CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s040

Trade Name: CHANTIX

Generic or Proper Name: varenicline tartrate

Sponsor: Pfizer, Inc.

Approval Date: 12/16/2016

Indication: CHANTIX is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928/S-040

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
REMS ASSESSMENT ACKNOWLEDGEMENT
RELEASE REMS REQUIREMENT

Pfizer, Inc.
235 E. 42nd Street
New York, NY 10017

Attention: Lilya I. Donohew, PhD
Senior Director, Worldwide Regulatory Affairs

Dear Dr. Donohew:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 18, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Chantix (varenicline) Tablets; 0.5 mg and 1 mg.

We also refer to our electronic communication dated December 1, 2016; and we acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated October 14, 2016. After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete.

This Prior Approval sNDA proposes changes to the package insert based on clinical trial data from the study titled, "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"; the supplement also proposes corresponding changes to the Medication Guide, and provides for proposed modification to the approved REMS for Chantix (varenicline).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submissions dated November 16, 2015, and February 18, 2016, reporting on and containing the final report for the following postmarketing requirement listed in the March 12, 2010, post-approval postmarketing requirements letter:

1544-4 A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric events, including but not limited to suicidality, in individuals using Chantix (varenicline), bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric events compared to individuals without prior history of psychiatric disorders while using Chantix (varenicline) as an aid to smoking cessation. The trial should be sufficiently powered to adequately assess clinically significant neuropsychiatric events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).

We have reviewed your submissions and conclude that the above requirement has been fulfilled.

We remind you that there are postmarketing requirements listed in the May 10, 2006, approval

letter, and the September 22, 2011, post-approval postmarketing requirement letter that are still open.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Chantix (varenicline) was originally approved on October 19, 2009, and the most recent modification was approved on August 12, 2016. The REMS consists of a Medication Guide, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of a revised Medication Guide to correspond to changes to the product label.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modification is necessary to minimize burden on the healthcare delivery system of complying with the REMS:

- Removal of the Medication Guide as an element of the REMS

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Chantix (varenicline) outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Therefore, because the Medication Guide as part of the REMS is no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS is no longer required for Chantix (varenicline).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Sharon H. Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON H HERTZ
12/16/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CHANTIX safely and effectively. See full prescribing information for CHANTIX.

CHANTIX® (varenicline) tablets, for oral use
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Boxed Warning-Removed	12/2016
Dosage and Administration, Usual Dosage for Adults (2.1)	8/2016
Warnings and Precautions,	
Neuropsychiatric Adverse Events including Suicidality (5.1)	12/2016
Warnings and Precautions, Somnambulism (5.6)	8/2016

----------INDICATIONS AND USAGE----------

CHANTIX is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment. (1 and 2.1)

----------DOSAGE AND ADMINISTRATION----------

- Begin CHANTIX dosing one week before the date set by the patient to stop smoking. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment. (2.1)
- Starting week: 0.5 mg once daily on days 1-3 and 0 5 mg twice daily on days 4-7. (2.1)
- Continuing Weeks: 1 mg twice daily for a total of 12 weeks. (2.1)
- An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence. (2.1)
- Consider a gradual approach to quitting smoking with CHANTIX for patients who are sure that they are not able or willing to quit abruptly. Patients should begin CHANTIX dosing and reduce smoking by 50% from baseline within the first four weeks, by an additional 50% in the next four weeks, and continue reducing with the goal of reaching complete abstinence by 12 weeks. Continue treatment for an additional 12 weeks, for a total of 24 weeks. (2.1)
- Severe Renal Impairment (estimated creatinine clearance less than 30 mL/min): Begin with 0.5 mg once daily and titrate to 0.5 mg twice daily. For patients with end-stage renal disease undergoing hemodialysis, a maximum of 0.5 mg daily may be given if tolerated. (2.2)
- Consider dose reduction for patients who cannot tolerate adverse effects. (2.1)
- Another attempt at treatment is recommended for those who fail to stop smoking or relapse when factors contributing to the failed attempt have been addressed. (2.1)
- Provide patients with appropriate educational materials and counseling to support the quit attempt. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 0.5 mg and 1 mg (3)

----------CONTRAINDICATIONS----------

History of serious hypersensitivity or skin reactions to CHANTIX. (4)

----------WARNINGS AND PRECAUTIONS----------

- Neuropsychiatric Adverse Events: Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Observe patients attempting to quit smoking with CHANTIX for the occurrence of such symptoms and instruct them to discontinue CHANTIX and contact a healthcare provider if they experience such adverse events. (5.1)
- Seizures: New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold. (5.2)
- Interaction with Alcohol: Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them. (5.3)
- Accidental Injury: Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (5.4)
- Cardiovascular Events: A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular (CV) disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their healthcare providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction (MI) or stroke. (5.5 and 6.1)
- Somnambulism: Cases of somnambulism have been reported in patients taking CHANTIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience somnambulism. (5.6 and 6.2)
- Angioedema and Hypersensitivity Reactions: Such reactions, including angioedema, infrequently life-threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur. (5.7 and 6.2)
- Serious Skin Reactions: Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.8 and 6.2)
- Nausea: Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Other Smoking Cessation Therapies: Safety and efficacy in combination with other smoking cessation therapies has not been established. Coadministration of varenicline and transdermal nicotine resulted in a high rate of discontinuation due to adverse events. (7.1)
- Effect of Smoking Cessation on Other Drugs: Pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) may be altered, necessitating dose adjustment. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CHANTIX is indicated for use as an aid to smoking cessation treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage for Adults

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Provide patients with appropriate educational materials and counseling to support the quit attempt.

The patient should set a date to stop smoking. Begin CHANTIX dosing one week before this date. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment.

CHANTIX should be taken orally after eating and with a full glass of water.

The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – end of treatment:	1 mg twice daily

Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence.

For patients who are sure that they are not able or willing to quit abruptly, consider a gradual approach to quitting smoking with CHANTIX. Patients should begin CHANTIX dosing and reduce smoking by 50% from baseline within the first four weeks, by an additional 50% in the next four weeks, and continue reducing with the goal of reaching complete abstinence by 12 weeks. Continue CHANTIX treatment for an additional 12 weeks, for a total of 24 weeks of treatment. Encourage patients to attempt quitting sooner if they feel ready *[see Clinical Studies (14.5)]*.

Patients who are motivated to quit, and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerability due to adverse events or who relapsed after treatment, should be encouraged to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed.

Consider a temporary or permanent dose reduction in patients who cannot tolerate the adverse effects of CHANTIX.

2.2 Dosage in Special Populations

Patients with Impaired Renal Function

No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance less than 30 mL per min), the recommended starting dose of CHANTIX is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice daily. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

Elderly and Patients with Impaired Hepatic Function

No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Use in Specific Populations (8.5)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsular, biconvex tablets: 0.5 mg (white to off-white, debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side) and 1 mg (light blue, debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side).

4 CONTRAINDICATIONS

CHANTIX is contraindicated in patients with a known history of serious hypersensitivity reactions or skin reactions to CHANTIX.

5 WARNINGS AND PRECAUTIONS

5.1 Neuropsychiatric Adverse Events including Suicidality

Serious neuropsychiatric adverse events have been reported in patients being treated with CHANTIX *[see Adverse Reactions (6.2)]*. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some patients who stopped smoking may have been experiencing symptoms of nicotine withdrawal, including depressed mood. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these adverse events occurred in patients taking CHANTIX who continued to smoke.

Neuropsychiatric adverse events occurred in patients without and with pre-existing psychiatric disease; some patients experienced worsening of their psychiatric illnesses. Some neuropsychiatric adverse events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol *[see Warnings and Precautions (5.3), Adverse Reactions (6.2)]*. Observe patients for the occurrence of neuropsychiatric adverse events. Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. The healthcare provider should evaluate the severity of the symptoms and the extent to which the patient is benefiting from treatment, and consider options including dose reduction, continued

treatment under closer monitoring, or discontinuing treatment. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported. However, the symptoms persisted in some cases; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The neuropsychiatric safety of CHANTIX was evaluated in a randomized, double-blind, active and placebo-controlled study that included patients without a history of psychiatric disorder (non-psychiatric cohort, N=3912) and patients with a history of psychiatric disorder (psychiatric cohort, N=4003). In the non-psychiatric cohort, CHANTIX was not associated with an increased incidence of clinically significant neuropsychiatric adverse events in a composite endpoint comprising anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, and irritability. In the psychiatric cohort, there were more events reported in each treatment group compared to the non-psychiatric cohort, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: Risk Differences (RDs) (95%CI) vs. placebo were 2.7% (-0.05, 5.4) for CHANTIX, 2.2% (-0.5, 4.9) for bupropion, and 0.4% (-2.2, 3.0) for transdermal nicotine. In the non-psychiatric cohort, neuropsychiatric adverse events of a serious nature were reported in 0.1% of CHANTIX-treated patients and 0.4% of placebo-treated patients. In the psychiatric cohort, neuropsychiatric events of a serious nature were reported in 0.6% of CHANTIX-treated patients, with 0.5% involving psychiatric hospitalization. In placebo-treated patients, serious neuropsychiatric events occurred in 0.6%, with 0.2% requiring psychiatric hospitalization *[see Clinical Studies (14.9)]*.

5.2 Seizures

During clinical trials and the post marketing experience, there have been reports of seizures in patients treated with CHANTIX. Some patients had no history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled. In most cases, the seizure occurred within the first month of therapy. Weigh this potential risk against the potential benefits before prescribing CHANTIX in patients with a history of seizures or other factors that can lower the seizure threshold. Advise patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment *[see Adverse Reactions (6.2)]*.

5.3 Interaction with Alcohol

There have been postmarketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some cases described unusual and sometimes aggressive behavior, and were often accompanied by amnesia for the events. Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol *[see Adverse Reactions (6.2)]*.

5.4 Accidental Injury

There have been postmarketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Advise patients to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

5.5 Cardiovascular Events

In a placebo-controlled clinical trial of CHANTIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX, but certain nonfatal cardiovascular events occurred more frequently in patients treated with CHANTIX than in patients treated with placebo *[see Adverse Reactions (6.1)]*. Table 1 below shows the incidence of deaths and of selected nonfatal serious cardiovascular events occurring more frequently in the CHANTIX arm compared to the placebo arm. These events were adjudicated by an independent blinded committee. Nonfatal serious cardiovascular events not listed occurred at the same incidence or more commonly in the placebo arm. Patients with more than one cardiovascular event of the same type are counted only once per row. Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina.

Table 1. Mortality and Adjudicated Nonfatal Serious Cardiovascular Events in the Placebo-Controlled CHANTIX Trial in Patients with Stable Cardiovascular Disease

Mortality and Cardiovascular Events	CHANTIX (N=353) n (%)	Placebo (N=350) n (%)
Mortality (Cardiovascular & All-cause up to 52 wks)		
Cardiovascular death	1 (0.3)	2 (0.6)
All-cause mortality	2 (0.6)	5 (1.4)
Nonfatal Cardiovascular Events (rate on CHANTIX > Placebo)		
Up to 30 days after treatment		
Nonfatal myocardial infarction	4 (1.1)	1 (0.3)
Nonfatal Stroke	2 (0.6)	0 (0)
Beyond 30 days after treatment & up to 52 weeks		
Nonfatal myocardial infarction	3 (0.8)	2 (0.6)
Need for coronary revascularization	7 (2.0)	2 (0.6)
Hospitalization for angina pectoris	6 (1.7)	4 (1.1)
Transient ischemia attack	1 (0.3)	0 (0)
New diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure	5 (1.4)	2 (0.6)

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHANTIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHANTIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis. There were lower rates of all-cause mortality (CHANTIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHANTIX 2 [0.05%]; placebo 2 [0.07%]) in the CHANTIX arms compared with the placebo arms in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small

number of MACE occurred in the trials included in the meta-analysis, as described in Table 2. These events occurred primarily in patients with known cardiovascular disease.

Table 2. Number of MACE cases, Hazard Ratio and Rate Difference in a Meta-Analysis of 15 Clinical Trials Comparing CHANTIX to Placebo*

	CHANTIX N=4190	**Placebo N=2812**
MACE cases, n (%)	13 (0.31%)	6 (0.21%)
Patient-years of exposure	1316	839
Hazard Ratio (95% CI)		
	1.95 (0.79, 4.82)	
Rate Difference per 1,000 patient-years (95% CI)		
	6.30 (-2.40, 15.10)	

*Includes MACE occurring up to 30 days post-treatment.

The meta-analysis showed that exposure to CHANTIX resulted in a hazard ratio for MACE of 1.95 (95% confidence interval from 0.79 to 4.82) for patients up to 30 days after treatment; this is equivalent to an estimated increase of 6.3 MACE events per 1,000 patient-years of exposure. The meta-analysis showed higher rates of CV endpoints in patients on CHANTIX relative to placebo across different time frames and pre-specified sensitivity analyses, including various study groupings and CV outcomes. Although these findings were not statistically significant they were consistent. Because the number of events was small overall, the power for finding a statistically significant difference in a signal of this magnitude is low.

CHANTIX was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a healthcare provider of new or worsening symptoms of cardiovascular disease. The risks of CHANTIX should be weighed against the benefits of its use in smokers with cardiovascular disease. Smoking is an independent and major risk factor for cardiovascular disease. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.

5.6 Somnambulism

Cases of somnambulism have been reported in patients taking CHANTIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience somnambulism *[see Adverse Reactions (6.2)]*.

5.7 Angioedema and Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX *[see Adverse Reactions (6.2), Patient Counseling Information (17)]*. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.

5.8 Serious Skin Reactions

There have been postmarketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients using CHANTIX *[see Adverse Reactions (6.2)]*. As these skin reactions can be life-threatening, instruct patients to stop taking CHANTIX and contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

5.9 Nausea

Nausea was the most common adverse reaction reported with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. For patients treated to the maximum recommended dose of 1 mg twice daily following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg twice daily following initial titration, the incidence was 16% compared with 11% for placebo. Approximately 3% of patients treated with CHANTIX 1 mg twice daily in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, a dose reduction should be considered.

6 ADVERSE REACTIONS

The following serious adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the labeling:

- Neuropsychiatric Adverse Events including Suicidality *[see Warnings and Precautions (5.1)]*
- Seizures *[see Warnings and Precautions (5.2)]*
- Interaction with alcohol *[see Warnings and Precautions (5.3)]*
- Accidental injury *[see Warnings and Precautions (5.4)]*
- Cardiovascular events *[see Warnings and Precautions (5.5)]*
- Somnambulism *[see Warnings and Precautions (5.6)]*
- Angioedema and hypersensitivity reactions *[see Warnings and Precautions (5.7)]*
- Serious skin reactions *[see Warnings and Precautions (5.8)]*

In the placebo-controlled premarketing studies, the most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

The treatment discontinuation rate due to adverse events in patients dosed with 1 mg twice daily was 12% for CHANTIX, compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates that are higher than placebo for the most common adverse events in CHANTIX-treated patients were as follows: nausea (3% vs. 0.5% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo).

Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the premarketing development of CHANTIX, over 4500 subjects were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less.

The most common adverse event associated with CHANTIX treatment is nausea, occurring in 30% of patients treated at the recommended dose, compared with 10% in patients taking a comparable placebo regimen *[see Warnings and Precautions (5.9)]*.

Table 3 shows the adverse events for CHANTIX and placebo in the 12- week fixed dose premarketing studies with titration in the first week [Studies 2 (titrated arm only), 4, and 5]. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

MedDRA High Level Group Terms (HLGT) reported in ≥ 5% of patients in the CHANTIX 1 mg twice daily dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥ 1% of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (HLGTs ≥5% of patients in the 1 mg BID CHANTIX Group and more commonly than Placebo and PT ≥ 1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1 mg BID N=821	Placebo N=805
GASTROINTESTINAL (GI)			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain *	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4
PSYCHIATRIC DISORDERS			
Sleep Disorder/Disturbances			
Insomnia **	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13
Neurological Disorders NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIR/THORACIC/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrition Disorders			
Increased appetite	4	3	2
Decreased appetite/ Anorexia	1	2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort

** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern and frequency of adverse events during the longer-term premarketing trials was similar to those described in Table 3, though several of the most common events were reported by a greater proportion of patients with long-term use (e.g., nausea was reported in 40% of patients treated with CHANTIX 1 mg twice daily in a one year study, compared to 8% of placebo-treated patients).

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all premarketing clinical trials and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline. Adverse events were categorized using MedDRA, Version 16.0. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Blood and Lymphatic System Disorders. *Infrequent* anemia, lymphadenopathy. *Rare* leukocytosis, splenomegaly, thrombocytopenia.
Cardiac Disorders. *Infrequent* angina pectoris, myocardial infarction, palpitations, tachycardia. *Rare* acute coronary syndrome, arrhythmia, atrial fibrillation, bradycardia, cardiac flutter, cor pulmonale, coronary artery disease, ventricular extrasystoles.
Ear and Labyrinth Disorders. *Infrequent* tinnitus, vertigo. *Rare* deafness, Meniere's disease.
Endocrine Disorders. *Infrequent* thyroid gland disorders.
Eye Disorders. *Infrequent* conjunctivitis, eye irritation, eye pain, vision blurred, visual impairment. *Rare* blindness transient, cataract subcapsular, dry eye, night blindness, ocular vascular disorder, photophobia, vitreous floaters.
Gastrointestinal Disorders. *Frequent* diarrhea, toothache. *Infrequent* dysphagia, eructation, gastritis, gastrointestinal hemorrhage, mouth ulceration. *Rare* enterocolitis, esophagitis, gastric ulcer, intestinal obstruction, pancreatitis acute.
General Disorders and Administration Site Conditions. *Frequent* chest pain. *Infrequent* chest discomfort, chills, edema, influenza-like illness, pyrexia.
Hepatobiliary Disorders. *Rare* gall bladder disorder.
Investigations. *Frequent* liver function test abnormal, weight increased. *Infrequent* electrocardiogram abnormal. *Rare* muscle enzyme increased, urine analysis abnormal.
Metabolism and Nutrition Disorders. *Infrequent* diabetes mellitus, hypoglycemia. *Rare* hyperlipidemia, hypokalemia.
Musculoskeletal and Connective Tissue Disorders. *Frequent*: arthralgia, back pain, myalgia. *Infrequent* arthritis, muscle cramp, musculoskeletal pain. *Rare* myositis, osteoporosis.
Nervous System Disorders. *Frequent* disturbance in attention, dizziness. *Infrequent* amnesia, convulsion, migraine, parosmia, syncope, tremor. *Rare* balance disorder, cerebrovascular accident, dysarthria, mental impairment, multiple sclerosis, VIIth nerve paralysis, nystagmus, psychomotor hyperactivity, psychomotor skills impaired, restless legs syndrome, sensory disturbance, transient ischemic attack, visual field defect.
Psychiatric Disorders. *Infrequent* dissociation, libido decreased, mood swings, thinking abnormal. *Rare* bradyphrenia, disorientation, euphoric mood.
Renal and Urinary Disorders. *Infrequent* nocturia, pollakiuria, urine abnormality. *Rare* nephrolithiasis, polyuria, renal failure acute, urethral syndrome, urinary retention.
Reproductive System and Breast Disorders. *Frequent* menstrual disorder. *Infrequent* erectile dysfunction. *Rare* sexual dysfunction.
Respiratory, Thoracic and Mediastinal Disorders. *Frequent* respiratory disorders. *Infrequent* asthma, epistaxis, rhinitis allergic, upper respiratory tract inflammation. *Rare* pleurisy, pulmonary embolism.
Skin and Subcutaneous Tissue Disorders. *Infrequent* acne, dry skin, eczema, erythema, hyperhidrosis, urticaria. *Rare* photosensitivity reaction, psoriasis.
Vascular Disorders. *Infrequent* hot flush. *Rare* thrombosis.

CHANTIX has also been studied in postmarketing trials including (1) a trial conducted in patients with chronic obstructive pulmonary disease (COPD), (2) a trial conducted in generally healthy patients (similar to those in the premarketing studies) in which they were allowed to select a quit date between days 8 and 35 of treatment ("alternative quit date instruction trial"), (3) a trial conducted in patients who did not succeed in stopping smoking during prior CHANTIX therapy, or who relapsed after treatment ("re-treatment trial"), (4) a trial conducted in patients with stable cardiovascular disease, (5) a trial conducted in patients with stable schizophrenia or schizoaffective disorder, (6) a trial conducted in patients with major depressive disorder, (7) a postmarketing neuropsychiatric safety outcome trial in patients without or with a history of psychiatric disorder, and (8) a trial in patients who were not able or willing to quit abruptly and who were instructed to quit gradually ("gradual approach to quitting smoking trial").

Adverse events in the trial of patients with COPD, in the alternative quit date instruction trial, and in the gradual approach to quitting smoking trial were similar to those observed in premarketing studies. In the re-treatment trial, the profile of common adverse events was similar to that previously reported, but, in addition, varenicline-treated patients also commonly reported diarrhea (6% vs. 4% in placebo-treated patients), depressed mood disorders and disturbances (6% vs. 1%), and other mood disorders and disturbances (5% vs. 2%).

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to premarketing studies. Treatment-emergent (on-treatment or 30 days after treatment) cardiovascular events reported with a frequency ≥ 1% in either treatment group in this study were angina pectoris (3.7% and 2.0% for varenicline and placebo, respectively), chest pain (2.5% vs. 2.3%), peripheral edema (2.0% vs. 1.1%), hypertension (1.4% vs. 2.6%), and palpitations (0.6 % vs. 1.1%). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment emergent and non-treatment emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency≥1% in either treatment group: nonfatal MI (1.1% vs. 0 3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow-up to 52 weeks, the adjudicated events included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1 1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

In the trial of patients with stable schizophrenia or schizoaffective disorder, 128 smokers on antipsychotic medication were randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up. The most common adverse events in patients taking varenicline were nausea (24% vs. 14.0% on placebo), headache (11% vs. 19% on placebo) and vomiting (11% vs. 9% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event that occurred in either treatment group in ≥5% of subjects at a rate higher in the varenicline group than in placebo (10% vs. 5%). These common and neuropsychiatric adverse events occurred on treatment or within 30 days after the last dose of study drug. There was no consistent worsening of schizophrenia in either treatment group as measured by the Positive and Negative Syndrome Scale. There were no overall changes in extra-pyramidal signs, as measured by the Simpson-Angus Rating Scale. The Columbia-Suicide Severity Rating Scale was administered at baseline and at clinic visits during the treatment and non-treatment follow-up phases. Over half of the patients had a lifetime history of suicidal behavior and/or ideation (62% on varenicline vs. 51% on placebo), but at baseline, no patients in the varenicline group reported suicidal behavior and/or ideation vs. one patient in the placebo group (2%). Suicidal behavior and/or ideation were reported in 11% of the varenicline-treated and 9% of the placebo-treated patients during the treatment phase. During the post-treatment phase, suicidal behavior and/or ideation were reported in 11% of patients in the varenicline group and 5% of patients in the placebo group. Many of the patients reporting suicidal behavior and ideation in the follow-up phase had not reported such experiences in the treatment phase. However, no new suicidal ideation or behavior emerged in either treatment group shortly (within one week) after treatment discontinuation (a phenomenon noted in postmarketing reporting). There were no completed suicides. There was one suicide attempt in a varenicline-treated patient. The limited data available from this single smoking cessation study are not sufficient to allow conclusions to be drawn.

In the trial of patients with major depressive disorder, the most common adverse events (≥ 10%) in subjects taking varenicline were nausea (27% vs. 10% on placebo), headache (17 vs. 11%), abnormal dreams (11% vs. 8%), insomnia (11% vs. 5%) and irritability (11% vs. 8%). Additionally, the following psychiatric AEs were reported in ≥ 2% of patients in either treatment group (varenicline or placebo, respectively): anxiety (7% vs. 9%), agitation (7% vs. 4%), depressed mood disorders and disturbances (11% vs. 9%), tension (4% vs. 3%), hostility (2% vs. 0.4%) and restlessness (2% vs. 2%). Patients treated with varenicline were more likely than patients treated with placebo to report one of various events related to hostility and aggression (3% vs. 1%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression during the study in either treatment group. The percentage of subjects with suicidal ideation and/or behavior was similar between the varenicline and placebo groups during treatment (6% and 8%, respectively) and the non-treatment follow-up (6% and 6%, respectively). There was one event of intentional self-injury/possible suicide attempt during treatment (Day 73) in a subject in the placebo group. Suicide could not be ruled out in one subject who died by an overdose of illicit drugs 76 days after last dose of study drug in the varenicline group.

In the trial of patients without or with a history of psychiatric disorder, the most common adverse events in subjects treated with varenicline were similar to those observed in premarketing studies. Adverse events reported in ≥ 10% of subjects treated with varenicline in the entire study population were nausea (25% vs. 7% on placebo) and headache (12% vs. 10% on placebo). Additionally, the following psychiatric adverse events were reported in ≥ 2% of patients in either treatment group (varenicline vs. placebo) by cohort. For the non-psychiatric cohort, these adverse events were abnormal dreams (8% vs. 4%), agitation (3% vs. 3%), anxiety (5% vs. 6%), depressed mood (3% vs. 3%), insomnia (10% vs. 7%), irritability (3% vs. 4%), sleep disorder (3% vs. 2%). For the psychiatric cohort, these adverse events were abnormal dreams (12% vs. 5%), agitation (5% vs. 4%), anxiety (8% vs. 6%), depressed mood (5% vs. 5%), depression (5% vs. 5%), insomnia (9% vs. 7%), irritability (5% vs. 7%), nervousness (2% vs. 3%), sleep disorder (3% vs. 2%).

6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking CHANTIX *[see Warnings and Precautions (5.1)]*.

There have been postmarketing reports of new or worsening seizures in patients treated with CHANTIX *[see Warnings and Precautions (5.2)]*.

There have been postmarketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior *[see Warnings and Precautions (5.1) and (5.3)]*.

There have been reports of hypersensitivity reactions, including angioedema *[see Warnings and Precautions (5.7)]*.

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX *[see Warnings and Precautions (5.8)]*.

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking CHANTIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out *[see Warnings and Precautions (5.5)]*.

There have been reports of hyperglycemia in patients following initiation of CHANTIX.

There have been reports of somnambulism, some resulting in harmful behavior to self, others, or property in patients treated with CHANTIX *[see Warnings and Precautions (5.6)]*.

7 DRUG INTERACTIONS

Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions *[see Clinical Pharmacology (12.3)]*.

7.1 Use with Other Drugs for Smoking Cessation

Safety and efficacy of CHANTIX in combination with other smoking cessation therapies have not been studied.

Bupropion

Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.

Nicotine replacement therapy (NRT)

Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. In this study, eight of twenty-two (36%) patients treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of patients treated with NRT and placebo.

7.2 Effect of Smoking Cessation on Other Drugs

Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available human data on the use of CHANTIX in pregnant women are not sufficient to inform a drug associated risk. Smoking during pregnancy is associated with maternal, fetal, and neonatal risks *[see Clinical Considerations]*. In animal studies, varenicline did not result in major malformations but caused decreased fetal weights in rabbits when dosed during organogenesis at exposures equivalent to 50 times the exposure at the maximum recommended human dose (MRHD). Additionally, administration of varenicline to pregnant rats during organogenesis through lactation produced developmental toxicity in offspring at maternal exposures equivalent to 36 times human exposure at the MRHD *[see Data]*.

The estimated background risk of oral clefts is increased by approximately 30% in infants of women who smoke during pregnancy, compared to pregnant women who do not smoke. The background risk of other major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk
Smoking during pregnancy causes increased risks of orofacial clefts, premature rupture of membranes, placenta previa, placental abruption, ectopic pregnancy, fetal growth restriction and low birth weight, stillbirth, preterm delivery and shortened gestation, neonatal death, sudden infant death syndrome and reduction of lung function in infants. It is not known whether quitting smoking with CHANTIX during pregnancy reduces these risks.

Data

Animal Data
Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD of 1 mg twice daily based on AUC). Fetal weight reduction did not occur in rabbits at exposures 23 times the human exposure at the MRHD based on AUC.

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain was observed at 15 mg/kg/day (36 times the human exposure at the MRHD based on AUC). However, decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

8.2 Lactation

Risk Summary

There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats *[see Data]*. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. The lack of clinical data during lactation precludes a clear determination of the risk of CHANTIX to an infant during lactation; however the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CHANTIX and any potential adverse effects on the breastfed child from CHANTIX or from the underlying maternal condition.

Clinical Considerations

Because there are no data on the presence of varenicline in human milk and the effects on the breastfed infant, breastfeeding women should monitor their infant for seizures and excessive vomiting, which are adverse reactions that have occurred in adults that may be clinically relevant in breastfeeding infants.

Data

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate through gestation and lactation Mean serum concentrations of varenicline in the nursing pups were 5-22% of maternal serum concentrations.

8.4 Pediatric Use

Safety and effectiveness of CHANTIX in pediatric patients have not been established.

8.5 Geriatric Use

A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 years) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.2)]*.

No dosage adjustment is recommended for elderly patients.

8.6 Renal Impairment

Varenicline is substantially eliminated by renal glomerular filtration along with active tubular secretion. Dose reduction is not required in patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), and for patients with end-stage renal disease undergoing hemodialysis, dosage adjustment is needed *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Varenicline is not a controlled substance.

9.3 Dependence

Humans

Fewer than 1 out of 1,000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction.

In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

Animals

Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine; however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

10 OVERDOSAGE

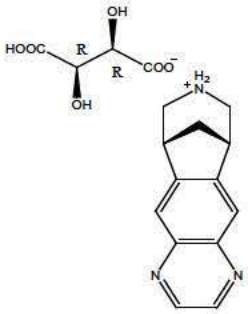
In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end-stage renal disease *[see Clinical Pharmacology (12.3)]*, however, there is no experience in dialysis following overdose.

11 DESCRIPTION

CHANTIX tablets contain varenicline (as the tartrate salt), which is a partial nicotinic agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes.

Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3- h][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361 35 Daltons, and a molecular formula of $C_{13}H_{13}N_3 \cdot C_4H_6O_6$. The chemical structure is:



CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1 mg CHANTIX tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's activity at α4β2 sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to these receptors.

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to α4β2 receptors than to other common nicotinic receptors (>500-fold α3β4, >3,500-fold α7, >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (>2,000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.

12.3 Pharmacokinetics

Absorption

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses.

In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%.

Food Effect
Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Distribution

Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

Elimination

The elimination half-life of varenicline is approximately 24 hours.

Metabolism
Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine.

Excretion
Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

Specific Populations

There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Age Geriatric Patients
A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 years) for 7 consecutive days was similar to that of younger subjects.

Age Pediatric Patients
Because the safety and effectiveness of CHANTIX in pediatric patients have not been established, CHANTIX is not recommended for use in patients under 18 years of age. Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight >55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population.

Renal Impairment
Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min). In subjects with moderate renal impairment (estimated creatinine clearance ≥30 mL/min and ≤50 mL/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min). In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD) undergoing a three-hour session of hemodialysis for three days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 days. The plasma Cmax and AUC of varenicline noted in this setting were similar to those of healthy subjects receiving 1 mg twice daily *[see Dosage and Administration (2.2), Use in Specific Populations (8.6)]*. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis *[see Overdosage (10)]*.

Hepatic Impairment
Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment.

Drug-Drug Interactions

In vitro studies demonstrated that varenicline does not inhibit the following cytochrome P450 enzymes (IC50 >6400 ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

In vitro studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g., metformin *[see below]*) are unlikely to be affected by varenicline.

In vitro studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter OCT2. Co-administration with inhibitors of OCT2 (e.g., cimeditine *[see below]*) may not necessitate a dose adjustment of CHANTIX as the increase in systemic exposure to CHANTIX is not expected to be clinically meaningful. Furthermore, since metabolism of varenicline represents less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of CHANTIX *[see Clinical Pharmacology (12.3)]*; therefore, a dose adjustment of CHANTIX would not be required.

Drug interaction studies were performed with varenicline and digoxin, warfarin, transdermal nicotine, bupropion, cimetidine, and metformin. No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

Metformin
When co-administered to 30 smokers, varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

Cimetidine
Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance.

Digoxin
Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

Warfarin
Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics *[see Drug Interactions (7.2)]*.

Use with Other Drugs for Smoking Cessation
Bupropion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers *[see Drug Interactions (7.1)]*.

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for NRT alone *[see Drug Interactions (7.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily (MRHD) exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the MRHD exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the MRHD exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis

Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Impairment of Fertility

There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the MRHD exposure based on AUC at 1 mg twice daily). Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day. However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day. This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the MRHD exposure based on AUC at 1 mg twice daily).

14 CLINICAL STUDIES

The efficacy of CHANTIX in smoking cessation was demonstrated in six clinical trials in which a total of 3659 chronic cigarette smokers (≥10 cigarettes per day) were treated with CHANTIX. In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide (CO≤10 ppm) at weekly visits. Among the CHANTIX-treated patients enrolled in these studies, the completion rate was 65%. Except for the dose-ranging study (Study 1) and the maintenance of abstinence study (Study 6), patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. Most patients enrolled in these trials were white (79-96%). All studies enrolled almost equal numbers of men and women. The average age of patients in these studies was 43 years. Patients on average had smoked about 21 cigarettes per day for an average of approximately 25 years. Patients set a date to stop smoking (target quit date) with dosing starting 1 week before this date.

Seven additional studies evaluated the efficacy of CHANTIX in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease *[see Clinical Studies (14.7)]*, in patients instructed to select their quit date within days 8 and 35 of treatment *[see Clinical Studies (14.4)]*, patients with major depressive disorder *[see Clinical Studies (14.8)]*, patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment *[see Clinical Studies (14.6)]*, in patients without or with a history of psychiatric disorder enrolled in a postmarketing neuropsychiatric safety outcome trial *[see Warnings and Precautions (5.1), Clinical Studies (14.9)]*, and in patients who were not able or willing to quit abruptly and were instructed to quit gradually *[see Clinical studies (14.5)]*.

In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines.

14.1 Initiation of Abstinence

Study 1

This was a six-week dose-ranging study comparing CHANTIX to placebo. This study provided initial evidence that CHANTIX at a total dose of 1 mg per day or 2 mg per day was effective as an aid to smoking cessation.

Study 2

This study of 627 patients compared CHANTIX 1 mg per day and 2 mg per day with placebo. Patients were treated for 12 weeks (including one-week titration) and then were followed for 40 weeks post-treatment. CHANTIX was given in two divided doses daily. Each dose of CHANTIX was given in two different regimens, with and without initial dose-titration, to explore the effect of different dosing regimens on tolerability. For the titrated groups, dosage was titrated up over the course of one week, with full dosage achieved starting with the second week of dosing. The titrated and nontitrated groups were pooled for efficacy analysis.

Forty-five percent of patients receiving CHANTIX 1 mg per day (0.5 mg twice daily) and 51% of patients receiving 2 mg per day (1 mg twice daily) had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% of patients in the placebo group (Figure 1). In addition, 31% of the 1 mg per day group and 31% of the 2 mg per day group were continuously abstinent from one week after TQD through the end of treatment as compared to 8% of the placebo group.

Study 3

This flexible-dosing study of 312 patients examined the effect of a patient-directed dosing strategy of CHANTIX or placebo. After an initial one-week titration to a dose of 0.5 mg twice daily, patients could adjust their dosage as often as they wished between 0.5 mg once daily to 1 mg twice daily per day. Sixty-nine percent of patients titrated to the maximum allowable dose at any time during the study. For 44% of patients, the modal dose selected was 1 mg twice daily; for slightly over half of the study participants, the modal dose selected was 1 mg/day or less.

Of the patients treated with CHANTIX, 40% had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% in the placebo group. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 9% of the placebo group.

Study 4 and Study 5

These identical double-blind studies compared CHANTIX 2 mg per day, bupropion sustained-release (SR) 150 mg twice daily, and placebo. Patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. The CHANTIX dosage of 1 mg twice daily was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg twice daily for the next 4 days. The bupropion SR dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Study 4 enrolled 1022 patients and Study 5 enrolled 1023 patients. Patients inappropriate for bupropion treatment or patients who had previously used bupropion were excluded.

In Study 4, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (17%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 12% of the placebo group and 23% of the bupropion SR group.

Similarly in Study 5, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (18%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 11% of the placebo group and 21% of the bupropion SR group.

Figure 1: Continuous Abstinence, Weeks 9 through 12

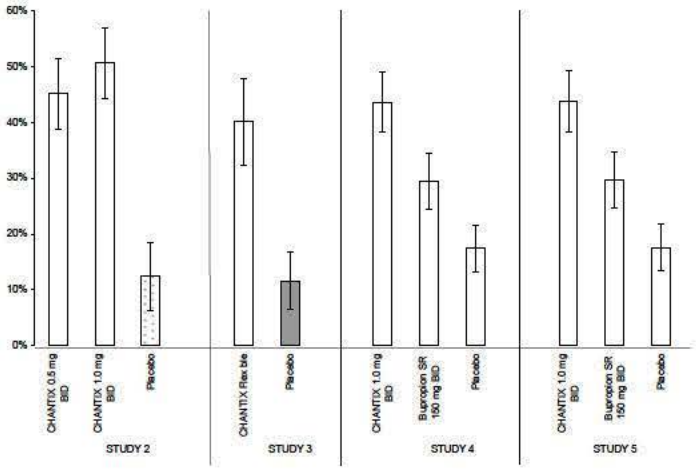


Table 4: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	CHANTIX 0.5 mg BID	CHANTIX 1 mg BID	CHANTIX Flexible	Bupropion SR	Placebo
Study 2	45% (39%, 51%)	51% (44%, 57%)			12% (6%, 18%)
Study 3			40% (32%, 48%)		12% (7%, 17%)
Study 4		44% (38%, 49%)		30% (25%, 35%)	17% (13%, 22%)
Study 5		44% (38%, 49%)		30% (25%, 35%)	18% (14%, 22%)

BID = twice daily

14.2 Urge to Smoke

Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale "urge to smoke" item, CHANTIX reduced urge to smoke compared to placebo.

14.3 Long-Term Abstinence

Studies 1 through 5 included 40 weeks of post-treatment follow-up. In each study, CHANTIX-treated patients were more likely to maintain abstinence throughout the follow-up period than were patients treated with placebo (Figure 2, Table 5).

Figure 2: Continuous Abstinence, Weeks 9 through 52

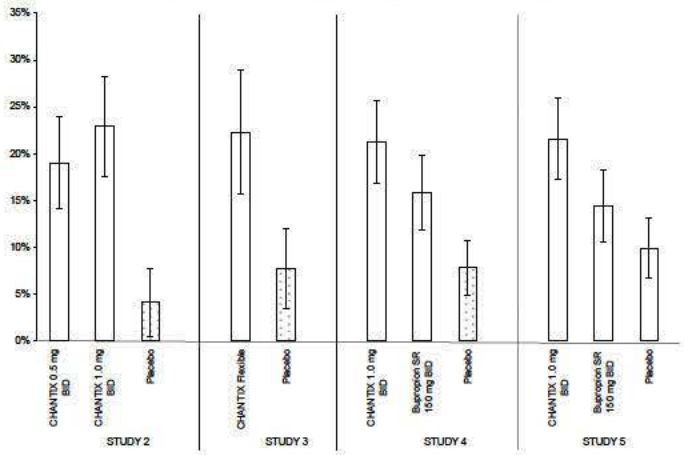


Table 5: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) Across Different Studies

	CHANTIX 0.5 mg BID	CHANTIX 1 mg BID	CHANTIX Flexible	Bupropion SR	Placebo
Study 2	19% (14%, 24%)	23% (18%, 28%)			4% (1%, 8%)
Study 3			22% (16%, 29%)		8% (3%, 12%)
Study 4		21% (17%, 26%)		16% (12%, 20%)	8% (5%, 11%)
Study 5		22% (17%, 26%)		14% (11%, 18%)	10% (7%, 13%)

BID = twice daily

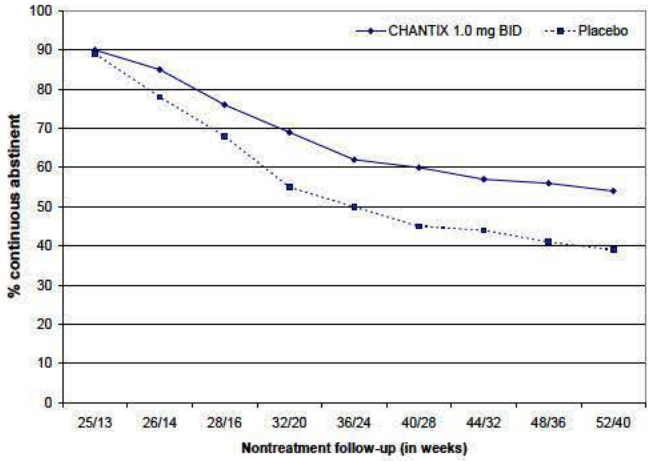
Study 6

This study assessed the effect of an additional 12 weeks of CHANTIX therapy on the likelihood of long-term abstinence. Patients in this study (N=1927) were treated with open-label CHANTIX 1 mg twice daily for 12 weeks. Patients who had stopped smoking for at least a week by Week 12 (N= 1210) were then randomized to double-blind treatment with CHANTIX (1 mg twice daily) or placebo for an additional 12 weeks and then followed for 28 weeks post-treatment.

The continuous abstinence rate from Week 13 through Week 24 was higher for patients continuing treatment with CHANTIX (70%) than for patients switching to placebo (50%). Superiority to placebo was also maintained during 28 weeks post-treatment follow-up (CHANTIX 54% versus placebo 39%).

In Figure 3 below, the x-axis represents the study week for each observation, allowing a comparison of groups at similar times after discontinuation of CHANTIX; post-CHANTIX follow-up begins at Week 13 for the placebo group and Week 25 for the CHANTIX group. The y-axis represents the percentage of patients who had been abstinent for the last week of CHANTIX treatment and remained abstinent at the given timepoint.

Figure 3: Continuous Abstinence Rate during Nontreatment Follow-Up



14.4 Alternative Instructions for Setting a Quit Date

CHANTIX was evaluated in a double-blind, placebo-controlled trial where patients were instructed to select a target quit date between Day 8 and Day 35 of treatment. Subjects were randomized 3:1 to CHANTIX 1 mg twice daily (N=486) or placebo (N=165) for 12 weeks of treatment and followed for another 12 weeks post-treatment. Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (54%) compared to patients treated with placebo (19%) and from weeks 9 through 24 (35%) compared to subjects treated with placebo (13%).

14.5 Gradual Approach to Quitting Smoking

CHANTIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomized to either CHANTIX 1 mg twice daily (N=760) or placebo (N=750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with CHANTIX had a significantly higher Continuous Abstinence Rate compared with placebo at weeks 15 through 24 (32% vs. 7%) and weeks 15 through 52 (24% vs. 6%).

14.6 Re-Treatment Study

CHANTIX was evaluated in a double-blind, placebo-controlled trial of patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment. Subjects were randomized 1:1 to CHANTIX 1 mg twice daily (N=249) or placebo (N=245) for 12 weeks of treatment and followed for 40 weeks post-treatment. Patients included in this study had taken CHANTIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks.

Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (45%) compared to patients treated with placebo (12%) and from weeks 9 through 52 (20%) compared to subjects treated with placebo (3%).

Table 6: Continuous Abstinence (95% confidence interval), Re-Treatment Study

	Weeks 9 through 12		Weeks 9 through 52	
	CHANTIX 1 mg BID	Placebo	CHANTIX 1 mg BID	Placebo
Retreatment Study	45% (39%, 51%)	12% (8%, 16%)	20% (15%, 25%)	3% (1%, 5%)

BID = twice daily

14.7 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 35 to 75 years with stable, documented cardiovascular disease (diagnoses other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomized to CHANTIX 1 mg twice daily (N=353) or placebo (N=350) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47%) compared to subjects treated with placebo (14%) and from week 9 through 52 (20%) compared to subjects treated with placebo (7%).

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged ≥ 35 years with mild-to-moderate COPD with post-bronchodilator FEV_1/FVC <70% and $FEV_1 \geq 50\%$ of predicted normal value. Subjects were randomized to CHANTIX 1 mg twice daily (N=223) or placebo (N=237) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (41%) compared to subjects treated with placebo (9%) and from week 9 through 52 (19%) compared to subjects treated with placebo (6%).

Table 7: Continuous Abstinence (95% confidence interval), Studies in Patients with Cardiovascular Disease (CVD) and Chronic Obstructive Pulmonary Disease (COPD)

	Weeks 9 through 12		Weeks 9 through 52	
	CHANTIX 1 mg BID	Placebo	CHANTIX 1 mg BID	Placebo
CVD Study	47% (42%, 53%)	14% (11%, 18%)	20% (16%, 24%)	7% (5%, 10%)
COPD Study	41% (34%, 47%)	9% (6%, 13%)	19% (14%, 24%)	6% (3%, 9%)

BID = twice daily

14.8 Subjects with Major Depressive Disorder

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 18 to 75 years with major depressive disorder without psychotic features (DSM-IV TR). If on medication, subjects were to be on a stable antidepressant regimen for at least two months. If not on medication, subjects were to have experienced a major depressive episode in the past 2 years, which was successfully treated. Subjects were randomized to CHANTIX 1 mg twice daily (N=256) or placebo (N=269) for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (36%) compared to subjects treated with placebo (16%) and from week 9 through 52 (20%) compared to subjects treated with placebo (10%).

Table 8: Continuous Abstinence (95% confidence interval), Study in Patients with Major Depressive Disorder (MDD)

	Weeks 9 through 12		Weeks 9 through 52	
	CHANTIX 1 mg BID	Placebo	CHANTIX 1 mg BID	Placebo
MDD Study	36% (30%, 42%)	16% (11%, 20%)	20% (15%, 25%)	10% (7%, 14%)

BID = twice daily

14.9 Postmarketing Neuropsychiatric Safety Outcome Trial

CHANTIX was evaluated in a randomized, double-blind, active and placebo-controlled trial that included subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3912) and with a history of psychiatric disorder (psychiatric cohort, N=4003). Subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomized 1:1:1:1 to CHANTIX 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment. *[See Warnings and Precautions (5.1)]*

A composite safety endpoint intended to capture clinically significant neuropsychiatric (NPS) adverse events included the following NPS adverse events: anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, irritability, suicidal ideation, suicidal behavior or completed suicide.

As shown in Table 9, the use of CHANTIX, bupropion, and NRT in the non-psychiatric cohort was not associated with an increased risk of clinically significant NPS adverse events compared with placebo. Similarly, in the non-psychiatric cohort, the use of CHANTIX was not associated with an increased risk of clinically significant NPS adverse events in the composite safety endpoint compared with bupropion or NRT.

Table 9. Number of Patients with Clinically Significant or Serious NPS Adverse Events by Treatment Group Among Patients without a History of Psychiatric Disorder

	CHANTIX (N=975) n (%)	**Bupropion (N=968) n (%)**	**NRT (N=987) n (%)**	**Placebo (N=982) n (%)**
Clinically significant NPS	30 (3.1)	34 (3.5)	33 (3 3)	40 (4.1)
Serious NPS	1 (0.1)	5 (0.5)	1 (0.1)	4 (0.4)
Psychiatric hospitalizations	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.1)

As shown in Table 10, there were more clinically significant NPS adverse events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort (Table 9). The incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: Risk Differences (RDs) (95%CI) vs placebo were 2.7% (-0.05, 5.4) for CHANTIX, 2.2% (-0.5, 4.9) for bupropion, and 0.4% (-2.2, 3.0) for NRT transdermal nicotine.

Table 10. Number of Patients with Clinically Significant or Serious NPS Adverse Events by Treatment Group Among Patients with a History of Psychiatric Disorder

	CHANTIX (N=1007) n (%)	**Bupropion (N=1004) n (%)**	**NRT (N=995) n (%)**	**Placebo (N=997) n (%)**
Clinically Significant NPS	123 (12.2)	118 (11.8)	98 (9.8)	95 (9.5)
Serious NPS	6 (0.6)	8 (0.8)	4 (0.4)	6 (0.6)
Psychiatric hospitalizations	5 (0.5)	8 (0.8)	4 (0.4)	2 (0.2)

There was one completed suicide, which occurred during treatment in a patient treated with placebo in the non-psychiatric cohort. There were no completed suicides reported in the psychiatric cohort.

In both cohorts, subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo.

Table 11: Continuous Abstinence (95% confidence interval), Study in Patients with or without a History of Psychiatric Disorder

	CHANTIX 1 mg BID	**Bupropion SR 150 mg BID**	**NRT 21 mg/day with taper**	**Placebo**
Weeks 9 through 12				
Non-Psychiatric Cohort	38% (35%, 41%)	26% (23%, 29%)	26% (24%, 29%)	14% (12%, 16%)
Psychiatric Cohort	29% (26%, 32%)	19% (17%, 22%)	20% (18%, 23%)	11% (10%, 14%)
Weeks 9 through 24				
Non-Psychiatric Cohort	25% (23%, 28%)	19% (16%, 21%)	18% (16%, 21%)	11% (9%, 13%)
Psychiatric Cohort	18% (16%, 21%)	14% (12%, 16%)	13% (11%, 15%)	8% (7%, 10%)

BID = twice daily

16 HOW SUPPLIED/STORAGE AND HANDLING

CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side. CHANTIX is supplied in the following package configurations:

	Description	NDC
Packs	Starting 2 week card: 0.5 mg x 11 tablets and 1 mg x 14 tablets	NDC 0069-0471-01
	Continuing 2 week card: 1 mg x 28 tablets	NDC 0069-0469-11
	Starting 4-week card: 0.5 mg x 11 tablets and 1 mg x 42 tablets	NDC 0069-0471-03
	Continuing 4-week card: 1 mg x 56 tablets	NDC 0069-0469-03
	Starting Month Box: 0.5 mg x 11 tablets and 1 mg x 42 tablets	NDC 0069-0471-02; NDC 0069-0471-03
	Continuing Month Box: 1 mg x 56 tablets	NDC 0069-0469-12; NDC 0069-0469-03
Bottles	0.5 mg - bottle of 56	NDC 0069-0468-56
	1 mg - bottle of 56	NDC 0069-0469-56

Store at 25 C (77 F); excursions permitted to 15–30 C (59–86 F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Initiate Treatment and Continue to Attempt to Quit if Lapse

Instruct patients to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date. Alternatively, the patient can begin CHANTIX dosing and then set a date to quit smoking between days 8 and 35 of treatment. Encourage patients to continue to attempt to quit if they have early lapses after quit day *[see Dosage and Administration (2.1)]*.

For patients who are sure that they are not able or willing to quit abruptly, a gradual approach to quitting smoking with CHANTIX may be considered. Patients should begin CHANTIX dosing and reduce smoking during the first 12 weeks of treatment, then quit by the end of that period and continue treatment for an additional 12 weeks for a total of 24 weeks *[see Dosage and Administration (2.1)]*.

Encourage patients who are motivated to quit and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerability due to adverse events, or who relapsed after treatment to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed *[see Dosage and Administration (2.1), Clinical Studies (14.6)]*.

How to Take

Advise patients that CHANTIX should be taken orally after eating, and with a full glass of water *[see Dosage and Administration (2.1)]*.

Starting Week Dosage

Instruct patients on how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening *[see Dosage and Administration (2.1)]*.

Continuing Weeks Dosage

Advise patients that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening *[see Dosage and Administration (2.1)]*.

Dosage Adjustment for CHANTIX or Other Drugs

Inform patients that nausea and insomnia are side effects of CHANTIX and are usually transient; however, advise patients that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.

Inform patients that some drugs may require dose adjustment after quitting smoking *[see Dosage and Administration (2.1)]*.

Counseling and Support

Provide patients with educational materials and necessary counseling to support an attempt at quitting smoking *[see Dosage and Administration (2.1)]*.

Neuropsychiatric Adverse Events

Inform patients that some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. Instruct patients to discontinue CHANTIX and contact a healthcare professional if they experience such symptoms *[see Warnings and Precautions (5.1), Adverse Reactions (6.2)]*.

History of Psychiatric Illness

Encourage patients to reveal any history of psychiatric illness prior to initiating treatment.

Nicotine Withdrawal

Inform patients that quitting smoking, with or without CHANTIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric illness.

Seizures

Encourage patients to report any history of seizures or other factors that can lower seizure threshold. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment *[see Warnings and Precautions (5.2)]*.

Interaction with Alcohol

Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol *[see Warnings and Precautions (5.3), Adverse Reactions (6.2)]*.

Driving or Operating Machinery

Advise patients to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them *[see Warnings and Precautions (5.4)]*.

Cardiovascular Events

Patients should be instructed to notify their healthcare providers of symptoms of new or worsening cardiovascular events and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.

Somnambulism

Patients should be instructed to discontinue CHANTIX and notify their healthcare providers if they experience somnambulism *[see Warnings and Precautions (5.6)]*.

Angioedema

Inform patients that there have been reports of angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms *[see Warnings and Precautions (5.7), Adverse Reactions (6.2)]*.

Serious Skin Reactions

Inform patients that serious skin reactions, such as Stevens-Johnson Syndrome and erythema multiforme, were reported by some patients taking CHANTIX. Advise patients to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a healthcare provider immediately *[see Warnings and Precautions (5.8), Adverse Reactions (6.2)]*.

Vivid, Unusual, or Strange Dreams

Inform patients that they may experience vivid, unusual or strange dreams during treatment with CHANTIX.

Pregnancy and Lactation

Patients who are pregnant or breastfeeding or planning to become pregnant should be advised of: the risks of smoking to a pregnant mother and her developing baby, the potential risks of CHANTIX use during pregnancy and breastfeeding, and the benefits of smoking cessation with and without CHANTIX. Advise breastfeeding women to monitor the infant for seizures and vomiting *[see Use in Specific Populations (8.1 and 8.2)]*.

This product's label may have been updated. For full prescribing information, please visit www.pfizer.com

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MEDICATION GUIDE
CHANTIX® (CHANT-iks)
(varenicline)
Tablets

What is the most important information I should know about CHANTIX?

When you try to quit smoking, with or without CHANTIX, you may have symptoms that may be due to nicotine withdrawal, including:

- urge to smoke
- depressed mood
- trouble sleeping
- irritability
- frustration
- anger
- feeling anxious
- difficulty concentrating
- restlessness
- decreased heart rate
- increased appetite
- weight gain

Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Some people have had serious side effects while taking CHANTIX to help them quit smoking, including:

New or worse mental health problems, such as changes in behavior or thinking, aggression, hostility, agitation, depressed mood, or suicidal thoughts or actions. Some people had these symptoms when they began taking CHANTIX, and others developed them after several weeks of treatment, or after stopping CHANTIX. These symptoms happened more often in people who had a history of mental health problems before taking CHANTIX, than in people without a history of mental health problems.

Stop taking CHANTIX and call your healthcare provider right away if you, your family, or caregiver notice any of these symptoms. Work with your healthcare provider to decide whether you should continue to take CHANTIX. In many people, these symptoms went away after stopping CHANTIX, but in some people symptoms continued after stopping CHANTIX. It is important for you to follow-up with your healthcare provider until your symptoms go away.

Before taking CHANTIX, tell your healthcare provider if you have ever had depression or other mental health problems. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without CHANTIX.

What is CHANTIX?

CHANTIX is a prescription medicine to help people stop smoking.

Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that are related to smoking.

It is not known if CHANTIX is safe and effective in children.

It is not known if CHANTIX is safe and effective when used with other stop smoking medicines.

Who should not take CHANTIX?

Do not take CHANTIX if you have had a serious allergic or skin reaction to CHANTIX. Symptoms may include:

- swelling of the face, mouth (tongue, lips, gums), throat or neck
- trouble breathing
- rash, with peeling skin
- blisters in your mouth

What should I tell my healthcare provider before taking CHANTIX?

See "What is the most important information I should know about CHANTIX?"

Before you take CHANTIX, tell your healthcare provider if you:

- use other treatments to quit smoking. Using CHANTIX with a nicotine patch may cause nausea, vomiting, headache, dizziness, upset stomach, and tiredness to happen more often than if you just use a nicotine patch alone.
- have kidney problems or get kidney dialysis. Your healthcare provider may prescribe a lower dose of CHANTIX for you.
- have a history of seizures
- drink alcohol
- have heart or blood vessel problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if CHANTIX will harm your unborn baby.
- are breastfeeding. It is not known if CHANTIX passes into breast milk. If you breastfeed and take CHANTIX, monitor your baby for seizures as well as spitting up or vomiting more than normal.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Your healthcare provider may need to change the dose of some of your medicines when you stop smoking.

You should not use CHANTIX while using other medicines to quit smoking. Tell your healthcare provider if you use other treatments to quit smoking.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take CHANTIX?

- There are 3 ways that you can use CHANTIX to help you quit smoking. Talk to your healthcare provider about the following 3 ways to use CHANTIX:
  - Choose a **quit date** when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your **quit date**. Take CHANTIX for 12 weeks.

    OR
  - Start taking CHANTIX before you choose a **quit date.** Pick a date to quit smoking that is between days 8 and 35 of treatment. Take CHANTIX for 12 weeks.

    OR
  - If you are sure that you are not able or willing to quit smoking right away, start taking CHANTIX and reduce smoking during the first 12 weeks of treatment, as follows:

Weeks 1 through 4	Reduce your smoking to reach one-half of your starting daily number of cigarettes. Example: If you usually smoke 20 cigarettes each day, reduce your smoking to 10 cigarettes each day during weeks 1 through 4.
Weeks 5 through 8	Reduce your smoking to reach one-quarter of your starting daily number of cigarettes. Example: If you usually smoked 20 cigarettes each day, reduce your smoking to 5 cigarettes each day during weeks 5 through 8.
Weeks 9 through 12	Keep reducing your smoking until you are no longer smoking (you reach zero cigarettes each day).

    Aim to quit by the end of the 12th week of treatment, or sooner if you feel ready. Continue to take CHANTIX for another 12 weeks, for a total of 24 weeks of treatment.

  Starting CHANTIX before your **quit date** gives CHANTIX time to build up in your body. You can keep smoking during this time. Take CHANTIX exactly as prescribed by your healthcare provider.
- CHANTIX comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then usually go to the blue tablet. See the chart below for dosing instructions for adults.

Day 1 to Day 3	o White tablet (0.5 mg) o Take 1 tablet each day
Day 4 to Day 7	o White tablet (0.5 mg) Take 1 in the morning and 1 in the evening
Day 8 to end of treatment	o Blue tablet (1 mg) o Take 1 in the morning and 1 in the evening

- Make sure that you try to stop smoking on your quit date. If you slip-up and smoke, try again. Some people need to take CHANTIX for a few weeks for CHANTIX to work best.
- Most people will take CHANTIX for up to 12 weeks. If you have completely quit smoking by 12 weeks, your healthcare provider may prescribe CHANTIX for another 12 weeks to help you stay cigarette-free.
- Take CHANTIX after eating and with a full glass (8 ounces) of water.
- This dosing schedule may not be right for everyone. Talk to your healthcare provider if you are having side effects such as nausea, strange dreams, or sleep problems. Your healthcare provider may want to reduce your dose.
- If you miss a dose of CHANTIX, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take your next dose at your regular time.

What should I avoid while taking CHANTIX?

- Use caution when driving or operating machinery until you know how CHANTIX affects you. CHANTIX may make you feel sleepy, dizzy, or have trouble concentrating, making it hard to drive or perform other activities safely.
- Decrease the amount of alcoholic beverages that you drink during treatment with CHANTIX until you know if CHANTIX affects your ability to tolerate alcohol. Some people have experienced the following when drinking alcohol during treatment with CHANTIX:
  - o increased drunkenness (intoxication)
  - o unusual or sometimes aggressive behavior
  - o no memory of things that have happened

What are the possible side effects of CHANTIX?

Serious side effects of CHANTIX may include:

- **See "What is the most important information I should know about CHANTIX?"**
- **Seizures**. Some people have had seizures during treatment with CHANTIX. In most cases, the seizures have happened during the first month of treatment with CHANTIX. If you have a seizure during treatment with CHANTIX, stop taking CHANTIX and contact your healthcare provider right away.
- **New or worse heart or blood vessel (cardiovascular) problems**, mostly in people, who already have cardiovascular problems. Tell your healthcare provider if you have any changes in symptoms during treatment with CHANTIX.

  Get emergency medical help right away if you have any of the following symptoms of a heart attack, including:
  - o chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
  - o pain or discomfort in one or both arms, back, neck, jaw or stomach
  - o shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort
- **Sleepwalking** can happen with CHANTIX, and can sometimes lead to behavior that is harmful to you or other people, or to property. Stop taking CHANTIX and tell your healthcare provider if you start sleepwalking.
- **Allergic reactions** can happen with CHANTIX. Some of these allergic reactions can be life-threatening.
- **Serious skin reactions**, including rash, swelling, redness, and peeling of the skin. Some of these skin reactions can become life-threatening.

Stop taking CHANTIX and get medical help right away if you have any of the following symptoms:

- o swelling of the face, mouth (tongue, lips, and gums), throat or neck
- o trouble breathing
- o rash with peeling skin
- o blisters in your mouth

The most common side effects of CHANTIX include:

- nausea
- sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
- constipation
- gas
- vomiting

Tell your healthcare provider about side effects that bother you or that do not go away.

These are not all the side effects of CHANTIX. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CHANTIX?

- Store CHANTIX at room temperature, between 68°F to 77°F (20°C to 25°C).
- **Keep CHANTIX and all medicines out of the reach of children.**

General information about the safe and effective use of CHANTIX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CHANTIX for a condition for which it was not prescribed. Do not give your CHANTIX to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CHANTIX that is written for healthcare professionals.

For more information about CHANTIX and tips on how to quit smoking, go to www.CHANTIX.com or call 1-877-242-6849.

If you are motivated to quit smoking and did not succeed during prior CHANTIX treatment for reasons other than side effects, or if you returned to smoking after treatment, speak with your healthcare provider about whether another course of CHANTIX therapy may be right for you.

What are the ingredients in CHANTIX?

Active ingredient: varenicline tartrate

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA#/Supplement #	021928/ S040
Applicant Name	Pfizer, Inc.
Date of Submission	February 18, 2016
PDUFA Goal Date	December 18, 2016
Proprietary Name / Established (USAN) Name	Chantix (varenicline tartrate) tablet, film coated
Dosage Forms / Strength	Oral tablets, 0.5 mg and 1 mg
Proposed Indication(s)	Aid to smoking cessation treatment (approved)
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Sarah Arnold, MD, Celia Winchell, MD
Statistical Review	Yi Ren, PhD, David Petullo, MS Eugenio Andraca-Carrera, PhD, Mat Soukup, PhD
OSE/DEPI	Natasha Pratt, PhD, Judy Staffa, PhD
OSI	John Lee, MD, Janice Pohlman, MD, MPH, Kassa Ayalew, MD, MPH
CDTL Review	Celia Winchell, MD
OSE/DPVII	Martin Pollock, PharmD, Sara Camilli, PharmD, BCPS, S. Christopher Jones, PharmD, MS, MPH
OMP/DMPP	Sharon R. Mills, BSN, RN, CCRP , L. Shenee' Toombs, PharmD, LaShawn Griffiths, MSHS-PH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

Pfizer (the Applicant) has submitted supplement S-040 to NDA 21928, Chantix (varenicline tartrate), approved as an aid to smoking cessation treatment. The supplement seeks removal of the boxed warning for the risk of neuropsychiatric adverse events and was supported by a single new, randomized, placebo-controlled safety trial, Study A3051123, in which a cohort of patients without a history of psychiatric diagnoses and a cohort of patients with current or past diagnoses were randomized to treatment with standard regimens of Chantix, sustained-release bupropion, or transdermal nicotine and closely monitored for the emergence of neuropsychiatric adverse events. This trial was conducted in response to an Agency requirement to evaluate the risk of serious neuropsychiatric effects. No new chemistry, manufacturing, and control information, nonclinical data, or clinical pharmacology data were submitted in support of this supplemental application. Sections of Dr. Winchell's CDTL review and primary review have been incorporated into this memo.

2. Background

Chantix was developed under IND 58,994 and originally approved on May 10, 2016. Varenicline is a high-affinity selective partial agonist of the α4β2 nicotinic receptor, previously designated CP526-555. The α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine in animal models. Based on the activity at the nicotinic receptor, varenicline could be expected to mitigate withdrawal symptoms and reduce the reinforcing effects of nicotine, leading to efficacy in helping smokers stop smoking.

Chantix was originally approved based on the results from 30 completed clinical studies, including eight Phase 2/3 trials, as well as data from three clinical studies ongoing at the time of NDA submission. The safety database consisted of a total of 4690 subjects including 456 subjects treated with varenicline at the highest proposed marketed dose, 1 mg twice a day, for at least 24 weeks, and 112 for 364 days or more. Varenicline appeared relatively safe, with no consistent effects on any laboratory parameters, cardiac conduction parameters, or vital sign measurements. The initial study populations did not include patients with psychiatric diagnoses.

After careful consideration, a boxed warning describing a risk for serious neuropsychiatric events was added to the labeling for Chantix in July 2009. Concerns arose following including notification from the European Medicines Agency (EMA) of an investigation of a signal of suicidality-related adverse events in 2007, and postmarketing reports of bizarre and aggressive behavior by Chantix-treated patients in the U.S. Reviews of post-marketing data for Zyban (Bupropion Hydrochloride Sustained Release tablets, NDA 020711)[1] and various nicotine

replacement therapies conducted FDA identified similar cases in Zyban-treated patients. In May 2008, FDA issued a letter notifying Pfizer that a risk evaluation and mitigation strategy (REMS) was required to help mitigate the risks of neuropsychiatric adverse events and of a new postmarketing requirement (PMR) for a clinical trial to further assess the risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions related to the use of varenicline products. A similar REMS and PMR was required of Glaxo SmithKline for Zyban.

When the postmarketing study, Study A3051123, was in development, it was recognized that there was no clear definition for what would constitute the clinically significant neuropsychiatric (NPS) adverse events of interest, and that it would be difficult to capture such events with traditional MedDRA coding[2]. FDA worked with the Applicant to define a novel composite endpoint, that captured 16 main conceptual "components". Selection of the specific MedDRA terms was left to the sponsor, and following FDA review, some additional terms were identified for inclusion and incorporated into the primary endpoint before the final analysis. One the challenges of defining this endpoint is the overlap with symptoms of nicotine withdrawal, particularly symptoms such as irritability and impaired concentration, which occur independently of the use of pharmacotherapy as an aid to cease smoking. The novel instrument developed for the study, the Neuropsychiatric Event Interview (NAEI) was designed to be used as a semi-structured interview. A critical feature was intended to be follow up of any positive responses in order to provide the context of the symptom, co-occurring symptoms, and an informative narrative of the event. Investigator assessments of severity were incorporated into the endpoint to avoid inclusion of events without clinical importance. Unfortunately, a number of study sites failed to implement the NAEI in the manner intended and the review team used a variety of other methods to capture events of a clinically significant nature for analysis.

3. CMC

Not applicable.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

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[1] ZYBAN, Bupropion HCl Sustained Release tablets, also studied in the clinical trial supporting this supplement, is an aminoketone antidepressant originally approved under the proprietary name Wellbutrin. As an antidepressant, Wellbutrin is thought to act primarily via noradrenergic mechanisms, but also has some dopaminergic activity. Its mechanism of action as an aid to smoking cessation is not known. The NDA for ZYBAN (20711, Glaxo SmithKline) was approved in May 1997.

[2] MedDRA (Medical Dictionary for Regulatory Activities) is an international standardized lexicon of medical terms used to code adverse events. http://www.meddra.org/sites/default/files/guidance/file/intguide_17_1_english.pdf

5. Clinical Pharmacology/Biopharmaceutics

Not applicable.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The details of the protocol, study conduct, and results of Study A3051123 can be found in the primary and CDTL reviews by Dr. Winchell and the statistics review by Dr. Andraca-Carrera. Key study protocol details, problems with the study conduct, and the results will be summarized in this memo. Study A3051123 was a 24-week, randomized, double-blind, active- and placebo-controlled multi-center study evaluating the neuropsychiatric safety and efficacy of varenicline and bupropion for smoking cessation in subjects with and without a history of psychiatric disorders. The treatment arms were varenicline 1 mg twice a day, bupropion hydrochloride 150 mg twice a day, nicotine replacement therapy (NRT), and placebo, and a triple-dummy design was used to maintain the study blind. The treatment period was 12 weeks on active treatment and 12 weeks of non-treatment follow-up. The study was conducted by the Applicant and Glaxo SmithKline, the sponsor of Zyban.

Patients were randomized to one of the four treatment arms and were stratified by the presence or absence of psychiatric disorder, and with respect to the four major diagnosis groups listed below, from page 11 of Dr. Winchell's CDTL review:

> Eligible patients were adult smokers of at least 10 cigarettes/day (on average, over the past year and during the month prior to screening) who were motivated to stop smoking.
>
> All potential participants were screened using the Structured Clinical Interview for DSM-IV (SCID). Subjects were to be included in the psychiatric cohort, if they were considered clinically stable and met criteria, either current (meeting criteria in past month) or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and had met diagnostic criteria before the initiation of study treatment.
>
> Psychotic Disorders limited to:
> - Schizophrenia
> - Schizoaffective
>
> Affective Disorders limited to:
> - Major Depression
> - Bipolar-I, Bipolar-II
>
> Anxiety Disorders limited to:

- Panic Disorder with or without Agoraphobia
- Post-Traumatic Stress Disorder
- Obsessive-Compulsive Disorder
- Social Phobia
- Generalized Anxiety Disorder

Personality Disorders limited to past history of:

- Borderline Personality Disorder

All subjects with an Axis I or II diagnosis were to be judged to be clinically stable including the following no exacerbations in the prior 6 months, stable medication regimen in the prior 3 months, no anticipated change in treatment, and not at high risk for suicide per investigator.

Key exclusion criteria were pregnancy, nursing, psychiatric conditions not included in the above list[3], substance use disorders (unless in remission), Clinical Global Impression of Severity (CGI-S) rated 5 or higher, past year suicidal ideation with intent or plan (C-SSRS Item 5), past year suicidal behavior, self-injuring behaviors, positive urine drug screen, medical conditions (severe COPD, recent significant cardiovascular or cerebrovascular disease, recent cancer, ECG or LFT abnormalities). Additionally, exclusions related to bupropion (seizure disorder, anorexia, bulimia, abrupt discontinuation of sedatives) were described.

In addition to the NAEI, outcome measures included the Hospital Anxiety and Depression Scale (HADS), the Columbia Suicide Severity Rating Scale (C-SSRS) and a Clinical Global Impression of Improvement (CGI-I). As noted above, the NAEI was intended to be a structured interview that would elicit questioning for additional information in response to any positive responses. Study personnel administering the NAEI were supposed to have been trained and sample follow-up questions were provided in the training materials. The interviewer was instructed to "probe as needed to assess the subject's experiences and to make an appropriate assessment." Narratives were to be constructed for NPS cases that pulled together all relevant information from reporters who could include the patient, significant others, health care providers, or other sources.

The NAEI is reproduced in the following figure.

Figure 1. Neuropsychiatric Adverse Event Interview

Neuropsychiatric Adverse Events Interview Questions
· Have you felt depressed (sad, blue, down, empty, as if you didn't care)? · Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy? · Have you cried or felt like crying?
· Have you been worried or scared? · Have you been nervous or anxious? · Have you felt panicky at all? · Some people have panic attacks when they suddenly feel very frightened and have physical symptoms like heart palpitations (your heart is pounding and/or beating rapidly), shortness of breath and chest pains. Have you had

[3] Detailed inclusion and exclusion criteria and excluded medications are listed in the primary review

	this?
·	Have you had times when you felt extremely agitated? · Have you had times when you felt like you had to be always moving or even pacing?
·	Have you felt unusually cheerful, or happy, not just your normal self, so that other people noticed? · Have you had much more energy than usual to do things? · Have you needed less sleep than usual to feel rested?
·	Have you felt hostile towards others? · Have you been involved in any serious arguments or fights? · Have you had the urge to injure or harm someone?
·	Have you felt that people have been talking about you? · Have you felt that someone may be after you, or trying to harm you in some way?
·	Has there been anything unusual about the way things look or sound or smell? · Have you heard things that other people couldn't hear, like noises or voices of people talking when there was no one around? · Have you seen things that other people couldn't see?
·	Has your mind been playing tricks on you in any way? · Have you had any ideas that other people might not understand or might find strange?
·	Have things seemed unreal to you? · Have you felt that you are detached from or have trouble connecting with other people? · Have you felt strange or unnatural in any other way?

The protocol called for recording verbatim text for adverse events reported by the subject, and as well as adverse events reported by a household member of the subject, personal physician, or others.

Assessments were to be done in the following order:
1. Volunteered AE report – opening question on how the subject has been feeling in general
2. Follow up on previously reported AEs that are still ongoing
3. Clinical rating scales as specified in the protocol
4. NAEI
5. Columbia Suicide Severity Rating Scale.

Efficacy for smoking cessation was assessed using a Nicotine Use Inventory and end-expiratory exhaled carbon monoxide (exhaled CO) monitoring.

There were study endpoints for the neuropsychiatric events and for smoking cessation. The primary pre-specified safety endpoint for neuropsychiatric adverse events was a 16 component composite of the following elements:

- 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.

This composite endpoint includes 241 MedDRA preferred terms in the 16. This endpoint is referred to as the Neuropsychiatric (NPS) endpoint.

Secondary safety endpoints included the components of the NPS endpoint as well as the scores of three questionnaires: Hospital Anxiety and Depression Scale (HADS), Columbia Suicide Severity Rating Scale (C-SSRS), and the Clinical Global Impression of Improvement (CGI-I). Deaths were also analyzed as a secondary safety endpoint of interest.

The primary efficacy endpoint was the 4-week CO-confirmed continuous abstinence for Weeks 9 through 12. The primary measures of efficacy were CO-confirmed CA (Continuous Abstinence) from Week 9 through Week 12 (CA 9-12) and CO-confirmed CA from Week 9 through Week 24 (CA 9-24). Smoking status was assessed by use of the Nicotine Use Inventory (NUI) questionnaire, and confirmed by CO levels measured at in-clinic visits.

A total of 8144 subjects were enrolled at 140 investigative centers in 16 countries. As described by Dr. Winchell (page 19):

> The treatment groups were similar at baseline with respect to demographic characteristics and smoking history. About 20% in each arm of the non-PHx cohort and about 16-17% in each arm of the PHx cohort had never made a 24 hour attempt to quit smoking, The group mean scores on the Fagerstrom Test of Nicotine Dependence (FTND) were approximately 5.5 in the non-PHx cohort and 6 in the PHx, denoting a fairly low level of dependence, and some people in each cohort scored 0 on the FTND. The motivation of these patients who had never attempted to quit smoking for enrolling in a clinical trial is not clear.
>
> Of those who had made at least one prior attempt in the NPHx cohort, ~17% had used varenicline on their most recent quit attempt, 11% had used bupropion, and nearly 40% had used NRT. In the PHx cohort, 17-20% of those with a prior quit attempt had used varenicline, about 12% had used bupropion, and 40% had used NRT. The willingness of these experienced patients to enroll in the study suggests that they tolerated the medication previously and may have been at lower risk for serious events. Sensitivity analyses excluding these patients are described below.

Completers of the 12 weeks of treatment and the full 24 weeks of the study were similar across treatment groups, approximately 80%.

Efficacy – Smoking Cessation

The primary efficacy results for smoking cessation are presented in the following table from page 35 of Dr. Winchell's review, and show that the continuous abstinence rates were highest for varenicline, followed by similar rates for bupropion and NRT, and lowest for placebo. Subjects in the non-PHX group had higher abstinence rates across the four treatment groups than subjects in the PHX group.

Table 10 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - FAS Population							
Cohort	**Varenicline**	**Bupropion**	**NRT**	**Placebo**	**Odds ratio**		
	(%)	**(%)**	**(%)**	**(%)**	**V/P**	**B/P**	**N/P**
Overall							
CAR 9-12	33.5	22.6	23.4	12.5	3.60*	2.06*	2.14*
CAR 9-24	21.9	16.2	15.7	9.4	2.73*	1.88*	1.80*
Non-PHx							
CAR 9-12	38.0	26.1	26.4	13.7	4.00*	2.26*	2.30*
CAR 9-24	25.5	18.8	18.5	10.5	2.99*	2.00*	1.96*
PHx							
CAR 9-12	29.2	19.3	20.4	11.4	3.25*	1.87*	2.00*
CAR 9-24	18.3	13.8	13.0	8.3	2.50*	1.77*	1.65*
V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo * p-value <0.001, using a logistic regression with terms treatment, cohort, region, and treatment by cohort interaction, and region by cohort interaction. Region used 2-level classification (US, non-US).							

Numerous sensitivity analyses were conducted, including an analysis excluding data from two sites identified as unreliable (1077 and 1002), sites that reported financial relationships with Pfizer (generally via participation in a speakers bureau), and based on prior experience with the study drugs. The overall outcomes were unchanged.

8. Safety

The analysis of the neuropsychiatric adverse event outcomes will be discussed in this section. As Dr. Winchell conducted her review, she identified a number of problems with the way in which the Applicant and investigators conducted the study and collected the study data. The nature of these problems were categorized by Dr. Winchell in her review, pages 22-23, as follows.

7.3.1 Incomplete/inadequate data collection

7.3.1.1. Ineffective Use of NAEI

The NAEI was intended to be used as a starting point to identify symptoms of potential concern, and then the full description of the patient's experience was to be sought and recorded. The investigator was to determine whether the solicited symptom did or did not qualify as an adverse event. It appears that, at many sites, the NAEI was, instead, used as a checklist. No additional information was recorded beyond the patient endorsing one of the symptoms mentioned.

7.3.1.2 Inadequate Capture of Patient Verbatim

It was expected that the events were to be recorded in the reporter's words, in order to ensure that difficult-to-characterize events were adequately described. At three sites, and sporadically at other sites, no patient verbatim (described in the database as

"event as described by reporter" was recorded at all so it is not possible to determine how the investigator verbatim term was selected or how severity was assessed. Across all sites, in many cases, the recorded "event as described by reporter" is a single word (identical to the investigator verbatim term) such as "anxiety," giving no additional insight.

7.3.1.3 Inadequate Capture of Information About Circumstances of Events

Several narratives had insufficient information to understand the context of the event and whether it occurred in the setting of the type of neuropsychiatric problems that are of interest in the trial. Specific examples are provided in my primary review.

7.3.2 Data Coding Issues

7.3.2.1 Inconsistent Investigator Assessment of Severity

The investigator assessment of severity was intended to distinguish adverse events that reached a certain threshold of interference of a patient's usual functioning. However, some narratives suggest a level of interference in the patient's usual functioning not reflected in the investigator's rating of severity. Some of these cases are included in the NPS primary endpoint because they were assigned codes and severity ratings included in the composite, whereas other cases in which the narratives describe very similar symptoms and impacts are not, either because the term selected is not in the composite (e.g., irritability) or because the investigator rating of severity did not meet criteria for inclusion in the NPS primary endpoint. In a number of cases, subjects reported events that were coded to terms such as depression and mood disturbance which had a documented interference in their functioning but were only rarely assessed as "severe." Some are assessed as "mild" despite the patient report of missing days of work or other significant impact. Specific examples are included in my primary review.

Cases of events coded to a new psychiatric diagnosis in subjects who were in the non-psychiatric cohort were noted. These cases did not meet the "severity" criterion based on investigator severity rating and were not flagged as NPS cases, although the onset of a new psychiatric condition would generally be considered quite significant. These types of cases further underscored the concern that the severity criterion for inclusion in the NPS endpoint may have been inappropriate to capture events of concern. There may have been a disconnect between what subjects with no previous psychiatric issues consider severe (even missing a day of work) and what a health care provider accustomed to caring for seriously mentally ill patients would regard as "severe" (possibly only an event requiring hospitalization). Even one hospitalization was assessed as "mild" by the investigator. Because the primary endpoint relied on investigator assessment of severity, which was clearly problematic, our confidence in the analyses based on the protocol-specified primary NPS endpoint is undermined by these findings. An expanded analysis which included patients who experienced events coded as "moderate" but also experienced symptoms captured by other clinical assessments or MHP evaluation is described below.

7.3.2.2 Lack of Integration of Different Data Streams

Although C-SSRS, HADS, and CGI scores were recorded, patients could have had significant indicators of distress on one or more of these instruments and no adverse event recorded. Patients could also have been evaluated by the MHP and information

recorded in the evaluation was not recorded as an adverse event. In some cases (as noted above) a new diagnosis was recorded as an adverse event. Some subjects had AEs reported based on C-SSRS results while others did not. A subject who endorsed suicidal ideation during the protocol-specified mental health evaluation prompted by his NPS-endpoint qualifying event was not coded as having suicidal ideation. The expanded analysis attempts to capture these patients.

7.3.2.3 Inconsistent Mapping of Events to Sub-Components of the Composite

The endpoint was a composite of various emotional, cognitive, and perceptual experiences that subjects might experience because the post-marketing adverse events typically described patients experiencing multiple symptoms simultaneously. However, the coding of events did not facilitate identification of subjects who might have been experiencing a cluster of symptoms. Pfizer's analysis included tabulation of events separated out into categories such as agitation, depression, psychosis, and panic.

Review of the narratives, where sufficient information about the patient report is provided to assess the coding, reveals a number of issues. Overall, the mapping of events to the sub-components was not consistent. There are subjects whose events included a constellation of cognitive and emotional and behavioral experiences but the investigator may not have coded all of the events such that the NPS threshold was reached for all of them. Additionally, there are errors in the assignment of terms to components (for some reason, "dysphoria" is included in the aggression component), and, unfortunately, there is no cognitive component at all. Cognitive symptoms are included in the "agitation" component. Therefore, it does not appear helpful or informative to analyze the cases by component of the NPS endpoint.

7.3.2.4 Inconsistent Application of Coding

Some terms, notably "agitation," appear to have been applied inconsistently to a variety of symptoms. In a number of cases, there is sufficient information to determine that the term was interpreted to refer to motor agitation (akathisia); in others it refers to emotional upset and distress (which was the intended meaning in the protocol stage). In some cases another term in another component of the NPS endpoint (e.g., "anger") was stated by the patient but the term "agitation" was chosen for coding. In still other cases, the patient reported insomnia, leading to selection of the term "restlessness" (i.e., the patient was not getting "rest"), which then coded to "agitation"—clearly not what was intended.

For many subjects whose only event is "moderate agitation," there is virtually no additional information on the event to allow us to understand how that was manifested and in what way it was disruptive to the patient's functioning (which is what makes it "moderate").

Additionally, in some cases, subject verbatim terms containing concepts in NPS endpoint (e.g. "anger") were coded to terms not in the NPS endpoint (irritability). There are also many subjects with verbatim terms coded to the term "irritability" where the description of the event is identical to other subjects coded to "agitation," but they are not considered NPS cases. However, it is not possible to re-adjudicate all cases coded to "irritability" because many lack further information. Although irritability was

intentionally excluded from the endpoint because of its well-known association with nicotine withdrawal, the expanded analysis included subjects with moderate to severe events coded to "irritability" who also had other indicators of clinically significant findings (e.g., clinical scales or significant findings by MHP). Only a very few patients had irritability as their only symptom.

7.3.2.4 Miscellaneous Coding Errors

As with any large dataset, other coding errors were identified, examples of which are given in my primary review.

7.3.3 Data Reporting Issues

The case narratives provided by Pfizer presented a barrier to review. Pfizer submitted the study report prior to submitting the supplement, and gave the Division an opportunity to comment. The original submitted narratives did not include relevant information and provided no insight beyond the MedDRA terms and the timing of the events, along with investigator assessment of relatedness. Even where available, the patient's own words describing the event were not included in the narrative, or any context/background for the event. The Division requested revised narratives which were improved, but nevertheless, not as informative or as logically constructed as expected for NDA case narratives. The chronology of different streams of data was presented separately, rather than integrating the scores on clinical assessments and the smoking behavior reported together with the timeline of the adverse events. The information presented was also limited by the problems noted above related to data capture. Ultimately, it was determined that it was neither feasible nor possible to attempt to independently adjudicate the cases based on the provided information. It also became apparent on inspection of the Adverse Event datasets that many events of potential interest were not flagged, and no narratives had been constructed. This appears to have been related to issues noted above of data coding, primarily involving investigator assessment of severity. As described below, sensitivity analyses to capture more of the cases of interest were performed to address this issue.

7.3.4 Issues raising concerns of data reliability

Pfizer identified two sites that were identified as having significant protocol violations leading to concerns about data reliability. These issues are described in detail in my primary review. There were also a number of sites at which Pfizer noted that individuals without the appropriate qualifications were performing the role of MHP and sites where investigators needed to be re-trained on administering the SCID. These observations were taken into consideration in choosing sites for inspection by the Office of Scientific Investigations. OSI confirmed significant violations at the two sites (1077 and 1002) but assessed the data from six other sites as reliable.

The statistical reviewers were able to replicate the Applicant's results as shown in the following two figures from Dr. Andraca-Carrera's review for patient cohorts with no prior psychiatric history (non-PHx) and with prior psychiatric history (PHx). The results differed by psychiatric history. For the non-PHx cohort, the observed cumulative rate of NPS events among subjects was lowest among subjects randomized to varenicline, and was similar for subjects randomized to bupropion, NRT, or placebo. For the PHx cohort, the observed cumulative rate of NPS events was highest among subjects randomized to varenicline and bupropion and was lowest among subjects randomized to placebo. Patients randomized to

bupropion or varenicline in the PHx cohort experienced more NPS events within the first 7 days after randomization (21 subjects on bupropion, 12 on varenicline) than subjects randomized to NRT (4) or placebo (4).

Figure 5 NPS Events in the Non-PHx Cohort

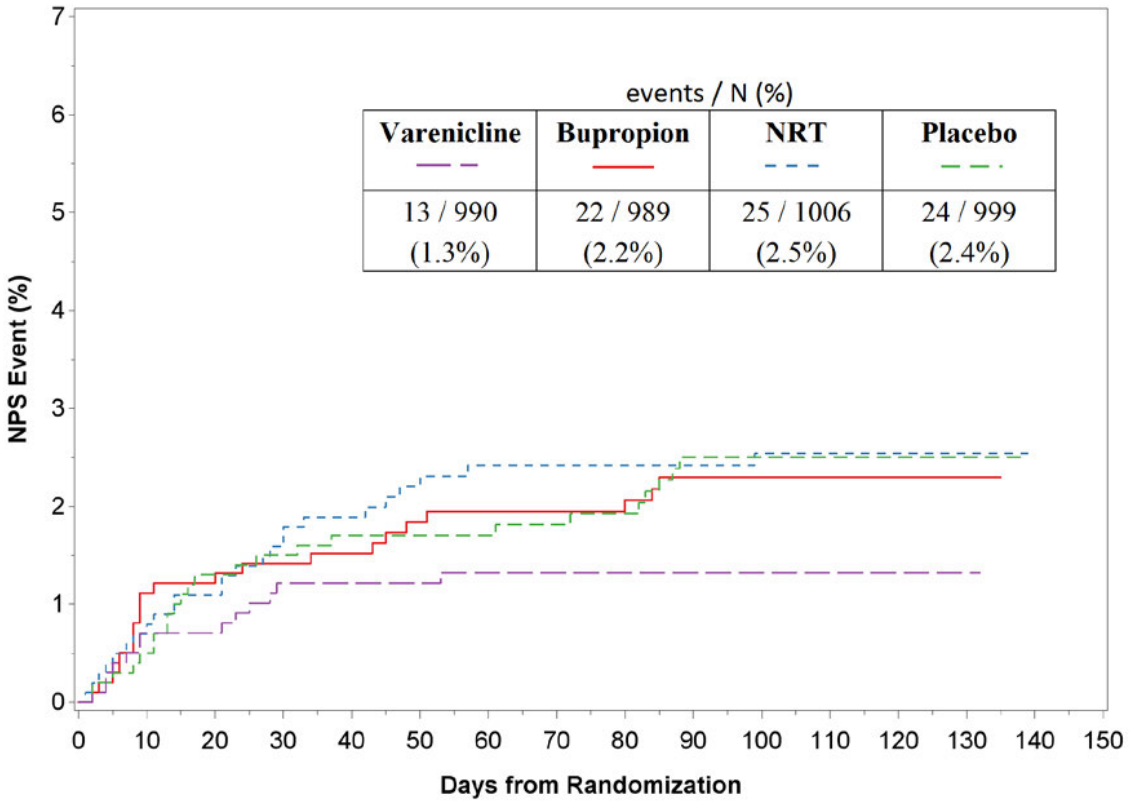
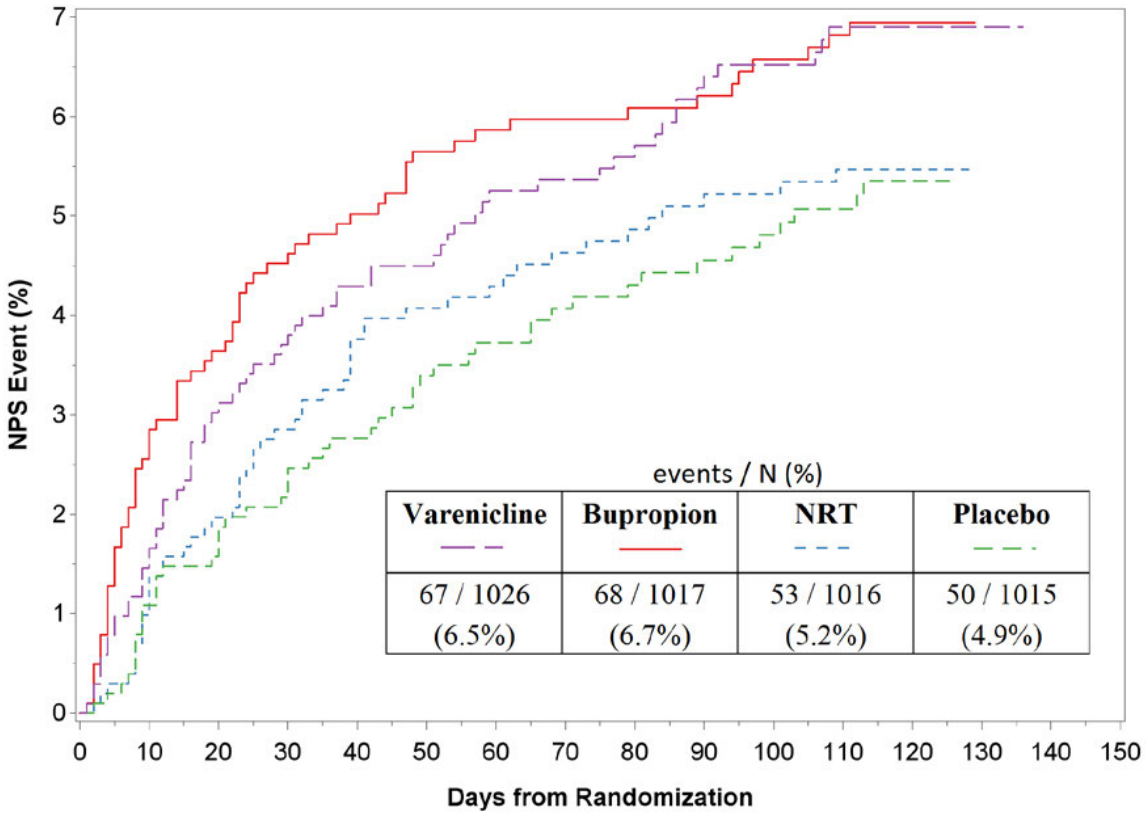


Figure 6 NPS Events in the PHx Cohort



Drs. Winchell and Andraca-Carrera undertook extensive reanalyses of the data to evaluate whether the problems identified had an impact on the study outcomes, and if so, the nature of that impact. The Applicant also reanalyzed the data after hearing of the problems identified by the Agency review team. Several analyses used expanded definitions of the NPS AE endpoint. Beyond the Applicant's analysis, the results of the additional analyses using expanded definitions of the safety outcome conducted by the Agency review team did not change the conclusions of the study. Key results from the Agency review team will be described below.

The following tables are from Dr. Andraca-Carrera's review. The first two analyses represent treatment emergent neuropsychiatric events of all severity and of those categorized as severe. The third table represents an analysis termed "NPS plus" (NPS+) which included all primary NPS events plus moderate or severe adverse events with an associated MedDRA Preferred Term (PT) of 'Irritability' or a High Level Group Term (HGLT) of 'Depressed mood disorders'.

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Table 18. Treatment Emergent Neuropsychiatric Events of All Severities by Cohort

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	148 / 990 (14.9%)	161 / 989 (16.3%)	131 / 1006 (13.0%)	151 / 999 (15.1%)
PHx Cohort	289 / 1026 (28.2%)	289 / 1017 (28.4%)	255 / 1016 (25.1%)	239 / 1015 (23.5%)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Table 19. Severe Treatment Emergent Neuropsychiatric Events by Cohort

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	1 / 990 (0.1%)	4 / 989 (0.4%)	3 / 1006 (0.3%)	5 / 999 (0.5%)
PHx Cohort	14 / 1026 (1.4%)	14 / 1017 (1.4%)	14 / 1016 (1.4%)	13 / 1015 (1.3%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

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Table 20. Treatment Emergent NPS+ Events by Treatment and Cohort

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	32 / 990 (3.2%)	35 / 989 (3.5%)	38 / 1006 (3.8%)	44 / 999 (4.4%)
PHx Cohort	118 / 1026 (11.5%)	109 / 1017 (10.7%)	89 / 1016 (8.8%)	100 / 1015 (9.9%)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Analyses were conducted that excluded patients who had previous experience with the study drugs.

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Table 25. NPS events in treatment-naïve subjects

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	6 / 673 (0.9%)	17 / 632 (2.7%)	12 / 649 (1.8%)	9 / 658 (1.4%)
PHx Cohort	37 / 631 (5.9%)	37 / 609 (6.1%)	20 / 631 (3.2%)	23 / 638 (3.6%)

*Treatment-naïve subjects are defined as those without recorded exposure to varenicline, bupropion or NRT at the time of randomization.
Source: Created by reviewer using datasets cnmedp.xpt, smkhst.xpt, demog.xpt, subevg.xpt, advers.xpt

Table 26. NPS events in treatment-experienced subjects

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	7 / 317 (2.2%)	5 / 357 (1.4%)	13 / 357 (3.6%)	15 / 341 (4.4%)
PHx Cohort	30 / 395 (7.6%)	31 / 408 (7.6%)	33 / 385 (8.6%)	27 / 377 (7.2%)

*Treatment-experienced subjects are defined as subjects with exposure to at least one of varenicline, bupropion or NRT at the time of randomization

Analyses were conducted that excluded the three study sites identified as potentially problematic (Sites 1002, 1063, and 1077)[4], and excluding sites with disclosed financial arrangements exceeding the threshold for disclosure and sites where investigators were involved in an ongoing way as speakers or consultants.

None of these analyses changed the overall conclusions. In each analysis, there did not appear to be a difference across treatment groups in the non-psychiatric cohort but there were small, but consistent increases in rates of events in the patients treated with varenicline or bupropion in the psychiatric cohort.

The table below from Dr. Winchell's review illustrates the findings across different analyses including the original NPS outcome, an expanded analysis by the Applicant, and two of the additional analyses by FDA. As summarized by Dr. Winchell, "In all analyses, there appears to be no increased risk of NPS events in patients without psychiatric diagnoses who are treated with any of the medications for smoking cessation. However, neuropsychiatric adverse events of a clinically significant, if not serious, nature are relatively common, occurring in 3-5% of the non-psychiatric population when trying to quit smoking without medication. There is also a small, but consistent, finding in the population of patients with psychiatric diagnoses that events are more common during treatment with varenicline or bupropion than with NRT or placebo."

[4] Note that the Applicant identified probles at Sites 1002 and 1077. Dr. Andraca-Carrera also excluded 1063 from his analyses because this site failed to record patient verbatim terms.

Table 9 Comparison of NPS Rates Using Different Analyses

Non-PHx Cohort								
	Varenicline		Bupropion		NRT		Placebo	
	N = 990		N = 989		N = 1006		N = 999	
NPS (Protocol)	13	1.31%	22	2.22%	25	2.49%	24	2.40%
NPS Expanded (Pfizer)	45	4.55%	50	5.06%	51	5.07%	56	5.61%
NPS+ (FDA)	32	3.23%	35	3.54%	38	3.78%	44	4.40%
NPS Expanded (FDA)	31	3.13%	35	3.54%	33	3.28%	40	4.00%
PHx Cohort								
	Varenicline		Bupropion		NRT		Placebo	
	N = 1026		N = 1017		N = 1016		N = 1015	
NPS (Protocol)	67	6.53%	68	6.69%	53	5.22%	50	4.93%
NPS Expanded (Pfizer)	140	13.65%	138	13.57%	130	12.80%	123	12.12%
NPS+ (FDA)	118	11.50%	109	10.72%	89	8.76%	100	9.85%
NPS Expanded (FDA)	126	12.28%	121	11.90%	98	9.65%	96	9.46%

Information about deaths and serious adverse events were reviewed. None of the ten deaths in the study occurred in patients treated with Chantix. There were 72 patients with treatment-emergent SAEs in the non-PHx cohort and 101 in the PHx cohort. Dr. Winchell notes that there were 36 cases of NPS events for which a relationship to study drug could not be ruled out. She summarizes these as follows, "[n]otably, one of these cases was not included in the NPS endpoint because the investigator rated the event of depression as "mild" although it resulted in hospitalization. Cases of both treatment-emergent and discontinuation-emergent symptoms were noted. NPS events in bupropion-treated patients in the PHx cohort included cases that appear to be precipitation of mania in patients with bipolar disorder, a known and labeled risk of bupropion and other antidepressants. Two additional cases involving deliberate overdose were identified that were not flagged as serious by Pfizer. One was included in the SAE cases because the patient was hospitalized for a medical problem; one was not flagged as an SAE at all (and was coded as an accidental overdose) but was added to the table below."

As summarized by Dr. Winchell, "[o]verall, adverse events leading to temporary or permanent discontinuation of study drug or to dose reduction were reported in 115 subjects. In the non-PHx group, all active treatment arms had a higher rate of dose reductions or discontinuations than the placebo arm; in the PHx cohort, rates were similar."

Common adverse events were consistent with the events known for the study drugs. Standardized MedDRA Queries were conducted for certain types of neuropsychiatric events including Depression and Suicide/Self-Injury; Psychosis and Psychotic Disorders; Accidents and Injuries; and Hostility/Aggression. The findings were generally consistent with the analysis of the composite endpoint, with no obvious differences across groups in the non-psychiatric cohort, and small increases in varenicline-treated and bupropion-treated groups compared to placebo in the psychiatric cohort.

9. Advisory Committee Meeting

The following has been excerpted verbatim from Dr. Winchell's review.

> In October 2014, in the context of a previous labeling supplement submitted by Pfizer proposing to remove the boxed warning from the Chantix labeling, data from randomized controlled trial (RCT) meta-analyses, and observational studies were discussed at a joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). The committees were asked to discuss how they would weigh the evidence contributed by the meta-analyses, observational studies, and spontaneous case reports when they were evaluating the risk of serious neuropsychiatric adverse events in patients taking varenicline. In general, many of the committee members expressed concern with the quality of the data presented. The committee members were also asked based on the data presented on the risk of serious neuropsychiatric adverse events with Chantix, whether they would they recommend removal or modification of the boxed warning statements regarding risk of serious neuropsychiatric adverse events, or retention of the current boxed warning statements with a reassessment once the ongoing post-market safety outcome trial was completed.
>
> The majority of the committee agreed that more data were needed and recommended to retain the current boxed warning statements and reassess once the post-market safety outcome trial results were available.
>
> Accordingly, the results of the trial, and updated reviews of observational studies, were discussed at a second joint meeting of the PDAC and the DSaRM AC on September 14, 2016. Because of the specific concerns to be discussed, SGEs with a variety of backgrounds were also added as voting members for this meeting. These included individuals with general internal medicine background, as well as clinicians involved in smoking control and smoking cessation research. Experts who had attended the meeting to discuss the previous labeling supplement were invited; some were not available.
>
> Key issues to be discussed at the meeting included the Committees' opinion on the following topics:
>
> - The strengths and weaknesses of the completed randomized controlled trial (RCT) with regard to the study design including the novel primary endpoint.
> - The potential impact of the variability in data collection, adverse event coding, and case definition on the primary endpoint.

- Which analysis and results most appropriately described the effect of the smoking cessation therapies on neuropsychiatric events.
- The contribution of the evidence from observational studies when evaluating the risk of serious neuropsychiatric adverse events in patients taking smoking cessation products.
- The impact of psychiatric history on the occurrence of neuropsychiatric adverse events during smoking cessation therapy.
- Whether the boxed warning should be removed, modified, or retained, and whether any additional labeling changes should be made.

Overall, panel members agreed that the trial design was good and applauded the completion of a randomized controlled trial to add to prior studies. There were concerns regarding the number of sites and difficulty with data monitoring and control across so many countries, languages, cultures, and investigators. The committee members also expressed concerns with the lack of power to address suicidal events. Some panel members noted the need for having a design that holds to rigorous standards for safety related outcomes, and stated power calculations a priori for this deserved closer attention. Some of the committee members expressed concerns regarding the inclusion of patients who were not naïve to treatment with the drugs under study, which may have enriched the population for individuals able to tolerate the drugs. However, following the advisory committee, FDA obtained a data set from Pfizer that excluded the patients who had prior exposure to the study drugs, and the results of the primary analysis in this population of patients naïve to the study drugs were similar to what was observed in the full population.

Most committee members did not have specific recommendations regarding which of the analyses best represented the data, although there was support for using an expanded outcome definition and for using the alternate statistical approach employed by the FDA team. The potential impact of the variability of data collection practices and coding of adverse events was discussed, but some committee members noted that they did not expect that the variability would affect the adverse event (AE) data differentially across treatment arms.

The committee members did not think emphasis should be placed on the observational studies and concluded that they did not contribute additional insight beyond the findings of the RCT.

Committee members noted the increased risk for neuropsychiatric events in the population with a psychiatric history. Several committee members who noted this difference recommended that this information needs to be described in product labeling.

The committee members were asked to vote for one of the following options:
A. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events (10 members voted for this option)
B. Modify the language in the boxed warning (4 members voted for this option)
C. Keep the current boxed warning (5 members voted for this option)

Some committee members who voted to remove the boxed warning noted that the decision was difficult due to their concerns with the limitations from the study results

presented. Some also noted the public health importance of effective smoking cessation therapies being available for patients who need smoking cessation aids, especially those with psychiatric illness.

Several members who voted to retain or modify the boxed warning voiced that their reason was not related to the study, but due to a concern that removing a boxed warning would be misinterpreted as communicating a complete absence of risk. There was also concern about the potential precedent-setting nature of the removal of the boxed warning for other products in the future. A few members of the committee voted to keep the boxed warning, citing concerns about the study endpoint, study conduct, and the inadequate statistical power to detect more rare events, or simply noted that they were unconvinced by the study.

10. Pediatrics

No new pediatric information was submitted. The Applicant is completing pediatric studies as requested in a Pediatric Written Request.

11. Other Relevant Regulatory Issues

Financial Disclosure
Financial disclosures identified six sites with payments exceeding the threshold for reporting. Analyses without these sites did not change the conclusions.

OSI Inspections
OSI inspection confirmed GCP violations at the two sites identified by the Applicant. Analyses without these two sites did not change the conclusions.

Observational Studies
The Division of Epidemiology II (DEPI II) was consulted to review observational studies submitted by the Applicant, as well as any additional published observational studies on neuropsychiatric risk associated with smoking cessation prescription medications. Based on limitations associated with the designs of the six observational studies identified for in-depth review, it was concluded that, "[t]he evidence from the existing observational studies, alone, is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline use or bupropion use. Observational data alone also are inadequate to inform whether or not neuropsychiatric risk associated with varenicline or bupropion could be different between smokers with and without psychiatric history. Neuropsychiatric safety of smoking cessation products should be assessed based on the totality of data streams, including case reports, observational and clinical trial data."

REMS
Because of the post-marketing safety signal of neuropsychiatric adverse events, Chantix is currently marketed under a REMS. The goal of the REMS is to inform patients about the potential serious risk of serious neuropsychiatric adverse events associated with the use of

Chantix. The elements of the REMS are limited to a Medication Guide (MG) and a timetable for submission of assessments.

Previous assessment reports have concluded that the risk of neuropsychiatric adverse events is understood by 70-80% of patients. Moreover, the results of this PMR trial indicate that the risk of events of a serious nature is lower than previously suspected. Although disturbances in mood, thinking, and behavior are not uncommon, the vast majority of these events are not serious. Therefore, consistent with our conclusion that the boxed warning is no longer warranted in the package insert, it is appropriate that the REMS no longer be required. A MedGuide will still be distributed which informs patients about these risks, but FDA will not require this under a REMS with periodic assessments.

Similarly, the results of the study support making analogous changes to the labeling of Zyban to remove the boxed warning and to incorporate the results of the PMR study, and to remove the requirement for a REMS. The labels for the antidepressant bupropion products will retain the antidepressant class label boxed warning but may have the language pertaining to smoking cessation use removed from the box.

There are no other unresolved relevant regulatory issues.

12. Labeling

The Applicant proposed a number of changes to the labeling including deleting the boxed warning. The data from the clinical trial A3051123 support the removal of the boxed warning and additional labeling changes. In addition, Section 5.1 has been edited with removal of reference to the observational studies and addition of language from the new clinical trial, as follows:

5.1 Neuropsychiatric Adverse Events including Suicidality

Serious neuropsychiatric adverse events have been reported in patients being treated with CHANTIX *[see Adverse Reactions (6.2)]*. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some patients who stopped smoking may have been experiencing symptoms of nicotine withdrawal, including depressed mood. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these adverse events occurred in patients taking CHANTIX who continued to smoke.

Neuropsychiatric adverse events occurred in patients without and with pre-existing psychiatric disease; some patients experienced worsening of their psychiatric illnesses. Some neuropsychiatric adverse events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol *[see Warnings and Precautions (5.3), Adverse Reactions (6.2)]*. Observe patients for the occurrence of neuropsychiatric adverse events. Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. The healthcare provider should evaluate the severity of the symptoms and the extent to which the patient is benefiting from treatment, and consider options including dose reduction, continued treatment under

closer monitoring, or discontinuing treatment. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported. However, the symptoms persisted in some cases; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The neuropsychiatric safety of CHANTIX was evaluated in a randomized, double-blind, active and placebo-controlled study that included patients without a history of psychiatric disorder (non-psychiatric cohort, N=3912) and patients with a history of psychiatric disorder (psychiatric cohort, N=4003). In the non-psychiatric cohort, CHANTIX was not associated with an increased incidence of clinically significant neuropsychiatric adverse events in a composite endpoint comprising anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, and irritability. In the psychiatric cohort, there were more events reported in each treatment group compared to the non-psychiatric cohort, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: Risk Differences (RDs) (95%CI) vs. placebo were 2.7% (-0.05, 5.4) for CHANTIX, 2.2% (-0.5, 4.9) for bupropion, and 0.4% (-2.2, 3.0) for transdermal nicotine. In the non-psychiatric cohort, neuropsychiatric adverse events of a serious nature were reported in 0.1% of CHANTIX-treated patients and 0.4% of placebo-treated patients. In the psychiatric cohort, neuropsychiatric events of a serious nature were reported in 0.6% of CHANTIX-treated patients, with 0.5% involving psychiatric hospitalization. In placebo-treated patients, serious neuropsychiatric events occurred in 0.6%, with 0.2% requiring psychiatric hospitalization *[see Clinical Studies (14.9)]*.

Study A3051123 has also been added to Section 14 Clinical Trials.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

The clinical trial data from Study A3051123 have provided evidence that, for patients without a psychiatric history, the neuropsychiatric adverse events that occur in a population attempting to quit smoking are no greater for patients treated with Chantix or other drug products approved as an aide to smoking cessation. However, for patients with a history of psychiatric disorders, there is a greater risk for clinically significant neuropsychiatric adverse events from the study composite endpoint: anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, and irritability. This risk was higher for each of the active treatments compared to placebo, particularly for Chantix and bupropion. This information will remain in the labeling, but does not require a boxed warning.

The importance of smoking cessation for the health of an individual is well known. Even with the increased risk for the clinically significant neuropsychiatric adverse events described for patients with prior psychiatric disorders, the importance of quitting smoking outweighs that risk. These patients should be followed by their healthcare providers for any of these symptoms.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

No new requirements are being added.

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/s/

SHARON H HERTZ
12/16/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

CROSS DISCIPLINE TEAM LEADER REVIEW

Tracked Safety Issue (TSI) Integrated Review Memorandum

Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

NDA/BLA	*21-928; 20-* (b) (4)
Drug name	*Chantix (varenicline)* *Zyban (bupropion)*
TSI #	*260*
Safety Issue Name	*Neuropsychiatric adverse events*
Author name	*Judith A. Racoosin, MD, MPH*
Date	*See DARRTS signature block*

I. OVERALL ASSESSMENT AND RECOMMENDATIONS

Serious neuropsychiatric adverse events emerged as a safety concern for smoking cessation drugs Chantix and Zyban in the postmarketing period. Concurrent with adding warnings to the product labeling and requiring a REMS for each product, the Division required a placebo-controlled PMR trial to assess serious neuropsychiatric adverse events in a defined population of smoking cessation patients without and with a history of psychiatric illness.

Based on the team's review and analysis, including sensitivity analyses, and the discussion at the September 14, 2016 advisory committee meeting, the Division has determined that it is appropriate to remove the boxed warning language for serious neuropsychiatric adverse events from Chantix labeling. The language describing the serious neuropsychiatric adverse events seen in patients quitting smoking will also be removed from the Boxed Warning in the Zyban label.[1] Additionally, we will revise the Warnings and Precautions 5.1 statement in both labels to include the results of the postmarket safety outcome trial, including the frequencies of the neuropsychiatric adverse events and the efficacy measures. The Medication Guide that explains the neuropsychiatric adverse events associated with the use of Chantix and Zyban will be maintained as part of labeling; however, the REMS requirement will be removed.

II. BACKGROUND

Varenicline, marketed by Pfizer as Chantix in the US and Champix globally, is a partial α4β2 acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation. The treatment regimen is (b) (4)

[1] The active ingredient in Zyban (bupropion) is in the antidepressant class; therefore the label carries the class Boxed Warning for suicidality and antidepressant drugs. This language will remain in a Boxed Warning in the labels for Zyban and other bupropion products.

(b) (4) A second 12-week course may be taken to increase the chance of maintenance of abstinence.

Bupropion HCl is an aminoketone antidepressant originally approved under the proprietary name Wellbutrin. As an antidepressant, Wellbutrin is thought to act primarily via noradrenergic mechanisms, but also has some dopaminergic activity. Its mechanism of action as an aid to smoking cessation is not known. The new drug application (NDA) for Bupropion HCl Sustained Release Tablets (marketed by GSK under the proprietary name Zyban for this indication) was approved in May 1997. The treatment regimen is 150 mg twice daily for 7-12 weeks (with an initial three-day titration).

In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events with Chantix (marketed in the EU as Champix). Later that same summer, a fatal case involving bizarre and aggressive behavior by a Chantix-treated patient became highly-publicized. FDA subsequently undertook evaluations of the postmarketing data regarding cases of suicide and cases of neuropsychiatric adverse events and concluded that there were cases that could be attributed to Chantix treatment. In a number of cases, the reporters provided rich and detailed narratives about the events, describing experiences involving symptoms in a variety of neuropsychiatric domains, including cognition, perception, mood, and general functioning. A series of incremental changes to labeling were made to address the emerging understanding of the nature of the risk. A subsequent review of postmarketing data on Zyban and various nicotine replacement therapies identified similar cases associated with Zyban. A chronology of the subsequent regulatory actions and public communications that followed is shown below.

May 1997	NDA approval of bupropion[2] for smoking cessation (tradename "Zyban")
May 2006	NDA approval of varenicline in the U.S. (tradename "Chantix")
September 2006	Approval of varenicline in the European Union (tradename "Champix")
May 2007	European Medicines Agency informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a postmarketing suicidal-event analysis.
Nov 2007	Information added to ADVERSE REACTIONS section of varenicline labeling; Early communication of an ongoing safety review
Jan/Feb 2008	Serious neuropsychiatric adverse events information upgraded to the WARNINGS AND PRECAUTIONS section of the varenicline labeling; Public health advisory issued
April 2008	Center Director briefing to discuss varenicline and serious neuropsychiatric adverse events, the benefits of varenicline to help patients achieve smoking cessation vs. the risk of serious neuropsychiatric adverse events
May 2008	Division required Risk Evaluation and Mitigation Strategy (REMS) for varenicline; issued a postmarketing requirement (PMR) to assess the serious

[2] NDA approval for bupropion first occurred in December 1985 for major depressive disorder (tradename "Wellbutrin").

	risk of neuropsychiatric symptoms with varenicline; Public health advisory updated. FAA bans use of varenicline by pilots and air traffic controllers
Feb 2009	Division required Risk Evaluation and Mitigation Strategy (REMS) for bupropion and issued a postmarketing requirement (PMR) to assess the serious risk of neuropsychiatric symptoms with bupropion
July 2009	Added BOXED WARNING section to varenicline and bupropion labeling; Public health advisory issued regarding addition of boxed warning to both varenicline and bupropion
March 2010	Formalized PMR description and milestone dates for varenicline and bupropion to require a placebo- and active- controlled randomized controlled trial (RCT) to assess the serious risk of neuropsychiatric symptoms with treatments for smoking cessation
Oct 2011	Drug Safety Communication reported the results of two FDA-sponsored epidemiology studies that evaluated the risk of serious neuropsychiatric adverse events associated with varenicline
Oct 2014	Joint meeting of Psychiatric Drugs Advisory Committee/Drug Safety and Risk Management Committee to consider Pfizer's request to remove the boxed warning from the Chantix label based on meta-analyses of randomized controlled trials and observational studies. Committee voted to wait until the PMR RCT results were available.

As described above, based on postmarketing adverse event reports, both Chantix and Zyban labeling carry boxed warnings regarding the risk of serious neuropsychiatric events. In 2008, using the postmarketing safety authorities included in the FDA Amendments Act of 2007, FDA imposed a post marketing requirement (PMR), which required Pfizer and GSK to conduct a placebo-controlled postmarketing safety outcome trial to further characterize the risk of neuropsychiatric adverse events and to evaluate whether a prior history of psychiatric illness was a risk modifier. Because patients with a history of psychiatric illness did not participate in the initial clinical efficacy trials that supported approval of the NDA, it was also important to ascertain whether the medications were effective in these patients, in order to understand the balance of risks and benefits. An active comparator of transdermal nicotine was included in the clinical trial design to determine whether nicotine replacement, another pharmacologic option for treating tobacco dependence, offered any advantage or disadvantage with respect to neuropsychiatric effects.

Specifically, the trial had to be a large randomized, double-blind, active- and placebo-controlled trial, with the following treatment arms: varenicline, bupropion, NRT, and placebo. It needed to compare the risk of clinically significant neuropsychiatric adverse events, including, but not limited to, suicidality, and also determine whether individuals with prior history of psychiatric disorders are at greater risk for such adverse events compared to individuals without prior history of psychiatric disorders. Finally, the trial needed to be sufficiently powered to adequately assess clinically significant neuropsychiatric events with each treatment and in both of the two subgroups (those without and with a history of psychiatric disorder).

In October 2014, in the context of a labeling supplement submitted by Pfizer proposing to remove the boxed warning from the Chantix labeling, data from randomized controlled trial (RCT) meta-analyses and observational studies were discussed at a joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM AC). The committees were asked to discuss how they would weigh the evidence contributed by the meta-analyses, observational studies, and spontaneous case reports when they were evaluating the risk of serious neuropsychiatric adverse events in patients taking varenicline. In general, many of the committee members expressed concern with the quality of the data presented. The committee members were also asked based on the data presented on the risk of serious neuropsychiatric adverse events with Chantix, whether they would they recommend removal or modification of the boxed warning statements regarding risk of serious neuropsychiatric adverse events, or retention of the current boxed warning statements with a reassessment once the ongoing postmarket safety outcome trial was completed.

The majority of the committee agreed that more data were needed and recommended to retain the current boxed warning statement and reassess once the postmarket safety outcome trial results were available.

III. SIGNIFICANT REVIEW FINDINGS

Results of the Postmarket Safety Outcome Trial

The clinical study report and accompanying labeling supplement were reviewed by Dr. Celia Winchell, DAAAP's Addiction Team Leader. See Dr. Winchell's review dated 11/14/16 for a detailed discussion of the postmarket safety outcome trial.

Briefly, the trial was a 24-week, double-blind, active- and placebo-controlled, multi-center, parallel group trial designed to assess the safety and efficacy of Chantix 1 mg twice daily and Zyban 150 mg twice daily for smoking cessation. Nicotine replacement therapy (NRT) was included as an active control. The duration of active treatment was 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks. Patients were classified into one of two cohorts— those without a diagnosis of a psychiatric disorder and those with an established and stable diagnosis of psychiatric disorder confirmed by the Structured Clinical Interview for DSM-IV Axis 1 and 2 Disorders (SCID I and II) conducted at screening; an equal number of patients without or with a diagnosis of a psychiatric disorder were enrolled and randomized among the four treatment arms in a 1:1:1:1 ratio.

The trial enrolled 8,144 patients at 140 centers in 16 countries, including the U.S., of which 8,058 patients were randomized to Chantix (n=2,016), Zyban (n=2,006), NRT (n=2,022), and placebo (n=2,014). Among the 4,074 patients in the psychiatric history cohort, approximately 70 percent had affective disorders, 19 percent had anxiety disorders, 9 percent had psychotic disorders, and less than 1 percent had borderline personality disorder.

FDA's review of this trial revealed several issues limiting the review team's confidence in the Applicants' reported frequencies of primary neuropsychiatric outcome events[3]. However, a variety of sensitivity analyses conducted to address the trial conduct issues did not change the overall conclusion of the primary analysis.[4] Regardless of the sensitivity analysis approach, the relative frequencies of the primary outcomes were similar. None of the smoking cessation treatments appeared to increase the risk of neuropsychiatric events in patients without a history of psychiatric disorders, and in patients with a history of psychiatric disorders or current illness, both varenicline and bupropion had numerically higher frequencies of events in all analyses. Some of the bupropion-related neuropsychiatric adverse events appeared to involve precipitation of mania in patients with a known affective disorder; this is a labeled risk of bupropion.

Based on the sensitivity analyses, the review team thought it was likely that the frequency of primary outcome events was likely higher than what was measured in the trial. Just prior to the advisory committee, Pfizer submitted an analysis that expanded the definition of the primary endpoint. After the advisory committee meeting, the review team further assessed Pfizer's expanded endpoint definition and refined it further. Dr. Winchell described the final expanded endpoint definitions in her 11/14/16 review on page 78-80, including a comparison of the frequency of the primary endpoint by the various outcome definitions.

As shown in Table 1 below, clinically significant neuropsychiatric adverse effects occurred at a similar frequency of about 3 percent across treatment groups in patients without psychiatric diagnoses. In the cohort of patients with psychiatric diagnoses, there was a higher incidence across groups, and a numerically increased risk associated with Chantix and with Zyban (approximately 12 percent), compared to placebo (approximately 10 percent). There was no meaningful difference in risk between Chantix and Zyban (see Table 1).

Table 1. Incidence of Clinically Significant Neuropsychiatric Adverse Events^

	Chantix 1 mg BID*	**Zyban 150 mg BID***	**NRT 21 mg/day with taper**	**Placebo**
Non-psychiatric cohort	3.1%	3.5%	3.3%	4.1%
Psychiatric cohort	12.2%	11.8%	9.8%	9.5%

^ Using FDA expanded analysis definition; *BID – twice daily

Serious adverse events (i.e., events of a life-threatening nature, or resulting in hospitalization or death) in the psychiatric history cohort primarily involved psychiatric

[3] For additional details, see Dr. Celia Winchell's review (dated 11/14/16; section 6.1.3, pp. 59-65)
[4] For additional details, see Dr. Winchell's review (dated 11/14/16; section 6.1.3, pp. 72-84) and Dr. Eugenio Andraca-Carrera's biostatistics review dated 11/10/16 and addendum dated 11/21/16.

decompensation. Other reported events had an impact on patient functioning; however, most events were not serious (as defined above) and were usually transient.

The trial evaluated efficacy by comparing smoking abstinence rates of Chantix and Zyban relative to placebo for the last 4 weeks of the 12-week treatment and continuously through Week 24, as measured by carbon monoxide (CO)-confirmed continuous abstinence rate. In both cohorts, patients treated with Chantix, Zyban, or nicotine patch (NRT) had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and weeks 9 through 24 compared to patients treated with placebo (see Table 2).

Table 2. Continuous Abstinence (95% Confidence Interval)

	Chantix 1 mg BID	**Zyban 150 mg BID**	**NRT 21 mg/day with taper**	**Placebo**
Weeks 9 through 12				
Non-psychiatric cohort	38% (35%, 41%)	26% (23%, 29%)	26% (24%, 29%)	14% (12%, 16%)
Psychiatric cohort	29% (26%, 32%)	19% (17%, 22%)	20% (18%, 23%)	11% (10%, 14%)
Weeks 9 through 24				
Non-psychiatric cohort	25% (23%, 28%)	19% (16%, 21%)	18% (16%, 21%)	11% (9%, 13%)
Psychiatric cohort	18% (16%, 21%)	14% (12%, 16%)	13% (11%, 15%)	8% (7%, 10%)

Advisory committee discussion

The results of the postmarket safety outcome trial and updated reviews of observational studies were discussed at a second joint meeting of the PDAC and the DSaRM AC on September 14, 2016. Because of the specific concerns to be discussed, special government employees with a variety of backgrounds were also added as voting members to the advisory committee for this meeting. These included individuals with general internal medicine background, as well as clinicians involved in smoking control and smoking cessation research. Experts who had attended the meeting to discuss the previous labeling supplement were invited; some were not available.

Overall, committee members applauded the completion of a randomized controlled trial to add to prior studies. There were concerns regarding the difficulty with data monitoring and control across so many trial sites located in several countries with different languages, cultures, and investigators. The committee members also expressed concerns with the lack of statistical power to detect suicidal events. Some panel members noted the need for having a design that holds to rigorous standards for safety related outcomes, and stated power calculations a priori for this deserved closer attention. Some of the committee members expressed concerns regarding the inclusion of patients who were not naïve to treatment with the drugs under study, which may have enriched the population for individuals able to tolerate the drugs. However, following the advisory committee, FDA

performed an analysis that confirmed that exclusion of patients who had prior exposure to the study drugs did not change results of the primary endpoint analysis.

Most committee members did not have specific recommendations regarding which of the analyses best represented the data, although there was support for using an expanded outcome definition and for using the alternate statistical approach employed by the FDA team. The potential impact of the variability of data collection practices and coding of adverse events was discussed, but some committee members noted that they did not expect that the variability would affect the adverse event data differentially across treatment arms.

The committee members did not think emphasis should be placed on the observational studies and concluded that they did not contribute additional insight beyond the findings of the postmarket safety outcome trial.

Committee members noted the increased risk for neuropsychiatric events in the population with a psychiatric history. Several committee members who noted this difference recommended that this information needed to be described in product labeling.

The committee members were asked to vote for one of the following options:

A. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events (10 members voted for this option)
B. Modify the language in the boxed warning (4 members voted for this option)
C. Keep the current boxed warning (5 members voted for this option)

Some committee members who voted to remove the boxed warning noted that the decision was difficult due to their concerns with the limitations from the study results presented. Some also noted the public health importance of effective smoking cessation therapies being available for patients who need smoking cessation aids, especially those with psychiatric illness.

Several members who voted to retain or modify the boxed warning voiced that their reason was not related to the study, but due to a concern that removing a boxed warning would be misinterpreted as communicating a complete absence of risk. There was also concern about the potential precedent-setting nature of the removal of the boxed warning for other products in the future. A few members of the committee voted to keep the boxed warning, citing concerns about the study endpoint, study conduct, and the inadequate statistical power to detect more rare events, or simply noted that they were unconvinced by the study.

IV. CONCLUSIONS

Based on the review of the postmarket safety outcome trial, we have determined the risk of serious neuropsychiatric adverse events with Chantix and Zyban is lower than previously suspected. Although there is still a risk of neuropsychiatric adverse events with Chantix and Zyban, most people who had changes in mood, behavior, or thinking

did not have serious consequences such as hospitalization. Therefore, given the robust efficacy results, we believe this trial confirms that the benefits of taking these drugs for smoking cessation outweigh the risk of neuropsychiatric adverse events.

V. RECOMMENDED REGULATORY ACTION(S)

Based on the team's review and analysis, including sensitivity analyses, and the discussion at the September 14, 2016 advisory committee meeting, the Division has determined that it is appropriate to remove the boxed warning for serious neuropsychiatric adverse events from the Chantix labeling. The language describing the serious neuropsychiatric adverse events seen in patients quitting smoking will also be removed from the Boxed Warning in the Zyban label.[5] Additionally, we will revise the Warnings and Precautions 5.1 statement in both labels to include the results of the postmarket safety outcome trial, including the frequencies of the neuropsychiatric adverse events and the efficacy measures. The Medication Guides that explain the neuropsychiatric adverse events associated with the use of Chantix and Zyban will be maintained as part of labeling for each product; however, the REMS requirement for each product will be removed.

[5] The active ingredient in Zyban (bupropion) is in the antidepressant class; therefore the label carries the class Boxed Warning for suicidality and antidepressant drugs. This language will remain in a Boxed Warning in the labels for Zyban and other bupropion products.

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/s/

JUDITH A RACOOSIN
12/07/2016

Cross-Discipline Team Leader Review

Date	November 21, 2016
From	Celia Winchell, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/Supplement#	021928 S040
Applicant	Pfizer, Inc.
Date of Submission	February 18, 2016
PDUFA Goal Date	December 18, 2016
Proprietary Name / Established (USAN) names	CHANTIX (varenicline tartrate) tablet, film coated
Dosage forms / Strength	Oral tablets, 0.5 mg and 1 mg
Indication(s)	Aid to smoking cessation treatment (approved)
Recommended:	*Approval*

Contents

1. Introduction

This memo serves as the supervisory review for a supplement submitted to Pfizer's NDA 21928, an aid to smoking cessation treatment marketed as Chantix. The supplement was supported by a single new, randomized, placebo-controlled safety trial, Study A3051123, in which a cohort of patients without a history of psychiatric diagnoses and a cohort of patients with current or past diagnoses were randomized to treatment with standard regimens of Chantix, sustained-release bupropion, or transdermal nicotine and closely monitored for the emergence of neuropsychiatric adverse events. This trial was conducted in response to an Agency requirement to evaluate the risk of serious neuropsychiatric effects. I conducted the primary clinical review with assistance from Sarah Arnold, M.D. The statistical review of the safety endpoint was conducted by Eugenio Andraca-Carrera, Ph.D., supervised by Mat Soukup, Ph.D.; and the statistical review of the

efficacy was conducted by Yi Ren, Ph.D., supervised by David Petullo, M.S. Additional observational study results from published literature were reviewed by Natasha Pratt, Ph.D., supervised by Judy Staffa, Ph.D. The supplement seeks to remove the Boxed Warning concerning the risk of neuropsychiatric adverse events from labeling, and to add detailed results of the study to Section 5.1 (Warnings and Precautions) as well as to add the efficacy results to the Clinical Trials section of labeling.

2. Background

Varenicline is a high-affinity selective partial agonist of the α4β2 nicotinic receptor, previously designated CP526-555 and developed under IND 58,994, opened on 9/14/1999. The α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine in animal models. Based on the activity at the nicotinic receptor, varenicline could be expected to mitigate withdrawal symptoms and reduce the reinforcing effects of nicotine, leading to efficacy in helping smokers stop smoking. NDA 21,928 was submitted by Pfizer on 11/11/05 and approved on 5/10/06.

2.1 Original NDA Findings

The initial approval was based on results from 30 completed (24 Phase 1, 8 Phase 2/3) and 3 ongoing clinical studies. The studied population included adult smokers of at least 10 cigarettes/day, generally in good health, with exclusions for laboratory abnormalities, psychiatric conditions, hypertension, significant cardiovascular history (remote history allowable in Phase 3), or other significant medical illnesses.

The main smoking cessation studies in the original NDA were basically similar in design. After initial screening assessments and a baseline visit, subjects were randomized to one of the treatment arms, which included placebo, varenicline (various doses in Phase 2; 1 mg b.i.d. in Phase 3), and, in several studies, Zyban at labeled doses (i.e., 150 mg b.i.d. with initial dose titration). Subjects attended study visits weekly visits during treatment (12 weeks in most studies), and were to quit smoking on treatment day 7. Smoking status was assessed at each visit via self-report (nicotine use inventory) and exhaled carbon monoxide. The protocol also called for provision of an educational booklet on smoking cessation (National Cancer Institute's "Clearing the Air" booklet) and were provided with up to 10 minutes of counseling at each visit following Agency for Healthcare Research and Quality guidelines. Subjects who completed the 12 weeks of the treatment phase (even those who discontinued using study medication but elected to stay in the study) were then followed for an additional 40 weeks with clinic visits at roughly 12 week intervals, supplemented with intervening telephone contacts.
The pre-specified primary endpoint was the 4-week Continuous Quit Rate (CQR) for the last four weeks of treatment (for most studies, Weeks 9 to 12). Subjects were to be classified as responders if they were able to maintain complete abstinence from cigarette smoking and other nicotine use for the last 4 weeks of treatment with end-expiratory exhaled CO measurements ≤ 10 ppm.

In the Phase 2 and 3 studies, varenicline treated patients were more likely to achieve the protocol-specified definition of abstinence than patients treated with placebo or with Zyban in all studies, demonstrating substantial evidence of efficacy and of superiority over existing treatment. The table below shows the abstinence rates in the two trials designated as pivotal in the original NDA.

	Chantix	Placebo
Study 28	N = 349	N = 344
Continuous Abstinence Weeks 9-12	44%	17%
Continuous Abstinence Weeks 9-52	21%	8%
Study 36	N = 343	N = 340
Continuous Abstinence Weeks 9-12	44%	18%
Continuous Abstinence Weeks 9-52	22%	10%

In the original NDA submission, the overall safety database included 4690 individuals who were exposed to varenicline, including 456 subjects treated with varenicline 1 mg b.i.d. (the highest proposed marketed dose) for at least 24 weeks, and 112 for 364 days or more. Treatment-related adverse events included nausea, vomiting, flatulence, constipation, insomnia, abnormal dreams, dysgeusia, and increased appetite (leading, in longer-term treatment, to weight gain). Approximately 13% of subjects in short-term studies discontinued due to adverse events, although only nausea, headache, and insomnia accounted for discontinuation in >1% of subjects, and only nausea was clearly a more common cause of treatment discontinuation in active-treated subjects compared to placebo-treated. Varenicline did not have consistent effects on any laboratory parameters, cardiac conduction parameters, or vital sign measurements. Notably, patients with psychiatric diagnoses were not included.

2.2 Regulatory History of Neuropsychiatric Adverse Event Signal and Labelng

In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events involving varenicline (approved for marketing in the EU in September 2006 under the name "Champix"). Later that same summer, a fatal case involving bizarre and aggressive behavior by a Chantix-treated patient in the U.S. became highly-publicized. FDA then undertook evaluations of the post-marketing data regarding both cases of suicide and cases of bizarre and aggressive behavior and concluded that there were cases that could be attributed to Chantix treatment. In a number of cases, the reporters provided rich and detailed narratives about the events, describing experiences involving symptoms in a variety of neuropsychiatric domains, including cognition, perception, mood, and general functioning. A subsequent review of post-marketing data on Zyban[1] and various nicotine replacement therapies identified similar cases associated with Zyban.

[1] ZYBAN, Bupropion HCl Sustained Release tablets, also studied in the clinical trial supporting this supplement, is an aminoketone antidepressant originally approved under the proprietary name Wellbutrin. As an antidepressant, Wellbutrin is thought to act primarily via noradrenergic mechanisms, but also has some dopaminergic activity. Its mechanism of action as an aid to smoking cessation is not known. The NDA for ZYBAN (20711, Glaxo SmithKline) was approved in May 1997.

Two reviews of AERS[2] cases were completed by the Division of Adverse Event Analysis II[3] - one focused on suicidality events (finalized July 2008) and the other focused on neuropsychiatric adverse events not related to suicidality (finalized Dec 2008). These are summarized in my primary review.

A chronology of the regulatory actions and public communications that followed is provided in my primary review. In addition to labeling actions taken as the understanding of the serious neuropsychiatric adverse events with varenicline evolved, FDA determined that a REMS was necessary to ensure that the benefits of varenicline outweighed the risks. In May 2008, FDA issued a letter to Pfizer that required a REMS and also included issuance of a postmarketing requirement (PMR) for a clinical trial to assess the known serious risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions related to the use of varenicline products. A similar REMS and PMR for Zyban was required of Glaxo SmithKline.

A series of incremental changes to labeling were made to address the emerging understanding of the nature of the risk, ultimately leading to the placement of a Boxed Warning in July 2009 The need for a boxed warning was discussed extensively at the highest levels of Center management and it was determined that the events met criteria for placement in a boxed warning. Specifically, because the events were of a serious nature and had adverse consequences that could be prevented by close monitoring.

[2] The FDA Adverse Events Reporting System was called "Adverse Event Reporting System (AERS)" at the time these reviews were done.
[3] The Division of Adverse Event Analysis II is now called the "Division of Pharmacovigilance II".

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2.3 Regulatory History of PMR Trial

After issuance of the PMR letter, the considerable deliberation inside CDER and with the Sponsors took place. The design of the study presented a number of challenges. The fundamental problem was that the types of cases reported in the postmarket setting were of a heterogeneous nature and subsumed a variety of disturbing symptoms. Focus on a single endpoint, such as suicide or psychiatric hospitalization, was considered but it was felt that this would miss the full range of neuropsychiatric symptoms that were reported, and additionally, that the sample size for such a study might need to be so large as to be impracticable. Instead, a composite endpoint would be needed that could capture the types of events reported in the AERS cases—events often involving a cluster of emotional, cognitive, perceptual, and behavioral symptoms that were identified by the patient or the patient's family as unusual, out of character, and extremely disturbing.

After internal deliberation and discussion with Pfizer and GlaxoSmithKline (sponsor of bupropion), further guidance on the PMR was issued in a letter dated June 2, 2009. As seen in the description below, FDA determined that a randomized controlled clinical trial would be required to meet the PMR goals:

A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric adverse events, including but not limited to suicidality, in individuals using varenicline, bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric adverse events compared to individuals without prior history of psychiatric disorders while using varenicline as an aid to smoking cessation. The study should be sufficiently powered to adequately assess clinically significant neuropsychiatric adverse events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).

The Sponsors were encouraged to collaborate on this trial. Pfizer took the lead on designing and conducting the PMR trial, with financial support and study drug supplied by GSK (who also markets nicotine transdermal products). After a series of discussions internally and with the sponsors, the PMR protocol was found acceptable around July 2010. In recognition of the variable and ill-defined nature of the neuropsychiatric adverse events reported, and the difficulty of capturing such events in traditional MedDRA coding[4], a composite endpoint was developed specifically for the PMR trial and instruments to solicit relevant events were included in the trial procedures. Sixteen main conceptual "components" of the endpoint were agreed-upon in the protocol—however, selection of the specific MedDRA terms was left to

[4] MedDRA (Medical Dictionary for Regulatory Activities) is an international standardized lexicon of medical terms used to code adverse events. MedDRA was developed by the ICH (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and released in 1999. MedDRA contains about 21,000 different preferred terms (PTs, e.g., nausea, hypotension) for various adverse events. These PTs are vertically grouped into 3 levels. The highest level for a PT is the System Organ Class, of which there are 26 (e.g., Cardiac disorders, Infections and infestations). http://www meddra.org/sites/default/files/guidance/file/intguide_17_1_english.pdf

to the sponsors to determine and included in the statistical analysis plan (SAP). Following FDA review, some additional terms were identified for inclusion and incorporated into the primary endpoint before the final analysis.

In pre-submission discussions, it was conveyed that the intent for this endpoint was to avoid "noise" by excluding mild events, because some emotional and cognitive symptoms such as irritability and impaired concentration are well-recognized symptoms of nicotine withdrawal. Such symptoms may be expected in patients quitting smoking without pharmacotherapy. The instrument developed for the study, the Neuropsychiatric Event Interview (NAEI) was intended to be used as a semi-structured interview, wherein any positive responses would be followed up in order to get a full picture of the context of the symptom, co-occurring symptoms, and a rich narrative of the event. Additionally, investigator assessments of severity were incorporated into the endpoint with the aim of filtering out events that did not have any impact on patient functioning. This was intended to facilitate identification of clinically significant events and to differentiate minor, expected symptoms from the unusual and disturbing findings seen in the postmarketing reports. As described below, this intent was not fully realized, and other methods to capture events of a clinically significant nature were explored in the analysis.

3. CMC/Device

No new CMC issues were raised by this supplement.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical issues were raised by this supplement

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics information was included in this supplement. The text below, adapted from the approved labeling, summarizes the clinical pharmacology of Chantix:

Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking.

Absorption of varenicline is virtually complete after oral administration and systemic bioavailability is ~90%. Cmax occurs within 3-4 hours of administration, T1/2 is approximately 24 hours, and steady-state conditions are reached in 4 days. Bioavailability is unaffected by food or time of day. Plasma protein binding is low and independent of age and renal function. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender,

smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

In subjects with moderate renal impairment, varenicline exposure increased 1.5-fold compared with subjects with normal renal function. In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. Dose reduction is recommended for patients with renal impairment. Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment.

No clinically meaningful pharmacokinetic drug-drug interactions have been identified. In vitro studies demonstrated that varenicline does not inhibit renal transport systems or the following cytochrome P450 enzymes (IC50 >6400 ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes in vitro, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for NRT alone.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Primary Safety Endpoint and Efficacy

Phase 4, Randomized, Double Blind, Active- and Placebo-Controlled Multi-Center Study Evaluating the Neuropsychiatric Safety and Efficacy of Varenicline and Buproprion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders[5]

Protocol # A3051123
Conducted November 30 2011-January 13 2015

8144 subjects at 140 investigative centers in 16 countries[6] *(Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Denmark, Finland, Germany, Mexico, New Zealand, Russia, Slovakia, South Africa, Spain, U.S.)*

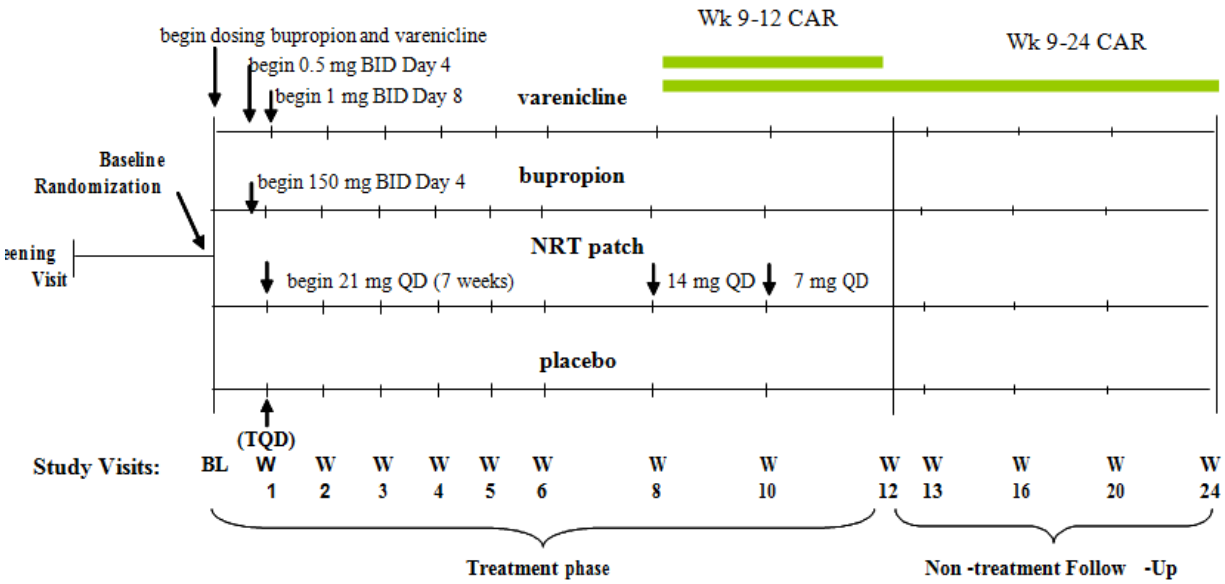
This supplement included the results of one new clinical trial, Study A3051123, and sought, on the basis of the data submitted, to delete the boxed warning concerning serious NPS from the Chantix labeling, as well as to include the results of the study in detail in several places in labeling. Pfizer proposed to retain a (significantly shortened) description of neuropsychiatric symptoms that have been reported in patients being treated with Chantix. However, a statement that "A causal relationship between these reports and CHANTIX treatment has not been established" was proposed for inclusion in this warning, and the instruction that patients should discontinue Chantix if symptoms occur was proposed for deletion.

7.1 Study Design

Study A3051123 The study was a 24-week, double-blind, NRT and placebo-controlled, multi-center, parallel group study designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion hydrochloride 150 mg BID for smoking cessation. The study design, dosing regimen, efficacy endpoints, and analyses were mostly similar to the Phase 3 studies used to support the initial application in 2005. The primary comparisons were to be varenicline vs. placebo and bupropion vs. placebo. NRT was included as active control and study medications were to be given via a triple-dummy design. The duration of active treatment was 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks (Figure 1).

[5] The sponsor refers to this trial as the "EAGLES" trial.
[6] Ten additional centers did not enroll any subjects; one center enrolled only a single subject who did not take any study medication, and therefore did not contribute to the Safety population.

Figure 1. Study Diagram



W = Week; BL = Baseline; TQD = Target quit date; CAR= Continuous abstinence rate

Eligible patients were adult smokers of at least 10 cigarettes/day (on average, over the past year and during the month prior to screening) who were motivated to stop smoking.

All potential participants were screened using the Structured Clinical Interview for DSM-IV (SCID). Subjects were to be included in the psychiatric cohort, if they were considered clinically stable and met criteria, either current (meeting criteria in past month) or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and had met diagnostic criteria before the initiation of study treatment.

Psychotic Disorders limited to:

- Schizophrenia
- Schizoaffective

Affective Disorders limited to:

- Major Depression
- Bipolar-I, Bipolar-II

Anxiety Disorders limited to:

- Panic Disorder with or without Agoraphobia
- Post-Traumatic Stress Disorder
- Obsessive-Compulsive Disorder
- Social Phobia
- Generalized Anxiety Disorder

Personality Disorders limited to past history of:

- Borderline Personality Disorder

All subjects with an Axis I or II diagnosis were to be judged to be clinically stable including the following no exacerbations in the prior 6 months, stable medication regimen in the prior 3 months, no anticipated change in treatment, and not at high risk for suicide per investigator.

Key exclusion criteria were pregnancy, nursing, psychiatric conditions not included in the above list[7], substance use disorders (unless in remission), Clinical Global Impression of Severity (CGI-S) rated 5 or higher, past year suicidal ideation with intent or plan (C-SSRS Item 5), past year suicidal behavior, self-injuring behaviors, positive urine drug screen, medical conditions (severe COPD, recent significant cardiovascular or cerebrovascular disease, recent cancer, ECG or LFT abnormalities). Additionally, exclusions related to bupropion (seizure disorder, anorexia, bulimia, abrupt discontinuation of sedatives) were described.

[7] Detailed inclusion and exclusion criteria and excluded medications are listed in the primary review

Disallowed concomitant medications included other smoking cessation aids, as well as some other medications thought to affect or be affected by smoking cessation[1].

Patients were randomly assigned to treatment at a 1:1:1:1 ratio, with stratification by the presence or absence of a diagnosis of psychiatric disorder. Within the cohort with a diagnosis of a psychiatric disorder, treatment assignment was stratified with respect to the four major diagnosis groups (Psychotic, Affective, Anxiety and Personality Disorders).

The study utilized a triple-dummy design. Subjects randomized to one of the three active dosing groups were to take that active medication and the other two medications in matching placebo form. Because both varenicline and bupropion are initiated before quit day while NRT is initiated on quit day, during the first week of treatment no patches were applied. All subjects began their transdermal medication (active or placebo) in Week 2. Varenicline was titrated to the full dose during the first week in the usual manner described in labeling (0.5 mg QD x 3 days, 0.5 mg BID x 4 days, then 1 mg BID for 11 weeks). Bupropion was titrated as in labeling, with 150 mg QD x 3 days and then150 mg BID for the remainder of the treatment period (11 weeks and 4 days). NRT treatment began at the Week 1 visit with 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.

Dosing continued until the Week 12 visit. All subjects were then to be followed for an additional 12 weeks in the non-treatment phase of the protocol. At the discretion of the Investigator, dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may have been reduced, temporarily discontinued or stopped for subjects who had intolerable adverse events (e.g., nausea); or for subjects who in the opinion of the Investigator required a dose reduction due to use of concurrent medications. Dosing with blinded NRT (NRT or matching placebo) may have been temporarily discontinued or stopped for subjects who had intolerable adverse events. It was not possible to reduce the dose of blinded NRT. If any of the study drugs needed to be permanently discontinued then all 3 blinded study medications (varenicline/placebo, bupropion/placebo, and NRT/placebo) were to be permanently discontinued.

Study visits occurred weekly through Week 6, then biweekly through Week 12, with telephone contacts in intervening weeks. During the post-treatment period, in-clinic visits occurred at Weeks 13, 16, 20, and 24, with weekly telephone contacts.

The following assessments were used to collect information about patient experiences:

- Hospital Anxiety and Depression Scale (HADS) at baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24
    - 14 individual item responses, ranging in increasing severity from 0 to 3.
    - Anxiety subscale score (sum of the 7 odd-numbered item response scores; ranges: 0-7 = normal, 8-10 = suggestive, 11-21 = probable).
    - Depression subscale score (sum of the 7 even-numbered item response scores; ranges: 0-7 = normal, 8-10 = suggestive, 11-21 = probable).
- C-SSRS at baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24.

- Clinical Global Impression of Improvement (CGI-I) at Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24
    - A single item response (a 7-point rating, with 4 being no change and 1 to 3 being levels of improvement and 5 to 7 being levels of worsening).

Figure 2. Neuropsychiatric Adverse Event Interview

)Neuropsychiatric Adverse Events Interview Questions
· Have you felt depressed (sad, blue, down, empty, as if you didn't care)? · Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy? · Have you cried or felt like crying?
· Have you been worried or scared? · Have you been nervous or anxious? · Have you felt panicky at all? · Some people have panic attacks when they suddenly feel very frightened and have physical symptoms like heart palpitations (your heart is pounding and/or beating rapidly), shortness of breath and chest pains. Have you had this?
· Have you had times when you felt extremely agitated? · Have you had times when you felt like you had to be always moving or even pacing?
· Have you felt unusually cheerful, or happy, not just your normal self, so that other people noticed? · Have you had much more energy than usual to do things? · Have you needed less sleep than usual to feel rested?
· Have you felt hostile towards others? · Have you been involved in any serious arguments or fights? · Have you had the urge to injure or harm someone?
· Have you felt that people have been talking about you? · Have you felt that someone may be after you, or trying to harm you in some way?
· Has there been anything unusual about the way things look or sound or smell? · Have you heard things that other people couldn't hear, like noises or voices of people talking when there was no one around? · Have you seen things that other people couldn't see?
· Has your mind been playing tricks on you in any way? · Have you had any ideas that other people might not understand or might find strange?
· Have things seemed unreal to you? · Have you felt that you are detached from or have trouble connecting with other people? · Have you felt strange or unnatural in any other way?

The NAEI (above) was intended to be used as a semi-structured interview, wherein any positive responses would be followed up in order to get a full picture of the context of the symptom, co-occurring symptoms, and a rich narrative of the event. To accomplish this, the protocol stipulated that NAEI was to be administered by trained interviewers. Follow-up questions were to be used for "clarification, frequency/duration, severity, and degree of functional impairment related to the symptom." Sample follow-up questions were provided in the training materials. The interviewer was instructed to "probe as needed to assess the subject's experiences and to make an appropriate assessment." Narratives were to be constructed for NPS cases that pulled together all relevant information from reporters who could include the patient, significant others, health care providers, or other sources.

When reporting an AE, verbatim text was also to be recorded on a supplemental AE reporting page. Reported events by a household member of the subject, personal physician, or other, that were judged to be AEs by the investigator were to be captured as AEs, and the reporters' verbatim texts of these events were also to be captured.

At each visit, assessments were to be done in the following order:
1. Volunteered AE report – opening question on how the subject has been feeling in general
2. Follow up on previously reported AEs that are still ongoing
3. Clinical rating scales as specified in the protocol
4. NAEI
5. Columbia Suicide Severity Rating Scale.

All assessment instruments used in the A3051123 study were translated into the local language and were administered in that language, and the results were recorded on worksheets that were replicas of the case report forms translated into the local language. Conversations between the site staff and the study subjects regarding their volunteered adverse events and conversations intended to gain more details about the subjects' positive responses on the NAEI were conducted in the local language. The results of those assessments and conversations were then to be translated by the site staff and were entered into the electronic case report form in English.

All participants were to receive up to 10 minutes of smoking cessation counseling in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines[8] or similar local guidelines, at each clinic visit.

Efficacy was assessed using a Nicotine Use Inventory and end-expiratory exhaled carbon monoxide (exhaled CO) monitoring.

The primary pre-specified safety endpoint was a 16 component composite of the following elements:

[8] Fiore MC, Jaen CR, Baker TB, et al. Clinical practice guideline; U.S. Department of Health and Human Services, DHHS publication no. (CDC) 88-8406, 2000 referenced.

- 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.

This composite endpoint includes 241 MedDRA preferred terms in the 16. This endpoint is referred to as the Neuropsychiatric (NPS) endpoint.

Treatment emergent events were defined as events that occurred after the first dose of randomized study treatment and before the last dose of study treatment plus 30 days. Note that this means that the primary NPS endpoint was based on events observed only during the 12 week treatment phase of the trial plus 30 days.

Adverse events were classified as Mild, Moderate or Severe according to the following definitions:

- Mild – does not interfere with subject's usual function.

- Moderate – interferes to some extent with subject's usual function.

- Severe – interferes significantly with subject's usual function.

According to the study protocol, NPS events were collected through any of the following means:

- Volunteered adverse event.

- Actively collected adverse event. NPS events were collected through a neuropsychiatric adverse event interview at each clinic visit.

- Report by a family member and judged to be an adverse event by the investigator.

- Suicide related AEs solicited through the C-SSRS questionnaire at each clinic visit.

Secondary safety endpoints included the components of the NPS endpoint as well as the scores of three questionnaires: Hospital Anxiety and Depression Scale (HADS), Columbia Suicide Severity Rating Scale (C-SSRS), and the Clinical Global Impression of Improvement (CGI-I). Deaths were also analyzed as a secondary safety endpoint of interest.

Efficacy:

The primary efficacy endpoint was the 4-week CO-confirmed continuous abstinence for Weeks 9 through 12.

The primary measures of efficacy were CO-confirmed CA (Continuous Abstinence) from Week 9 through Week 12 (CA 9-12) and CO-confirmed CA from Week 9 through Week 24

(CA 9-24). Smoking status was assessed by use of the Nicotine Use Inventory (NUI) questionnaire, which was administered at each study visit (in-clinic visits and telephone contacts) and confirmed by CO levels measured at in-clinic visits. Subjects were considered responders (abstainers) if they answered 'no' to questions 1 and 2 on the NUI at each week included in the assessment period and had CO levels ≤10 ppm. The questions asked whether the subject had smoked any cigarettes ('even a puff') since the last visit/contact and whether they had used any other nicotine-containing products including other tobacco products and NRT products (other than the study medication) for Weeks 9 through 12, and any tobacco products for Weeks 13 through 24.

7.2 Population

A total of 11,186 subjects were screened for participation in the study, of which 8144 subjects subjects at 140 investigative centers (in 16 countries) were randomized in an approximate 1:1:1:1 ratio; 8058 ultimately received treatment distributed as varenicline (n=2016), bupropion (n=2006), NRT (n=2022), and placebo (n=2014). At one site, a single patient was randomized but not treated, so the number sites which treated patients is 139.

Demographics

Selected demographic and baseline characteristics of the subjects are shown in the tables below.

Table 1 Summary of Baseline Characteristics (Non-PHx Cohort) – Safety Population

Baseline Characteristics	Varenicline (N = 990)	Bupropion (N = 989)	NRT (N = 1006)	Placebo (N = 999)
Age (years)				
Mean (SD)	45.8 (13.0)	46.0 (13.0)	46.1 (12.8)	45.9 (12.8)
Min, Max	18, 73	18, 75	18, 75	18, 74
Gendera, n (%)				
Male 510 (51.5)	503 (50.9)	497 (49.4)	489 (48.9)	
Female	480 (48.5)	486 (49.1)	509 (50.6)	510 (51.1)
Race, n (%)				
White	819 (82.7)	820 (82.9)	837 (83.2)	817 (81.8)
Black	135 (13.6)	116 (11.7)	127 (12.6)	126 (12.6)
Asian	14 (1.4)	16 (1.6)	13 (1.3)	19 (1.9)
Other	22 (2.2)	37 (3.7)	29 (2.9)	37 (3.7)
Weight (kg)				
N	980	984	1000	992
Mean (SD)	80.0 (19.5)	80.4 (20.1)	81.6 (19.6)	80.6 (19.3)
Min, Max	39.8, 176.8	40.5, 171.5	38.4, 201.8	42.0, 169.2
Prior psychiatric medications, n (%)				
Psychoanaleptics	27 (2.7)	27 (2.7)	33 (3.3)	36 (3.6)
Psycholeptics	61 (6.2)	58 (5.9)	68 (6.8)	73 (7.3)
Total number of years subject smoked				
Mean (SD)	27.8 (12.8)	28.2 (13.0)	28.2 (12.8)	28.2 (12.6)
Min, Max	2, 64	2, 60	1, 63	2, 62
Total number of lifetime serious quit attemptsb				
None, n (%)	181 (18.3)	181 (18.3)	174 (17.3)	204 (20.4)
≥1 previous serious quit attempt, n (%)	809 (81.7)	808 (81.7)	832 (82.7)	795 (79.6)
Mean (SD)	3.3 (13.8)	3.4 (10.3)	3.1 (4.2)	3.2 (7.4)
Min, Max	0, 400	0, 300	0, 31	0, 108
Previous use of medication for quit attempt (most recent attempt), n (%)				
Varenicline	132 (13.3)	144 (14.6)	152 (15.1)	136 (13.6)
Bupropion	92 (9.3)	91 (9.2)	93 (9.2)	90 (9.0)
NRT	272 (27.5)	307 (31.0)	325 (32.3)	305 (30.5)
Average number of cigarettes per day over the last month prior to study entry				
N	990	989	1005	999
Mean (SD)	20.8 (8.3)	20.6 (7.8)	20.8 (8.2)	20.5 (7.9)
Min, Max	10, 80	6, 60	10, 60	10, 60
FTND (Total Score)				
N	989	987	1006	998
Mean (SD)	5.49 (1.98)	5.50 (2.02)	5.56 (1.95)	5.51 (2.01)
Min, Max	0, 10	0, 10	0, 10	0, 10
C-SSRS Lifetime				
n (%)	49 (4.9)	44 (4.4)	52 (5.2)	49
HADS (Total Score)				
Mean (SD) 4.35 (4.44)		4.08 (4.09)	4.20 (4.11)	4.50 (4.33)
Min, Max 0, 28	0, 24	0, 25	0, 22	

Abbreviations: C-SSRS = Columbia–Suicide Severity Rating Scale; FTND = Fagerström Test for Nicotine Dependence; HADS = Hospital Anxiety and Depression Scale

a. The gender for 4 subjects randomized to treatment was inaccurately recorded (see ERRATA). b. Serious quit attempt = more than 24 hours.

c. Positive C-SSRS response for suicidal behavior or/and ideation.

Source: Pfizer's Section 14, Tables 14.1.2.1, 14.1.2.4, 14.1.2.6.1, 14.1.2.6.2, 14.1.2.6.3, 14.1.2.9.1, 14.4.3, 14.5.1.1, and 14.5.2.

Table 2 Summary of Baseline Characteristics (PHx Cohort) – Safety Population

Baseline Characteristics	Varenicline (N = 1026)	Bupropion (N = 1017)	NRT (N = 1016)	Placebo (N = 1015)
Age (years)				
Mean (SD)	47.2 (11.8)	46.7 (12.2)	47.6 (11.5)	46.9 (11.5)
Min, Max	18, 74	18, 75	18, 75	18, 75
Gendera, n (%)				
Male	392 (38.2)	387 (38.1)	384 (37.8)	387 (38.1)
Female	634 (61.8)	630 (61.9)	632 (62.2)	628 (61.9)
Race, n (%)				
White	849 (82.7)	816 (80.2)	804 (79.1)	822 (81.0)
Black	145 (14.1)	165 (16.2)	176 (17.3)	155 (15.3)
Asian	5 (0.5)	10 (1.0)	11 (1.1)	7 (0.7)
Other	27 (2.6)	26 (2.6)	25 (2.5)	30 (3.0)
Unspecified	0	0	0	1 (0.1)
Weight (kg)				
N	1024	1014	1015	1012
Mean (SD)	83.0 (21.5)	82.5 (21.3)	80.8 (20.1)	82.7 (21.3)
Min, Max	43.0, 230.0	43.2, 174.3	39.6, 191.5	44.6, 189.1
Prior psychiatric medications, n (%)				
Psychoanaleptics	423 (41.2)	354 (34.8)	369 (36.3)	380 (37.4)
Psycholeptics	309 (30.1)	298 (29.3)	326 (32.1)	295 (29.1)
Total number of years subject smoked				
Mean (SD)	28.9 (11.8)	28.2 (12.4)	28.9 (11.9)	28.3 (11.6)
Min, Max	2, 60	2, 56	2, 58	2, 56
Total number of lifetime serious quit attempts				
None, n (%)	171 (16.7)	174 (17.1)	165 (16.2)	161 (15.9)
≥1 previous serious quit attempt, n (%)	855 (83.3)	843 (82.9)	851 (83.8)	854 (84.1)
Mean (SD)	3.4 (7.7)	3.5 (6.9)	3.3 (5.3)	3.6 (10.9)
Min, Max	0, 200	0, 100	0, 77	0, 300
Previous use of medication for quit attempt (most recent attempt), n (%)				
Varenicline	149 (14.5)	194 (19.1)	168 (16.5)	161 (15.9)
Bupropion	102 (9.9)	114 (11.2)	101 (9.9)	101 (10.0)
NRT	372 (36.3)	326 (32.1)	356 (35.0)	338 (33.3)
Average number of cigarettes per day over the last month prior to study entry				
Mean (SD)	20.6 (8.0)	20.5 (8.2)	20.8 (9.1)	20.7 (8.2)
Min, Max	5, 70	10, 60	10, 120	10, 70
FTND (Total Score)				
N	1025	1017	1016	1015
Mean (SD)	6.04 (1.93)	6.06 (1.91)	5.96 (1.95)	5.91 (2.02)
Min, Max	0, 10	0, 10	0, 10	0, 10
HADS (Total Score)				
N	1026	1017	1015	1015
Mean (SD)	8.26 (6.45)	8.74 (6.92)	8.37 (6.58)	8.21 (6.22)
Min, Max	0, 30	0, 36	0, 31	0, 36
C-SSRS Lifetimeb				
n (%)	353 (34.4)	363 (35.7)	339 (33.4)	358 (35.3)

Abbreviations: C-SSRS = Columbia–Suicide Severity Rating Scale; FTND = Fagerström Test for Nicotine Dependence; HADS = Hospital Anxiety and Depression Scale;

a. The gender for 2 subjects randomized to treatment was inaccurately recorded (see ERRATA). b. C-SSRS (positive response for suicidal behavior or/and ideation).

Source: Pfizer's Section 14, Tables 14.1.2.1, 14.1.2.4, 14.1.2.6.1, 14.1.2.6.2, 14.1.2.6.3, 14.1.2.9.1, 14.4.3, 14.5.1.1, and 14.5.2.

Table 3 Summary of Baseline Psychiatric Characteristics (PHx Cohort) - FAS Population

Baseline Psychiatric Characteristics	Varenicline	Bupropion	NRT	Placebo
Primary Diagnosis in SCID, N	1032	1033	1025	1026
Affective disorders, n (%)	734 (71.1)	729 (70.6)	721 (70.3)	726 (70.8)
Anxiety disorders, n (%)	196 (19.0)	201 (19.5)	196 (19.1)	199 (19.4)
Psychotic disorders, n (%)	95 (9.2)	98 (9.5)	99 (9.7)	98 (9.6)
Borderline personality disorder, n (%)	7 (0.7)	5 (0.5)	9 (0.9)	3 (0.3)

Abbreviations: FAS = full analysis set; N = number of subjects randomized to study treatment; n = number of subjects with observation of interest; NRT = nicotine replacement therapy; SCID = Structured Clinical Interview for DSM-IV.
Note: Columns many not add up to 100% due to rounding error. Source: Section 14, Table 14.2.1.1a and Section 16, Table 16.2.6.11.

The treatment groups were similar at baseline with respect to demographic characteristics and smoking history. About 20% in each arm of the non-PHx cohort and about 16-17% in each arm of the PHx cohort had never made a 24 hour attempt to quit smoking, The group mean scores on the Fagerstrom Test of Nicotine Dependence (FTND) were approximately 5.5 in the non-PHx cohort and 6 in the PHx, denoting a fairly low level of dependence, and some people in each cohort scored 0 on the FTND. The motivation of these patients who had never attempted to quit smoking for enrolling in a clinical trial is not clear.

Of those who had made at least one prior attempt in the NPHx cohort, ~17% had used varenicline on their most recent quit attempt, 11% had used bupropion, and nearly 40% had used NRT. In the PHx cohort, 17-20% of those with a prior quit attempt had used varenicline, about 12% had used bupropion, and 40% had used NRT. The willingness of these experienced patients to enroll in the study suggests that they tolerated the medication previously and may have been at lower risk for serious events. Sensitivity analyses excluding these patients are described below.

Patient Disposition

Patient disposition is shown in the tables below. Subjects could discontinue study treatment but remain in the study; additionally, because of the prolonged post-treatment follow-up observation period, subjects could also complete treatment but not complete the study.

Table 4. Disposition in the Non-PHx Cohort

	Pooled	Varenicline	Bupropion	NRT	Placebo
Treated	**3984**	990	989	1006	999
Completed Study (24 wks)	**3124 (78.4%)**	787 (79.5%)	783 (79.2%)	767 (76.2%)	787 (78.8%)
Discontinued Study:					
No longer willing	**439 (11.0%)**	94 (9.5%)	103 (10.4%)	118 (11.7%)	124 (12.4%)
Lost to follow-up	**266 (6.7%)**	68 (6.9%)	67 (6.8%)	72 (7.2%)	59 (5.9%)
Completed Treatment (12 wks)	**3145 (78.9%)**	793 (80.1%)	772 (78.1%)	777 (77.2%)	803 (80.4%)
Discontinued Treatment:					
No longer willing	**292 (7.3%)**	61 (6.2%)	63 (6.4%)	79 (7.9%)	89 (8.9%)
Adverse Events	**230 (5.8%)**	57 (5.8%)	74 (7.5%)	73 (7.3%)	26 (2.6%)

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt and Subevg.xpt

Table 5. Disposition in the PHx Cohort

	Pooled	Varenicline	Bupropion	NRT	Placebo
Treated	**4074**	1026	1017	1016	1015
Completed Study (24 wks)	**3169 (77.8%)**	811 (79.0%)	803 (79.0%)	790 (77.8%)	765 (75.4%)
Discontinued Study:					
No longer willing	**446 (10.9%)**	101 (9.8%)	115 (11.3%)	106 (10.4%)	124 (12.2%)
Lost to follow-up	**266 (6.5%)**	67 (6.5%)	59 (5.8%)	72 (7.1%)	68 (6.7%)
Completed Treatment (12 wks)	**3023 (74.2%)**	772 (75.2%)	765 (75.2%)	761 (74.9%)	725 (71.4%)
Discontinued Treatment:					
No longer willing	**281 (6.9%)**	62 (6.0%)	70 (6.9%)	66 (6.5%)	83 (8.2%)
Adverse Events	**388 (9.5%)**	108 (10.5%)	101 (9.9%)	85 (8.4%)	94 (9.3%)

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt and Subevg.xpt

7.3 Study Conduct

My review of the submitted data revealed several issues and concerns with data collection, data coding, and data reporting that created obstacles to review and limited the extent to which we can place confidence in the protocol-specified primary endpoint and in certain other analyses, such as tabulations of events in various sub-components of the primary endpoint. The review team performed various sensitivity analyses and identified an alternative approach we believe more accurately captures the rates of clinically significant NPS events, which is described below.

Issues fell into the following broad categories

- Incomplete/inadequate data collection
- Data coding issues
- Data reporting issues
- Issues raising concerns of data reliability

Specific examples of these issues are described in detail in my primary review. Briefly, problems included the following:

7.3.1 Incomplete/inadequate data collection

7.3.1.1. Ineffective Use of NAEI

The NAEI was intended to be used as a starting point to identify symptoms of potential concern, and then the full description of the patient's experience was to be sought and recorded. The investigator was to determine whether the solicited symptom did or did not qualify as an adverse event. It appears that, at many sites, the NAEI was, instead, used as a checklist. No additional information was recorded beyond the patient endorsing one of the symptoms mentioned.

7.3.1.2 Inadequate Capture of Patient Verbatim

It was expected that the events were to be recorded in the reporter's words, in order to ensure that difficult-to-characterize events were adequately described. At three sites, and sporadically at other sites, no patient verbatim (described in the database as "event as described by reporter" was recorded at all so it is not possible to determine how the investigator verbatim term was selected or how severity was assessed. Across all sites, in many cases, the recorded "event as described by reporter" is a single word (identical to the investigator verbatim term) such as "anxiety," giving no additional insight.

7.3.1.3 Inadequate Capture of Information About Circumstances of Events

Several narratives had insufficient information to understand the context of the event and whether it occurred in the setting of the type of neuropsychiatric problems that are of interest in the trial. Specific examples are provided in my primary review.

7.3.2 Data Coding Issues

7.3.2.1 Inconsistent Investigator Assessment of Severity

The investigator assessment of severity was intended to distinguish adverse events that reached a certain threshold of interference of a patient's usual functioning. However, some narratives suggest a level of interference in the patient's usual functioning not reflected in the investigator's rating of severity. Some of these cases are included in the NPS primary endpoint because they were assigned codes and severity ratings included in the composite, whereas other cases in which the narratives describe very similar symptoms and impacts are not, either because the term selected is not in the composite (e.g., irritability) or because the investigator rating of severity did not meet criteria for inclusion in the NPS primary endpoint. In a number of cases, subjects reported events that were coded to terms such as depression and mood disturbance which had a documented interference in their functioning but were only

rarely assessed as "severe." Some are assessed as "mild" despite the patient report of missing days of work or other significant impact. Specific examples are included in my primary review.

Cases of events coded to a new psychiatric diagnosis in subjects who were in the non-psychiatric cohort were noted. These cases did not meet the "severity" criterion based on investigator severity rating and were not flagged as NPS cases, although the onset of a new psychiatric condition would generally be considered quite significant.

These types of cases further underscored the concern that the severity criterion for inclusion in the NPS endpoint may have been inappropriate to capture events of concern. There may have been a disconnect between what subjects with no previous psychiatric issues consider severe (even missing a day of work) and what a health care provider accustomed to caring for seriously mentally ill patients would regard as "severe" (possibly only an event requiring hospitalization). Even one hospitalization was assessed as "mild" by the investigator.

Because the primary endpoint relied on investigator assessment of severity, which was clearly problematic, our confidence in the analyses based on the protocol-specified primary NPS endpoint is undermined by these findings. An expanded analysis which included patients who experienced events coded as "moderate" but also experienced symptoms captured by other clinical assessments or MHP evaluation is described below.

7.3.2.2 Lack of Integration of Different Data Streams

Although C-SSRS, HADS, and CGI scores were recorded, patients could have had significant indicators of distress on one or more of these instruments and no adverse event recorded. Patients could also have been evaluated by the MHP and information recorded in the evaluation was not recorded as an adverse event. In some cases (as noted above) a new diagnosis was recorded as an adverse event. Some subjects had AEs reported based on C-SSRS results while others did not. A subject who endorsed suicidal ideation during the protocol-specified mental health evaluation prompted by his NPS-endpoint qualifying event was not coded as having suicidal ideation. The expanded analysis attempts to capture these patients.

7.3.2.3 Inconsistent Mapping of Events to Sub-Components of the Composite

The endpoint was a composite of various emotional, cognitive, and perceptual experiences that subjects might experience because the post-marketing adverse events typically described patients experiencing multiple symptoms simultaneously. However, the coding of events did not facilitate identification of subjects who might have been experiencing a cluster of symptoms. Pfizer's analysis included tabulation of events separated out into categories such as agitation, depression, psychosis, and panic.

Review of the narratives, where sufficient information about the patient report is provided to assess the coding, reveals a number of issues. Overall, the mapping of events to the sub-components was not consistent. There are subjects whose events included a constellation of cognitive and emotional and behavioral experiences but the investigator may not have coded all of the events such that the NPS threshold was reached for all of them. Additionally, there are errors in the assignment of terms to components (for some reason, "dysphoria" is included

in the aggression component), and, unfortunately, there is no cognitive component at all. Cognitive symptoms are included in the "agitation" component.
Therefore, it does not appear helpful or informative to analyze the cases by component of the NPS endpoint.

7.3.2.4 Inconsistent Application of Coding

Some terms, notably "agitation," appear to have been applied inconsistently to a variety of symptoms. In a number of cases, there is sufficient information to determine that the term was interpreted to refer to motor agitation (akathisia); in others it refers to emotional upset and distress (which was the intended meaning in the protocol stage). In some cases another term in another component of the NPS endpoint (e.g., "anger") was stated by the patient but the term "agitation" was chosen for coding. In still other cases, the patient reported insomnia, leading to selection of the term "restlessness" (i.e., the patient was not getting "rest"), which then coded to "agitation"—clearly not what was intended.
For many subjects whose only event is "moderate agitation," there is virtually no additional information on the event to allow us to understand how that was manifested and in what way it was disruptive to the patient's functioning (which is what makes it "moderate").
Additionally, in some cases, subject verbatim terms containing concepts in NPS endpoint (e.g. "anger") were coded to terms not in the NPS endpoint (irritability). There are also many subjects with verbatim terms coded to the term "irritability" where the description of the event is identical to other subjects coded to "agitation," but they are not considered NPS cases. However, it is not possible to re-adjudicate all cases coded to "irritability" because many lack further information. Although irritability was intentionally excluded from the endpoint because of its well-known association with nicotine withdrawal, the expanded analysis included subjects with moderate to severe events coded to "irritability" who also had other indicators of clinically significant findings (e.g., clinical scales or significant findings by MHP). Only a very few patients had irritability as their only symptom.

7.3.2.4 Miscellaneous Coding Errors

As with any large dataset, other coding errors were identified, examples of which are given in my primary review.

7.3.3 Data Reporting Issues

The case narratives provided by Pfizer presented a barrier to review. Pfizer submitted the study report prior to submitting the supplement, and gave the Division an opportunity to comment. The original submitted narratives did not include relevant information and provided no insight beyond the MedDRA terms and the timing of the events, along with investigator assessment of relatedness. Even where available, the patient's own words describing the event were not included in the narrative, or any context/background for the event. The Division requested revised narratives which were improved, but nevertheless, not as informative or as logically constructed as expected for NDA case narratives. The chronology of different streams of data was presented separately, rather than integrating the scores on clinical assessments and the smoking behavior reported together with the timeline of the adverse events. The information presented was also limited by the problems noted above related to data capture. Ultimately, it

was determined that it was neither feasible nor possible to attempt to independently adjudicate the cases based on the provided information.
It also became apparent on inspection of the Adverse Event datasets that many events of potential interest were not flagged, and no narratives had been constructed. This appears to have been related to issues noted above of data coding, primarily involving investigator assessment of severity. As described below, sensitivity analyses to capture more of the cases of interest were performed to address this issue.

7.3.4 Issues raising concerns of data reliability

Pfizer identified two sites that were identified as having significant protocol violations leading to concerns about data reliability. These issues are described in detail in my primary review. There were also a number of sites at which Pfizer noted that individuals without the appropriate qualifications were performing the role of MHP and sites where investigators needed to be re-trained on administering the SCID. These observations were taken into consideration in choosing sites for inspection by the Office of Scientific Investigations. OSI confirmed significant violations at the two sites (1077 and 1002) but assessed the data from six other sites as reliable.

7.4 Statistical Methodologies

The primary analysis of the NPS endpoint was conducted on the Safety Analysis Population (defined as all treated subjects (i.e. received at least one partial dose of randomized study drug) based on events observed only during the 12 week treatment phase of the trial plus 30 days. The trial was not designed to rule out a pre-specified risk margin of NPS events. The applicant sized the trial based on the desired precision of the estimated risk difference (RD) for the NPS event comparing varenicline to placebo.
In the cohort with no-prior history of psychiatric disease (Non-PHx cohort), the applicant assumed a true incidence rate (IR) of 3.5 events per 100 subjects in the placebo arm and an IR of 6.13% in the varenicline arm, equivalent to an incidence rate ratio of 1.75. Under these assumptions, and with a sample size of 1,000 subjects per treatment arm in the Non-PHx cohort, the expected RD and corresponding 95% confidence interval for the NPS event comparing varenicline to placebo was 2.63% (0.75%, 4.50%).
In the cohort with a prior history of psychiatric disease (PHx cohort), the applicant assumed a true IR of 7.0% in the placebo arm and 12.25% in the varenicline arm, also equivalent to an incidence rate ratio of 1.75. Under these assumptions, and with a sample size of 1,000 subjects per treatment arm in the PHx cohort, the expected RD and corresponding 95% confidence interval for the NPS event comparing varenicline to placebo was 5.25% (2.34%, 5.52%).

Primary Safety Analysis
The primary safety analysis estimated the risk difference of NPS events for all 6 pairwise treatment comparisons (varenicline - placebo, bupropion - placebo, etc) by cohort of previous diagnosis of a psychiatric disorder. The risk difference of NPS events was estimated through a generalized linear model for binary data with an identity link function. The model included covariates for treatment (4 levels), cohort (2 levels), treatment by cohort interaction, and region of randomization (2 levels: USA vs. non-USA). The SAP did not pre-specify any

safety-related statistical hypotheses to be tested and therefore no the statistical review team did not discuss p-values for safety outcomes. The estimated treatment risk differences of NPS events and their corresponding confidence intervals are considered to be descriptive. All confidence intervals for safety endpoints were calculated at a nominal 95% confidence level and no corrections were made for multiple comparisons.

Efficacy
The primary efficacy analysis (CAR 9-12) was evaluated using a logistic regression model on the Full Analysis Set (all randomized subjects). The model included treatment (varenicline, bupropion, NRT, and placebo), cohort (PHx and non-PHx), region (US and non-US), plus the 2-way and 3-way interactions, with possible model reduction by removal of non-significant interaction terms at the 10% level. The analysis of the secondary endpoint, CAR 9-24, was based on the same logistic regression as the primary analysis. The odds ratio (OR) and its 95% confidence interval (CI) were estimated for all pairwise comparisons of treatment groups. This estimation was done both overall and by cohort. The primary efficacy hypotheses were to test the superiority of varenicline versus placebo and bupropion versus placebo, respectively, with respect to CAR 9-12 in PHx and non-PHx cohorts. The key secondary hypotheses were to test the superiority of varenicline versus placebo and bupropion versus placebo, respectively, with respect to CAR 9-24 in each cohort. All other treatment pairwise comparisons were considered secondary hypotheses and were tested using the same scheme as in the primary and key secondary hypotheses. Each hypothesis was tested individually at a 5% level without any adjustment for multiplicity.
Subjects who discontinued the trial or were lost to follow-up were assumed to be non-responder (smokers) for the remainder of the trial. Missing NUI data were imputed using the next non-missing NUI response to the respective question separately for the treatment period and follow-up period. If no response was available, the default imputation was as a non-responder. The protocol stipulated that missing CO values were imputed as negative. This is not the customary approach to analysis of smoking cessation studies. An analysis imputing missing values as positive was performed by the statistical review team.

7.5 Results and Conclusions

7.5.1 Primary Safety Results

7.5.1.1 Protocol-Specified Primary Endpoint

The analysis of the safety results was conducted by Dr. Eugenio Andraca-Carerra from the Division of Biometrics 7 (DB7) and much of the text below is from the statistical review.
The table below shows the number and proportion of subjects who experienced a treatment-emergent NPS event in the trial by treatment arm and cohort of psychiatric history diagnosis at baseline (PHx and Non-PHx). The observed rate of NPS events among subjects in the Non-PHx cohort was lowest among subjects randomized to varenicline (1.3%) and was similar for subjects randomized to bupropion, NRT, or placebo (2.2% to 2.5%). The observed rate of NPS events in the PHx cohort was highest among subjects randomized to varenicline and bupropion (6.5% and 6.7% respectively) and was lowest among subjects randomized to placebo (4.9%).

Table 6 Primary NPS Endpoint by Cohort of Psychiatric History

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	13 / 990 (1.3%)	22 / 989 (2.2%)	25 / 1006 (2.5%)	24 / 999 (2.4%)
PHx Cohort	67 / 1026 (6.5%)	68 / 1017 (6.7%)	53 / 1016 (5.2%)	50 / 1015 (4.9%)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Dr. Andraca-Carrera also constructed Kaplan-Meyer curves to illustrate the timing of events, and noted that subjects randomized to bupropion or varenicline in the PHx cohort experienced more NPS events within the first 7 days after randomization (21 subjects on bupropion, 12 on varenicline) than subjects randomized to NRT (4) or placebo (4). These analyses are shown as Figure 6 and 7 in my primary review.

Dr. Andraca-Carrera evaluated the estimated risk differences and corresponding nominal 95% confidence intervals for the risk difference of treatment-emergent NPS events for each of the 6 pairwise treatment comparisons in each of the two cohorts based on the pre-specified primary analysis. He observed a nominally protective effect associated with varenicline relative to placebo: RD = -1.28 NPS events per 100 subjects, 95% CI (-2.40,-0.15) in the Non-PHx cohort, and a numerically increased risk associated with varenicline: RD = 1.59 NPS events per 100 subjects, 95% CI (-0.42, 3.59) and bupropion: RD = 1.78 NPS events per 100 subjects, 95% CI (-0.24, 3.81) relative to placebo in the PHx cohort. Varenicline showed a nominally protective effect relative to bupropion in the Non-PHx cohort: RD = -1.19 NPS events per 100 subjects, 95% CI (-2.30, -0.09) and no meaningful difference in the PHx cohort: RD = -0.20, 95% CI (-2.34, 1.95). A figure illustrating the risk differences may be found in my primary review (Figure 5).

The 261 MedDRA preferred terms in the NPS composite were grouped into 16 categories, and analyses of the number of subjects in the trial with at least one qualifying treatment emergent NPS event in each of these categories were presented in the statistical review. However, as noted above, concerns about the way the data were captured and coded render these particular analyses less informative and they are not reproduced here.

7.5.1.2 Sensitivity Analyses

Dr. Andraca-Carrera also performed a number of sensitivity analyses. These included:

1. An alternative statistical model intended to account for higher-than-anticipated heterogeneity across sites.
2. Analyses of events of all severities and analyses of only events coded as “severe”
3. Analyses excluding sites with disclosed financial arrangements exceeding the threshold for disclosure and sites where investigators were involved in an ongoing way as speakers or consultants

4. Analyses excluding patients who had previous experience with the study drugs

None of these changed the overall conclusions. In each analysis, there did not appear to be a difference across treatment groups in the non-psychiatric cohort but there were small, but consistent increases in rates of events in the patients treated with varenicline or bupropion in the psychiatric cohort.

Pfizer also graphically displayed the relationship between reported NPS events and smoking status at the time of the event, in an attempt to link symptoms to changes in smoking behavior. No clear patterns are evident. These figures are included in my primary review.

To address the concerns noted above that the coding issues (particularly the investigator rating of severity and the inconsistent coding to the term "irritability") led to an underestimate of the rates of NPS, Dr. Andraca-Carrera performed an analysis that included all primary NPS events plus moderate or severe adverse events with an associated MedDRA Preferred Term (PT) of 'Irritability' or a High Level Group Term (HGLT) of 'Depressed mood disorders.' This "NPS+" analysis was presented at the Advisory Committee meeting. However, while a step in the right direction, the analysis did not successfully integrate all data streams such as the clinical rating scales and the mental health professional evaluations. The results are shown in the table below.

7.5.1.3 Pfizer's Expanded Analysis

After becoming aware of the FDA review team's findings concerning the study conduct and the potential incomplete of capture of clinically significant neuropsychiatric adverse events, Pfizer conducted their own re-examination of the study data to identify additional cases of NPS events that may have been missed due to investigator severity assessment issues, lack of consistency across data streams (e.g., the HADS scores, clinical global assessments, C-SSRS assessments, evaluations by MHP) and adverse event reporting, and submitted a sensitivity analysis incorporated an expanded definition of NPS. The analysis was described as follows:

> The expanded definition included the original primary NPS AE endpoint plus the following:
>
> 1. Clinical consensus cases based on a blind review of the patient health information provided by the CGI-I, the HADS-A and HADS-D and the C-SSRS scales, as well as the Mental Health psychiatric evaluations that were required as part of the protocol. Specifically, data listings were prepared for subjects meeting any of the following criteria during the treatment emergent period (through end of treatment plus 30 days):
>
> a) Adverse event of any severity in the MedDRA Suicide and Self-Injury SMQ (all terms in the primary NPS endpoint plus "intentional overdose")
> b) CGI-I of much worse or very much worse
> c) C-SSRS of ideation 4 or 5 or any behavior
> d) HADS score of >15 for either subscale, depression or anxiety

e) A psychiatric evaluation by a MHP that resulted in a new DSM-IV diagnosis, represented an exacerbation of a pre-existing condition, or the MHP said the subject should not continue in the study

Two Pfizer clinicians separately identified subjects as potential 'events' based on blinded review of the data listings prepared based on the above criteria. Lists of subjects identified by each clinician were then forwarded to a third clinician for blinded review and final determination of clinical consensus as to whether the subject should be included as having an expanded NPS event for this sensitivity analysis. It should be noted that this review also included all the cases for which narratives have been submitted to FDA

Or, if not identified by clinical consensus,

2."Moderate" AEs coded to any one or more of the MedDRA components of "Anxiety", "Depression", Feeling Abnormal" or "Hostility". Please note that subjects with "severe" adverse events coded to any one or more of these MedDRA components were already included in the pre-specified primary composite NPS endpoint.

Or, if not identified by clinical consensus or the moderate ratings for the above four components,

3. "Moderate" or "severe" AEs events coded to a MedDRA preferred term of "Irritability".

Pfizer reported that 480 patients were identified for clinical review and that the process of review identified only 10 patients (all in the psychiatric cohort) who were assessed as having had experiences intended to be captured by the *primary* NPS endpoint. The *expanded* endpoint added moderate events of depression, anxiety, hostility, and feeling abnormal, as well as moderate or severe events coded to the term "irritability." This was applied across the entire population, not just those patients identified for clinical review. Although this is similar to the "NPS+" approach taken previously, the review team was concerned that a wholesale expansion would be over-inclusive and would incorporate too much "noise." Pfizer's process identified the following:

Table 7 Pfizer's Expanded NPS Endpoint--Non-PHx Cohort

	Varenicline N = 990	Bupropion N = 989	NRT N = 1006	Placebo N = 999
Expanded NPS	**45**	**50***	**51**	**56**
Primary NPS	13	22	25	24
Identified by clinical review	0	0	0	0
Flagged for review; anxiety, depression, hostility, feeling abnormal, irritability (irritability only)	12 (0)	9 (0)	6 (0)	13 (1)
Not flagged for review; anxiety, depression, hostility, feeling abnormal, irritability (irritability only)	20 (4)	18 (5)	20 (4)	19 (4)

*1 subject was recorded as having an expanded NPS event due to clinical review even though he/she did not undergo clinical review (flag for clinical review = 0)
Table constructed by Dr. Andraca-Carrera

Table 8 Pfizer's Expanded NPS Endpoint--PHx Cohort

	Varenicline N = 1026	Bupropion N = 1017	NRT N = 1016	Placebo N = 1015
Expanded NPS	**140**	**138**	**130**	**123**
Primary NPS	67	68	54*	50
Identified by clinical review	3	1	2	4
Flagged for review; anxiety, depression, hostility, feeling abnormal, irritability (irritability only)	43 (1)	41 (2)	31 (1)	33 (1)
Not flagged for review; anxiety, depression, hostility, feeling abnormal, irritability (irritability only)	27 (0)	28 (3)	43 (4)	36 (6)

*The original analysis included 53 NPS endpoint in the NRT arm of the PHx cohort, this dataset lists 54
Table constructed by Dr. Andraca-Carrera

7.5.1.4 FDA Expanded Analysis

Some patients were not included in Pfizer's expanded endpoint even if they had elevations on HADS scales or were assessed as significantly worsened on the clinical global assessment. If no adverse events were recorded using MedDRA terms in the NPS endpoint, or if the severity was assessed as "mild" by the investigator, patients were not included in the expanded analysis. These cases potentially represent situations in which there is a disconnect between the investigator's assessment of severity and the actual impact on the patient. Moreover, the review team learned that free-text fields containing the information from the MHP evaluations had not been provided to the clinicians performing the blind review and had not been taken into consideration. Inspection of the text fields identified additional patients whose new diagnosis, exacerbation, or recommendation to discontinue medication occurred in the context of what appeared to be a clinically significant NPS event appropriate for inclusion in an expanded analysis. In some cases, information included in the text fields had not be captured as an AE in the AE dataset.

Therefore, the review team undertook a blinded review of the text fields to identify other patients whose clinically significant NPS events had not been captured in the expanded analysis. Only patients not already added to the expanded endpoint based on AEs recorded in the dataset were evaluated. For the purposes of this review, the following case definitions were used:

In the Non-PHx cohort, a case was defined as having one or more of the following:

1. New Axis I psychiatric diagnosis in the diagnosis column (including adjustment disorders)[9].
2. Psychotropic medication initiated or recommended (usually in the recommendations field)
3. Recommendation to discontinue study drug ("opinion of MHP to remain on Study Drug" = NO)
4. Patient reports discontinuing study drug due to NPS

AND

The events began during treatment (even if the time criterion for diagnosis was met later), or the events are described as beginning in the context of study drug discontinuation.

In the PHx cohort, a case was defined as having one or more of the following:

1. New DSM-IV psychiatric diagnosis flag AND text in DSM diagnosis field is an Axis I diagnosis involving depression, anxiety, or psychosis
2. New or changed medication in context of exacerbation
   a. A recommendation is made for a psychiatric medication (new or changed) by the MHP
   b. A new/changed psychiatric medication initiated by someone else is documented (e.g., patient reports personal physician started/changed psychiatric medication)
3. Recommendation to discontinue study drug ("opinion of MHP to remain on Study Drug" = NO)
4. Patient reports discontinuing study drug due to NPS

[9] DSM-IV diagnoses include a component of interference with the patient's function and therefore new diagnoses were considered, by definition, clinically significant

AND
The events began during treatment (even if the time criterion for diagnosis was met later), or the events are described as beginning in the context of study drug discontinuation.

A total of 300 MHP evaluations were documented, of which 151 were added to the expanded endpoint by Pfizer on the basis of documented adverse events. Blinded review of the line listings for the MHP evaluations for the remaining 149 patients (32 Non-PHx and 117 PHx) was performed by two independent clinicians. Cases that were not identified by both clinicians were evaluated by a third blind clinician as a "tie-breaker." This process identified 14 patients in the Non-PHx cohort and 44 patients in the PHx cohort. These were then incorporated into an expanded analysis.

The review team determined that a reasonable approach to expanding the NPS endpoint without being over-inclusive would be as follows:

1. Patients who met the original protocol-specified criteria based on event type and investigator severity rating
2. Patients identified by Pfizer's clinical consensus process
3. Patients (identified by Pfizer's process) who had recorded adverse events in the NPS endpoint that were rated moderate, but also had one or more of the criteria indicating clinical significance:
    a. Adverse event of any severity in the MedDRA Suicide and Self-Injury SMQ (all terms in the primary NPS endpoint plus "intentional overdose")
    b. CGI-I of much worse or very much worse
    c. C-SSRS of ideation 4 or 5 or any behavior
    d. HADS score of >15 for either subscale, depression or anxiety
    e. A psychiatric evaluation by a MHP that resulted in a new DSM-IV diagnosis, represented an exacerbation of a pre-existing condition, or the MHP said the subject should not continue in the study
4. Patients identified by FDA review of MHP evaluation line-listings who had not been included in Pfizer's expanded analysis, but met the case definitions above.

This expanded analysis identified the following distribution of patients experiencing clinically significant NPS events. Notably, most of the events are still not of a serious nature per regulatory definition (see below). Because of the concern that inclusion of patients whose only reported symptom was "irritability" might introduce noise into the analysis, the tables below also show how many patients in each arm were included in the expanded analysis solely based on report of irritability. There are very few such patients.

Table 6 Components of the FDA Expanded NPS Endpoint in the Non-PHx Cohort

	Varenicline	**Bupropion**	**NRT**	**Placebo**
	N = 990	**N = 989**	**N = 1006**	**N = 999**
Expanded NPS	**31 (3.1%)**	**35* (3.5%)**	**33 (3.3%)**	**40 (4.0%)**
Primary NPS	13	22	25	24
Identified by Pfizer's clinical consensus review	0	0	0	0
Identified by Pfizer's flags + AEs anxiety, depression, hostility, feeling abnormal,	12 (0)	9 (0)	6 (0)	13 (1)

irritability (irritability only)				
Identified by FDA process	6	3	2	3

*1 subject was recorded as having an expanded NPS event due to Pfizer clinical review even though he/she did not undergo clinical review (flag for clinical review = 0)

Table 7 Components of FDA Expanded NPS in PHx Cohort

	Varenicline	**Bupropion**	**NRT**	**Placebo**
	N = 1026	**N = 1017**	**N = 1016**	**N = 1015**
Expanded NPS	**125 (12.3%)**	**1221 (11.9%)**	**98 (9.7%)**	**96 (9.5%)**
Primary NPS	67	68	54*	50
Identified by Pfizer's clinical consensus review	3	1	2	4
Identified by Pfizer's flags + AEs anxiety, depression, hostility, feeling abnormal, irritability (irritability only)	43 (1)	41 (2)	31 (1)	33 (1)
Identified by FDA process	12	11	11	9

*The original analysis included 53 NPS endpoint in the NRT arm of the PHx cohort, this dataset lists 54

7.5.1.5 Comparison of NPS Rates Using Different Analyses

The table below illustrates the findings across different analyses. In all analyses, there appears to be no increased risk of NPS events in patients without psychiatric diagnoses who are treated with any of the medications for smoking cessation. However, neuropsychiatric adverse events of a clinically significant, if not serious, nature are relatively common, occurring in 3-5% of the non-psychiatric population when trying to quit smoking without without medication. There is also a small, but consistent, finding in the population of patients with psychiatric diagnoses that events are more common during treatment with varenicline or bupropion than with NRT or placebo.

Table 9 Comparison of NPS Rates Using Different Analyses

Non-PHx Cohort								
	Varenicline		Bupropion		NRT		Placebo	
	N = 990		N = 989		N = 1006		N = 999	
NPS (Protocol)	13	1.31%	22	2.22%	25	2.49%	24	2.40%
NPS Expanded (Pfizer)	45	4.55%	50	5.06%	51	5.07%	56	5.61%
NPS+ (FDA)	32	3.23%	35	3.54%	38	3.78%	44	4.40%
NPS Expanded (FDA)	31	3.13%	35	3.54%	33	3.28%	40	4.00%
PHx Cohort								
	Varenicline		Bupropion		NRT		Placebo	
	N = 1026		N = 1017		N = 1016		N = 1015	
NPS (Protocol)	67	6.53%	68	6.69%	53	5.22%	50	4.93%
NPS Expanded (Pfizer)	140	13.65%	138	13.57%	130	12.80%	123	12.12%
NPS+ (FDA)	118	11.50%	109	10.72%	89	8.76%	100	9.85%
NPS Expanded (FDA)	126	12.28%	121	11.90%	98	9.65%	96	9.46%

7.2 Primary Efficacy Results

The efficacy results were reviewed by Dr. Yi Ren of the Division of Biometrics 2 (DB2). Dr. Ren was able to replicate the Sponsor's analyses and confirm the conclusions regarding efficacy for rates of continuous abstinence during weeks 9-12 (CAR 9-12) and during weeks 9-24 (CAR 9-24).

Table 10 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - FAS Population

Cohort	Varenicline (%)	Bupropion (%)	NRT (%)	Placebo (%)	Odds ratio V/P	B/P	N/P
Overall							
CAR 9-12	33.5	22.6	23.4	12.5	3.60*	2.06*	2.14*
CAR 9-24	21.9	16.2	15.7	9.4	2.73*	1.88*	1.80*
Non-PHx							
CAR 9-12	38.0	26.1	26.4	13.7	4.00*	2.26*	2.30*
CAR 9-24	25.5	18.8	18.5	10.5	2.99*	2.00*	1.96*
PHx							
CAR 9-12	29.2	19.3	20.4	11.4	3.25*	1.87*	2.00*
CAR 9-24	18.3	13.8	13.0	8.3	2.50*	1.77*	1.65*

V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* p-value <0.001, using a logistic regression with terms treatment, cohort, region, and treatment by cohort interaction, and region by cohort interaction. Region used 2-level classification (US, non-US).

Source: Statistical reviewer Yi Ren

These results were consistent with Pfizer's conclusion that varenicline was superior to bupropion, NRT, and placebo with respect to smoking cessation. Bupropion was also considered superior to placebo. Although the observed rates for CAR 9-12 and CAR 9-24 were numerically lower in the PHx cohort than in the non-PHx cohort, there was no statistically significant interaction between treatment and cohort.

Pfizer's analysis considered missing CO values as negative, i.e. a subject could be considered a non-smoker according only to self-report. Although this is not the customary approach to analysis of smoking cessation studies, the conclusion did not change when these subjects were considered non-responders (results not shown). A total of 53 subjects (0.7%) and 128 subjects (1.6%), respectively, were considered non-responders and when CAR 9-12 and CAR 9-24 were reanalyzed.

Sensitivity analyses were performed excluding the data from the two sites identified as unreliable (1077 and 1002), and excluding sites which reported financial involvement with Pfizer. These analyses also did not change the conclusions.

The treatment effect for varenicline, bupropion, and NRT was also examined for differences due to age (18-44 years, 45-64 years, and > 64 years), sex (male and female), race (White, Black, and Other), and region (US and non-US) based on the FAS population. The treatment effects on CAR 9-12 were consistent across these subgroups.

An additional exploratory analysis excluded patients with prior experience with the study drugs. In a study primarily designed to assess comparative efficacy, patients already known to be intolerant to one of the study drugs would have been screened out. To explore the impact of this possibility, these subjects were excluded and the data was reanalyzed. This modified population is referred as the modified Full Analysis Set (mFAS). The table below provides a summary of the number of patients in the FAS and mFAS datasets.

Table 11 Number of Subjects in FAS and mFAS Datasets

Treatment/Cohort	Number of Subjects				
	Varenicline	**Bupropion**	**NRT**	**Placebo**	**Total**
Overall					
FAS Population	2037	2034	2038	2035	8144
mFAS Population	1333	1262	1296	1322	5213
Non-PHx					
FAS Population	1005	1001	1013	1009	4028
mFAS Population	690	641	656	670	2657
PHx					
FAS Population	1032	1033	1025	1026	4116
mFAS Population	643	621	640	652	2556

Source: Statistical reviewer Yi Ren

The primary comparisons of varenicline versus placebo and bupropion versus placebo and the secondary comparison of NRT versus placebo for CAR 9-12 and CAR 9-24 using the mFAS are summarized by psychiatric cohort below

Table 12 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - mFAS Population†

Cohort	Varenicline (%)	Bupropion (%)	NRT (%)	Placebo (%)	Odds ratio		
					V/P	B/P	N/P
Overall							
CAR 9-12	31.9	22.8	22.1	12.5	3.39*	2.09*	1.98*
CAR 9-24	21.5	15.5	15.4	9.8	2.60*	1.70*	1.68*
Non-PHx							
CAR 9-12	34.9	26.2	26.5	14.3	3.33*	2.14*	2.16*
CAR 9-24	23.8	18.3	18.3	11.6	2.42*	1.70*	1.68**
PHx							
CAR 9-12	28.6	19.3	17.5	10.6	3.45*	2.04*	1.82*
CAR 9-24	19.0	12.6	12.3	7.8	2.78*	1.70**	1.68**

V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo

* p-value < 0.001, using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction.

** p-value < 0.05, using the same model above.

† FAS population excluding those subjects who used concomitant medications and/or had failed lifetime serious quit attempts on the study medications.

Source: Statistical reviewer Yi Ren

This analysis shows that the effect of the medications is similar in a population naïve to treatment. This addresses a concern regarding the comparative efficacy conclusions in this study. The consistent results in the two cohorts provide replicated evidence that varenicline was superior to the other two active treatments. The labeling for varenicline already includes study results supporting a claim of superior efficacy over bupropion based on appropriately-designed comparative efficacy trials submitted with the original NDA. This is the first demonstration of superiority over transdermal nicotine.

8. Safety

The size of the database was sufficient to characterize the safety profile, although the size of individual sub-cohorts in the psychiatric cohort may have been too small to draw definitive conclusions.

Exposure by duration is shown in tables below from Pfizer's submission.

Table 13 Exposure to Treatment, Non-PHx - Safety Population

	Varenicline N = 990	Bupropion N = 989	NRT N = 1006	Placebo N = 999
Exposure in Days*	Number (%) of Subjects			
1 – 7	17 (1.7)	18 (1.8)	15 (1.5)	7 (0.7)
8 – 14	16 (1.6)	25 (2.5)	32 (3.2)	28 (2.8)
15 – 21	22 (2.2)	30 (3.0)	25 (2.5)	21 (2.1)
22 – 28	25 (2.5)	22 (2.2)	27 (2.7)	27 (2.7)
29 - 35	17 (1.7)	20 (2.0)	14 (1.4)	16 (1.6)
36 - 42	19 (1.9)	16 (1.6)	12 (1.2)	13 (1.3)
43 - 49	14 (1.4)	13 (1.3)	16 (1.6)	20 (2.0)
50 - 56	15 (1.5)	12 (1.2)	13 (1.3)	11 (1.1)
57 - 63	15 (1.5)	17 (1.7)	30 (3.0)	19 (1.9)
64 - 70	11 (1.1)	17 (1.7)	18 (1.8)	14 (1.4)
71 - 77	28 (2.8)	31 (3.1)	34 (3.4)	24 (2.4)
78+	791 (79.9)	768 (77.7)	770 (76.5)	799 (80.0)
Statistics (Days)				
Mean	75.92	74.61	74.53	76.13
Q1 - Q3	83 - 86	81 - 86	80 - 86	82 - 86
Median	85	85	85	85
Standard deviation	21.59	22.87	22.82	21.44
Range	2 - 103	1 - 96	1 - 100	1 - 110

Abbreviations: N = number of subjects randomized to study treatment who received at least 1 partial dose of study medication; NRT = nicotine replacement therapy.
*Note: May not sum to total due to rounding.
Q1 and Q3 are the first quartile and third quartile statistics, respectively.
Lost-to-follow-up subjects were imputed as having used all study drug dispensed at last contact visit in a per protocol manner.
Source: Pfizer's Section 14, Table 14.4.1.2.

Table 14 Exposure to Treatment, PHx - Safety Population

	Varenicline N = 1026	Bupropion N = 1017	NRT N = 1016	Placebo N = 1015
Exposure in Days*	Number (%) of Subjects			
1 - 7	24 (2.3)	25 (2.5)	21 (2.1)	21 (2.1)
8 - 14	38 (3.7)	39 (3.8)	36 (3.5)	35 (3.4)
15 - 21	34 (3.3)	24 (2.4)	32 (3.1)	44 (4.3)
22 - 28	21 (2.0)	29 (2.9)	24 (2.4)	32 (3.2)
29 - 35	23 (2.2)	24 (2.4)	21 (2.1)	24 (2.4)
36 - 42	9 (0.9)	18 (1.8)	27 (2.7)	25 (2.5)
43 - 49	19 (1.9)	15 (1.5)	9 (0.9)	24 (2.4)
50 - 56	17 (1.7)	12 (1.2)	9 (0.9)	16 (1.6)
57 - 63	25 (2.4)	26 (2.6)	23 (2.3)	18 (1.8)
64 - 70	16 (1.6)	14 (1.4)	20 (2.0)	24 (2.4)
71 - 77	32 (3.1)	24 (2.4)	31 (3.1)	35 (3.4)
78+	768 (74.9)	767 (75.4)	763 (75.1)	717 (70.6)
Statistics (Days)				
Mean	72.95	72.76	72.93	71.05
Q1 - Q3	77 - 86	78 - 86	78 - 86	68 - 85
Median	85	85	85	85
Standard deviation	24.46	24.69	24.33	25.37
Range	1 - 107	1 - 98	1 - 98	1 - 103

Abbreviations: N = number of subjects randomized to study treatment who received at least 1 partial dose of study medication; NRT = nicotine replacement therapy.
*Note: May not sum to total due to rounding.
Q1 and Q3 are the first quartile and third quartile statistics, respectively.
Lost-to-follow-up subjects were imputed as having used all study drug dispensed at last contact visit in a per protocol manner.
Source: Section 14, Table 14.4.1.2.

8.1 Deaths

There were ten deaths in the study; one occurred possibly prior to initiation of study treatment and two were recorded post-study (~6 months after last dose of study treatment). No deaths occurred in patients treated with Chantix. The table below gives an event description for each of the fatal events.

Table 15 Fatal Adverse Events

Cohort/ Subject ID	Treatment Group	Sex/Age at Death/ Race	Day of Last Dose	Day of Death	Event Description
Non-Psychiatric History					
(b) (6)	Bupropion	M/32/White	19	19	Heroin Overdose
	NRT	M/62/White	77	208	Prostate Cancer
	Placebo	M/64/Asian	86	128	Myocardial Infarction
	Placebo	F/30/White	29	32	Suicide
	Placebo	M/32/White	85	258	Road Traffic Accident[10]
Psychiatric History					
(b) (6)	Bupropion	M/52/White	77	77	"Cardiovascular Disorder" (No additional information provided)[11]
	NRT	M/62/White	64	238	Esophageal cancer
Randomized but not treated:					
(b) (6)	NRT	F/57/Black	N/A	N/A[c]	Possible[12] overdose (coded as sepsis but no information supporting this diagnosis)
	Placebo	F/42/Black	60	60	Pulmonary Embolism

[10] The narrative provides no information about the circumstances of the accident, described as a "head on collision," even whether or not the patient was the driver of the vehicle.

[11] The narratives provides only this information: "On (b) (6) 2014, the subject experienced a fatal event of cardiovascular disorder which was considered severe in intensity and serious (due to death) by the investigator. No action was taken with the study drug due to the event. The subject received no treatment for the event. The outcome of the event was death on the same day (b) (6) 2014). At the time of the event, average daily cigarette use was 12 (b) (6) 2014). The investigator considered the cardiovascular disorder to be not related to the study drug but due to other illness related to background of cardiovascular risk."

[12] The narrative indicates that the 57-year-old black female subject with current major depressive disorder and no recorded history of drug use was randomized to NRT on (b) (6) 2014. She experienced an event of "septic shock" two days later, and ultimately died 10 days afterwards. The narrative provides the information that "A heroin overdose was suspected as the emergency medical technicians (EMTs) found her in the front yard of a suspected drug house. Multisystem organ failure ensued with ultimate full septic shock. The subject received treatment for the event with norepinephrine bitartrate and bicarbonate infusion." There is no information explaining why this event was coded as "septic" shock or "sepsis", and it does not appear that the patient was treated for an infectious process. It is not known whether or not the patient had taken study drug, and it is reported as occurring prior to initiation of study drug.

8.2 SAEs

There were 72 patients with treatment-emergent SAEs in the non-PHx cohort and 101 in the PHx cohort. All 173 patients were reviewed with an eye towards identifying NPS cases of interest. A number of serious adverse events in other domains (e.g., cardiovascular) were also reported but this review focuses on the NPS events. After reviewing the SAE narratives for potential NPS cases, the review team identified 36 cases for which a relationship to study drug could not be ruled out. Notably, one of these cases was not included in the NPS endpoint because the investigator rated the event of depression as "mild" although it resulted in hospitalization. Cases of both treatment-emergent and discontinuation-emergent symptoms were noted. NPS events in bupropion-treated patients in the PHx cohort included cases that appear to be precipitation of mania in patients with bipolar disorder, a known and labeled risk of bupropion and other antidepressants. Two additional cases involving deliberate overdose were identified that were not flagged as serious by Pfizer. One was included in the SAE cases because the patient was hospitalized for a medical problem; one was not flagged as an SAE at all (and was coded as an accidental overdose) but was added to the table below.

Treatment-Emergent psychiatric hospitalizations, an endpoint of particular interest, were reported in 23 patients, distributed as follows. The table below illustrates the distribution of all SAEs, NPS SAEs, and psychiatric hospitalizations. No patients from the two excluded sites had SAEs identified; the denominator excludes these two sites.

Table 16 Number of Serious Adverse Events, NPS SAEs, and Psychiatric Hospitalizations

	Varenicline		Bupropion		NRT		Placebo	
Non-PHx (N)	975		968		987		982	
Any SAE	16	1.6%	19	2.0%	21	2.1%	16	1.6%
Any NPS SAEs	1	0.1%	5	0.5%	1	0.1%	4	0.4%
Psychiatric hospitalizations	1	0.1%	2	0.2%	0	0.0%	1	0.1%
PHx (N)	1007		1004		995		997	
Any SAE	23	2%	29	3%	24	2%	26	3%
Any NPS SAE	6	0.6%	8	0.8%	4	0.4%	6	0.6%
Psychiatric hospitalizations	5	0.5%	8	0.8%	4	0.4%	2	0.2%

A table providing brief descriptions of the events is included in the Appendix.

8.3 Discontinuations and Dose Reductions

Overall, adverse events leading to temporary or permanent discontinuation of study drug or to dose reduction were reported in 115 subjects. In the non-PHx group, all active treatment arms had a higher rate of dose reductions or discontinuations than the placebo arm; in the PHx cohort, rates were similar.

Table 17 Patients with Treatment-Emergent Adverse Events Leading to Dose Reductions or Discontinuations

	Varenicline	Bupropion	NRT*	Placebo
Non-PHx Cohort	N = 990	N = 989	N = 1006	N = 999
	122 (12%)	141 (14%)	152 (15%)	76 (8%)
PHx Cohort	N = 1026	N = 1017	N = 1016	N = 1015
	179 (17%)	153 (15%)	152 (15%)	140 (14%)

*Only discontinuation was possible
Prepared by clinical reviewer from Sponsor's dataset

The tables below, grouped by MedDRA Higher Level Group Term (HLGT), show types of events leading to reduction or discontinuation in at least 1% of subjects in any of the treatment arms. As in previous studies, gastrointestinal symptoms and sleep disturbances are the most common reason for study drug reduction or discontinuation.

Table 18 Adverse Events Leading to Study Drug Reduction or Discontinuation in ≥1% in Any Arm; Non-Phx Cohort

SOC	HLGT	Varenicline N = 990		Bupropion N = 989		NRT N = 1006		Placebo N = 999	
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	1	0%	5	1%	1	0%	0	0%
Gastrointestinal disorders	GI motility & defaecation conditions	8	1%	1	0%	6	1%	3	0%
	GI signs and symptoms	49	5%	16	2%	20	2%	13	1%
General disorders and administration site conditions	Administration site reactions	2	0%	6	1%	32	3%	3	0%
	General system disorders NEC	10	1%	14	1%	10	1%	5	1%
Infections and infestations	Infections - pathogen unspec	7	1%	14	1%	6	1%	5	1%
Nervous system disorders	Headaches	12	1%	5	1%	15	1%	3	0%
	Neurological disorders NEC	10	1%	13	1%	10	1%	7	1%
Psychiatric disorders	Anxiety disorders & symptoms	10	1%	19	2%	12	1%	7	1%
	Depressed mood disorders and disturbances	9	1%	4	0%	4	0%	6	1%
	Mood disorders and disturbances NEC	7	1%	3	0%	3	0%	3	0%
Psychiatric disorders	Sleep disorders and disturbances	17	2%	26	3%	33	3%	14	1%
Skin and subcutaneous tissue disorders	Angioedema and urticaria	0	0%	6	1%	0	0%	0	0%
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	6	1%	15	2%	15	1%	3	0%

Table 19 Adverse Events Leading to Study Drug Reduction or Discontinuation in ≥1% in Any Arm; PHx Cohort

SOC	HLGT	Varenicline N = 1026		Bupropion N = 1017		NRT N =1016		Placebo N = 1015	
Cardiac disorders	Cardiac arrhythmias	3	0%	2	0%	0	0%	6	1%
Gastrointestinal disorders	GI motility & defaecation conditions	10	1%	0	0%	4	0%	6	1%
	GI signs and symptoms	62	6%	19	2%	20	2%	13	1%
General disorders and administration site conditions	Administration site reactions	0	0%	4	0%	19	2%	2	0%
	General system disorders NEC	12	1%	4	0%	14	1%	14	1%
Infections and infestations	Infections - pathogen unspec	9	1%	8	1%	7	1%	9	1%
Nervous system disorders	Headaches	5	0%	2	0%	7	1%	5	0%
	Neurological disorders NEC	13	1%	15	1%	9	1%	8	1%
Psychiatric disorders	Anxiety disorders and symptoms	16	2%	26	3%	19	2%	14	1%
	Depressed mood disorders and disturbances	21	2%	17	2%	13	1%	24	2%
	Mood disorders & disturbances NEC	10	1%	5	0%	7	1%	10	1%
	Sleep disorders and disturbances	11	1%	22	2%	31	3%	17	2%
Skin and subcutaneous tissue disorders	Angioedema and urticaria	1	0%	12	1%	2	0%	2	0%
	Epidermal and dermal conditions	9	1%	11	1%	19	2%	9	1%

Prepared by Clinical Reviewer from Sponsor's Dataset
Adverse Events Leading to Study Drug Discontinuation

Compared to the experience in a pooled dataset of other clinical trials, a higher proportion of both varenicline and placebo subjects in this study had AEs leading to dose reduction or temporary discontinuations (varenicline: 12% in the Non-PHx, 17% in the PHx cohort vs 8.2% in the pooled data; placebo: 8% in the Non-PHx, 14% in the PHx cohort, vs 4.7%). The rates are higher in both the active and placebo arms, potentially reflecting differences in the monitoring or the willingness of patients to continue on-treatment in the face of side effects.

8.4 Common Adverse Events

The overall profile of common adverse events was similar in this study to the established AE profile for each of the active treatments. I generated a tabulation of treatment-emergent events at the HLGT level occurring in at least 5% of subjects in any active treatment arm and included PTs within the HLGT that were reported by at least 1% in any active treatment arm. These tables may be found in the Appendix. The most commonly-reported AEs in Chantix-treated patients that exceeded placebo rates in the non-psychiatric cohort were nausea (25% vs 6% in placebo); headache (12% vs 10% in placebo) HLGT sleep disorders and disturbances (21% --primarily insomnia (10%) and abnormal dreams (8%) vs 14% (insomnia 7%, abnormal dreams 4%) in placebo; GI motility disorders (diarrhea/constipation) 9% vs 5% in placebo. Similarly, in the psychiatric cohort, the most commonly-reported in Chantix-treated patients that exceeded placebo rates were nausea (26% vs 7% in placebo), HLGT sleep disorders and disturbances (22% --primarily abnormal dreams (12%) and insomnia (9%) and vs 15% (abnormal dreams 5%, insomnia 7%) in placebo; HLGT anxiety disorders and symptoms (15% vs 13%); headache (13% vs 10%); GI motility disorders (diarrhea/constipation) 9% vs 6% in placebo.

8.5 Special Safety Topics

To supplement the analysis of the composite safety endpoint, analyses employing the Standardized MedDRA Queries for certain types of neuropsychiatric events were also conducted. The findings are generally consistent with the analysis of the composite endpoint, with no obvious differences across groups in the non-psychiatric cohort, and small increases in varenicline-treated and bupropion-treated groups compared to placebo in the psychiatric cohort.

Tables showing results for SMQ analysis for Depression and Suicide/Self-Injury; Psychosis and Psychotic Disorders; Accidents and Injuries; and Hostility/Aggression are shown in the Appendix.

8.6 Vital Signs, Laboratory Assessments, ECGs

No consistent trends were noted in vital signs, laboratory assessments, or ECGs.

9. Advisory Committee Meeting

In October 2014, in the context of a previous labeling supplement submitted by Pfizer proposing to remove the boxed warning from the Chantix labeling, data from randomized controlled trial (RCT) meta-analyses, and observational studies were discussed at a joint meeting of the

Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). The committees were asked to discuss how they would weigh the evidence contributed by the meta-analyses, observational studies, and spontaneous case reports when they were evaluating the risk of serious neuropsychiatric adverse events in patients taking varenicline. In general, many of the committee members expressed concern with the quality of the data presented. The committee members were also asked based on the data presented on the risk of serious neuropsychiatric adverse events with Chantix, whether they would they recommend removal or modification of the boxed warning statements regarding risk of serious neuropsychiatric adverse events, or retention of the current boxed warning statements with a reassessment once the ongoing post-market safety outcome trial was completed.

The majority of the committee agreed that more data were needed and recommended to retain the current boxed warning statements and reassess once the post-market safety outcome trial results were available.

Accordingly, the results of the trial, and updated reviews of observational studies, were discussed at a second joint meeting of the PDAC and the DSaRM AC on September 14, 2016. Because of the specific concerns to be discussed, SGEs with a variety of backgrounds were also added as voting members for this meeting. These included individuals with general internal medicine background, as well as clinicians involved in smoking control and smoking cessation research. Experts who had attended the meeting to discuss the previous labeling supplement were invited; some were not available.

Key issues to be discussed at the meeting included the Committees' opinion on the following topics:

- The strengths and weaknesses of the completed randomized controlled trial (RCT) with regard to the study design including the novel primary endpoint.
- The potential impact of the variability in data collection, adverse event coding, and case definition on the primary endpoint.
- Which analysis and results most appropriately described the effect of the smoking cessation therapies on neuropsychiatric events.
- The contribution of the evidence from observational studies when evaluating the risk of serious neuropsychiatric adverse events in patients taking smoking cessation products.
- The impact of psychiatric history on the occurrence of neuropsychiatric adverse events during smoking cessation therapy.
- Whether the boxed warning should be removed, modified, or retained, and whether any additional labeling changes should be made.

Overall, panel members agreed that the trial design was good and applauded the completion of a randomized controlled trial to add to prior studies. There were concerns regarding the number of sites and difficulty with data monitoring and control across so many countries, languages, cultures, and investigators. The committee members also expressed concerns with the lack of power to address suicidal events. Some panel members noted the need for having a design that holds to rigorous standards for safety related outcomes, and stated power calculations a priori for this deserved closer attention. Some of the committee members expressed concerns regarding the inclusion of patients who were not naïve to treatment with the drugs under study, which may have enriched the population for individuals able to tolerate the drugs. However, following the advisory committee, FDA obtained a data set from Pfizer that excluded the patients who had prior exposure to the study drugs, and the results of the primary analysis in this population of patients naïve to the study drugs were similar to what was observed in the full population.

Most committee members did not have specific recommendations regarding which of the analyses best represented the data, although there was support for using an expanded outcome definition and for using the alternate statistical approach employed by the FDA team. The potential impact of the variability of data collection practices and coding of adverse events was discussed, but some committee members noted that they did not expect that the variability would affect the adverse event (AE) data differentially across treatment arms.

The committee members did not think emphasis should be placed on the observational studies and concluded that they did not contribute additional insight beyond the findings of the RCT.

Committee members noted the increased risk for neuropsychiatric events in the population with a psychiatric history. Several committee members who noted this difference recommended that this information needs to be described in product labeling.

The committee members were asked to vote for one of the following options:

A. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events (10 members voted for this option)
B. Modify the language in the boxed warning (4 members voted for this option)
C. Keep the current boxed warning (5 members voted for this option)

Some committee members who voted to remove the boxed warning noted that the decision was difficult due to their concerns with the limitations from the study results presented. Some also noted the public health importance of effective smoking cessation therapies being available for patients who need smoking cessation aids, especially those with psychiatric illness.

Several members who voted to retain or modify the boxed warning voiced that their reason was not related to the study, but due to a concern that removing a boxed warning would be misinterpreted as communicating a complete absence of risk. There was also concern about the potential precedent-setting nature of the removal of the boxed warning for other products in the future. A few members of the committee voted to keep the boxed warning, citing concerns about the study endpoint, study conduct, and the inadequate statistical power to detect more rare events, or simply noted that they were unconvinced by the study.

10. Pediatrics

No new pediatric information was submitted. Pfizer is completing pediatric studies as requested in a Pediatric Written Request.

11. Other Relevant Regulatory Issues

11.1 Financial Disclosures

Financial disclosures identified six sites with payments exceeding the threshold for reporting. Analyses without these sites did not change the conclusions.

11.2 OSI Inspections

OSI inspection confirmed GCP violations at the two sites identified by Pfizer. Analyses without these two sites did not change the conclusions.

11.3 Review of Observational Studies

The labeling for Chantix currently includes descriptions of some observational studies in Section 5.1. These were added as a result of a labeling supplement submitted by Pfizer while awaiting the results of the PMR safety trial. However, the studies all had a number of limitations. In this submission, additional language describing some additional studies was proposed. The Division of Epidemiology II (DEPI II) was consulted to review the observational studies submitted by Pfizer, as well as any additional published observational studies on neuropsychiatric risk associated with smoking cessation prescription medications. The text below, from Dr. Natasha Pratt's review, summarizes their conclusions.

> DEPI II's literature search identified a total of six observational studies for in-depth review. The findings of the reviewed epidemiological studies showed inconsistent results. Four of the studies did not observe a statistically significant difference in the risk of neuropsychiatric adverse events between varenicline and NRT, varenicline and bupropion, or between bupropion and NRT; the point estimates did not suggest a consistent trend of association. One study found a significant reduction in neuropsychiatric risk among varenicline users (34% reduction in risk of outpatient depression visit and 44% reduction in the risk of outpatient visit for suicide or non-fatal self- harm) and a 25% reduction in risk of depression visit in bupropion users, comparing to NRT users. Yet, another study observed that while varenicline use was not associated with significant risk of suicide-related behaviors, the risk of neuropsychiatric in- or out-patient visits significantly increased by 18% during varenicline-exposed time compared to unexposed time in varenicline users.
>
> Each of the reviewed studies had key study design limitations. The most important limitations were: 1) use of outcome measures with suboptimal sensitivity and specificity, 2) residual confounding, 3) use of bupropion (another smoking cessation drug with neuropsychiatric risk labeled in a boxed warning) as a reference group to examine varenicline's neuropsychiatric risk and 4) inability to assess the influence of pre-existing psychiatric illness on the association between smoking cessation treatments and neuropsychiatric outcomes. All studies relied on diagnostic codes to capture

neuropsychiatric adverse outcomes, which likely underestimated the absolute risk of events. It is difficult to estimate how many outcome events were missed in each study, or to know whether or not the proportion of outcome under-ascertainment varied among study drugs resulting in decreased precision of estimates and unpredictable direction of bias. In the studies that included data from the timeframe after the publicity of the neuropsychiatric safety concern associated with varenicline and, to a lesser degree, with bupropion, the potential for residual confounding was due to differential prescribing of smoking cessation therapies based on a physician or patient's perceived underlying risk of neuropsychiatric outcomes (i.e., channeling bias); in the other studies, it was due to the impact of other unmeasured factors, such as nicotine withdrawal syndrome. "Channeling bias" makes varenicline or bupropion appear to reduce neuropsychiatric risk when compared to another prescription smoking cessation therapy. "Confounding by nicotine withdrawal syndrome" makes all smoking cessation drugs appear to elevate neuropsychiatric risk (relative to non-users), even if they were in fact risk-neutral. When the potential biases are considered in combination, they restrict our ability to predict the direction of the relative risk associated with any smoking cessation product. One study's use of bupropion as the reference group to examine varenicline's neuropsychiatric risk was problematic because finding no increased risk of NPS events comparing to bupropion does not reassure us of varenicline's neuropsychiatric safety, given that both products are labeled for these adverse events. The inability to assess the risk among those with pre-existing psychiatric illness further restricts the generalizability of the findings. The evidence from the existing observational studies, alone, is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline use or bupropion use. Observational data alone also are inadequate to inform whether or not neuropsychiatric risk associated with varenicline or bupropion could be different between smokers with and without psychiatric history. Neuropsychiatric safety of smoking cessation products should be assessed based on the totality of data streams, including case reports, observational and clinical trial data.

Consistent with this assessment of the observational literature and the Advisory Committee's opinion that observational literature does not add to the understanding of risk beyond the findings of the PMR trial, the team recommended deleting descriptions of observational studies from the labeling.

12. Labeling

Pfizer proposed to make the following changes in labeling:
Boxed warning deleted – Review team concurs

New language for 5.1:
Significant (b) (4) text from body of warning include text communicating the following concepts:

(b) (4)

(b) (4)

The review team does not concur with deleting all of these messages. Recommended wording is shown below.

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Additions to 5.1
Section 5.1 currently contains text describing metaanalysis of RCTs and descriptions of observational studies. Pfizer's proposal includes (b) (4)

The review team does not concur with (b) (4)

(b) (4)

General Safety and Efficacy findings from PMR RCT
Adverse event rates from PMR study added to the Adverse Reactions section in text. Review team concurs.

Clinical Trials Section: Description and quit rate table added
Review team concurs, and proposes to add NPS safety results to this section as well, using Expanded NPS rates.

Patient Counseling [redacted] (b) (4) if patients develop neuropsychiatric symptoms. Patients directed only to "contact a health care professional" if they develop symptoms. [redacted] (b) (4) .

Patient Labeling

Pfizer's labeling proposal included [redacted] (b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  I recommend approval of this supplement.

- Risk Benefit Assessment

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Because of the post-marketing safety signal of neuropsychiatric adverse events, Chantix is currently marketed under a REMS. The goal of the REMS is to inform patients about the potential serious risk of serious neuropsychiatric adverse events associated with the use of Chantix. The elements of the REMS are limited to a Medication Guide (MG) and a timetable for submission of assessments.

Previous assessment reports have concluded that the risk of neuropsychiatric adverse events is understood by 70-80% of patients. Moreover, the results of this PMR trial indicate that the risk of events of a serious nature is lower than previously suspected. Although disturbances in mood, thinking, and behavior are not uncommon, the vast majority of these events are not serious. Therefore, consistent with our conclusion that the boxed warning is no longer warranted in the package insert, it is appropriate that the REMS no longer be required. A MedGuide will still be distributed which informs patients about these risks, but FDA will not require this under a REMS with periodic assessments.

Similarly, the results of the study support making analogous changes to the labeling of Zyban to removed the boxed warning and to incorporate the results of the PMR study, and to remove the requirement for a REMS. The labels for the antidepressant bupropion products will retain the antidepressant class label boxed warning but may have the language pertaining to smoking cessation use removed from the box.

APPEARS THIS WAY ON ORIGINAL

APPENDIX

Table 20 Description of NPS SAEs

Patient #, demographics, primary diagnosis	Description of event
Non-PHx Cohort	
Varenicline	
(b) (6) WF 58	After three months on study drug, subject was **hospitalized** for "alcohol abuse" for three days. No other information provided.
Bupropion	
(b) (6) WM 53	Treatment Day 13, subject was **hospitalized** for ~2 days for evaluation after mentioning that he "felt like blowing his brains out." This was later dismissed by the subject as a "misunderstanding." He was started on an antidepressant and declined further participation in the study.
(b) (6) WF 74	After ~1 month on study drug, subject first noticed "intermittent left hemiparesthesia and subjective confusion." Symptoms resolved and then recurred, with four instances in a month of "a foggy feeling in my head" and "stabbing cold pains." Symptoms became persistent after ~2 months on study drug; she was admitted to the hospital to be evaluated for stroke. Workup negative; study drug discontinued.
(b) (6) WM 32	On Treatment Day 19, subject was found dead (reported by his sister). Toxicology report showed opiates. Patient had history of occasional use of heroin. (Not enough information to rule out NPS event.)
(b) (6) BM 40	After 24 days of study drug treatment "the subject experienced depression which was considered mild in intensity and serious due to **hospitalization** or prolonged hospitalization by the investigator." Study drug was discontinued, patient was treated with psychotropic medication. Patient had reduced smoking from 28 to cigarettes/day 5 at the time of event. No other information is provided.

(b) (6) WM 23	Subject was randomized into non-PHx cohort; after events occurred MHP in retrospect felt subject had "underlying mood disorder (probably bipolar) and PTSD." After five days of study drug, patient reported that he had experienced three days of worsening symptoms, including sweating and pacing, "I felt like I took drugs." "Mild anxiety" and "moderate hostility" were also recorded with no detail. Study drug was decreased and then discontinued. He had reduced smoking from BL 15 to 9-10 cigarettes/day. About a month after discontinuing study drug, the subject revealed that he had been hitting himself in the head with his fists and had repeatedly placed a loaded gun into his mouth with intent to commit suicide. He had been taken to see a psychiatrist outside the study and was taking quetiapine. He completed the study off treatment.
NRT	
(b) (6) WF 47	After three weeks of treatment with NRT, in the context of drinking alcohol, subject "decided on the spur of the moment to pack and leave her apartment. In the process of packing, she saw a knife and impulsively started to cut herself. She said her husband saw her cutting, stopped her, and took her to the ER. She shared that she did feel that the combination of the alcohol and the drug trial she was on may have caused her to be more emotional than usual during the time when she cut herself." Study drug was discontinued; subject had a second episode of suicidal ideation with plan a month later. Smoking was decreased from BL 20 to 6-9 cigarettes/day at the time of the events.
Placebo	
(b) (6) WM 34	(Subject was randomized to NRT but event occurred during initial week of placebo pill dosing before patch began) After a week of study drug (placebo pills) treatment, patient "reported a panic attack that led to binge drinking", and that he was **hospitalized** for five days for treatment. Smoking had not changed.
(b) (6) WF 30 *completed suicide*	Subject began taking study drug and stopped smoking between the Week 1 and Week 2 visits. She had no complaints other than insomnia reported during the first week of treatment. She did not appear for the Week 5 visit, and the site subsequently learned she had committed suicide by jumping from a high monument three days after her Week 4 visit, leaving a note saying "everything was too much." The subject had no prior psychiatric history and no lifetime suicidal attempts or ideation.
(b) (6) WM 47	After ~2 months of study medication and ~2 weeks after last dose, the subject was hospitalized for orthostatic hypotension and numbness in his hand. He required treatment with dopamine and adjustment of his

	antihypertensives, and was hospitalized for four days. After discharge from the hospital, he reported "physical problems overwhelming, ganging up on me," and endorsed suicidal ideation about twice a week without plan. About 10 days later he endorsed suicidal thoughts of overdosing; he required **crisis assessment at a local psychiatric facility**. He had reduced smoking but not quit.
(b) (6) WM 33	Subject completed 85 days of study drug. At the Week 13 (post-treatment visit) the site documented "since stopping the meds, subject reports depression," and that symptoms of a prior eating disorder had re-emerged "appetite down, fasting, binging, and purging," and that two days after completing the course of treatment, he experienced vague suicidal ideation with no intent or plan; on C-SSRS he endorsed "easier to be dead." This suicidal ideation was assessed by the investigator as "moderate in intensity and serious." No change in smoking level. He was referred to a psychiatrist but the nature of treatment is not documented; narrative states that the event resolved.
PHx Cohort	
Varenicline	
(b) (6) WM 34 bipolar disorder	Treatment Day 58, subject reported increased anxiety, auditory hallucinations, and "checked himself into" a psychiatric **hospital**. Study drug discontinued. Investigator believed complaints were factitious. Subject also reported command hallucinations and suicide attempt by jumping in front of a bus.
(b) (6) WM 19 major depressive disorder	Subject completed 87 days of study drug treatment. Approximately two weeks after discontinuing study drug, subject "did not sleep for three nights" and experienced symptoms described as "panicky, nervous, anxious," and cut his wrists "as an act of self-mutilation and not as a suicide attempt." He was **psychiatrically hospitalized** for three days. He was smoking 3 cigarettes/day (Baseline [BL]: 15) at the time of the events.
(b) (6) WM 33 schizoaffective/bipolar	After four weeks of study drug, subject presented to an emergency room after a fight with his parents, seeking admission, stating he was depressed; he reported suicidal thoughts but it was believed this claim was factitious. However, he reported that while on study drug "his depression had gotten worse." Study medications were discontinued; patient did not return for further visits. He was **psychiatrically hospitalized** for approximately a week.

(b) (6) WM 47 bipolar disorder, PTSD, panic	Subject took study medication for ~16 days. A few days after discontinuing medication, he relapsed to alcohol use reportedly "due to the death of his father" and was lost to follow-up to the study site. Approximately two weeks after resuming drinking he was found unconscious and **hospitalized** for alcohol poisoning and management of withdrawal.
(b) (6) WM 36 bipolar disorder	After 20 days of study drug, subject "was upset and had brief thought of death ("I had a suicide thought about taking my sleeping medication"), called a crisis line, and went into an **outpatient stabilization unit**." He had missed two doses of his mood stabilizer (valproate) and antidepressant (citalopram). Smoking decreased from 20 to 5 cigarettes/day at time of event. Study medication was continued. Event resolved.
(b) (6) WF 37 bipolar disorder	After 53 days of study drug treatment, subject was **psychiatrically hospitalized**, and gave retrospective report of three weeks of impulsive thoughts of suicide by taking all of her medication. Complaints at admission included "becoming more aggressive in her thoughts and behavior." Site investigator noted that symptoms occurred in the context of ex-husband returning to live with the patient after being released from jail and that symptoms had not been reported during visits prior to hospitalization, and that the complaints may have been factitious. Smoking at time of the event reduced from 20 to 10 cigarettes/day.
Bupropion	
(b) (6) WM 58 bipolar disorder, panic	Treatment Day 14, subject began a four-day alcohol binge (a quart of vodka/day) and was hospitalized. The subject's sister reported that he was **hospitalized** for an exacerbation of his bipolar disorder. No details about affective symptoms were obtained.
(b) (6) WF 45 bipolar disorder	After ~3 weeks of study drug treatment, the subject was **psychiatrically hospitalized** for symptoms that her husband reported retrospectively had begun "a couple of weeks" earlier. He reported agitation for "a couple of weeks," worsening to her becoming "out of control," he was worried she might hurt herself or others. Presenting symptoms included aggression and anger. The subject had significantly decreased her cigarette use (2-3/day from BL 15) and stated that she felt exactly the same when she tried to quit smoking before without any medications. Subject remained hospitalized for a week; study drug discontinued. Urine screen positive for methamphetamine at admission and two days after discharge; cross-reactivity with bupropion evidently not considered[13]. No prior or subsequent methamphetamine positive screens. Two months later, subject reported

[13] Therapeutic use of bupropion may be a cause of false-positive urine screens for amphetamines

	agitation and panic attacks at a study visit, and two weeks later was re-hospitalized for ~1 week.
(b) (6) WM 36 major depressive disorder	One day after completing the course of study drug treatment, the subject (who was without any psychiatric symptoms at baseline) made a suicide attempt by inhaling butane from a cigarette lighter; this was attributed to a reaction to his girlfriend's suicide attempt two days earlier. The subject was **evaluated in an inpatient crisis setting** and referred for ongoing day treatment; a diagnosis of schizoaffective disorder was made but no information is provided to explain this diagnosis (e.g. presence of ongoing psychotic symptoms in absence of mood symptoms).
(b) (6) WF 59 bipolar disorder	When the site attempted to contact the subject to confirm her Week 2 visit, they were informed she had been **arrested and subsequently hospitalized**. Medication may have been taken for two weeks. Subject had been found walking naked in her neighborhood and "mooned" a neighbor. She was delusional and tangential during admission and refused voluntary admission. Study medication was discontinued.
(b) (6) WM 45 Major depressive disorder (recurrent); alcohol dependence (past)	On Study Day 84, subject was **psychiatrically hospitalized** for a relapse to alcohol dependence. Paroxetine was initiated for depression. Smoking had been reduced to 5 cigarettes/day at the time of the event.
(b) (6) WF 25 bipolar disorder	After four days of study drug treatment (first day of b.i.d. dosing), the subject experienced increased activity, tachycardia, racing thoughts, and pressured speech. She was "a bit more excited and irritated" at the Week 1 study visit but the mental health professional did not recommend any action be taken. On Study Day 12, the patient experienced symptoms of irritability, decreased mood, and anxiety and discontinued taking study drug. A few days later at a study visit, the mental health professional noted her to be in a mixed state of bipolar disorder and recommended she be withdrawn from the trial. Symptoms continued and the subject required **hospitalization** approximately 2 weeks later. She had increased her smoking above baseline levels.
(b) (6) WF 64 Depression, past alcoholism	The subject completed 85 days of study drug treatment; during treatment reported adverse events included irritability, panic attack, and depression, all assessed as “mild.” MHP evaluations at Study Day 29 and 36 record a recommendation for “medication;” it is not clear if any medication was initiated. (Baseline concomitant medications included mirtazapine and flupentixol.) Approximately 12 days later she was

	hospitalized for "alcoholism" for approximately two weeks.
(b) (6) WM 37 schizophrenia	The subject completed the course of treatment with study drug and reduced smoking from 26 to 10 cigarettes/day. Six days after completing treatment he was **hospitalized** so that treatment with clozapine could be re-initiated after having been discontinued three days earlier. The narrative summary did not provide a reason for admission.
NRT	
(b) (6) WM 28 schizophrenia	After ~8 weeks on study drug (7 weeks on NRT), subject reported anxiety and noted his mother had recently died, and that his personal physician had made some changes to his medications; anxiety worsened and approximately 10 days later he was **psychiatrically hospitalized** for a week. Smoking at the time of the event was 4 cigarettes/day (BL = 13). Study medication was discontinued. Events resolved.
(b) (6) WM 53 major depressive disorder	After 37 days of study drug treatment (30 days of NRT), subject discontinued taking study drug. The reason was not recorded; on-treatment evaluations recorded gradually increasing anxiety scores but symptoms were not considered "clinically significant." Two days after discontinuing study drug he reported that "I am in the hospital for my anxiety." He remained **hospitalized** for a week. Study drug was not resumed; subject was not evaluated at the study site until ~5 weeks later at which time symptoms had resolved.
(b) (6) WM 46 Major depressive disorder (recurrent), PTSD, alcohol dependence (full remission)	After approximately one month of study treatment, the subject was **hospitalized** for relapse to alcohol dependence. He was discontinued from the study. Smoking at the time of the event was reduced to 2 cigarettes/day.
(b) (6) WF 38 major depressive disorder	On Study Day 42 after ~6 weeks of NRT, the subject reported that she felt depressed with a lack of energy; study drug was discontinued. ~2 weeks later, depression worsened (subject had omitted antidepressant for ~4 days) and subject required **hospitalization** for depression. Smoking was unchanged from baseline.
Placebo	

(b) (6) [14] schizophrenia	During Week 7, patient took 4 bottles of study drug, after which she vomited and then fell asleep and did not seek medical attention. She reported this at the Week 8 visit, at which time she endorsed on the C-SSRS that she had active suicidal ideation (wish to be dead) and had a specific plan and intent to commit suicide. "The investigator recorded the event as a mild accidental overdose and attributed causality to the subject's long history of impulsivity thought disorder and similar events in which the subject would overdose without it being a suicide attempt." A psychiatric evaluation was performed and no treatment changes were recommended.
(b) (6) WF 26 major depressive disorder	On Treatment Day 6, subject reported feeling "irritable over small things," 18 days later she reported feeling depressed and having suicidal thoughts. She reportedly was admitted to a psychiatric hospital and was **hospitalized** for a month. Study drug was discontinued. Smoking at time of hospitalization is not known.
(b) (6) BM 35[15] generalized anxiety disorder	Subject failed to return after the Week 4 visit; however, the site learned through subject's girlfriend (also a subject in the study) that he had hit her in the head with a gun and fractured her skull. She noted that he had been violent before. He had been drinking at the time of the event.
(b) (6) WF 43 schizophrenia	On Study Day 42, the subject began treatment with disulfiram "to control alcohol intake." (Alcohol abuse is noted as a "past" diagnosis; the implication is that the subject relapsed to serious alcohol use requiring treatment.) The subject discontinued using study drug at that time. A psychiatric evaluation was done "due to an increase of depressive and anxious symptoms" but no adverse event was reported. Approximately a month later, the subject took an impulsive overdose of clorazepate stating "I felt nervous and distressed...I felt very sad and anxious and decided to take some pills and not wake up." There were minimal sequelae of the overdose. Smoking was reduced from BL 25 to 12 cigarettes/day.
(b) (6) WF 42 major depressive disorder, borderline PD	After 9 days of study drug treatment, subject attempted suicide by ingesting 56 aripiprazole and 30 diazepam tablets along with her week's supply of blinded study medications together with alcohol. The subject was **hospitalized** very briefly. Study medications were discontinued. Her cigarette use was reduced from BL 24 cigarettes/day at baseline to 20 cigarettes/day. Approximately 10 days later, the subject was **rehospitalized** for "recurrent symptoms of borderline personality disorder," and a few days later had again been "monitored in the hospital psychiatric department." Smoking was increased to 30 cigarettes/day.

[14] Not flagged as serious by Sponsor. The outcome was not serious because the pills consumed were placebo.
[15] In this case the aggressive behavior was coded as serious because of the risk to the victim, not the patient

(b) (6) WM 49[16] major depression	Within two days of initiating study drug treatment, subject reported feeling more depressed since starting the study medication, and experiencing increasing anxiety after a couple of days of study drug treatment, and endorsed feeling that "it would be easier to be dead" on C-SSRS. He also reported insomnia. Study drug was discontinued. ~1 week later, the subject was hospitalized for a medical illness (shortness of breath diagnosed as pulmonary embolus and cardiac failure); while hospitalized, he left the hospital, went home, and took 20 tablets of paracetamol 500 mg/codeine 30 mg. He returned to the hospital and reported the overdose but denied intent to kill himself. The patient required treatment with n-acetylcysteine for elevated acetaminophen level. The investigator did not consider this serious and did not consider it a suicide attempt.

[16] Coded as serious by sponsor because of the hospitalization for medical problem; overdose of acetaminophen was not assessed by sponsor as serious.

Table 21 Frequency of Events in Selected SMQs--Non PHx cohort

Non-Psych Cohort	Varenicline 1.0 mg BID (N = 1005)			Bupropion 150 mg BID (N = 1001)			NRT 21/14/7 mg QD (N = 1013)			Placebo (N = 1009)		
	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%
Depression and suicide/self-injury (narrow)	96	67	7	55	41	4	57	42	4	92	60	6
Depression and suicide/self-injury (broad)	165	112	11	131	88	9	139	91	9	141	88	9
(Suicide/self-injury *(narrow)	2	2	0	5	4	0	4	2	0	5	4	0
Suicide/self-injury (broad)	2	2	0	5	4	0	4	2	0	5	4	0
Depression (excl suicide and self injury) (narrow)	94	67	7	50	37	4	53	40	4	87	58	6
Depression (excl suicide and self injury) (broad)	163	112	11	126	84	8	135	89	9	136	87	9
Psychosis and psychotic disorders (narrow)	1	1	0	3	3	0	2	2	0	1	1	0
Psychosis and psychotic disorders (broad)	19	14	1	11	10	1	13	12	1	17	13	1
Accidents and injuries	94	64	6	78	51	5	105	63	6	107	61	6
Hostility/aggression (narrow)	10	9	1	12	6	1	16	16	2	17	15	1
Hostility/aggression (broad)	115	84	8	98	69	7	122	92	9	103	77	8

Source: Prepared by Dr. Sarah Arnold from Sponsor's datasets

Table 22 Frequency of Events in Selected SMQs--PHx cohort

Psych Cohort	Varenicline 1.0 mg BID (N = 1032)			Bupropion 150 mg BID (N = 1033)			NRT 21/14/7 mg QD (N = 1025)			Placebo (N = 1026)		
	Events	N	(%)	Events	N	(%)	Events	N	(%)	Events	N	(%)
Depression and suicide/self-injury (narrow)	209	136	13.18	209	132	12.78	227	134	13.07	203	127	12.38
Depression and suicide/self-injury (broad)	336	200	19.38	333	196	18.97	343	192	18.73	296	174	16.96
Suicide/self-injury (narrow)	13	10	0.97	6	5	0.48	11	11	1.07	15	10	0.97
Suicide/self-injury (broad)	13	10	0.97	6	5	0.48	11	11	1.07	15	10	0.97
Depression (excl suicide and self injury) (narrow)	196	128	12.4	203	130	12.58	216	132	12.88	188	121	11.79
Depression (excl suicide and self injury)(broad)	323	194	18.8	327	194	18.78	332	190	18.54	281	169	16.47
Psychosis and psychotic disorders (narrow)	27	17	1.65	24	15	1.45	19	10	0.98	22	15	1.46
Psychosis and psychotic disorders (broad)	85	57	5.52	63	43	4.16	51	32	3.12	41	33	3.22
Accidents and injuries (narrow)	97	61	5.91	125	62	6	133	74	7.22	75	48	4.68
Accidents and injuries (broad)	108	66	6.4	139	69	6.68	144	79	7.71	85	53	5.17
Hostility/aggression (narrow)	34	26	2.52	29	22	2.13	19	18	1.76	33	19	1.85
Hostility/aggression (broad)	217	133	12.89	197	119	11.52	184	129	12.59	192	133	12.96

Source: Prepared by Dr. Sarah Arnold from Sponsor's datasets

Table 23 – Non Psychiatric Cohort—Treatment Emergent Adverse Events reported by ≥5% in any Active Treatment at HLGT level; PTs reported by at least 1%

SOC	HLGT	PT	Varenicline		Bupropion		NRT		Placebo	
			N = 990		N = 989		N = 1006		N = 999	
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions		88	9%	57	6%	58	6%	49	5%
		Constipation	39	4%	31	3%	17	2%	15	2%
		Diarrhoea	44	4%	24	2%	32	3%	31	3%
		Gastrooesophageal reflux disease	5	1%	3	0%	9	1%	6	1%
	Gastrointestinal signs and symptoms		304	31%	132	13%	146	15%	115	12%
		Abdominal discomfort	11	1%	4	0%	1	0%	5	1%
		Abdominal distension	6	1%	4	0%	1	0%	3	0%
		Abdominal pain	12	1%	6	1%	5	0%	11	1%
		Abdominal pain upper	18	2%	10	1%	12	1%	8	1%
		Dyspepsia	26	3%	11	1%	21	2%	17	2%
		Flatulence	17	2%	8	1%	8	1%	9	1%
		Nausea	243	25%	90	9%	95	9%	63	6%
		Vomiting	31	3%	14	1%	25	2%	15	2%
	Salivary gland conditions		29	3%	70	7%	33	3%	26	3%

	Dry mouth	29	3%	70	7%	31	3%	26	3%
General disorders and administration site conditions	Administration site reactions	27	3%	15	2%	117	12%	21	2%
	Application site erythema	5	1%	5	1%	38	4%	1	0%
	Application site irritation	4	0%	2	0%	17	2%	6	1%
	Application site pain	3	0%	0	0%	13	1%	2	0%
	Application site pruritus	11	1%	6	1%	51	5%	11	1%
	Application site rash	4	0%	2	0%	9	1%	2	0%
	General system disorders NEC	83	8%	88	9%	93	9%	69	7%
	Asthenia	4	0%	4	0%	7	1%	3	0%
	Chest discomfort	6	1%	5	1%	4	0%	3	0%
	Chest pain	6	1%	7	1%	11	1%	7	1%
	Crying	3	0%	3	0%	6	1%	5	1%
	Fatigue	39	4%	20	2%	28	3%	24	2%
	Feeling jittery	8	1%	10	1%	7	1%	4	0%
	Influenza like illness	1	0%	8	1%	6	1%	2	0%
	Malaise	6	1%	1	0%	6	1%	2	0%
Infections and	Infections - pathogen unspecified	228	23%	203	21%	205	20%	216	22%

infestations									
	Bronchitis	10	1%	15	2%	19	2%	16	2%
	Conjunctivitis	2	0%	1	0%	7	1%	3	0%
	Cystitis	5	1%	1	0%	2	0%	4	0%
	Gastroenteritis	15	2%	13	1%	23	2%	20	2%
	Nasopharyngitis	86	9%	79	8%	65	6%	73	7%
	Pneumonia	7	1%	1	0%	3	0%	2	0%
	Rhinitis	7	1%	5	1%	7	1%	4	0%
	Sinusitis	15	2%	17	2%	14	1%	14	1%
	Tooth infection	5	1%	4	0%	1	0%	9	1%
	Upper respiratory tract infection	47	5%	48	5%	40	4%	55	6%
	Urinary tract infection	12	1%	13	1%	6	1%	6	1%
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders NEC	46	5%	38	4%	34	3%	50	5%
	Back pain	22	2%	19	2%	20	2%	24	2%
	Musculoskeletal pain	5	1%	4	0%	4	0%	9	1%
	Neck pain	5	1%	6	1%	2	0%	6	1%
	Pain in extremity	13	1%	4	0%	7	1%	10	1%

Nervous system disorders	Headaches	121	12%	90	9%	136	14%	100	10%
	Headache	116	12%	87	9%	129	13%	95	10%
	Neurological disorders NEC	79	8%	103	10%	77	8%	58	6%
	Dizziness	33	3%	51	5%	38	4%	28	3%
	Dysgeusia	23	2%	43	4%	15	1%	10	1%
	Somnolence	16	2%	5	1%	16	2%	8	1%
Psychiatric disorders	Anxiety disorders and symptoms	87	9%	113	11%	79	8%	90	9%
	Agitation	32	3%	29	3%	28	3%	25	3%
	Anxiety	46	5%	64	6%	45	4%	57	6%
	Nervousness	14	1%	18	2%	11	1%	9	1%
	Panic attack	2	0%	7	1%	2	0%	3	0%
	Tension	2	0%	10	1%	2	0%	2	0%
	Depressed mood disorders and disturbances	60	6%	29	3%	39	4%	49	5%
	Depressed mood	31	3%	13	1%	27	3%	29	3%
	Depression	17	2%	13	1%	8	1%	15	2%
	Depressive symptom	5	1%	3	0%	2	0%	2	0%
	Mood disorders and disturbances NEC	55	6%	40	4%	62	6%	44	4%

	Apathy	7	1%	2	0%	3	0%	3	0%
	Irritability	34	3%	29	3%	47	5%	37	4%
	Sleep disorders and disturbances	209	21%	222	22%	217	22%	139	14%
	Abnormal dreams	83	8%	47	5%	111	11%	39	4%
	Initial insomnia	7	1%	6	1%	10	1%	4	0%
	Insomnia	95	10%	126	13%	91	9%	73	7%
	Middle insomnia	7	1%	15	2%	13	1%	6	1%
	Nightmare	9	1%	7	1%	26	3%	3	0%
	Sleep disorder	31	3%	37	4%	17	2%	19	2%
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	55	6%	51	5%	60	6%	53	5%
	Cough	17	2%	22	2%	23	2%	19	2%
	Dyspnoea	12	1%	7	1%	6	1%	7	1%
	Oropharyngeal pain	11	1%	6	1%	15	1%	14	1%
	Productive cough	5	1%	4	0%	5	0%	4	0%
	Respiratory tract congestion	5	1%	3	0%	2	0%	2	0%
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	39	4%	40	4%	79	8%	28	3%

Dermatitis contact	1	0%	3	0%	9	1%	3	0%
Eczema	3	0%	2	0%	6	1%	2	0%
Erythema	3	0%	1	0%	11	1%	4	0%
Pruritus	7	1%	6	1%	23	2%	4	0%
Pruritus generalised	1	0%	5	1%	0	0%	0	0%
Rash	8	1%	12	1%	12	1%	8	1%
Skin irritation	4	0%	3	0%	10	1%	3	0%

Table 24 –Psychiatric Cohort—Treatment Emergent Adverse Events reported by ≥5% in any Active Treatment at HLGT level; PTs reported by at least 1%

SOC	HLGT	PREFERRED TERM	Varenicline		Bupropion		NRT		Placebo	
			N = 1026		N = 1017		N = 1016		N = 1015	
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions		90	9%	83	8%	82	8%	58	6%
		Constipation	51	5%	45	4%	32	3%	22	2%
		Diarrhoea	31	3%	33	3%	44	4%	25	2%
		Gastrooesophageal reflux disease	10	1%	6	1%	7	1%	5	0%

	Gastrointestinal signs and symptoms	332	32%	180	18%	160	16%	136	13%
	Abdominal discomfort	11	1%	8	1%	5	0%	12	1%
	Abdominal distension	11	1%	6	1%	3	0%	5	0%
	Abdominal pain	19	2%	12	1%	5	0%	10	1%
	Abdominal pain upper	25	2%	13	1%	15	1%	17	2%
	Dyspepsia	20	2%	23	2%	24	2%	14	1%
	Flatulence	13	1%	10	1%	15	1%	9	1%
	Nausea	268	26%	111	11%	104	10%	74	7%
	Vomiting	38	4%	22	2%	22	2%	20	2%
	Salivary gland conditions	39	4%	77	8%	30	3%	38	4%
	Dry mouth	37	4%	76	7%	28	3%	38	4%
General disorders and administration site conditions	Administration site reactions	19	2%	15	1%	119	12%	23	2%
	Application site erythema	4	0%	3	0%	34	3%	7	1%
	Application site irritation	3	0%	5	0%	18	2%	4	0%
	Application site pain	1	0%	1	0%	11	1%	1	0%
	Application site pruritus	11	1%	6	1%	58	6%	5	0%
	Application site rash	1	0%	0	0%	9	1%	0	0%

	General system disorders NEC	140	14%	108	11%	102	10%	108	11%
	Asthenia	6	1%	4	0%	4	0%	5	0%
	Chest discomfort	1	0%	7	1%	0	0%	7	1%
	Chest pain	9	1%	8	1%	8	1%	10	1%
	Crying	10	1%	16	2%	16	2%	10	1%
	Energy increased	13	1%	12	1%	11	1%	4	0%
	Fatigue	85	8%	37	4%	47	5%	59	6%
	Feeling jittery	1	0%	12	1%	3	0%	1	0%
	Influenza like illness	4	0%	3	0%	6	1%	3	0%
	Pain	6	1%	4	0%	4	0%	6	1%
Infections and infestations	Infections - pathogen unspecified	231	23%	211	21%	212	21%	212	21%
	Bronchitis	17	2%	14	1%	19	2%	23	2%
	Ear infection	6	1%	8	1%	7	1%	6	1%
	Gastroenteritis	21	2%	19	2%	16	2%	15	1%
	Nasopharyngitis	88	9%	77	8%	61	6%	62	6%
	Pharyngitis	6	1%	3	0%	6	1%	3	0%
	Rhinitis	6	1%	0	0%	4	0%	2	0%
	Sinusitis	16	2%	13	1%	18	2%	10	1%

		Tooth abscess	6	1%	4	0%	8	1%	8	1%
		Tooth infection	2	0%	7	1%	4	0%	5	0%
		Upper respiratory tract infection	62	6%	56	6%	57	6%	60	6%
		Urinary tract infection	11	1%	8	1%	6	1%	11	1%
Injury, poisoning and procedural complications	Injuries NEC		38	4%	43	4%	55	5%	39	4%
		Contusion	4	0%	7	1%	7	1%	11	1%
		Fall	10	1%	9	1%	16	2%	10	1%
		Ligament sprain	6	1%	5	0%	8	1%	5	0%
		Muscle strain	4	0%	6	1%	3	0%	4	0%
Metabolism and nutrition disorders	Appetite and general nutritional disorders		47	5%	32	3%	26	3%	22	2%
		Decreased appetite	19	2%	17	2%	14	1%	7	1%
		Increased appetite	27	3%	12	1%	12	1%	16	2%
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders NEC		50	5%	58	6%	62	6%	40	4%
		Back pain	27	3%	29	3%	24	2%	16	2%

		Musculoskeletal pain	8	1%	8	1%	10	1%	4	0%
		Neck pain	5	0%	8	1%	8	1%	7	1%
		Pain in extremity	12	1%	13	1%	17	2%	10	1%
Nervous system disorders	Headaches		137	13%	105	10%	113	11%	109	11%
		Headache	129	13%	99	10%	104	10%	104	10%
		Migraine	6	1%	5	0%	8	1%	4	0%
	Neurological disorders NEC		101	10%	125	12%	102	10%	96	9%
		Dizziness	45	4%	47	5%	47	5%	38	4%
		Dysgeusia	30	3%	43	4%	25	2%	28	3%
		Paraesthesia	5	0%	6	1%	4	0%	7	1%
		Somnolence	13	1%	14	1%	13	1%	8	1%
Psychiatric disorders	Anxiety disorders and symptoms		149	15%	181	18%	160	16%	134	13%
		Agitation	47	5%	56	6%	39	4%	41	4%
		Anxiety	86	8%	105	10%	93	9%	63	6%
		Nervousness	21	2%	19	2%	17	2%	27	3%
		Panic attack	9	1%	19	2%	13	1%	11	1%
		Stress	9	1%	4	0%	7	1%	7	1%

Tension	9	1%	5	0%	10	1%	6	1%
Depressed mood disorders and disturbances	115	11%	114	11%	112	11%	112	11%
Decreased interest	4	0%	2	0%	7	1%	5	0%
Depressed mood	47	5%	47	5%	52	5%	52	5%
Depression	49	5%	45	4%	47	5%	46	5%
Depressive symptom	11	1%	8	1%	12	1%	13	1%
Major depression	7	1%	10	1%	4	0%	2	0%
Tearfulness	3	0%	6	1%	0	0%	3	0%
Mood disorders and disturbances NEC	81	8%	66	6%	80	8%	92	9%
Anger	11	1%	4	0%	4	0%	5	0%
Apathy	6	1%	3	0%	3	0%	5	0%
Euphoric mood	1	0%	6	1%	0	0%	2	0%
Irritability	48	5%	42	4%	61	6%	67	7%
Sleep disorders and disturbances	228	22%	234	23%	266	26%	156	15%
Abnormal dreams	118	12%	84	8%	140	14%	53	5%
Initial insomnia	15	1%	8	1%	10	1%	2	0%
Insomnia	94	9%	119	12%	104	10%	66	7%
Middle insomnia	11	1%	16	2%	13	1%	8	1%

		Nightmare	13	1%	9	1%	30	3%	14	1%
		Sleep disorder	34	3%	36	4%	28	3%	23	2%
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC		49	5%	41	4%	54	5%	50	5%
		Cough	18	2%	13	1%	15	1%	21	2%
		Dyspnoea	5	0%	4	0%	9	1%	10	1%
		Oropharyngeal pain	9	1%	15	1%	14	1%	13	1%
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions		49	5%	54	5%	93	9%	47	5%
		Dermatitis contact	4	0%	3	0%	7	1%	3	0%
		Eczema	3	0%	3	0%	8	1%	2	0%
		Erythema	6	1%	0	0%	9	1%	1	0%
		Pruritus	11	1%	17	2%	28	3%	12	1%
		Rash	16	2%	15	1%	21	2%	14	1%
		Skin irritation	3	0%	1	0%	10	1%	5	0%

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/s/

CELIA J WINCHELL
11/21/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Supplement
Application Number(s)	021928-S040
Priority or Standard	Standard
Submit Date(s)	February 18, 2016
Received Date(s)	February 18, 2016
PDUFA Goal Date	December 18, 2016
Division/Office	Division of Anesthesia, Analgesia, and Addiction Products
Reviewer Name(s)	Celia Winchell, M.D.
Review Completion Date	November 13, 2016
Established Name	Varenicline tartrate
(Proposed) Trade Name	Chantix
Applicant	Pfizer, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	0.5 mg once daily on days 1-3, 0.5 mg twice daily on days 4-7, then 1 mg twice daily for 12 weeks.
Applicant Proposed Indication(s)/Population(s)	Smoking Cessation
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Smoking Cessation

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Chantix (varenicline) is a partial α4β2 acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation. Approximately a year later, post-marketing signals involving suicidality and bizarre/aggressive behavior arose and evaluations of the postmarketing revealed cases that appeared to be drug-related involving symptoms in a variety of neuropsychiatric domains, including cognition, perception, mood, and general functioning. A subsequent review of post-marketing data on Zyban and various nicotine replacement therapies identified similar cases associated with Zyban. A series of incremental changes to labeling were made to address the emerging understanding of the nature of the risk, including the addition of a boxed warning concerning the risk of neuropsychiatric adverse events and a MedGuide-only REMS to inform patients and prescribers of the risk. FDA also required, under the authorities of FDAA, a safety outcome study a clinical trial to assess the known serious risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions related to the use of varenicline products. A similar REMS and PMR for Zyban was required of Glaxo SmithKline. The Sponsors were required to conduct

> A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric adverse events, including but not limited to suicidality, in individuals using varenicline, bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric adverse events compared to individuals without prior history of psychiatric disorders while using varenicline as an aid to smoking cessation. The study should be sufficiently powered to adequately assess clinically significant neuropsychiatric adverse events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).

The Sponsors were encouraged to collaborate on this trial. Pfizer took the lead on designing and conducting the PMR trial, with financial support and study drug supplied by GSK (who also markets nicotine transdermal products).In recognition of the variable and ill-defined nature of the neuropsychiatric adverse events reported, and the difficulty of capturing such events in traditional MedDRA coding, a composite endpoint was developed specifically for the PMR trial and instruments to solicit relevant events were included in the trial procedures.

This submission provides the results of the PMR trial. A number of barriers to review and concerns about the study conduct were identified, limiting confidence in some of the reported results. However,

after a series of sensitivity analyses and other approaches to capture cases of interest, the review team concluded that the data could be relied upon to support certain conclusions.

1.2. Conclusions

Across all analyses, consistent results were found despite issues with the data. In patients with no history of psychiatric diagnoses, the risk of clinically significant neuropsychiatric adverse effects does not appear to be increased in association with Chantix treatment. In patients with either a past or current (stable) psychiatric diagnosis,[1] there appears to be a small, but consistent, increase in risk of clinically-significant neuropsychiatric adverse events in patients treated with Chantix or bupropion as compared to patients treated with nicotine patch or placebo. The primary endpoint as defined in the protocol appears to have underestimated the frequency of clinically significant events, due to problems with data capture and coding. An analysis based on an approach to capturing all clinically significant events was undertaken by the review team.

Based on the review team's analysis, in patients without a history of psychiatric diagnoses, all groups, including patients treated with placebo, had similar incidence of clinically significant neuropsychiatric adverse events, at approximately 3-4%. Very few events met the regulatory criteria for seriousness, with serious events of a neuropsychiatric nature occurring at a rate of 1 per 1000 in Chantix-treated patients without psychiatric diagnoses, and 4 per 1000 in placebo-treated patients. The only completed suicide occurred in a placebo-treated patient with no psychiatric history.

In patients with psychiatric diagnoses, clinically significant neuropsychiatric adverse events occurred in approximately 12% of patients treated with Chantix or bupropion vs. approximately 10% treated with NRT or placebo. Again, events were almost all non-serious. Neuropsychiatric adverse events of a serious nature primarily involved psychiatric hospitalization in this cohort. Psychiatric hospitalizations were reported in 5 per 1000 patients treated with Chantix, 8 per 1000 treated with bupropion, and 4 per 1000 treated with NRT, as compared to 2 per 1000 patients treated with placebo.

Table 1 below summarizes the frequencies of clinically significant neuropsychiatric events, serious neuropsychiatric events, and events involving psychiatric hospitalization, which is of particular interest to clinicians.

[1] Specific diagnoses were eligible for inclusion and represented major Axis I affective, anxiety, and psychotic diagnoses

Table 1 Clinically Significant Neuropsychiatric (NPS) Events and Serious NPS Events

	Varenicline		Bupropion		NRT		Placebo	
Non-Psychiatric Cohort								
N	975		968		987		982	
Clinically significant NPS	30	3.1%	34	3.5%	33	3.3%	40	4.1%
Serious NPS	1	0.1%	5	0.5%	1	0.1%	4	0.4%
Psychiatric hospitalizations	1	0.1%	2	0.2%	0	0.0%	1	0.1%
Psychiatric Cohort								
N	1007		1004		995		997	
Clinically Significant NPS	123	12.2%	118	11.8%	98	9.8%	95	9.5%
Serious NPS	6	0.6%	8	0.8%	4	0.4%	6	0.6%
Psychiatric hospitalizations	5	0.5%	8	0.8%	4	0.4%	2	0.2%

All active treatments were superior to placebo in helping patients in both cohorts achieve and sustain abstinence from smoking. Chantix demonstrated statistically significantly better quit rates than the other two active medications; confirmation of this finding in both cohorts provides substantial evidence of this finding. Chantix has previously been shown to be superior to bupropion, but this is the first head-to-head comparison with transdermal nicotine to support this conclusion.

Table 2 below illustrates the proportion of patients continuously abstinent from Week 9 of treatment through the end of treatment at Week 12 (CAR 9-12) and the proportion continuously abstinent throughout the follow-up period (Weeks 9-24, CAR 9-24).

Table 2 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - FAS Population

Cohort	Varenicline (%)	Bupropion (%)	NRT (%)	Placebo (%)	Odds ratio V/P	Odds ratio B/P	Odds ratio N/P
Overall							
CAR 9-12	33.5	22.6	23.4	12.5	3.60*	2.06*	2.14*
CAR 9-24	21.9	16.2	15.7	9.4	2.73*	1.88*	1.80*
Non-PHx							
CAR 9-12	38.0	26.1	26.4	13.7	4.00*	2.26*	2.30*
CAR 9-24	25.5	18.8	18.5	10.5	2.99*	2.00*	1.96*
PHx							
CAR 9-12	29.2	19.3	20.4	11.4	3.25*	1.87*	2.00*
CAR 9-24	18.3	13.8	13.0	8.3	2.50*	1.77*	1.65*

V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* p-value <0.001, using a logistic regression with terms treatment, cohort, region, and treatment by cohort interaction, and region by cohort interaction. Region used 2-level classification (US, non-US).
Source: Statistical reviewer Yi Ren

1.3. Benefit-Risk Assessment

This study confirms that clinically significant neuropsychiatric events are not uncommon; in patients with psychiatric history they are frequent. Attempts to stop smoking may play a role in these symptoms because of the effects of nicotine withdrawal on mood and cognition; however, no clear relationship to smoking cessation or reduction was clear from the data. However, unlike the picture emerging from review of the post-marketing reports, it appears that events of a serious nature are less common than suspected.

The study also confirms that all three treatments are effective as aids to smoking cessation. The likelihood of a successful quit attempt is substantially higher than the likelihood of experiencing a serious adverse event of a neuropsychiatric nature. Given the known risks of smoking and benefits of quitting, the benefit-risk ratio is favorable for patients with and without psychiatric diagnoses.

2 Therapeutic Context

2.1. Analysis of Condition

Tobacco dependence is a serious and life-threatening condition due to the well-established link between smoking and cancer and a variety of cardiovascular and respiratory diseases.
Literature has shown that subjects with a current Axis I disorder are more likely to experience tobacco withdrawal symptoms and withdrawal-related discomfort and relapse.
Subjects with Axis I disorders may need more intensive and/or longer treatments to help them cope with withdrawal symptoms and prevent relapse.

2.2. Analysis of Current Treatment Options

Chantix® (varenicline tartrate) is a first in class, new molecular entity (NME) approved as an aid to smoking cessation. Varenicline is a partial nicotinic receptor agonist, selective for the α4β2 nicotinic acetylcholine receptor subtype. NDA 21928 was submitted by Pfizer on 11/11/05 and approved on 5/10/06.

- Trade name: Chantix®
- Drug established name: varenicline tartrate
- Chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1)
- Drug class: partial α4β2 nicotinic receptor agonist
- Indication: aid to smoking cessation in adult smokers. The recommended dose of Chantix is 1 mg orally twice daily following a 1-week titration as follows:

Days 1 – 3	0.5 mg once daily
Days 4 – 7	0.5 mg twice daily
Day 8 – end of treatment	1 mg twice daily

Chantix is supplied as an immediate release film-coated tablet in two strengths, 0.5 mg and 1 mg, and in blister card presentations providing appropriate combinations to initiate and continue treatment.

Table 3. Summary of Treatment Options for Smoking Cessation

DRUGS USED AS AIDS TO SMOKING CESSATION			
Generic/Chemical Name	**Trade Name**	**Sponsor(s)**	**Dosage form(s)**
Nicotine polacrilex	Nicorette gum, chewing (OTC; also generic)	GlaxoSmithKline Consumer Healthcare LP	• Chewing pieces (transmucosal)
Nicotine polacrilex	Nicorette (F/K/A Commit) Lozenge (OTC; also generic) Nicorette Mini-Lozenge	GlaxoSmithKline Consumer Healthcare LP	• Lozenges – buccal delivery system
Nicotine patch	Habitrol (also generic)	Dr. Reddy	• Transdermal • Film, extended release
Nicotine patch	Nicoderm CQ (also generic)*	Sanofi Aventis/Glaxo Smith Kline Consumer Healthcare LP	• Transdermal • Film, extended release
Nicotine oral inhaler	Nicotrol	Pfizer/Pharmacia and Upjohn	• Cartridge with mouthpieces – buccal delivery system
Nicotine nasal spray	Nicotrol	Pfizer/Pharmacia and Upjohn	• Solution with metered spray pump
Bupropion	Zyban	GlaxoSmithKline	• Oral tablets

*Other NDA transdermal products including Nicotrol TD, and ProStep are no longer marketed.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Chantix® (varenicline) is a partial α4β2 acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation. The treatment regimen is 1 mg twice daily for 12 weeks (with an initial one-week titration). A second 12-week course may be taken to increase the chance of maintenance of abstinence.

Bupropion HCl, also studied in the clinical trial supporting this supplement, is an aminoketone antidepressant originally approved under the proprietary name Wellbutrin. As an antidepressant, Wellbutrin is thought to act primarily via noradrenergic mechanisms, but also has some dopaminergic activity. Its mechanism of action as an aid to smoking cessation is not known. The NDA for Bupropion HCl Sustained Release Tablets (marketed under the proprietary name Zyban for this indication) was approved in May 1997.

In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events involving varenicline (approved for marketing in the EU in September 2006 under the name "Champix"). Later that same summer, a fatal case involving bizarre and aggressive behavior by a Chantix-treated patient in the U.S. became highly-publicized. FDA then undertook evaluations of the post-marketing data regarding both cases of suicide and cases of bizarre and aggressive behavior and concluded that there were cases that could be attributed to Chantix treatment. In a number of cases, the reporters provided rich and detailed narratives about the events, describing experiences involving symptoms in a variety of neuropsychiatric domains, including cognition, perception, mood, and general functioning. A series of incremental changes to labeling were made to address the emerging understanding of the nature of the risk. A subsequent review of post-marketing data on Zyban and various nicotine replacement therapies identified similar cases associated with Zyban. A chronology of the regulatory actions and public communications that followed is shown below.

May 2006	NDA approval for varenicline in the U.S. (trade name "Chantix")
September 2006	Approval in the European Union (trade name "Champix")
May 2007	European Medicines Agency informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a postmarketing suicidal-event analysis.
Nov 2007	Information added to ADVERSE REACTIONS section of labeling; Early communication of an ongoing safety review
Jan 2008	Serious neuropsychiatric adverse events information upgraded to the WARNINGS AND PRECAUTIONS section of the labeling
Feb 2008	Public health advisory issued
April 2008	Center Director briefing concerning varenicline and serious neuropsychiatric adverse events: discussed the benefits of varenicline to help patients achieve smoking cessation vs. the risk of serious neuropsychiatric adverse events
May 2008	Added Med Guide-only REMS; issued a postmarketing requirement (PMR) to assess the serious risk of neuropsychiatric symptoms with varenicline; Updated public health advisory; FAA bans use of varenicline by pilots and air traffic controllers
July 2009	Added BOXED WARNING section to varenicline and bupropion labeling; Public health advisory issued regarding addition of boxed warning to both varenicline and bupropion
Oct 2011	Drug Safety Communication issued reporting the results of two FDA-sponsored epidemiology studies that evaluated the risk of serious neuropsychiatric adverse events associated with varenicline

Oct 2014	Joint meeting of Psychiatric Drugs Advisory Committee/Drug Safety and Risk Management Committee to consider removing boxed warning from Chantix label based on meta-analyses and epidemiologic/observational studies. Committee voted to wait until randomized trial results were available.

Initial Postmarketing Safety Reviews

Prior to the addition of the boxed warning for serious neuropsychiatric adverse events, the Division of Adverse Event Analysis II[2] completed two reviews of AERS[3] cases- one focused on suicidality events (finalized July 2008) and the other focused on neuropsychiatric adverse events not related to suicidality (finalized Dec 2008).

Briefly, the review of suicidality events showed that from initial marketing through November 2007, AERS had 262 cases of suicidal-related events for the smoking cessation drugs as shown in the table below. Despite the shortest time on the market, varenicline had the highest number of cases. Median time to event was 8-14 days.

Table 4 Suicide-related Events in AERS, Initial Marketing-2007

	varenicline	bupropion[4]	NRT
# cases	153	75	34
Suicidal ideation (%)	76	61	47
Attempted/completed suicide or other self-injurious behavior (%)	24	39	53

Varenicline had the largest proportion of reports (24%) in which it was explicitly stated that the suicidal event(s) were a first-time significant behavior change from the past, followed by bupropion (15%) and nicotine (none). Varenicline cases had the most reports that described pre-existing disease worsening (17%) compared to nicotine (12%) and bupropion (8%); depression was the most common pre-existing psychiatric condition that worsened for all three drugs. The overall conclusion was that AERS data suggested a possible association between

[2] The Division of Adverse Event Analysis II is now called the "Division of Pharmacovigilance II".
[3] The FDA Adverse Events Reporting System was called "Adverse Event Reporting System (AERS)" at the time these reviews were done.
[4] Bupropion was approved for the treatment of depression as Wellbutrin about a decade before it was approved as Zyban for smoking cessation. In order to limit the review to those exposed to bupropion for the treatment of smoking cessation, included cases had to either reference bupropion by the trade name Zyban, or mention the indication of smoking cessation in the report.

suicidal events and the use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge and a few positive rechallenges, a close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history.

A recommendation was made to add a BOXED WARNING section to highlight the risk of serious neuropsychiatric adverse events and to request a PMR to determine the incidence of serious neuropsychiatric adverse events with varenicline, especially in patients with preexisting psychiatric disorders. For Zyban (bupropion), which was included as a comparator in this review, there was a similar recommendation to add language to the already existing BOXED WARNING section about the risk of suicidality in those using bupropion for smoking cessation.

A review of AERS cases describing neuropsychiatric adverse events other than suicidality was completed in December 2008. Because of the increased awareness that there was "stimulated" reporting[5] starting in September 2007, this review was conducted from market approval through August 2007. Additionally, because there were few evaluable cases reported with nicotine replacement therapies (NRT) the review focused on only case reports for varenicline and bupropion.

For both varenicline and bupropion, anxiety and depression were the two most commonly reported events. For both drugs, ~20% of the cases reported psychosis/mania or aggression-events. For varenicline, the most common event for the psychosis/mania and aggression groups was *hallucination* and *aggression* respectively; for bupropion, it was *paranoia* and *hostility* respectively. There was a temporal association between the two drugs and all groups of events with a median onset time between three and seven days. Positive dechallenge was reported in 33% and 63% of the varenicline and bupropion cases respectively.

For all event groups, patients with no reported psychiatric history ranged from 17 to 33% for varenicline and 13 to 30% for bupropion. For all event groups, patients with no reported concomitant psychiatric medications ranged from 4 % to 13% for varenicline and 0 to 25% for bupropion. There were more cases with varenicline (29-33%) that reported a behavioral change from the patient's past (i.e., either new experience or disease worsening) than with bupropion (0-9%).

More varenicline patients (27%-53%) had a history of psychiatric disease than bupropion (0%-20%); however, there was a portion of the bupropion population for which unknown medical history was very high (78%). The most commonly reported psychiatric history across the case

[5]Stimulated reporting is an increase in adverse event reporting that often occurs following any risk communication or media attention to a particular safety issue due to enhanced awareness.

series was depression and bipolar disorder. Psychiatric medication use ranged from 13% to 73% for varenicline and 21% to 70% for bupropion.

The recommendations included enhancements to the proposed BOXED WARNING section and other parts of labeling to warn of the risk of these other neuropsychiatric adverse events.

The need for a boxed warning was discussed extensively at the highest levels of Center management and it was determined that the events met criteria for placement in a boxed warning. Specifically, because the events were of a serious nature and had adverse consequences that could be prevented by close monitoring.

3.2. Summary of Presubmission/Submission Regulatory Activity

As the understanding of the serious neuropsychiatric adverse events with varenicline evolved, it was determined that a REMS was necessary to ensure that the benefits of varenicline outweighed the risks. In May 2008, FDA issued a letter to Pfizer that required REMS and also included issuance of a postmarketing requirement (PMR) for a clinical trial to assess the known serious risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions related to the use of varenicline products. A similar REMS and PMR for Zyban was required of Glaxo SmithKline.

The design of the study presented a number of challenges. The fundamental problem was that the types of cases reported in the postmarket setting were of a heterogeneous nature and subsumed a variety of disturbing symptoms. Focus on a single endpoint, such as suicide or psychiatric hospitalization, was considered but it was felt that this would miss the full range of neuropsychiatric symptoms that were reported, and additionally, that the sample size for such a study might need to be so large as to be impracticable. Instead, a composite endpoint would be needed that could capture the types of events reported in the AERS cases—events often involving a cluster of emotional, cognitive, perceptual, and behavioral symptoms that were identified by the patient or the patient's family as unusual, out of character, and extremely disturbing.

After internal deliberation and discussion with Pfizer and GlaxoSmithKline (sponsor of bupropion), further guidance on the PMR was issued in a letter dated June 2, 2009. As seen in the description below, FDA determined that a randomized controlled clinical trial would be required to meet the PMR goals:

> A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric adverse events, including but not limited to suicidality, in individuals using varenicline, bupropion, nicotine replacement therapy, or

> placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric adverse events compared to individuals without prior history of psychiatric disorders while using varenicline as an aid to smoking cessation. The study should be sufficiently powered to adequately assess clinically significant neuropsychiatric adverse events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).

The Sponsors were encouraged to collaborate on this trial. Pfizer took the lead on designing and conducting the PMR trial, with financial support and study drug supplied by GSK (who also markets nicotine transdermal products). After a series of discussions internally and with the sponsors, the PMR protocol was found acceptable around July 2010. In recognition of the variable and ill-defined nature of the neuropsychiatric adverse events reported, and the difficulty of capturing such events in traditional MedDRA coding[6], a composite endpoint was developed specifically for the PMR trial and instruments to solicit relevant events were included in the trial procedures. Sixteen main conceptual "components" of the endpoint were agreed-upon in the protocol—however, selection of the specific MedDRA terms were left to to the sponsors to determine and included in the statistical analysis plan (SAP). Following FDA review, some additional terms were identified for inclusion and incorporated into the primary endpoint before the final analysis.

In pre-submission discussions, it was conveyed that the intent for this endpoint was to avoid "noise" by excluding mild events, because some emotional and cognitive symptoms such as irritability and impaired concentration are well-recognized symptoms of nicotine withdrawal. Such symptoms may be expected in patients quitting smoking without pharmacotherapy.

[6] MedDRA (Medical Dictionary for Regulatory Activities) is an international standardized lexicon of medical terms used to code adverse events. MedDRA was developed by the ICH (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and released in 1999. MedDRA contains about 21,000 different preferred terms (PTs, e.g., nausea, hypotension) for various adverse events. These PTs are vertically grouped into 3 levels. The highest level for a PT is the System Organ Class, of which there are 26 (e.g., Cardiac disorders, Infections and infestations). http://www.meddra.org/sites/default/files/guidance/file/intguide_17_1_english.pdf

3.4. Foreign Regulatory Actions and Marketing History

In May 2016, EMA approved a change to the European Summary of Product Characteristics (SmPC; the package insert) for Champix to incorporate the results of the PMR trial and to remove the black triangle symbol that indicates a need for additional safety monitoring.

The text describing the risk of neuropsychiatric symptoms in the updated labeling now reads:

> Neuropsychiatric symptoms
> Changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with CHAMPIX in the post-marketing experience. A large randomised, double-blind, active and placebo-controlled study was conducted to compare the risk of serious neuropsychiatric events in patients with and without a history of psychiatric disorder treated for smoking cessation with varenicline, bupropion, nicotine replacement therapy patch (NRT) or placebo. The primary safety endpoint was a composite of neuropsychiatric adverse events that have been reported in post-marketing experience. The use of varenicline in patients with or without a history of psychiatric disorder was not associated with an increased risk of serious neuropsychiatric adverse events in the composite primary endpoint compared with placebo (See section 5.1 Pharmacodynamic properties - Study in Subjects with and without a History of Psychiatric Disorder). Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal. Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.
>
> History of psychiatric disorders
> Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression). CHAMPIX smoking cessation studies have provided data in patients with a history of psychiatric disorders (see section 5.1). In a smoking cessation clinical trial, neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

Section 5.1 in the SmPC includes a lengthy presentation of the results of the PMR trial as well as a summary of metaanalysis and observational studies pertaining to neuropsychiatric AEs.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Eight sites were inspected, including two sites identified by Pfizer as non-compliant and six other sites selected as a feasible sampling of the 150 sites in the study. The Clinical Inspection Summary confirmed GCP violations at the two Pfizer-identified sites. At Sites 1002 (Wombolt--VAI) and 1077 (Curtis--OAI), a Form FDA 483 was issued for GCP noncompliance. At the remaining six sites, study conduct appeared GCP-compliant and the data appear reliable.

4.2. Product Quality

No new information

4.3. Clinical Microbiology

N/A

4.4. Nonclinical Pharmacology/Toxicology

No new information

4.5. Clinical Pharmacology

No new information was submitted. The following summary of clinical pharmacology is from the package insert.

4.5.1. Mechanism of Action

Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors. The efficacy of Chantix in smoking cessation is believed to be the result of varenicline's activity at α4β2 sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to these receptors.

4.5.2. Pharmacodynamics

Electrophysiology studies in vitro and neurochemical studies in vivo have shown that varenicline binds to α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-

mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to α4β2 receptors than to other common nicotinic receptors (>500-fold α3β4, >3500-fold α7, >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (>2000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.

4.5.3. **Pharmacokinetics**

Absorption/Distribution: Maximum plasma concentrations of varenicline occur typically within 3–4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

Metabolism/Elimination: The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

Pharmacokinetics in Special Patient Populations: There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Renal Impairment: Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min). In subjects with moderate renal impairment (estimated creatinine clearance ≥30 mL/min and ≤50 mL/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min). In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD) undergoing a three-hour session of hemodialysis for three days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 days. The plasma Cmax and AUC of varenicline noted in this setting were similar to those of healthy subjects receiving 1 mg twice daily. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis.

Drug-Drug Interactions: Drug interaction studies were performed with varenicline and digoxin,

warfarin, transdermal nicotine, bupropion, cimetidine, and metformin. No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

In vitro studies demonstrated that varenicline does not inhibit the following cytochrome P450 enzymes (IC50 >6400 ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes in vitro, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

In vitro studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g., metformin) are unlikely to be affected by varenicline.

Use with Other Drugs for Smoking Cessation:

Bupropion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers.

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for NRT alone.

4.6. Devices and Companion Diagnostic Issues

N/A

4.7. Consumer Study Reviews

N/A

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The data in this supplement derives from a single study, Study A3051123.

Table 5. Chantix Supplement 040 Single Study

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
A3051123	Phase 4, randomized, double-blind, active- and placebo-controlled, multi-center, parallel group study designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion hydrochloride 150 mg BID for smoking cessation in subjects with and without a history of psychiatric disorders.	varenicline: 1 mg BID orally bupropion: 150 mg BID orally, NRT 21mg transdermal patch daily x 7 weeks, then 14 mg transdermal patch daily x 2 weeks, then 7 mg transdermal patch x 2 weeks	NPS endpoint: 241 MedDRA preferred terms, mapped to 16 components TEAEs, HADS, C-SSRS, CGI-I, CO-confirmed CA 9-12 weeks, and 9-24 weeks	12 weeks of active treatment followed by 12 weeks of non-treatment follow-up phase	8058 subjects	Subjects that smoke at least 10 cigarettes/day, CO > 10 ppm at screening Px Cohort: stable psych disorder Axis I or II NPx Cohort: no current or history of psychiatric illness	16 countries, 140 centers

5.2. Review Strategy

The supplement provides results from a single study whose primary objective was 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 with and without a diagnosis of psychiatric disorder and to characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).

The primary safety results as well as the efficacy results are described in Section 6. No integrated review of effectiveness was included. The following additional sections and subsections were not relevant to this review and were deleted:

- 4.2 Product Quality
- 4.3 Clinical Microbiology
- 4.4 Nonclinical Pharmacology/Toxicology
- 4.6 Devices and Companion Diagnostic Issues
- 4.7 Consumer Study Reviews
- 7. Integrated Review of Effectiveness
- 8.5 Specific Safety Studies
- 8.6.Additional Safety Explorations
- 8.7 Additional Safety Issues from Other Disciplines

The protocol, conduct, and demographic information for the trial are reviewed in subsection 6.1.2 and the efficacy data are reviewed in section 6.

Section 6.1.2 also contains several additional sensitivity analyses performed in this review, due to several issues regarding data quality and reviewability.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Phase 4, Randomized, Double Blind, Active and Placebo Controlled Multi-Center Study Evaluating the Neuropsychiatric Safety and Efficacy of Varenicline and Buproprion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders

6.1.1. Study Design

Overview and Objective

The purpose of the study was to assess varenicline and bupropion as aids to smoking cessation treatment in subjects with and without an established diagnosis of major psychiatric disorder and to characterize the neuropsychiatric (NPS) safety profile in both of these cohorts. This study was a United States Post-Marketing Requirement (PMR) for varenicline and bupropion and also qualified as a Post-Authorization Safety Study (PASS) in the European Union (EU) for varenicline and bupropion. The population was to be characterized by the presence or absence of an established and stable diagnosis of a major psychiatric disorder, current or past, as defined by the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR).

Primary Safety Objectives:

- 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:
    - With a diagnosis of psychiatric disorder;
    - Without a diagnosis of psychiatric disorder.

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

Primary 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) CAR 9-12 and CAR 9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

Secondary Efficacy Objective:

- To assess if there is a difference between cohorts in the placebo adjusted relative abstinence rates (CAR 9-12 and CAR 9-24) of varenicline and bupropion, separately.

Another secondary objective of the study was to perform the following comparisons with respect to the primary safety and efficacy endpoints:

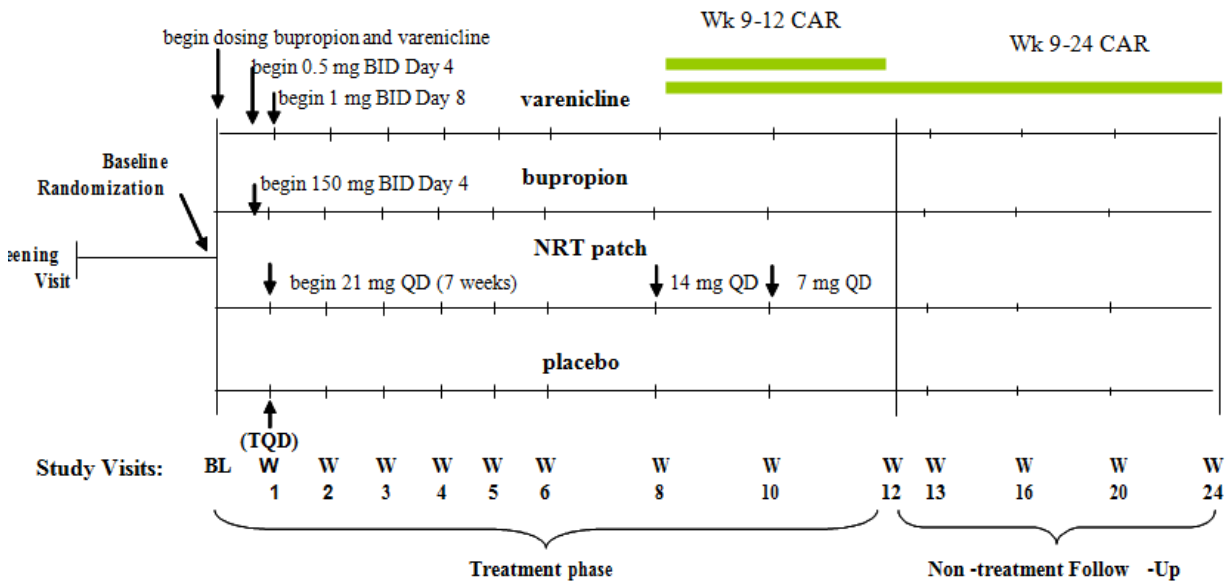
1. NRT vs. Placebo;
2. Varenicline vs. Bupropion;
3. Varenicline vs. NRT;
4. Bupropion vs NRT.

Trial Design

The study was a 24-week, double-blind, NRT and placebo-controlled, multi-center, parallel group study designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion hydrochloride 150 mg BID for smoking cessation. The primary comparisons were to be varenicline vs. placebo and bupropion vs. placebo. NRT was included as active control and study medications were to be given via a triple-dummy design. The duration of active treatment was 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks (Figure 1). Approximately 2000 subjects in each of 4 treatment arms were to be randomized, for a total of 8000 subjects at approximately 200 sites.

Subjects were to be classified into one of the two cohorts—those with an established and stable diagnosis of psychiatric disorder, confirmed by the Structured Clinical Interview for DSM-IV Axis 1 and 2 Disorders (SCID I and II) conducted at screening; and those without a diagnosis of psychiatric disorder. An equal number of subjects with or without a diagnosis of a psychiatric disorder were to be enrolled and randomized among the 4 treatment arms (varenicline, bupropion, NRT, and placebo) in 1:1:1:1 ratio. All clinic visits were in an outpatient clinic setting.

Figure 1. Study Diagram



W = Week; BL = Baseline; TQD = Target quit date; CAR= Continuous abstinence rate

Population and Procedures

Inclusion/Exclusion Criteria

Subjects both with and without a diagnosis of a major psychiatric disorder were eligible for this study. To be included in the non-psychiatric (Non-PHx) stratum, the subject must not have had any previous diagnosis of a psychiatric disorder confirmed by SCID I and II.

To be eligible for enrollment into the study, subjects were required to meet the following criteria:

- Male or female cigarette smokers, 18-75 years, motivated to stop smoking and considered suitable for a smoking cessation attempt.
- Smoked an average of at least 10 cigarettes per day during past year and during the month prior to the screening visit, and exhaled carbon monoxide (CO) >10 ppm at screening.
- Females who are of childbearing potential could be included provided that they were not pregnant or nursing, and agreed to use medically acceptable contraception[7]

Subjects were to be included in the psychiatric cohort, if they were considered clinically stable and met criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and had met diagnostic criteria before the initiation of study treatment.

Psychotic Disorders limited to:

- Schizophrenia
- Schizoaffective

Affective Disorders limited to:

- Major Depression
- Bipolar-I, Bipolar-II

Anxiety Disorders limited to:

- Panic Disorder with or without Agoraphobia
- Post-Traumatic Stress Disorder
- Obsessive-Compulsive Disorder

[7] Oral contraceptive, IUD, implantable or injectable contraceptive for at least a month before entering the study and through 30 days after the last dose; or a double barrier method during the study and 30 days after the last.

- Social Phobia
- Generalized Anxiety Disorder

Personality Disorders limited to past history of:

- Borderline Personality Disorder

Axis I and II diagnosis (current and/or past) were based on DSM IV TR criteria on clinical assessment and confirmed by SCID[8]

- A "current" diagnosis was defined as the subject meeting the established criteria in the prior month
- A "past" diagnosis ("lifetime" diagnosis where applicable) could have occurred anytime in the past medical history

All subjects with an Axis I or II diagnosis were to be judged to be clinically stable including the following:

- No acute exacerbation of their condition in the preceding 6 months
- If on treatment for their condition, must have been on stable treatment for a minimum of 3 months (e.g., stable drug and dose 3 months)
- No change in treatment was anticipated for the duration of the study
- In the opinion of the Investigator, the patient was not at high risk of self-injury or suicidal behavior
- In the event the Investigator was not a mental health professional (MHP), the subject was to be evaluated by a MHP to confirm the SCID I or II diagnosis and determine if the subject was stable. A MHP must be a psychiatrist or licensed PhD level clinical psychologist. A subject who required new treatment or was judged not to be clinically stable was not randomized.

Subjects who did not meet study inclusion criteria could be re-screened if deemed clinically stable at a later date.

Subjects who presented with a past or present diagnosis of any of the following disorders were to be excluded from the study:

- Schizophreniform Disorder
- Delusional Disorder

[8] Administered by a clinician or a qualified person trained in clinical mental health, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social worker] who have been trained to use the SCID2).

- Psychotic Disorder NOS
- All Delirium, Dementia, and Amnestic and Other Cognitive Disorders
- All Substance-Induced Disorders (Other than nicotine)
- All Factitious Disorders
- All Dissociative Disorders
- All Impulse Control Disorders
- Evidence of substance abuse/misuse or dependence severe enough to compromise the subject's ability to comply with the study requirements
- Subjects with antisocial, schizotypal, or any other personality disorder severe enough to compromise the subject's ability to comply with the study requirements
- Subjects with a past history of a comorbid condition listed in the above Exclusion Criteria were considered for inclusion in the study and placed in the "psychiatric stratum" if the subject was:
  - Concurrently diagnosed with an inclusionary diagnosis
  - Considered to be in sustained full remission for substance abuse or misuse (no criteria for abuse or dependency being met in the last 12 months), and the patient was not taking agonists or partial agonists (i.e., methadone, buprenorphine).

If the subjects described above (exclusionary co-morbid psychiatric condition) did not meet a primary diagnosis listed in inclusion criteria of the psychiatric arm, they were not to be eligible for the study. Subjects who met a primary diagnosis listed in the inclusion criteria of the psychiatric arm, and who had a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) were considered to be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent condition was stable and did not prevent the subject from safely complying with study procedures.

Subjects were also excluded for:

- Pregnancy or nursing
- Having an Axis I diagnosis according to DSM IV TR criteria, a rating of 5 or higher on the Clinical Global Impression- Severity (CGI-S)
- Being at risk for suicide at screening, baseline, or after assessment by a qualified MHP-(Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Suicidal ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS
- Previous history of suicide behaviors in the past year
- Displaying self-injuring behaviors, in the opinion of the investigator

- A positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition
- Taking an investigational drug within 30 days before the Baseline visit and at any time during the study period
- Taking varenicline, bupropion, or NRT within 30 days prior to Baseline visit
- Seizure disorder
- Abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
- Current or prior diagnosis of anorexia or bulimia nervosa
- Taking a monoamine oxidase (MAO) inhibitor within the past fourteen days (prior to the Baseline visit)
- Taking the following narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (eg, propafenone, flecainide), thioridazine.
- Intending to donate blood or blood components while receiving study drug or within 1 month of the completion of the treatment phase of the study
- Severe chronic obstructive pulmonary disease (COPD)[9]
- A recent (<5 years) history of cancer. Subjects with a remote (>5years) history of cancer were to be considered pending discussion with the study clinician. Subjects with cured basal cell or squamous cell carcinoma of the skin were allowed.
- Evidence or history of clinically significant allergic reactions to drugs (e.g., severe cutaneous and/or systemic allergic reactions).
- SGOT (AST) or SGPT (ALT) greater than 3 times the upper limit of normal (ULN) or total bilirubin greater than 2 times the ULN.
- Clinically significant cardiovascular disease in the past 2 months[10]
- Clinically significant cerebrovascular disease (CVA, TIA) in the past 2 months.
- Not agreeing to abstain from using non-cigarette tobacco products (including, e.g., pipe tobacco, cigars, snuff, chewing tobacco, hookah, etc.) or marijuana during study participation.
- Not agreeing to abstain from using nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during study participation (both the treatment phase and the post-treatment follow-up).
- Previously experiencing an adverse drug reaction that the investigator considered potentially due to treatment with any of the active drugs in this study.

[9] Defined as any subject who fulfills any of the following criteria: History of repeated exacerbations of COPD (greater than or equal to 3 in 3 years); Requires systemic corticosteroid maintenance (eg, oral prednisolone) for management of chronic symptoms;Is maintained on oxygen therapy for management of chronic symptoms.
[10] Myocardial infarction; Coronary artery bypass graft (CABG); Percutaneous transluminal coronary angioplasty (PTCA); Severe or unstable angina; A serious arrhythmia; Clinically significant ECG conduction abnormalities; Hospitalizations for heart failure.

- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
- Taking a concomitant medication that was prohibited by this protocol
- Skin conditions resulting in red, broken or irritated skin that may hinder the use of the nicotine replacement therapy (NRT) patch

Disallowed concomitant medications included:

- Drugs containing bupropion
- Varenicline (Chantix®/Champix®)
- Nicotine replacement therapy and other aids to smoking cessation
- Naltrexone
- Insulin
- Theophylline
- Warfarin
- Monoamine oxidase (MAO) inhibitors
- Over the counter and prescribed stimulants and anorectic agents
- Narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (e.g., propafenone, flecainide), thioridazine
- Milnacipran (Savella)

Procedures

The study began with a screening period of 3-14 days.. Results of screening laboratory evaluations and the electrocardiogram were reviewed during this period to assure subject eligibility. Determination of diagnosis of a psychiatric disorder for each subject was to be confirmed at screening using DSM IV TR based on clinical assessment and confirmed by SCID I and II.

Subjects who met all inclusion criteria at the screening visit then progressed to the baseline visit. At the baseline visit only those subjects who continued to meet all other criteria were to be randomized. A computer-generated randomization schedule was to be used to assign subjects to treatment, with two-level stratification by the presence or absence of a diagnosis of psychiatric disorder. An equal number of smokers were enrolled in each of the two cohorts. When the planned enrollment was achieved in one of the cohorts, enrollment was to continue only into the other cohort until recruitment goals were reached.

Within the cohort with a diagnosis of a psychiatric disorder, treatment assignment was stratified with respect to the four major diagnosis groups (Psychotic, Affective, Anxiety and Personality Disorders).

The 12-week placebo controlled treatment period had periodic clinic visits for safety and efficacy assessments and smoking cessation counseling. There were weekly clinic visits up to and including Week 6 and then biweekly clinic visits between Week 6 and Week 12. On weeks with no scheduled clinic visits, telephone contact visits occurred to collect smoking status.

During the active treatment phase, varenicline and bupropion dosing began on the Baseline day with a one-week titration followed by 11 weeks of 1 mg BID and 150 mg BID respectively. NRT dosing began at the Week 1 visit with a 21 mg patch per day for 7 weeks, followed by a 14 mg patch per day for 2 weeks, and then a 7 mg patch for 2 weeks. All subjects were to set a target quit date (TQD) to coincide with the Week 1 visit. The Week 1 visit occurred at the end of the first week of the treatment phase (Day 8).

STUDY TREATMENTS

The study utilized a triple-dummy design as shown in Table 3 (below). Subjects randomized to one of the three active dosing groups were to take that active medication and the other two medications in matching placebo form. Subjects randomized to placebo were to receive matching placebo for varenicline, bupropion, and NRT, and follow the same titration and dosing schedules as those randomized to each of the active medication groups. Because both varenicline and bupropion are initiated before quit day while NRT is initiated on quit day, during the first week of treatment no patches were applied. All subjects began their transdermal medication (active or placebo) in Week 2.

Table 6. Dosing Schedule (Protocol)

Treatment Group	Day 1-3	Day 4-7	Week 1*-8	Week 8-10	Week 10-12
Varenicline (V)	0.5 mg V QD 1 placebo B QD	0.5 mg V BID 1 placebo B BID	1 mg V BID 1 placebo B BID 1 placebo NRT QD	1 mg V BID 1 placebo B BID 1 placebo NRT QD	1 mg V BID 1 placebo B BID 1 placebo NRT QD
Bupropion (B)	150 mg B QD 1 placebo V QD	150 mg B BID 1 placebo V BID	150 mg B BID 1 placebo V BID 1 placebo NRT QD	150 mg B BID 1 placebo V BID 1 placebo NRT QD	150 mg B BID 1 placebo V BID 1 placebo NRT QD

NRT patch	1 placebo V QD 1 placebo B QD	1 placebo V BID 1 placebo B BID	21mg NRT QD 1 placebo V BID 1 placebo B BID	14 mg NRT QD 1 placebo V BID 1 placebo B BID	7 mg NRT QD 1 placebo V BID 1 placebo B BID
Placebo	1 placebo V QD 1 placebo B QD	1 placebo V BID 1 placebo B BID	1 placebo V BID 1 placebo B BID 1 placebo NRT QD	1 placebo V BID 1 placebo B BID 1 placebo NRT QD	1 placebo V BID 1 placebo B BID 1 placebo NRT QD

*On day of Week 1 visit, the varenicline dose will be taken as 2-0.5 mg tablets (or 2 placebo varenicline tablets) in the AM and 1 mg tablet (or 1 placebo varenicline tablet) in the PM.

Dosing Regimens:

- Subjects randomized to varenicline were 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.
- Subjects randomized to bupropion received 150 mg QD x 3 days and then took 150 mg BID for the remainder of the treatment period (11 weeks and 4 days).
- Subjects randomized to 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.

Dosing was to occur with 240 ml of water and it was recommended that subjects eat prior to dosing. It was recommended that there be at least 8 hours between the morning and evening dosing.

Dosing continued until the Week 12 visit. All subjects were then to be followed for an additional 12 weeks in the non-treatment phase of the protocol. At the discretion of the Investigator, dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may have been reduced, temporarily discontinued or stopped for subjects who had intolerable adverse events (e.g., nausea); or for subjects who in the opinion of the Investigator required a dose reduction due to use of concurrent medications.

If a subject endorsed suicidality on items 4, 5 or to any behavioral question on the CSSRS, the subject was to have a risk assessment by a qualified mental health professional to determine whether it was safe to continue active dosing in the trial. In the event the risk assessment could not be immediately performed, it would be at the discretion of the Investigator to determine if study drug was to be discontinued (temporarily or permanently) until the risk assessment was completed.

Study drug was to be discontinued immediately for any female subject who became pregnant during the treatment period of the study.

A dose reduction for tablet medication was performed by decreasing both blinded tablet medications to once per day dosing. If a dose reduction was required, both blinded tablet medications were to be reduced at the same time. Dosing with blinded NRT (NRT or matching placebo) may have been temporarily discontinued or stopped for subjects who had intolerable adverse events. It was not possible to reduce the dose of blinded NRT. If any of the study drugs needed to be permanently discontinued then all 3 blinded study medications (varenicline/placebo, bupropion/placebo, and NRT/placebo) were to be permanently discontinued.

Subjects who discontinued treatment were to be encouraged to continue participation in the study and all planned assessments/evaluations. Such subjects were referred to as "OTIS" (off-treatment, in study). If a subject withdrew from the study, but did not withdraw consent, he/she was to be contacted at the end of the trial to assess vital status/cardiovascular events. If the subject withdrew from the study, and also withdrew consent for disclosure of future information, no further evaluations were to be performed, and no additional data was to be collected. All reasonable efforts were to be made to contact subjects who are lost to follow up to ascertain their reason(s) for not continuing in the study. A determination was to be made that they are truly lost to follow up and not withdrawing for another reason (e.g., adverse event or lack of efficacy).

Allocation to Treatment

Subjects were to be stratified by diagnosis of psychiatric disorder or lack thereof and then randomized to varenicline, bupropion, NRT, or placebo in a 1:1:1:1 ratio. Overall enrollment was to be equal for the two cohorts (and within the cohort with a diagnosis of psychiatric disorder, balanced with respect to the major diagnosis groups). Investigators obtained subject identification numbers and study drug assignments utilizing a web-based or telephone call-in drug management system as directed by the sponsor. Identification numbers for the subjects were to be provided at the screening visit.

Behavioral Treatment

Smoking cessation counseling up to 10 min duration was to be provided at each clinic visit consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines beginning at Baseline, then during the treatment and non-treatment periods. The counseling was 1:1, and individually tailored to each subject's needs. Whenever possible, counseling was conducted by the same counselor throughout, so that the relationship was built and brought additional value to the sessions.

Participants were expected to abstain from the use of tobacco products such as pipe tobacco, cigars, snuff, chewing tobacco, hookah, and the use of marijuana. Subjects were expected to

refrain from using any form of nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during both the treatment and non-treatment follow-up phases.

The following time-and-events tables illustrate the planned schedule of assessments.

Table 7 Schedule of Activities- Study Treatment Period

Procedure	Screen	BL	Wk 1 (Day 8)	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7*	Wk 8	Wk 9*	Wk 10	Wk 11*	Wk 12	ET[a] 1
Informed Consent[b]	X														
Medical History, Cardiovascular Medical History, Demography, Smoking history/ height	X														
Physical Examination	X														
Vital Signs (PR, BP)		X	X	X	X	X	X	X		X		X		X	X
Weight		X												X	X
SCID I and II	X														
Adverse Events Volunteered reporting		X	X	X	X	X	X	X		X		X		X	X
Concomitant Medications and Non-Drug Treatment	X	X	X	X	X	X	X	X		X		X		X	X
CGI-S	X	X													
CGI-I			X	X	X	X	X	X		X		X		X	X
HADS		X	X	X	X	X	X	X		X		X		X	X
Aggression Questionnaire		X													
Neuropsychiatric Adverse Event Interview (NAEI)		X	X	X	X	X	X	X		X		X		X	X
SBQ-R	X														
C-SSRS	X	X	X	X	X	X	X	X		X		X		X	X
NUI		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fagerström Test	X														
Exhaled CO	X	X	X	X	X	X	X	X		X		X		X	X
Dispense Study Drugs		X	X	X	X	X	X	X		X		X			
EKG	X													X	X
CBC, Blood Chemistry	X													X	X
Pregnancy Test[c] (urine or serum)	X	X	X	X	X	X	X	X		X		X		X	X
Urine Drug Screen[d] (dipstick at site)	X	X													
Emergency Contact Information Card		X													
Counseling (≤10 minutes)		X	X	X	X	X	X	X		X		X		X	X
Psychiatric Evaluation[e]	X	X	X	X	X	X	X	X		X		X		X	X
Collect cardiovascular events of interest			X	X	X	X	X	X	X	X	X	X	X	X	X

* Designates telephone visit
[a] If ET is before the Week 12 visit.
[b] Must be signed prior to any protocol procedures being performed.
[c] All females unless surgically sterilized or at least 2 years postmenopausal.
[d] May be performed at other visits at investigator's discretion.
[e] If deemed needed per protocol section 7.1.10.

Table 8. Schedule of Activities- Post Treatment Period

Procedure	Wk 13	Wk 14*	Wk 15*	Wk 16	Wk 17*	Wk 18*	Wk 19*	Wk 20	Wk 21*	Wk 22*	Wk 23*	Wk 24	ET[a] 24
Vital Signs (PR, BP)	X			X				X				X	X
Weight												X	X
Adverse Events Volunteered reporting	X			X				X				X	X
CGI-I	X			X				X				X	X
HADS	X			X				X				X	X
Neuropsychiatric Adverse Event Interview	X			X				X				X	X
C-SSRS	X			X				X				X	X
NUI	X	X	X	X	X	X	X	X	X	X	X	X	X
Exhaled CO	X			X				X				X	X
Concomitant Medications and Non-Drug Treatment	X			X				X				X	X
Counseling (≤10 minutes)	X			X				X				X	X
Psychiatric Evaluation[b]	X			X				X				X	X
Collect cardiovascular events of interest	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[c] (urine or serum)				X									

* Designates telephone visit.
[a] If ET is after Week 12 visit and before Week 24 visit.
[b] If deemed needed per protocol section 7.1.10.
[c] All females unless surgically sterilized or at least 2 years postmenopausal.

The following assessments were used to collect information about patient experiences:

- Hospital Anxiety and Depression Scale (HADS) at baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24
  - 14 individual item responses, ranging in increasing severity from 0 to 3.
  - Anxiety subscale score (sum of the 7 odd-numbered item response scores; ranges: 0-7 = normal, 8-10 = suggestive, 11-21 = probable).
  - Depression subscale score (sum of the 7 even-numbered item response scores; ranges: 0-7 = normal, 8-10 = suggestive, 11-21 = probable).
- C-SSRS at baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24.
- Clinical Global Impression of Improvement (CGI-I) at Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24
  - A single item response (a 7-point rating, with 4 being no change and 1 to 3 being levels of improvement and 5 to 7 being levels of worsening).

Figure 2. Neuropsychiatric Adverse Event Interview

)Neuropsychiatric Adverse Events Interview Questions
· Have you felt depressed (sad, blue, down, empty, as if you didn't care)? · Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy? · Have you cried or felt like crying?
· Have you been worried or scared? · Have you been nervous or anxious? · Have you felt panicky at all? · Some people have panic attacks when they suddenly feel very frightened and have physical symptoms like heart palpitations (your heart is pounding and/or beating rapidly), shortness of breath and chest pains. Have you had this?
· Have you had times when you felt extremely agitated? · Have you had times when you felt like you had to be always moving or even pacing?
· Have you felt unusually cheerful, or happy, not just your normal self, so that other people noticed? · Have you had much more energy than usual to do things? · Have you needed less sleep than usual to feel rested?
· Have you felt hostile towards others? · Have you been involved in any serious arguments or fights? · Have you had the urge to injure or harm someone?
· Have you felt that people have been talking about you? · Have you felt that someone may be after you, or trying to harm you in some way?
· Has there been anything unusual about the way things look or sound or smell? · Have you heard things that other people couldn't hear, like noises or voices of people talking when there was no one around? · Have you seen things that other people couldn't see?
· Has your mind been playing tricks on you in any way? · Have you had any ideas that other people might not understand or might find strange?
· Have things seemed unreal to you? · Have you felt that you are detached from or have trouble connecting with other people? · Have you felt strange or unnatural in any other way?

The NAEI (above) was intended to be used as a semi-structured interview, wherein any positive responses would be followed up in order to get a full picture of the context of the symptom, co-

occurring symptoms, and a rich narrative of the event. To accomplish this, the protocol stipulated that NAEI was to be administered by trained interviewers. Follow-up questions were to be used for "clarification, frequency/duration, severity, and degree of functional impairment related to the symptom." Sample follow-up questions were provided in the training materials. The interviewer was instructed to "probe as needed to assess the subject's experiences and to make an appropriate assessment." Narratives were to be constructed for NPS cases that pulled together all relevant information from reporters who could include the patient, significant others, health care providers, or other sources.

When reporting an AE, verbatim text was also to be recorded on a supplemental AE reporting page. Reported events by a household member of the subject, personal physician, or other, that were judged to be AEs by the investigator were to be captured as AEs, and the reporters' verbatim texts of these events were also to be captured.

At each visit, assessments were to be done in the following order:
1. Volunteered AE report – opening question on how the subject has been feeling in general
2. Follow up on previously reported AEs that are still ongoing
3. Clinical rating scales as specified in the protocol
4. NAEI
5. Columbia Suicide Severity Rating Scale.

All assessment instruments used in the A3051123 study were translated into the local language and were administered in that language, and the results were recorded on worksheets that were replicas of the case report forms translated into the local language. Conversations between the site staff and the study subjects regarding their volunteered adverse events and conversations intended to gain more details about the subjects' positive responses on the NAEI were conducted in the local language. The results of those assessments and conversations were then to be translated by the site staff and were entered into the electronic case report form in English.

Safety:

The primary pre-specified safety endpoint was a 16 component composite of the following elements:

- 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.

This composite endpoint includes 241 MedDRA preferred terms in the 16. This endpoint is referred to as the Neuropsychiatric (NPS) endpoint.

Treatment emergent events were defined as events that occurred after the first dose of randomized study treatment and before the last dose of study treatment plus 30 days. Note that this means that the primary NPS endpoint was based on events observed only during the 12 week treatment phase of the trial plus 30 days.

Adverse events were classified as Mild, Moderate or Severe according to the following definitions:

- Mild – does not interfere with subject's usual function.
- Moderate – interferes to some extent with subject's usual function.
- Severe – interferes significantly with subject's usual function.

According to the study protocol, NPS events were collected through any of the following means:

- Volunteered adverse event.
- Actively collected adverse event. NPS events were collected through a neuropsychiatric adverse event interview at each clinic visit.
- Report by a family member and judged to be an adverse event by the investigator.
- Suicide related AEs solicited through the C-SSRS questionnaire at each clinic visit.

Secondary safety endpoints included the components of the NPS endpoint as well as the scores of three questionnaires: Hospital Anxiety and Depression Scale (HADS), Columbia Suicide Severity Rating Scale (C-SSRS), and the Clinical Global Impression of Improvement (CGI-I). Deaths were also analyzed as a secondary safety endpoint of interest.

Efficacy:

The primary efficacy endpoint was the 4-week CO-confirmed continuous abstinence for Weeks 9 through 12.

The primary measures of efficacy were CO-confirmed CA (Continuous Abstinence) from Week 9 through Week 12 (CA 9-12) and CO-confirmed CA from Week 9 through Week 24 (CA 9-24). Smoking status was assessed by use of the Nicotine Use Inventory (NUI) questionnaire, which was administered at each study visit (in-clinic visits and telephone contacts) and confirmed by

CO levels measured at in-clinic visits. Subjects were considered responders (abstainers) if they answered 'no' to questions 1 and 2 on the NUI at each week included in the assessment period and had CO levels $\leq$10 ppm. The questions asked whether the subject had smoked any cigarettes ('even a puff') since the last visit/contact and whether they had used any other nicotine-containing products including other tobacco products and NRT products (other than the study medication) for Weeks 9 through 12, and any tobacco products for Weeks 13 through 24.

Statistical Analysis Plan:

Safety:

The applicant defined two analysis populations:

- Full Analysis Set (FAS). Defined as all randomized subjects from the time of randomization to the last recorded trial visit, regardless of treatment adherence.

- Safety Analysis Population. Defined as all treated subjects (i.e. received at least one partial dose of randomized study drug) from the time of their first dose to the time of their last dose of study drug plus 30 days.

The primary analysis of the NPS endpoint was conducted on the Safety Analysis Population based on events observed only during the 12 week treatment phase of the trial plus 30 days. The primary analysis of the NPS endpoint did not include events observed during the 12 weeks of post-treatment follow-up.

Statistical Power

Trial A3051123 was not designed to rule out a pre-specified risk margin of NPS events. The applicant sized the trial based on the desired precision of the estimated risk difference (RD) for the NPS event comparing varenicline to placebo.

In the cohort with no-prior history of psychiatric disease (Non-PHx cohort), the applicant assumed a true incidence rate (IR) of 3.5 events per 100 subjects in the placebo arm and an IR of 6.13% in the varenicline arm, equivalent to an incidence rate ratio of 1.75. Under these assumptions, and with a sample size of 1,000 subjects per treatment arm in the Non-PHx cohort, the expected RD and corresponding 95% confidence interval for the NPS event comparing varenicline to placebo was 2.63% (0.75%, 4.50%).

In the cohort with a prior history of psychiatric disease (PHx cohort), the applicant assumed a true IR of 7.0% in the placebo arm and 12.25% in the varenicline arm, also equivalent to an incidence rate ratio of 1.75. Under these assumptions, and with a sample size of 1,000 subjects per treatment arm in the PHx cohort, the expected RD and corresponding 95% confidence interval for the NPS event comparing varenicline to placebo was 5.25% (2.34%, 5.52%).

Primary Safety Analysis

The primary safety analysis estimated the risk difference of NPS events for all 6 pairwise treatment comparisons (varenicline - placebo, bupropion - placebo, etc…) by cohort of previous diagnosis of a psychiatric disorder. The risk difference of NPS events was estimated through a

generalized linear model for binary data with an identity link function. The model included covariates for treatment (4 levels), cohort (2 levels), treatment by cohort interaction, and region of randomization (2 levels: USA vs. non-USA). The primary analysis of NPS events was conducted in the safety analysis population defined in Section 3.3.2.1.

The SAP did not pre-specify any safety-related statistical hypotheses to be tested and therefore no p-values for safety outcomes are discussed in this document. The estimated treatment risk differences of NPS events and their corresponding confidence intervals are considered to be descriptive. All confidence intervals for safety endpoints were calculated at a nominal 95% confidence level and no corrections were made for multiple comparisons.

Efficacy

The primary efficacy analysis (CAR 9-12) was evaluated using a logistic regression model on the Full Analysis Set (see definition below). The model included treatment (varenicline, bupropion, NRT, and placebo), cohort (PHx and non-PHx), region (US and non-US), plus the 2-way and 3-way interactions, with possible model reduction by removal of non-significant interaction terms at the 10% level. The analysis of the secondary endpoint, CAR 9-24, was based on the same logistic regression as the primary analysis. The odds ratio (OR) and its 95% confidence interval (CI) were estimated for all pairwise comparisons of treatment groups. This estimation was done both overall and by cohort. The primary efficacy hypotheses were to test the superiority of varenicline versus placebo and bupropion versus placebo, respectively, with respect to CAR 9-12 in PHx and non-PHx cohorts. The key secondary hypotheses were to test the superiority of varenicline versus placebo and bupropion versus placebo, respectively, with respect to CAR 9-24 in each cohort. All other treatment pairwise comparisons were considered secondary hypotheses and were tested using the same scheme as in the primary and key secondary hypotheses. Each hypothesis was tested individually at a 5% level without any adjustment for multiplicity.

Subjects who discontinued the trial or were lost to follow-up were assumed to be non-responder (smokers) for the remainder of the trial. Missing NUI data were imputed using the next non-missing NUI response to the respective question separately for the treatment period and follow-up period. If no response was available, the default imputation was as a non-responder. The protocol stipulated that missing CO values were imputed as negative. This is not the customary approach to analysis of smoking cessation studies. A sensitivity analysis imputing missing values as positive was performed and discussed later.

Protocol Amendments

Eight protocol amendments were documented for this study:
Amendments 1-4 were implemented before enrollment began.
Amendment 1 (dated 17 Jun 2010). The protocol was amended to incorporate changes

requested by the 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. The FDA asked that the following wording be added to the protocol: training and background requirements for administering the SCID; narratives for all moderate events included in the composite primary endpoint; instructions to record all AEs regardless of the mechanism for ascertainment in the AE CRF; description of AE collection using the NAEI, including guidelines to the investigator in the appendix; instructions in the appendices and text to instruct investigators that CGI-S and CGI-I ratings are in reference to psychiatric diagnoses; revision to the additional inclusion criteria for the NPS cohort to specify that both a current condition and a lifetime diagnosis are eligible for inclusion; reference to the pilot study to test the NAEI; and correction on schedule of activities to include C-SSRS assessment at Week 10.

Amendment 2 (dated 28 Jun 2011) amended the protocol to incorporate changes requested by the FDA and the 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.

Amendment 3 (dated 04 Oct 2011) amended the protocol to incorporate changes requested by the FDA. The protocol was amended to include detailed CV medical history, collection of CV events of interest during the study, and a Cardiovascular Event Adjudication Committee (CEAC)[11]. The protocol was also updated to be consistent with updated SOP CT 02 in regard to Section 15.1, Communication of Results to Pfizer.

Amendment 4 (dated 10 Oct 2011) amended the protocol to incorporate changes requested by the EMA for the countries of Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Slovakia, and Spain.
- Subjects with Bipolar I and II disorders were to be excluded from the study.
- The MHP was defined as a psychiatrist only.

Protocol amendments taking effect after enrollment began (amendments 5-8) were administrative in nature, and did not influence the study results. The protocol was reviewed and compared to the study report to ensure all amendments were incorporated. Neither changes in study endpoints, general safety measurements, nor changes in interim assessments were reported.

[11] This amendment was requested in order to gain further insight into a newly-identified concern about cardiovascular safety risk in this large, planned study.

Changes in the analysis plan are noted below:

There was 1 amendment (dated 21 Apr 2015, prior to database lock) to the SAP for Study A3051123. Revisions made included the following:

1) The MedDRA-based definition of the composite primary safety endpoint was updated
   a) to reflect 3 specific MedDRA PT changes from version 14.0 (initial) to version 18.0 (current) at the time of database lock:
   b) to contain 20 additional PTs, classified under the 'feeling abnormal' component, perFDA Advice Letter each requiring an intensity grade of severe.
2) Visit window rules were now included in Appendix 2 of the protocol, in lieu of their prior acknowledgment in a note to file. The Week 24 upper window boundary now extended days beyond Week 24 nominal time to provide greater inclusion of end of study data.
3) Study drug exposure imputation rule was included
4) Language was added regarding the presentation of the primary safety and efficacy endpoints by sub-cohort (according to diagnosis of psychiatric disorder) as a descriptive summary. Added a more detailed summary of multiple AEs included in the primary safety endpoint recorded for a subject.
5) Clarifying language was added regarding model assessment, which included a governing rule that if model convergence or poor diagnostics were evident, region would be assessed.
6) Clinical significance was defined for changes in blood pressure (systolic and diastolic), pulse rate and weight.
7) Clarifying language was added indicating that sample means will not be presented for the CGI-S and CGI-I responses due to a concern with representing these categorically scaled variables in a numerical manner.
8) For the 7-day point prevalence efficacy endpoint, a logistic regression secondary analysis was added for Weeks 12 and 24 as an aid in the interpretation of this endpoint at these key time points.

Data Quality and Integrity: Sponsor's Assurance

Pfizer provided the follwing information regarding data quality and integrity:

> All study sites were initiated during an investigator meeting or a site visit by Pfizer or its designated representative. Rater training for NPS assessments was provided by Worldwide Clinical Trials, Inc. Refresher training was provided to all NPS raters every 6 months during the conduct of the study. Pfizer or its designated representative monitored the study through routine center visits. At these visits, study procedures were reviewed, CRF data were compared with original clinical records, data queries were resolved, and protocol deviations were discussed with the investigator. In addition, the overall study conduct was subject to internal quality review by Pfizer.
>
> The sponsor Compliance Oversight Leads (COLs) provided study and site level oversight to ensure that the

study was delivered to high quality standards. COLs performed on-site and remote oversight to assess monitoring effectiveness and ensure compliance with the study protocol by investigational sites according to ICH/GCP, applicable standard operating procedures (SOPs) and local regulation.

Investigator site audits were performed by Pfizer Medical Quality Assurance at 26 sites: 1002, 1003, 1005, 1025, 1028, 1057, 1062, 1077, 1081, 1086, 1087, 1088, 1108, 1110, 1126, 1144, 1154, 1161, 1174, 1181, 1196, 1208, 1218, 1220, 1228, and 1232. These audits were conducted according to the sponsor's procedures and GCP guidelines. As a result of monitoring visits, compliance oversight visits, and Medical Quality Assurance audits, concerns about the reliability and overall quality of data from US sites 1002 and 1077 were documented. As a result, sensitivity analyses were performed on the primary safety endpoint and the main efficacy endpoint excluding the data from these 2 sites.

A central laboratory was used for all sites. Documentation of laboratory standardization methods and quality assurance procedures are available on request.

An Independent Data Monitoring Committee (IDMC) was established to assess safety data at regular intervals for the duration of the study and to make recommendations to the Executive Steering Committee on whether to continue, modify, or stop the study. An IDMC charter was authored *a priori* and was governed by the IDMC. In addition, the IDMC reviewed blinded 50% and unblinded 75% interim analysis results to determine if the number of NPS AEs was consistent with the planned sample size.

The committee was responsible for ongoing monitoring of the safety of subjects in the study. Any recommendation made by the committee to alter the conduct of the study was forwarded to the sponsor for final decision. The sponsor forwarded such decisions, which could include summaries of aggregate analyses of safety endpoint events, to regulatory authorities, as appropriate

Significant findings reported by Pfizer at two sites are described below.

6.1.3. Study Results

Compliance with Good Clinical Practices

The Sponsor conducted the study adhering to principles of GCP. Their quality management system included on-site monitoring, compliance oversight visits to the study sites, and investigator site audits. A total of 4451 on-site monitoring visits were conducted during the course of the study across all 142 sites that screened subjects**.** A total of 404 compliance oversight visits to assess study site adherence to the protocol and to ensure monitoring practices were completed at 140 sites during the conduct of the study.

Investigator site audits were conducted to assess compliance with GCP, International Conference on Harmonisation (ICH) Guidelines, the study protocol, Pfizer Corporate Policies and Procedures, and Pfizer Standard Operating Procedures (SOPs). Site audits were carried out at the investigator sites and included interviews with the investigator and site staff, facility tours where study activities were conducted, and reviews of source documentation and study subject data. A total of 26 investigator site audits were conducted over the study period (22 routine; 4 directed/for-cause), representing approximately 18% of sites that enrolled subjects. This represents approximately 70% of the top 10% of enrolling sites.

Pfizer's own audits of their clinical sites identified two sites with such significant violations that they concluded the data were not reliable. At these sites, 1002 and 1077, 7 NPS primary events in 105 subjects were reported at site 1002 and 0 events in 31 subjects at site 1077.

At Site 1002, the findings included:

> The Principal Investigator did not provide sufficient or effective support and guidance to his staff to fully oversee this clinical trial. For example, adverse events (AEs) and Neuropsychiatric Adverse Event Interviews (NAEIs) were not properly assessed for causality and severity by the Principal Investigator (PI) in a timely manner.
>
> The site changed data without appropriate substantiation. This occurred for AEs, source documentation, and investigational product (IP) compliance. It was also noted that entries were made more than a year later by site staff after subjects had completed the study, were lost to follow up (LTFU) or withdrawn from the study.

> Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID) data changes were made by the only MHP approved for the study up to 28 months after the original SCID was completed. The approved MHP reviewed the SCIDs for all subjects in the study. After concerns were raised by Pfizer regarding SCID assessments that had been performed at screening by a MHP not approved to work in the study. These reviews with changes involved 26 of 63 subjects randomized to the psychiatric cohort and resulted in 2 subjects no longer meeting study eligibility criteria.

Additionally, other violations observed included inconsistencies between electronic case report forms and source data, missing documents, missing safety assessments and failure to record adverse events, and personnel performing diagnostic interviews, mental health evaluations who did not meet the mental health professional qualification requirements.

At Site 1077, a for-cause audit was performed after the study monitor identified problems such as potentially fabricated weights, unreported AEs, late entry of data into the CRF, incomplete or missing SCID interviews, large gaps between event dates and the date of the PI's signature, signature dates that did not align with the signer's schedule at the site, assessments performed by staff member not approved for these tasks. The for-cause audit identified the following issues:

- Principal Investigator (PI) oversight of study conduct was inadequate in regard to ensuring accurate and complete study data, management of adverse events (AEs), and clinical assessments.

- Source data and documentation was inadequate for consistently confirming data integrity for 11 of 18 subjects reviewed.

- The clinical study was not conducted in accordance with the approved protocol and adherence to the approved protocol could not be confirmed with source data/documentation present at the time of the audit for 4 of 18 subjects reviewed.

- Adverse event (AE) assessment, reporting, and follow-up was inadequate for 5 of 18 subjects reviewed.

- Source data, documentation, and data reported on case report forms (CRFs) were inadequate for 9 of 18 subjects reviewed forms.

- Two (2) of 8 site study staff performed study related procedures and assessments although the procedures/assessments were not in accordance with site staff education, professional training, or scope of practice.

- The training and experience of the site's Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID I and II) ("SCID") Administrator was not in accordance with the approved protocol.

Pfizer reported that six sites had individuals performing the role of MHP (reviewing the SCID for subjects enrolled in the psychiatric cohort to confirm the diagnosis and the stability of the subject and evaluating the subject when needed, such as in the case of positive response on the C-SSRS or depression scores >11 on the HADS) who were not approved for the study because they did not meet study requirements, either based on professional training and experience or on failure to complete study-required training and certification. Pfizer also noted that the results of the SCID were reviewed by staff of Worldwide Clinical Trials before subjects could be randomized. Based on these reviews of completed SCIDs, 22 sites had individuals who required retraining on performing the SCID.

Office of Scientific Investigation inspections of the two problematic sites were requested and the significant violations were confirmed, with the data at Site 1077 in particular identified as unreliable. At Site 1002, the inspection noted that NPS adverse event monitoring may not have been GCP-compliant. Six other sites were also selected for inspection based on issues such as enrollment, reported protocol violations of unqualified personnel performing the MHP, or monitors noting that retraining was required for personnel performing the SCID. The inspection did not identify significant concerns.

Financial Disclosure

Seven investigators at six sites received payments in excess of $25,000 from Pfizer between November 2011 and October 2015. Of these, two reported multiple payments that represented an ongoing participation as a consultant or speaker. (One of these two investigators was the PI at Site (b) (6).)

On request, Pfizer identified other investigators with such a relationship. Investigators in 32 sites received payments from Pfizer that were either in excess of the $25,000 threshold for reporting to FDA or were received as part of speaking services related to CHANTIX (12 of 32 sites) and/or other products marketed by Pfizer (21 of 32 sites). We conducted sensitivity analysis of the primary NPS event excluding these 32 sites and found no difference in the overall conclusions.

Patient Disposition[12]

A total of 11,186 subjects were screened for participation in the study, of which 8144 subjects subjects at 140 investigative centers (in 16 countries) were randomized in an

approximate 1:1:1:1 ratio; 8058 ultimately received treatment distributed as varenicline (n=2016), bupropion (n=2006), NRT (n=2022), and placebo (n=2014). At one site, a single patient was randomized but not treated, so the number sites which treated patients is 139.

Approximately half the subjects (4260) were randomized at 65 sites in the US. Participating sites were located in the following countries. A complete listing of sites, investigators, and enrollment by center is found in the Appendix.

Table 9 Enrollment by Country

Country	Sites Enrolling Subjects	Number of Subjects Randomized
Argentina	2	333
Australia	2	57
Brazil	4	21
Bulgaria	10	490
Canada	6	279
Chile	2	17
Denmark	2	113
Finland	6	505
Germany	7	892
Mexico	4	188
New Zealand	1	125
Russian Federation	9	126
Slovakia	5	202
South Africa	9	296
Spain	6	240
United States	65	4260

Sites included contract research organizations (CROs), general medical centers, and specialty psychiatric centers. Sites enrolled as few as 1 and as many as 287 subjects. Some sites had 15 or more sub-investigators while at other sites, only one or two people were involved in administering the protocol. At one US site, 41 individuals were listed as sub-investigators.

As shown in the tables below, the proportion of subjects who were followed until the completion of the trial at 24 weeks was approximately 78% in both cohorts. The proportion of subjects who completed the 12 week treatment phase of the trial was approximately 79%

[12] N.B., Patient disposition tables and demographic tables include patients from the two excluded sites. These sites enrolled no more than 2% of any treatment group and are not expected to change the overall descriptive information.

among subjects in the non-PHx cohort and 74% in the PHx cohort. The two most common reasons given for study discontinuations were being "no longer willing to participate in the study" (11.0%) and being "lost to follow-up" (6.6%). Subjects in the Non-PHx cohort randomized to placebo were more likely to discontinue treatment due to being "no longer willing" (8.9%) and less likely to discontinue treatment due to adverse events (2.6%) than subjects randomized to varenicline, bupropion, or NRT. Subjects in the PHx cohort randomized to placebo were more likely to discontinue treatment due to being "no longer willing" (8.2%) than those randomized to any of the three active treatments (6.5%).

Table 10. Disposition in the Non-PHx Cohort

	Pooled	Varenicline	Bupropion	NRT	Placebo
Treated	**3984**	990	989	1006	999
Completed Study (24 wks)	**3124 (78.4%)**	787 (79.5%)	783 (79.2%)	767 (76.2%)	787 (78.8%)
Discontinued Study:					
No longer willing	**439 (11.0%)**	94 (9.5%)	103 (10.4%)	118 (11.7%)	124 (12.4%)
Lost to follow-up	**266 (6.7%)**	68 (6.9%)	67 (6.8%)	72 (7.2%)	59 (5.9%)
Completed Treatment (12 wks)	**3145 (78.9%)**	793 (80.1%)	772 (78.1%)	777 (77.2%)	803 (80.4%)
Discontinued Treatment:					
No longer willing	**292 (7.3%)**	61 (6.2%)	63 (6.4%)	79 (7.9%)	89 (8.9%)
Adverse Events	**230 (5.8%)**	57 (5.8%)	74 (7.5%)	73 (7.3%)	26 (2.6%)

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt and Subevg.xpt

Table 11. Disposition in the PHx Cohort

	Pooled	Varenicline	Bupropion	NRT	Placebo
Treated	**4074**	1026	1017	1016	1015
Completed Study (24 wks)	**3169 (77.8%)**	811 (79.0%)	803 (79.0%)	790 (77.8%)	765 (75.4%)
Discontinued Study:					
No longer willing	**446 (10.9%)**	101 (9.8%)	115 (11.3%)	106 (10.4%)	124 (12.2%)
Lost to follow-up	**266 (6.5%)**	67 (6.5%)	59 (5.8%)	72 (7.1%)	68 (6.7%)
Completed Treatment (12 wks)	**3023 (74.2%)**	772 (75.2%)	765 (75.2%)	761 (74.9%)	725 (71.4%)
Discontinued Treatment:					
No longer willing	**281 (6.9%)**	62 (6.0%)	70 (6.9%)	66 (6.5%)	83 (8.2%)
Adverse Events	**388 (9.5%)**	108 (10.5%)	101 (9.9%)	85 (8.4%)	94 (9.3%)

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt and Subevg.xpt

Table of Demographic Characteristics

Selected demographic and baseline characteristics of the subjects are shown in the tables below.

Table 12 Summary of Baseline Characteristics (Non-PHx Cohort) – Safety Population

Baseline Characteristics	Varenicline (N = 990)	Bupropion (N = 989)	NRT (N = 1006)	Placebo (N = 999)
Age (years)				
Mean (SD)	45.8 (13.0)	46.0 (13.0)	46.1 (12.8)	45.9 (12.8)
Min, Max	18, 73	18, 75	18, 75	18, 74
Gender[a], n (%)				
Male	510 (51.5)	503 (50.9)	497 (49.4)	489 (48.9)
Female	480 (48.5)	486 (49.1)	509 (50.6)	510 (51.1)
Race, n (%)				
White	819 (82.7)	820 (82.9)	837 (83.2)	817 (81.8)
Black	135 (13.6)	116 (11.7)	127 (12.6)	126 (12.6)
Asian	14 (1.4)	16 (1.6)	13 (1.3)	19 (1.9)
Other	22 (2.2)	37 (3.7)	29 (2.9)	37 (3.7)
Weight (kg)				
N	980	984	1000	992
Mean (SD)	80.0 (19.5)	80.4 (20.1)	81.6 (19.6)	80.6 (19.3)
Min, Max	39.8, 176.8	40.5, 171.5	38.4, 201.8	42.0, 169.2
Prior psychiatric medications, n (%)				
Psychoanaleptics	27 (2.7)	27 (2.7)	33 (3.3)	36 (3.6)
Psycholeptics	61 (6.2)	58 (5.9)	68 (6.8)	73 (7.3)
Total number of years subject smoked				
Mean (SD)	27.8 (12.8)	28.2 (13.0)	28.2 (12.8)	28.2 (12.6)
Min, Max	2, 64	2, 60	1, 63	2, 62
Total number of lifetime serious quit attempts[b]				
None, n (%)	181 (18.3)	181 (18.3)	174 (17.3)	204 (20.4)
≥1 previous serious quit attempt, n (%)	809 (81.7)	808 (81.7)	832 (82.7)	795 (79.6)
Mean (SD)	3.3 (13.8)	3.4 (10.3)	3.1 (4.2)	3.2 (7.4)
Min, Max	0, 400	0, 300	0, 31	0, 108
Previous use of medication for quit attempt (most recent attempt), n (%)				
Varenicline	132 (13.3)	144 (14.6)	152 (15.1)	136 (13.6)
Bupropion	92 (9.3)	91 (9.2)	93 (9.2)	90 (9.0)
NRT	272 (27.5)	307 (31.0)	325 (32.3)	305 (30.5)
Average number of cigarettes per day over the last month prior to study entry				
N	990	989	1005	999
Mean (SD)	20.8 (8.3)	20.6 (7.8)	20.8 (8.2)	20.5 (7.9)
Min, Max	10, 80	6, 60	10, 60	10, 60
FTND (Total Score)				
N	989	987	1006	998
Mean (SD)	5.49 (1.98)	5.50 (2.02)	5.56 (1.95)	5.51 (2.01)
Min, Max	0, 10	0, 10	0, 10	0, 10
C-SSRS Lifetime				
n (%)	49 (4.9)	44 (4.4)	52 (5.2)	49 (4.9)
HADS (Total Score)				
Mean (SD)	4.35 (4.44)	4.08 (4.09)	4.20 (4.11)	4.50 (4.33)
Min,Max	0,28	0,24	0,25	0,22

Abbreviations: C-SSRS = Columbia–Suicide Severity Rating Scale; FTND = Fagerström Test for Nicotine Dependence; HADS = Hospital Anxiety and Depression Scale

a. The gender for 4 subjects randomized to treatment was inaccurately recorded (see ERRATA). b. Serious quit attempt = more than 24 hours.
c. Positive C-SSRS response for suicidal behavior or/and ideation.
Source: Pfizer's Section 14, Tables 14.1.2.1, 14.1.2.4, 14.1.2.6.1, 14.1.2.6.2, 14.1.2.6.3, 14.1.2.9.1, 14.4.3, 14.5.1.1, and

14.5.2.

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Table 13 Summary of Baseline Characteristics (PHx Cohort) – Safety Population

Baseline Characteristics	Varenicline (N = 1026)	Bupropion (N = 1017)	NRT (N = 1016)	Placebo (N = 1015)
Age (years)				
Mean (SD)	47.2 (11.8)	46.7 (12.2)	47.6 (11.5)	46.9 (11.5)
Min, Max	18, 74	18, 75	18, 75	18, 75
Gender[a], n (%)				
Male	392 (38.2)	387 (38.1)	384 (37.8)	387 (38.1)
Female	634 (61.8)	630 (61.9)	632 (62.2)	628 (61.9)
Race, n (%)				
White	849 (82.7)	816 (80.2)	804 (79.1)	822 (81.0)
Black	145 (14.1)	165 (16.2)	176 (17.3)	155 (15.3)
Asian	5 (0.5)	10 (1.0)	11 (1.1)	7 (0.7)
Other	27 (2.6)	26 (2.6)	25 (2.5)	30 (3.0)
Unspecified	0	0	0	1 (0.1)
Weight (kg)				
N	1024	1014	1015	1012
Mean (SD)	83.0 (21.5)	82.5 (21.3)	80.8 (20.1)	82.7 (21.3)
Min, Max	43.0, 230.0	43.2, 174.3	39.6, 191.5	44.6, 189.1
Prior psychiatric medications, n (%)				
Psychoanaleptics	423 (41.2)	354 (34.8)	369 (36.3)	380 (37.4)
Psycholeptics	309 (30.1)	298 (29.3)	326 (32.1)	295 (29.1)
Total number of years subject smoked				
Mean (SD)	28.9 (11.8)	28.2 (12.4)	28.9 (11.9)	28.3 (11.6)
Min, Max	2, 60	2, 56	2, 58	2, 56
Total number of lifetime serious quit attempts				
None, n (%)	171 (16.7)	174 (17.1)	165 (16.2)	161 (15.9)
≥1 previous serious quit attempt, n (%)	855 (83.3)	843 (82.9)	851 (83.8)	854 (84.1)
Mean (SD)	3.4 (7.7)	3.5 (6.9)	3.3 (5.3)	3.6 (10.9)
Min, Max	0, 200	0, 100	0, 77	0, 300
Previous use of medication for quit attempt (most recent attempt), n (%)				
Varenicline	149 (14.5)	194 (19.1)	168 (16.5)	161 (15.9)
Bupropion	102 (9.9)	114 (11.2)	101 (9.9)	101 (10.0)
NRT	372 (36.3)	326 (32.1)	356 (35.0)	338 (33.3)
Average number of cigarettes per day over the last month prior to study entry				
Mean (SD)	20.6 (8.0)	20.5 (8.2)	20.8 (9.1)	20.7 (8.2)
Min, Max	5, 70	10, 60	10, 120	10, 70
FTND (Total Score)				
N	1025	1017	1016	1015
Mean (SD)	6.04 (1.93)	6.06 (1.91)	5.96 (1.95)	5.91 (2.02)
Min, Max	0, 10	0, 10	0, 10	0, 10
HADS (Total Score)				
N	1026	1017	1015	1015
Mean (SD)	8.26 (6.45)	8.74 (6.92)	8.37 (6.58)	8.21 (6.22)
Min, Max	0, 30	0, 36	0, 31	0, 36
C-SSRS Lifetime[b]				
n (%)	353 (34.4)	363 (35.7)	339 (33.4)	358 (35.3)

Abbreviations: C-SSRS = Columbia–Suicide Severity Rating Scale; FTND = Fagerström Test for Nicotine Dependence; HADS = Hospital Anxiety and Depression Scale;

a. The gender for 2 subjects randomized to treatment was inaccurately recorded (see ERRATA). b. C-SSRS (positive response for suicidal behavior or/and ideation).
Source: Pfizer's Section 14, Tables 14.1.2.1, 14.1.2.4, 14.1.2.6.1, 14.1.2.6.2, 14.1.2.6.3, 14.1.2.9.1, 14.4.3, 14.5.1.1, and 14.5.2.

Table 14 Summary of Baseline Psychiatric Characteristics (PHx Cohort) - FAS Population

Baseline Psychiatric Characteristics	Varenicline	Bupropion	NRT	Placebo
Primary Diagnosis in SCID, N	1032	1033	1025	1026
Affective disorders, n (%)	734 (71.1)	729 (70.6)	721 (70.3)	726 (70.8)
Anxiety disorders, n (%)	196 (19.0)	201 (19.5)	196 (19.1)	199 (19.4)
Psychotic disorders, n (%)	95 (9.2)	98 (9.5)	99 (9.7)	98 (9.6)
Borderline personality disorder, n (%)	7 (0.7)	5 (0.5)	9 (0.9)	3 (0.3)

Abbreviations: FAS = full analysis set; N = number of subjects randomized to study treatment; n = number of subjects with observation of interest; NRT = nicotine replacement therapy; SCID = Structured Clinical Interview for DSM-IV.
Note: Columns many not add up to 100% due to rounding error.
Source: Section 14, Table 14.2.1.1a and Section 16, Table 16.2.6.11.

The treatment groups were similar at baseline with respect to demographic characteristics and smoking history. About 20% in each arm of the non-PHx cohort and about 16-17% in each arm of the PHx cohort had never made a 24 hour attempt to quit smoking, The group mean scores on the Fagerstrom Test of Nicotine Dependence (FTND) were approximately 5.5 in the non-PHx cohort and 6 in the PHx, denoting a fairly low level of dependence, and some people in each cohort scored 0 on the FTND. The motivation of these patients who had never attempted to quit smoking for enrolling in a clinical trial is not clear.

Of those who had made at least one prior attempt in the NPHx cohort, ~17% had used varenicline on their most recent quit attempt, 11% had used bupropion, and nearly 40% had used NRT. In the PHx cohort, 17-20% of those with a prior quit attempt had used varenicline, about 12% had used bupropion, and 40% had used NRT. The willingness of these experienced patients to enroll in the study suggests that they tolerated the medication previously and may have been at lower risk for serious events. Sensitivity analyses excluding these patients are described below.

Treatment Compliance

The table below from the Sponsor's study report illustrates compliance with study medication

Table 15. Study Drug Compliance by cohort and Treatment Group-Safety Population (Study Report, Table 13)

Compliant to Treatment[a]/Cohort	Varenicline n/N (%)	Bupropion n/N (%)	NRT n/N (%)	Placebo n/N (%)
Overall	1630/2016 (80.9)	1605/2006 (80.0)	1617/2022 (80.0)	1593/2014 (79.1)
Non-Psychiatric History	822/990 (83.0)	807/989 (81.6)	811/1006 (80.6)	829/999 (83.0)
Psychiatric History	808/1026 (78.8)	798/1017 (78.5)	806/1016 (79.3)	764/1015 (75.3)

Abbreviations: N = number of subjects randomized to study treatment who received at least 1 partial dose of study medication; n = number of subjects with observation of interest; NRT = nicotine replacement therapy.
a. Compliance was defined as having any (partial or full) daily dose of study drug for 80% of the planned treatment period (ie, a minimum of 68 days).
Source: Section 14, Table 14.4.1.2.

Protocol Violations/Deviations

Table 16, below, (from Pfizer's table 8 of study report) summarizes the major protocol deviations by issue category and treatment group for the safety population. The most frequently reported major protocol deviations were categorized as inclusion/exclusion criteria (352[4.37%]), disallowed medications (217[2.69%]), and procedures/tests (126[1.56%]).

Table 16. Summary of Major Protocol Deviations by Issue Category and Treatment Group-Safety Population

Issue Category	Total (%) N=8058	Varenicline(%) N=2016	Bupropion(%) N=2006	NRT (%) N=2022	Placebo (%) N=2014
AE/SAE	11 (0.14)	3 (0.15)	3 (0.15)	3 (0.15)	2 (0.10)
Disallowed Medications	217 (2.69)	60 (2.98)	47 (2.34)	52 (2.57)	58 (2.88)
Inclusion/Exclusion Criteria	352 (4.37)	84 (4.17)	96 (4.79)	87 (4.30)	85 (4.22)
Informed Consent	7 (0.09)	1 (0.05)	2 (0.10)	2 (0.10)	2 (0.10)
Treatment	51 (0.63)	7 (0.35)	12 (0.60)	16 (0.79)	16 (0.79)
Procedures/Tests	126 (1.56)	25 (1.74)	35 (1.74)	32 (1.58)	34 (1.69)
Other	49 (0.61)	9 (0.45)	18 (0.90)	6 (0.30)	16 (0.79)

Abbreviations: AE= adverse event, N= number of subjects randomized to study treatment who received at least 1 partial dose of study drug; SAE = Serious Adverse Event.
Tabulations were made based ons ubject counts, so subjects were counted only once per issue category and

major PD designation. Percentages were calculated in reference to N. Source: Section 14, Table 14.1.1.13.1 and Section 16, Table 16.2.2.1.

According to the Sponsor, these errors did not affect the safety of subjects or the interpretation of safety or efficacy results

Review Findings Concerning Data Quality and Reviewability

Review of the submitted data revealed several issues and concerns with data collection, data coding, and data reporting that created obstacles to review and limited the extent to which we can place confidence in the protocol-specified primary endpoint and in certain other analyses, such as tabulations of events in various sub-components of the primary endpoint. The review team performed various sensitivity analyses and identified an alternative approach we believe more accurately captures the rates of clinically significant NPS events, which is described below.

Issues fell into the following broad categories

- Incomplete/inadequate data collection
- Data coding issues
- Data reporting issues
- Issues raising concerns of data reliability

Specific examples of these issues are described below.

Incomplete/inadequate data collection

Ineffective Use of NAEI

The NAEI was intended to be used as a starting point to identify symptoms of potential concern, and then the full description of the patient's experience was to be sought and recorded. The investigator was to determine whether the solicited symptom did or did not qualify as an adverse event. It appears that, at many sites, the NAEI was, instead, used as a checklist. No additional information was recorded beyond the patient endorsing one of the symptoms mentioned. It appears that some sites or investigators may have entered any endorsed symptom into the database as an adverse event. The dataset includes some events where no verbatim term whatsoever is recorded (this was the case at some sites throughout the trial) or where the verbatim is simply the NAEI term (e.g. "moderate agitation") without any context or description. Many narratives are therefore unhelpful in providing insight into the nature of the adverse event or the impact on the patient.

Inadequate Capture of Patient Verbatim

It was expected that the events were to be recorded in the reporter's words, in order to ensure that difficult-to-characterize events were adequately described. Pfizer stated that the "requirement to record subject verbatim terms as part of AE collection was an important and novel aspect of this protocol. Moreover, many site investigators and staff did not have prior experience recording subject verbatims in this manner. Training on how to promptly and accurately record subject verbatims was given at the Investigator Meetings and Site Initiation visits. The importance of the collection of subject verbatims was reinforced and emphasized via newsletters and monitor interactions with the sites. This continued site education improved the collection rate of subject verbatims as the study progressed." At three sites, and sporadically at other sites, no patient verbatim (described in the database as "event as described by reporter" was recorded at all so it is not possible to determine how the investigator verbatim term was selected or how severity was assessed. Frequently, the recorded "event as described by reporter" is a single word (identical to the investigator verbatim term) such as "anxiety," or, at some sites, if the investigator verbatim was "anxiety," the "event as described by reporter" would read "as anxiety." In some cases, the medical monitor instructed the site to rephrase an entry in "event as described by reporter" from third person (i.e., "patient reports…") to first person.

Inadequate Capture of Information About Circumstances of Events

Several narratives had insufficient information to understand the context of the event and whether it occurred in the setting of the type of neuropsychiatric problems that are of interest in the trial. A patient who was killed in a motor vehicle accident is described as having an event of "head-on collision" and information about whether or not the patient was the driver is missing from the narrative.

A subject sustained a fractured skull when her boyfriend (also a trial participant, although per protocol this should not have occurred) hit her in the head with a gun. The narrative for the event (reported for both subjects) does not capture whether this occurred in the context of an altercation, was associated with treatment-emergent symptoms of anger/hostility/aggression, etc., or was otherwise an event of relevance to the NPS primary endpoint.

In one case (b) (6), a subject with a prior psychiatric diagnosis of a single, remote, past episode of major depression and a past diagnosis of obsessive-compulsive disorder who was not symptomatic or ill at baseline, made a suicide attempt one day after completing study treatment (with bupropion) and received a diagnosis of schizoaffective disorder. This was reported as an NPS event. However, no explanation of this diagnosis, which requires the presence of psychotic symptoms over a period of time without affective symptoms, appears to have been sought, and no description of any such symptoms is provided.

Data Coding Issues

Inconsistent Investigator Assessment of Severity

The investigator assessment of severity was intended to distinguish adverse events that reached a certain threshold of interference of a patient's usual functioning. However, some narratives suggest a level of interference in the patient's usual functioning not reflected in the investigator's rating of severity. Some of these cases are included in the NPS primary endpoint because they were assigned codes and severity ratings included in the composite, whereas other cases in which the narratives describe very similar symptoms and impacts are not, either because the term selected is not in the composite (e.g., irritability) or because the investigator rating of severity did not meet criteria for inclusion in the NPS primary endpoint.

In a number of cases, subjects reported events that were coded to terms such as depression and mood disturbance which had a documented interference in their functioning but were only rarely assessed as "severe." Some are assessed as "mild" despite the patient report of missing days of work or other significant impact. A patient (b) (6)) reporting "Severe change in my mood. Low patience for others, no hope for my future. I was more argumentative. I've noticed less pleasure from spending time with my family and my work. I have thought about crying," on treatment Day 31 was not included in the depression component. The patient had a HADS depression score of 14 (from 0 at baseline) and endorsed a wish to be dead on the C-SSRS, but this was rated as "moderate" and not considered treatment-related. This patient, as well as some other similar cases, was flagged as having an NPS events by virtue of a co-occurring symptom (in this case, disturbance in attention) but others who probably should have been flagged as having an NPS event were not.

In reviewing the dataset for events in the domains of interest that were not coded to the NPS endpoint, several cases of events coded to a new psychiatric diagnosis (major depression) in subjects who were in the non-psychiatric cohort were noted. These cases did not meet the "severity" criterion and were not flagged as NPS cases, and no narratives were prepared[13].

These types of cases further underscored the concern that the severity criterion for inclusion in the NPS endpoint may have been inappropriate to capture events of concern. There may have been a disconnect between what subjects with no previous psychiatric issues consider severe (even missing a day of work) and what a health care provider accustomed to caring for seriously mentally ill patients would regard as "severe" (possibly only an event requiring

[13] An example of a case located in review of the verbatim terms in the dataset and *not* coded to the NPS endpoint or selected for construction of a narrative is a case in which the subject reported the following: "I think I am having a major depression. I am worried, I cry easily, I have apathy, I have no desire to do things, insomnia, increased apetite [sic], guilt, I have death thoughts (without suicidal ideation)"

hospitalization). However, even hospitalization may not have been assessed as "severe" by some investigators; an additional case was identified among the SAE narratives, where a subject appears to have been hospitalized for depression after about 3 weeks of treatment with bupropion, but the event was assessed as "mild" by the investigator. ("On 02 Nov 2012, the subject experienced depression which was considered mild in intensity and serious due to hospitalization or prolonged hospitalization by the investigator.")

Because the primary endpoint relied on investigator assessment of severity, which was clearly problematic, our confidence in the analyses based on the protocol-specified primary NPS endpoint is undermined by these findings. An expanded analysis which included patients who experienced events coded as "moderate" but also experienced symptoms captured by other clinical assessments or MHP evaluation is described below.

Lack of Integration of Different Data Streams

Although C-SSRS, HADS, and CGI scores were recorded, patients could have had significant indicators of distress on one or more of these instruments and no adverse event recorded. Patients could also have been evaluated by the MHP and information recorded in the evaluation was not recorded as an adverse event. In some cases (as noted above) a new diagnosis was recorded as an adverse event. A patient without psychiatric history meeting criteria for a new diagnosis of major depression would be considered clinically significant, but such patients were not consistently coded as having an NPS event. Some subjects had AEs reported based on C-SSRS results while others did not. A subject described above who endorsed suicidal ideation during the protocol-specified mental health evaluation prompted by his NPS-endpoint qualifying event was not coded as having suicidal ideation. The expanded analysis attempts to capture these patients.

Inconsistent Mapping of Events to Sub-Components of the Composite

The endpoint was a composite of various emotional, cognitive, and perceptual experiences that subjects might experience because the post-marketing adverse events typically described patients experiencing multiple symptoms simultaneously. However, the coding of events did not facilitate identification of subjects who might have been experiencing a cluster of symptoms. Pfizer's analysis included tabulation of events separated out into categories such as agitation, depression, psychosis, and panic.

Review of the narratives, where sufficient information about the patient report is provided to assess the coding, reveals a number of issues. Overall, the mapping of events to the sub-components was not consistent. There are subjects whose events included a constellation of cognitive and emotional and behavioral experiences but the investigator may not have coded all of the events such that the NPS threshold was reached for all of them. Additionally, there are errors in the assignment of terms to components (for some reason, "dysphoria" is

included in the aggression component), and, unfortunately, there is no cognitive component at all. Cognitive symptoms are included in the “agitation” component.

Therefore, it does not appear helpful or informative to analyze the cases by component of the NPS endpoint.

Inconsistent Application of Coding

Some terms, notably “agitation,” appear to have been applied inconsistently to a variety of symptoms. In a number of cases, there is sufficient information to determine that the term was interpreted to refer to motor agitation (akathisia); in others it refers to emotional upset and distress (which was the intended meaning in the protocol stage). In some cases another term in another component of the NPS endpoint (e.g., “anger”) was stated by the patient but the term “agitation” was chosen for coding. In still other cases, the patient reported insomnia, leading to selection of the term “restlessness” (i.e., the patient was not getting “rest”), which then coded to “agitation”—clearly not what was intended.

For many subjects whose only event is “moderate agitation,” there is virtually no additional information on the event to allow us to understand how that was manifested and in what way it was disruptive to the patient’s functioning (which is what makes it “moderate”). The only information recorded appears to be that the patient endorsed this symptom on the “checklist.”

In some cases, subject verbatim terms containing concepts in NPS endpoint (e.g. “anger”) were coded to terms not in the NPS endpoint (irritability). There are also many subjects with verbatim terms coded to the term “irritability” where the description of the event is identical to other subjects coded to “agitation,” but they are not considered NPS cases. However, it is not possible to re-adjudicate all cases coded to “irritability” because many lack further information. Although irritability was intentionally excluded from the endpoint because of its well-known association with nicotine withdrawal, the expanded analysis included subjects with moderate to severe events coded to “irritability” who also had other indicators of clinically significant findings (e.g., clinical scales or significant findings by MHP). Only a very few patients had irritability as their only symptom.

Miscellaneous Coding Errors

As with any large dataset, other coding errors were identified, such as a case included in the “psychosis” component in which the subject did not experience psychosis. The subject was appropriately included in the NPS endpoint because of suicidal ideation, but the narrative shows that the subject reported being "down and lonely," investigator term was "depressed affect" and this was coded to "flat affect," which is a symptom of psychosis. Similarly, a subject who reported withdrawing from social activity was coded to the term “detachment”

which was interpreted as “flat affect” and therefore psychosis. As noted above, insomnia was sometimes translated to “restlessness” and then to “agitation.” The study was conducted globally in a variety of languages not all site personnel were trained mental health care professionals. This may have complicated the coding of the collected AE data relevant to the NPS endpoint.

Data Reporting Issues

Prior to submitting this supplement, Pfizer provided a final study report and case narratives for Division comment. Initially, the submitted narratives did not include relevant information and provided no insight beyond the MedDRA terms and the timing of the events, along with investigator assessment of relatedness. Even where available, the patient’s own words describing the event were not included in the narrative, or any context/background for the event. Extreme examples of the unhelpfulness of the narratives included the event below, in which the term “skull fracture” is reported in the narrative without providing any context for how the patient came to sustain the skull fracture. (Subsequent information requests revealed the injury was sustained in an altercation with her boyfriend, a potentially relevant piece of information.)

> The subject was randomized to varenicline 1 mg twice a day (BID) treatment, and received the first dose of double blind study drug on 20 Dec 2011. The final dose of study drug was received on 03 Feb 2012 after 40 days of actual treatment. The subject was withdrawn from the study drug on 02 Feb 2012 due to an adverse event of skull fracture and completed the study on 05 Jun 2012.

On (b) (6) 2012, the subject experienced skull fracture which was considered severe in intensity and serious (due to hospitalization or prolonged hospitalization) by the investigator. Study drug was permanently stopped on (b) (6) 2012 due to the event though it resolved on (b) (6) 2012. Concurrent with the event, the subject also experienced moderate ear injury, moderate ear pain, moderate dizziness, mild depression and mild insomnia. The subject underwent suture insertion on (b) (6) 2012 for laceration left ear. The subject received treatment with ondansetron hydrochloride for the nausea on (b) (6) 2012; hydromorphone hydrochloride for the headache/left ear pain from (b) (6) 2012 to (b) (6) 2012; meclozine for the dizziness from (b) (6) 2012 to (b) (6) 2012; cefazolin for the skull fracture from (b) (6) 2012 to (b) (6) 2012; fluoxetine for the situational depression and a dose change for trazodone for insomnia, both since (b) (6) 2012 (and ongoing). The events of ear injury, ear pain and skull fracture resolved on (b) (6) 2012; the dizziness on (b) (6) 2012; and the depression, the headache and the insomnia were still present at the end of the study. The investigator considered the events of ear injury, ear pain, skull fracture, dizziness, depression and headache to be not related to the study drug[14] but due to trauma and the insomnia to be

[14] Investigator assessment of relatedness was guided by directions provided to investigators which appear to have instructed them to provide any plausible alternative explanation. Thus, emotional symptoms were often attributable to “stress” or to specific social situations, worsening symptoms of a pre-existing psychiatric illness

related to head injury.

The review team then asked Pfizer to construct new, more informative narratives for all NPS events. Pfizer had also created narratives for other events they deemed potentially of interest, including traumatic injuries (which could have occurred in the context of violence-related symptoms or cognitive impairment) and some cases coded to terms such as irritability or terms in the endpoint that did not meet the severity threshold; the FDA clinical team reviewed this list and identified cases that needed new narratives to be constructed. New more informative narratives were submitted for all NPS cases and a subset of events of potential interest numbering over 500 cases; these were included with the Supplement. . Review of a sample of approximately 100 case narratives was undertaken. The newly-constructed narratives were improved, but still presented barriers to review. The chronology of different streams of data was presented separately, rather than integrating the scores on clinical assessments and the smoking behavior reported together with the timeline of the adverse events. The information presented was also limited by the problems noted above related to data *capture.* Ultimately, it was determined that it was neither feasible nor possible to attempt to independently adjudicate the cases based on the provided information.

Following submission of the Supplement, the full dataset was also probed to determine whether additional cases that should have had narratives prepared based on the reporter's verbatim or the adverse event coding had been omitted from the group of events of potential interest; it was apparent that many events of potential interest were not flagged, and no narratives had been constructed. As discussed further below, once it became apparent that not all cases of potential NPS events had been identified by the investigators or Sponsors, rather than request multiple additional narratives, certain sensitivity analyses were conducted to estimate the impact of potential NPS events having been omitted.

Issues raising concerns of data reliability

As described above, Pfizer identified two sites that were identified as having significant protocol violations leading to concerns about data reliability. There were also a number of sites at which Pfizer noted that individuals without the appropriate qualifications were performing the role of MHP and sites where investigators needed to be re-trained on administering the SCID. These observations were taken into consideration in choosing sites for inspection by the Office of Scientific Investigations. (See 4.1, above.)

Primary Safety Results

The analyses were conducted by the FDA review team based on the datasets submitted by the Sponsor. The analysis of the safety results was conducted by Dr. Eugenio Andraca-Carerra

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were almost always coded as "not related to study drug," and unhelpful assessments such as "The investigator considered the SAE of foot fracture to be not related to the study drug but due to fractured right heel" were provided. For this reason, investigator assessment of relatedness in the narratives has been altogether disregarded in this review

from the Division of Biometrics 7 (DB7) and much of the text below is from the statistical review.

Analysis of the Primary Neuropsychiatric Event

Table 17 shows the number and proportion of subjects who experienced a treatment-emergent NPS event in the trial by treatment arm and cohort of psychiatric history diagnosis at baseline (PHx and Non-PHx). The observed rate of NPS events among subjects in the Non-PHx cohort was lowest among subjects randomized to varenicline (1.3%) and was similar for subjects randomized to bupropion, NRT, or placebo (2.2% to 2.5%). The observed rate of NPS events in the PHx cohort was highest among subjects randomized to varenicline and bupropion (6.5% and 6.7% respectively) and was lowest among subjects randomized to placebo (4.9%).

Table 17. Primary NPS Endpoint by Cohort of Psychiatric History

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	13 / 990 (1.3%)	22 / 989 (2.2%)	25 / 1006 (2.5%)	24 / 999 (2.4%)
PHx Cohort	67 / 1026 (6.5%)	68 / 1017 (6.7%)	53 / 1016 (5.2%)	50 / 1015 (4.9%)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Figure **3** and

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Figure 4 show the timing of these events, by treatment arm and cohort of psychiatric history diagnosis at baseline (PHx and Non-PHx). Subjects randomized to bupropion or varenicline in the PHx cohort (

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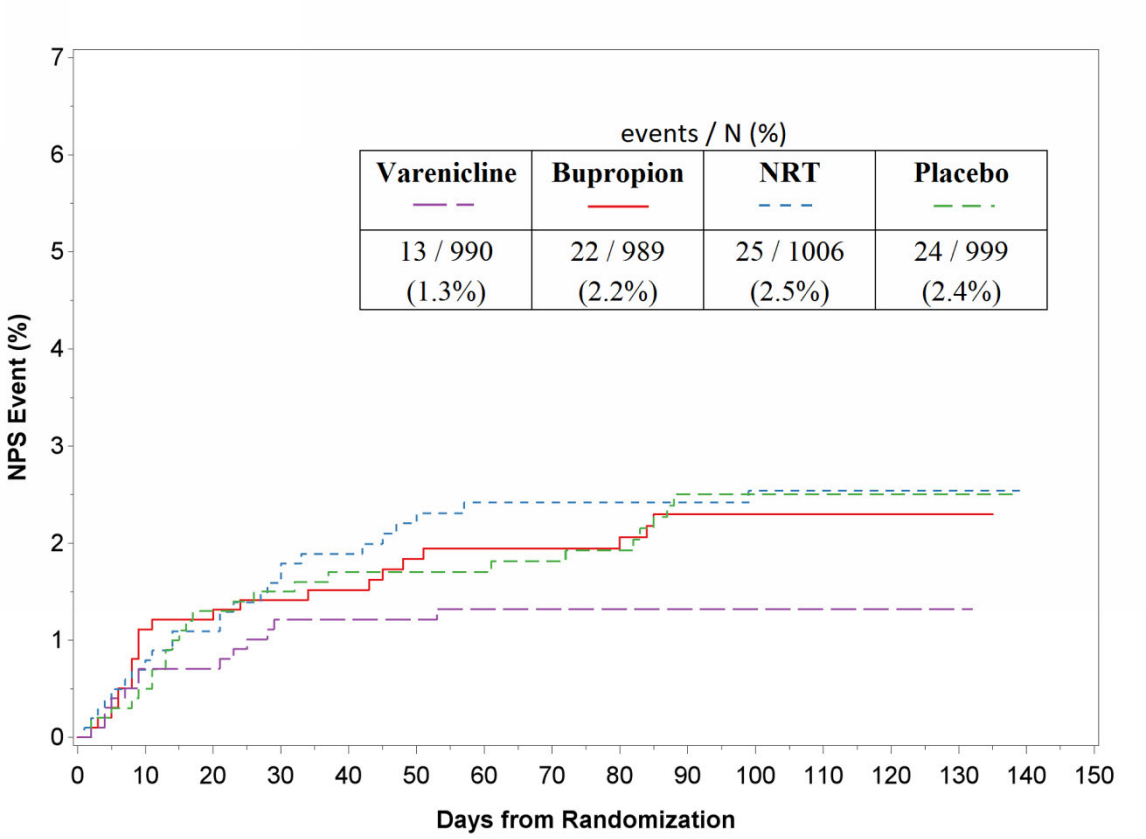
Figure 4) experienced more NPS events within the first 7 days after randomization (21 subjects on bupropion, 12 on varenicline) than subjects randomized to NRT (4) or placebo (4).

Figure 3. NPS Events in the Non-PHx Cohort



Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

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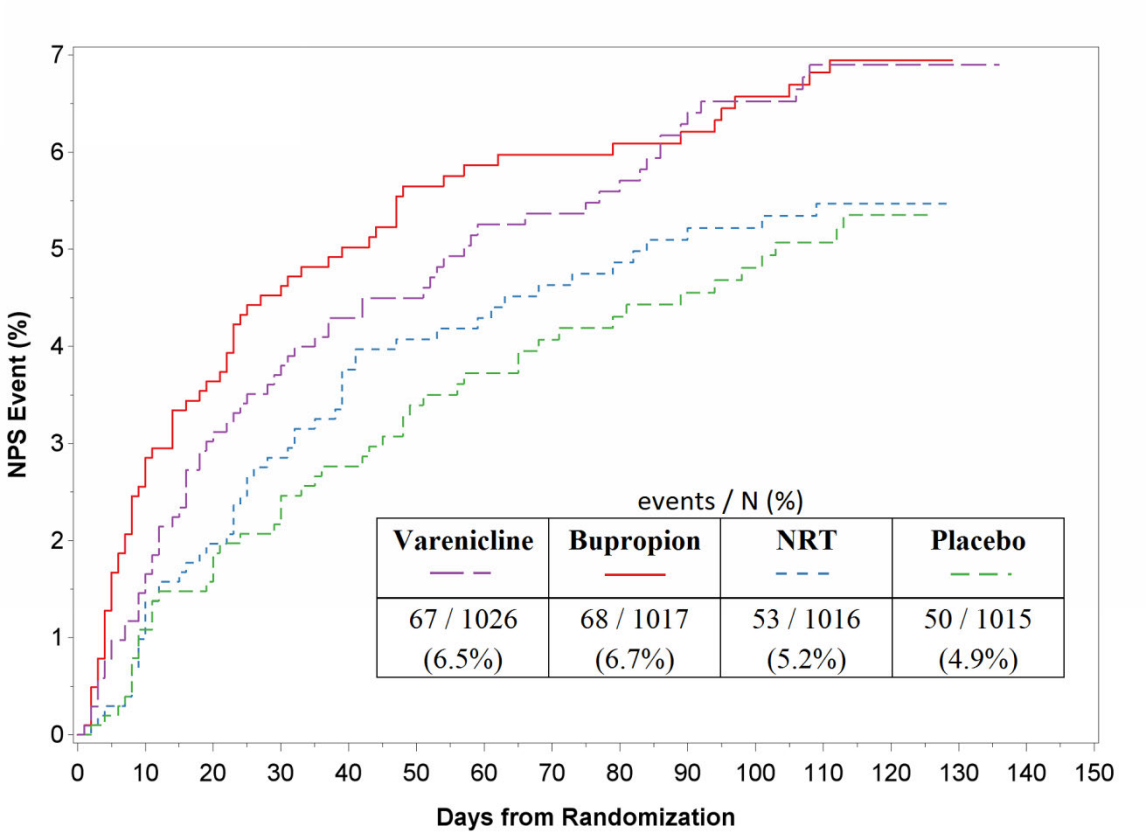
Figure 4. NPS Events in the PHx Cohort



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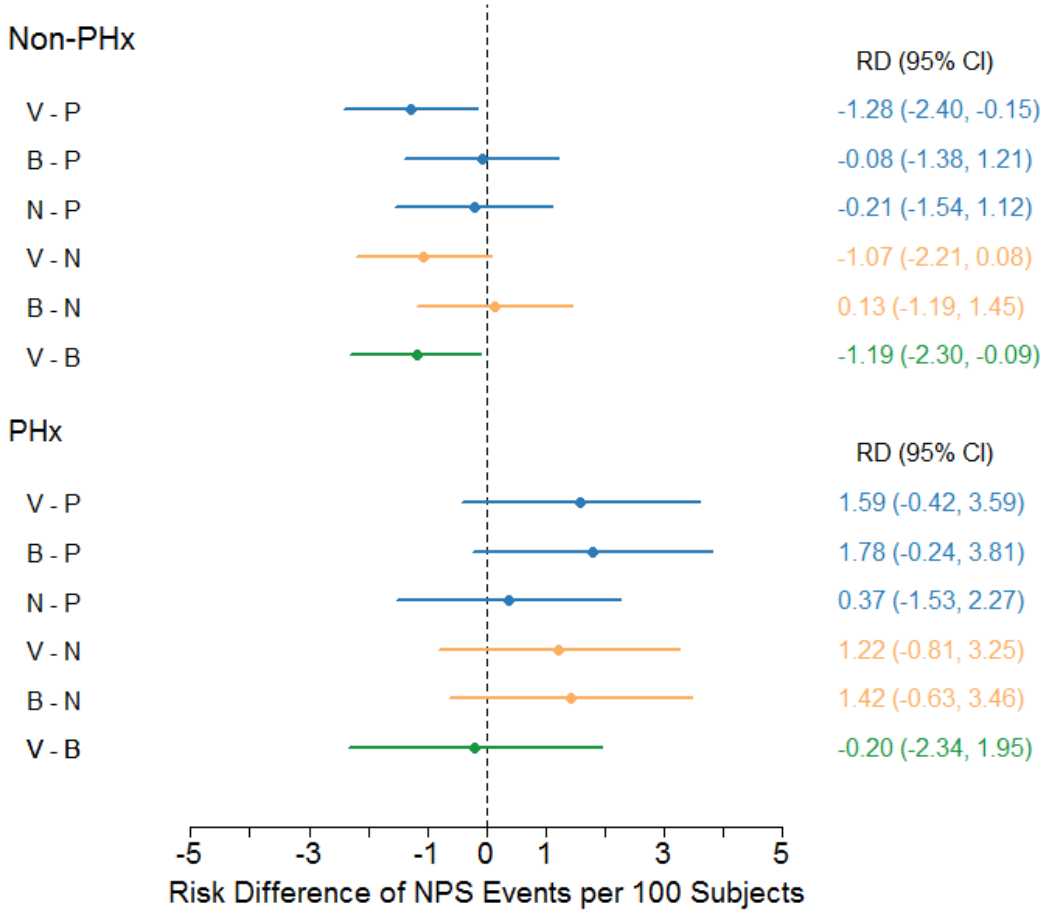
Error! Reference source not found. shows the estimated risk differences and corresponding nominal 95% confidence intervals for the risk difference of treatment-emergent NPS events for each of the 6 pairwise treatment comparisons in each of the two cohorts based on the pre-specified primary analysis. The figure shows a nominally protective effect associated with varenicline relative to placebo: RD = -1.28 NPS events per 100 subjects, 95% CI (-2.40,-0.15) in the Non-PHx cohort, and a numerically increased risk associated with varenicline: RD = 1.59 NPS events per 100 subjects, 95% CI (-0.42, 3.59) and bupropion: RD = 1.78 NPS events per 100 subjects, 95% CI (-0.24, 3.81) relative to placebo in the PHx cohort. Varenicline showed a nominally protective effect relative to bupropion in the Non-PHx cohort: RD = -1.19 NPS events per 100 subjects, 95% CI (-2.30, -0.09) and no meaningful difference in the PHx cohort: RD = -0.20, 95% CI (-2.34, 1.95).

Dr. Andraca-Carrera noted that the observed incidence rates of NPS events in both cohorts were smaller than anticipated in the Statistical Analysis Plan (SAP) described in Section **Error!**

Reference source not found.. Consequently, the widths of the 95% confidence intervals for the Risk Difference of NPS events comparing varenicline to placebo were narrower than anticipated in the SAP. The sample size of trial A3051123 was adequate to evaluate the risk difference of NPS events based on the pre-specified precision in the SAP. However, the widths of the confidence intervals on a relative scale (relative risk) were wider due to the smaller total number of observed events.

Figure 5. Primary Analysis: Risk Difference of NPS Events by Cohort



V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

Source: Created by statistical reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

The 261 MedDRA preferred terms in the NPS composite were grouped into 16 categories, and analyses of the number of subjects in the trial with at least one qualifying treatment emergent NPS event in each of these categories were presented in the statistical review.

However, as noted above, concerns about the way the data were captured and coded render these particular analyses less informative and they are not reproduced here.

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NPS Event by Sub-Cohorts of Psychiatric History at Baseline

Subjects in the PHx cohort were categorized into 4 sub-cohorts based on their diagnosis of psychiatric disorder at baseline: affective disorder, anxiety disorder, psychotic disorder, or borderline personality disorder. Dr. Andraca-Carrera also presented analyses of NPS events by sub-cohort of psychiatric history.

Table 18 shows the number and percentage of subjects with at least one treatment emergent NPS event in each of these sub-cohorts by randomized treatment arm. The statistical review notes that any differences in the observed rates of events across sub-cohorts within each randomized treatment are reasonably explained by chance.

Table 18. Primary NPS Event by Sub-Cohort of the PHx Cohort

	Varenicline **events / N (%)**	**Bupropion** **events / N (%)**	**NRT** **events / N (%)**	**Placebo** **events / N (%)**
Affective Disorder	**50/731 (6.8%)**	**46/716 (6.4%)**	**39/713 (5.5%)**	**33/722 (4.6%)**
Anxiety Disorder	**11/193 (5.7%)**	**16/200 (8.0%)**	**9/195 (4.6%)**	**11/194 (5.7%)**
Psychotic Disorder	**6/95 (6.3%)**	**6/96 (6.3%)**	**5/99 (5.1%)**	**6/96 (6.3%)**
Borderline Personality Disorder	**0/7**	**0/5**	**0/9**	**0/3**

Source: Created by DB7 reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

NPS Event by Investigative Sites

Dr. Andraca-Carrera noted that the results by site exhibited a great deal of heterogeneity, suggesting that the protocol-specified analysis might not have been the appropriate approach. His review includes figures illustrating a 95% (99%) prediction band for the expected number of subjects with an NPS event under the assumption that the number of subjects who experience an event in any given site follows a binomial distribution with a common rate of events for all sites in the same cohort. He shows that sites in the PHx cohort exhibited high heterogeneity in NPS event rates and more sites with 0 NPS events than would be expected under the assumption of a binomial distribution for the number of events within sites (45 expected sites with no events vs. 60 sites observed). He notes:

> This level of site heterogeneity is highly improbable to have occurred by chance alone under the assumption of a common rate of NPS events. One potential concern is that the subjective nature of the NPS endpoint may have led to different interpretations of what constitutes an event across sites and that this may diminish the generalizability of the trial findings. [Text below] discusses sensitivity analyses that account for extra-binomial variation of NPS events across sites, and analyses that explore the influence of specific sites, such as sites 1002 and 1077 previously identified as 'problematic' by the applicant.
>
> An evaluation of whether the observed heterogeneity in the rate of NPS events by site within the PHx cohort could be partly or fully explained by differences in covariates between sites was performed looking at various factors. We found no evidence of an association between site heterogeneity and country of randomization, sub-cohort of the PHx cohort, or treatment allocation. These analyses are not shown in this review.

Sensitivity Analyses of Neuropsychiatric Events

The DB7 review team conducted a variety of sensitivity analyses to explore the results of the study.

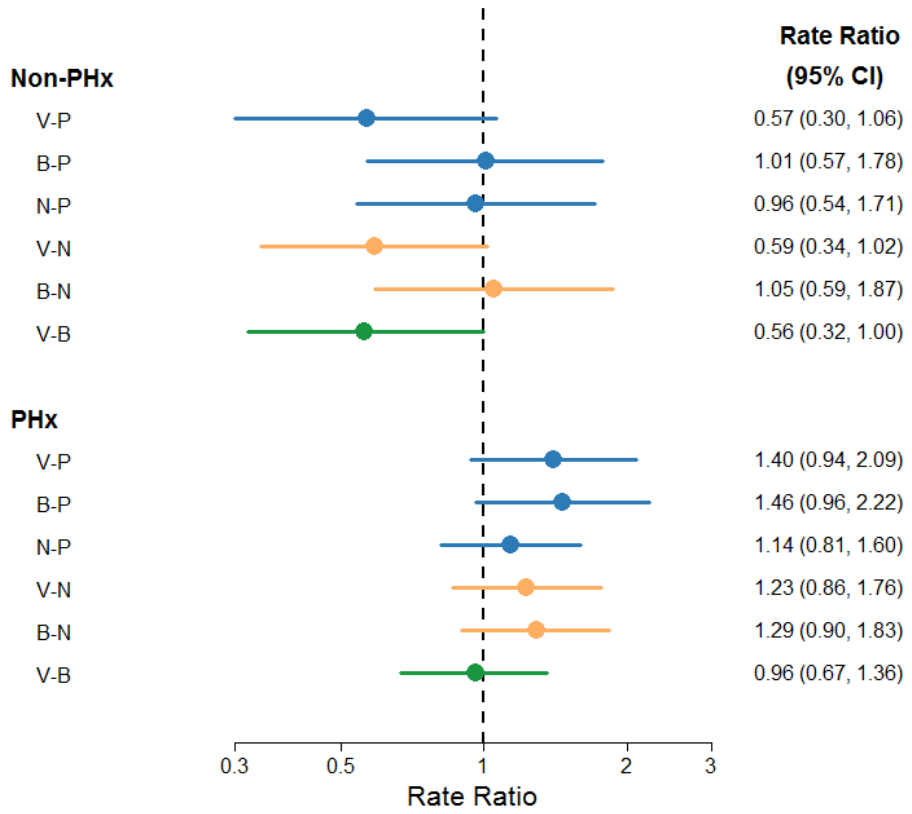
Statistical Models to Account for Extra Binomial Variation between Sites

In order to evaluate whether different statistical models adequately account for the site heterogeneity described above, the DB7 team fit four different statistical models, including a binomial model (equivalent to the primary pre-specified model), a Poisson Model, a Negative Binomial Model (NB) for the rate ratio of subjects with an NPS event, and a Zero Inflated

Negative Binomial Model (ZINB) for a “mixture” of distributions. These are described in detail in the statistical review. The review noted that the BB and ZINB models fit the data better than the primary binomial model and the Poisson model. These results suggest that the primary binomial model may underestimate the heterogeneity of NPS rates across sites and also that the risk ratio (RR) estimated by the NB model may be a more appropriate measure of risk to summarize these data than the risk difference (RD) estimated by the primary binomial model. The NB model fit the data slightly better than the ZINB model, and has the added advantage of easier interpretation and fewer parameters.

The results of this analysis show that even though the rate of NPS events in the PHx cohort was more heterogeneous than originally anticipated in the primary binomial model, the interpretations of the NB model and the primary binomial model are consistent. Both models show a numerically lower rate of events observed in the varenicline arm in the Non-PHx cohort and a numerically higher rate of events in the varenicline and bupropion arms in the PHx cohort**.**

Figure 6. Rate Ratio for NPS Events from a Negative Binomial Model



Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Dr. Andraca-Carrera also performed various other sensitivity analyses, including an analysis including adverse events of all severities in the composite, and an analysis of only events rated as "severe." These are described in the statistical review and did not change the conclusions overall. Additionally, to address concerns identified in the clinical review of the datasets, the team defined an alternative composite endpoint, referred to here as NPS+, that included all primary NPS events plus moderate or severe adverse events with an associated MedDRA Preferred Term (PT) of 'Irritability' or a High Level Group Term (HGLT) of 'Depressed mood disorders'. The primary endpoint required a rating of "severe" for AEs involving depression, but the lack of consistency between patient reports and investigator ratings suggested that patient with clinically significant depression were missed in this analysis. NPS+ also added irritability (excluded from the primary endpoint as an attempt to avoid "noise") to address the observation that some patients who reported anger or hostility were being coded as experiencing "irritability" This NPS+ analysis was presented at the Advisory Committee meeting.

Table 19 shows a summary of NPS+ events by cohort and randomized treatment arm. The overall frequency of NPS+ events was approximately twice as large as the frequency of NPS events in all treatment arms in both cohorts. The estimated risk differences of NPS+ events were generally consistent with the estimated risk differences of the primary NPS endpoint (risk differences not shown). The observed cumulative rate of NPS+ events in the Non-PHx cohort was lowest among subjects randomized to varenicline. The observed cumulative rate of NPS+ events in the PHx cohort was highest among subjects randomized to varenicline and bupropion.

Table 19. Treatment Emergent NPS+ Events by Treatment and Cohort

	Varenicline **events / N (%)**	**Bupropion** **events / N (%)**	**NRT** **events / N (%)**	**Placebo** **events / N (%)**
Non-PHx Cohort	**32 / 990** **(3.2%)**	**35 / 989** **(3.5%)**	**38 / 1006** **(3.8%)**	**44 / 999** **(4.4%)**
PHx Cohort	**118 / 1026** **(11.5%)**	**109 / 1017** **(10.7%)**	**89 / 1016** **(8.8%)**	**100 / 1015** **(9.9%)**

Source: Created by DB7 reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

The statistical review also evaluated the effect of including sites identified as problematic by Pfizer, and excluding sites with potential financial conflicts or involvements. The results of all these analyses were consistent with previous analyses and did not alter the conclusions.

Additionally, Dr. Andraca-Carrera evaluated whether the inclusion of patients who had previous experience with one or more of the study drugs might have yielded a population enriched for the ability to tolerate the drugs and decreased the observed rate of adverse events. In this analysis, previous users of smoking cessation products were defined as subjects with at least one recorded use of varenicline, bupropion or NRT as a concomitant medication (dataset Cnmedp.xpt), or at least one reported smoking cessation attempt using any of these products (dataset Smkhst.xpt) prior to randomization. Approximately 30% of the population had documented prior experience with one or more of the study drugs.

The analysis revealed that subjects without prior documented experience with the study drugs had a lower observed pooled rate of NPS events than treatment-experienced subjects in both study cohorts: 1.7% vs. 2.9% respectively in the Non-PHx cohort; 4.7% vs. 7.7% in the PHx cohort. Overall, the data showed no evidence to suggest that treatment-naïve subjects may be at higher risk of NPS events than treatment-experienced subjects. Detailed tables are found in the statistics review.

Expanded NPS Analysis

After becoming aware of the FDA review team's findings concerning the study conduct and the potential incomplete of capture of clinically significant neuropsychiatric adverse events, Pfizer conducted their own re-examination of the study data to identify additional cases of NPS events that may have been missed due to investigator severity assessment issues, lack of consistency across data streams (e.g., the HADS scores, clinical global assessments, C-SSRS assessments, evaluations by MHP) and adverse event reporting, and submitted a sensitivity analysis incorporated an expanded definition of NPS. The analysis was described as follows:

> The expanded definition included the original primary NPS AE endpoint plus the following:
>
> 1. Clinical consensus cases based on a blind review of the patient health information provided by the CGI-I, the HADS-A and HADS-D and the C-SSRS scales, as well as the Mental Health psychiatric evaluations that were required as part of the protocol. Specifically, data listings were prepared for subjects meeting any of the following criteria during the treatment emergent period (through end of treatment plus 30 days):
>
> a) Adverse event of any severity in the MedDRA Suicide and Self-Injury SMQ (all terms in the primary NPS endpoint plus "intentional overdose")
>
> b) CGI-I of much worse or very much worse
>
> c) C-SSRS of ideation 4 or 5 or any behavior
>
> d) HADS score of >15 for either subscale, depression or anxiety

e) A psychiatric evaluation by a MHP that resulted in a new DSM-IV diagnosis, represented an exacerbation of a pre-existing condition, or the MHP said the subject should not continue in the study

Two Pfizer clinicians separately identified subjects as potential 'events' based on blinded review of the data listings prepared based on the above criteria. Lists of subjects identified by each clinician were then forwarded to a third clinician for blinded review and final determination of clinical consensus as to whether the subject should be included as having an expanded NPS event for this sensitivityanalysis. It should be noted that this review also included all the cases for which narratives have been submitted to FDA.

Or, if not identified by clinical consensus,

2."Moderate" AEs coded to any one or more of the MedDRA components of "Anxiety", "Depression", Feeling Abnormal" or "Hostility". Please note that subjects with "severe" adverse events coded to any one or more of these MedDRA components were already included in the pre-specified primary composite NPS endpoint.

Or, if not identified by clinical consensus or the moderate ratings for the above four components,

3. "Moderate" or "severe" AEs events coded to a MedDRA preferred term of "Irritability".

Pfizer reported that 480 patients were identified for clinical review and that the process of review identified only 10 patients (all in the psychiatric cohort) who were assessed as having had experiences intended to be captured by the *primary* NPS endpoint. An *expanded* endpoint was also constructed which added moderate events of depression, anxiety, hostility, and feeling abnormal, as well as moderate or severe events coded to the term "irritability." In situations where patients reported significant symptomatology on the HADS scales or were assessed as significantly worsened on the clinical global assessment, if no adverse events were recorded using MedDRA terms in the NPS endpoint, or if the severity was assessed as "mild" by the investigator, patients were not included in the expanded analysis. Pfizer explained the process as follows:

While an expanded NPS endpoint was explored in a sensitivity analysis, it should be noted that inclusion of subjects in the primary NPS endpoint was determined by pre-specified criteria based on specific events and severities, which were determined by investigators' interactions with their subjects and by investigators' clinical judgment. The intent of the clinical review component of the expanded analysis was not to override the investigators' judgment, which was fundamental to how the primary NPS endpoint was defined. This review was conducted to ascertain whether other sources of data collected as part of the A3051123 clinical study from subjects that did not meet the endpoint revealed cases clearly consistent with the intent of the primary endpoint and if so, the primary endpoint could be augmented with these cases identified based on the totality of the information available as part of the A3051123 clinical study.

All 480 subjects meeting the specified criteria and not identified as having a primary NPS endpoint event were sent for clinical review. Of these, 10 subjects were identified by the clinical review process as potential cases that were consistent with those that met the pre- specified primary endpoint criteria.

For the remaining 470 subjects that were reviewed and were not considered to be consistent with the primary NPS endpoint, 188 were included in the expanded NPS endpoint based on moderate anxiety, depression, hostility, and feeling abnormal and moderate or severe irritability. Of the remaining 282, 133 had events that were of the type included in the primary NPS endpoint but were assessed as mild and therefore did not qualify for the expanded endpoint. The remaining 149 did not have any events recorded that were consistent with the primary NPS endpoint.

At Agency request, Pfizer provided a dataset listing flags for all of the criteria used to determine whether patients should be added to the expanded analysis, and tabulations of the MHP comments on the evaluations. This identified a number of patients for whom the MHP text fields documented adverse events that were not in the AE dataset. Pfizer revealed that the free-text fields containing the information from the MHP evaluations had not been provided to the clinicians performing the blind review and had not been taken into consideration. Inspection of the text fields identified additional patients whose new diagnosis, exacerbation, or recommendation to discontinue medication occurred in the context of what appeared to be a clinically significant NPS event. It is not clear why patients who received new diagnoses of, for example, major depression and were started on antidepressants did not have adverse events of "depression" captured in the database; this is a further illustration of the inconsistency in capture and coding of AEs in the study. Diagnostic criteria for major depression and even for adjustment disorder include the concept of impairment of function; therefore a patient with a new Axis I diagnosis involving depression, anxiety, or psychosis—even an adjustment disorder diagnosis—would be considered to have had relevant symptoms affecting function. In the case of patients with pre-existing diagnoses, symptoms requiring a change of therapy may be assumed to have been clinically significant. Finally, any patient discontinuing study drug due to NPS may be assumed to have experienced clinically significant symptoms. Therefore, the review team undertook a blinded review of the text fields to identify other patients whose clinically significant NPS events had not been captured in the expanded analysis. Only patients not already added to the expanded endpoint based on AEs recorded in the dataset were evaluated. For the purposes of this review, the following case definitions were used:

In the Non-PHx cohort, a case was defined as having one or more of the following:

1. New Axis I psychiatric diagnosis in the diagnosis column (including adjustment disorders).
2. Psychotropic medication initiated or recommended (usually in the recommendations field)
3. Recommendation to discontinue study drug ("opinion of MHP to remain on Study Drug" = NO)
4. Patient reports discontinuing study drug due to NPS

AND

The events began during treatment (even if the time criterion for diagnosis was met later), or the events are described as beginning in the context of study drug discontinuation.

In the PHx cohort, a case was defined as having one or more of the following:

1. New DSM-IV psychiatric diagnosis flag AND text in DSM diagnosis field is an Axis I diagnosis involving depression, anxiety, or psychosis
2. New or changed medication in context of exacerbation
    a. A recommendation is made for a psychiatric medication (new or changed) by the MHP
    b. A new/changed psychiatric medication initiated by someone else is documented (e.g., patient reports personal physician started/changed psychiatric medication)
3. Recommendation to discontinue study drug ("opinion of MHP to remain on Study Drug" = NO)
4. Patient reports discontinuing study drug due to NPS

AND

The events began during treatment (even if the time criterion for diagnosis was met later), or the events are described as beginning in the context of study drug discontinuation.

A total of 300 MHP evaluations were documented, of which 151 were added to the expanded endpoint by Pfizer on the basis of documented adverse events. Blinded review of the line listings for the MHP evaluations for the remaining 149 patients (32 Non-PHx and 117 PHx) was performed by two independent clinicians. Cases that were not identified by both clinicians were evaluated by a third blind clinician with psychiatric expertise as a "tie-breaker."

This process identified 14 patients in the Non-PHx cohort and 44 patients in the PHx cohort. The distribution across treatment arms is shown in **Table 20** and 21, below.

FDA Expanded Analysis

The review team determined that a reasonable approach to expanding the NPS endpoint without being over-inclusive would be as follows:

1. Patients who met the original protocol-specified criteria based on event type and investigator severity rating

2. Patients identified by Pfizer's clinical consensus process

3. Patients (identified by Pfizer's process) who had recorded adverse events in the NPS endpoint that were rated moderate, but also had one or more of the criteria indicating clinical significance:

    a. Adverse event of any severity in the MedDRA Suicide and Self-Injury SMQ (all terms in the primary NPS endpoint plus "intentional overdose")

    b. CGI-I of much worse or very much worse

    c. C-SSRS of ideation 4 or 5 or any behavior

d. HADS score of >15 for either subscale, depression or anxiety

e. A psychiatric evaluation by a MHP that resulted in a new DSM-IV diagnosis, represented an exacerbation of a pre-existing condition, or the MHP said the subject should not continue in the study

4. Patients (identified by FDA adjudication process) who had a psychiatric evaluation by a MHP that resulted in a new DSM-IV diagnosis, represented an exacerbation of a pre-existing condition, or the MHP said the subject should not continue in the study and did not have recorded adverse events in the NPS endpoint that were rated moderate, but had documented clinically significant events in the MHP evaluation line listings, meeting the case definition above.

This expanded analysis identified the following distribution of patients experiencing clinically significant NPS events. Notably, most of the events are still not of a serious nature per regulatory definition. Because of the concern that inclusion of patients whose only reported symptom was "irritability" might introduce noise into the analysis, the tables below also show how many patients in each arm were included in the expanded analysis solely based on report of irritability. There are very few such patients.

Table 20 Components of the Expanded NPS Endpoint in the Non-PHx Cohort

	Varenicline	**Bupropion**	**NRT**	**Placebo**
	N = 990	**N = 989**	**N = 1006**	**N = 999**
Expanded NPS	**31 (3.1%)**	**35* (3.5%)**	**33 (3.3%)**	**40 (4.0%)**
Primary NPS	13	22	25	24
Identified by Pfizer's clinical consensus review	0	0	0	0
Identified by Pfizer's flags + AEs anxiety, depression, hostility, feeling abnormal, irritability (irritability only)	12 (0)	9 (0)	6 (0)	13 (1)
Identified by FDA process	6	3	2	3

*1 subject was recorded as having an expanded NPS event due to Pfizer clinical review even though he/she did not undergo clinical review (flag for clinical review =

Table 21 Components of Expanded NPS in PHx Cohort

	Varenicline	**Bupropion**	**NRT**	**Placebo**
	N = 1026	**N = 1017**	**N = 1016**	**N = 1015**
Expanded NPS	**125 (12.3%)**	**1221 (11.9%)**	**98 (9.7%)**	**96 (9.5%)**
Primary NPS	67	68	54*	50
Identified by Pfizer's clinical consensus review	3	1	2	4
Identified by Pfizer's flags + AEs anxiety, depression, hostility, feeling abnormal, irritability (irritability only)	43 (1)	41 (2)	31 (1)	33 (1)
Identified by FDA process	12	11	11	9

*The original analysis included 53 NPS endpoint in the NRT arm of the PHx cohort, this dataset lists 54

The table below illustrates the findings across different analyses. In all analyses, there appears to be no increased risk of NPS events in patients without psychiatric diagnoses who are treated with any of the medications for smoking cessation. However, neuropsychiatric adverse events of a clinically significant,

if not serious, nature are relatively common, occurring in 3-5% of the non-psychiatric population when trying to quit smoking without without medication. There is also a small, but consistent, finding in the population of patients with psychiatric diagnoses that events are more common during treatment with varenicline or bupropion than with NRT or placebo.

Table 22 Comparison of NPS Rates Using Different Analyses

Non-PHx Cohort								
	Varenicline		Bupropion		NRT		Placebo	
	N = 990		N = 989		N = 1006		N = 999	
NPS (Protocol)	13	1.31%	22	2.22%	25	2.49%	24	2.40%
NPS Expanded (Pfizer)	45	4.55%	50	5.06%	51	5.07%	56	5.61%
NPS+ (FDA)	32	3.23%	35	3.54%	38	3.78%	44	4.40%
NPS Expanded (FDA)	31	3.13%	35	3.54%	33	3.28%	40	4.00%
PHx Cohort								
	Varenicline		Bupropion		NRT		Placebo	
	N = 1026		N = 1017		N = 1016		N = 1015	
NPS (Protocol)	67	6.53%	68	6.69%	53	5.22%	50	4.93%
NPS Expanded (Pfizer)	140	13.65%	138	13.57%	130	12.80%	123	12.12%
NPS+ (FDA)	118	11.50%	109	10.72%	89	8.76%	100	9.85%
NPS Expanded (FDA)	126	12.28%	121	11.90%	98	9.65%	96	9.46%

Effect of Smoking vs Abstinence

When the safety signal for neuropsychiatric adverse events with Chantix originally came to light, Pfizer (and others, including smoking cessation researchers) theorized that the events were related not to the drug itself, but due to smoking cessation. Mood changes such as depression and irritability have been observed in association with nicotine withdrawal, and the possibility existed that the events could be explained by this phenomenon. However, case review revealed that many people reporting neuropsychiatric events had not stopped smoking; some had reduced their smoking but others were smoking at their baseline level. In most cases, however, the smoking status at the time of the event was not recorded. In this study, it was emphasized that the smoking status at the time of the event should be captured and described. This was not always the case, moreover, case narratives did not place the smoking status into the chronological narrative in a way that allowed the temporal relationship between smoking, study drug, and adverse events to be understood.

At best, it is possible to view the relationship between smoking and Sponsor-designated NPS events, where smoking status is known, in the graphic displays shown below (constructed by Pfizer). These analyses used information from the NUI, which was

administered weekly during the study, to determine smoking status and AE data to determine the onset of the NPS AE endpoint event.

The figures below illustrate the relationship between smoking status by week and the onset of NPS events. Smoking status is classified as completely abstinent for the week, abstinent during part of the week (≥2 days), smoked during the entire week (abstinent <1 day) – with the occurrence of the NPS AE superimposed on the week it started (**Error! Reference source not found.**) for each subject who reported an NPS AE endpoint event. Data are shown through Week 16 to cover the treatment-emergent period of 12 weeks plus 30 days.

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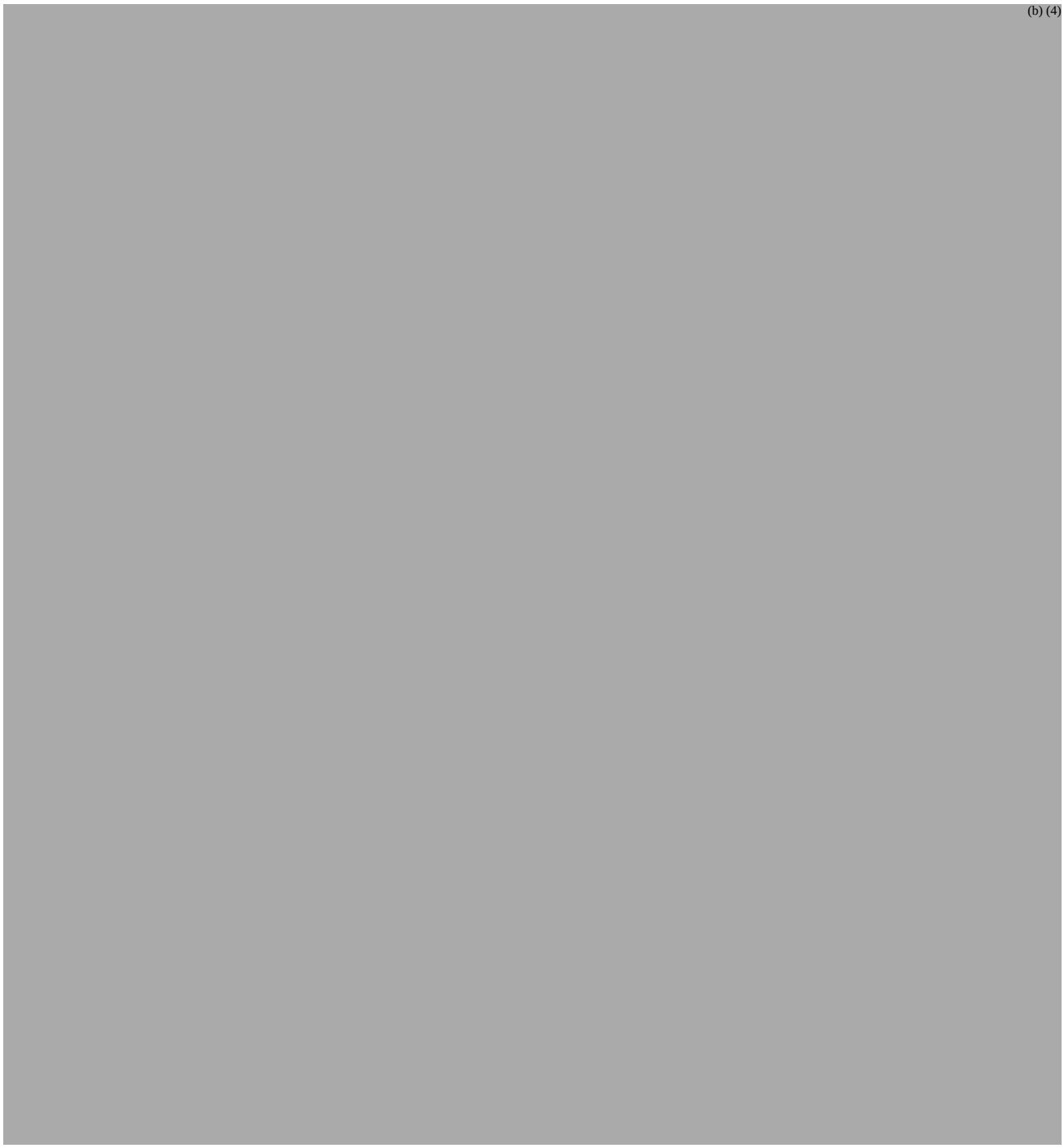
Figure 7. Primary NPS AE Endpoint – Smoking Status by Week and Onset of AE - Non-Psychiatric History Cohort, Safety Population

Black=smoker, dark grey=partial abstainer, light grey=abstainer, white=no further Nicotine Use Inventory data available.
Red diamonds show onset of NPS AE.
NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy.

Source: A3051123 CSR Appendix 16, Figures 16.2.7.4a, 16.2.7.4b, 16.2.7.4c, and 16.2.7.4d.

Figure 8 Primary NPS AE Endpoint – Smoking Status by Week and Onset of AE - Psychiatric History Cohort, Safety Population



Black=smoker, dark grey=partial abstainer, light grey=abstainer, white=no further Nicotine Use Inventory data available.
Red diamonds show onset of NPS AE.
NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy.
Source: A3051123 Clinical Study Report Appendix 16, Figures 16.2.7.4e, 16.2.7.4f, 16.2.7.4g, and 16.2.7.4h,

Although some subjects in each treatment group had NPS AEs that occurred during or following a week of partial or complete abstinence, these graphs showed no consistent association between the occurrence of an NPS AE in the composite endpoint and abstinence in any of the treatment groups. The analysis is also affected by lack of specificity of actual days in the week a subject was abstinent, missing data imputation methods which did not account for partial abstinence, and the lack of consideration for reduction in the number of cigarettes smoked.

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Efficacy Results – Primary Endpoint

The efficacy results were reviewed by Dr. Yi Ren of the Division of Biometrics 2 (DB2). Dr. Ren was able to replicate the Sponsor's analyses and confirm the conclusions regarding efficacy for rates of continuous abstinence during weeks 9-12 (CAR 9-12) and during weeks 9-24 (CAR 9-24). The results of the analyses for CAR 9-12 and CAR 9-24 are presented in **Table 23** by psychiatric cohort using the FAS population. The primary comparisons of varenicline versus placebo and bupropion versus placebo and the secondary comparison of NRT versus placebo for CAR 9-12 and CAR 9-24 were statistically significant ($p < 0.001$). All other pairwise comparisons were also considered statistically significant except for bupropion versus NRT (results not shown).

Table 23 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - FAS Population

Cohort	Varenicline (%)	Bupropion (%)	NRT (%)	Placebo (%)	Odds ratio V/P	Odds ratio B/P	Odds ratio N/P
Overall							
CAR 9-12	33.5	22.6	23.4	12.5	3.60*	2.06*	2.14*
CAR 9-24	21.9	16.2	15.7	9.4	2.73*	1.88*	1.80*
Non-PHx							
CAR 9-12	38.0	26.1	26.4	13.7	4.00*	2.26*	2.30*
CAR 9-24	25.5	18.8	18.5	10.5	2.99*	2.00*	1.96*
PHx							
CAR 9-12	29.2	19.3	20.4	11.4	3.25*	1.87*	2.00*
CAR 9-24	18.3	13.8	13.0	8.3	2.50*	1.77*	1.65*

V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* p-value <0.001, using a logistic regression with terms treatment, cohort, region, and treatment by cohort interaction, and region by cohort interaction. Region used 2-level classification (US, non-US).
Source: Statistical reviewer Yi Ren

These results were consistent with Pfizer's conclusion that varenicline was superior to bupropion, NRT, and placebo with respect to smoking cessation. Bupropion was also considered superior to placebo. Although the observed rates for CAR 9-12 and CAR 9-24 were numerically lower in the PHx cohort than in the non-PHx cohort, there was no statistically significant interaction between treatment and cohort.

Pfizer's analysis considered missing CO values as negative, i.e. a subject could be considered a non-smoker according only to self-report. Although this is not the customary approach to analysis of smoking cessation studies, the conclusion did not change when these subjects were considered non-responders (results not shown). A total of 53 subjects (0.7%) and 128 subjects (1.6%), respectively, were considered non-responders and when CAR 9-12 and CAR 9-24 were reanalyzed.

The results indicated that varenicline, bupropion, and NRT were all superior to placebo with respect to smoking cessation, p-value < 0.05. Even though the observed rates of CAR 9-12 and CAR 9-24 were lower in the PHx cohort than in the non-PHx cohort, there was no statistically

significant interaction between treatment and cohort. The observed rates and estimated odds ratios for CAR 9-24 were lower than those reported for CAR 9-12.

Data Quality and Integrity – Reviewers' Assessment

See above.

Efficacy Results – Secondary and other relevant endpoints

No other efficacy endpoints were reviewed.

Dose/Dose Response

Only one dose was evaluated.

Durability of Response

Not evaluated in this study.

Persistence of Effect

Not evaluated in this study.

Additional Analyses Conducted on the Individual Trial

The review team undertook an additional exploratory analysis to address the possibility that some subjects had tried the various study drugs before the trial. If by chance these subjects were randomized to a drug they were previously unable to tolerate, they would likely drop out and be considered non-responders. In a study primarily designed to assess comparative efficacy, patients already known to be intolerant to one of the study drugs would have been screened out. To explore the impact of this possibility, these subjects were excluded and the data was reanalyzed. This modified population is referred as the modified Full Analysis Set (mFAS). The table below provides a summary of the number of patients in the FAS and mFAS datasets.

Table 24 Number of Subjects in FAS and mFAS Datasets

Treatment/Cohort	Number of Subjects				
	Varenicline	Bupropion	NRT	Placebo	Total
Overall					
FAS Population	2037	2034	2038	2035	8144
mFAS Population	1333	1262	1296	1322	5213
Non-PHx					
FAS Population	1005	1001	1013	1009	4028
mFAS Population	690	641	656	670	2657
PHx					
FAS Population	1032	1033	1025	1026	4116
mFAS Population	643	621	640	652	2556

Source: Statistical reviewer Yi Ren

The primary comparisons of varenicline versus placebo and bupropion versus placebo and the secondary comparison of NRT versus placebo for CAR 9-12 and CAR 9-24 using the mFAS are summarized by psychiatric cohort in **Table 25**

Table 25 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - mFAS Population†

Cohort	Varenicline	Bupropion	NRT	Placebo	Odds ratio		
	(%)	(%)	(%)	(%)	V/P	B/P	N/P
Overall							
CAR 9-12	31.9	22.8	22.1	12.5	3.39*	2.09*	1.98*
CAR 9-24	21.5	15.5	15.4	9.8	2.60*	1.70*	1.68*
Non-PHx							
CAR 9-12	34.9	26.2	26.5	14.3	3.33*	2.14*	2.16*
CAR 9-24	23.8	18.3	18.3	11.6	2.42*	1.70*	1.68**
PHx							
CAR 9-12	28.6	19.3	17.5	10.6	3.45*	2.04*	1.82*
CAR 9-24	19.0	12.6	12.3	7.8	2.78*	1.70**	1.68**

V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo

* p-value < 0.001, using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction.

** p-value < 0.05, using the same model above.

† FAS population excluding those subjects who used concomitant medications and/or had failed lifetime serious quit attempts on the study medications.

Source: Statistical reviewer Yi Ren

This analysis shows that the effect of the medications is similar in a population naïve to treatment. This addresses a concern regarding the comparative efficacy conclusions in this study. The consistent results in the two cohorts provide replicated evidence that varenicline was superior to the other two active treatments. The labeling for varenicline already includes study results supporting a claim of superior efficacy over bupropion based on appropriately-designed comparative efficacy trials submitted with the original NDA. This is the first demonstration of superiority over transdermal nicotine.

As mentioned above, Pfizer conducted investigator site audits at 26 sites and showed concerns with two US sites (1002 and 1077) in terms of reliability and overall data quality. To examine the impact of this finding, a sensitivity analysis was performed excluding the data from these two sites using the mFAS population. The treatment effect was not dependent on the presence of data from these two sites.

Excluding sites which reported financial involvement with Pfizer also did not change the conclusions.

The treatment effect for varenicline, bupropion, and NRT was also examined for differences due to age (18-44 years, 45-64 years, and > 64 years), sex (male and female), race (White, Black, and Other), and region (US and non-US) based on the FAS population. The treatment effects on CAR 9-12 were consistent across these subgroups.

7 Integrated Review of Effectiveness

No integrated review of effectiveness was performed.

8 Review of Safety

The review of the primary safety composite endpoint is described in Section 6, above. Below, the general safety findings are described.

8.1. Safety Review Approach

The results of the analysis of the primary safety endpoint are discussed above. This section describes the review of the general safety data from this single trial. The aggregate analyses and tabulations do include the two excluded sites, which contributed no more than 2% to any treatment group.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Exposure by duration is shown in tables below from Pfizer's submission.

Table 26 Exposure to Treatment, Non-PHx - Safety Population

	Varenicline N = 990	Bupropion N = 989	NRT N = 1006	Placebo N = 999
Exposure in Days*	Number (%) of Subjects			
1 - 7	17 (1.7)	18 (1.8)	15 (1.5)	7 (0.7)
8 - 14	16 (1.6)	25 (2.5)	32 (3.2)	28 (2.8)
15 - 21	22 (2.2)	30 (3.0)	25 (2.5)	21 (2.1)
22 - 28	25 (2.5)	22 (2.2)	27 (2.7)	27 (2.7)
29 - 35	17 (1.7)	20 (2.0)	14 (1.4)	16 (1.6)
36 - 42	19 (1.9)	16 (1.6)	12 (1.2)	13 (1.3)
43 - 49	14 (1.4)	13 (1.3)	16 (1.6)	20 (2.0)
50 - 56	15 (1.5)	12 (1.2)	13 (1.3)	11 (1.1)
57 - 63	15 (1.5)	17 (1.7)	30 (3.0)	19 (1.9)
64 - 70	11 (1.1)	17 (1.7)	18 (1.8)	14 (1.4)
71 - 77	28 (2.8)	31 (3.1)	34 (3.4)	24 (2.4)
78+	791 (79.9)	768 (77.7)	770 (76.5)	799 (80.0)
Statistics (Days)				
Mean	75.92	74.61	74.53	76.13
Q1 - Q3	83 - 86	81 - 86	80 - 86	82 - 86
Median	85	85	85	85
Standard deviation	21.59	22.87	22.82	21.44
Range	2 - 103	1 - 96	1 - 100	1 - 110

Abbreviations: N = number of subjects randomized to study treatment who received at least 1 partial dose of study medication; NRT = nicotine replacement therapy.
*Note: May not sum to total due to rounding.
Q1 and Q3 are the first quartile and third quartile statistics, respectively.
Lost-to-follow-up subjects were imputed as having used all study drug dispensed at last contact visit in a per protocol manner.
Source: Pfizer's Section 14, Table 14.4.1.2.

Table 27 Exposure to Treatment, PHx - Safety Population

	Varenicline N = 1026	Bupropion N = 1017	NRT N = 1016	Placebo N = 1015
Exposure in Days*	Number (%) of Subjects			
1 - 7	24 (2.3)	25 (2.5)	21 (2.1)	21 (2.1)
8 - 14	38 (3.7)	39 (3.8)	36 (3.5)	35 (3.4)
15 - 21	34 (3.3)	24 (2.4)	32 (3.1)	44 (4.3)
22 - 28	21 (2.0)	29 (2.9)	24 (2.4)	32 (3.2)
29 - 35	23 (2.2)	24 (2.4)	21 (2.1)	24 (2.4)
36 - 42	9 (0.9)	18 (1.8)	27 (2.7)	25 (2.5)
43 - 49	19 (1.9)	15 (1.5)	9 (0.9)	24 (2.4)
50 - 56	17 (1.7)	12 (1.2)	9 (0.9)	16 (1.6)
57 - 63	25 (2.4)	26 (2.6)	23 (2.3)	18 (1.8)
64 - 70	16 (1.6)	14 (1.4)	20 (2.0)	24 (2.4)
71 - 77	32 (3.1)	24 (2.4)	31 (3.1)	35 (3.4)
78+	768 (74.9)	767 (75.4)	763 (75.1)	717 (70.6)
Statistics (Days)				
Mean	72.95	72.76	72.93	71.05
Q1 - Q3	77 - 86	78 - 86	78 - 86	68 - 85
Median	85	85	85	85
Standard deviation	24.46	24.69	24.33	25.37
Range	1 - 107	1 - 98	1 - 98	1 - 103

Abbreviations: N = number of subjects randomized to study treatment who received at least 1 partial dose of study medication; NRT = nicotine replacement therapy.
*Note: May not sum to total due to rounding.
Q1 and Q3 are the first quartile and third quartile statistics, respectively.
Lost-to-follow-up subjects were imputed as having used all study drug dispensed at last contact visit in a per protocol manner.
Source: Section 14, Table 14.4.1.2.

8.2.2. Relevant characteristics of the safety population:

See Table 12 Summary of Baseline Characteristics (Non-PHx Cohort) – Safety Population and **Table 13 Summary of Baseline Characteristics (PHx Cohort) – Safety Population**, above.

8.2.3. Adequacy of the safety database:

The size of the database was sufficient to characterize the safety profile, although the size of individual sub-cohorts in the psychiatric cohort may have been too small to draw definitive conclusions.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

See above

8.3.2. Categorization of Adverse Events

All adverse events were coded using MedDRA version 18.0. A discussion on coding concerns can be found in section 6.1.2. Issues with interpretation of subject verbatim statements and accuracy of coding preferred terms is presented in section 6.1.2.

8.3.3. **Routine Clinical Tests**

8.3.4. **Deaths**

There were ten deaths in the study; one occurred possibly prior to initiation of study treatment and two were recorded post-study (~6 months after last dose of study treatment). No deaths occurred in patients treated with Chantix. The table below gives an event description for each of the fatal events.

Table 28 Fatal Adverse Events

Cohort/ Subject ID	Treatment Group	Sex/Age at Death/ Race	Day of Last Dose	Day of Death	Event Description
Non-Psychiatric History					
(b) (6)	Bupropion	M/32/White	19	19	Heroin Overdose
	NRT	M/62/White	77	208	Prostate Cancer
	Placebo	M/64/Asian	86	128	Myocardial Infarction
	Placebo	F/30/White	29	32	Suicide
	Placebo	M/32/White	85	258	Road Traffic Accident
Psychiatric History					
(b) (6)	Bupropion	M/52/White	77	77	"Cardiovascular Disorder" (No additional information provided)
	NRT	M/62/White	64	238	Esophageal cancer
Randomized but not treated:					
(b) (6)	NRT	F/57/Black	N/A	N/A[c]	Possible overdose (coded as sepsis but no information supporting this diagnosis)
	Placebo	F/42/Black	60	60	Pulmonary Embolism

Three of these cases illustrate the review team's concerns about lack of rigor regarding the Sponsor's data collection, reporting, and coding. In one case, it is not known whether or not the

patient had taken study drug, and it is reported as occurring prior to initiation of study drug. The narrative indicates that the 57-year-old black female subject with current major depressive disorder and no recorded history of drug use was randomized to NRT on (b) (6) 2014. She experienced an event of “septic shock” two days later, and ultimately died 10 days afterwards. The narrative provides the information that “A heroin overdose was suspected as the emergency medical technicians (EMTs) found her in the front yard of a suspected drug house. Multisystem organ failure ensued with ultimate full septic shock. The subject received treatment for the event with norepinephrine bitartrate and bicarbonate infusion.” There is no information explaining why this event was coded as “septic” shock or “sepsis”, and it does not appear that the patient was treated for an infectious process.

Another example of incomplete documentation by the sponsor is a patient who was in the placebo arm who completed study treatment and several months of follow-up, and on Study Day 258 was killed in a car accident. The narrative provides the following information:

> On (b) (6), the subject was in a "head on car collision" that resulted in death at the scene of the accident. The subject died on (b) (6). An autopsy was performed and determined the cause of death was multiple blunt force trauma to the chest and abdomen and hemorrhage. The toxicology evaluation was negative for drugs or other substances. No relevant tests were reported. The action taken in response to the event for study drug was “post-therapy”. Outcome of the SAE "head on car collision" was fatal. The investigator considered there was not a reasonable possibility that the event "head on car collision" was related to the study drug, concomitant medications or a study procedure.

Notably, no information is provided about the circumstances of the accident, even whether or not the patient was the driver of the vehicle.

Finally, the narrative for Subject (b) (6) (bupropion arm/PHx cohort) provides only this information:

> On (b) (6), the subject experienced a fatal event of cardiovascular disorder which was considered severe in intensity and serious (due to death) by the investigator. No action was taken with the study drug due to the event. The subject received no treatment for the event. The outcome of the event was death on the same day (b) (6) At the time of the event, average daily cigarette use was 12 (b) (6) 2014). The investigator considered the cardiovascular disorder to be not related to the study drug but due to other illness related to background of cardiovascular risk.

8.3.6. **Serious Adverse Events**

There were 72 patients with treatment-emergent SAEs in the non-PHx cohort and 101 in the PHx cohort. All 173 patients were reviewed with an eye towards identifying NPS cases of interest. A number of serious adverse events in other domains (e.g., cardiovascular) were also reported but this review focuses on the NPS events. After reviewing the SAE narratives for potential NPS cases, the review team identified 36 cases for which a relationship to study drug could not be ruled out. Notably, one of these cases was not included in the NPS endpoint because the investigator rated the event of depression as "mild" although it resulted in hospitalization. Cases of both treatment-emergent and discontinuation-emergent symptoms were noted. NPS events in bupropion-treated patients in the PHx cohort included cases that appear to be precipitation of mania in patients with bipolar disorder, a known and labeled risk of bupropion and other antidepressants.Two additional cases involving deliberate overdose were identified that were not flagged as serious by Pfizer. One was included in the SAE cases because the patient was hospitalized for a medical problem; one was not flagged as an SAE at all (and was coded as an accidental overdose) but was added to the table below.

Treatment-Emergent psychiatric hospitalizations, an endpoint of particular interest, were reported in 23 patients, distributed as follows. The table below illustrates the distribution of all SAEs, NPS SAEs, and psychiatric hospitalizations. No patients from the two excluded sites had SAEs identified; the denominator excludes these two sites.

Table 29 Number of Serious Adverse Events, NPS SAEs, and Psychiatric Hospitalizations

	Varenicline		Bupropion		NRT		Placebo	
Non-PHx (N)	975		968		987		982	
Any SAE	16	1.6%	19	2.0%	21	2.1%	16	1.6%
Any NPS SAEs	1	0.1%	5	0.5%	1	0.1%	4	0.4%
Psychiatric hospitalizations	1	0.1%	2	0.2%	0	0.0%	1	0.1%
PHx (N)	1007		1004		995		997	
Any SAE	23	2%	29	3%	24	2%	26	3%
Any NPS SAE	6	0.6%	8	0.8%	4	0.4%	6	0.6%

Psychiatric hospitalizations	5	0.5%	8	0.8%	4	0.4%	2	0.2%

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The following table includes a description of 35 NPS SAEs

Table 30 Description of NPS SAEs

Patient #, demographics, primary diagnosis	Description of event
Non-PHx Cohort	
Varenicline	
(b) (6) WF 58	After three months on study drug, subject was **hospitalized** for “alcohol abuse” for three days. No other information provided.
Bupropion	
(b) (6) WM 53	Treatment Day 13, subject was **hospitalized** for ~2 days for evaluation after mentioning that he "felt like blowing his brains out." This was later dismissed by the subject as a "misunderstanding." He was started on an antidepressant and declined further participation in the study.
(b) (6) WF 74	After ~1 month on study drug, subject first noticed "intermittent left hemiparesthesia and subjective confusion." Symptoms resolved and then recurred, with four instances in a month of "a foggy feeling in my head" and "stabbing cold pains." Symptoms became persistent after ~2 months on study drug; she was admitted to the hospital to be evaluated for stroke. Workup negative; study drug discontinued.
(b) (6) WM 32	On Treatment Day 19, subject was found dead (reported by his sister). Toxicology report showed opiates. Patient had history of occasional use of heroin. (Not enough information to rule out NPS event.)
(b) (6) BM 40	After 24 days of study drug treatment "the subject experienced depression which was considered mild in intensity and serious due to **hospitalization** or prolonged hospitalization by the investigator." Study drug was discontinued, patient was treated with psychotropic medication. Patient had reduced smoking from 28 to

	cigarettes/day 5 at the time of event. No other information is provided.
(b) (6) WM 23	Subject was randomized into non-PHx cohort; after events occurred MHP in retrospect felt subject had "underlying mood disorder (probably bipolar) and PTSD." After five days of study drug, patient reported that he had experienced three days of worsening symptoms, including sweating and pacing, "I felt like I took drugs." "Mild anxiety" and "moderate hostility" were also recorded with no detail. Study drug was decreased and then discontinued. He had reduced smoking from BL 15 to 9-10 cigarettes/day. About a month after discontinuing study drug, the subject revealed that he had been hitting himself in the head with his fists and had repeatedly placed a loaded gun into his mouth with intent to commit suicide. He had been taken to see a psychiatrist outside the study and was taking quetiapine. He completed the study off treatment.
NRT	
(b) (6) WF 47	After three weeks of treatment with NRT, in the context of drinking alcohol, subject "decided on the spur of the moment to pack and leave her apartment. In the process of packing, she saw a knife and impulsively started to cut herself. She said her husband saw her cutting, stopped her, and took her to the ER. She shared that she did feel that the combination of the alcohol and the drug trial she was on may have caused her to be more emotional than usual during the time when she cut herself." Study drug was discontinued; subject had a second episode of suicidal ideation with plan a month later. Smoking was decreased from BL 20 to 6-9 cigarettes/day at the time of the events.
Placebo	
(b) (6) WM 34	(Subject was randomized to NRT but event occurred during initial week of placebo pill dosing before patch began) After a week of study drug (placebo pills) treatment, patient "reported a panic attack that led to binge drinking", and that he was **hospitalized** for five days for treatment. Smoking had not changed.
(b) (6) WF 30 *completed suicide*	Subject began taking study drug and stopped smoking between the Week 1 and Week 2 visits. She had no complaints other than insomnia reported during the first week of treatment. She did not appear for the Week 5 visit, and the site subsequently learned she had committed suicide by jumping from a high monument three days after her Week 4 visit, leaving a note saying "everything was too much." The subject

	had no prior psychiatric history and no lifetime suicidal attempts or ideation.
(b) (6) WM 47	After ~2 months of study medication and ~2 weeks after last dose, the subject was hospitalized for orthostatic hypotension and numbness in his hand. He required treatment with dopamine and adjustment of his antihypertensives, and was hospitalized for four days. After discharge from the hospital, he reported "physical problems overwhelming, ganging up on me," and endorsed suicidal ideation about twice a week without plan. About 10 days later he endorsed suicidal thoughts of overdosing; he required **crisis assessment at a local psychiatric facility**. He had reduced smoking but not quit.
(b) (6) WM 33	Subject completed 85 days of study drug. At the Week 13 (post-treatment visit) the site documented "since stopping the meds, subject reports depression," and that symptoms of a prior eating disorder had re-emerged "appetite down, fasting, binging, and purging," and that two days after completing the course of treatment, he experienced vague suicidal ideation with no intent or plan; on C-SSRS he endorsed "easier to be dead." This suicidal ideation was assessed by the investigator as “moderate in intensity and serious.” No change in smoking level. He was referred to a psychiatrist but the nature of treatment is not documented; narrative states that the event resolved.
PHx Cohort	
Varenicline	
(b) (6) WM 34 bipolar disorder	Treatment Day 58, subject reported increased anxiety, auditory hallucinations, and "checked himself into" a psychiatric **hospital**. Study drug discontinued. Investigator believed complaints were factitious. Subject also reported command hallucinations and suicide attempt by jumping in front of a bus.
(b) (6) WM 19 major depressive disorder	Subject completed 87 days of study drug treatment. Approximately two weeks after discontinuing study drug, subject "did not sleep for three nights" and experienced symptoms described as "panicky, nervous, anxious," and cut his wrists "as an act of self-mutilation and not as a suicide attempt." He was **psychiatrically hospitalized** for three days. He was smoking 3 cigarettes/day (Baseline [BL]: 15) at the time of the events.

(b) (6) WM 33 schizoaffective/bipolar	After four weeks of study drug, subject presented to an emergency room after a fight with his parents, seeking admission, stating he was depressed; he reported suicidal thoughts but it was believed this claim was factitious. However, he reported that while on study drug "his depression had gotten worse." Study medications were discontinued; patient did not return for further visits. He was **psychiatrically hospitalized** for approximately a week.
(b) (6) WM 47 bipolar disorder, PTSD, panic	Subject took study medication for ~16 days. A few days after discontinuing medication, he relapsed to alcohol use reportedly "due to the death of his father" and was lost to follow-up to the study site. Approximately two weeks after resuming drinking he was found unconscious and **hospitalized** for alcohol poisoning and management of withdrawal.
(b) (6) WM 36 bipolar disorder	After 20 days of study drug, subject "was upset and had brief thought of death ("I had a suicide thought about taking my sleeping medication"), called a crisis line, and went into an **outpatient stabilization unit**." He had missed two doses of his mood stabilizer (valproate) and antidepressant (citalopram). Smoking decreased from 20 to 5 cigarettes/day at time of event. Study medication was continued. Event resolved.
(b) (6) WF 37 bipolar disorder	After 53 days of study drug treatment, subject was **psychiatrically hospitalized**, and gave retrospective report of three weeks of impulsive thoughts of suicide by taking all of her medication. Complaints at admission included "becoming more aggressive in her thoughts and behavior." Site investigator noted that symptoms occurred in the context of ex-husband returning to live with the patient after being released from jail and that symptoms had not been reported during visits prior to hospitalization, and that the complaints may have been factitious. Smoking at time of the event reduced from 20 to 10 cigarettes/day.
Bupropion	
(b) (6) WM 58 bipolar disorder, panic	Treatment Day 14, subject began a four-day alcohol binge (a quart of vodka/day) and was hospitalized. The subject's sister reported that he was **hospitalized** for an exacerbation of his bipolar disorder. No details about affective symptoms were obtained.
(b) (6) WF 45 bipolar disorder	After ~3 weeks of study drug treatment, the subject was **psychiatrically hospitalized** for symptoms that her husband reported retrospectively had begun "a couple of weeks" earlier. He reported agitation for "a couple of weeks," worsening to her becoming "out of control," he was worried she might hurt herself or others.

	Presenting symptoms included aggression and anger. The subject had significantly decreased her cigarette use (2-3/day from BL 15) and stated that she felt exactly the same when she tried to quit smoking before without any medications. Subject remained hospitalized for a week; study drug discontinued. Urine screen positive for methamphetamine at admission and two days after discharge; cross-reactivity with bupropion evidently not considered[15]. No prior or subsequent methamphetamine positive screens. Two months later, subject reported agitation and panic attacks at a study visit, and two weeks later was re-hospitalized for ~1 week.
(b) (6) WM 36 major depressive disorder	One day after completing the course of study drug treatment, the subject (who was without any psychiatric symptoms at baseline) made a suicide attempt by inhaling butane from a cigarette lighter; this was attributed to a reaction to his girlfriend's suicide attempt two days earlier. The subject was **evaluated in an inpatient crisis setting** and referred for ongoing day treatment; a diagnosis of schizoaffective disorder was made but no information is provided to explain this diagnosis (e.g. presence of ongoing psychotic symptoms in absence of mood symptoms).
(b) (6) WF 59 bipolar disorder	When the site attempted to contact the subject to confirm her Week 2 visit, they were informed she had been **arrested and subsequently hospitalized**. Medication may have been taken for two weeks. Subject had been found walking naked in her neighborhood and "mooned" a neighbor. She was delusional and tangential during admission and refused voluntary admission. Study medication was discontinued.
(b) (6) WM 45 Major depressive disorder (recurrent); alcohol dependence (past)	On Study Day 84, subject was **psychiatrically hospitalized** for a relapse to alcohol dependence. Paroxetine was initiated for depression. Smoking had been reduced to 5 cigarettes/day at the time of the event.

[15] Therapeutic use of bupropion may be a cause of false-positive urine screens for amphetamines

(b) (6) WF 25 bipolar disorder	After four days of study drug treatment (first day of b.i.d. dosing), the subject experienced increased activity, tachycardia, racing thoughts, and pressured speech. She was "a bit more excited and irritated" at the Week 1 study visit but the mental health professional did not recommend any action be taken. On Study Day 12, the patient experienced symptoms of irritability, decreased mood, and anxiety and discontinued taking study drug. A few days later at a study visit, the mental health professional noted her to be in a mixed state of bipolar disorder and recommended she be withdrawn from the trial. Symptoms continued and the subject required **hospitalization** approximately 2 weeks later. She had increased her smoking above baseline levels.
(b) (6) WF 64 Depression, past alcoholism	The subject completed 85 days of study drug treatment; during treatment reported adverse events included irritability, panic attack, and depression, all assessed as “mild.” MHP evaluations at Study Day 29 and 36 record a recommendation for “medication;” it is not clear if any medication was initiated. (Baseline concomitant medications included mirtazapine and flupentixol.) Approximately 12 days later she was **hospitalized** for “alcoholism” for approximately two weeks.
(b) (6) WM 37 schizophrenia	The subject completed the course of treatment with study drug and reduced smoking from 26 to 10 cigarettes/day. Six days after completing treatment he was **hospitalized** so that treatment with clozapine could be re-initiated after having been discontinued three days earlier. The narrative summary did not provide a reason for admission.
NRT	
(b) (6) WM 28 schizophrenia	After ~8 weeks on study drug (7 weeks on NRT), subject reported anxiety and noted his mother had recently died, and that his personal physician had made some changes to his medications; anxiety worsened and approximately 10 days later he was **psychiatrically hospitalized** for a week. Smoking at the time of the event was 4 cigarettes/day (BL = 13). Study medication was discontinued. Events resolved.
(b) (6) WM 53 major depressive disorder	After 37 days of study drug treatment (30 days of NRT), subject discontinued taking study drug. The reason was not recorded; on-treatment evaluations recorded gradually increasing anxiety scores but symptoms were not considered "clinically significant." Two days after discontinuing study drug he reported that "I am in the hospital for my anxiety." He remained **hospitalized** for a week. Study drug was not resumed; subject was not evaluated at the study site until ~5 weeks later at which time symptoms had resolved.

(b) (6) WM 46 Major depressive disorder (recurrent), PTSD, alcohol dependence (full remission)	After approximately one month of study treatment, the subject was **hospitalized** for relapse to alcohol dependence. He was discontinued from the study. Smoking at the time of the event was reduced to 2 cigarettes/day.
(b) (6) WF 38 major depressive disorder	On Study Day 42 after ~6 weeks of NRT, the subject reported that she felt depressed with a lack of energy; study drug was discontinued. ~2 weeks later, depression worsened (subject had omitted antidepressant for ~4 days) and subject required **hospitalization** for depression. Smoking was unchanged from baseline.
Placebo	
(b) (6) [16] schizophrenia	During Week 7, patient took 4 bottles of study drug, after which she vomited and then fell asleep and did not seek medical attention. She reported this at the Week 8 visit, at which time she endorsed on the C-SSRS that she had active suicidal ideation (wish to be dead) and had a specific plan and intent to commit suicide. "The investigator recorded the event as a mild accidental overdose and attributed causality to the subject's long history of impulsivity thought disorder and similar events in which the subject would overdose without it being a suicide attempt." A psychiatric evaluation was performed and no treatment changes were recommended.
(b) (6) WF 26 major depressive disorder	On Treatment Day 6, subject reported feeling "irritable over small things," 18 days later she reported feeling depressed and having suicidal thoughts. She reportedly was admitted to a psychiatric hospital and was **hospitalized** for a month. Study drug was discontinued. Smoking at time of hospitalization is not known.
(b) (6) BM 35[17] generalized anxiety disorder	Subject failed to return after the Week 4 visit; however, the site learned through subject's girlfriend (also a subject in the study) that he had hit her in the head with a gun and fractured her skull. She noted that he had been violent before. He had been drinking at the time of the event.

[16] Not flagged as serious by Sponsor. The outcome was not serious because the pills consumed were placebo.
[17] In this case the aggressive behavior was coded as serious because of the risk to the victim, not the patient

(b) (6) WF 43 schizophrenia	On Study Day 42, the subject began treatment with disulfiram "to control alcohol intake." (Alcohol abuse is noted as a "past" diagnosis; the implication is that the subject relapsed to serious alcohol use requiring treatment.) The subject discontinued using study drug at that time. A psychiatric evaluation was done "due to an increase of depressive and anxious symptoms" but no adverse event was reported. Approximately a month later, the subject took an impulsive overdose of clorazepate stating "I felt nervous and distressed...I felt very sad and anxious and decided to take some pills and not wake up." There were minimal sequelae of the overdose. Smoking was reduced from BL 25 to 12 cigarettes/day.
(b) (6) WF 42 major depressive disorder, borderline PD	After 9 days of study drug treatment, subject attempted suicide by ingesting 56 aripiprazole and 30 diazepam tablets along with her week's supply of blinded study medications together with alcohol. The subject was **hospitalized** very briefly. Study medications were discontinued. Her cigarette use was reduced from BL 24 cigarettes/day at baseline to 20 cigarettes/day. Approximately 10 days later, the subject was **rehospitalized** for "recurrent symptoms of borderline personality disorder," and a few days later had again been "monitored in the hospital psychiatric department." Smoking was increased to 30 cigarettes/day.
(b) (6) WM 49[18] major depression	Within two days of initiating study drug treatment, subject reported feeling more depressed since starting the study medication, and experiencing increasing anxiety after a couple of days of study drug treatment, and endorsed feeling that "it would be easier to be dead" on C-SSRS. He also reported insomnia. Study drug was discontinued. ~1 week later, the subject was hospitalized for a medical illness (shortness of breath diagnosed as pulmonary embolus and cardiac failure); while hospitalized, he left the hospital, went home, and took 20 tablets of paracetamol 500 mg/codeine 30 mg. He returned to the hospital and reported the overdose but denied intent to kill himself. The patient required treatment with n-acetylcysteine for elevated acetaminophen level. The investigator did not consider this serious and did not consider it a suicide attempt.

[18] Coded as serious by sponsor because of the hospitalization for medical problem; overdose of acetaminophen was not assessed by sponsor as serious.

8.3.7. **Dropouts and/or Discontinuations Due to Adverse Effects**

Overall, adverse events leading to temporary or permanent discontinuation of study drug or to dose reduction were reported in 115 subjects. In the non-PHx group, all active treatment arms had a higher rate of dose reductions or discontinuations than the placebo arm; in the PHx cohort, rates were similar.

Table 31 Patients with Treatment-Emergent Adverse Events Leading to Dose Reductions or Discontinuations

	Varenicline	Bupropion	NRT*	Placebo
Non-PHx Cohort	N = 990	N = 989	N = 1006	N = 999
	122 (12%)	141 (14%)	152 (15%)	76 (8%)
PHx Cohort	N = 1026	N = 1017	N = 1016	N = 1015
	179 (17%)	153 (15%)	152 (15%)	140 (14%)

*Only discontinuation was possible
Prepared by clinical reviewer from Sponsor's dataset

The tables below, grouped by MedDRA Higher Level Group Term (HLGT), show types of events leading to reduction or discontinuation in at least 1% of subjects in any of the treatment arms.

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Table 32 Adverse Events Leading to Study Drug Reduction or Discontinuation in ≥1% in Any Arm; Non-Phx Cohort

SOC	HLGT	Varenicline N = 990		Bupropion N = 989		NRT N = 1006		Placebo N = 999	
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	1	0%	5	1%	1	0%	0	0%
Gastrointestinal disorders	GI motility & defaecation conditions	8	1%	1	0%	6	1%	3	0%
	GI signs and symptoms	49	5%	16	2%	20	2%	13	1%
General disorders and administration site conditions	Administration site reactions	2	0%	6	1%	32	3%	3	0%
	General system disorders NEC	10	1%	14	1%	10	1%	5	1%
Infections and infestations	Infections - pathogen unspec	7	1%	14	1%	6	1%	5	1%
Nervous system disorders	Headaches	12	1%	5	1%	15	1%	3	0%
	Neurological disorders NEC	10	1%	13	1%	10	1%	7	1%
Psychiatric disorders	Anxiety disorders & symptoms	10	1%	19	2%	12	1%	7	1%
	Depressed mood disorders and disturbances	9	1%	4	0%	4	0%	6	1%
	Mood disorders and disturbances NEC	7	1%	3	0%	3	0%	3	0%
Psychiatric disorders	Sleep disorders and disturbances	17	2%	26	3%	33	3%	14	1%
Skin and subcutaneous tissue disorders	Angioedema and urticaria	0	0%	6	1%	0	0%	0	0%
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	6	1%	15	2%	15	1%	3	0%

Table 33 Adverse Events Leading to Study Drug Reduction or Discontinuation in ≥1% in Any Arm; PHx Cohort

SOC	HLGT	Varenicline N = 1026		Bupropion N = 1017		NRT N =1016		Placebo N = 1015	
Cardiac disorders	Cardiac arrhythmias	3	0%	2	0%	0	0%	6	1%
Gastrointestinal disorders	GI motility & defaecation conditions	10	1%	0	0%	4	0%	6	1%
	GI signs and symptoms	62	6%	19	2%	20	2%	13	1%
General disorders and administration site conditions	Administration site reactions	0	0%	4	0%	19	2%	2	0%
	General system disorders NEC	12	1%	4	0%	14	1%	14	1%
Infections and infestations	Infections - pathogen unspec	9	1%	8	1%	7	1%	9	1%
Nervous system disorders	Headaches	5	0%	2	0%	7	1%	5	0%
	Neurological disorders NEC	13	1%	15	1%	9	1%	8	1%
Psychiatric disorders	Anxiety disorders and symptoms	16	2%	26	3%	19	2%	14	1%
	Depressed mood disorders and disturbances	21	2%	17	2%	13	1%	24	2%
	Mood disorders & disturbances NEC	10	1%	5	0%	7	1%	10	1%
	Sleep disorders and disturbances	11	1%	22	2%	31	3%	17	2%
Skin and subcutaneous tissue disorders	Angioedema and urticaria	1	0%	12	1%	2	0%	2	0%
	Epidermal and dermal conditions	9	1%	11	1%	19	2%	9	1%

Prepared by Clinical Reviewer from Sponsor's Dataset

8.3.8. **Significant Adverse Events**

Neuropsychiatric adverse events are discussed above in Section 6.

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8.3.10. **Treatment Emergent Adverse Events and Adverse Reactions**

Within the non-psychiatric history cohort, the three most frequent treatment-emergent adverse events in each of the four treatment groups were:

- Varenicline: nausea (243 [24.5%]), headache (116 [11.7%]), and insomnia (95 [9.6%]);
- Bupropion: insomnia (126 [12.7%]), nausea (90 [9.1%]), and headache (87 [8.8%]);
- NRT: headache (129 [12.8%]), abnormal dreams (111 [11.0%]), and nausea (95 [9.4%]); and
- Placebo: headache (95 [9.5%]), insomnia (73 [7.3%]), and nasopharyngitis (73 [7.3%]).

Within the psychiatric history cohort, the most frequent treatment-emergent adverse events in the four treatment groups were:

- Varenicline: nausea (268 [26.1%]), headache (129 [12.6%]), and abnormal dreams (118 [11.5%]);
- Bupropion: insomnia (119 [11.7%]), nausea (111 [10.9%]), and anxiety (105 [10.3%]);
- NRT: abnormal dreams (140 [13.8%]), headache (104 [10.2%]), insomnia (104 [10.2%]), and nausea (104 [10.2%]); and
- Placebo: headache (104 [10.2%]), nausea (74 [7.3%]), and irritability (67 [6.6%]).

Table 34, below, from Pfizer's submission below lists MedDRA Higher Level Group Terms (HLGT) reported by at least 5% of the varenicline-treated group (pooled cohorts) and more commonly than the placebo group. Within each HLGT, Preferred Terms (PTs) reported by at least 1% in the varenicline-treated group are shown. The overall profile of adverse events is similar to that established in previous trials

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Table 34 Most Frequent All Causality Treatment –Emergent Adverse Events (HLGT≥ 5% in Varenicline Group and More Commonly than Placebo Group, and PT ≥ 1% in Varenicline Group

	Varenicline 1.0 mg BID		Bupropion 150 mg BID		NRT 21/14/7 mg QD		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of Subjects:								
Evaluable for adverse events	2016		2006		2022		2014	
With adverse events	1503	(74.6)	1446	(72.1)	1435	(71.0)	1345	(66.8)
Discontinued due to adverse events	166	(8.2)	176	(8.8)	162	(8.0)	122	(6.1)
Number (%) of Subjects with Adverse Events by: System Organ Class and High Level Group Term and MedDRA (v18.0) Preferred Term								
GASTROINTESTINAL DISORDERS	786	(39.0)	527	(26.3)	480	(23.7)	414	(20.6)
Gastrointestinal motility and defaecation conditions	178	(8.8)	140	(7.0)	140	(6.9)	107	(5.3)
Constipation	90	(4.5)	76	(3.8)	49	(2.4)	37	(1.8)
Diarrhoea	75	(3.7)	57	(2.8)	76	(3.8)	56	(2.8)
Gastrointestinal signs and symptoms	636	(31.5)	312	(15.6)	306	(15.1)	251	(12.5)
Abdominal discomfort	22	(1.1)	12	(0.6)	6	(0.3)	17	(0.8)
Abdominal pain	31	(1.5)	18	(0.9)	10	(0.5)	21	(1.0)
Abdominal pain upper	43	(2.1)	23	(1.1)	27	(1.3)	25	(1.2)
Dyspepsia	46	(2.3)	34	(1.7)	45	(2.2)	31	(1.5)
Flatulence	30	(1.5)	18	(0.9)	23	(1.1)	18	(0.9)
Nausea	511	(25.3)	201	(10.0)	199	(9.8)	137	(6.8)
Vomiting	69	(3.4)	36	(1.8)	47	(2.3)	35	(1.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	270	(13.4)	241	(12.0)	404	(20.0)	229	(11.4)
General system disorders NEC	223	(11.1)	196	(9.8)	195	(9.6)	177	(8.8)
Fatigue	124	(6.2)	57	(2.8)	75	(3.7)	83	(4.1)
INFECTIONS AND INFESTATIONS	533	(26.4)	475	(23.7)	494	(24.4)	506	(25.1)
Infections - pathogen unspecified	459	(22.8)	414	(20.6)	417	(20.6)	428	(21.3)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
HLGTs with incidences > 4.95% and < 5% appear through rounding as 5%,but do not meet the cut-off point of >= 5% to be included in this table.
MedDRA (v18.0) coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.2 Date of Reporting Dataset Creation: 28MAY2015 Date of Table Generation: 13JAN2016 (13:40)

	Varenicline 1.0 mg BID		Bupropion 150 mg BID		NRT 21/14/7 mg QD		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of Subjects with Adverse Events by: System Organ Class and High Level Group Term and MedDRA (v18.0) Preferred Term								
Bronchitis	27	(1.3)	29	(1.4)	38	(1.9)	39	(1.9)
Gastroenteritis	36	(1.8)	32	(1.6)	39	(1.9)	35	(1.7)
Nasopharyngitis	174	(8.6)	156	(7.8)	126	(6.2)	135	(6.7)
Sinusitis	31	(1.5)	30	(1.5)	32	(1.6)	24	(1.2)
Upper respiratory tract infection	109	(5.4)	104	(5.2)	97	(4.8)	115	(5.7)
Urinary tract infection	23	(1.1)	21	(1.0)	12	(0.6)	17	(0.8)
NERVOUS SYSTEM DISORDERS	440	(21.8)	440	(21.9)	443	(21.9)	374	(18.6)
Headaches	258	(12.8)	195	(9.7)	249	(12.3)	209	(10.4)
Headache	245	(12.2)	186	(9.3)	233	(11.5)	199	(9.9)
Neurological disorders NEC	180	(8.9)	228	(11.4)	179	(8.9)	154	(7.6)
Dizziness	78	(3.9)	98	(4.9)	85	(4.2)	66	(3.3)
Dysgeusia	53	(2.6)	86	(4.3)	40	(2.0)	38	(1.9)
Somnolence	29	(1.4)	19	(0.9)	29	(1.4)	16	(0.8)
PSYCHIATRIC DISORDERS	720	(35.7)	767	(38.2)	721	(35.7)	613	(30.4)
Anxiety disorders and symptoms	236	(11.7)	294	(14.7)	239	(11.8)	224	(11.1)
Agitation	79	(3.9)	85	(4.2)	67	(3.3)	66	(3.3)
Anxiety	132	(6.5)	169	(8.4)	138	(6.8)	120	(6.0)
Nervousness	35	(1.7)	37	(1.8)	28	(1.4)	36	(1.8)
Depressed mood disorders and disturbances	175	(8.7)	143	(7.1)	151	(7.5)	161	(8.0)
Depressed mood	78	(3.9)	60	(3.0)	79	(3.9)	81	(4.0)
Depression	66	(3.3)	58	(2.9)	55	(2.7)	61	(3.0)
Sleep disorders and disturbances	437	(21.7)	456	(22.7)	483	(23.9)	295	(14.6)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
HLGTs with incidences > 4.95% and < 5% appear through rounding as 5%,but do not meet the cut-off point of >= 5% to be included in this table.
MedDRA (v18.0) coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.2 Date of Reporting Dataset Creation: 28MAY2015 Date of Table Generation: 13JAN2016 (13:40)

	Varenicline 1.0 mg BID		Bupropion 150 mg BID		NRT 21/14/7 mg QD		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of Subjects with Adverse Events by: System Organ Class and High Level Group Term and MedDRA (v18.0) Preferred Term								
Abnormal dreams	201	(10.0)	131	(6.5)	251	(12.4)	92	(4.6)
Initial insomnia	22	(1.1)	14	(0.7)	20	(1.0)	6	(0.3)
Insomnia	189	(9.4)	245	(12.2)	195	(9.6)	139	(6.9)
Nightmare	22	(1.1)	16	(0.8)	56	(2.8)	17	(0.8)
Sleep disorder	65	(3.2)	73	(3.6)	45	(2.2)	42	(2.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	146	(7.2)	127	(6.3)	149	(7.4)	141	(7.0)
Respiratory disorders NEC	104	(5.2)	92	(4.6)	114	(5.6)	103	(5.1)
Cough	35	(1.7)	35	(1.7)	38	(1.9)	40	(2.0)
Oropharyngeal pain	20	(1.0)	21	(1.0)	29	(1.4)	27	(1.3)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
HLGTs with incidences > 4.95% and < 5% appear through rounding as 5%,but do not meet the cut-off point of >= 5% to be included in this table.
MedDRA (v18.0) coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.2 Date of Reporting Dataset Creation: 28MAY2015 Date of Table Generation: 13JAN2016 (13:40)

8.3.11. Laboratory Findings

Common laboratory test abnormalities included increased eosinophils, cholesterol, low-density lipoprotein cholesterol, and triglycerides and decreased high-density lipoprotein cholesterol. The proportion of these laboratory test abnormalities was comparable to placebo across the active treatment groups, and also by cohort. Median changes from baseline to last observation in laboratory test data were small and comparable across treatment groups and cohorts.

8.3.12. Vital Signs

Median changes from baseline to last observations (weeks 12 and 24) in sitting blood pressure (systolic and diastolic) and heart rate were small and not clinically important across treatment groups and cohorts.

Adverse events leading to permanent discontinuation of study drug that were potentially associated with a clinically significant change in vital signs were reported in 12 subjects, 4 from the non-psychiatric cohort, and 8 from the psychiatric cohort distributed across treatment groups.

8.3.13. Electrocardiograms (ECGs)

No new safety signals were found in any of the treatment arms for either cohort.

8.3.14. QT

No new safety signals were found in any of the treatment arms for either cohort.

8.3.15. Immunogenicity

N/A

8.4. Analysis of Submission-Specific Safety Issues

To supplement the analysis of the composite safety endpoint, analyses employing the Standardized MedDRA Queries for certain types of events were also conducted. The findings are generally consistent with the analysis of the composite endpoint, with no obvious differences across groups in the non-psychiatric cohort, and small increases in varenicline-treated and bupropion-treated groups compared to placebo in the psychiatric cohort.

Table 35 Frequency of Events in Selected SMQs--Non PHx cohort

Non-Psych Cohort	Varenicline 1.0 mg BID (N = 1005)			Bupropion 150 mg BID (N = 1001)			NRT 21/14/7 mg QD (N = 1013)			Placebo (N = 1009)		
	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%
Depression and suicide/self-injury (narrow)	96	67	7	55	41	4	57	42	4	92	60	6
Depression and suicide/self-injury (broad)	165	112	11	131	88	9	139	91	9	141	88	9
(Suicide/self-injury *(narrow)	2	2	0	5	4	0	4	2	0	5	4	0
Suicide/self-injury (broad)	2	2	0	5	4	0	4	2	0	5	4	0
Depression (excl suicide and self injury) (narrow)	94	67	7	50	37	4	53	40	4	87	58	6
Depression (excl suicide and self injury) (broad)	163	112	11	126	84	8	135	89	9	136	87	9
Psychosis and psychotic disorders (narrow)	1	1	0	3	3	0	2	2	0	1	1	0
Psychosis and psychotic disorders (broad)	19	14	1	11	10	1	13	12	1	17	13	1
Accidents and injuries	94	64	6	78	51	5	105	63	6	107	61	6
Hostility/aggression (narrow)	10	9	1	12	6	1	16	16	2	17	15	1
Hostility/aggression (broad)	115	84	8	98	69	7	122	92	9	103	77	8

Source: Prepared by Dr. Sarah Arnold from Sponsor's datasets

Table 36 Frequency of Events in Selected SMQs--PHx cohort

Psych Cohort	Varenicline 1.0 mg BID (N = 1032)			Bupropion 150 mg BID (N = 1033)			NRT 21/14/7 mg QD (N = 1025)			Placebo (N = 1026)		
	Events	N	(%)	Events	N	(%)	Events	N	(%)	Events	N	(%)
Depression and suicide/self-injury (narrow)	209	136	13.18	209	132	12.78	227	134	13.07	203	127	12.38
Depression and suicide/self-injury (broad)	336	200	19.38	333	196	18.97	343	192	18.73	296	174	16.96
Suicide/self-injury (narrow)	13	10	0.97	6	5	0.48	11	11	1.07	15	10	0.97
Suicide/self-injury (broad)	13	10	0.97	6	5	0.48	11	11	1.07	15	10	0.97
Depression (excl suicide and self injury) (narrow)	196	128	12.4	203	130	12.58	216	132	12.88	188	121	11.79
Depression (excl suicide and self injury)(broad)	323	194	18.8	327	194	18.78	332	190	18.54	281	169	16.47
Psychosis and psychotic disorders (narrow)	27	17	1.65	24	15	1.45	19	10	0.98	22	15	1.46
Psychosis and psychotic disorders (broad)	85	57	5.52	63	43	4.16	51	32	3.12	41	33	3.22
Accidents and injuries (narrow)	97	61	5.91	125	62	6	133	74	7.22	75	48	4.68
Accidents and injuries (broad)	108	66	6.4	139	69	6.68	144	79	7.71	85	53	5.17
Hostility/aggression (narrow)	34	26	2.52	29	22	2.13	19	18	1.76	33	19	1.85
Hostility/aggression (broad)	217	133	12.89	197	119	11.52	184	129	12.59	192	133	12.96

Source: Prepared by Dr. Sarah Arnold from Sponsor's datasets

8.5. Safety in the Postmarket Setting

8.5.1. Safety Concerns Identified Through Postmarket Experience

This supplement focuses on a specific safety concern identified through postmarket experience.

8.6. Integrated Assessment of Safety

Supplement is based on a single study

9 Advisory Committee Meeting and Other External Consultations

In October 2014, in the context of a previous labeling supplement submitted by Pfizer proposing to remove the boxed warning from the Chantix labeling, data from randomized controlled trial (RCT) meta-analyses, and observational studies were discussed at a joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). The committees were asked to discuss how they would weigh the evidence contributed by the meta-analyses, observational studies, and spontaneous case reports when they were evaluating the risk of serious neuropsychiatric adverse events in patients taking varenicline. In general, many of the committee members expressed concern with the quality of the data presented. The committee members were also asked based on the data presented on the risk of serious neuropsychiatric adverse events with Chantix, whether they would they recommend removal or modification of the boxed warning statements regarding risk of serious neuropsychiatric adverse events, or retention of the current boxed warning statements with a reassessment once the ongoing post-market safety outcome trial was completed.

The majority of the committee agreed that more data were needed and recommended to retain the current boxed warning statements and reassess once the post-market safety outcome trial results were available.

Accordingly, the results of the trial, and updated reviews of observational studies, were discussed at a second joint meeting of the PDAC and the DSaRM AC on September 14, 2016. Because of the specific concerns to be discussed, SGEs with a variety of backgrounds were also added as voting members for this meeting. These included individuals with general internal medicine background, as well as clinicians involved in smoking control and smoking cessation research. Experts who had attended the meeting to discuss the previous labeling supplement were invited; some were not available.

Key issues to be discussed at the meeting included the Committees' opinion on the following topics:

- The strengths and weaknesses of the completed randomized controlled trial (RCT) with regard to the study design including the novel primary endpoint.
- The potential impact of the variability in data collection, adverse event coding, and case definition on the primary endpoint.
- Which analysis and results most appropriately described the effect of the smoking cessation therapies on neuropsychiatric events.
- The contribution of the evidence from observational studies when evaluating the risk of serious neuropsychiatric adverse events in patients taking smoking cessation products.
- The impact of psychiatric history on the occurrence of neuropsychiatric adverse events during smoking cessation therapy.
- Whether the boxed warning should be removed, modified, or retained, and whether any additional labeling changes should be made.

Overall, panel members agreed that the trial design was good and applauded the completion of a randomized controlled trial to add to prior studies. There were concerns regarding the number of sites and difficulty with data monitoring and control across so many countries, languages, cultures, and investigators. The committee members also expressed concerns with the lack of power to address suicidal events. Some panel members noted the need for having a design that holds to rigorous standards for safety related outcomes, and stated power calculations a priori for this deserved closer attention. Some of the committee members expressed concerns regarding the inclusion of patients who were not naïve to treatment with the drugs under study, which may have enriched the population for individuals able to tolerate the drugs. However, following the advisory committee, FDA obtained a data set from Pfizer that excluded the patients who had prior exposure to the study drugs, and the results of the primary analysis in this population of patients naïve to the study drugs were similar to what was observed in the full population.

Most committee members did not have specific recommendations regarding which of the analyses best represented the data, although there was support for using an expanded outcome definition and for using the alternate statistical approach employed by the FDA team. The potential impact of the variability of data collection practices and coding of adverse events was discussed, but some committee members noted that they did not expect that the variability would affect the adverse event (AE) data differentially across treatment arms.

The committee members did not think emphasis should be placed on the observational studies and concluded that they did not contribute additional insight beyond the findings of the RCT.

Committee members noted the increased risk for neuropsychiatric events in the population with a psychiatric history. Several committee members who noted this difference recommended that this information needs to be described in product labeling.

The committee members were asked to vote for one of the following options:
A. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events (10 members voted for this option)
B. Modify the language in the boxed warning (4 members voted for this option)
C. Keep the current boxed warning (5 members voted for this option)

Some committee members who voted to remove the boxed warning noted that the decision was difficult due to their concerns with the limitations from the study results presented. Some also noted the public health importance of effective smoking cessation therapies being available for patients who need smoking cessation aids, especially those with psychiatric illness.

Several members who voted to retain or modify the boxed warning voiced that their reason was not related to the study, but due to a concern that removing a boxed warning would be misinterpreted as communicating a complete absence of risk. There was also concern about the potential precedent-setting nature of the removal of the boxed warning for other products in the future. A few members of the committee voted to keep the boxed warning, citing concerns about the study endpoint, study conduct, and the inadequate statistical power to detect more rare events, or simply noted that they were unconvinced by the study.

10 Labeling Recommendations

10.1. Prescribing Information

Pfizer proposed to make the following changes in labeling:
Boxed warning deleted – Review team concurs

New language for 5.1:
Significant (b) (4) text from body of warning include text communicating the following concepts:

(b) (4)

- (b) (4)
- (b) (4)
- (b) (4)

The review team does not concur with deleting all of these messages. Recommended wording is shown below.

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3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Additions to 5.1

Section 5.1 currently contains text describing metaanalysis of RCTs and descriptions of observational studies. Pfizer's proposal includes (b) (4)

The review team does not concur with (b) (4)

(b) (4)

General Safety and Efficacy findings from PMR RCT
Adverse event rates from PMR study added to the Adverse Reactions section in text.
Review team concurs.

Clinical Trials Section: Description and quit rate table added
Review team concurs, and proposes to add NPS safety results to this section as well, using Expanded NPS rates.

Patient Counseling (b) (4) if patients develop neuropsychiatric symptoms. Patients directed only to "contact a health care professional" if they develop symptoms. (b) (4)

10.2. Patient Labeling

Pfizer's labeling proposal included (b) (4)

10.3. Nonprescription Labeling

N/A

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11 Risk Evaluation and Mitigation Strategies (REMS)

Because of the post-marketing safety signal of neuropsychiatric adverse events, Chantix is currently marketed under a REMS. The goal of the REMS is to inform patients about the potential serious risk of serious neuropsychiatric adverse events associated with the use of Chantix. The elements of the REMS are limited to a Medication Guide (MG) and a timetable for submission of assessments.

Previous assessment reports have concluded that the risk of neuropsychiatric adverse events is understood by 70-80% of patients. Moreover, the results of this PMR trial indicate that the risk of events of a serious nature is lower than previously suspected. Although disturbances in mood, thinking, and behavior are not uncommon, the vast majority of these events are not serious. Therefore, consistent with our conclusion that the boxed warning is no longer warranted in the package insert, it is appropriate that the REMS no longer be required. A MedGuide will still be distributed which informs patients about these risks, but FDA will not require this under a REMS with periodic assessments.

12 Postmarketing Requirements and Commitments

No new PMRs or PMCs are recommended.

13 Appendices

13.1. References

N/A

13.2. Financial Disclosure

A Form FDA 3455, Disclosure Statement was provided for each clinical investigator who, or whose spouse or dependent child, had disclosable financial interests in and/or arrangements with any sponsor of the covered clinical study. As noted in section 6.1.2, additional sensitivity analyses were conducted excluding the 32 sites involved.

Phase 4, Randomized, Double Blind, Active and Placebo Controlled Multi-Center Study Evaluating the Neuropsychiatric Safety and Efficacy of Varenicline and Buproprion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 975		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 7 Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	YesX☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes X☐	No ☐ (Request explanation from Applicant)

13.3. List of Investigators and Centers

Investigator and Site List

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/s/

CELIA J WINCHELL
11/14/2016

Medical Officer Review of Periodic Adverse Drug Experience Report

NDA Number(s)/Submission: NDA-21928/ PADER-23; SD-1739
Trade/Drug Name: Chantix/Champix
Date Submitted: 7/7/2016
Date Completed: 9/6/2016
Reviewer: Sarah Arnold, MD/MPH

REVIEW: This is a Periodic Adverse Drug Experience Report covering the period from May 23, 2015 to April 23, 2016

The safety update contains 3 sets of data:

- Clinically important follow up received for the time period for death and nonfatal SAE cases reported in study A3051123.
- New death and nonfatal SAE cases reported during the time period for subjects enrolled in study A3051123 who did not enroll in study A3051148.
- All death and nonfatal SAE cases reported as part of Study A3051148 for the time period.

Clinically Important Follow-up to Deaths and Nonfatal SAEs

- 11 cases were identified with clinically important follow-up. Of these, 6 were placebo (2 NonPHx cohort, 4 PHx cohort). Of the remaining 5 cases, 1 was varenicline, 2 bupropion, 2 NRT, all from the PHx cohort.

New Deaths and Nonfatal SAEs for Subjects in study A3051123 not enrolled in study A3051148
No deaths or nonfatal SAEs reported.

Deaths and Nonfatal SAEs for study A3051148

- 140 cases, including 4 deaths identified.
- The 140 cases involved 124 unique subjects as summarized, along with deaths, in Table 1 below based on cohort and study arm.

Table 1. Subjects Reporting Serious Adverse Events Including Deaths in Study A3051148, from Informed Consent for A3051148 through 23 April 2016

	Varenicline	Bupropion	NRT	Placebo
Non PHx Cohort	**N=564**	**N=547**	**N=515**	**N=534**
Number of subjects reporting any SAE	10	13	15	14
Number of deaths	0	0	0	0
Number of subjects reporting an SAE included in the NPS primary endpoint	0	0	0	1
PHx Cohort	**N=628**	**N=619**	**N=601**	**N=587**
Number of subjects reporting an SAE	17	14	24	17[a]
Number of deaths	2	1	1	0
Number of subjects reporting an SAE included in the NPS primary endpoint	2	3	3	2

a. Includes one exposure in utero case resulting in a premature birth which was assigned to the baby rather than the mother who was enrolled in the study.
Source: Appendix 4, Appendix 5, Appendix 6 and A3051123 CSR Table 16.2.4.1

Table 2 summarizes subjects reporting SAEs by MedDRA SOC.

Table 2. Subjects with Serious Adverse Events Reported in Study A3051148 through 23 April 2016 by System Organ Class

	Non-PHx Cohort				PHx Cohort			
System Organ Class	Var	Bup	NRT	Pbo	Var	Bup	NRT	Pbo
Cardiac disorders		5	4	3	1	1[a]	5	3
Congenital, familial and genetic disorders	1							
Ear and labyrinth disorders		1						1
Endocrine disorders					1			
Eye disorders		1				1		
Gastrointestinal disorders			2	2	3[a]	2	2	1
General disorders and administration site conditions					1[a]	2	2	1
Hepatobiliary disorders	1		1		1		2	
Immune system disorders			1					
Infections and infestations	3	1	1	2	4	1	5	3
Injury, poisoning and procedural complications	2	1		2	1	1		2
Investigations		1						
Metabolism and nutrition disorders			1					
Musculoskeletal and connective tissue disorders	1		2		1		1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1		1	5	1	1	1	3
Nervous system disorders		1	1	1	1	2		2
Pregnancy, puerperium and perinatal conditions	1						1	1[b]
Psychiatric disorders				1	2	4	3[a]	2
Renal and urinary disorders						1	2	1
Respiratory, thoracic and mediastinal disorders		2	2		1	1	2	
Surgical and medical procedures								1
Vascular disorders		1	2			1	1	

a. 1 death case.
b. exposure in utero case assigned to baby of mother enrolled in the study.
Var=varenicline; Bup=bupropion, NRT=nicotine replacement therapy; Pbo=placebo
Source: Appendix 5; A3051123 CSR Table 16.2.4.1
MedDRA v 18.1

Conclusion

This 4-month safety update to the varenicline sNDA (S-040) based on study A3051123 provides updated information on deaths and nonfatal SAEs for subjects enrolled in study A3051123. There were 11 cases reported with clinically important follow-up during the time period noted, 1 of which involved 1 varenicline subject. There were no new cases reported during the same period for subjects in study A3051123 who did not enroll in the extension study, A3051148. For subjects who did enroll in study A3051148, 124 subjects experienced an SAE after consent, including 4 deaths. A total of 11 of the 124 subjects experienced an SAE that was of the type and severity included in the NPS AE endpoint study A3051123; the number of subjects reporting these events was similar across treatment arms and included 2 varenicline subjects. No new safety concerns for varenicline were identified.

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/s/

SARAH J ARNOLD
09/06/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

STATISTICAL REVIEW(S)

STATISTICS REVIEW

AMENDMENT TO 11/10/2016 STATISTICS REVIEW

Date:	11/21/2017
To:	Project Manager: Ayanna Augustus, PhD, RAC Team Lead: Celia Winchell, M.D. Deputy Director of Safety: Judy Racoosin, M.D. Division of Anesthesia, Analgesia, and Addiction Products
From:	Eugenio Andraca-Carrera, Ph.D., Primary Reviewer, DB7
Through:	Mat Soukup, Ph.D., Team Lead, DB7
NDA #:	21-928
Supplement #:	S040
Drug Name:	Chantix (varenicline) tablet; 0.5 mg and 1.0 mg
Indication(s):	Aid to smoking cessation
Applicant:	Pfizer, Inc.
Subject:	Updated analysis of neuropsychiatric safety in trial A3051123 based on newly defined endpoints.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

1 INTRODUCTION

In May 2008, the FDA issued a post-marketing requirement (PMR) for a clinical study or trial to assess the risk of serious neuropsychiatric adverse events associated with the use of varenicline, bupropion, nicotine replacement therapy (NRT), or placebo as aids to smoking cessation over 12 weeks of treatment. Trial A3051123 was a large randomized, double-blind trial designed to fulfill the PMR. The trial was completed in 2015. In February 2016, Pfizer submitted a supplemental NDA requesting updates to the Chantix labeling relating to the risk of NPS events based on the outcomes of the trial. A statistical review of trial A3051123 co-authored by Eugenio Andraca-Carrera and Dr. Yi Ren (Team Leads Dr. Mat Soukup and Dr. David Petullo) was signed on 10 November 2016.

The primary safety endpoint in trial A3051123 was a composite of treatment emergent moderate and severe adverse events in 261 MedDRA preferred terms corresponding to 16 components. This endpoint is referred to as the neuropsychiatric or 'NPS' endpoint. Multiple issues related to the evaluation of neuropsychiatric safety were identified during the review process. The clinical review team identified potential data coding errors of the NPS endpoint and deficient adverse event narratives throughout the trial, and the statistics review team found high heterogeneity in the rate of NPS events by trial sites in the cohort of subjects with a history with psychiatric illness at baseline. In order to address these limitations and to assess the robustness of the primary NPS safety results to changes in the endpoint definition, the statistics review team conducted sensitivity analyses of alternative composite neuropsychiatric endpoints which are discussed in the 11/10/2016 review.

On 7 September 2016 Pfizer submitted the results of their own sensitivity analysis using an expanded NPS endpoint[1]. This amendment to the 11/10/2016 statistical review discusses the analysis of 2 endpoints: the expanded NPS proposed by the sponsor based on their 7 September 2016 submission, and an expanded endpoint defined by the clinical review team at the FDA. The dataset scs719.xpt submitted on 21 October 2016 was used to conduct the analyses on this addendum.

2 Expanded Endpoints

2.1 Sponsor's Expanded NPS Endpoint

The expanded NPS endpoint was defined by the sponsor as follows[2]:

> The expanded definition included the original primary NPS AE endpoint plus the following:
>
> 1. Clinical consensus cases based on a blind review of the patient health information provided by the CGI-I, the HADS-A and HADS-D and the C-SSRS scales, as well as the Mental Health psychiatric evaluations that were required as part of the protocol.

[1] The sponsor submitted additional tables and datasets to support the analyses of their expanded endpoint in October 2016.
[2] Source: a3051123-sensitivity-analysis.pdf submitted to NDA 21928, eCTD Sequence Number 0414 on 9/7/2016

Specifically, data listings were prepared for subjects meeting any of the following criteria during the treatment emergent period (through end of treatment plus 30 days):

a) Adverse event of any severity in the MedDRA Suicide and Self-Injury SMQ (all terms in the primary NPS endpoint plus "intentional overdose")
b) CGI-I of much worse or very much worse
c) C-SSRS of ideation 4 or 5 or any behavior
d) HADS score of >15 for either subscale, depression or anxiety
e) A psychiatric evaluation by a MHP that resulted in a new DSM-IV diagnosis, represented an exacerbation of a pre-existing condition, or the MHP said the subject should not continue in the study.

Two Pfizer clinicians separately identified subjects as potential 'events' based on blinded review of the data listings prepared based on the above criteria. Lists of subjects identified by each clinician were then forwarded to a third clinician for blinded review and final determination of clinical consensus as to whether the subject should be included as having an expanded NPS event for this sensitivity analysis. It should be noted that this review also included all the cases for which narratives have been submitted to FDA.

Or, if not identified by clinical consensus,

2. "Moderate" AEs coded to any one or more of the MedDRA components of "Anxiety", "Depression", Feeling Abnormal" or "Hostility". Please note that subjects with "severe" adverse events coded to any one or more of these MedDRA components were already included in the pre-specified primary composite NPS endpoint.

Or, if not identified by clinical consensus or the moderate ratings for the above four components,

3. "Moderate" or "severe" AEs events coded to a MedDRA preferred term of "Irritability".

One potential limitation of this expanded endpoint is that subjects who were not identified by clinical consensus provided by the CGI-I, the HADS-A and HADS-D and the C-SSRS scales, as well as the Mental Health psychiatric evaluations, who contributed adverse events of anxiety, depression, hostility, feeling abnormal, or irritability to the expanded endpoint may not represent clinically significant neuropsychiatric adverse events. In order to address this limitation of the sponsor's expanded NPS endpoint, the clinical review team at the FDA defined a new 'FDA expanded NPS endpoint'.

2.2 FDA Expanded NPS Endpoint

The clinical review team at the FDA constructed a similar expanded NPS endpoint defined as follows[3]:

[3] Source: Clinical review authored by Dr. Celia Winchell dated 14 November 2016

1. Subjects who met the original protocol-specified criteria based on event type and investigator severity rating

2. Subjects identified by Pfizer's clinical consensus process

3. Subjects (identified by Pfizer's process) who had recorded adverse events in the NPS endpoint that were rated moderate, but also had one or more of the criteria indicating clinical significance:

    a. Adverse event of any severity in the MedDRA Suicide and Self-Injury SMQ (all terms in the primary NPS endpoint plus "intentional overdose")
    b. CGI-I of much worse or very much worse
    c. C-SSRS of ideation 4 or 5 or any behavior
    d. HADS score of >15 for either subscale, depression or anxiety
    e. A psychiatric evaluation by a MHP that resulted in a new DSM-IV diagnosis, represented an exacerbation of a pre-existing condition, or the MHP said the subject should not continue in the study

4. Subjects (identified by FDA adjudication process) who had a psychiatric evaluation by a MHP that resulted in a new DSM-IV diagnosis, represented an exacerbation of a pre-existing condition, or the MHP said the subject should not continue in the study and did not have recorded adverse events in the NPS endpoint that were rated moderate, but had documented clinically significant events in the MHP evaluation line listings, meeting the case definition above.

The two main differences between the FDA expanded endpoint and the sponsor's expanded endpoint are:

1. The FDA expanded endpoint does not include moderate AEs coded to anxiety, depression, feeling abnormal or hostility, or moderate or severe AEs coded to irritability among subjects who were not identified by the CGI-I, HADS-A, HADS-D, or C-SSRS scales, or by the Mental Health psychiatric evaluations.
2. The FDA expanded endpoint includes an additional adjudication process to identify clinically significant events as described in item (4) above.

These two changes in the endpoint definition were made to increase the specificity of the FDA expanded endpoint relative to the sponsor's expanded endpoint to capture clinically significant neuropsychiatric adverse events.

3 Statistical Methodology

The analyses of the sponsor's expanded NPS endpoint and the FDA expanded NPS endpoint were conducted in the Safety Analysis Population, which is defined as all treated subjects from the time of their first dose to the time of their last dose of study drug plus 30 days.

The analysis of the sponsor's expanded NPS endpoint will be limited to descriptive statistics of the number of observed events by component of the endpoint, randomized treatment arm, and

cohort of psychiatric illness at baseline: subjects with no prior history of psychiatric illness at baseline (Non-PHx) and subjects with a history of psychiatric illness at baseline (PHx).

The FDA expanded endpoint will be summarized by component of the FDA expanded endpoint, treatment arm, and psychiatric cohort at baseline. A statistical model will be fit to estimate the risk difference of the FDA expanded endpoint for all 6 pairwise treatment comparisons (varenicline - placebo, bupropion - placebo, etc…) by cohort of previous diagnosis of a psychiatric disorder. The risk difference will be estimated through a generalized linear model for binary data with an identity link function and a binomial error function. The model will include covariates for treatment (4 levels), cohort (2 levels), treatment by cohort interaction, and region of randomization (2 levels: USA vs. non-USA). This statistical model is consistent with the primary statistical model used in the analysis of the primary NPS endpoint.

4 Results

4.1 Analysis of the Sponsor's Expanded NPS Endpoint

Table 1 and Table 2 show the number of subjects with at least one observed sponsor's expanded NPS event by treatment arm and cohort of psychiatric history at baseline.

In the Non-PHx cohort (Table 1), subjects randomized to varenicline (45) observed fewer events than those randomized to bupropion (50), NRT (51), or placebo (56). Approximately 42% (84/212) of the expanded events in the Non-PHx cohort across all treatment arms were primary NPS events. The majority of the additional events (117/212) were added to the expanded endpoint due to adverse events of anxiety, depression, hostility, feeling abnormal, or irritability, as shown in the last two rows of Table 1.

In the PHx cohort (Table 2) subjects randomized to varenicline (140 events) and bupropion (138) experienced more expanded NPS events than subjects randomized to NRT (130) or placebo (123). Approximately 45% (239/531) of the expanded events in the PHx cohort across all treatment arms were primary NPS events. Ten events were added based on clinical review conducted by the sponsor and 282 events were added based on adverse events of anxiety, depression, hostility, feeling abnormal, or irritability.

The last row of Table 1 and Table 2 show subjects who were not identified by clinical consensus but nevertheless contributed events of anxiety, depression, hostility, feeling abnormal, or irritability to the expanded NPS endpoint. These events may not necessarily represent clinically significant neuropsychiatric adverse events as discussed in Section 2.1. In order to address this potential limitation of the sponsor's expanded NPS endpoint, Section 4.2 discusses analyses of the FDA expanded NPS endpoint.

Table 1. Expanded NPS Endpoint in the Non-PHx Cohort

	Varenicline N = 990	Bupropion N = 989	NRT N = 1006	Placebo N = 999
Expanded NPS	**45 (4.5%)**	**50 (5.1%)**	**51 (5.1%)**	**56 (5.6%)**
Primary NPS	13	22	25	24
Identified by Pfizer's clinical review	0	1*	0	0
Clinically reviewed by Pfizer + anxiety, depression, hostility, feeling abnormal, irritability	12	9	6	13
Not clinically reviewed with anxiety, depression, hostility, feeling abnormal, irritability	20	18	20	19

*1 subject was recorded as having an expanded NPS event due to clinical review even though he/she did not undergo clinical review (flag for clinical review = 0)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Scs719.xpt

Table 2. Expanded NPS Endpoint in the PHx Cohort

	Varenicline N = 1026	Bupropion N = 1017	NRT N = 1016	Placebo N = 1015
Expanded NPS	**140 (13.6%)**	**138 (13.6%)**	**130 (12.8%)**	**123 (12.1%)**
Primary NPS	67	68	54*	50
Identified by Pfizer's clinical review	3	1	2	4
Clinically reviewed by Pfizer + anxiety, depression, hostility, feeling abnormal, irritability	43	41	31	33
Not clinically reviewed + anxiety, depression, hostility, feeling abnormal, irritability	27	28	43	36

*The original analysis included 53 NPS events in the NRT arm of the PHx cohort, this dataset lists 54

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Scs719.xpt

4.2 Analysis of the FDA Expanded Endpoint

Table 3 and Table 4 show the number of subjects with at least one observed FDA expanded NPS event by treatment arm and cohort of psychiatric history at baseline. The FDA adjudication process contributed 14 events in the Non-PHx cohort and 43 events in the PHx cohort. These tables show a similar pattern of events by treatment arm and cohort as Table 1 and Table 2. In the Non-PHx cohort, fewer subjects on varenicline (3.1%) experienced an event than on bupropion (3.5%), NRT (3.3%), or placebo (4.0%). In the PHx cohort, subjects randomized to varenicline (12.2%) and bupropion (11.9%) experienced a higher rate of events than subjects randomized to NRT (9.6%) or placebo (9.5%).

Table 3. FDA Expanded NPS Endpoint in the Non-PHx Cohort

	Varenicline N = 990	Bupropion N = 989	NRT N = 1006	Placebo N = 999
FDA Expanded NPS	**31 (3.1%)**	**35 (3.5%)**	**33 (3.3%)**	**40 (4.0%)**
Primary NPS	13	22	25	24
Identified by Pfizer's clinical review	0	1	0	0
Clinically reviewed by Pfizer + anxiety, depression, hostility, feeling abnormal, irritability	12	9	6	13
Adjudicated by FDA clinicians	6	3	2	3

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Scs719.xpt

Table 4. FDA Expanded NPS Endpoint in the PHx Cohort

	Varenicline N = 1026	Bupropion N = 1017	NRT N = 1016	Placebo N = 1015
FDA Expanded NPS	**125 (12.2%)**	**121 (11.9%)**	**98 (9.6%)**	**96 (9.5%)**
Primary NPS	67	68	54	50
Identified by Pfizer's clinical review	3	1	2	4
Clinically reviewed by Pfizer + anxiety, depression, hostility, feeling abnormal, irritability	43	41	31	33
Adjudicated by FDA clinicians	12	11	11	9

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Scs719.xpt

A site audit conducted by the Office of Scientific Investigations at the FDA identified important problems in the conduct of the trial at site 1077 and suggested that data from this site may not be interpretable. Site 1002 was also identified by OSI and by an internal audit conducted by the sponsor as having experienced similar problems. Table 5 shows a summary of FDA expanded NPS events by treatment arm and cohort excluding these 2 problematic sites.

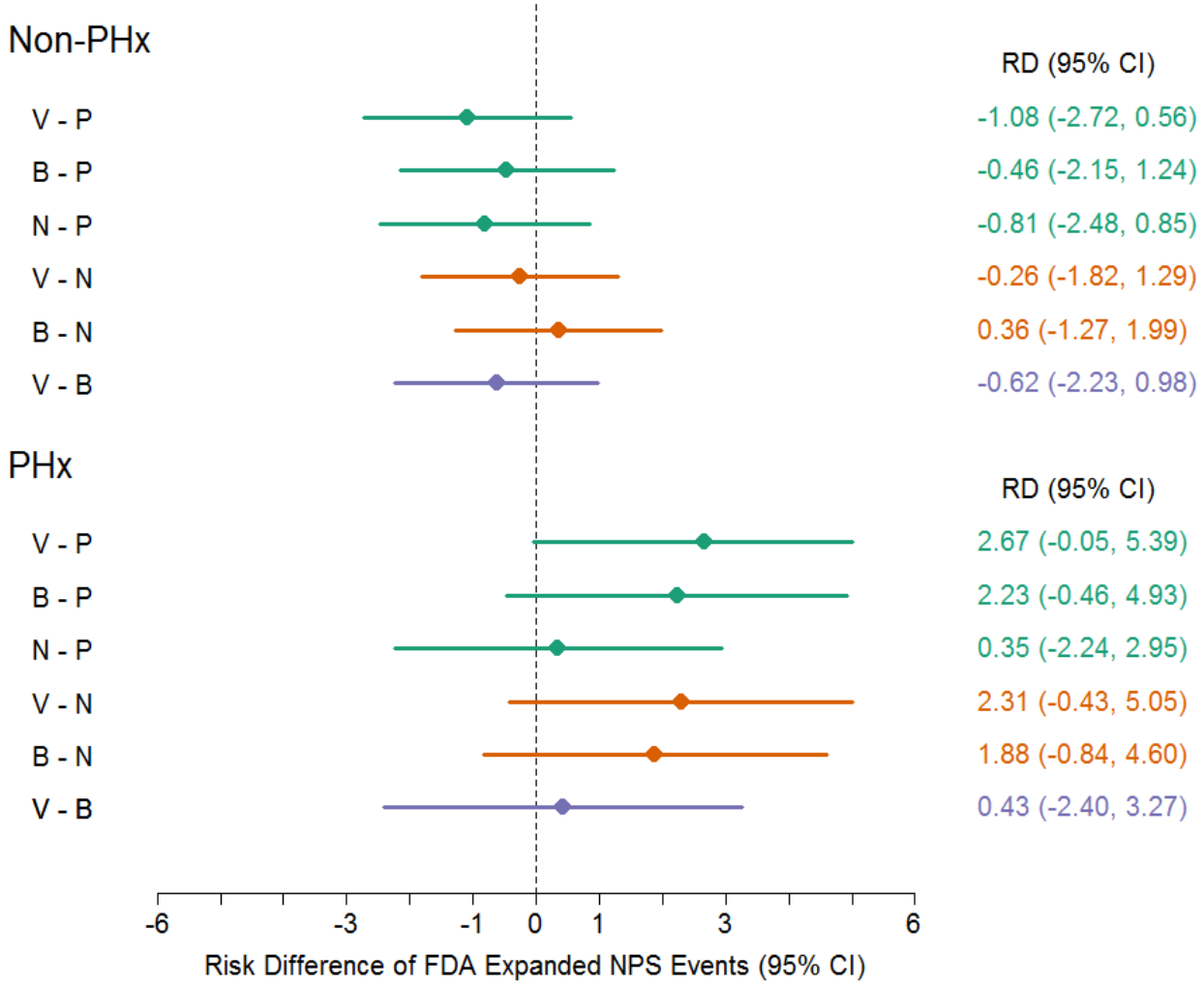
Table 5. FDA Expanded NPS Event Excluding Sites 1002 and 1077

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	30 / 975 (3.1%)	34 / 968 (3.5%)	33 / 987 (3.3%)	40 / 982 (4.1%)
PHx Cohort	123 / 1007 (12.2%)	118 / 1004 (11.8%)	98 / 995 (9.8%)	95 / 997 (9.5%)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Scs719.xpt

Figure 1 shows the estimated risk differences and corresponding 95% confidence intervals for the risk of FDA expanded NPS events for each of the 6 pairwise treatment comparisons in each of the two cohorts. This analysis excludes all subjects and events in sites 1002 and 1077. In the Non-PHx cohort, Figure 1 shows no evidence of increased risk associated with varenicline relative to placebo: RD = -1.08 events per 100 subjects, 95% CI (-2.72,0.56), bupropion relative to placebo: RD = -0.46 (-2.15, 1.24), or NRT relative to placebo: RD = -0.81 (-2.48, 0.85). In the PHx cohort varenicline and bupropion observed a numerically increased risk relative to placebo: RD = 2.67 (-0.05, 5.39) for varenicline and RD = 2.23 (-0.46, 4.93) for bupropion.

Figure 1. Risk Difference of FDA Expanded NPS Events Excluding Sites 1002 and 1077

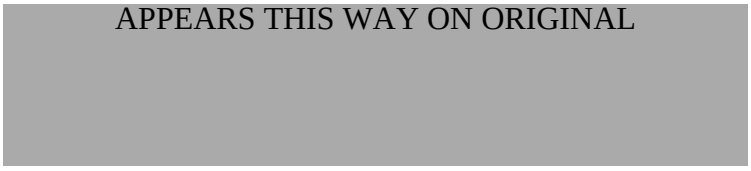


V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Scs719.xpt

5 Conclusions

The clinical review team at the FDA defined an updated neuropsychiatric safety endpoint, referred to in this addendum as the 'FDA expanded NPS endpoint'. This endpoint is based on a similar expanded endpoint proposed by Pfizer. The estimated risk differences of FDA expanded NPS events were generally consistent with those of the primary NPS endpoint discussed in the 11/10/2016 statistical review. The observed rate of FDA expanded NPS events in the Non-PHx cohort was lowest among subjects randomized to varenicline. The observed rate of FDA expanded NPS events in the PHx cohort was highest among subjects randomized to varenicline and bupropion.



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/s/

EUGENIO ANDRACA-CARRERA
11/21/2016

MATTHEW J SOUKUP
11/21/2016

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	21-928
Supplement #:	S040
Drug Name:	Chantix (varenicline) tablet; 0.5 mg and 1.0 mg
Indication(s):	Aid to smoking cessation
Applicant:	Pfizer, Inc.
Date(s):	**Submitted**: 2/18/2016 **Primary Review Goal Date**: 11/13/2016 **PDUFA Goal Date**: 12/18/2016
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 2 and 7
Statistical Reviewers:	Yi Ren, Ph.D., Primary Reviewer, DB2 Eugenio Andraca-Carrera, Ph.D., Primary Reviewer, DB7
Concurring Reviewers:	David Petullo, M.S., Team Lead, DB2 Mat Soukup, Ph.D., Team Lead, DB7 Mark Levenson, Ph.D., Division Direction (acting), DB7
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Team Lead: Celia Winchell, M.D. Deputy Director of Safety: Judy Racoosin, M.D.
Project Manager:	Ayanna Augustus

Keywords: neuropsychiatric safety, safety trial, smoking cessation

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1 EXECUTIVE SUMMARY

Chantix® (varenicline) and Zyban® (bupropion) were approved as aids to smoking cessation in adults in 2006 and 1997, respectively. Serious neuropsychiatric adverse events associated with the use of both products were first reported in 2007 and a boxed warning describing this risk was added to the labels of both Chantix and Zyban in July 2009. On May 16, 2008, the FDA issued a post-marketing requirement (PMR) for a clinical study or trial to assess the risk of clinically significant neuropsychiatric events in individuals using bupropion, varenicline, nicotine replacement therapy (NRT), or placebo as aids to smoking cessation over 12 weeks of treatment. Trial A3051123 was designed to fulfill the PMR and compare the safety and efficacy of varenicline, bupropion, NRT and placebo. The trial was completed in 2015 and its results were submitted by the sponsor Pfizer in February 2016 under NDA 21928. This review discusses the efficacy and the neuropsychiatric safety of varenicline and bupropion based on the results of trial A3051123.

1.1 Statistical Issues and Findings

No major issues that impact the evaluation and interpretation of efficacy findings were identified in the review of trial A3051123. Efficacy findings showed that varenicline had a superior rate of carbon monoxide (CO)-confirmed abstinence during weeks 9 through 12 and weeks 9 through 24 regardless of previous psychiatric history when compared to bupropion, NRT, and placebo. Abstinence rate for bupropion and NRT were also superior to placebo and did not differ based on previous psychiatric history.

Table 1. Comparison of CO-Confirmed Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 by Cohort and Overall

Cohort	Varenicline	Bupropion	NRT	Placebo	Odds ratio		
	(%)	(%)	(%)	(%)	V/P	B/P	N/P
Overall							
CAR 9-12	33.5	22.6	23.4	12.5	3.60*	2.06*	2.14*
CAR 9-24	21.9	16.2	15.7	9.4	2.73*	1.88*	1.80*
Non-PHx							
CAR 9-12	38.0	26.1	26.4	13.7	4.00*	2.26*	2.30*
CAR 9-24	25.5	18.8	18.5	10.5	2.99*	2.00*	1.96*
PHx							
CAR 9-12	29.2	19.3	20.4	11.4	3.25*	1.87*	2.00*
CAR 9-24	18.3	13.8	13.0	8.3	2.50*	1.77*	1.65*

V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
Non-PHx = non-psychiatric history, PHx = psychiatric history
* p-value <0.001, using a logistic regression with terms treatment, cohort, region, and treatment by cohort interaction, and region by cohort interaction. Region used 2-level classification (US, non-US).

The neuropsychiatric safety of varenicline and bupropion was evaluated based on the final results of trial A3051123. The primary safety endpoint in the trial was a composite of treatment-emergent moderate and severe adverse events in 261 MedDRA preferred terms corresponding to

the following 16 components: anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, and completed suicide. This endpoint is referred to as the neuropsychiatric safety (NPS) endpoint. The trial enrolled and treated 3984 subjects without a history of psychiatric illness at baseline (Non-PHx cohort) and 4074 subjects with a history of psychiatric illness at baseline (PHx cohort). These 8058 total subjects were randomized in approximately equal ratios to varenicline, bupropion, NRT, and placebo. Table 2 shows the number of subjects and observed NPS events by treatment arm in each of the two cohorts of the trial.

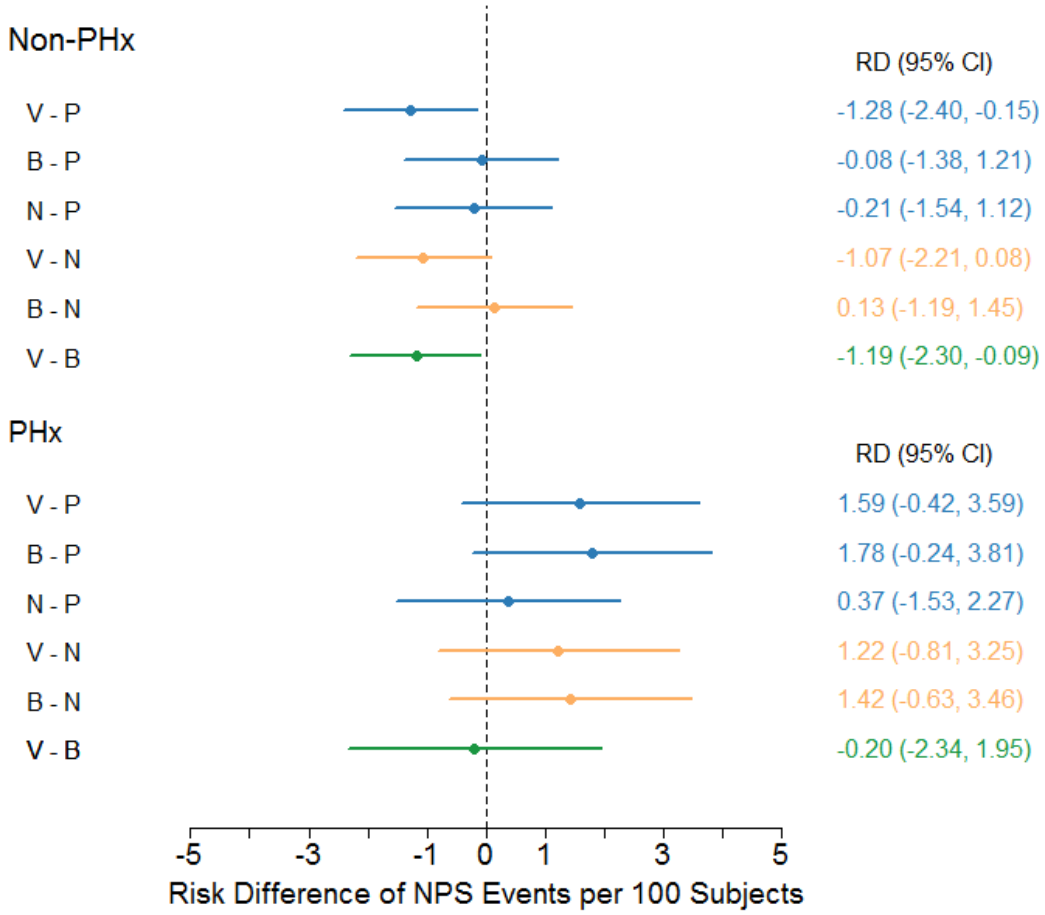
Table 2. Primary NPS Event by Cohort of Psychiatric Illness and Treatment

	Varenicline events / N (%)	**Bupropion events / N (%)**	**NRT events / N (%)**	**Placebo events / N (%)**
Non-PHx Cohort	13 / 990 (1.3%)	22 / 989 (2.2%)	25 / 1006 (2.5%)	24 / 999 (2.4%)
PHx Cohort	67 / 1026 (6.5%)	68 / 1017 (6.7%)	53 / 1016 (5.2%)	50 / 1015 (4.9%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

The primary pre-specified safety analysis estimated the risk difference of NPS events and the corresponding nominal 95% confidence interval for each of the six pairwise treatment comparisons (varenicline - placebo, bupropion - placebo, etc…) by cohort of previous diagnosis of psychiatric illness. The results of the primary safety analysis are summarized in Figure 1. Varenicline showed a nominally protective effect relative to placebo in the Non-PHx cohort: RD = **-1.28 NPS events per 100 subjects, 95% CI (-2.40,-0.15).** Varenicline and bupropion showed a numerically higher risk of NPS events relative to placebo in the PHx cohort: RD = **1.59 NPS events per 100 subjects, 95% CI (-0.42, 3.59)** for varenicline and RD = **1.78 NPS events per 100 subjects, 95% CI (-0.24, 3.81)** for bupropion.

Figure 1. Primary Analysis: Risk Difference of NPS Events by Cohort



V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Multiple issues related to the evaluation of neuropsych safety were identified during the review of trial A3051123. The applicant conducted an audit of 26 of the 139 sites in trial A3051123 and identified inconsistencies between CRFs and source data, missing documentation, inadequate documentation of subject eligibility, and unqualified personnel serving as 'mental health professionals' in 2 sites. Additionally, the clinical review team identified potential data coding errors of the primary safety endpoint and deficient adverse event narratives throughout the trial. A statistical analysis of the primary neuropsych safety (NPS) endpoint by investigative site showed a high level of heterogeneity in the rate of NPS events across sites. As a result of these findings, sensitivity analyses were conducted which included using an alternative negative binomial model to account for heterogeneity in the rate of NPS events between sites, and an array of analyses to evaluate the sensitivity of safety results to different endpoint definitions.

A negative binomial model for the rate of NPS events was found to fit the data significantly better than the primary pre-specified model, which implicitly assumes that the number of NPS events within each site follows a binomial distribution. The negative binomial model estimated

the rate ratio of NPS events for each pair-wise treatment comparison in each of the two study cohorts. The results of this model were generally consistent with the primary model and are presented in Section 3.6.1.2.1.

Sensitivity analyses that evaluated neuropsychiatric safety based on alternate endpoint definitions were generally consistent with the findings of the primary analysis of the NPS endpoint. These sensitivity analyses are presented in Sections 3.6.1.2.2 through 3.6.1.2.4.

1.2 Conclusions and Recommendations

The results from the PMR trial A3051123 provided substantial evidence of the efficacy of varenicline and bupropion in smoking cessation compared with placebo for both weeks 9-12 and 9-24 regardless of psychiatric history. In addition, the results confirmed that subjects treated with varenicline had significant improvement in smoking cessation compared to subjects treated with bupropion and NRT in both cohorts (PHx and Non-PHx).

The results of trial A3051123 were discussed at a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on September 14, 2016. The Advisory Committee was asked to vote on the following question:

VOTE: Based on the data presented on the risk of serious neuropsychiatric adverse events with smoking cessation products, what would you recommend?

A. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events.

B. Modify the language in the boxed warning.

C. Keep the current boxed warning.

The committee voted in the following way: **A**: 10 **B**: 4 **C**: 5 Abstain: 0.

Based on our review of trial A3051123, we believe that sufficient evidence exists to support the removal of the current boxed warning for neuropsychiatric adverse events from the labels of both Chantix and Zyban. We recommend that the potential risk of neuropsychiatric adverse events associated with Chantix and Zyban in patients with prior history of psychiatric illness be described in the WARNINGS section of the label. However, since the PMR trial was only designed to estimate the risk of serious neuropsychiatric adverse events and not to rule out a pre-specified risk margin, we believe that the interpretation of the trial results and potential labeling changes are a matter of clinical judgement.

2 INTRODUCTION

2.1 Overview

Chantix (varenicline) was approved as an aid to smoking cessation for adults by the Food and Drug Administration (FDA) in May 2006 and shortly thereafter in September 2006 was approved by the European Medicines Agency (EMA) as CHAMPIX. The approved dosing regimen is 1 mg twice daily (BID) for 12 weeks starting with a 1-week titration. An additional 12 weeks of treatment may be taken to increase the chance of maintaining long-term abstinence. Varenicline is a selective partial agonist at the $\alpha_4\beta_2$-subtype neuronal nicotinic acetylcholine receptor and is claimed to have "the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving during abstinence while blocking the reinforcing effects of chronic nicotine".
Wellbutrin® (bupropion) was first approved for the treatment of depression in Dec 1985 by the FDA and was approved for smoking cessation under the trade name of Zyban in 1997. The dosing regimen is 150 mg BID for 7 to 12 weeks. Bupropion, a selective inhibitor of the neuronal re-uptake of with minimal effect on the re-uptake of indolamines and does not inhibit monoamine oxidase, was the first approved non-nicotine treatment for nicotine dependence as an aid to smoking cessation.

In May 2007, the EMA informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a post-marketing analysis. Later that year in November, information was added on reports of neuropsychiatric events under ADVERSE REACTIONS/POST-MARKETING EXPERIENCE section of labeling.

In January 2008, serious neuropsychiatric (NPS) symptoms had been reported in varenicline-treated patients. The event-related information was added to the WARNINGS section of labeling. Similar issues associated with bupropion were identified.

In July 2009, as per FDA's request, a boxed warning was added to both varenicline and bupropion labeling to highlight information regarding serious NPS events and suicidality on the basis of the post-marketing reports.

To address these concerns, FDA issued a post-marketing requirement (PMR) clinical study or trial to compare the risk of clinically significant NPS events in subjects with and without a history of psychiatric disorders over 12 weeks of treatment. Trial A3051123 was a large randomized, double-blind, active- and placebo-controlled PMR trial and also qualified as a post-authorization safety study (PASS) in the European Union, used to determine whether subjects with a history of psychiatric disorders are at greater risk for development of clinically significant NPS events compared to smokers without a history of psychiatric disorders, while treated with varenicline, bupropion, nicotine replacement therapy (NRT), or placebo as aids to smoking cessation. The trial was sponsored by Pfizer in collaboration with GSK. The trial was designed in consultation with the FDA and EMA.

Prior to the completion of trial A3051123, on April 8, 2014, Pfizer submitted the results of a retrospective meta-analysis of 18 phase II-IV clinical trials to evaluate the risk of suicidal

ideation, suicidal behavior, and hostility associated with varenicline relative to placebo in two sets of trials:

- A set of 5 Phase III/IV clinical trials that prospectively captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS).
- A set of 18 Phase II-IV clinical trials which captured psychiatric adverse events through routine adverse events reports coded using the Medical Dictionary for Regulatory Activities (MedDRA).

These meta-analyses showed no evidence of increased risk of neuropsychiatric adverse events associated with varenicline relative to placebo. The main limitations of the meta-analysis were that the trials were not designed to collect and adjudicate neuropsychiatric adverse events.

Based on these findings, Pfizer proposed to remove the boxed warning. The results of the meta-analysis and the proposal to remove the boxed warning were discussed at a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on October 16, 2014.

The Advisory Committee was asked to vote on the following question:

VOTE: Based on the data presented on the risk of serious neuropsychiatric adverse events with varenicline, what would you recommend?

A. Removal of the boxed warning statements regarding risk of serious neuropsychiatric adverse events.

B. Modification of the language in the boxed warning.

C. Retain the current boxed warning statements and reassess once the ongoing post-marketing randomized controlled trial designed to capture serious neuropsychiatric adverse events is completed.

The committee voted in the following way: **A**: 1 **B**: 6 **C**: 11 Abstain: 0. The Summary Minutes of the meeting include the following comment regarding this vote:

"The majority of the committee agreed that more data are needed and recommended to retain the current boxed warning statements and reassess once the ongoing post-marketing randomized controlled trial designed to capture serious neuropsychiatric adverse events is complete."

Ultimately the Division of Anesthesia, Analgesia, and Addiction Products revised the Chantix label to include the meta-analysis results in Section 5 of the product label. However, the boxed warning was retained in the label.

Trial A3051123 was completed in 2015. In February 2016, Pfizer submitted to FDA a supplemental NDA requesting updates to the Chantix labeling relating to the risk of NPS events based on the outcomes of the PMR trial. The labeling updates proposed by Pfizer included

removal of the boxed warning regarding serious NPS adverse events (AEs), revisions to the corresponding WARNINGS AND PRECAUTIONS section of the label based on the findings of this trial, and inclusion of the trial safety and efficacy outcomes in appropriate sections of the product label.

On September 14, 2016, FDA sought advice from the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss this completed PMR trial to determine whether to remove the boxed warning. The Advisory Committee was asked to vote on the following question:

VOTE: Based on the data presented on the risk of serious neuropsychiatric adverse events with smoking cessation products, what would you recommend?

A. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events.

B. Modify the language in the boxed warning.

C. Keep the current boxed warning.

The committee voted in the following way: **A**: 10 **B**: 4 **C**: 5 Abstain: 0.

The review for trial A3051123 primarily focuses on the evaluation of the NPS safety of varenicline and bupropion. Even though not the focus of this trial, the results of evaluation of efficacy are also presented.

2.2 Data Sources

Datasets were submitted by the applicant to the CDER electronic data room in SAS transport format. The documentation (protocol, SAP, and study reports) were submitted under the network path \\CDSESUB1\evsprod\NDA021928\0346. All datasets and literature referenced were submitted under the network path \\CDSESUB1\evsprod\NDA021928\0351. In response to the information request sent on March 7, 2016, subgroup analyses for primary safety and efficacy endpoints, as well as the programs used to generate the efficacy analysis datasets and efficacy tables were submitted under the network path \\CDSESUB1\evsprod\NDA021928\0360.

The following datasets were used to conduct the analyses of safety endpoints, including the primary neuropsychiatric safety endpoint:

- Demog.xpt contains baseline and demographic characteristics of subjects in the trial.
- Cnmedp.xpt contains history of concomitant medications used before randomization.
- Smkhst.xpt contains history of smoking cessation attempts.
- Pidcha.xpt contains additional characteristics not included in the Demog.xpt dataset, such as country of randomization.
- Subevg.xpt contains data on subjects' final treatment and study dispositions and reasons for discontinuation.
- Advers.xpt contains data on adverse events, including but not limited to the primary

NPS endpoint.

- Death.xpt contains data on deaths observed in the trial.
- Css1 and Css2.xpt contain data on the C-SSRS instrument to assess suicidality.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets were of acceptable quality and were adequately documented to conduct a review of efficacy. We were able to reproduce the results of all primary and secondary efficacy analyses. All results in this review were based on the modified dataset created by correcting sex for 6 subjects and with missing CO data imputed as positive (non-responder). This is discussed in Section 3.5.1.

The applicant conducted an audit of 26 sites from trial A3051123 and identified problems in two, sites 1002 and 1077. The problems included inconsistencies between CRFs and source data, missing documentation, inadequate documentation of subject eligibility, and unqualified personnel serving as 'mental health professionals'. The FDA clinical review team identified similar problems in the conduct of the trial at one more site (1063). A site audit conducted by the Office of Scientific Investigations at the FDA identified important problems at site 1077 and suggested that data from this site may not be interpretable. Table 3 summarizes the total number of subjects in these three potentially problematic sites. Note that site 1077, which was suggested to be considered for removal by the Office of Scientific Investigations, enrolled only 31 total subjects across both cohorts and did not report any primary safety events.

Table 3. Sample Size of Potentially Problematic Sites

Site:	Non-PHx Cohort	PHx Cohort
1002	49	63
1063	79	15
1077	23	8

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt

All safety analyses in this review are based on the totality of Trial A3051123, including sites 1002, 1063 and 1077. A sensitivity analysis of neuropsychiatric safety that excludes these potentially problematic sites is discussed in Section 3.6.1.2.6.

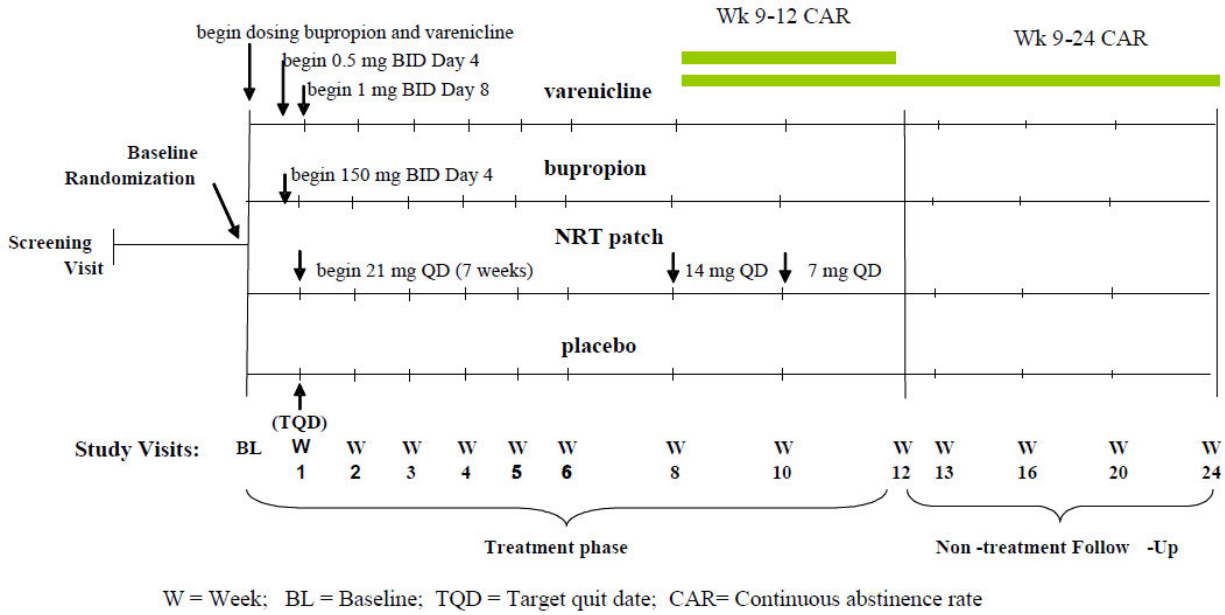
3.2 Trial Design and Endpoints

3.2.1 Trial Design

Trial A3051123 was a 24-week, double-blind, active- and placebo-controlled, multi-center, parallel-group trial designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion HCl 150 mg BID for smoking cessation. Figure 2 shows a schematic diagram of the trial. The trial duration for active treatment was 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks. In addition to the in-clinic visits shown in the diagram, telephone contacts occurred at Weeks 7, 9, 11, 14, 15, 17, 18, 19, 21, 22, and 23.

The trial used a triple dummy design that randomly assigned subjects to one of the three active treatment groups, varenicline, bupropion, and NRT or placebo. Subjects randomized to an active treatment group received that active treatment and the other two in matching placebo form. Subjects randomly assigned to placebo received matching placebo for all three active treatments and followed the same titration and dosing schedules as those randomized to the active treatment groups.

Figure 2. Trial Diagram



W = Week; BL = Baseline; TQD = Target quit date; CAR= Continuous abstinence rate

Source: CSR Section 16.1.1

The trial included two cohorts, those with a diagnosed history of psychiatric disorders, psychiatric (PHx) cohort, and those without a history of psychiatric disorders, non-psychiatric (non-PHx) cohort. Diagnoses of psychiatric history were confirmed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders 4th Edition-Text Revision Axis I and II disorders, which was conducted at the screening visit. Subjects in the psychiatric cohort were further classified into 4 sub-cohorts by diagnosis of psychiatric disorder: affective, anxiety, psychotic and borderline personality disorders. The trial was designed to randomize 8000 subjects among the 4 treatment arms in a 1:1:1:1 ratio, stratified by cohort and by sub-cohort.

3.2.2 Primary Efficacy Endpoint

The main efficacy objective of trial A3051123 was to compare smoking abstinence rates of varenicline and bupropion to placebo for the last 4 weeks of treatment, weeks 9 through 12 (CAR 9-12). A secondary objective was to assess abstinence rates for weeks 9 through 24 (CAR 9-24). Abstinence was confirmed by negative CO reading. Results were presented separately for psychiatric cohort and non-psychiatric cohort, respectively. A secondary efficacy objective was to assess if there was a difference between cohorts in the placebo adjusted CAR 9-12 and CAR 9-24 for either varenicline or bupropion. Other secondary efficacy objectives included an assessment of the above two objectives with respect to each of the remaining four pairwise treatment comparisons, i.e. NRT versus placebo, varenicline versus bupropion, varenicline versus NRT, and bupropion versus NRT.

3.2.3 Primary Safety Endpoint

The primary pre-specified safety endpoint in trial A3051123 is a composite 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." This composite endpoint includes 261 MedDRA preferred terms in the 16 components listed above. This endpoint is referred to as the neuropsychiatric safety (NPS) endpoint.

Adverse events were classified as mild, moderate or severe according to the following definitions:

- Mild – does not interfere with subject's usual function.
- Moderate – interferes to some extent with subject's usual function.
- Severe – interferes significantly with subject's usual function.

According to the trial protocol, NPS events were collected through any of the following means:

- Volunteered adverse event.
- Actively collected adverse event. NPS events were collected through a neuropsychiatric adverse event interview at each clinic visit.
- Report by a family member and judged to be an adverse event by the investigator.
- Suicide related AEs solicited through the C-SSRS questionnaire at each clinic visit.

3.2.4 Secondary Safety Endpoints

Pre-specified secondary safety endpoints include the components of the NPS endpoint as well as the scores of three questionnaires: Hospital Anxiety and Depression Scale (HADS), Columbia

Suicide Severity Rating Scale (C-SSRS), and the Clinical Global Impression of Improvement (CGI-I).

The C-SSRS score was the primary endpoint in the meta-analysis of neuropsychiatric events conducted by the applicant in 2014. In this review, we will discuss the results of the C-SSRS assessment in trial A3051123 as a secondary safety endpoint.

Deaths observed in the trial were also analyzed as a secondary safety endpoint of interest in this review.

3.3 Statistical Methodologies

3.3.1 Methods Related to the Analysis of Efficacy

The primary efficacy analysis (CAR 9-12) was evaluated using a logistic regression model on the Full Analysis Set (see definition below). The model included treatment (varenicline, bupropion, NRT, and placebo), cohort (PHx and non-PHx), region (US and non-US), plus the 2-way and 3-way interactions, with possible model reduction by removal of non-significant interaction terms at the 10% level. The analysis of the secondary endpoint, CAR 9-24, was based on the same logistic regression as the primary analysis. The odds ratio (OR) and its 95% confidence interval (CI) were estimated for all pairwise comparisons of treatment groups. This estimation was done both overall and by cohort. The primary efficacy hypotheses were to test the superiority of varenicline versus placebo and bupropion versus placebo, respectively, with respect to CAR 9-12 in PHx and non-PHx cohorts. The key secondary hypotheses were to test the superiority of varenicline versus placebo and bupropion versus placebo, respectively, with respect to CAR 9-24 in each cohort. All other treatment pairwise comparisons were considered secondary hypotheses and were tested using the same scheme as in the primary and key secondary hypotheses. Each hypothesis was tested individually at a 5% level without any adjustment for multiplicity.

Subjects who discontinued the trial or were lost to follow-up were assumed to be non-responder (smokers) for the remainder of the trial. Missing data on Nicotine Use Inventory (NUI) were imputed using the next non-missing NUI response to the respective question separately for the treatment period and follow-up period. If no response was available, the default imputation was as a non-responder. The protocol stipulated that missing CO values were imputed as negative. This is not the customary approach to analysis of smoking cessation studies. A sensitivity analysis imputing missing values as positive was performed and discussed later.

3.3.2 Methods Related to the Analysis of Safety

3.3.2.1 Analysis Populations

The applicant defined two analysis populations:

- Full Analysis Set (FAS). Defined as all randomized subjects from the time of randomization to the last recorded trial visit, regardless of treatment adherence.
- Safety Analysis Population. Defined as all treated subjects (i.e. received at least one partial dose of randomized study drug) from the time of their first dose to the time of their last dose of study drug plus 30 days.

The primary analysis of the NPS endpoint was conducted on the Safety Analysis Population based on events observed only during the 12 week treatment phase of the trial plus 30 days. The primary analysis of the NPS endpoint did not include events observed during the 12 weeks of post-treatment follow-up.

3.3.2.2 Statistical Power

Trial A3051123 was not designed to rule out a pre-specified risk margin of NPS events. The applicant sized the trial based on the desired precision of the estimated risk difference (RD) for the NPS event comparing varenicline to placebo.

In the cohort with no-prior history of psychiatric disease (Non-PHx cohort), the applicant assumed a true incidence rate (IR) of 3.5 events per 100 subjects in the placebo arm and an IR of 6.13% in the varenicline arm, equivalent to an incidence rate ratio of 1.75. Under these assumptions, and with a sample size of 1,000 subjects per treatment arm in the Non-PHx cohort, the expected RD and corresponding 95% confidence interval for the NPS event comparing varenicline to placebo was 2.63% (0.75%, 4.50%).

In the cohort with a prior history of psychiatric disease (PHx cohort), the applicant assumed a true IR of 7.0% in the placebo arm and 12.25% in the varenicline arm, also equivalent to an incidence rate ratio of 1.75. Under these assumptions, and with a sample size of 1,000 subjects per treatment arm in the PHx cohort, the expected RD and corresponding 95% confidence interval for the NPS event comparing varenicline to placebo was 5.25% (2.34%, 5.52%).

3.3.2.3 Primary Safety Analysis

The primary safety analysis estimated the risk difference of NPS events for all 6 pairwise treatment comparisons (varenicline - placebo, bupropion - placebo, etc…) by cohort of previous diagnosis of a psychiatric disorder. The risk difference of NPS events was estimated through a generalized linear model for binary data with an identity link function and a binomial error function. The model included covariates for treatment (4 levels), cohort (2 levels), treatment by cohort interaction, and region of randomization (2 levels: USA vs. non-USA). The primary analysis of NPS events was conducted in the safety analysis population defined in Section 3.3.2.1.

The SAP did not pre-specify any safety-related statistical hypotheses to be tested and therefore no p-values for safety outcomes are discussed in this document. The estimated treatment risk differences of NPS events and their corresponding confidence intervals are considered to be

descriptive. All confidence intervals for safety endpoints were calculated at a nominal 95% confidence level and no corrections were made for multiple comparisons.

3.3.2.4 Secondary Safety Analyses

The following sensitivity analyses of the primary NPS event were conducted by the FDA statistics review team and are discussed in this document:

- Descriptive analysis of NPS events by sub-cohort of psychiatric history diagnosis at baseline.
- Analysis of NPS events by investigative site and cohort to evaluate potential heterogeneity in the rate NPS events across sites.
- Analysis of NPS events through alternative statistical models to account for extra binomial variation between sites.

Three sites were identified as having experienced potential problems in the conduct of the trial as discussed in Section 3.1. Additionally, the clinical review team identified potential data coding errors of the primary safety endpoint and deficient adverse event narratives throughout the trial. In order to try to address these limitations and to assess the robustness of the primary NPS safety results to changes in the endpoint definition or to the analysis population of interest, the following sensitivity analyses were conducted:

- Analysis of an alternative composite neuropsychiatric event that includes events of all severities.
- Analysis of an alternative composite neuropsychiatric event that includes only events classified as severe.
- Analysis of NPS+, an exploratory composite neuropsychiatric event that includes the primary NPS event plus moderate or severe adverse events coded to the MedDRA Preferred Term “Irritability” plus moderate or severe adverse events in the “Depressed mood disorders” MedDRA High-Level Group Term (HGLT).
- Analysis of the primary NPS event in the FAS population.
- Analysis of the primary NPS event excluding sites identified as having experienced problems in the conduct of the trial.
- Analysis of the primary NPS endpoint by previous use of smoking cessation products.

Descriptive safety analyses were also conducted on two secondary safety endpoints of interest: deaths and suicidality evaluated through the C-SSRS instrument.

3.4 Patient Disposition, Demographic and Baseline Characteristics

A total of 8144 subjects at 140 investigative sites (there were 150 sites in total, 10 of which did not randomize subjects) in 16 countries were randomized. Of these subjects, 8058 subjects in 139 sites (98.9%) received randomized treatment. The overall subject disposition from randomization is summarized in Table 4. The subject population included male or female cigarette smokers

aged from 18 to 75 years at screening, motivated to stop smoking and considered suitable for a smoking cessation attempt, smoked an average of at least 10 cigarettes per day during the past year and during the month prior to the screening visit, and had an exhaled carbon monoxide > 10 ppm at screening.

Overall, the subject disposition was similar across treatment groups. A total of 1890 subjects discontinued treatment; approximately 23% of subjects in each treatment group with a slightly higher percentage (24.1%) in the placebo group. The most common reasons for treatment discontinuation were adverse event, lack of efficacy, lost to follow-up, medication error, no longer meet eligibility criteria, protocol violation, withdrawal of consent, and death. A total of 1765 subjects discontinued from the trial: 418 subjects (20.7%) received varenicline, 420 subjects (20.9%) received bupropion, 465 subjects (23.0%) received NRT and 462 subjects (22.9%) received placebo.

Table 4. Subject Disposition, Overall

Treatment/Cohort	Number (%) of Subjects			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Overall				
Randomized to Study Treatment[a]	2037	2034	2038	2035
Randomized but Not Treated	21	28	16	21
Randomized and Treated[b]	2016 (100)	2006 (100)	2022 (100)	2014 (100)
Completed treatment	1565 (77.6)	1537 (76.6)	1538 (76.1)	1528 (75.9)
Discontinued treatment	451 (22.4)	469 (23.4)	484 (23.9)	486 (24.1)
Completed Trial	1598 (79.3)	1586 (79.1)	1557 (77.0)	1552 (77.1)
OTIS completers	138	152	145	123
Discontinued Trial	418 (20.7)	420 (20.9)	465 (23.0)	462 (22.9)
During treatment phase	293 (70.1)	281 (66.9)	303 (65.2)	335 (72.5)
Post-treatment phase	125 (29.9)	139 (33.1)	162 (34.8)	127 (27.5)

a. FAS population
b. Safety population
Source: Modified from CSR Table 5

The subject disposition was also summarized by cohort, with and without a history of psychiatric disorders (Table 5). Of subjects treated, the non-psychiatric cohort included a total of 3984 subjects: 990 received varenicline, 989 received bupropion, 1006 received NRT and 999 received placebo. The psychiatric cohort included a total of 4074 subjects: 1026 received varenicline, 1017 to bupropion, 1016 received NRT and 1015 received placebo.

In both cohorts, the subject disposition was similar across treatment groups. In the non-psychiatric cohort, approximately 21% of subjects in each treatment group did not complete treatment. In the psychiatric cohort, approximately 25% of subjects discontinued treatment where there was a higher percentage (28.6%) in the placebo group. In particular, compared to non-psychiatric group there was greater discontinuation due to adverse event in the psychiatric group.

Table 5. Subject Disposition, by Cohort

Treatment/Cohort	Number (%) of Subjects			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Non-Psychiatric Cohort				
Randomized to Study Treatment[a]	1005	1001	1013	1009
Randomized but Not Treated	15	12	7	10
Randomized and Treated[b]	990 (100)	989 (100)	1006 (100)	999 (100)
Completed treatment	793 (80.1)	772 (78.1)	777 (77.2)	803 (80.4)
Discontinued treatment	197 (19.9)	217 (21.9)	229 (22.8)	196 (19.6)
Adverse event	57 (5.8)	74 (7.5)	73 (7.3)	26 (2.6)
Insufficient clinical response	6 (0.6)	3 (0.3)	9 (0.9)	7 (0.7)
Lost to follow-up	42 (4.2)	39 (3.9)	37 (3.7)	38 (3.8)
Medication error without associated adverse event	0	1 (0.1)	0	0
No longer meets eligibility criteria	0	3 (0.3)	0	2 (0.2)
No longer willing to participate in study	61 (6.2)	63 (6.4)	79 (7.9)	89 (8.9)
Other	29 (2.9)	29 (2.9)	26 (2.6)	26 (2.6)
Protocol violation	1 (0.1)	3 (0.3)	4 (0.4)	5 (0.5)
Withdrawn due to pregnancy	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)
Subject died	0	1 (0.1)	0	1 (0.1)
Completed Trial	787 (79.5)	783 (79.2)	767 (76.2)	787 (78.8)
OTIS completers	52	68	61	35
Discontinued Trial	203 (20.5)	206 (20.8)	239 (23.8)	212 (21.2)
During treatment phase	139 (68.5)	130 (63.1)	157 (65.7)	154 (72.6)
Post-treatment phase	64 (31.5)	76 (36.9)	82 (34.3)	58 (27.4)
Psychiatric Cohort				
Randomized to Study Treatment[a]	1032	1033	1025	1026
Randomized but Not Treated	6	16	9	11
Randomized and Treated[b]	1026 (100)	1017 (100)	1016 (100)	1015 (100)
Completed treatment	772 (75.2)	765 (75.2)	761 (74.9)	725 (71.4)
Discontinued treatment	254 (24.8)	252 (24.8)	255 (25.1)	290 (28.6)
Adverse event	108 (10.5)	101 (9.9)	85 (8.4)	94 (9.3)
Insufficient clinical response	4 (0.4)	4 (0.4)	8 (0.8)	10 (1.0)
Lost to follow-up	44 (4.3)	37 (3.6)	36 (3.5)	44 (4.3)
Medication error without associated adverse event	1 (0.1)	0	0	1 (0.1)
No longer meets eligibility criteria	1 (0.1)	6 (0.6)	4 (0.4)	3 (0.3)
No longer willing to participate in study	62 (6.0)	70 (6.9)	66 (6.5)	83 (8.2)
Other	30 (2.9)	30 (2.9)	49 (4.8)	49 (4.8)
Protocol violation	4 (0.4)	1 (0.1)	6 (0.6)	4 (0.4)
Withdrawn due to pregnancy	0	2 (0.2)	1 (0.1)	1 (0.1)
Subject died	0	1 (0.1)	0	1 (0.1)
Completed Trial	811 (79.0)	803 (79.0)	790 (77.8)	765 (75.4)
OTIS completers	86	84	84	88
Discontinued Trial	215 (21.0)	214 (21.0)	226 (22.2)	250 (24.6)
During treatment phase	154 (71.6)	151 (70.6)	146 (64.6)	181 (72.4)
Post-treatment phase	61 (28.4)	63 (29.4)	80 (35.4)	69 (27.6)

a. FAS population
b. Safety population
Source: Modified from CSR Table 5

The tables below provide baseline demographics, psychiatric characteristics, and smoking history information for the safety population by cohort.

In the non-psychiatric cohort, demographic characteristics were similar across treatment groups. The mean age was 46, the majority of subjects were white (approximately 83%), and gender was approximately evenly split. The baseline smoking history was similar across groups: approximately 28 smoking years, approximately 21 cigarettes on average per day, approximately 3 serious quit attempts.

In the psychiatric cohort, demographic characteristics were similar across treatment groups. The mean age was 47, the majority of subjects were white (approximately 81%) and 38% of subjects were male. Approximately 35% of subjects had positive responses for lifetime suicidal behavior and/or ideation at screening. The baseline smoking characteristics were similar as non-psychiatric cohort.

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Table 6. Summary of Baseline Characteristics, Non-PHx Cohort

Baseline Characteristics	Varenicline (N = 990)	Bupropion (N = 989)	NRT (N = 1006)	Placebo (N = 999)
Age (years)				
Mean (SD)	45.8 (13.0)	46.0 (13.0)	46.1 (12.8)	45.9 (12.8)
Min, Max	18, 73	18, 75	18, 75	18, 74
Gender[a], n (%)				
Male	510 (51.5)	503 (50.9)	497 (49.4)	489 (48.9)
Female	480 (48.5)	486 (49.1)	509 (50.6)	510 (51.1)
Race, n (%)				
White	819 (82.7)	820 (82.9)	837 (83.2)	817 (81.8)
Black	135 (13.6)	116 (11.7)	127 (12.6)	126 (12.6)
Asian	14 (1.4)	16 (1.6)	13 (1.3)	19 (1.9)
Other	22 (2.2)	37 (3.7)	29 (2.9)	37 (3.7)
Weight (kg)				
n	980	984	1000	992
Mean (SD)	80.0 (19.5)	80.4 (20.1)	81.6 (19.6)	80.6 (19.3)
Min, Max	39.8, 176.8	40.5, 171.5	38.4, 201.8	42.0, 169.2
Prior psychiatric medications, n (%)				
Psychoanaleptics	27 (2.7)	27 (2.7)	33 (3.3)	36 (3.6)
Psycholeptics	61 (6.2)	58 (5.9)	68 (6.8)	73 (7.3)
Total number of years subject smoked				
Mean (SD)	27.8 (12.8)	28.2 (13.0)	28.2 (12.8)	28.2 (12.6)
Min, Max	2, 64	2, 60	1, 63	2, 62
Total number of lifetime serious quit attempts[b]				
None, n (%)	181 (18.3)	181 (18.3)	174 (17.3)	204 (20.4)
≥1 previous serious quit attempt, n (%)	809 (81.7)	808 (81.7)	832 (82.7)	795 (79.6)
Mean (SD)	3.3 (13.8)	3.4 (10.3)	3.1 (4.2)	3.2 (7.4)
Min, Max	0, 400	0, 300	0, 31	0, 108
Previous use of medication for quit attempt (most recent attempt), n (%)				
Varenicline	132 (13.3)	144 (14.6)	152 (15.1)	136 (13.6)
Bupropion	92 (9.3)	91 (9.2)	93 (9.2)	90 (9.0)
NRT	272 (27.5)	307 (31.0)	325 (32.3)	305 (30.5)
Average number of cigarettes per day over the last month prior to study entry				
n	990	989	1005	999
Mean (SD)	20.8 (8.3)	20.6 (7.8)	20.8 (8.2)	20.5 (7.9)
Min, Max	10, 80	6, 60	10, 60	10, 60
FTND (Total Score)				
n	989	987	1006	998
Mean (SD)	5.49 (1.98)	5.50 (2.02)	5.56 (1.95)	5.51 (2.01)
Min, Max	0, 10	0, 10	0, 10	0, 10
HADS (Total Score)				
Mean (SD)	4.35 (4.44)	4.08 (4.09)	4.20 (4.11)	4.50 (4.33)
Min, Max	0, 28	0, 24	0, 25	0, 22

Source: CSR Table 10

Table 7. Summary of Baseline Characteristics, PHx Cohort

Baseline Characteristics	Varenicline (N = 1026)	Bupropion (N = 1017)	NRT (N = 1016)	Placebo (N = 1015)
Age (years)				
Mean (SD)	47.2 (11.8)	46.7 (12.2)	47.6 (11.5)	46.9 (11.5)
Min, Max	18, 74	18, 75	18, 75	18, 75
Gender[a], n (%)				
Male	392 (38.2)	387 (38.1)	384 (37.8)	387 (38.1)
Female	634 (61.8)	630 (61.9)	632 (62.2)	628 (61.9)
Race, n (%)				
White	849 (82.7)	816 (80.2)	804 (79.1)	822 (81.0)
Black	145 (14.1)	165 (16.2)	176 (17.3)	155 (15.3)
Asian	5 (0.5)	10 (1.0)	11 (1.1)	7 (0.7)
Other	27 (2.6)	26 (2.6)	25 (2.5)	30 (3.0)
Unspecified	0	0	0	1 (0.1)
Weight (kg)				
n	1024	1014	1015	1012
Mean (SD)	83.0 (21.5)	82.5 (21.3)	80.8 (20.1)	82.7 (21.3)
Min, Max	43.0, 230.0	43.2, 174.3	39.6, 191.5	44.6, 189.1
Prior psychiatric medications, n (%)				
Psychoanaleptics	423 (41.2)	354 (34.8)	369 (36.3)	380 (37.4)
Psycholeptics	309 (30.1)	298 (29.3)	326 (32.1)	295 (29.1)
Total number of years subject smoked				
Mean (SD)	28.9 (11.8)	28.2 (12.4)	28.9 (11.9)	28.3 (11.6)
Min, Max	2, 60	2, 56	2, 58	2, 56
Total number of lifetime serious quit attempts				
None, n (%)	171 (16.7)	174 (17.1)	165 (16.2)	161 (15.9)
≥1 previous serious quit attempt, n (%)	855 (83.3)	843 (82.9)	851 (83.8)	854 (84.1)
Mean (SD)	3.4 (7.7)	3.5 (6.9)	3.3 (5.3)	3.6 (10.9)
Min, Max	0, 200	0, 100	0, 77	0, 300
Previous use of medication for quit attempt (most recent attempt), n (%)				
Varenicline	149 (14.5)	194 (19.1)	168 (16.5)	161 (15.9)
Bupropion	102 (9.9)	114 (11.2)	101 (9.9)	101 (10.0)
NRT	372 (36.3)	326 (32.1)	356 (35.0)	338 (33.3)
Average number of cigarettes per day over the last month prior to study entry				
Mean (SD)	20.6 (8.0)	20.5 (8.2)	20.8 (9.1)	20.7 (8.2)
Min, Max	5, 70	10, 60	10, 120	10, 70
FTND (Total Score)				
n	1025	1017	1016	1015
Mean (SD)	6.04 (1.93)	6.06 (1.91)	5.96 (1.95)	5.91 (2.02)
Min, Max	0, 10	0, 10	0, 10	0, 10
HADS (Total Score)				
n	1026	1017	1015	1015
Mean (SD)	8.26 (6.45)	8.74 (6.92)	8.37 (6.58)	8.21 (6.22)
Min, Max	0, 30	0, 36	0, 31	0, 36
C-SSRS Lifetime[b]				
n (%)	353 (34.4)	363 (35.7)	339 (33.4)	358 (35.3)

a. The gender for 2 subjects randomized to treatment was inaccurately recorded.
b. C-SSRS (positive response for suicidal behavior or/and ideation).

Source: CSR Table 11

3.5 Evaluation of Efficacy

3.5.1 Results and Conclusions

The reviewer replicated the results of the analyses for CAR 9-12 and CAR 9-24. Results are presented in Table 8 and Table 9 by psychiatric cohort using the FAS population. At a 10% level, the interactions of treatment by region and treatment by cohort by region were not statistically significant and were removed from the model. The final model included treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction.

The primary comparisons of varenicline versus placebo and bupropion versus placebo with respect to CAR 9-12 were statistically significant (p-values < 0.001) by cohort and overall. All other pairwise comparisons with respect to CAR 9-12 were also considered statistically significant except for bupropion versus NRT (overall p=0.58, OR=0.96), both overall and by cohort. The results were consistent with the applicant's conclusion that varenicline (and separately, bupropion) was superior to placebo with respect to CAR 9-12. The odds of varenicline were statistically significant greater than bupropion, NRT, and placebo, respectively, with respect to smoking cessation for weeks 9-12.

Table 8. Treatment Comparison of Continuous Abstinence, Weeks 9-12, CO-Confirmed, by Cohort and Overall - FAS Population

	Overall	**Non-Psychiatric History**	**Psychiatric History**
CAR 9-12(%)		n/N	
Varenicline	33.5%	38.0%	29.2%
Bupropion	22.6%	26.1%	19.3%
NRT	23.4%	26.4%	20.4%
Placebo	12.5%	13.7%	11.4%
Treatment Comparisons	Estimated odds ratio in CAR 9-12 (95% CI)		
Primary Comparisons			
Varenicline vs Placebo	3.60* (3.06, 4.24)	4.00* (3.20, 5.00)	3.25* (2.56, 4.11)
Bupropion vs Placebo	2.06* (1.74, 2.44)	2.26* (1.80, 2.85)	1.87* (1.46, 2.39)
Secondary Comparisons			
NRT vs Placebo	2.14* (1.81, 2.54)	2.30* (1.83, 2.90)	2.00* (1.56, 2.56)
Varenicline vs Bupropion	1.75* (1.52, 2.02)	1.77* (1.46, 2.14)	1.74* (1.41, 2.14)
Varenicline vs NRT	1.68* (1.46, 1.93)	1.73* (1.43, 2.11)	1.63* (1.33, 1.99)
Bupropion vs NRT	0.96 (0.83, 1.11)	0.98 (0.80, 1.20)	0.94 (0.75, 1.16)

* p-value <0.05, using a logistic regression with terms treatment, cohort, region, and treatment by cohort interaction, and region by cohort interaction. Region used 2-level classification (US, non-US).
Source: Reviewer program main.sas

Table 9. Treatment Comparison of Continuous Abstinence, Weeks 9-24, CO-Confirmed, by Cohort and Overall - FAS Population

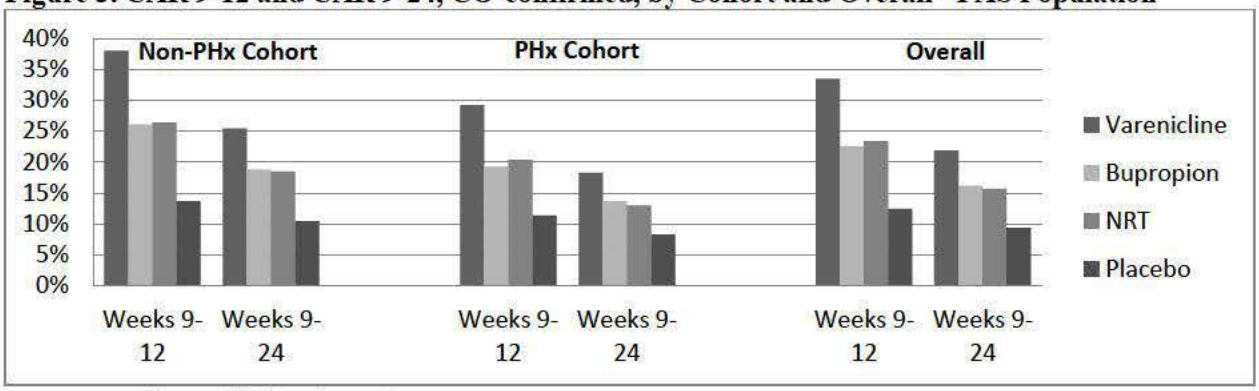
	Overall	Non-Psychiatric History	Psychiatric History
CAR 9-24(%)		n/N	
Varenicline	21.9%	25.5%	18.3%
Bupropion	16.2%	18.8%	13.8%
NRT	15.7%	18.5%	13.0%
Placebo	9.4%	10.5%	8.3%
Treatment Comparisons		Estimated odds ratio in CAR 9-24 (95% CI)	
Primary Comparisons			
Varenicline vs Placebo	2.73* (2.27, 3.29)	2.99* (2.33, 3.83)	2.50* (1.90, 3.29)
Bupropion vs Placebo	1.88* (1.55, 2.28)	2.00* (1.54, 2.59)	1.77* (1.33, 2.36)
Secondary Comparisons			
NRT vs Placebo	1.80* (1.48, 2.18)	1.96* (1.51, 2.54)	1.65* (1.24, 2.20)
Varenicline vs Bupropion	1.45* (1.24, 1.71)	1.50* (1.20, 1.86)	1.41* (1.11, 1.79)
Varenicline vs NRT	1.52* (1.29, 1.79)	1.52* (1.23, 1.89)	1.52* (1.19, 1.93)
Bupropion vs NRT	1.05 (0.88, 1.24)	1.02 (0.81, 1.28)	1.07 (0.83, 1.39)

* p-value <0.05, using a logistic regression with terms treatment, cohort, region, and treatment by cohort interaction, and region by cohort interaction. Region used 2-level classification (US, non-US).

Source: Reviewer program main.sas

The primary comparisons of varenicline versus placebo and bupropion versus placebo with respect to CAR 9-24 were statistically significant (p-values < 0.001) by cohort and overall. All other pairwise comparisons with respect to CAR 9-24 were also considered statistically significant except for bupropion versus NRT (overall p=0.60, OR=1.05), both overall and by cohort. The results were consistent with the applicant's conclusion that varenicline (and separately, bupropion) was superior to placebo with respect to CAR 9-24. The odds of varenicline were statistically significant greater than bupropion, NRT, and placebo, respectively, with respect to smoking cessation for weeks 9 through 24.

Figure 3. CAR 9-12 and CAR 9-24, CO-confirmed, by Cohort and Overall - FAS Population



Source: Reviewer file barchart.xlsx

Although the observed rates for CAR 9-12 and CAR 9-24 were numerically lower in the PHx cohort than in the non-PHx cohort, there was no statistically significant interaction between treatment and cohort (p-values of 0.62 and 0.79, respectively).

During the review, there were several discrepancies noted in the FAS population. Eight subjects were identified as having their genders reported incorrectly, and among them, two subjects had screen failures (see applicant's ERRATA). Therefore, genders of the remaining six subjects were corrected.

Exhaled CO was measured at the baseline visit and at Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24. Pfizer's analysis considered missing CO values as negative (responder), i.e. a subject could be considered a responder (non-smoker) based only on self-report. Since this is not the customary approach to analysis of smoking cessation studies, the reviewer imputed subjects with missing CO values as non-responders and reanalyzed CAR 9-12 and CAR 9-24. However, only 53 subjects (0.7%) and 128 subjects (1.6%), respectively, were considered non-responders and when CAR 9-12 and CAR 9-24 were reanalyzed, the conclusion did not change.

Another concern noted was that some subjects had prior exposure to varenicline, bupropion, or NRT and failed to tolerate the medication. If by chance these subjects were randomized to a drug they were previously unable to tolerate, they would likely drop out and be considered non-responders. In a trial primarily designed to assess comparative efficacy, subjects already known to be intolerant to one of the study drugs would have been screened out. To explore the impact of this possibility, these subjects were excluded and the data was reanalyzed. This modified population is referred as the modified Full Analysis Set (mFAS). The table below provides a summary of the number of patients in the FAS and mFAS datasets by cohort.

Table 10. Number of Subjects in FAS and mFAS Datasets, by Cohort

Treatment/Cohort	Number of Subjects				
	Varenicline	**Bupropion**	**NRT**	**Placebo**	**Total**
Overall					
FAS Population	2037	2034	2038	2035	8144
mFAS Population	1333	1262	1296	1322	5213
Non-Psychiatric History					
FAS Population	1005	1001	1013	1009	4028
mFAS Population	690	641	656	670	2657
Psychiatric History					
FAS Population	1032	1033	1025	1026	4116
mFAS Population	643	621	640	652	2556

Source: Reviewer program main.sas

The results of the analyses of CAR 9-12 and CAR 9-24 using the mFAS population both overall and by cohort are summarized in Table 11 and Table 12.

Table 11. Comparison of Continuous Abstinence, Weeks 9-12, CO-Confirmed, by Cohort and Overall - mFAS Population†

	Overall	Non-Psychiatric History	Psychiatric History
CAR 9-12(%)		n/N	
Varenicline	31.9%	34.9%	28.6%
Bupropion	22.8%	26.2%	19.3%
NRT	22.1%	26.5%	17.5%
Placebo	12.5%	14.3%	10.6%
Treatment Comparisons	Estimated odds ratio in CAR 9-12 (95% CI)		
Primary Comparisons			
Varenicline vs Placebo	3.39* (2.77, 4.16)	3.33* (2.54, 4.37)	3.45* (2.54, 4.68)
Bupropion vs Placebo	2.09* (1.69, 2.59)	2.14* (1.62, 2.84)	2.04* (1.48, 2.82)
Secondary Comparisons			
NRT vs Placebo	1.98* (1.60, 2.46)	2.16* (1.63, 2.86)	1.82* (1.32, 2.52)
Varenicline vs Bupropion	1.62* (1.35, 1.94)	1.55* (1.22, 1.97)	1.69* (1.30, 2.20)
Varenicline vs NRT	1.71* (1.43, 2.05)	1.54* (1.22, 1.96)	1.90* (1.45, 2.48)
Bupropion vs NRT	1.06 (0.87, 1.28)	0.99 (0.77, 1.28)	1.12 (0.84, 1.50)

* p-value < 0.05, using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction.

† FAS population excluding those subjects who used concomitant medications and/or had failed lifetime serious quit attempts on the study medications.
Source: Reviewer program main.sas

In the primary comparisons, all odds of varenicline and bupropion were significantly greater than placebo overall and within cohorts ($p<0.001$). All other comparisons was statistically significant except for bupropion versus NRT (overall $p=0.57$). The results indicated that varenicline and bupropion were superior to placebo with respect to smoking cessation. The observed rates of continuous abstinence were lower in the PHx cohort than in the non-PHx cohort. However, there was no statistically significant interaction between treatment and cohort ($p=0.71$).

Similarly, analysis of CAR 9-24 (Table 12) using the mFAS population indicated that the odds of quitting were significantly better for varenicline and bupropion versus placebo. Results were consistent for the overall population and within cohorts ($p<0.001$). All other comparisons were statistically significant except for bupropion versus NRT (overall $p=0.92$). In general the observed rates of continuous abstinence were lower in the PHx cohort than in the non-PHx cohort. However, there was no statistically significant interaction between treatment and cohort ($p=0.87$). The observed rates and estimated odds ratios of CAR 9-24 were lower than those of CAR 9-12 (Figure 4).

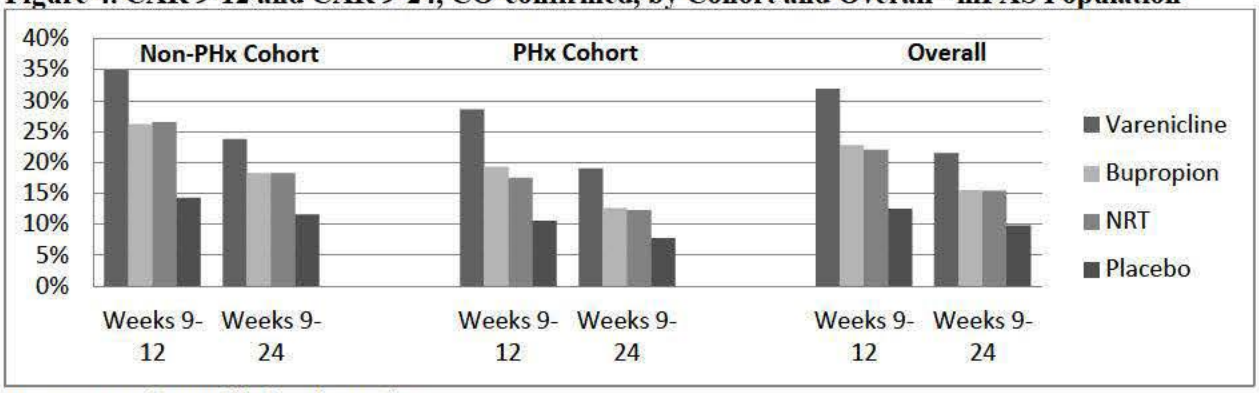
Table 12. Comparison of Continuous Abstinence, Weeks 9-24, CO-Confirmed, by Cohort and Overall - mFAS Population†

	Overall	Non-Psychiatric History	Psychiatric History
CAR 9-24(%)		n/N	
Varenicline	21.5%	23.8%	19.0%
Bupropion	15.5%	18.3%	12.6%
NRT	15.4%	18.3%	12.3%
Placebo	9.8%	11.6%	7.8%
Treatment Comparisons	Estimated odds ratio in CAR 9-24 (95% CI)		
Primary Comparisons			
Varenicline vs Placebo	2.60* (2.07, 3.27)	2.42* (1.80, 3.26)	2.78* (1.96, 3.95)
Bupropion vs Placebo	1.70* (1.33, 2.17)	1.70* (1.24, 2.32)	1.70* (1.17, 2.47)
Secondary Comparisons			
NRT vs Placebo	1.68* (1.32, 2.14)	1.68* (1.23, 2.30)	1.68* (1.16, 2.43)
Varenicline vs Bupropion	1.53* (1.25, 1.88)	1.43* (1.09, 1.87)	1.64* (1.20, 2.23)
Varenicline vs NRT	1.55* (1.26, 1.90)	1.44* (1.10, 1.88)	1.66* (1.22, 2.26)
Bupropion vs NRT	1.01 (0.81, 1.26)	1.01 (0.76, 1.34)	1.01 (0.73, 1.42)

* p-value < 0.05, using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction.

† FAS population excluding those subjects who used concomitant medications and/or had failed lifetime serious quit attempts on the study medications.
Source: Reviewer program main.sas

Figure 4. CAR 9-12 and CAR 9-24, CO-confirmed, by Cohort and Overall - mFAS Population



Source: Reviewer file barchart.xlsx

Pfizer conducted site audits at 26 sites and found concerns with reliability and data quality at 2 sites in the United States (1002 and 1077). As a result, a sensitivity analysis was performed on the primary endpoint (CAR 9-12) by removing the data from these two sites. The reviewer also conducted a sensitivity analysis on CAR 9-12 using the mFAS population.

Regardless of exclusion of the data from sites 1002 and 1077, the observed and estimated values from sensitivity analysis were similar to the results of primary efficacy analysis including all

sites. The applicant's results were confirmed that the treatment effect was not dependent on the presence of data from these two sites.

Table 13. Sensitivity Analysis of Continuous Abstinence, Weeks 9-12, CO-Confirmed, With Sites 1002 and 1077 Removed, by Cohort and Overall - mFAS Population†

	Overall	Non-Psychiatric History	Psychiatric History
CAR 9-12(%)		n/N	
Varenicline	32.0%	35.1%	28.8%
Bupropion	22.7%	26.1%	19.1%
NRT	22.2%	26.6%	17.7%
Placebo	12.4%	14.2%	10.6%
Treatment Comparisons		Estimated odds ratio in CAR 9-12 (95% CI)	
Primary Comparisons			
Varenicline vs Placebo	3.43* (2.80, 4.21)	3.39* (2.58, 4.46)	3.47* (2.55, 4.72)
Bupropion vs Placebo	2.08* (1.68, 2.58)	2.16* (1.63, 2.88)	2.00* (1.45, 2.77)

† FAS population excluding those subjects who used concomitant medications and/or had failed lifetime serious quit attempts on the study medications.
Source: Reviewer program main.sas

3.6 Evaluation of Safety

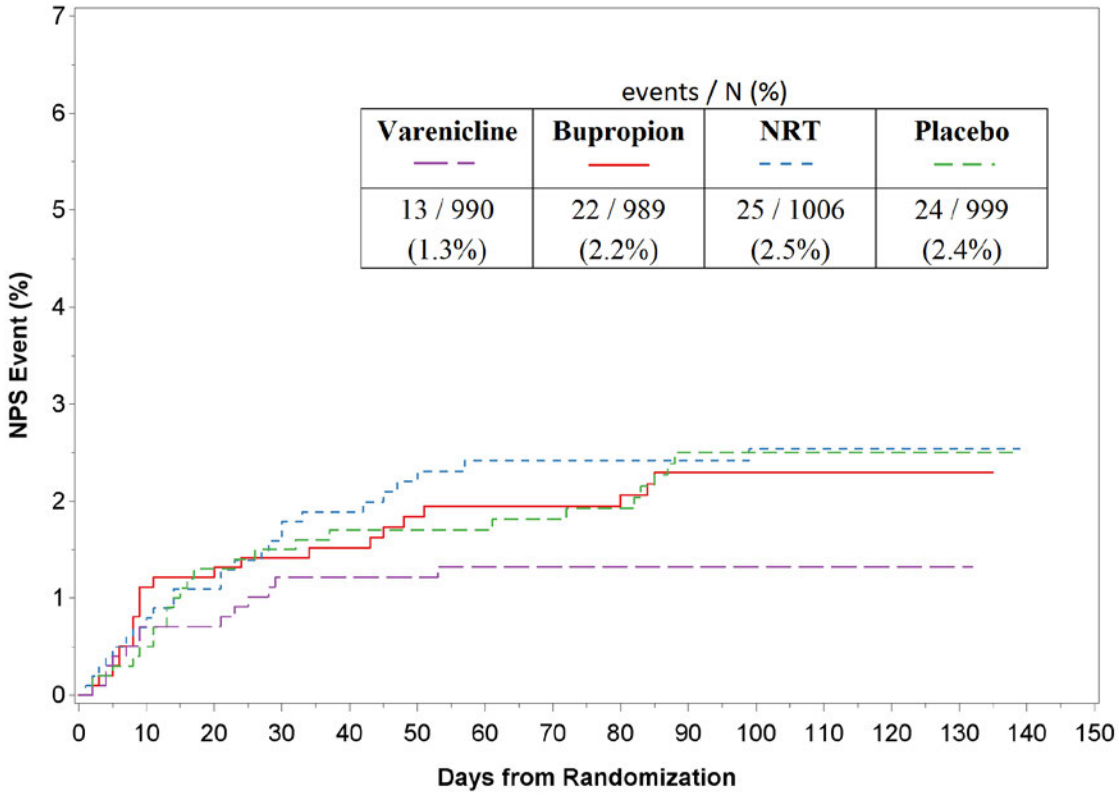
3.6.1 Results and Conclusions

In this section we discuss the analyses of the NPS endpoint and secondary safety endpoints described in Section 3.3.2. All analyses were conducted by the FDA's statistical review team based on the datasets submitted by the applicant and described in Section 2.2.

3.6.1.1 Analysis of the Primary Neuropsychiatric Safety (NPS) Endpoint

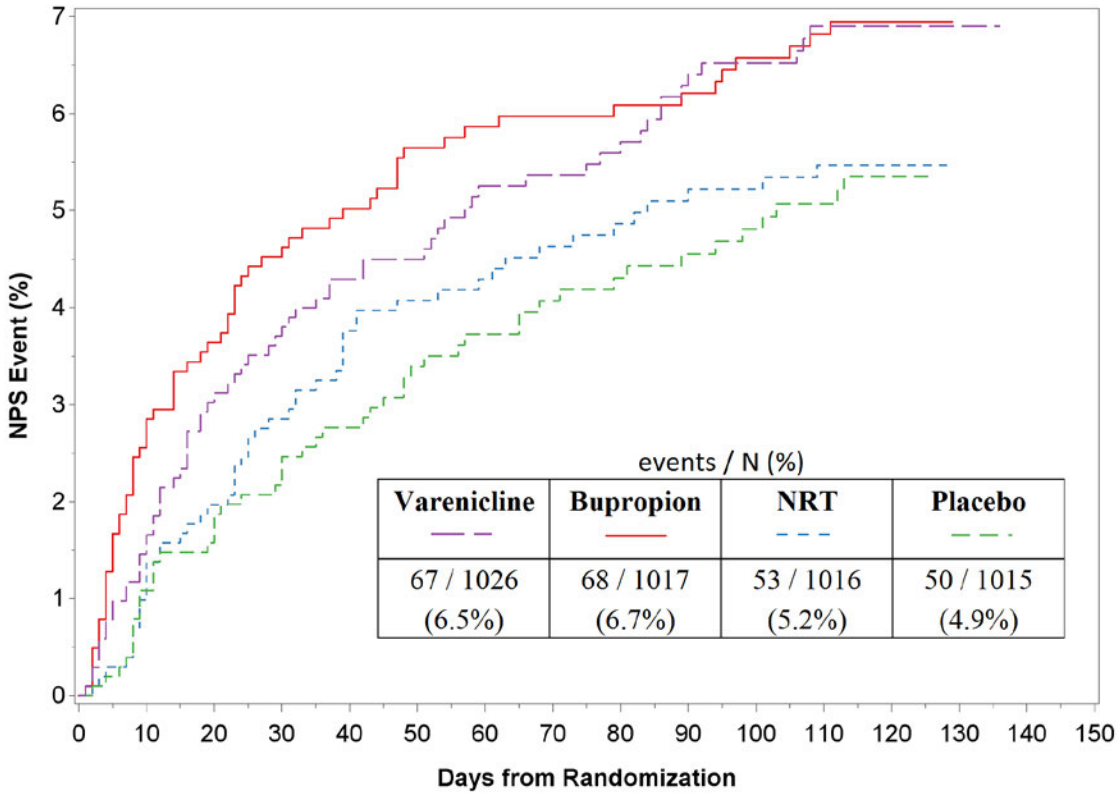
Figure 5 and Figure 6 show the number and proportion of subjects who experienced a treatment-emergent NPS event in trial A3051123, as well as the timing of these events, by treatment arm and cohort of psychiatric history diagnosis at baseline (PHx and Non-PHx). The observed cumulative rate of NPS events among subjects in the Non-PHx cohort was lowest among subjects randomized to varenicline (1.3%) and was similar for subjects randomized to bupropion, NRT, or placebo (2.2% to 2.5%). The observed cumulative rate of NPS events in the PHx cohort was highest among subjects randomized to varenicline and bupropion (6.5% and 6.7% respectively) and was lowest among subjects randomized to placebo (4.9%). Subjects randomized to bupropion or varenicline in the PHx cohort (Figure 6) experienced more NPS events within the first 7 days after randomization (21 subjects on bupropion, 12 on varenicline) than subjects randomized to NRT (4) or placebo (4).

Figure 5. NPS Events in the Non-PHx Cohort



Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Figure 6. NPS Events in the PHx Cohort

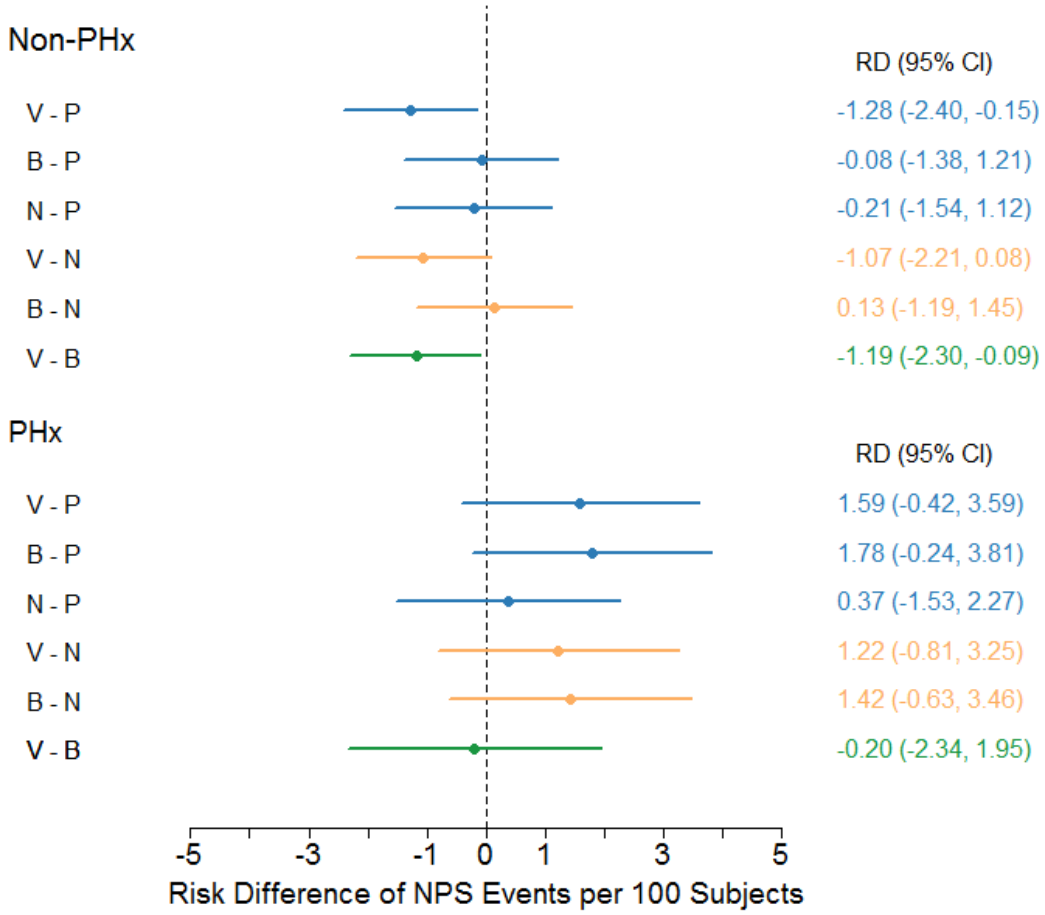


Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Figure 7 shows the estimated risk differences and corresponding nominal 95% confidence intervals for the risk difference of treatment-emergent NPS events for each of the 6 pairwise treatment comparisons in each of the two cohorts based on the pre-specified primary analysis. The figure shows a nominally protective effect associated with varenicline relative to placebo: RD = -1.28 NPS events per 100 subjects, 95% CI (-2.40,-0.15) in the Non-PHx cohort, and a numerically increased risk associated with varenicline: RD = 1.59 NPS events per 100 subjects, 95% CI (-0.42, 3.59) and bupropion: RD = 1.78 NPS events per 100 subjects, 95% CI (-0.24, 3.81) relative to placebo in the PHx cohort. Varenicline showed a nominally protective effect relative to bupropion in the Non-PHx cohort: RD = -1.19 NPS events per 100 subjects, 95% CI (-2.30, -0.09) and no meaningful difference in the PHx cohort: RD = -0.20, 95% CI (-2.34, 1.95).

Reviewer's Comment**:** *The observed incidence rates of NPS events in both cohorts were smaller than anticipated in the Statistical Analysis Plan (SAP) described in Section 3.3.2.2. Consequently, the widths of the 95% confidence intervals for the Risk Difference of NPS events comparing varenicline to placebo were narrower than anticipated in the SAP. The sample size of trial A3051123 was adequate to evaluate the risk difference of NPS events based on the pre-specified precision in the SAP. However, the widths of the confidence intervals on a relative scale (relative risk) were wider due to the smaller total number of observed events.*

Figure 7. Primary Analysis: Risk Difference of NPS Events by Cohort



V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

The 261 MedDRA preferred terms in the NPS composite were grouped into 16 categories, as described in Section 3.2.3 of this review. Table 14 and Table 15 show the number of subjects in the trial with at least one qualifying treatment emergent NPS event in each of these categories. Note that subjects may have experienced events in multiple categories and therefore may be counted in multiple rows. The categories with the largest number of subjects with at least one NPS event in the PHx cohort were: agitation (97 subjects), panic (43), aggression (38), and mania (25). In the Non-PHx cohort, the most common categories were: agitation (51 subjects), aggression (11), panic (8), and suicidal ideation (6). Only 1 completed suicide was recorded in the trial (the subject was randomized to placebo in the Non-PHx cohort). Two subjects exhibited suicidal behavior in the Non-PHx cohort (1 bupropion, 1 NRT) and 3 in the PHx cohort (1 varenicline, 1 bupropion, 1 placebo). The number of subjects with multiple qualifying NPS events by treatment arm and cohort is shown in Appendix 6.1.

Table 14. Number of Subjects who Experienced Individual Components of the NPS Endpoint in the Non-PHx Cohort

	Varenicline N = 990	Bupropion N = 989	NRT N = 1006	Placebo N = 999
NPS Endpoint Overall	**13 (1.3%)**	**22 (2.2%)**	**25 (2.5%)**	**24 (2.4%)**
Agitation	10	11	19	11
Aggression	3	3	2	3
Panic	0	4	1	3
Suicidal Ideation	0	1	2	3
Mania	0	1	2	2
Anxiety	0	1	0	3
Suicidal Behavior	0	1	1	0
Hostility	0	1	1	0
Depression	1	0	0	0
Hallucination	1	0	0	0
Psychosis	0	0	1	0
Paranoia	0	1	0	0
Delusions	0	0	1	0
Homicidal Ideation	0	0	1	0
Suicide	0	0	0	1
Feeling Abnormal	0	0	0	0

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Table 15. Number of Subjects who Experienced Individual Components of the NPS Endpoint in the PHx Cohort

	Varenicline N = 1026	Bupropion N = 1017	NRT N = 1016	Placebo N = 1015
NPS Endpoint Overall	**67 (6.5%)**	**68 (6.7%)**	**53 (5.2%)**	**50 (4.9%)**
Agitation	25	29	21	22
Panic	7	16	13	7
Aggression	14	9	7	8
Mania	7	9	3	6
Depression	6	4	7	6
Anxiety	5	4	6	2
Hallucination	5	4	2	2
Suicidal Ideation	5	2	3	2
Psychosis	4	2	3	1
Paranoia	1	0	0	2
Suicidal Behavior	1	1	0	1
Delusions	1	1	1	0
Feeling Abnormal	0	1	0	0
Homicidal Ideation	0	0	0	0
Hostility	0	0	0	0
Suicide	0	0	0	0

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.1.1 NPS Event by Sub-Cohorts of Psychiatric History at Baseline

Subjects in the PHx cohort were categorized into 4 sub-cohorts based on their diagnosis of psychiatric disorder at baseline: affective disorder, anxiety disorder, psychotic disorder, or borderline personality disorder. Table 16 shows the number and percentage of subjects with at least one treatment emergent NPS event in each of these sub-cohorts by randomized treatment arm. The most common sub-cohort consisted of subjects with a baseline diagnosis of affective disorder (2882 subjects), followed by subjects with anxiety disorder (782 subjects), and psychotic disorder (386 subjects). Only 24 subjects had a baseline diagnosis of borderline personality disorder. We conducted a post-hoc analysis to evaluate the interaction between sub-cohort and treatment on the risk of NPS events among subjects in the PHx cohort. This analysis found no statistical evidence of an interaction between treatment and sub-cohort on the risk of NPS events (nominal p-value 0.93). Any differences in the observed rates of events across sub-cohorts within each randomized treatment are reasonably explained by chance.

Table 16. Primary NPS Event by Sub-Cohort of the PHx Cohort

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Affective Disorder	50/731 (6.8%)	46/716 (6.4%)	39/713 (5.5%)	33/722 (4.6%)
Anxiety Disorder	11/193 (5.7%)	16/200 (8.0%)	9/195 (4.6%)	11/194 (5.7%)
Psychotic Disorder	6/95 (6.3%)	6/96 (6.3%)	5/99 (5.1%)	6/96 (6.3%)
Borderline Personality Disorder	0/7	0/5	0/9	0/3

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.1.2 NPS Event by Investigative Sites

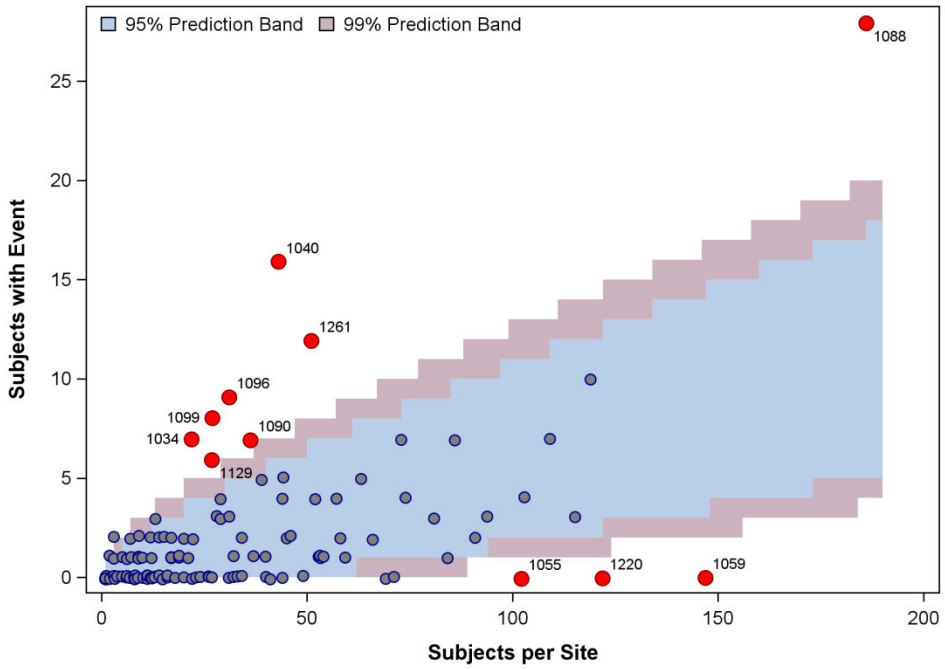
Trial A3051123 randomized and treated subjects in 139 sites in 16 countries (117 sites with subjects in the Non-PHx cohort, 127 sites with subjects in the PHx cohort). Prior to the submission of the trial results on 2/18/2016, Pfizer informed the Agency of problems regarding the conduct of the trial at two sites (site 1002 with 112 subjects, and site 1077 with 31 subjects). Because of this report, the review team at the FDA conducted analyses of various endpoints by site, including the primary NPS endpoint.

Figure 8 and Figure 9 show the number of subjects who were treated in each investigative site on the horizontal axis, and the number of subjects who experienced at least one treatment-emergent NPS event on the vertical axis. The blue (red + blue) shaded area in these figures shows a 95% (99%) prediction band for the expected number of subjects with an NPS event under the assumption that the number of subjects who experience an event in any given site follows a binomial distribution with a common rate of events for all sites in the same cohort. The sites identified by a red solid circle fall outside of the 99% prediction band, i.e. they had either fewer or more subjects with an event than would be expected for a site with the same number of subjects 99% of the time. Figure 8 shows that sites in the PHx cohort exhibited high heterogeneity in NPS event rates. Figure 9 shows that the Non-PHx cohort showed less heterogeneity between sites than the PHx cohort. One example of the high heterogeneity observed in the PHx cohort is that the largest site, site 1088, recorded an NPS event in 28 out of 186 subjects (15.1%), but the second largest site, site 1059, recorded 0 events in 147 subjects. The PHx cohort also observed more sites with 0 NPS events than would be expected under the assumption of a binomial distribution for the number of events within sites (45 expected sites with no events vs. 60 sites observed).

This level of site heterogeneity is highly improbable to have occurred by chance alone under the assumption of a common rate of NPS events. One potential concern is that the subjective nature of the NPS endpoint may have led to different interpretations of what constitutes an event across sites and that this may diminish the generalizability of the trial findings. Section 3.6.1.2 discusses sensitivity analyses that account for extra-binomial variation of NPS events across sites, and analyses that explore the influence of specific sites, such as sites 1002 and 1077 previously identified as 'problematic' by the applicant.

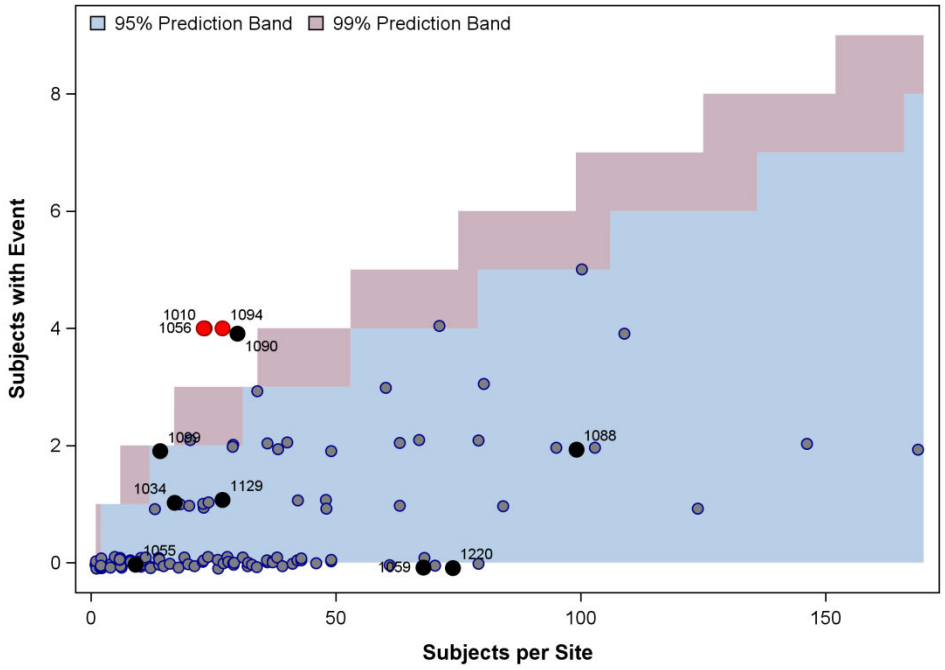
An evaluation of whether the observed heterogeneity in the rate of NPS events by site within the PHx cohort could be partly or fully explained by differences in covariates between sites was performed looking at various factors. We found no evidence of an association between site heterogeneity and country of randomization, sub-cohort of the PHx cohort, or treatment allocation. These analyses are not shown in this review.

Figure 8. Site Size and NPS Events in the PHx Cohort



[1]Red circles represent sites that fall outside of the 99% prediction band
[2]The pooled rate of subjects with an NPS event across all sites in the PHx cohort was 5.8%
Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Figure 9. Site Size and NPS Events in the Non-PHx Cohort



[1]Red circles represent sites that fall outside of the 99% prediction band
[2]Black circles represent sites that fell outside of the 99% prediction band in the PHx cohort (Figure 8)
[3]The pooled rate of subjects with an NPS event across all sites in the Non-PHx cohort was 2.1%
Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.2 Sensitivity Analyses of Neuropsychiatric Events

3.6.1.2.1 Statistical Models to Account for Extra Binomial Variation between Sites

The Akaike information criterion (AIC) is a measure of the goodness of fit of a statistical model to a given set of data. It is an increasing function of the number of parameters in the model (*k*) and a decreasing function of the maximized likelihood function (*L*): AIC = 2k – 2log (L). A smaller AIC implies a better model fit. In order to evaluate whether different statistical models adequately account for the site heterogeneity described in Section 3.6.1.1.2 we fit 4 post-hoc statistical models using the following site-specific variables:

- N_{ijk} is the number of subjects in site *i*, cohort *j*, randomized to treatment *k*.
- Y_{ijk} is the number of subjects with at least one NPS event in site *i*, cohort *j*, randomized to treatment *k* $(0 \leq Y_{ijk} \leq N_{ijk})$.

The 4 statistical models are as follows:

- Binomial Model for the risk difference of NPS events assuming that the number of subjects (Y_{ijk}) with an event within a site, given cohort (Non-PHx or PHx), country (US vs Non-US) and treatment follows a binomial distribution. To fit this model, we used a dependent variable given by Y_{ijk}/N_{ijk} and corresponding independent variables for cohort, country of randomization, and randomized treatment. This model uses a logit link function and is equivalent to the primary pre-specified model. The parameter estimated under this model is the risk difference of NPS events for each pair-wise treatment comparison in each cohort.

- Poisson Model for the number of subjects Y_{ijk} with an NPS event, with covariates for cohort, country of randomization (USA vs. Others) and randomized treatment. This model uses a log link function and $\log(N_{ijk})$ as an offset. The parameter estimated is the rate ratio of NPS events comparing two treatments.

- Negative Binomial Model (NB) for the rate ratio of subjects with an NPS event, with covariates for cohort, country of randomization (USA vs. Others) and randomized treatment. This model assumes a negative binomial distribution a log link function and uses $\log(N_{ijk})$ as an offset. The parameter estimated is the rate ratio of NPS events comparing two treatments.

- Zero Inflated Negative Binomial Model (ZINB) for a "mixture" of distributions, where one group of sites have counts of subjects with NPS events generated by a Negative Binomial model, and another group of sites have 0 events with probability equal to 1. This model estimates two sets of parameters: one set for the rate ratio of NPS events and another set for the probability of belonging to the group of sites with zero events.

The NB and ZINB models allow for extra-binomial variation in the rate of NPS events across sites whereas the Binomial model does not. Note that the Poisson and NB models estimate rate ratios (RR) of NPS events, unlike the primary pre-specified Binomial model which estimated the risk difference (RD). The binomial model assumes that the RD of NPS events associated with treatment is the same in all sites within a cohort and country.

Table 17 shows the AIC for these 4 models. The NB and ZINB models had a smaller AIC and therefore fit the data better than the primary binomial model and the Poisson model. These results suggest that the primary binomial model may underestimate the heterogeneity of NPS rates across sites and also that the RR estimated by the NB model may be a more appropriate measure of risk to summarize these data than the RD estimated by the primary binomial model. The NB model fit the data slightly better than the ZINB model, and has the added advantage of easier interpretation and fewer parameters.

Table 17. Model Fit for Alternative Models for the Distribution of NPS Events Accounting for Covariates and Site

Distribution of NPS Events[1]	AIC (Smaller is better)
Binomial (primary)	1288.13
Poisson	1274.28
Negative Binomial	**1212.48**
Zero-Inflated Negative Binomial	1215

[1]Conditional on values for cohort, treatment, cohort x treatment, and country (USA vs others).
*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Figure 10 shows estimated rate ratios and corresponding 95% confidence intervals for the risk of NPS events for each pair-wise treatment comparison by cohort from the Negative Binomial model for correlated data with observations clustered by site with covariates for cohort, country of randomization (USA vs. Others), and randomized treatment. Parameter estimates from this model were obtained through generalized estimating equations using SAS 9.4 PROC GENMOD.

The results of this analysis show that even though the rate of NPS events in the PHx cohort was more heterogeneous than originally anticipated in the primary binomial model, the interpretations of the NB model and the primary binomial model are consistent. Both models show a numerically lower rate of events observed in the varenicline arm in the Non-PHx cohort and a numerically higher rate of events in the varenicline and bupropion arms in the PHx cohort.

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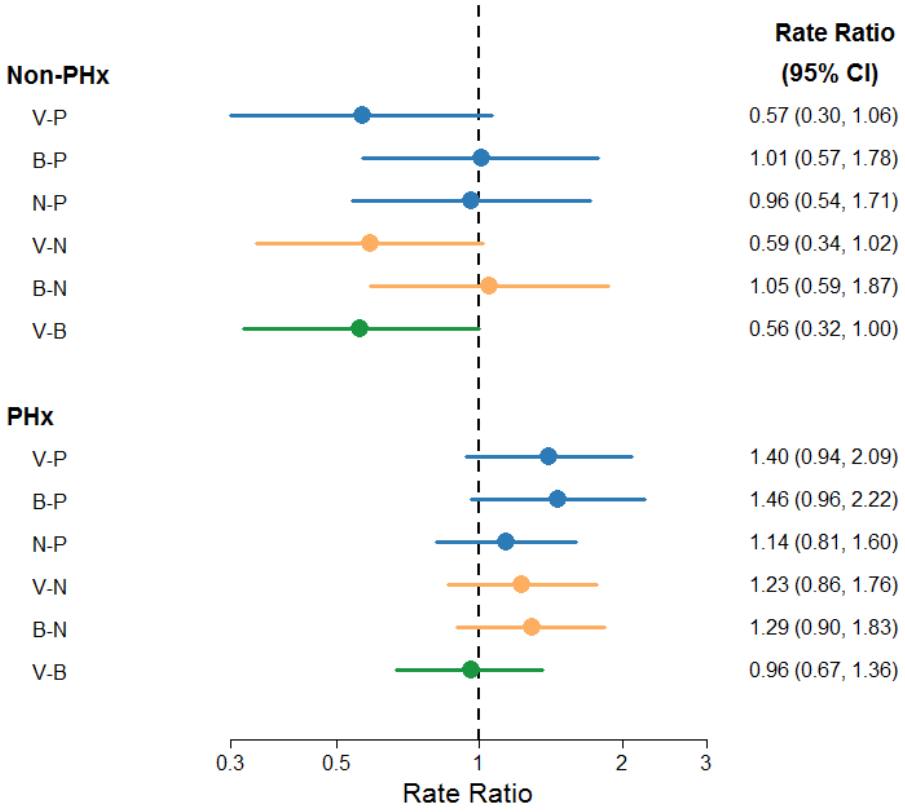
Figure 10. Rate Ratio for NPS Events from a Negative Binomial Model



V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.2.2 Composite Neuropsychiatric Event Including Adverse Events of All Severities

The primary composite NPS event only included treatment emergent adverse events that met a minimum severity threshold as described in Section 3.2.3. We conducted a sensitivity analysis of treatment emergent neuropsychiatric adverse events that included events of all severities, from mild to severe. Table 18 shows the number of subjects with at least one treatment emergent neuropsychiatric event of any severity by treatment arm and cohort. The most common categories for these events in both cohorts were anxiety, depression, and agitation (counts by individual components are not shown in tables). There were 7 times as many events of all severities as there were primary NPS events in the Non-PHx cohort, and 4.5 times as many in the PHx cohort.

Table 18 shows similar observed rates of events among subjects randomized to varenicline, bupropion, or placebo in the Non-PHx cohort, and a numerically higher rate of events among subjects randomized to varenicline or bupropion in the PHx cohort relative to placebo.

Table 18. Treatment Emergent Neuropsychiatric Events of All Severities by Cohort

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	148 / 990 (14.9%)	161 / 989 (16.3%)	131 / 1006 (13.0%)	151 / 999 (15.1%)
PHx Cohort	289 / 1026 (28.2%)	289 / 1017 (28.4%)	255 / 1016 (25.1%)	239 / 1015 (23.5%)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.2.3 Composite Neuropsychiatric Event Including Only Severe Adverse Events

The primary composite NPS event included treatment emergent adverse events that met a minimum severity threshold. We conducted a sensitivity analysis of treatment emergent neuropsychiatric adverse events that included only severe events. Table 19 shows a summary of subjects with at least one severe treatment emergent neuropsychiatric event by treatment arm and cohort. The most common categories for these severe events in the Non-PHx cohort were anxiety (4 subjects), panic (3), and suicidal ideation and behavior (3). The most common categories in the PHx cohort were depression (23 subjects), anxiety (17), and agitation (8).

Table 19 shows no evidence of an increased risk in severe treatment emergent neuropsychiatric events associated with any treatment arm in either cohort. In the cohort without a history of psychiatric illness, the observed frequency of severe NPS events was lower than 0.5% in all treatment arms. In the cohort with a history of psychiatric illness, the observed frequency was approximately 1.4% across all treatment arms in the trial.

Table 19. Severe Treatment Emergent Neuropsychiatric Events by Cohort

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	1 / 990 (0.1%)	4 / 989 (0.4%)	3 / 1006 (0.3%)	5 / 999 (0.5%)
PHx Cohort	14 / 1026 (1.4%)	14 / 1017 (1.4%)	14 / 1016 (1.4%)	13 / 1015 (1.3%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.2.4 Composite NPS+ Event

In order to better understand the neuropsychiatric safety profile of smoking cessation products in trial A3051123, the clinical review team at the FDA defined an alternative composite endpoint, referred to here as NPS+, that included all primary NPS events plus moderate or severe adverse events with an associated MedDRA Preferred Term (PT) of 'Irritability' or a High Level Group Term (HGLT) of 'Depressed mood disorders'. Table 20 shows a summary of NPS+ events by cohort and randomized treatment arm. The overall frequency of NPS+ events was approximately twice as large as the frequency of NPS events in all treatment arms in both cohorts. The estimated risk differences of NPS+ events were generally consistent with the estimated risk differences of the primary NPS endpoint (risk differences not shown). The observed cumulative

rate of NPS+ events in the Non-PHx cohort was lowest among subjects randomized to varenicline. The observed cumulative rate of NPS+ events in the PHx cohort was highest among subjects randomized to varenicline and bupropion.

Table 20. Treatment Emergent NPS+ Events by Treatment and Cohort

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	32 / 990 (3.2%)	35 / 989 (3.5%)	38 / 1006 (3.8%)	44 / 999 (4.4%)
PHx Cohort	118 / 1026 (11.5%)	109 / 1017 (10.7%)	89 / 1016 (8.8%)	100 / 1015 (9.9%)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.2.5 Analysis of the Primary NPS event in the Full Analysis Set

The primary analysis of NPS events was conducted in the Safety Analysis Population defined as all treated subjects from the time of their first dose to the time of their last dose of study drug plus 30 days. Table 21 shows the number of subjects who experienced at least one NPS event in the FAS population defined as the full study follow-up from randomization to the last recorded study visit. These results are consistent with the primary analysis of NPS events and show a smaller observed number of subjects with an NPS event among those randomized to varenicline in the Non-PHx cohort and a higher observed number of events among subjects on varenicline and bupropion in the PHx cohort. Note that the majority of the subjects who experienced at least one NPS event did so during the treatment phase of the trial (plus a window of 30 days): 92% in the Non-PHx cohort and 88% in the PHx cohort. Few events were observed in the post-treatment phase of the trial.

Table 21. NPS Endpoint by Cohort in the FAS Population

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	15 / 990 (1.5%)	24 / 989 (2.4%)	26 / 1006 (2.6%)	26 / 999 (2.6%)
PHx Cohort	72 / 1026 (7.0%)	76 / 1017 (7.5%)	63 / 1016 (6.2%)	60 / 1015 (5.9%)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.2.6 Sensitivity of Parameter Estimates to Potentially Problematic Sites

Section 3.1 discussed some of the potential problems identified in sites 1002, 1063, and 1077. Table 22 shows that these sites contributed only 9 total NPS events to the trial. Table 23 and Table 24 show the estimated risk differences for treatment emergent NPS events and their corresponding 95% confidence intervals comparing varenicline to placebo (Table 23) and bupropion to placebo (Table 24) excluding these three potentially problematic sites. The

estimated risk differences of NPS events excluding these sites are consistent with the results of the primary analysis, which are shown in the top row of each table. The results show a nominally significant reduction in the risk of NPS events associated with varenicline relative to placebo in the Non-PHx cohort, and numerically higher rates of NPS events in the PHx cohort observed in both varenicline and bupropion relative to placebo. These results suggest that the three sites identified as potentially problematic have only a small impact on the estimated risk difference of NPS events, and no meaningful impact on the conclusions of trial A3051123.

Table 22. Sample Size and NPS Events in Potentially Problematic Sites

Site:	Non-PHx Cohort NPS events / N	PHx Cohort NPS events / N
1002	2 / 49	5 / 63
1063	0 / 79	2 / 15
1077	0 / 23	0 / 8

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Table 23. Estimated Risk Difference per 100 Subjects (95% CI) of NPS Events Associated with Varenicline Relative to Placebo Excluding Potentially Problematic Sites

	Non-PHx Cohort	PHx Cohort
All sites	-1.28 (-2.40, -0.15)	1.59 (-0.42, 3.59)
Excluding sites 1002, 1077	-1.36 (-2.49, -0.23)	1.62 (-0.40, 3.65)
Excluding sites 1002, 1063, 1077	-1.39 (-2.54, -0.24)	1.52 (-0.50, 3.54)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Table 24. Estimated Risk Difference per 100 Subjects (95% CI) of NPS Events Associated with Bupropion Relative to Placebo Excluding Potentially Problematic Sites

	Non-PHx Cohort	PHx Cohort
All sites	-0.08 (-1.38, 1.21)	1.78 (-0.24, 3.81)
Excluding sites 1002, 1077	-0.15 (-1.46, 1.15)	1.60 (-0.43, 3.62)
Excluding sites 1002, 1063, 1077	-0.16 (-1.49, 1.16)	1.52 (-0.50, 3.54)

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.6.1.2.7 Analysis of the NPS Endpoint by Previous Use of Smoking Cessation Products

Previous users of smoking cessation products were defined as subjects with at least one recorded use of varenicline, bupropion or NRT as a concomitant medication (dataset Cnmedp.xpt), or at least one reported smoking cessation attempt using any of these products (dataset Smkhst.xpt)

prior to randomization. The objective of this secondary analysis was to assess whether treatment-naïve subjects had a different observed rate of NPS events than treatment-experienced subjects.

Table 25 and Table 26 show that treatment naïve subjects had a lower observed pooled rate of NPS events than treatment-experienced subjects in both study cohorts: 1.7% vs. 2.9% respectively in the Non-PHx cohort; 4.7% vs. 7.7% in the PHx cohort. Overall, the data showed no evidence to suggest that treatment-naïve subjects may be at higher risk of NPS events than treatment-experienced subjects.

Table 25. NPS events in treatment-naïve subjects

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	6 / 673 (0.9%)	17 / 632 (2.7%)	12 / 649 (1.8%)	9 / 658 (1.4%)
PHx Cohort	37 / 631 (5.9%)	37 / 609 (6.1%)	20 / 631 (3.2%)	23 / 638 (3.6%)

*Treatment-naïve subjects are defined as those without recorded exposure to varenicline, bupropion or NRT at the time of randomization.
Source: Created by reviewer using datasets cnmedp.xpt, smkhst.xpt, demog.xpt, subevg.xpt, advers.xpt

Table 26. NPS events in treatment-experienced subjects

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	7 / 317 (2.2%)	5 / 357 (1.4%)	13 / 357 (3.6%)	15 / 341 (4.4%)
PHx Cohort	30 / 395 (7.6%)	31 / 408 (7.6%)	33 / 385 (8.6%)	27 / 377 (7.2%)

*Treatment-experienced subjects are defined as subjects with exposure to at least one of varenicline, bupropion or NRT at the time of randomization.
Source: Created by reviewer using datasets cnmedp.xpt, smkhst.xpt, demog.xpt, subevg.xpt, advers.xpt

3.6.1.3 Analyses of Secondary Safety Endpoints

3.6.1.3.1 Analysis of Death

Table 27 summarizes all deaths observed in trial A3051123 in the FAS population. The cause of death reported for each of these subjects is shown in Appendix 6.3. Additionally, one subject not shown in Table 27 died before randomization and one subject randomized to placebo delivered a premature baby which resulted in the baby's death. The small number of observed deaths in the trial precludes a precise analysis of the risk of death associated with any of these treatments.

Table 27. Deaths by Cohort and Treatment

	Varenicline deaths / N	Bupropion deaths / N	NRT deaths / N	Placebo deaths / N
Non-PHx Cohort	0 / 990	1 / 989	1 / 1006	3 / 999
PHx Cohort	0 / 1026	2 / 1017	1 / 1016	1 / 1015

Source: Created by reviewer using dataset Death.xpt

3.6.1.3.2 Analysis of the C-SSRS Instrument

Suicidal behavior, suicidal ideation, and completed suicide are three components of the primary NPS endpoint as shown earlier in Table 14 and Table 15. Adverse events that are part of these components were captured through several mechanisms in trial A3051123, including routine collection of adverse events, investigator reports, and responses to the C-SSRS questionnaire. The C-SSRS is a validated questionnaire designed to evaluate suicide-related ideation and behavior. The results of the C-SSRS questionnaire were the primary endpoint of a meta-analysis of 5 Phase III/IV trials discussed at the October 16, 2014 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. In trial A3051123, the C-SSRS questionnaire was routinely collected at every clinic visit during the 12 week treatment phase.

Table 28 and Table 29 show the number of subjects with treatment emergent suicidal behavior, suicidal ideation, and self-injurious behavior based on the results of the C-SSRS questionnaire in trial A3051123. Note that episodes of suicidal ideation or behavior that were categorized as "mild" were counted in the C-SSRS instrument, but did not contribute an event to the primary NPS composite, which included only moderate or severe suicidal ideation and behavior. Analyses of the C-SSRS instrument show no conclusive evidence of a treatment effect on the risk of suicidal ideation, suicidal behavior, or self-injurious behavior.

Table 28. Results of the C-SSRS in the Non-PHx Cohort – Treatment Emergent Events

	Varenicline N = 990	Bupropion N = 989	NRT N = 1006	Placebo N = 999
Suicidal Behavior	0	0	1	1
Suicidal Ideation	7	4	3	6
Self-Injurious Behavior	0	0	0	0

Source: Created by reviewer using datasets Css1.xpt and Css2.xpt

Table 29. Results of the C-SSRS in the PHx Cohort – Treatment Emergent Events

	Varenicline N = 1026	Bupropion N = 1017	NRT N = 1016	Placebo N = 1015
Suicidal Behavior	0	1	0	2
Suicidal Ideation	27	15	20	25
Self-Injurious Behavior	2	1	0	1

Source: Created by reviewer using datasets Css1.xpt and Css2.xpt

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analyses of Efficacy by Gender, Race, Age, and Geographic Region

As per FDA's information request on March 8, 2016, the applicant submitted the subgroup analyses of CAR 9-12 and CAR 9-24 by age (18-44 years, 45-64 years, and > 64 years), sex (male and female), race (White, Black, and Other), and region (US and non-US) based on the FAS population. Similar subgroup analyses were conducted on CAR 9-12 for the mFAS population using the following subgroup categories:

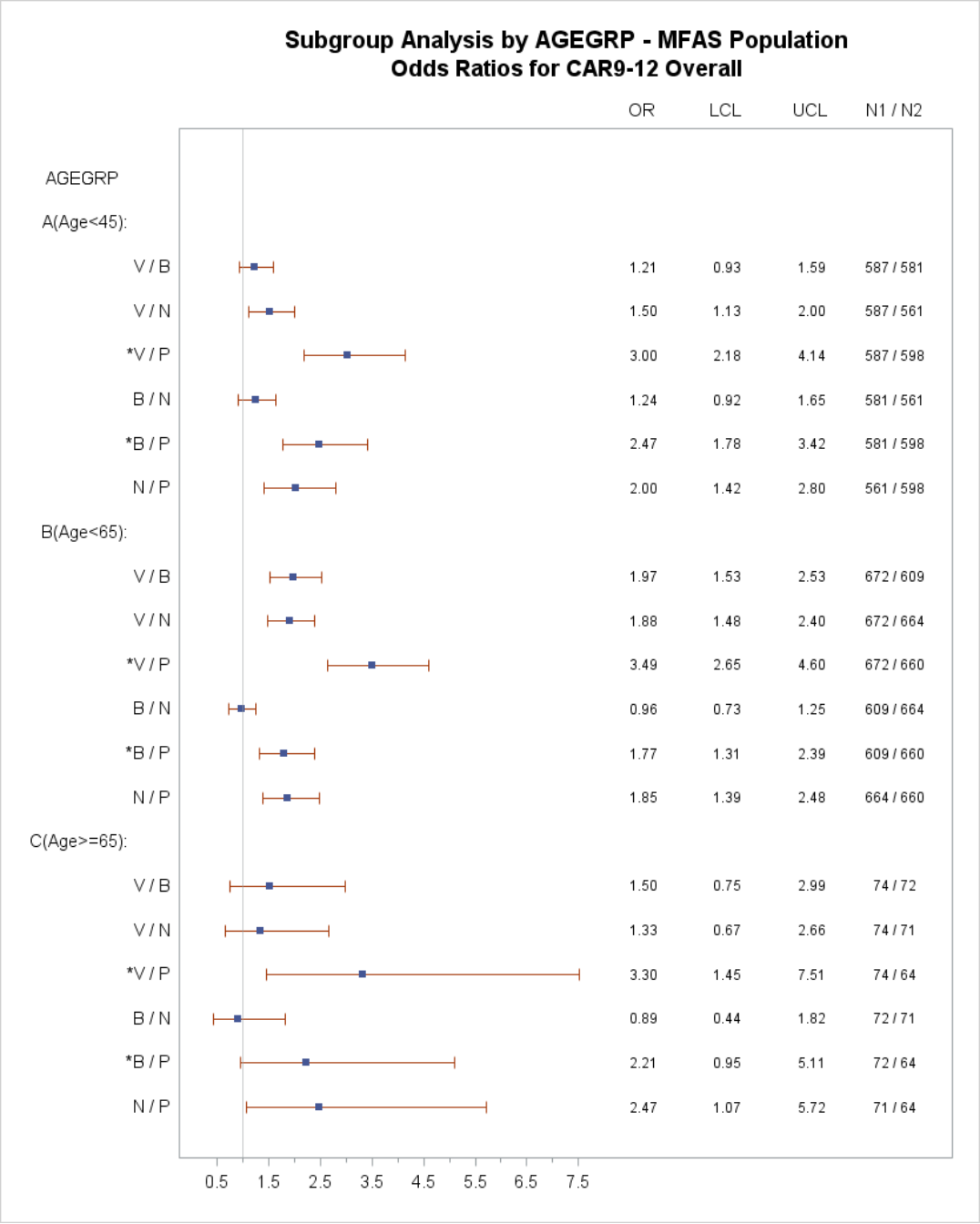
- Age: 18-44 years, 45-64 years, and > 64 years
- Sex: male and female
- Race: White, Black, and Other
- Region (binary): US and non-US
- Regions (categorical):
    - US/CA: United States, Canada
    - LA: Argentina, Brazil, Chile, Mexico
    - SA: South Africa
    - WE: Denmark, Finland, Germany, Spain, Australia, New Zealand
    - EE: Bulgaria, Slovakia, Russian Federation

Note that due to small sample sizes, Australia and New Zealand were combined into Western Europe category.

Interactions with treatment for these subgroups were not statistically significant ($p>0.1$). The estimated odds ratios for CAR 9-12 for primary comparisons were consistent across these subgroups.

For age subgroup, the estimated odds ratios were in the same direction and of similar magnitude for age categories 18-44 years and 45-64 years (Figure 11). There was a large variability with wide confidence intervals in age>64 years category due to limited numbers of subjects.

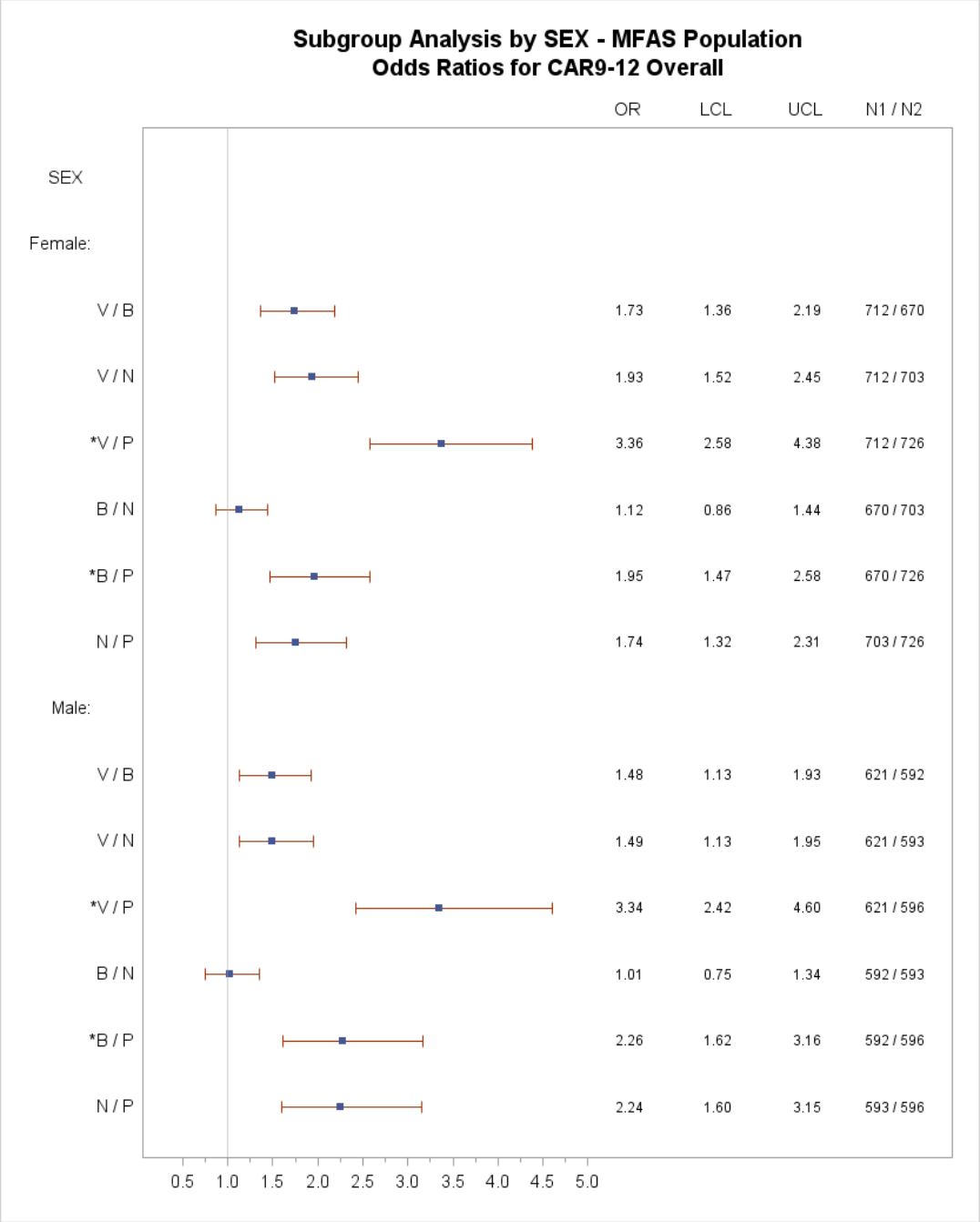
Figure 11. Forest Plot of Estimated Odds Ratios for CAR9-12 for the mFAS Population by Age Subgroup



V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* Primary comparisons: varenicline vs placebo, bupropion vs placebo
Source: Reviewer program main.sas

The estimated odds ratios for all treatment comparisons were largely consistent for females and males (Figure 12).

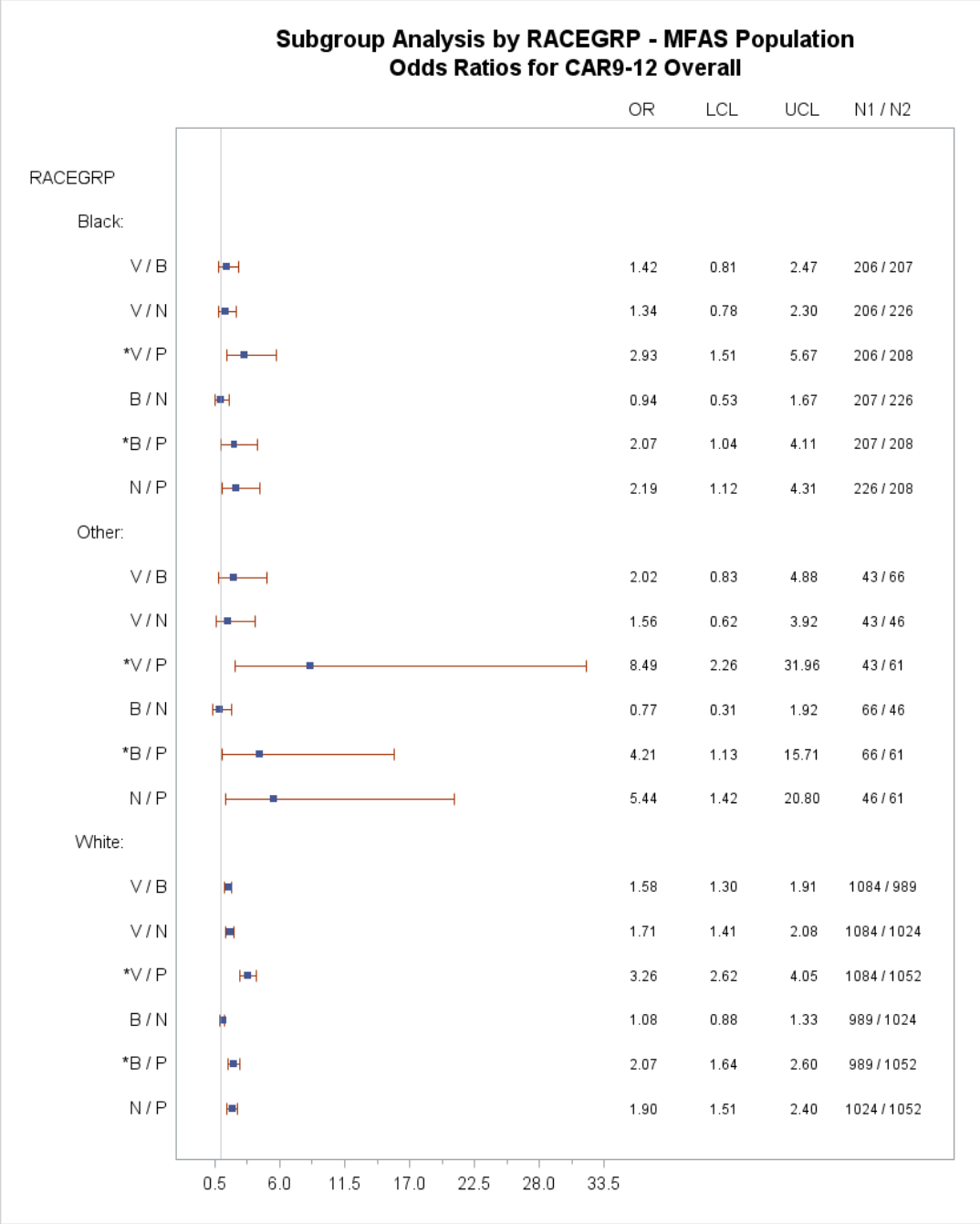
Figure 12. Forest Plot of Estimated Odds Ratios for CAR9-12 for the mFAS Population by Sex Subgroup



V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* Primary comparisons: varenicline vs placebo, bupropion vs placebo
Source: Reviewer program main.sas

For race subgroup, although the estimated odds ratios were larger in magnitude for the other category (Asian, other, and unspecified), given the small sample size, they were still consistent in the direction of benefit.

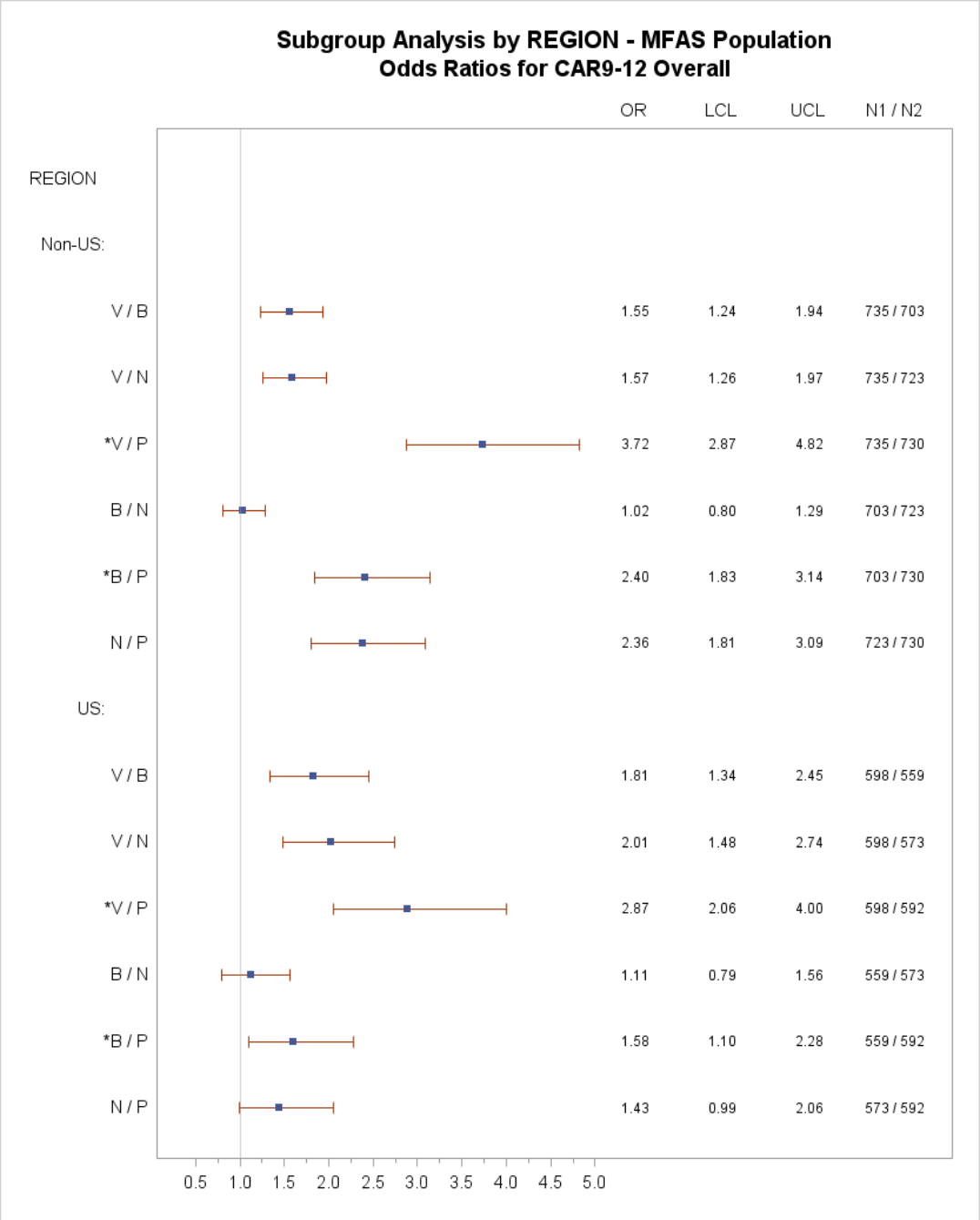
Figure 13. Forest Plot of Estimated Odds Ratios for CAR9-12 for the mFAS Population by Race Subgroup



V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* Primary comparisons: varenicline vs placebo, bupropion vs placebo
Source: Reviewer program main.sas

When region was examined as US and non-US, the treatment effect was in the same direction and of similar magnitude regardless of region. Results (Figure 14) indicated, there were slightly greater treatment effects demonstrated in subjects from non-US than those from US for both primary comparisons.

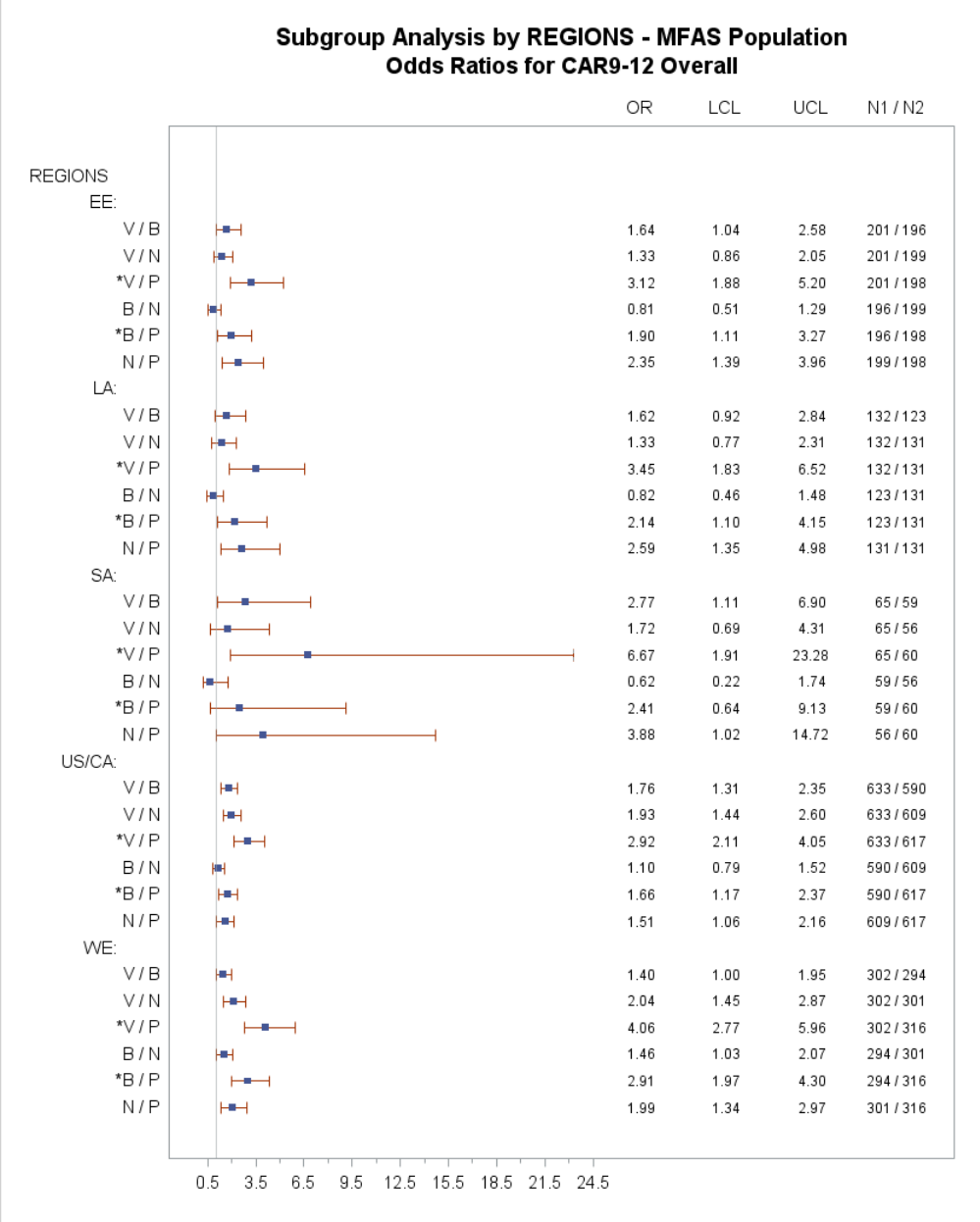
Figure 14. Forest Plot of Estimated Odds Ratios for CAR9-12 for the mFAS Population by Region (Binary) Subgroup



V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* Primary comparisons: varenicline vs placebo, bupropion vs placebo
Source: Reviewer program main.sas

When region was examined as US/CA, LA, SA, WE, EE, the estimated odds ratios were in the same direction and of similar magnitude for other categories (Figure 15). Among all categories, the greatest treatment comparisons in varenicline and bupropion compared to placebo were observed in Western Europe category. This is also the only category that demonstrates significant improvement comparing bupropion to NRT. The numbers of South Africa subjects were too small to obtain reliable estimates.

Figure 15. Forest Plot of Estimated Odds Ratios for CAR9-12 for the mFAS Population by Regions (Categorical) Subgroup



V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* Primary comparisons: varenicline vs placebo, bupropion vs placebo
Source: Reviewer program main.sas

4.2 Subgroup Analyses of Safety

The sections below present summary tables of the primary NPS event by cohort, treatment, and subgroups defined by gender, age race, and country of randomization. Appendix 6.4 shows estimated risk differences for NPS events and their corresponding 95% confidence intervals for each pair-wise treatment comparison by cohort of psychiatric illness at baseline and subgroup.

4.2.1 Subgroup Analysis by Gender

Among the 3984 randomized subjects in the Non-PHx cohort, 50.2% were male (N=1999) and 49.8% were female (N=1985). In the PHx cohort 62.0% of the 4074 subjects were female (N=2524).

Females randomized to bupropion had a higher observed risk of NPS events than males in both cohorts (Table 30 and Table 31). However this difference may reasonably be explained by chance. We found no conclusive evidence of an increased risk of NPS events associated with either gender (nominal p-value 0.2240) and no evidence of an interaction between gender and treatment on the risk of NPS events (nominal p-value 0.1796). The analyses of treatment by gender on the risk of NPS events were generally consistent with the primary analysis (Appendix 6.4).

Table 30. Primary NPS Event by Gender in the Non-PHx Cohort

	Varenicline	Bupropion	NRT	Placebo
Male	8/510 (1.6%)	9/503 (1.8%)	12/497 (2.4%)	14/489 (2.9%)
Female	5/480 (1.0%)	13/486 (2.7%)	13/509 (2.6%)	10/510 (2.0%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Table 31. Primary NPS Event by Gender in the PHx Cohort

	Varenicline	Bupropion	NRT	Placebo
Male	22/392 (5.6%)	15/387 (3.9%)	17/384 (4.4%)	17/387 (4.4%)
Female	45/634 (7.1%)	53/630 (8.4%)	36/632 (5.7%)	33/628 (5.3%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

4.2.2 Subgroup Analysis by Age

Table 32 and Table 33 show the number of total subjects and subjects with NPS events by cohort and by three subgroups defined by subjects' age at baseline: ages between 18 and 44, 45 and 64, and 65 or older.

The analyses of treatment by age group on the risk of NPS events were generally consistent with the primary analysis (Appendix 6.4). We found no evidence of an increased risk of NPS events associated with age (p-value 0.1004) and no evidence of an interaction between age and treatment on the risk of NPS events (p-value 0.2864).

Table 32. Primary NPS Event by Age Groups in the Non-PHx Cohort

	Varenicline	Bupropion	NRT	Placebo
18-44	6/431 (1.4%)	11/431 (2.6%)	9/432 (2.1%)	11/432 (2.5%)
45-64	5/487 (1.0%)	8/479 (1.7%)	13/499 (2.6%)	13/499 (2.6%)
65+	2/72 (2.8%)	3/79 (3.8%)	3/75 (4.0%)	0/68 (0.0%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Table 33. Primary NPS Event by Age Groups in the PHx Cohort

	Varenicline	Bupropion	NRT	Placebo
18-44	37/377 (9.8%)	28/412 (6.8%)	25/367 (6.8%)	29/406 (7.1%)
45-64	25/589 (4.2%)	37/537 (6.9%)	26/589 (4.4%)	21/562 (3.7%)
65+	5/60 (8.3%)	3/68 (4.4%)	2/60 (3.3%)	0/47 (0.0%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

4.2.3 Subgroup Analysis by Race

Table 34 and Table 35 show the total number of subjects and subjects with NPS events by cohort and race. Subjects identified as "White" comprised 81.7% of all randomized subjects and 87.9% of all subjects with events in trial A3051123. Due to the small number of subjects whose race was not White, it was not possible to accurately compare the risk of NPS events between subjects of different races based on these data.

Table 34. Primary NPS Event by Race in the Non-PHx Cohort

	Varenicline	Bupropion	NRT	Placebo
White	13/819 (1.6%)	20/820 (2.4%)	23/837 (2.7%)	23/817 (2.8%)
Black	0/135 (0.0%)	0/116 (0.0%)	2/127 (1.6%)	0/126 (0.0%)
Other	0/36 (0.0%)	2/53 (3.8%)	0/42 (0.0%)	1/56 (1.8%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Table 35. Primary NPS Event by Race in the PHx Cohort

	Varenicline	Bupropion	NRT	Placebo
White	60/849 (7.1%)	57/816 (7.0%)	45/804 (5.6%)	42/822 (5.1%)
Black	4/145 (2.8%)	5/165 (3.0%)	7/176 (4.0%)	8/155 (5.2%)
Other	3/32 (9.4%)	6/36 (16.7%)	1/36 (2.8%)	0/37 (0.0%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

4.2.4 Subgroup Analysis by Country of Randomization

Among the 3984 subjects in the Non-PHx cohort, 47.1% were randomized in the US (N=1875). In the PHx cohort, 57.2% (N=2332) of the subjects were randomized in the US. Table 36 and Table 37 show that the percentage of subjects with at least one NPS event, pooled across treatments, was higher in the US than in other countries. In the Non-PHx cohort, 2.7% of the subjects in the US and 1.6% of the subjects outside the US experienced an NPS event. In the PHx cohort, 6.3% of the subjects in the US and 5.3% outside the US experienced an event. These data show some nominally significant evidence that the rate of subjects with an NPS event may be higher in the US than outside the US (nominal p-value 0.0090); however we found no evidence of an interaction between country and treatment on the risk of NPS events (p-value 0.2036). This suggests that if the rate of NPS events is truly higher in the US, the data show no evidence that this increase is associated with any particular treatment.

Table 36. Primary NPS Event by Country of Randomization in the Non-PHx Cohort

	Varenicline	Bupropion	NRT	Placebo
US	10/464 (2.2%)	9/466 (1.9%)	19/476 (4.0%)	12/469 (2.6%)
Outside US	3/526 (0.6%)	13/523 (2.5%)	6/530 (1.1%)	12/530 (2.3%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Table 37. Primary NPS Event by Country of Randomization in the PHx Cohort

	Varenicline	Bupropion	NRT	Placebo
US	43/590 (7.3%)	41/586 (7.0%)	30/575 (5.2%)	32/581 (5.5%)
Outside US	24/436 (5.5%)	27/431 (6.3%)	23/441 (5.2%)	18/434 (4.1%)

*Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues identified in the evaluation of efficacy using data collected in PMR trial A3051123.

The neuropsychiatric safety of varenicline and bupropion was evaluated based on the final results of PMR trial A3051123. A site audit conducted by the applicant identified data inconsistencies and missing documentation for the primary safety endpoint in 2 trial sites. The clinical review team also found potential data coding errors and incomplete adverse event narratives throughout the trial. High heterogeneity in the rate of NPS events between sites in the cohort of subjects with a history of psychiatric illness was identified during review of the trial. As such, sensitivity analyses of additional statistical models and alternative endpoint definitions were conducted to try to address these issues and assess their impacts on trial findings.

Alternate statistical models were explored to account for the extra binomial variation observed in the rate of NPS events between sites in the PHx cohort. Findings from these alternate statistical

models suggest that the primary binomial model may underestimate the heterogeneity of NPS rates across sites and that a negative binomial model for the rate of NPS events was a better fit than other models. Findings based on the estimated rate ratios of NPS events obtained from the negative binomial model were generally consistent with risk differences estimated from the primary binomial model in the PHx cohort: the estimated rate ratios (95% CI) comparing varenicline to placebo and bupropion to placebo based on the negative binomial model were 1.40 (0.94, 2.09) and 1.46 (0.96, 2.22) respectively.

Sensitivity analyses that evaluated neuropsych safety based on alternate endpoint definitions were generally consistent with the findings of the primary analysis of the NPS endpoint. These sensitivity analyses are presented in Sections 3.6.1.2.2 through 3.6.1.2.4.

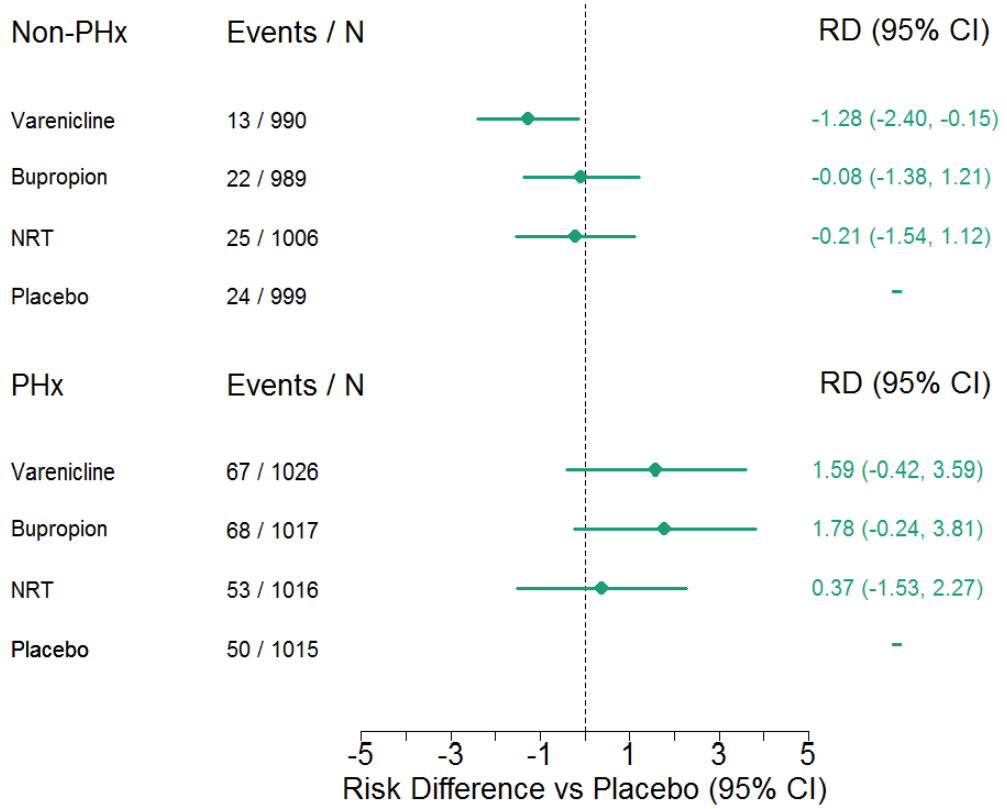
5.2 Collective Evidence

The results from the PMR trial A3051123 provided substantial evidence of the efficacy of varenicline and bupropion in smoking cessation compared with placebo for both weeks 9-12 and 9-24 regardless of psychiatric history. In addition, the results confirmed that subjects treated with varenicline had significant improvement in smoking cessation compared to subjects treated with bupropion and NRT in both cohorts (PHx and Non-PHx).

The primary safety endpoint in the trial was a composite of treatment-emergent moderate and severe adverse events in 261 MedDRA preferred terms. This endpoint is referred to as the neuropsychiatric safety (NPS) endpoint. The primary pre-specified safety analysis based on a binomial model estimated the risk difference of treatment emergent NPS events for each pairwise treatment comparison by cohort. Figure 16 summarizes the number of subjects and the number of NPS events by treatment arm and cohort as well as the estimated risk differences and corresponding 95% confidence intervals for the risk of NPS events associated with varenicline, bupropion, and NRT relative to placebo. Varenicline showed a nominally protective effect relative to placebo in the Non-PHx cohort: **RD = -1.28 NPS events per 100 subjects, 95% CI (-2.40,-0.15)**. Varenicline and bupropion showed a numerically increased risk relative to placebo in the PHx cohort: **RD = 1.59 NPS events per 100 subjects, 95% CI (-0.42, 3.59)** for varenicline and **RD = 1.78 NPS events per 100 subjects, 95% CI (-0.24, 3.81)** for bupropion.

Overall, the data from trial A3051123 showed no evidence of an increased neuropsychiatric risk associated with either varenicline or bupropion relative to placebo in subjects without prior history of psychiatric illness. In subjects with prior history of psychiatric illness, both bupropion and varenicline observed a numerically higher rate of events than placebo.

Figure 16. Analysis of Primary Safety NPS Endpoint by Treatment and Cohort



Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

5.3 Conclusions and Recommendations

The review team found issues associated with the quality of data collection and event narratives of the primary neuropsychiatric safety endpoint in the PMR trial. The trial also showed a high degree of heterogeneity in the rate of NPS events between sites in the PHx cohort. The review team conducted sensitivity analyses that allowed for extra-binomial variation in the rate of NPS events between sties, and analyses of additional endpoint definitions and safety endpoints. The results of these sensitivity analyses were generally consistent with the results of the primary analysis.

In the Non-PHx cohort, the trial observed a lower incidence of NPS events among subjects on varenicline. In this cohort, the rates of severe NPS events and of suicidal ideation and behavior as captured in the C-SSRS were low and balanced across treatment arms.

In the PHx cohort, subjects randomized to varenicline and bupropion observed a higher rate of NPS events than subjects randomized to placebo. The trial was not designed to rule out an upper margin of neuropsychiatric risk. Therefore the interpretation of the estimated risk differences of NPS events associated with varenicline: -1.28 events per 100 subjects, 95% CI (-2.40,-0.15) and bupropion: 1.78 (-0.24, 3.81) should be interpreted based on clinical and public health

considerations. The rates of severe NPS events (1.4%) and of suicidal ideation (2.1%) and behavior (0.1%) as captured in the C-SSRS were similar in all treatment arms and relatively low.

5.4 Labeling Recommendations

The applicant's proposed labeling includes efficacy results on observed continuous abstinence rate for Weeks 9-12 and 9-24 in patients with or without a history of psychiatric disorder while treated with varenicline, bupropion, NRT, or placebo (Table 38). The reviewer concurs with applicant's conclusions that varenicline was superior to bupropion, NRT and placebo in both cohorts; bupropion was superior to placebo in both cohorts.

Table 38. Continuous Abstinence (95% confidence interval), Study in Patients with or without a History of Psychiatric Disorder

	CHANTIX 1 mg BID	**Bupropion SR 150 mg BID**	**NRT 21 mg/day with taper**	**Placebo**
Weeks 9 through 12				
Non-PHx Cohort	38% (35% 41%)	26% (23% 29%)	26% (24% 29%)	14% (12% 16%)
PHx Cohort	29% (26% 32%)	19% (17% 22%)	20% (18% 23%)	11% (10% 14%)
Weeks 9 through 24				
Non-PHx Cohort	25% (23% 28%)	19% (16% 21%)	18% (16% 21%)	11% (9% 13%)
PHx Cohort	18% (16% 21%)	14% (12% 16%)	13% (11% 15%)	8% (7% 10%)

BID = twice daily

The results of trial A3051123 were discussed at a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on September 14, 2016. The Advisory Committee was asked to vote on the following question:

VOTE: Based on the data presented on the risk of serious neuropsychiatric adverse events with smoking cessation products, what would you recommend?

A. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events.

B. Modify the language in the boxed warning.

C. Keep the current boxed warning.

The committee voted in the following way: **A**: 10 **B**: 4 **C**: 5 Abstain: 0.

Based on our review of trial A3051123, we believe that sufficient evidence exists to support the removal of the current boxed warning for neuropsychiatric adverse events from the labels of both Chantix and Zyban. We recommend that the potential risk of neuropsychiatric adverse events associated with Chantix and Zyban in patients with prior history of psychiatric illness be described in the WARNINGS section of the label. However, since the PMR trial was only designed to estimate the risk of serious neuropsychiatric adverse events and not to rule out a pre-specified risk margin, we believe that the interpretation of the trial results and potential labeling changes are a matter of clinical judgement.

APPEARS THIS WAY ON ORIGINAL

6 APPENDIX

6.1 Number of Qualifying NPS Events by Subject

Table 39. Number of Qualifying NPS Events per Subject in the Non-PHx Cohort

	NPS Events per Subject				
	0	1	2	3	4+
Varenicline	977	8	5	0	0
Bupropion	967	15	4	1	2
NRT	981	17	6	2	0
Placebo	975	19	5	0	0

Source: Created by reviewer using datasets Subevg.xpt and Advers.xpt

Table 40. Number of Qualifying NPS Events per Subject in the PHx Cohort

	NPS Events per Subject				
	0	1	2	3	4+
Varenicline	959	47	12	6	2
Bupropion	949	43	17	6	2
NRT	963	36	12	3	2
Placebo	965	35	14	1	0

Source: Created by reviewer using datasets Subevg.xpt and Advers.xpt

6.2 NPS Events by Country of Randomization

Table 41. Treatment Emergent NPS Events by Country and Cohort

	Non-PHx		PHx	
Country:	**events / n**	**%**	**events / n**	**%**
UNITED STATES	50 / 1875	2.7%	146 / 2332	6.3%
GERMANY	15 / 400	3.8%	50 / 476	10.5%
FINLAND	3 / 178	1.7%	15 / 323	4.6%
BULGARIA	0 / 260	0.0%	1 / 230	0.4%
CANADA	3 / 136	2.2%	4 / 141	2.8%
ARGENTINA	2 / 218	0.9%	1 / 111	0.9%
SPAIN	2 / 147	1.4%	1 / 90	1.1%
SLOVAKIA	0 / 118	0.0%	0 / 84	0.0%
SOUTH AFRICA	4 / 224	1.8%	10 / 71	14.1%
NEW ZEALAND	2 / 67	3.0%	2 / 58	3.4%
RUSSIAN FEDERATION	0 / 68	0.0%	1 / 58	1.7%
MEXICO	3 / 133	2.3%	1 / 54	1.9%
AUSTRALIA	0 / 31	0.0%	3 / 24	12.5%
BRAZIL	0 / 9	0.0%	2 / 12	16.7%
DENMARK	0 / 107	0.0%	1 / 6	16.7%
CHILE	0 / 13	0.0%	0 / 4	0.0%

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

6.3 Causes of Death by Treatment and Cohort

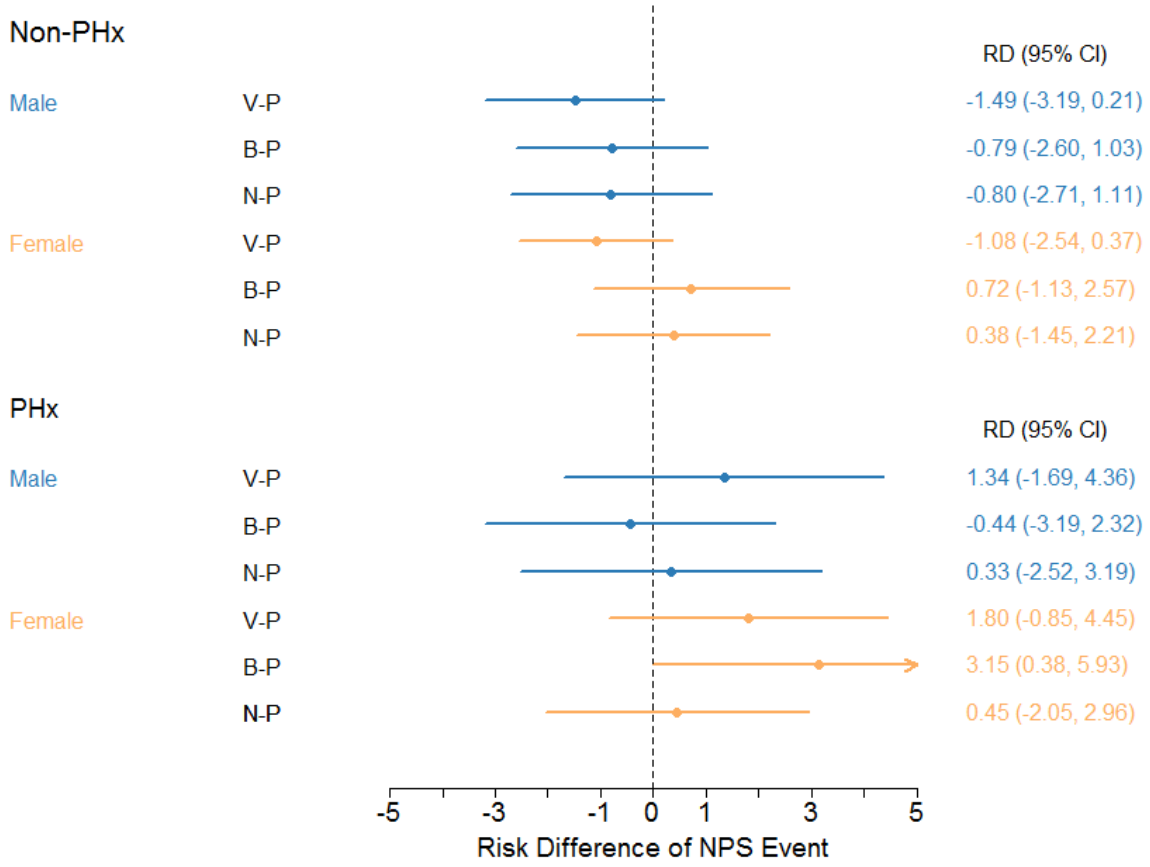
Table 42. Number of Deaths and Causes of Death in the EAGLES trial

Cohort	Treatment Group	Cause of Death
Non-PHx Cohort	Bupropion	Heroin Overdose
	NRT	Cancer of Prostate Gland
	Placebo	Head on Car Collision
	Placebo	Myocardial Infarction
	Placebo	Suicide
PHx Cohort	Bupropion	Lung Cancer
	Bupropion	Cardiovascular Event
	NRT	Severe Sepsis
	NRT	Adenocarcinoma
	Placebo	Thromboembolism

Source: Created by reviewer based on Table 47 (Page 134) of the applicant's Clinical Study Report

6.4 Risk Difference of the Primary NPS Event by Subgroups

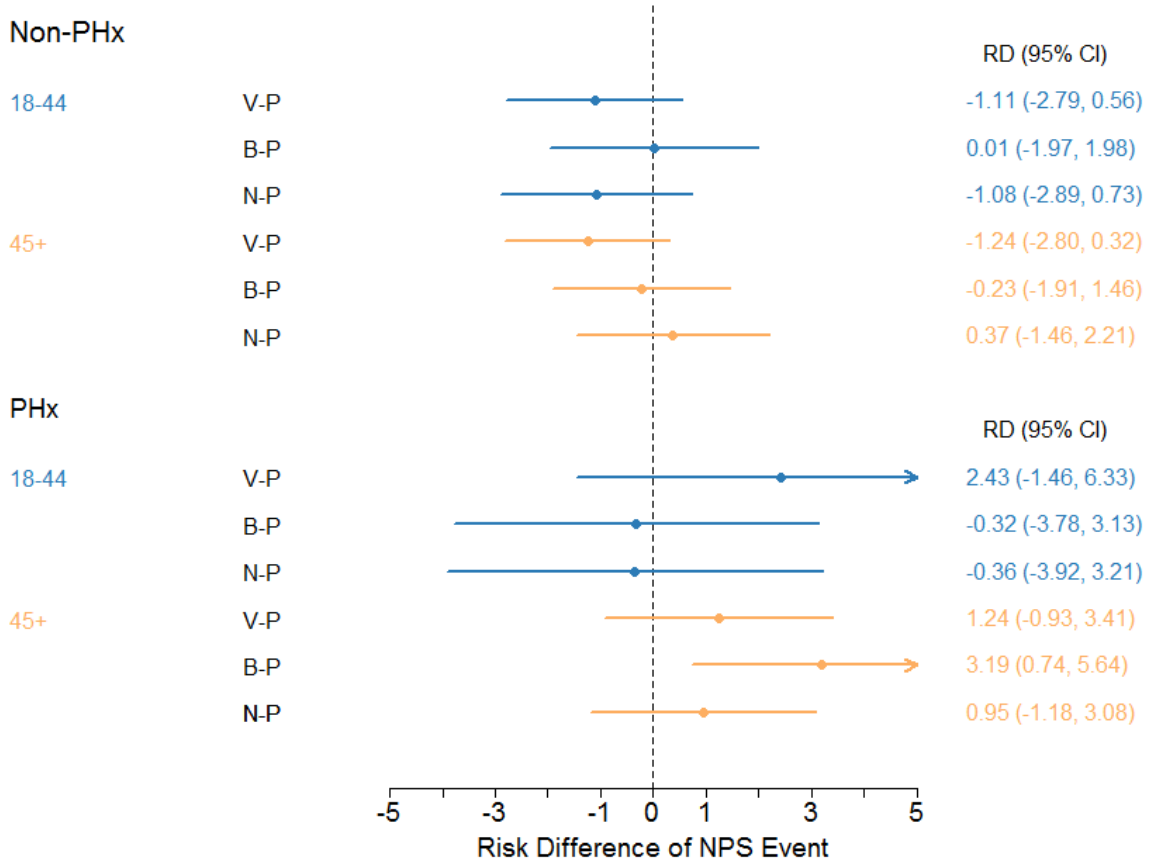
Figure 17. Risk Difference by Gender and Cohort



V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Figure 18. Risk Difference by Age Category and Cohort

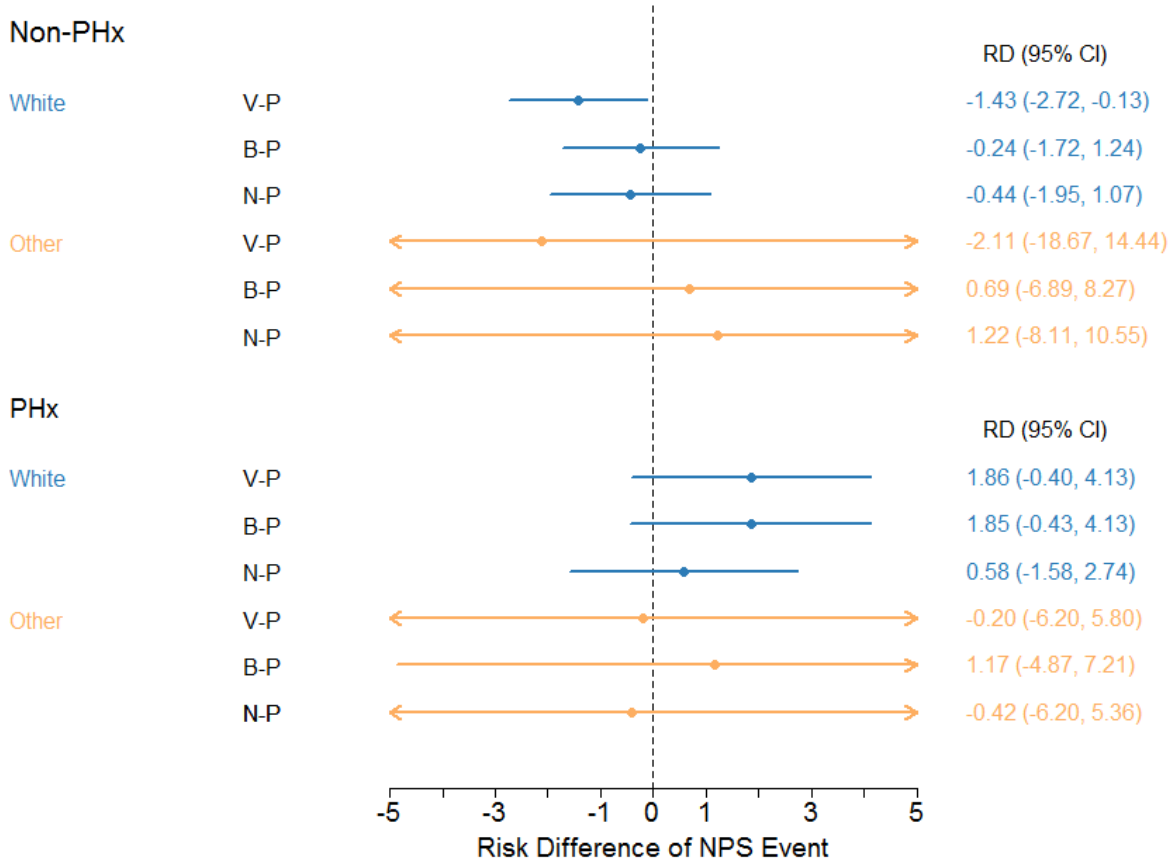


V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

*Age groups 45-64 and 65+ were combined due to the small sample size in the subgroup of subjects ages 65 and over.

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

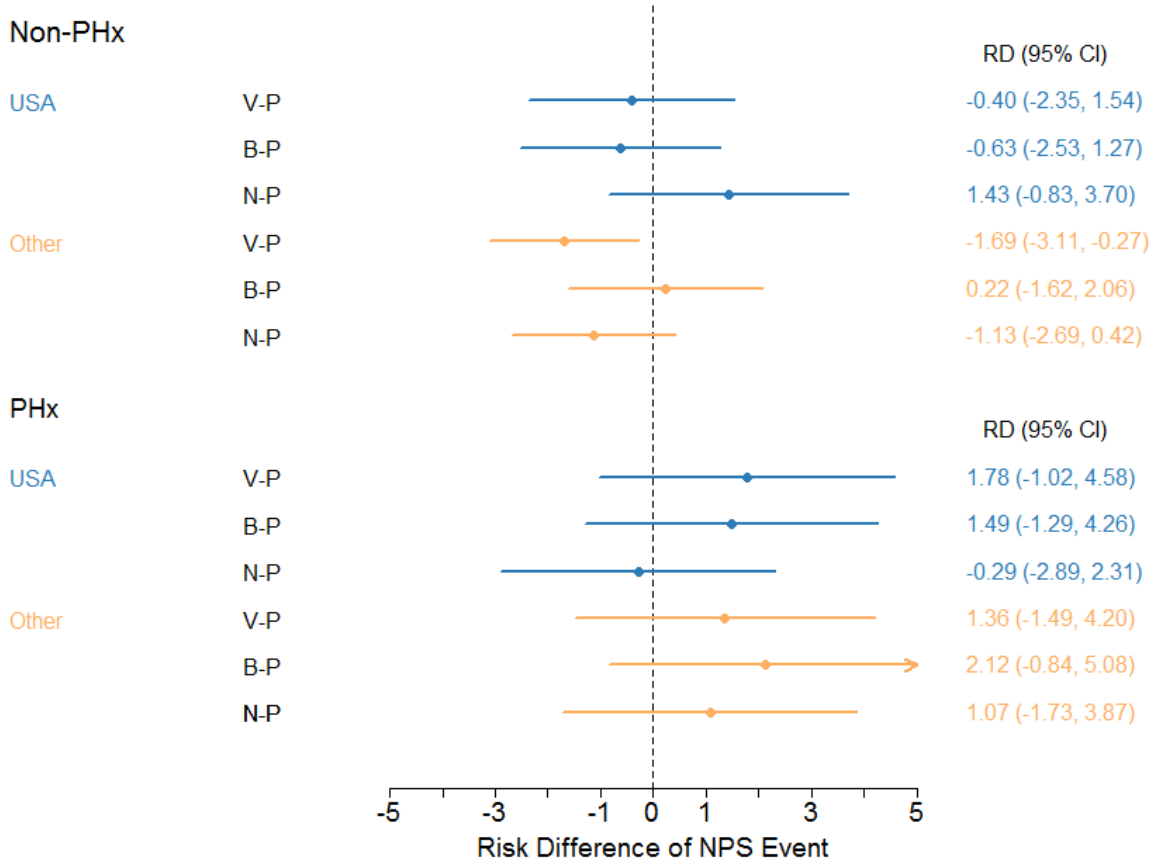
Figure 19. Risk Difference by Race and Cohort



V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Figure 20. Risk Difference by Region and Cohort



V = Varenicline, **B** = Bupropion, **N** = Nicotine Replacement Therapy, **P** = Placebo

Source: Created by reviewer using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

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/s/

EUGENIO ANDRACA-CARRERA
11/10/2016

YI N REN
11/10/2016

MATTHEW J SOUKUP
11/10/2016

DAVID M PETULLO
11/10/2016
I concur.

MARK S LEVENSON
11/10/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 21928/ S-040
Name of Drug: Chantix (varenicline) Tablets; 0.5 mg and 1 mg
Applicant: Pfizer, Inc.

Labeling Reviewed

Submission and Receipt Date: S-040; February 18, 2016

Background and Summary Description:

Supplement S-040 proposes changes to the **BOXED WARNING, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS**, C**LINICAL STUDIES**, **PATIENT COUNSELLING INFORMATION** sections of the Package Insert, and revisions to the Medication Guide based on the results from the postmarketing required trial titled, "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."

Review

The revised labeling submitted under S-040 on February 18, 2016, was compared to labeling approved on August 12, 2016, for S-041.

Please note that the omissions are indicated by strikeovers, inclusions by underlined text. See the attached revised label.

Recommendations

These supplements are recommended for approval.

Ayanna Augustus, Ph.D., RAC	November 10, 2016
Regulatory Project Manager	Date
ASA on behalf of Parinda Jani	December 15, 2016
Chief, Project Management Staff	Date

30 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AYANNA S AUGUSTUS
12/15/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of epidemiological studies on neuropsychiatric events associated with smoking cessation products

Date:	October 12, 2016
Reviewer(s):	Chih-Ying Chen, Ph.D. Division of Epidemiology II
Team Leader	Tamra Meyer, Ph.D., M.P.H. Division of Epidemiology II
Division Director	David Moeny, R.Ph. M.P.H. Division of Epidemiology II
Drug Name(s):	Varenicline (Chantix)
Subject:	Review of epidemiological studies on neuropsychiatric events associated with smoking cessation products
Application Type/Number:	NDA 21-928
Submission Number:	040
Applicant/sponsor:	Pfizer
OSE RCM #:	2016-640

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EXECUTIVE SUMMARY

In February (b) (4), Pfizer submitted a labeling supplement with regard to varenicline's neuropsychiatric safety, including data from a completed postmarketing requirement trial and published observational studies. The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Epidemiology II (DEPI II) to review the observational studies submitted by Pfizer, as well as any additional published observational studies on neuropsychiatric risk associated with smoking cessation prescription medications. This document describes DEPI II's literature search and assessment of all three FDA approved prescription smoking cessation products—varenicline, bupropion and nicotine replacement therapy (NRT).

DEPI II's literature search identified a total of six observational studies for in-depth review. The findings of the reviewed epidemiological studies showed inconsistent results. Four of the studies did not observe a statistically significant difference in the risk of neuropsychiatric adverse events between varenicline and NRT, varenicline and bupropion, or between bupropion and NRT; the point estimates did not suggest a consistent trend of association. One study found a significant reduction in neuropsychiatric risk among varenicline users (34% reduction in risk of outpatient depression visit and 44% reduction in the risk of outpatient visit for suicide or non-fatal self-harm) and a 25% reduction in risk of depression visit in bupropion users, comparing to NRT users. Yet, another study observed that while varenicline use was not associated with significant risk of suicide-related behaviors, the risk of neuropsychiatric in- or out-patient visits significantly increased by 18% during varenicline-exposed time compared to unexposed time in varenicline users.

Each of the reviewed studies had key study design limitations. The most important limitations were: 1) use of outcome measures with suboptimal sensitivity and specificity, 2) residual confounding, 3) use of bupropion (another smoking cessation drug with neuropsychiatric risk labeled in a boxed warning) as a reference group to examine varenicline's neuropsychiatric risk and 4) inability to assess the influence of pre-existing psychiatric illness on the association between smoking cessation treatments and neuropsychiatric outcomes. All studies relied on diagnostic codes to capture neuropsychiatric adverse outcomes, which likely underestimated the absolute risk of events. It is difficult to estimate how many outcome events were missed in each study, or to know whether or not the proportion of outcome under-ascertainment varied among study drugs resulting in decreased precision of estimates and unpredictable direction of bias. In the studies that included data from the timeframe after the publicity of the neuropsychiatric safety concern associated with varenicline and, to a lesser degree, with bupropion, the potential for residual confounding was due to differential prescribing of smoking cessation therapies based on a physician or patient's perceived underlying risk of neuropsychiatric outcomes (i.e., channeling bias); in the other studies, it was due to the impact of other unmeasured factors, such as nicotine withdrawal syndrome. "Channeling bias" makes varenicline or bupropion appear to reduce neuropsychiatric risk when compared to another prescription smoking cessation therapy. "Confounding by nicotine withdrawal syndrome" makes all smoking cessation drugs appear to elevate neuropsychiatric risk (relative to non-users), even if they were in fact risk-neutral. When the potential biases are considered in combination, they restrict our ability to predict the direction of the relative risk associated with any smoking cessation product. One study's use of bupropion as the reference group to examine varenicline's neuropsychiatric risk was problematic because

finding no increased risk of NPS events comparing to bupropion does not reassure us of varenicline's neuropsychiatric safety, given that both products are labeled for these adverse events. The inability to assess the risk among those with pre-existing psychiatric illness further restricts the generalizability of the findings. The evidence from the existing observational studies, alone, is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline use or bupropion use. Observational data alone also are inadequate to inform whether or not neuropsychiatric risk associated with varenicline or bupropion could be different between smokers with and without psychiatric history. Neuropsychiatric safety of smoking cessation products should be assessed based on the totality of data streams, including case reports, observational and clinical trial data.

APPEARS THIS WAY ON ORIGINAL

1. INTRODUCTION

Varenicline was approved in the US under the trade name of Chantix as an aid to smoking cessation treatment for adults in May 2006. In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events with varenicline (marketed in the EU as Champix). While FDA was assessing the potential association of neuropsychiatric adverse events with varenicline, the mainstream media in the US reported a highly publicized case of erratic behavior in a patient using varenicline for smoking cessation in September 2007. This case received considerable public attention.[1] Two months later (November 2007), FDA issued an Early Communication about this ongoing safety review of varenicline.[2] At the same time, the information regarding the neuropsychiatric adverse events was added to ADVERSE REACTIONS section of varenicline's labeling. After FDA completed the evaluation of the postmarketing data, neuropsychiatric events were added to the Warnings and Precautions section of the labeling of varenicline in January 2008, a medication guide was approved in May 2008 and a boxed warning was added to the labeling in July 2009.[3,4] A subsequent review of post-marketing data on the other smoking cessation products (i.e. bupropion and various nicotine replacement therapies) identified similar cases of neuropsychiatric adverse events associated with bupropion use, a boxed warning was also added to bupropion's labeling in July 2009.[4] Additionally, a postmarketing requirement (PMR) was issued in May 2008 to the sponsor, Pfizer, to conduct a large randomized, double-blind, active- and placebo-controlled study to compare the risk of clinically significant neuropsychiatric (NPS) events, including but not limited to, events related to suicide in smokers using varenicline, bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation. Another important aim was to determine whether individuals with a history of psychiatric disorders are at greater risk for development of clinically significant NPS events compared to smokers without a history of psychiatric disorders, while using these smoking cessation treatments.

In (b) (4)

FDA updated the Warnings and Precautions section of the label to include information about these studies, including the limitations of their findings. FDA also held an Advisory Committee (AC) meeting in October 2014 to discuss the (b) (4). The AC voted against the proposal and suggested revisiting the issue after the completion of the required postmarketing clinical trial.

In February (b) (4), the sponsor submitted another labeling supplement, including data from the completed PMR trial (Study A3051123, EAGLES trial) and additional observational studies published after their previous submission in 2014. They again proposed revisions to the Warnings and Precautions section of the label regarding the risk of neuropsychiatric adverse events with Chantix and removal of the boxed warning. The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Epidemiology II (DEPI II) to

review the observational studies submitted by Pfizer and to conduct a literature review of any published observational studies on neuropsychiatric risk associated with any smoking cessation product. Smoking cessation products other than varenicline were considered since the PMR trial results included new safety information that pertained to bupropion (Zyban) and nicotine replacement therapy (NRT). This document reports the results of DEPI II's literature search and assessment of current observational epidemiologic literature on neuropsychiatric risk associated with all three smoking cessation products—varenicline, bupropion and NRT.

2. REVIEW METHODS AND MATERIALS

DEPI II conducted a search of the National Library of Medicine's PubMed database on June 17th 2016. The search strategy is described in detail in Appendix I. Briefly, we first used search strings of smoking cessation products names and the neuropsychiatric adverse events to identify English language observational epidemiologic studies that examined neuropsychiatric adverse outcomes associated with a smoking cessation product. Studies were selected for review if they reported the relative risk of neuropsychiatric events between smoking cessation product and used an adequate design and analytical approach to examine the association.

3. REVIEW RESULTS

Using search strings of smoking cessation products names and the neuropsychiatric adverse events, we identified 412 English language articles. We excluded:

- 48 Animal studies, cell studies, pharmacokinetic studies, or pharmacodynamics studies
- 271 Publications that did not report on a research study (e.g., commentaries and reviews), non-observational studies (e.g., randomized control trials), or non-comparative studies (e.g., case reports, case series)
- 67 Studies that did not examine drug-related neuropsychiatric risk (e.g., studies that examined predictors of smoking cessation drug use among smokers with a mental disorder, studies that examined how pre-existing mental disorders impact success of smoking cessation treatment)
- 17 Studies that did not report relative risk of neuropsychiatric events between smoking cessation products or studies that did not use adequate designs and analytical approaches to examine neuropsychiatric risk of smoking cessation products, for example:
    - Cross-sectional studies
    - Studies without comparator groups
    - Studies that did not account for confounding when comparing risk of neuropsychiatric events between smoking cessation products

Among a total of eight articles that were eligible for in-depth review, we further excluded two publications:

- The publication by Gibbons et al.[5] used the same study dataset (i.e., the same data from the same patients during the same study timeframe) as a prior publication by Meyer et al.[6] to examine the association between varenicline and several neuropsychiatric disorders. The analyses in the Gibbons et al.[5] study were similar to analyses conducted in the Meyer

et al.[6] study[ab]. The only difference was that the Gibbons et al.[5] analyses included fewer covariates than the Meyer et al.[6] analyses. Because the Gibbons et al.[5] study was a re-analysis of a study already included in the in-depth review, and because they did not control for as many potential confounding variables as in the Meyer et al.[6] analysis, we excluded the Gibbons et al.[5] study from our in-depth analysis.

- The publication by Gunnell et al.[7] utilized the same data source and had overlapping data time frames as a later publication by Thomas et al.[8] which was included in our in-depth review.

Two of the six articles included in the in-depth review describe studies that were collaborative research projects between the FDA and other federal agencies through Inter-Agency Agreements: the Meyer et al.[6] publication described the study by the U.S. Army Office of the Surgeon General (OTSG) U.S. ARMY MEDICAL COMMAND (U.S. Army Medical Command MEDCOM)'s Pharmacovigilance Center (PVC) (referred to hereafter as the "DoD study")[b] and the Cunningham et al.[9] publication described the study by the Department of Veterans Affairs (VA) Center for Medication Safety (VAMedSAFE) (referred to hereafter as the "VA study"). DEPI also reviewed information from the following documents relevant to the DoD and VA studies that were submitted to the FDA:

- Final report of the DoD study: Rate of Neuropsychiatric Events in Varenicline Users Compared to Nicotine Replacement Therapy Patch Users, Military Health System, August 1, 2006 to August 31, 2007, dated May 04, 2012
- Draft protocol of the VA study: Varenicline and Mental Health Disorders, dated March 2009
- Final report of the VA study: Varenicline and Mental Health Disorders, dated May 2011, revised June 2011

3.1 OVERVIEW OF STUDIES EVALUATED

The six reviewed studies included five which assessed the risk of neuropsychiatric medical encounters associated with smoking cessation products (VA study/Cunningham et al.,[9] DoD study/Meyer et al.,[6] Kotz et al.[10], Molero et al.[11] and Pasternak et al.[12]), and three which evaluated the association between smoking cessation products and risk of suicide or non-fatal self-harm (Thomas et al.,[8] Kotz et al.,[10] Molero et al.[11]). All reviewed studies were retrospective, population-based, cohort studies. DEPI II consulted the Division of Biostatistics (DB7) to evaluate the advanced statistical methods used in the publications by Molero et al.[11] and Kotz et al.[10] The statistical review of these two studies will be submitted separately. Although some studies[8,10,11] examined risk of non-neuropsychiatric events associated with smoking cessation drugs, we focused on the study methods and findings that were relevant to neuropsychiatric risk in this review. One of the studies (Thomas et al.[8]) reported the association between smoking

[a] Although Meyer et al. did not report certain analyses in their publication, the FDA received the full report of the findings from the Meyer study.

[b] Two members of the DEPI review team are listed as authors on the Meyer et al. study. Dr. Meyer was the primary investigator, and David Moeny was a co-author.

cessation drug use and the likelihood of antidepressant initiation, as a proxy for incident depression. Prescribing of antidepressants is not a specific measure of incident depression, since antidepressants are also used to treat other disorders, including non-psychiatric indications like pain. Therefore, we did not discuss those findings in this review.

The design, data sources, methods, and main findings of the six included studies are summarized in Appendix II Table 1, Appendix II Table 2, Figure 3-1 and Figure 3-2. We summarized the VA study methods and findings based mostly on the pre-specified analytical plan described within the protocol and final report that were submitted to the FDA. This is because the VA study had two objectives. Objective one resulted in the final report submitted to FDA in 2011; this was based on the findings of the analyses for the first objective, which examined the risk of inpatient neuropsychiatric events associated with varenicline. The Cunningham publication[9] included additional findings of the second objective, which expanded the scope to examine the risk of outpatient neuropsychiatric events associated with varenicline.

To briefly summarize the findings:

- Four studies (DoD study/Meyer et al.,[6] VA study, Thomas et al.,[8] and Kotz et al.[10]) compared varenicline-associated neuropsychiatric risk to NRT. Their findings did not suggest a consistent trend of association—some effect estimates (Hazard ratios) were above, and some were below the null (1.0). Most of the effect estimates were imprecise, and their confidence intervals crossed the null. Only the study by Kotz et al.[10] found a statistically significant difference between varenicline and NRT. They reported that varenicline use was associated with a 34% reduction in risk of an outpatient depression visit and 44% reduction in the risk of an outpatient visit for suicide or non-fatal self-harm within six months after treatment initiation.
- One study by Pasternak et al.[12] used bupropion as the reference group to evaluate risk of emergency department visit or hospitalization for neuropsychiatric events. Varenicline use was shown to be associated with a 15% lowered neuropsychiatric risk compared with bupropion use, but the confidence interval of the point estimate was wide and crossed the null.
- One study by Molero et al.[11] used a self-controlled design that compared varenicline exposed time to un-exposed time among varenicline users. They observed that while varenicline use was not associated with significant risk of suicide-related behaviors, the risk of a neuropsychiatric in- or out-patient visit significantly increased by 18% during varenicline-exposed time.
- Two studies also examined bupropion-associated neuropsychiatric risk relative to NRT:
    - Thomas et al.[8] suggested an inverse association between bupropion use and neuropsychiatric adverse outcomes; however, the effect estimate was imprecise and did not reach statistical significance in most analyses.
    - Kotz et al.[10] reported a 25% reduction in the risk of an outpatient visit for depression in bupropion users, which reached statistical significance

- Four studies (Meyer et al.,[6] VA study, Pasternak et al.[12], and Molero et al.[11]) examined the risk of neuropsychiatric adverse outcomes among users of smoking cessation treatment with and/or without prior mental illness history:
    - The Meyer et al.[6] and the VA study both were unable to report the neuropsychiatric risk in all the subgroups stratified by psychiatric history because of small sample size or small observed numbers of outcome events in one of the subgroups.
    - Pasternak et al.[12] reported that the observed HRs of psychiatric events associated with varenicline, compared to bupropion, appeared lower in participants without a history of psychiatric disorder than in participants with a history, but the point estimates were imprecise and the confidence intervals both crossed one.
    - In the Molero et al.[11] study, the increased risk of psychiatric conditions were only among people with pre-existing psychiatric disorders. Most of the effect estimates of neuropsychiatric risk associated with varenicline exposed time (relative to varenicline unexposed time) were numerically higher among patients without history of psychiatric disorder, but the confidence intervals of the point estimates were wide and crossed the null.

We will describe each study in more detail in the following sections.

3.2 FINDINGS OF INDIVIDUAL STUDIES

3.2.1 Effect of smoking cessation treatment among overall study population

The Meyer study[6]

The study by Meyer et al.[6] compared the rates of hospitalizations for neuropsychiatric adverse events among new users of varenicline and the NRT patch (i.e., no varenicline or NRT patch use in the prior 6 months) that started therapy between August 1, 2006 and August 31, 2007 in the Military Health System. The study time frame was restricted to the period before the first FDA warning[2] on varenicline-related neuropsychiatric risk to reduce the potential of channeling bias (further discussed in section 4.2). Varenicline users were matched using propensity scores (reflecting demographic characteristics, health insurance benefits, psychiatric history, chronic pain diagnosis history, past neuropsychiatric or pain medication use and past healthcare utilizations), to NRT users. After propensity score matching, there were 11,978 varenicline users and an equal number of NRT users in the study sample. The main outcome was a primary hospital discharge diagnosis for one of a number of neuropsychiatric conditions (Appendix II Table 1) within 30 days of drug initiation. In the study's propensity score matched samples there were 16 psychiatric hospitalizations among varenicline users and 14 among NRT users. Comparing to NRT users, risk of neuropsychiatric hospitalization was numerically higher in varenicline users (HR=1.14; 95% CI=0.56 to 2.34), however, the effect estimate was unstable and the confidence interval crossed the null (i.e., 1.0). The finding was similar when patients were followed for 60 days after drug initiation instead of 30 days. Findings were similar when using any inpatient diagnosis as the outcome measure (HR=0.79; 95% CI=0.50-1.24). The HR estimate was within the range reported for the main outcome, but indicated a lowered risk of outpatient neuropsychiatric visits (HR=0.71, 95% CI=0.60-0.84) for varenicline users compared to NRT users.

The VA study

The VA study evaluated the incidence of neuropsychiatric hospitalizations among veterans using varenicline or NRT. Patients starting varenicline or NRT between May 1, 2006 and September 30, 2007, but with no varenicline or NRT use in the previous year, were selected and matched in a 1:1 ratio by use of propensity scores (reflecting demographic characteristics, comorbidities, psychiatric history and past psychotropic use). Similar to the Meyer et al. study,[6] the study time frame was restricted to the period before the first FDA warning[2] on varenicline-related neuropsychiatric risk to reduce the potential of channeling bias. The study's pre-specified main outcome was 30-day risk of psychiatric hospitalization, defined as hospitalizations with a primary discharge diagnosis of a range of mental health disorders (Appendix II). The study population included 14,131 varenicline users and an equal number of NRT users. Among these patients, there were 16 psychiatric hospitalizations in varenicline-treated patients, and 21 in NRT patients. The HRs for the composite outcome (0.76; 95% CI=0.40 to 1.46) of any hospitalized mental health disorder and for each component of the composite were not increased for varenicline compared with NRT use, except for the risk of hospitalization due to depression (Appendix Table II), however, the confidence intervals of the point estimates were all wide and crossed the null (i.e., 1.0).

Findings on primary outcomes (i.e., inpatient neuropsychiatric visit) in the Cunningham et al.[9] publication were similar to what was reported in the VA study final report. In contrast, a positive association was reported between varenicline use and outpatient neuropsychiatric visit in the Cunningham et al.[9] study, although most of the effect estimates did not reach statistical significance. One estimate showed a significantly elevated risk of outpatient visits for schizophrenia (HR=1.27, 95% CI=1.07-51).[9]

The Pasternak study[12]

The study by Pasternak et al. compared the rates of emergency department visit or hospital admission for a psychiatric diagnosis (Appendix II) that had occurred within 30 days of treatment initiation among new users of varenicline or bupropion who started therapy between January 1st 2007 and December 31 2010 in Denmark. Patients who had fewer than two years of registered residence in Denmark prior to the cohort entry and those with use of varenicline or bupropion prior to 2007 were excluded. Overall, 59,790 new users of varenicline and 17,936 new users of bupropion were identified. In this unmatched cohort, the distribution of baseline characteristics was generally similar between the two groups. To further control for confounders, 17,935 varenicline users were matched 1:1 to bupropion users based on a propensity score. The propensity score was estimated based on a range of variables, including age, sex, place of birth, place of living, medical history, comorbidities, selected prescription medications use and indicators of health-care use. A total of 85 psychiatric events occurred (39 events in varenicline group versus 46 events in bupropion group). There were three cases of suicide attempt or completed suicide among varenicline users and one case among bupropion users. Varenicline use was shown to be associated with a 15% lower neuropsychiatric risk compared with bupropion use (HR: 0.85. 95% CI: 0.55- 1.30), but the confidence interval of the point estimate was wide and crossed the null.

The Thomas study[8]

Thomas et al.[8] examined the 3-month risk of suicide-related outcomes and all-cause mortality among adults in 31,260 varenicline users, 6,741 bupropion users and 81,545 NRT users who

received their first prescription between September 01, 2006 and October 31, 2011 (no use of varenicline, bupropion, or NRT in past year). Ninety-two cases of suicide and non-fatal self-harm were identified from the linked UK CPRD, Office for National Statistics (ONS) mortality data and Health Episode Statistics (HES) data during 3 months of follow-up after the date of treatment initiation: 69 among NRT users, 4 among bupropion users and 19 among varenicline users. The multivariate-adjusted HR for fatal and non-fatal self-harm included the null when comparing varenicline users to NRT users (HR=0.88, 0.52 to 1.49), as well as when comparing bupropion users to NRT users (HR=0.83, 0.30 to 2.31). Similar findings were reported using propensity score-adjusted methods, but not in the instrumental variable analyses (Table 3-1, See section 4.2 for further discussions). The trend did not change in most of the sensitivity analyses that extended the follow-up to 6-, or 9-months, as well as when restricting to first-time users of smoking cessation drugs.

The Kotz study[10]

The Kotz study[10] is a retrospective cohort study that used UK QResearch database (National Health Service general practices) to compare neuropsychiatric and cardiovascular events among new users (ages 18-100 years) of varenicline (N=51,450), bupropion (N=6,557) and NRT (N=106,759) between Jan 1, 2007, and June 30, 2012. The study excluded patients if they had used one of the drugs during the 12 months before the start date of the study, had received overlapping prescriptions for these drugs during the follow-up period (indicating that they were on concomitant therapy), or were temporary residents. Patients were followed up for 6 months to estimate risk of neuropsychiatric events using Cox proportional hazards models (reference group: NRT), adjusted for potential confounders. Varenicline was associated with a significantly reduced risk of depression (HR=0·66; 95% CI=0·63 to 0·69), and self-harm (HR= 0·56; 95% CI= 0·46 to 0·68), while bupropion was associated with a significant reduction in depression risk (HR= 0.75; 95% CI=0.67 to 0.83) and a reduction of risk of self-harm that did not reach statistical significance (HR=0.74; 95% CI=0.48 to 1.16), which could be due to lack of power, given the wide confidence interval. The trend was similar in the analyses using propensity score matching to account for confounding. All of the analyses yielded similar results when the investigators examined neuropsychiatric events during 3 months of follow-up. The authors also used an approach described by Lin and colleagues[13] to model the effects of any potential unmeasured confounding. The modeling explores the range of the HRs and 95% CIs in varenicline versus NRT users for each of the events for a hypothetical, unmeasured, binary confounder, with an HR of 3 and various combinations of prevalence in the two exposure groups. According to the authors, the modelling of unmeasured confounding showed that missing a true increased risk of any of the neuropsychiatric events due to a single unmeasured confounder was very unlikely. For example, it would have required an unmeasured confounder to be very strongly associated with the outcome (hypothetical HR of 3) for the direction of the association with self-harm to be reversed from a reduced risk to an increased risk. The hypothetical unmeasured confounder would need to be distributed very differently among the two exposure groups (i.e., the prevalence of this confounder would need to be only 10% in varenicline users and be in at least 80% among NRT users) to achieve this reversing of the association.

The Molero study[11]

The Molero study[11] is a cohort study that used the Swedish population-based health care data to examine the association of varenicline use and several outcomes, including three psychiatric

conditions (psychoses, mood conditions, and anxiety conditions) and suicidal behavior. The study implemented within-person comparison (i.e., using patients as their own control to compare a varenicline-exposed period to an unexposed period) as their primary analysis in order to control for bias due to channeling and other unmeasured confounders that do not change over time. The study identified 69,757 people (ages 15 years and older) who had varenicline prescribed between November 22, 2006 (that is, the introduction of varenicline in Sweden) and December 31 2009 from the Swedish Prescribed Drug Register. Varenicline exposed periods were defined as starting at the date of the first collected prescription and ending 12 weeks later. No exclusions for prior varenicline use were made. Because varenicline is often divided into several prescriptions for the same 12-week treatment, all prescriptions within the12 weeks after the first collected prescription were considered to be part of the same treatment period. Patients were allowed to contribute multiple exposed periods if they had a varenicline prescription(s) after a 12-week window from the first prescription. The unexposed period included the time before the first observed varenicline-exposed period, between varenicline-exposed periods and after the last observed varenicline-exposed period. The studied neuropsychiatric outcomes were medical encounters for new psychiatric conditions and suicidal behavior. Information on the incidence of new psychiatric conditions came from the Swedish Patient Register, which includes diagnoses from both hospital admissions and outpatient visits for specialized care. Diagnoses received during planned visits (that is, follow-ups and referrals) were excluded from the analyses. Psychiatric conditions included three diagnostic categories: psychoses (ICD-10 (international classification of diseases, 10th revision) codes: F20-F29), mood conditions (F30-F39), and anxiety conditions (F40-F45, F48). Suicidal behavior included suicide attempts and suicides, defined as emergency inpatient or outpatient hospital visits or death due to intentional self-harm (ICD-10: X60-X84). The information on suicide attempts was collected from the Patient Register and information on suicides was collected from the Cause of Death Register. Stratified cox proportional-hazards regression, adjusted for age as a time-varying covariate, was used to estimate the risk of an outcome comparing between varenicline-exposed time and unexposed time. The analyses were repeated in patients with and without pre-existing psychiatric diagnoses (ICD-9: 295-302, 307-316; ICD-10: F20-F48, F50-F69, F90-F98; diagnosed before 1 November 2006). The findings showed that being treated with varenicline was not associated with significantly increased risk of suicidal behavior, but varenicline was associated with an increased hazard of new psychiatric conditions (HR=1.18, 95% CI=1.05 to 1.31). When further examining the associations by analyzing each diagnostic category separately, the results showed that varenicline was associated with increased risk for anxiety (HR=1.27, 95% CI=1.06 to 1.51) and mood conditions (HR=1.28; 95% CI= 1.07 to 1.52), but did not appear to be associated with the psychoses risk (HR= 0.94; 95% CI= 0.73 to 1.20) (Table 3-2).

3.2.2 Effect of smoking cessation treatment among patients with and/or without psychiatric history

The Meyer study[6]

Psychiatric history was defined as having one inpatient or two outpatient codes (the same ICD-9 codes as those used to identify the study outcome, Appendix Table I) on different days within the 365 days prior to the index prescription date. Most of the 55 primary outcome events (30-day neuropsychiatric hospitalization, 18 of the 23 with varenicline exposure, and 25 of the 32 with NRT exposure, Table 3-2) occurred in patients with psychiatric history, although such patients formed a minority of the cohorts (2,595 in the varenicline cohort and 1,762 in the NRT cohort).

The effect estimates among the population with a history of psychiatric disease could not be calculated in the propensity-matched cohort because of the small sample size. However, the effect estimates among the population without a history of psychiatric disease (HR = 0.80; 95% CI=0.21 to 2.98, Table 3-2) were numerically lower than that of the overall population in the propensity-matched cohort (HR=1.14; 95% CI=0.56 to 2.34, Table 3-2). Nevertheless, both estimates had wide confidence intervals that crossed the null. The researcher also calculated the HRs among the subgroups from a model that included the propensity score as a continuous variable (i.e., propensity score-adjusted analyses). The effect estimates were not significantly different between patients with (HR = 0.93, 95% CI: 0.48 to 1.82, Table 3-2) or without (HR = 0.77, 95% CI: 0.21 to 2.84, Table 3-2) psychiatric history, although the HRs were numerically lower among patients without prior psychiatric disease.

The VA study

In the VA study, patients with psychiatric history were defined as having been hospitalized with an inpatient diagnosis for mental health disorders (Appendix Table I) within the 24 months prior to the index date. Patients without psychiatric history were defined as having no mental health diagnoses, identified by ICD-9-CM codes in inpatient and outpatient records, and no prescriptions for medications used to treat mental health disorders within the 24 months prior to the index date. Among patients without psychiatric history, there was only one case of hospitalization for a mental health disorder (in the varenicline group); therefore, the HRs of inpatient mental disorder cannot be calculated among this subgroup. The effect estimates among the population with a history of psychiatric disease (HR = 1.07; 95% CI=0.46 to 2.46, Table 3-2) was numerically higher than that of the overall population in the propensity-matched cohort (HR=0.76; 95% CI=0.40 to 1.46, Table 3-2), but both were with wide confidence intervals that crossed the null.

The sample size and outcome event numbers were slightly different between the Cunningham et al. publication[9] and the VA study report, because of the changes in the propensity score matching approach,[c] however, the subgroup findings on the primary outcomes were similar. The point estimates of the HRs were generally higher among patients with psychiatric history than the overall population, although they were all imprecise and did not reach statistical significance.[9] There was a significant difference in outpatient visits for schizophrenia between varenicline and NRT (HR=1.40, 95% CI=1.09-1.80) in the subgroup with psychiatric history.[9] No patients in either the varenicline or NRT groups presented with outpatient visits for schizophrenia in the subgroup without psychiatric history.[9]

The Pasternak study[12]

Using the propensity score matched cohort, the study estimated HRs in participants with and without a history of psychiatric disorder. The history of psychiatric disorder was defined as any psychiatric diagnosis listed in Appendix II, or antidepressant or antipsychotic drug use within the one year before varenicline or bupropion initiation. The risk of psychiatric events associated with varenicline compared with bupropion appeared lower in participants without a history of psychiatric disorder (HR=0.33, 95% CI=0.09-1.22, Table 3-2) than in participants with a history

[c] The publication by Cunningham et al. reported results based on a 1:2 propensity score-matching instead of a 1:1 propensity score-matched cohort as specified in the VA study protocol.

(HR=1.01, 95% CI=0.64-1.59, Table 3-2) although this was based on few cases, and the difference in risk of psychiatric events associated with varenicline versus bupropion by history of psychiatric disorder was not statistically significant (P=0.12).

The Molero study[11]

This study reported the risk of each psychiatric diagnostic category (mood condition, anxiety condition and psychosis) in patients with and without pre-existing psychiatric diagnoses (ICD-9: 295-302, 307-316; ICD-10: F20-F48, F50-F69, F90-F98; diagnosed before 1 November 2006). Similar to the findings in the overall population, varenicline use was associated with an increased risk for anxiety and mood conditions, although the effect estimates were not statistically significant among users without prior psychiatric illness (Table 3-2). The trend of psychosis risk was opposite when the analyses were stratified by prior psychiatric illness, but both effect estimates were wide and crossed null (HR=0.90, 95% CI=0.70-1.16 among users with prior psychiatric illness versus HR=3.52, 95% CI= 0.81-15.27 among users without prior psychiatric illness, Table 3-2).

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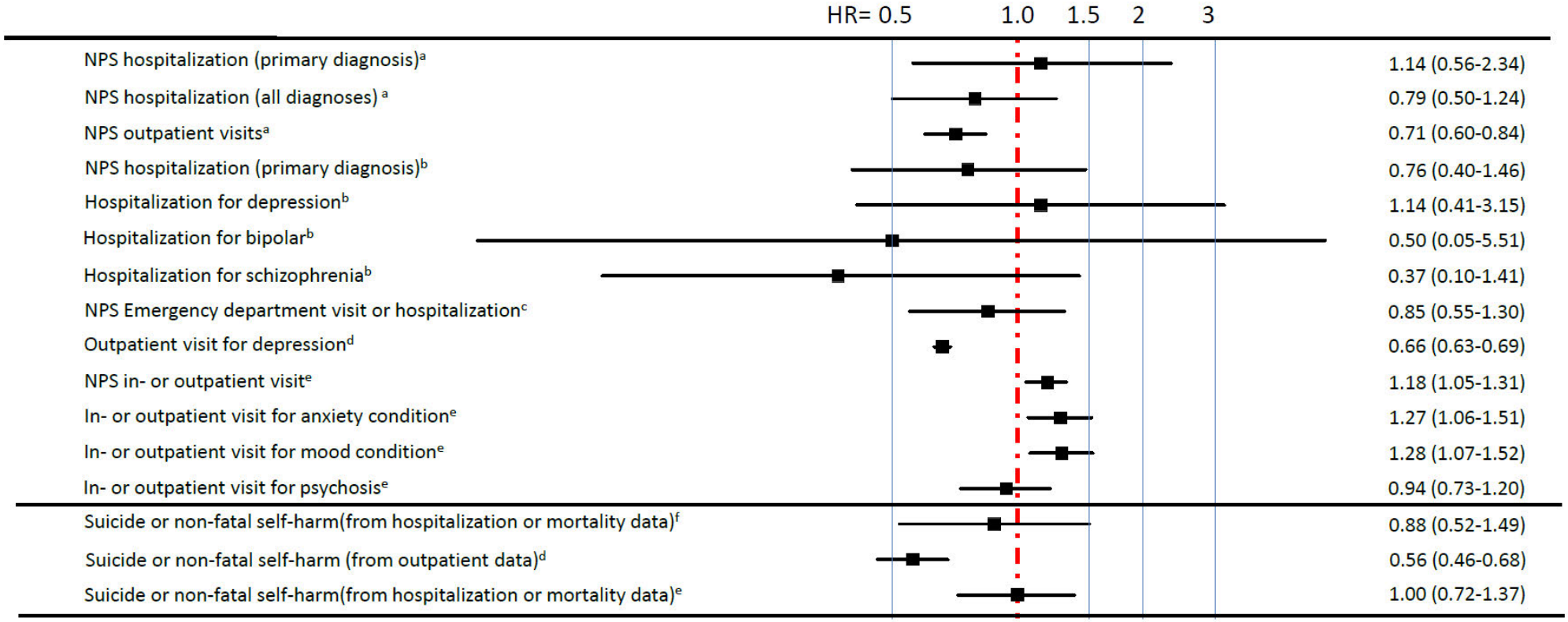
Figure 3-1 Reviewer-generated forest plot of varenicline-associated neuropsychiatric (NPS) risk observed in all reviewed studies (reference group: nicotine replacement therapy,[a,b,d,f] bupropion,[c] or person-time that was unexposed to varenicline[e])



NPS: Neuropsychiatric; HR: Hazard ratio; PTSD: Posttraumatic stress disorder

[a] Meyer TE, Taylor LG, Xie S et al. Neuropsychiatric events in varenicline and nicotine replacement patch users in the Military Health System. *Addiction* 2013;108:203-210. doi:10.1111/j.1360-0443.2012.04024.x [doi].

[b] Final report of the VA study: Varenicline and Mental Health Disorders, dated May 2011, revised June 2011

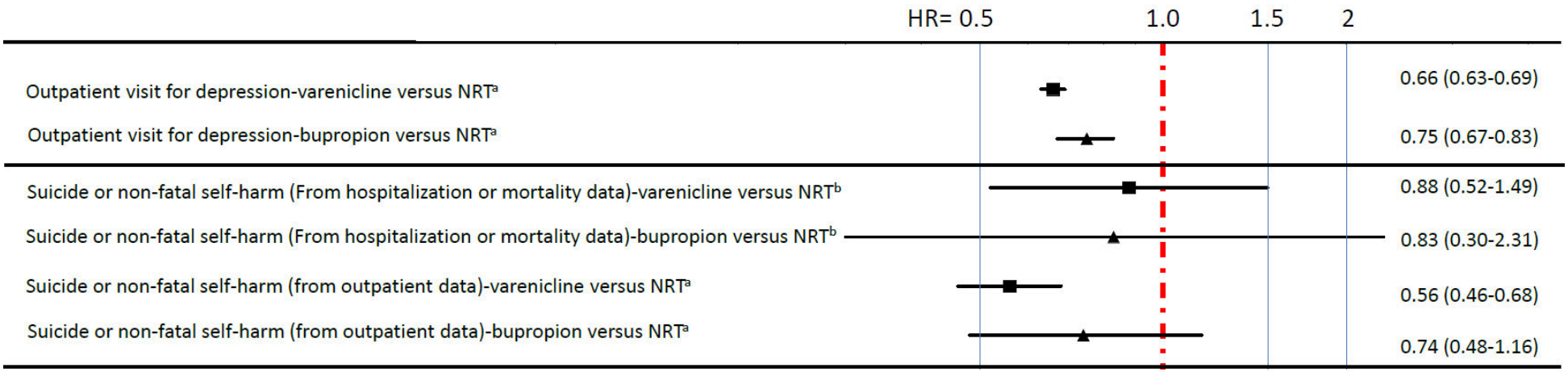
[c] Pasternak B, Svanstrom H, Hviid A. Use of varenicline versus bupropion and risk of psychiatric adverse events. Addiction. 2013;108(7):1336-1343.

[d] Kotz D, Viechtbauer W, Simpson C, van Schayck OC, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. *Lancet Respir Med.* 2015;3(10):761-768.

[e] Molero Y, Lichtenstein P, Zetterqvist J, Gumpert CH, Fazel S. Varenicline and risk of psychiatric conditions, suicidal behaviour, criminal offending, and transport accidents and offences: population based cohort study. *BMJ.* 2015;350:h2388.

[f] Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ.* 2013;347:f57

Figure 3-2 Reviewer-generated forest plot of neuropsychiatric (NPS) risk observed in all reviewed studies that examined both varenicline- and bupropion- associated risk[a,b]



NRT: nicotine replacement therapy

[a] Kotz D, Viechtbauer W, Simpson C, van Schayck OC, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. *Lancet Respir Med.* 2015;3(10):761-768.

[b] Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self-harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ.* 2013;347:f57

Table 3-1 Reviewer-generated summary table of the risks of suicide and non-fatal self-harm among varenicline users and bupropion users observed in the Thomas et al. study[a]

Analytical approaches	Exposure	Effect estimate (95% Confidence interval) Reference (NRT)	
		3-month suicide and non-fatal self-harm	
		Hazard ratio	Risk difference per 1000 person-year
Cox regression analyses	Varenicline	0.88 (0.52 to 1.49)	-0.1[c]
Propensity score matching analyses		0.87 (0.51 to 1.48)	-0.1[c]
Instrumental variable analyses		-	0.4 (-0.8 to 1.5)
Cox regression analyses	Bupropion	0.83 (0.30 to 2.31)	-0.1 to -0.2[c]
Propensity score matching analyses		0.87 (0.31 to 2.4)	0.1[c]
Instrumental variable analyses		-	-3.9[b] (-7.0 to -0.9)

[a] Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ.* 2013;347:f57

[b] p value < 0.05.

[c] see the calculation from HRs to risk differences in Appendix III

Table 3-2 Reviewer-generated summary table of varenicline-associated neuropsychiatric risk stratified by psychiatric history

	Overall cohort		**Cohort WITHOUT psychiatric history**		**Cohort WITH psychiatric history**	
Meyer et al.[a]	**Varenicline**	**NRT**	**Varenicline**	**NRT**	**Varenicline**	**NRT**
Sample size	N=19,933	N=15,867	N=17,338	N=14,105	N=2,595	N=1,762
NPS hospitalization	23	32	5	7	18	25
HR 95% CI	1.14 (0.56-2.34)		0.80 (0.21-2.98)		NA	
VA study[b]	**Varenicline**	**NRT**	**Varenicline**	**NRT**	**Varenicline**	**NRT**
Sample size[e]	N=14,131	N=14,131	N=13,811	N=13,811	N=2,034	N=2,034
NPS hospitalization	16	21	1	0	11	11
HR 95% CI	0.76 (0.40-1.46)		NA		1.07 (0.46-2.46)	
Pasternak et al. [c]	Varenicline	Bupropion	Varenicline	Bupropion	Varenicline	Bupropion
Sample size[e]	17,935	17,935	14,089	13,962	3,846	3,973
NPS hospitalization	39	46	3	9	36	37
HR 95% CI	0.85 (0.55 to 1.30)		0.33 (0.09 to 1.22)		1.01 (0.64 to 1.59)	
Molero et al.[d]	**All Varenicline users**		**Varenicline user WITHOUT psychiatric history**		**Varenicline user WITH psychiatric history**	
Sample size	N=69,757		N=60,366		N=9,391	
Anxiety conditions	1.27[f] (1.06 to 1.51)		1.41 (0.99 to 2.00)		1.23[f] (1.01 to 1.51)	
Mood conditions	1.28[f] (1.07 to 1.52)		1.17 (0.86 to 1.60)		1.31[f] (1.06 to 1.63)	
Psychosis	0.94 (0.73 to 1.20)		3.52 (0.81 to 15.27)		0.90 (0.70 to 1.16)	

[a] Meyer TE, Taylor LG, Xie S et al. Neuropsychiatric events in varenicline and nicotine replacement patch users in the Military Health System. *Addiction* 2013;108:203-210. doi:10.1111/j.1360-0443.2012.04024.x [doi].
[b] Final report of the VA study: Varenicline and Mental Health Disorders, dated May 2011, revised June 2011
[c] Pasternak B, Svanstrom H, Hviid A. Use of varenicline versus bupropion and risk of psychiatric adverse events. Addiction. 2013;108(7):1336-1343.
[d] Molero Y, Lichtenstein P, Zetterqvist J, Gumpert CH, Fazel S. Varenicline and risk of psychiatric conditions, suicidal behaviour, criminal offending, and transport accidents and offences: population based cohort study. *BMJ.* 2015;350:h2388.
[e] Based on propensity score-matched cohort
[f] p value < 0.05.

4. DISCUSSION

The findings were conflicting across studies, and each of the reviewed studies had a number of study design limitations that complicate the interpretation of their results. We will address the specific limitations of the existing observational studies in sections 4.1 to 4.3.

4.1 CONCERNS ON VALIDITY OF OUTCOME MEASURES

The outcomes examined in these studies—suicide, self-harm and neuropsychiatric medical encounters—did not cover the full range of the neuropsychiatric adverse events that have been seen in post-marketing spontaneous adverse event reports associated with smoking cessation products.[d] Furthermore, all studies relied primarily on diagnostic codes recorded during medical encounters (ICD-9, ICD-10, or Read codes) to ascertain outcomes; only one study[12] reported some measure of validity for some of the ICD-10 codes used to identify their outcomes.[e] We are concerned that diagnostic codes cannot accurately capture and characterize all of the neuropsychiatric adverse events that have been associated with varenicline. The events described in the adverse event reports have involved abrupt behavioral and/or mood changes, which are difficult to accurately translate into a medical coding system. Adverse events may have also resulted in patient contact with legal, rather than medical, systems. Without a detailed exploration of medical charts to identify all codes that might have been used to capture these outcomes, as well as patient and provider interviews to determine behavior and coding practices, it is not possible to estimate how many events are misclassified or not captured in these studies. Such problems are inherent to the study of behavioral and psychiatric outcomes, which present different challenges than studying other medical diagnoses.

In the studies that examined the association between smoking cessation products and neuropsychiatric hospitalizations or emergency room visits,[6,9,12] clinically important psychiatric events that did not include emergency room visit or hospitalization (such as a successful suicide without hospitalization) were not captured. Although both the Meyer and the VA studies[6,9] also examined a secondary outcome that included outpatient visits with a neuropsychiatric diagnosis, this metric may be simply capturing pre-existing psychiatric comorbidities, rather than treatment emergent psychiatric events. Moreover, an acute worsening of a psychiatric condition without a health care professional encounter would be missed. In light of the stigma that can be attached to psychiatric diagnoses in medical records, particularly in the military, this possibility cannot be ruled out.

Undercounting of the outcome is also a concern with respect to the Thomas study[8] that examined suicide-related outcomes due to the stigma that can be attached to such diagnoses, the difficulty in determining intentionality of injury, and the fact that such attempts are not always brought to medical attention. Although Thomas et al.[8] used both the hospital admission data and the UK

[d] For example, some adverse events that have been reported among patients who used varenicline include changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide

[e] Pasternak et al. had reported high positive predictive value (>90%) for the ICD-10 codes used to identify a schizophrenia-spectrum disorder and a single depressive episode. However, the two conditions are only some of several psychiatric adverse events that the study targeted.

mortality records to capture suicide-related outcomes (fatal/non-fatal self-harm), this approach only enhanced the capture of a part of the outcome—fatal self-harm, but not the other part that still relied on diagnostic codes used in hospital records (i.e., attempted suicide). In fact, a high proportion (approximately 90%) of the observed suicide-related outcome in the Thomas et al.[8] study were non-fatal self-harm. The author reported that a total of 92 cases of suicide and non-fatal self-harm were identified from the study population, but only six suicides were recorded in the NRT group, two in the varenicline group and none in the bupropion group.[8]

The Read codes used by the Kotz study[10] have been shown to be unreliable for detecting suicide death and under-report non-fatal self-harm.[14] The authors did not address the validity of Read codes to identify depression. In addition, the study was based on the general practitioner (GP) encounter data; suicide death, as well as severe cases of depression or suicide attempt that lead to emergency room visits, hospitalizations or requiring treatment by a psychiatrist were likely missed in the study. If varenicline or bupropion causes more severe neuropsychiatric adverse events than NRT, this under-ascertainment of outcome would be more pronounced in the varenicline or bupropion group than NRT groups. Furthermore, the study did not differentiate depression visits for new or existing conditions. The fact that varenicline and bupropion use significantly decreased the number of depression visits could be evidence of an adverse effect if planned follow-up visits for a pre-existing condition were missed (i.e., could be evidence of worsening depression).

Although Molero et al.[11] used both hospital and outpatient data to identify neuropsychiatric events, and excluded diagnoses during planned visits such as follow-up or referral, only some of the inpatient diagnosis codes (for schizophrenia and personality disorder) used by Molero et al.[11] were previously validated[15]. The validity of the majority of the diagnostic codes, especially those occurring in the outpatient setting, is still unclear. Under-ascertainment of suicide attempt is still likely for the reasons that have been addressed previously, even though the study used hospital and mortality records to identify suicide-related outcomes.

4.2 CHANNELING BIAS AND RESIDUAL CONFOUNDING

Another major concern of the existing observational data is residual confounding and channeling bias, especially, among the three studies by Thomas et al.[8] Kotz et al.,[10] and Molero et al.[11] that included data from the timeframe after the publicity of the neuropsychiatric safety concern associated with varenicline and bupropion.[16] Adverse publicity may have resulted in patients with a history of neuropsychiatric illness being preferentially prescribed NRT, and healthier patients or patients at lower risk of neuropsychiatric events being preferentially prescribed the other two drugs (i.e., channeling bias). In fact, varenicline users and bupropion users in the Thomas study and the Kotz study were less likely to have a history of chronic disease or psychiatric illness,[8,10] or had a lower frequency of previous use of hypnotics, antipsychotics, and antidepressants;[8] these patients were shown to be less likely to be at risk for neuropsychiatric event compared to NRT users. The study by Pasternak et al. also included data after the publicity of varenicline and bupropion's neuropsychiatric risk. Because the publicity on varenicline's neuropsychiatric safety concern was more widespread than that of bupropion, channeling bias could have existed in the Pasternak study[8,12] and led to a healthier varenicline group with lower baseline neuropsychiatric risk than the bupropion group. However, the distribution of baseline psychiatric history and psychotropic drug use was generally similar between the two groups in the study. The preferential prescribing of bupropion over varenicline among patients with higher

neuropsychiatric risk, if it existed, may not have biased the findings of the Pasternak study significantly.

The three studies by Thomas et al.,[8] by Kotz et al.,[10] and by Molero et al.[11] implemented advanced designs or advanced analytical approaches to handle the potential bias due to baseline patient selection, but we cannot be sure that their analyses adequately controlled for the baseline differences in patients due to channeling. We will comment on the methods of each study in the following section.

The Thomas study[8]

Thomas et al. conducted three analyses: a conventional Cox regression analysis, and two advanced analyses—a propensity score [PS] matched analysis and an instrumental variable [IV] analysis—in order to attempt to account for the potential bias due to baseline selection into treatment cohorts. Despite using multiple analytical approaches, their findings are still likely to be biased due to residual confounding. The issue of residual confounding was illustrated by the findings of their secondary analysis that examined all-cause mortality risk associated with the study drugs as described in the following paragraphs.

As shown in Table 4-1, the all-cause mortality risk at 3 months from their Cox regression and PS matching analyses were significantly lower among both varenicline users and bupropion users, compared to NRT users. Given that three months is too short of a timeframe for realizing the survival benefits of smoking cessation, the reduced risk in all-cause mortality seen in the Cox regression and PS matching analyses most likely indicates that varenicline users and bupropion users are generally healthier than NRT users. Therefore, the effect estimates of the suicide-related outcome (Table 3-1) from those two analyses would likely carry the impact of the residual baseline differences.

Table 4-1 Potential channeling bias in the Thomas et al. study[a] illustrated by their findings of the all-cause mortality risk among varenicline users and bupropion users

Analytical approaches	Exposure	Effect estimate (95% Confidence interval) (Reference: NRT users)	
		3-month all-cause mortality	
		Hazard ratio	Risk difference per 1000 person-year
Cox regression analyses	Varenicline	0.44[b] (0.30 to 0.63)	-1.4 to -2[c]
Propensity score matching analyses		0.37[b] (0.26 to 0.53)	~-2[c]
Instrumental variable analyses		-	-0.8 (-2.8 to 1.1)
Cox regression analyses	Bupropion	0.39[b] (0.16 to 0.95)	-1 to -2[c]
Propensity score matching analyses		0.34[b] (0.14 to 0.82)	-2 to -3[c]
Instrumental variable analyses		-	-4.2 (-10.5 to 2.1)

[a] Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ.* 2013;347:f57

[b] p value < 0.05.

[c] see the calculation from HRs to risk differences in Appendix III

Their third analysis using an IV approach appeared to reduce the impact of residual confounding when comparing varenicline users to NRT users, because the difference in 3-month mortality risk between varenicline and NRT users became smaller (from ~-1.4 to -2 per 1,000 patient-years based on Cox regression or PS matching analyses, to -0.8 per 1,000 patient-years in the IV analysis, Table 4-1). However, the IV analyses might still carry bias in estimating varenicline's effect on suicide-related outcome. In order for IV analysis to work well, the chosen IV needs to be strongly associated with the actual treatment and be independent of any factors that have impact on the targeted outcome (i.e. suicide or self-harm). Thomas et al.[8] choose physician' prescribing preference as the IV and they used physicians' prescribing patterns as the proxy of "prescribing preference". We noticed that physicians' characteristics, something that can influence prescribing preferences, are not used to estimate physician's preference. If the prescribing preferences are related to a physician's familiarity with current literature and the ability to make use of the information, physicians who prefer varenicline over NRT because of its higher efficacy[17] could be more vigilant of the risk of smoking cessation itself on depression or suicide and monitor their patients more frequently. In this scenario, patients who were seen by physicians who prefer varenicline or bupropion would have lower suicide risk that is unrelated to drug effect. The implication is that the effect estimates from IV analyses can still be biased by differences in the physician characteristics, and this study may have under-estimated the true suicide risk associated with varenicline.

With regard to the bupropion findings, the IV analyses did not seem to reduce the impact of residual confounding. Although we do not expect a reduction of all-cause mortality within three months of bupropion use because it is too short of a timeframe for realizing the survival benefits of smoking cessation, the IV findings indicated that bupropion is associated with an even larger reduction in 3-month mortality than the findings from the Cox regression and PS matching analyses (~-1 to -3 per 1,000 patient-years based on Cox regression or PS matching analyses, to -4.2 per 1,000 patient-years in the IV analysis, Table 4-1). Nevertheless, the effect estimate of all-cause mortality risk in the IV analysis was not statistically significant. The reduced risk of suicide-related outcome associated with bupropion in the IV analyses might still be biased due to the healthier bupropion users than NRT users.

The Kotz study[10]

Similar to the Thomas study,[8] the baseline characteristics of the study population indicated potential differential prescribing, i.e., varenicline and bupropion seems to be given to patients who were younger, less socioeconomically deprived and less likely to have a history of psychiatric illness. Although the author stated that those measured baseline differences were balanced in the statistical models (i.e., multivariable Cox regression and propensity score matching) used for their analyses, some important confounders were unmeasured and could still have biased the study findings. One such unmeasured confounder is prior or concurrent use of psychotropic medications, which had been reported to be imbalanced among smoking cessation product users in the aforementioned Thomas study,[8] which was based on a similar data source (i.e., UK general practices data) as the Kotz[10] study and likely had similar prescribing and utilization patterns. Recognizing the potential of residual confounding from unmeasured confounders, the authors conducted a sensitivity analysis and concluded that the observed reduced risk associated with varenicline use is unlikely to be reversed by unmeasured confounder(s). This is because the distribution of the unmeasured confounder would need to be extremely imbalanced among comparison groups to reverse the findings.[10] One caveat of this

sensitivity analysis[13] is that it only models the impact of a single unmeasured confounder that is not associated with the any measured confounders in the study; therefore, it does not address the impact of the unmeasured psychotropic medication use, which is likely to be associated with psychiatric comorbidities. In this case, the distribution of the unmeasured psychotropic medication use might not need to be as imbalanced between the comparison groups to reverse the effect estimates.

The Molero study[11]

Molero et al.[11] implemented a "within-person comparison" (i.e., self-controlled design using patients as their own controls) as the principle analysis instead of the "between-person" comparison that compared users of different smoking cessation products) that was used in the other reviewed studies.[8,10] The self-controlled design handled the concern of the confounding due to the potential differential prescribing of smoking cessation products based on a patient's baseline mental comorbidities because varenicline users were compared to themselves. However, the self-controlled design introduced a different type of confounding. Specifically, this design is unable to account for confounding that can change over time. As the author acknowledged, one of the potential time-varying confounders was the impact of nicotine withdrawal syndrome.[11] Because nicotine includes psychoactive compounds that mimic an antidepressant effect, smoking cessation could induce nicotine withdrawal symptoms that include depression and anxiety. It was unclear whether the increased neuropsychiatric risk that was observed in the Molero study[11] was due to varenicline use or to the choice of the comparison periods. The comparison periods could have included periods of smoking cessation attempts without medications, with other medications, or periods during which the patient was not trying to quit smoking.

4.3 OTHER DESIGN OR METHODOLOGICAL ISSUES

The study by Pasternak et al.[12] compared risk of neuropsychiatric emergency department visits or hospitalizations between varenicline users and bupropion users; the study found a non-significant 15% lower risk associated with varenicline use compared with bupropion use (HR: 0.85. 95% CI: 0.55- 1.30; Table 3-1, Appendix II). However, given that bupropion also has been associated with psychiatric adverse events and carries a boxed warning alerting about this possibility,[16]this finding does not provide reassurance of varenicline's neuropsychiatric safety.

All of the reviewed studies included patients with pre-existing psychiatric disorders with the intention to improve the generalizability over the premarketing trials, because these patients were typically excluded from the clinical trials conducted with varenicline before it was approved. However, not all of the studies examined the impact of psychiatric history on smoking cessation products' neuropsychiatric risk. Additionally, the four studies that had investigated the impact of psychiatric history all had limitations. We are unable to evaluate the impact of psychiatric history on varenicline-associated neuropsychiatric risk because the subgroup findings carried bias. For Molero et al.,[11] the bias was due to the impact of nicotine withdrawal syndrome, because of the self-controlled design (as addressed in section 4.2). Findings of the Meyer study[6] and VA study both suggest that varenicline users with psychiatric history might have a higher neuropsychiatric risk than those without because the majority of the neuropsychiatric events were observed among patients with psychiatric history. In both studies, HRs of the patients with psychiatric history were also numerically higher than that of the overall cohort. However, the small cohort of patients with psychiatric history and/or the few observed outcomes in the subgroup without

psychiatric history prevented a definitive conclusion about the additional impact of psychiatric history on the association between smoking cessation products and neuropsychiatric events. The Pasternak et al.[12] study reported a similar trend that the observed HRs of psychiatric events associated with varenicline appeared lower in participants without a history of psychiatric disorder than in participants with a history, but the point estimates were imprecise and the confidence intervals both crossed one. As addressed earlier, the choice of bupropion as the reference group to examine varenicline's neuropsychiatric risk also make it difficult to interpret the findings. All of the reviewed studies included patients with pre-existing psychiatric disorders with the intention to improve the generalizability over the premarketing trials, because these patients were typically excluded from the clinical trials conducted with varenicline before it was approved. However, not all of the studies examined the impact of psychiatric history on smoking cessation products' neuropsychiatric risk. Additionally, the four studies that investigated the impact of psychiatric history all had limitations. We are unable to evaluate the impact of psychiatric history on varenicline-associated neuropsychiatric risk because the subgroup findings carried bias. For Molero et al.,[11] the bias was due to the impact of nicotine withdrawal syndrome, because of the self-controlled design (as addressed in section 4.2). Findings of the Meyer study[6] and VA study both suggest that varenicline users with psychiatric history might have a higher neuropsychiatric risk than those without because the majority of the neuropsychiatric events were observed among patients with psychiatric history. In both studies, HRs of the patients with psychiatric history were also numerically higher than that of the overall cohort. However, the small cohort of patients with psychiatric history and/or the few observed outcomes in the subgroup without psychiatric history prevented a definitive conclusion about the additional impact of psychiatric history on the association between smoking cessation products and neuropsychiatric events. The Pasternak et al.[12] study reported a similar trend that the observed HRs of psychiatric events associated with varenicline appeared lower in participants without a history of psychiatric disorder than in participants with a history, but the point estimates were imprecise and the confidence intervals both crossed one. As addressed earlier, the choice of bupropion as the reference group to examine varenicline's neuropsychiatric risk also made it difficult to interpret the findings.

4.4 SUMMARY ASSESSMENT

To briefly summarize our assessment of the six reviewed observational studies:

- Studies that examined varenicline's neuropsychiatric risk
    - The studies by Meyer et al.[6] and VA study that examined risk of neuropsychiatric hospitalizations found "no increased risk" associated with varenicline relative to NRT, but those findings were not reassuring of varenicline's neuropsychiatric safety. The use of diagnostic codes to capture neuropsychiatric events in these studies is likely to have under-ascertained true events. Under-ascertainment of events that did not differ by cohort would result in an imprecise relative effect estimate with wide confidence intervals, as observed in the two studies. Those imprecise effect estimates did not suggest a consistent trend of association between varenicline and neuropsychiatric risk.
    - The study by Pasternak et al.[12] compared risk of neuropsychiatric emergency department visits or hospitalizations between varenicline users and bupropion users; the study found a non-significant 15% lowered risk associated with

varenicline use compared with bupropion use. Given that bupropion also has been associated with psychiatric adverse events and carries a boxed warning alerting about this possibility,[16] this finding does not provide reassurance of varenicline's neuropsychiatric safety.

- In the study by Thomas et al.,[8] the two analyses (Cox regression and PS matching analysis) that indicated a negative association for suicide/non-fatal self-harm risk for varenicline use both carried bias due to baseline patient selection into the treatment groups due to channeling. The third analysis (IV analysis) appeared to have reduced some of the bias in the comparison between varenicline to NRT, but not in the comparison between bupropion and NRT. The IV-based analyses suggested varenicline might have a higher risk of fatal or non-fatal self-harm than NRT. Although the risk increase was numerically small, it was likely an under-estimation of true risk because of the under-ascertainment of non-fatal self-harm. However, because the effect estimate of varenicline-associated neuropsychiatric risk was imprecise and the confidence interval crossed zero, the data are inconclusive.
- The significant reduction of neuropsychiatric risk associated with varenicline observed in the Kotz study[10] needs to be interpreted cautiously, due to the fact that the severe neuropsychiatric events that lead to hospitalization or death were not captured in the study since it was solely based on general practitioner data. In addition, the study did not differentiate whether depression visits were for a new or existing condition. The fact that varenicline use significantly decreased the occurrence of a depression visit could be an adverse effect if those visits were meant for following up a pre-existing condition, rather than treatment emergent events. Despite the authors' effort to address possible influence from unmeasured confounding, their sensitivity analyses did not examine the impact of multiple unmeasured confounders or those that are associated with the captured confounders, such as previous or concurrent use of psychotropic drugs. The potential differential patient selection at baseline could still explain the observation of a reduced risk of neuropsychiatric risk among varenicline users. Lastly, the study excluded patients who had received overlapping prescriptions for smoking cessation drugs during the follow-up period to focus the assessment on patients received single smoking cessation treatment. Because this approach also excluded patients who switched from one smoking cessation drug to another, it would likely under-estimate the risk associated with varenicline, if the reason for switching was because of neuropsychiatric adverse events.
- The self-controlled designed used by Molero et al.[11] might have inadvertently introduced confounding due to the impact from nicotine withdrawal syndrome if comparison periods did not also occur during treated smoking cessation attempts. It is unclear whether the increased neuropsychiatric risk that was observed in the study was due to varenicline use, the choice of comparator periods, or both.

- Studies that examined bupropion-associated neuropsychiatric risk
  - Although all three analyses in the Thomas et al. study[8] consistently found a negative association between bupropion use and suicide/non-fatal self-harm risk,

they also suggested that bupropion use was associated with a reduced 3-month all-cause mortality risk, which is unlikely. The reduced risk might be due to the bias from the potential baseline patient selection, rather than bupropion use.

- The limitations of the Kotz et al.[10] study in assessing varenicline's neuropsychiatric risk are all applicable to the assessment of bupropion-associated risk. The study may have missed more severe events that led to hospitalization or death, could not determine whether the identified outpatient depression visit was for new or existing condition. It also may have been vulnerable to residual confounding due to the differential patient selection at baseline. The exclusion of patients who switched from one smoking cessation drug to another would likely under-estimate the risk associated with bupropion, if the reason for switching was because of neuropsychiatric adverse events.

- In all reviewed studies
  - The impact of psychiatric history on the neuropsychiatric risk associated with varenicline or bupropion use was either not examined (Thomas et al.[8] and Kotz et al.[10]) or could not be appropriately assessed; either due to small sample size or small observed events in the subgroup (Meyer et al.[6], VA study, and Pasternak et al.[12]) or because of inappropriate study design that could not rule out confounding by nicotine withdrawal syndrome (Molero et al.[11]).
  - The outcomes examined did not cover the full range of the neuropsychiatric adverse events that have been associated with varenicline in the spontaneous case reports.

5. CONCLUSION

The reported results with respect to varenicline- or bupropion- associated neuropsychiatric risk in the reviewed studies varied considerably. All studies had a number of study design limitations; the biases within each study complicated interpretation of the result individually, and as a whole. The inability to assess the risk among those with pre-existing psychiatric illness further restricted the generalizability of the findings. The evidence from the existing observational studies alone is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline or bupropion use. Observational data alone also are inadequate to inform whether or not neuropsychiatric risk associated with varenicline or bupropion could be different between smokers with and without psychiatric history. Neuropsychiatric safety of smoking cessation products should be assessed based on the totality of data streams, including case reports, observational and clinical trial data.

Appendix I Literature search strategy and search terms

Search and screening process of identifying articles for in-depth review (Steps and number of articles left)

		N
1.	Search articles mentioned " smoking cessation drugs" AND "Neuropsychiatric adverse outcomes", identified	425
2.	Exclude animal studies, cell studies, pharmacokinetic/pharmacodynamics studies	377
3.	Excluded wrong publication or study type in title or abstract	140
4.	Excluded non-English articles	127
5.	Excluded 119 articles after reviewer screening	8

- Wrong publication or study type (N=34)
  (e.g., case series, RCT, reviews, letter)
- Studies that did not examine drug-related neuropsychiatric risk (N=68)
  (e.g., studies that examined predictors of smoking cessation drug use among smokers with mental disorders, studies that examined how existing mental disorder impacts outcomes of smoking cessation treatment)
- Studies that did not report relative risk of neuropsychiatric events between smoking cessation drugs or studies that did not use adequate design and analytical approach to examine neuropsychiatric risk among smoking cessation products, for example: cross-sectional analyses; studies without (concurrent) comparator groups, studies that did not account for confounding when comparing risk between studied drugs (N=17)

→**8 articles for in-depth review**

Search terms

- Smoking cessation products

((varenicline[All Fields] OR champix[All Fields] OR chantix[All Fields]) OR ((bupropion[All Fields] OR aplesnin[All Fields] OR budeprion[All Fields] OR bu phoban[All Fields] OR forgive[All Fields] OR wellbutrin[All Fields] OR wellbutrin[All Fields] OR zyban[All Fields]) AND and[All Fields] AND (smoking[All Fields] OR smoker[All Fields])) OR ("nicotine replacement therapy"[All Fields] OR NRT[All Fields] OR "nicotine replacement product"[All Fields])) AND

- Neuropsychiatric adverse outcomes

("mental disorders"[All Fields] OR "mental disease"[All Fields] OR "psychiatric disorder"[All Fields] OR "neuropsychiatric disorder"[All Fields] OR "neuropsychiatric safety"[All Fields] OR (suicide[All Fields] OR suicidal[All Fields] OR "self harm"[All Fields] OR "self-harm"[All Fields]) OR (depression[All Fields] OR "mood disorder"[All Fields]) OR (schizophrenia[All Fields] OR schizophrenic[All Fields] OR hallucination[All Fields] OR delusion[All Fields] OR psychosis[All Fields] OR paranoia[All Fields] OR mania[All Fields] OR "manic disorder"[All Fields] OR "bipolar disorder"[All Fields]) OR (anxiety[All Fields] OR panic[All Fields] OR agitation[All Fields] OR aggression[All Fields] OR "aggressive behavior"[All Fields]) OR hostility[All Fields] OR "abnormal behavior"[All Fields] OR ("change behavior"[All Fields]) OR "personality disorder"[All Fields])

- Animal study

(animals[tiab] OR animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent[Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[Tiab] OR "guinea pig"[Tiab] OR cavia[Tiab] OR callithrix[Tiab] OR marmoset[Tiab] OR marmosets[Tiab] OR cebuella[Tiab] OR hapale[Tiab] OR octodon[Tiab] OR chinchilla[Tiab] OR chinchillas[Tiab] OR gerbillinae[Tiab] OR gerbil[Tiab] OR gerbils[Tiab] OR jird[Tiab] OR jirds[Tiab] OR merione[Tiab] OR meriones[Tiab] OR rabbits[Tiab] OR rabbit[Tiab] OR hares[Tiab] OR hare[Tiab] OR diptera[Tiab] OR flies[Tiab] OR fly[Tiab] OR dipteral[Tiab] OR drosphila[Tiab] OR drosophilidae[Tiab] OR cats[Tiab] OR cat[Tiab] OR carus[Tiab] OR felis[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematodes[Tiab] OR sipunculida[Tiab] OR dogs[Tiab] OR dog[Tiab] OR canine[Tiab] OR canines[Tiab] OR canis[Tiab] OR sheep[Tiab] OR sheeps[Tiab] OR mouflon[Tiab] OR mouflons[Tiab] OR ovis[Tiab] OR goats[Tiab] OR goat[Tiab] OR capra[Tiab] OR capras[Tiab] OR rupicapra[Tiab] OR chamois[Tiab] OR haplorhini[Tiab] OR monkey[Tiab] OR monkeys[Tiab] OR anthropoidea[Tiab] OR anthropoids[Tiab] OR saguinus[Tiab] OR tamarin[Tiab] OR tamarins[Tiab] OR leontopithecus[Tiab] OR hominidae[Tiab] OR ape[Tiab] OR apes[Tiab] OR pan[Tiab] OR paniscus[Tiab] OR "pan paniscus"[Tiab] OR bonobo[Tiab] OR bonobos[Tiab] OR troglodytes[Tiab] OR "pan troglodytes"[Tiab] OR gibbon[Tiab] OR gibbons[Tiab] OR siamang[Tiab] OR siamangs[Tiab] OR nomascus[Tiab] OR symphalangus[Tiab] OR chimpanzee[Tiab] OR chimpanzees[Tiab] OR prosimians[Tiab] OR "bush baby"[Tiab] OR prosimian[Tiab] OR bush babies[Tiab] OR galagos[Tiab] OR galago[Tiab] OR pongidae[Tiab] OR gorilla[Tiab] OR gorillas[Tiab] OR pongo[Tiab] OR pygmaeus[Tiab] OR "pongo pygmaeus"[Tiab] OR orangutans[Tiab] OR pygmaeus[Tiab] OR lemur[Tiab] OR lemurs[Tiab] OR lemuridae[Tiab] OR horse[Tiab] OR horses[Tiab] OR pongo[Tiab] OR

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- Cell study

cell[tiab] OR "cell line"[tiab] OR cellular[tiab] OR tissue[tiab] OR "in vitro"[tiab] OR spectroscopic[tiab] OR spectrometer[tiab] OR spectrophotometry[tiab] OR "transformation products"[tiab] OR synthesized[tiab] OR "gene variants"[tiab] OR polymorphism[tiab] OR plant[tiab]

- Pharmacokinetics/Pharmacodynamics studies

pharmacokinetics[tiab] OR pharmacokinetic[tiab] OR pharmacodynamic[tiab] OR pharmacodynamics[tiab])

- Excluded study type or publication type

autobiography[tiab] OR bibliography[tiab] OR biography[tiab] OR books[tiab] OR "case reports"Â[tiab] OR "clinical conference"[tiab] OR "clinical trial"[tiab] OR "phase I"[tiab] OR "phase II"[tiab] OR "phase III"[tiab] OR comment[tiab] OR "consensus development"[tiab] OR "controlled clinical trial"[tiab] OR editorial[tiab] OR guideline[tiab] OR interview[tiab] OR news[tiab] OR newspaper[tiab] OR "patient education handout"[tiab] OR "practice guideline"[tiab] OR "randomized controlled"[tiab] OR "randomised controlled"[tiab] OR â€œcase seriesâ€[tiab] OR â€œcase-seriesâ€ [tiab] OR webcast[tiab] OR ((Addresses[ptyp] OR Autobiography[ptyp] OR Bibliography[ptyp] OR Biography[ptyp] OR pubmed books[filter] OR Case Reports[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Comment[ptyp] OR Congresses[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Controlled Clinical Trial[ptyp] OR Dictionary[ptyp] OR Directory[ptyp] OR Editorial[ptyp] OR Government Publications[ptyp] OR Guideline[ptyp] OR Historical Article[ptyp] OR Interactive Tutorial[ptyp] OR Interview[ptyp] OR Lectures[ptyp] OR Legal Cases[ptyp] OR Legislation[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper Article[ptyp] OR Review[ptyp]))
OR “animals”[MeSH Terms:noexp]

Appendix II Summary tables for study design, methods and findings of the reviewed studies

Table 1 Design and methods of the observational studies on smoking cessation product use and neuropsychiatric risk

	DoD study/Meyers et al.	**VA Study**	**Pasternak et al.**	**Thomas et al.**	**Molero et al.**	**Kotz et al.**
Design	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Time frame	Aug 01 2006 to Aug 31 2007	May 01 2006 to Sep 30 2007	Jan 1 2007 to Dec 31 2010	Sep 01 2006 to Oct 31 2011	November 2006 to December 2009	January 2007 to June 2012
Data sources	Military health system data (Claims and administrative data)	VA health care data bases (claims and administrative data)	Nation-wide linked health care data in Denmark including information on prescription drug use, emergency department visits, hospital admissions, neuropsychiatric diagnosis, etc.	UK CPRD linked to Office for National Statistics (ONS) mortality data and Health Episode Statistics (HES) data	Nation-wide linked health care data in Sweden including information on prescription drug use, emergency department visit, hospital admission, outpatient visit, neuropsychiatric diagnosis, mortality information, including cause of death, etc.	QResearch database (version 36, upload July 31, 2013), which holds anonymised health records from 753 National Health Service general practices (GPS) from across England.
Exposure	Varenicline or NRT	Varenicline or NRT	Varenicline or bupropion	Varenicline, bupropion, or NRT	Varenicline-exposed period: 12-weeks after the first observed varenicline dispensing.	Varenicline, bupropion, or NRT
Reference group	NRT	NRT	Bupropion	NRT	Unexposed period	NRT
Main Outcomes	30-day Neuropsychiatric hospitalizations • Primary definition:	30-day Neuropsychiatric hospitalizations • hospitalization with a	30-day Neuropsychiatric emergency department visits or hospitalizations with	90-day Suicide, non-fatal self-harm, depression, all-cause mortality • Suicide was	<u>New psychiatric conditions</u> Inpatient or outpatient diagnosis of psychiatric	6-month GP visits for depression or self-harm identified using READ codes

	hospitalization with a primary discharge diagnosis from among the ICD-9 codes of the following conditions: • Drug-induced mental disorders (292.xx) • Transient mental disorders (293.xx) • Schizophrenia (295.xx) • Episodic and mood disorders (296.xx) • Delusional disorders (297.xx) • Other nonorganic psychoses (298.xx) • Anxiety disorders (300.xx) • Personality disorders (301.xx)	primary discharge diagnosis from among the ICD-9 codes of the following conditions: • Depression (296.3, 300.4, 311) • Schizophrenia (295.xx) • Bipolar disorder (296.xx) • Suicide attempt (E950-E959, E980-E982) • Psychosis excluding bipolar, depression and schizophrenia (292.xx ,293.xx, 294.xx, 297.xx, 298.xx, 299.xx)	a primary diagnosis of the following diagnoses identified using ICD-10 codes • Mood disorder • Psychotic disorder • Substance abuse • Neurotic, stress-related or somatoform disorder • Behavioral syndromes associated with physiological disturbances and physical factors, disorders of adult personality and behavior • unspecified mental disorder, confusion, hallucinations, • symptoms and signs involving emotional state and symptoms and signs involving appearance and behavior	defined as death from suicide in the ONS mortality database, using ICD-10 codes of intentional self-harm and undetermined deaths • Non-fatal self-harm was identified from hospital admission for self-harm from the HES data • Depression was defined as the initiation of antidepressant therapy	conditions that was not occurred during planned visits (i.e. follow-ups and referrals), the conditions included three categories • Psychosis (ICD-10: F20-F29) • Mood conditions (ICD-10:F30-F39) • Anxiety conditions (ICD-10:F40-F45, F48) <u>Suicidal behavior</u> Suicide and suicide attempt defined as emergency inpatients or outpatient hospital visits or death due to intentional self-harm (ICD-10: X60-X84)	

	• Posttraumatic stress disorder (PTSD) (309.81) • Depressive disorders (311.xx) • Suicide attempt (E950-E959). • Secondary definition: hospitalization with a neuropsychiatric condition in any discharge diagnoses, or, any neuropsychiatric diagnoses in outpatient records that occurred twice on different days					
Study population	New users (17+ years-old) of varenicline and NRT patch (no smoking cessation medicine for 6 months) during the study time frame	Primary: New users of varenicline or NRT (no smoking cessation medicine for 12 months) during the study	New users (18+ years-old) of varenicline and bupropion during the study time frame and matched 1:1 by propensity scores	Primary: New users (18+ years-old) of varenicline, bupropion, and NRT (no smoking cessation medicine	Primary (Within person comparison): Users (15+ years-old) of varenicline during the study time frame	New users (18-100 years-old) of varenicline, bupropion, and NRT (no smoking cessation medicine for 12 months)

	and matched 1:1 by propensity scores	timeframe and matched in a 1:1 ratio by propensity scores Secondary: Prevalent users of NRT who initiated varenicline or continue on NRT during the study timeframe, matched on 1:2 ratio by propensity score		for 12 months) during the study timeframe Secondary: First-time users of varenicline, bupropion and NRT during the study timeframe (no prior use of smoking cessation medicines in the database)	Secondary (Between person comparison): Overall population in Sweden who were over 15+ years-old during the study time frame	during the study timeframe, and did not use combination of the studied smoking cessation drugs during the 6 months after the first identified prescription
Follow-up	Follow-up continued for 30 days after this prescription with censoring for deployment, stationing overseas, loss of MHS eligibility, death or event, whichever came first	Follow-up continued for 30 days after this prescription with censoring for death, end of study periods or event, whichever came first	Follow-up started from the date when the first prescription was filled and censored at the respective date of death, disappearance, immigration, end of study (31 December 2010), switching to the other study drug or psychiatric adverse event, whichever occurred first	Follow-up continued for 90 days after first prescription with censoring for death, left the practice, primary event (suicide or non-fatal self-harm), end of study period, whichever came first	The observed time period was censored at outcome event, or end of study period or death, whichever happened first The time abroad, in prison or in hospital was also removed from the analyses	Follow-up continued for 6 months after first prescription with censoring for death, left the practice, primary event, end of study period, whichever came first
Main Analyses	Cox proportional-hazards regression	Cox proportional-hazards regression	Cox proportional-hazards regression	Cox proportional-hazards regression Propensity score matching and Cox proportional-hazards regression Instrumental variable analysis	Stratified cox proportional-hazards regression adjusted for age as a time-varying covariate	Cox proportional-hazards regression Propensity score matching and Cox proportional-hazards regression

Stratified analyses by psychiatric history	Yes Psychiatric history was defined as having the diagnostic codes that were used to identify the outcome events within a year prior to the initiation of varenicline or NRT	Yes Patients with a history of psychiatric illness were defined as having been hospitalized with an inpatient diagnosis for mental health disorders (identified by the same as the outcome events) within the 24 months prior to the initiation of varenicline or NRT Patients with no psychiatric history were defined as having no mental health diagnoses, as in inpatient and outpatient records, and no prescriptions for medications used to treat mental health disorders within the 24 months prior to the initiation of varenicline or NRT	Yes The history of psychiatric disorder was defined as any psychiatric diagnosis listed in "main outcomes", or antidepressant or antipsychotic drug use within the year before varenicline or bupropion initiation.	No	Yes Psychiatric history was defined as having the following diagnostic codes before November 1, 2006: ICD-9: 295-302, 307-316; ICD-10: F20-F48, F50-F69, F90-F98	No

*Non-fatal self-harm: suicide attempt that did not result in death

Table 2-1 Main study findings of the observational studies on smoking cessation products neuropsychiatric risk (statistically significant findings [p<0.05] are bolded)

Study	Outcome	Target drug (N event/total/IR)		Reference group (N event/total/IR)	Varenicline Fully-adjusted Hazard Ratio	Bupropion Fully-adjusted Hazard Ratio
		Varenicline	Bupropion			
Meyer et al. 2013	30-day NPS hospitalization (primary diagnosis)	16/ 10,814/ 18 per 1,000 person-years	-	NRT 14/ 10,814/ 16 per 1,000 person-years	1.14[a](0.56-2.34)	-
Meyer et al. 2013	30-day NPS hospitalization (any diagnosis)	34/ 10,710/ 39 per 1,000 person-years	-	NRT 43/ 10,710/ 49 per 1,000 person-years	0.79[a] (0.50-1.24)	-
Meyer et al. 2013	30-day NPS outpatient visits	234/ 10,710/ 269 per 1,000 person-years	-	NRT 327/ 10,710/ 378 per 1,000 person-years	**0.71[a] (0.60-0.84)**	-
VA study	30-day NPS hospitalization	16/ 14,131/ 16 per 1,000 person-years	-	NRT 21/ 14,131/ 21 per 1,000 person-years	0.76[a] (0.40-1.46)	-
VA study	30-day hospitalization for depression	8/ 14,131/ 12 per 1,000 person-years	-	NRT 7/ 14,131/ 7 per 1,000 person-years	1.14 (0.41-3.15)	-
VA study	30-day hospitalization for bipolar disorder	1/ 14,131/ 1 per 1,000 person-years	-	NRT 2/ 14,131/ 2 per 1,000 person-years	0.50 (0.05-5.51)	-
VA study	30-day hospitalization for schizophrenia	3/ 14,131/ 3 per 1,000 person-years	-	NRT 8/ 14,131/ 8 per 1,000 person-years	0.37 (0.10-1.41)	-
Pasternak et al. 2013	30-day NPS emergency room visit or hospitalization	39/ 17,935/ 27 per 1,000 person-years	-	Bupropion 46/ 17,935/ 31 per 1,000 person-years	0.85 (0.55-1.30)	
Molero et al. 2015	New NPS inpatient or outpatient visit during exposed period	3,213/ 69,757/ NA	-	Unexposed time NA/ NA/ NA	**1.18 (1.05-1.31)**	-
Kotz et al. 2015	180-day outpatient visits for depression	2,395/ 51,450/ 95.9 per 1,000 person-years	357/ 6,557/ 112.9 per 1,000 person-years	NRT 8,274/ 106,759/ 163.7 per 1,000 person-years	**0.66[b] (0.63-0.69)**	**0.75[b] (0.67-0.83)**
Thomas et al. 2013	90-day Suicide or non-fatal self-harm	19/ 31,260/ 3 per 1,000 person-years	4/ 6,741/ 2.5 per 1,000 person-years	NRT 69/ 81,545/ 4 per 1,000 person-years	0.88[c] (0.52-1.49)	0.83[c] (0.30-2.31)
Kotz et al. 2015	180-day Outpatient suicide or non-fatal self-harm	119/ 51,450/ 4.7 per 1,000 person-years	20/ 6,557/ 6.1 per 1,000 person-years	NRT 540/ 106,759/ 10.2 per 1,000 person-years	**0.56[b] (0.46-0.68)**	0.74[b] (0.48-1.16)
Molero et al. 2015	Suicide or non-fatal self-harm during exposed period	657/ 69,757/ NA	-	Unexposed time NA/ NA/ NA	1.00 (0.72-1.37)	

NRT: Nicotine replacement therapy; IR: Incidence Rate; NPS: neurologic/psychiatric; PS: propensity score; PTSD: post-traumatic stress disorder
Hazard Ratios calculated using Cox proportional hazards regression model
[a]Based on propensity score-matched cohort
[b]Adjusted for age; sex; socioeconomic status, relevant comorbidities from the Charlson Index (i.e. chronic obstructive pulmonary disease, diabetes, peptic ulcer disease, renal disease, rheumatological disease, cancer) and alcohol misuse, previous diagnosis of ischemic heart disease, cerebral infarction, heart failure, peripheral vascular disease, arrhythmia, depression and self-harm; previous suicide related event; previous smoking cessation therapy; psychiatric consultation; date of initial exposure to product, number of general practice visits per year, index of multiple deprivation, UK region.
[c]Adjusted for sex; age; previous psychiatric illness or consultation; previous use of psychotropic drugs such as hypnotics, antipsychotics and antidepressants; previous self-harm; socioeconomic position; major chronic illness; number of general practice consultations in the year before the prescription; exposure to the drug before or after 2008; year of first prescription; and previous use of a smoking cessation product.

Appendix III Calculation of the risk differences of study outcomes based on the hazard ratios of the Cox regression and propensity score matching analyses of the Thomas et al. study

Fatal and non-fatal self-harm (varenicline versus NRT)

1. **Calculate the crude outcome rates from event counts and follow-up person-time in population used for COX regression**

   NRT group =69/19196*1000 = 3.59 per 1,000 patient-year
   Varenicline group =19/7363*1000 = 2.58 per 1,000 patient-year

   in population used for PS matching

   NRT group =61/17026*1000 = 3.58 per 1,000 patient-year
   Varenicline group =19/7241*1000 = 2.62 per 1,000 patient-year

2. **Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching**

   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression

   NRT group =3.59 * 1 = 3.59
   Varenicline group =3.59 * (0.88) = 3.16

   -Adjusted outcome rates calculated based on the crude rate of varenicline or bupropion group and the HR of COX regression

   Varenicline group =2.58 * 1 = 2.58
   NRT group =2.58 / 0.88 = 2.93

   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching

   NRT group =3.58 * 1 = 3.58
   Varenicline group =3.58 * (0.87) = 3.11

   -Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching

   Varenicline group =2.62 * 1 = 2.62
   NRT group =2.62 / 0.87 = 3.01

3. **Calculate the adjusted risk differences between varenicline and NRT reflected by the risk ratio of COX regression or PS matching**

   -Adjusted risk differences based on risk ratio of COX regression=

   3.16-3.59= -0.43 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months) **OR**
   2.58-2.93= -0.35 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months)

   -Adjusted risk differences based on risk ratio of PS matching regression=

   3.11-3.58= -0.47 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months) **OR**
   2.62-3.01= -0.39 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months)

Mortality (varenicline versus NRT)

1. **Calculate the crude outcome rates from event counts and follow-up person-time in population used for COX regression**

   NRT group =292/19947*1000 = 14.64 per 1,000 patient-year
   Varenicline group =33/7575*1000 = 4.36 per 1,000 patient-year

   in population used for PS matching

   NRT group =260/17715*1000 = 14.68 per 1,000 patient-year
   Varenicline group =33/7447*1000 = 4.43 per 1,000 patient-year

2. **Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching**

   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression

   NRT group =14.64 * 1 = 14.64
   Varenicline group =14.64 * (0.44)= 6.44

   -Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of COX regression

   Varenicline group =4.36 * 1 = 4.36
   NRT group =4.36 / 0.44 = 9.90

   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching

   NRT group =14.68 * 1 = 14.68
   Varenicline group =14.68 * (0.37)= 5.43

   -Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching

   Varenicline group =4.43 * 1 = 4.43
   NRT group =4.43 / 0.37 = 11.97

3. **Calculate the adjusted risk differences between varenicline and NRT reflected by the risk ratio of COX regression or PS matching**

   -Adjusted risk differences based on risk ratio of COX regression=

   6.44-14.64= -8.2 (per 1,000 patient-year)= ~-2.1 (per 1,000 patients per 3 months) **OR**
   4.36-9.90= -5.5 (per 1,000 patient-year)= ~-1.4 (per 1,000 patients per 3 months)

   -Adjusted risk differences based on risk ratio of PS matching=

   5.43-14.68= -9.3 (per 1,000 patient-year)= ~-2.3 (per 1,000 patients per 3 months) **OR**
   4.36-11.78= -7.5(per 1,000 patient-year)= ~-1.9 (per 1,000 patients per 3 months

Fatal and non-fatal self-harm (bupropion versus NRT)

1. **Calculate the crude outcome rates from event counts and follow-up person-time in population used in COX regression**

   NRT group =69/19196*1000 = 3.59 per 1,000 patient-year
   Bupropion group =4/1662*1000 = 2.4 per 1,000 patient-year

   population used in PS matching

   NRT group =69/18806*1000 = 3.66 per 1,000 patient-year

Bupropion group =4/1570*1000 = 2.55 per 1,000 patient-year

2. **Calculate the <u>adjusted outcome rates</u> from the <u>crude outcome rates</u> and <u>risk ratios of COX regression or PS matching</u>**
   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression
   NRT group =3.59 * 1 = 3.59
   Bupropion group =3.59 * (0.83) = 2.98

   -Adjusted outcome rates calculated based on the crude rate of varenicline or bupropion group and the HR of COX regression
   Bupropion group =2.4 * 1 = 2.4
   NRT group =2.4/ 0.83 = 2.89

   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching
   NRT group =3.66 * 1 = 3.66
   Bupropion group =3.66 * (0.87) = 3.18

   -Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching
   Bupropion group =2.55 * 1 = 2.55
   NRT group =2.55 / 0.87 = 2.93

3. **Calculate the <u>adjusted risk differences</u> between varenicline and NRT reflected by the risk ratio of COX regression or PS matching**
   -Adjusted risk differences based on risk ratio of COX regression=
   2.98-3.59= -0.61 (per 1,000 patient-year)= ~-0.15 (per 1,000 patients <u>per 3 months</u>) **OR**
   2.4-2.89= -0.49 (per 1,000 patient-year)= ~-0.12 (per 1,000 patients <u>per 3 months</u>)
   -Adjusted risk differences based on risk ratio of PS matching regression=
   3.18-3.66= -0.48 (per 1,000 patient-year)= ~-0.12 (per 1,000 patients <u>per 3 months</u>) **OR**
   2.55-2.93= -0.36 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients <u>per 3 months</u>)

<u>Mortality (bupropion versus NRT)</u>

1. **Calculate the <u>crude outcome rates</u> from <u>event counts</u> and <u>follow-up person-time in population used for COX regression</u>**
   NRT group =292/19947*1000 = 14.64 per 1,000 patient-year
   Bupropion group =5/1665*1000 = 3 per 1,000 patient-year
   <u>in population used for PS matching</u>
   NRT group =292/19543*1000 = 14.94 per 1,000 patient-year
   Bupropion group =5/1612*1000 = 3.1 per 1,000 patient-year

2. **Calculate the <u>adjusted outcome rates</u> from the <u>crude outcome rates</u> and <u>risk ratios of COX regression or PS matching</u>**
   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression

NRT group =14.64 * 1 = 14.64
Bupropion group =14.64 * (0.39)= 5.71

-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of COX regression
Bupropion group =3 * 1 = 3
NRT group =3 / 0.39 = 7.69

-Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching
NRT group =14.94 * 1 = 14.94
Bupropion group =14.94 * (0.34)= 5.08

-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching
Bupropion group =3.1 * 1 = 3.1
NRT group =3.1 / 0.34 = 9.12

3. **Calculate the <u>adjusted risk differences</u> between varenicline and NRT reflected by the risk ratio of COX regression or PS matching**

-Adjusted risk differences based on risk ratio of COX regression=
5.71 -14.64= -8.93 (per 1,000 patient-year)= ~-2.2 (per 1,000 patients <u>per 3 months</u>) **OR**
3 -7.69= -4.69 (per 1,000 patient-year)= ~-1.2 (per 1,000 patients <u>per 3 months</u>)
-Adjusted risk differences based on risk ratio of PS matching=
5.08-14.94= -9.86 (per 1,000 patient-year)= ~-2.5 (per 1,000 patients <u>per 3 months</u>) **OR**
3.1 -9.12= -6.02(per 1,000 patient-year)= ~-1.5 (per 1,000 patients <u>per 3 months</u>

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/s/

CHIH-YING CHEN
10/12/2016

TAMRA E MEYER
11/07/2016

DAVID G MOENY
11/07/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 20, 2016

To: Ayanna Augustus, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 021928/S-040
OPDP labeling comments for CHANTIX® (varenicline) tablets
Labeling Review

OPDP has reviewed the proposed package insert (PI) for CHANTIX® (varenicline) tablets (Chantix) that was submitted for consult on March 16, 2016. Comments on the proposed PI are based on the version sent via email from Ayanna Augustus (RPM) on October 5, 2016 entitled “draft chantix label 09 26.doc”.

Comments regarding the PI are provided on the marked version below.

Please note that comments on the Medication Guide will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee’ Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
10/20/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 19, 2016
To:	Sharon Hertz, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Shenee' Toombs, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	CHANTIX (varenicline)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 021928
Supplement Number:	S-040
Applicant:	Pfizer, Inc.

On February 18, 2016, Pfizer, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 021928/S-040 for CHANTIX (varenicline) tablets. In this supplement the Applicant proposes changes to the CHANTIX (varenicline) tablets Prescribing Information based on clinical data from a post marketing requirement study (A3051123) evaluating the neuropsychiatric safety and efficacy of CHANTIX (varenicline) 1 mg BID and Zyban (bupropion hydrochloride) 150 mg BID for smoking cessation in subjects with and without a history of psychiatric disorders. The Applicant also proposes modifications to the approved Risk Evaluation and Mitigation Strategy (REMS), which includes proposed revisions to the Medication Guide (MG). Chantix (varenicline) Tablets was originally approved on May 10, 2006, and is indicated for use as an aid to smoking cessation treatment.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on March 17, 2016, and March 16, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed MG for CHANTIX (varenicline) tablets.

The REMS is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

1 MATERIAL REVIEWED

- Draft CHANTIX (varenicline) tablets MG received on February 18, 2016, further revised on August 22, 2016, and received by DMPP and OPDP on October 5, 2016.
- Draft CHANTIX (varenicline) tablets Prescribing Information (PI) received on February 18 2016, revised by the Review Division throughout the review cycle, and received by DMPP on October 5, 2016.
- Approved CHANTIX (varenicline) tablets labeling dated August 12, 2016.

2 REVIEW METHODS

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

3 CONCLUSIONS

The MG is acceptable with our recommended changes.

4 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
10/19/2016

LATOYA S TOOMBS
10/19/2016

BARBARA A FULLER
10/19/2016

LASHAWN M GRIFFITHS
10/20/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 11, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 21928/S-040
Product Name and Strength:	Chantix (varenicline tartrate) tablet, 0.5 mg and 1 mg
Submission Date:	February 18, 2016
Applicant/Sponsor Name:	Pfizer, Inc.
OSE RCM #:	2016-532
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Pfizer, Inc. submitted revised full prescribing information (FPI) as part of a prior approval supplement (S-040) for Chantix. The prior approval supplement provides for labeling revisions based on varenicline clinical data from the study, "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." Thus, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised FPI to determine if it is acceptable from a medication error perspective.

2 CONCLUSIONS

The revised FPI does not include revisions to the Dosage and Administration, Dosage Forms and Strengths, or How Supplied/Storage and Handling sections; therefore, we have no recommendations at this time.

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/s/

MILLIE C BRAHMBHATT
05/11/2016

BRENDA V BORDERS-HEMPHILL
05/11/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

RISK MITIGATION and RISK ASSESSMENT REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	November 10, 2016
Reviewers:	Sangeeta Tandon, PharmD, MPH Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Kim Lehrfeld, PharmD DRISK
Division Director:	Cynthia LaCivita, PharmD DRISK
Subject:	Review of REMS requirement release
Drug Name(s):	Chantix (varenicline)
Therapeutic class:	Smoking cessation agent
Dosage and Route:	tablet
Application Type/Number:	NDA 21928
Applicant/Sponsor:	Pfizer, Inc.
OSE RCM #:	2015-2499; 2015-2501

1 INTRODUCTION

The purpose of this review is to provide the Division of Risk Management's (DRISK) re-evaluation of the need for the risk evaluation and mitigation strategy (REMS) for Chantix (varenicline), NDA 21928.

The Agency has removed the boxed warning informing patients about the neuropsychiatric events that have been reported in patients taking Chantix. Given the available clinical data, stakeholder feedback and revised labeling for Chantix, there has not been an identified and emerging safety issue that may constitute a need for a REMS. The Agency has determined a REMS is no longer necessary to ensure the benefits of of Chantix outweigh the risks.

1.1 PRODUCT BACKGROUND

Chantix (varenicline) is a high-affinity selective partial agonist of the α4β2 nicotinic receptor. The α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine in animal models. Based on the activity at the nicotinic receptor, varenicline could be expected to mitigate withdrawal symptoms and reduce the reinforcing effects of nicotine, leading to efficacy in helping smokers stop smoking.

Chantix was originally approved on May 10, 2006 and is indicated for use as an aid to smoking cessation treatment. Chantix is available in 0.5 mg and 1 mg capsules. Chantix dosing should begin one week before the date set by the patient to stop smoking or alternatively, the patient can begin dosing, and then quit smoking between days 8 and 35 of treatment. The starting week dose is 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7. Continuing weeks dosing is 1 mg twice daily for a total of 12 weeks. An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence.

Chantix was originally approved on May 10, 2006 without a REMS. On May 16, 2008, in addition to the approval of a Medication Guide (MG) for Chantix, the Agency communicated to the Sponsor that under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), a REMS should be submitted. The Agency cited that "since Chantix was approved on May 10, 2006, as an aid to smoking cessation treatment, we have become aware of post-marketing reports of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions associated with Chantix. This information was not available when Chantix was granted marketing authorization as an aid to smoking cessation treatment. Therefore, we consider this information to be "new safety information" as defined in FDAAA."

The Chantix REMS was approved on October 19, 2009. The goal of the REMS was "to inform patients about the serious risks associated with the use of Chantix, including the potential risk of serious neuropsychiatric symptoms in patients taking Chantix". The REMS elements include a MG and a timetable for submission of assessments (18 months, 3- and 7-years after the approval of the REMS).

At the time the REMS was approved, the Agency also required a PMR to further evaluate this risk of neuropsychiatric adverse events.

On October 16, 2014, the Agency held a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss safety data from observational studies and a meta-analysis of randomized controlled clinical trials that were conducted since the original signal of serious neuropsychiatric adverse events with Chantix. The committee then discussed whether an action needed to be taken with regard to how the risk is described in product labeling. At this time, the majority of the committee agreed that more data are needed and recommended to retain the current boxed warning statements and reassess once the ongoing post-marketing randomized controlled trial designed to capture serious neuropsychiatric adverse events is complete.

1.2 REGULATORY HISTORY

August 22, 2016: The sponsor submitted prior approval supplement 40/ REMS Modification which proposes to remove the box warning of serious neuropsychiatric events based on clinical data and to modify the MG. This submission contained data from the PMR required clinical trial which the Sponsor proposed supported their proposal to remove the boxed warning.

2 MATERIALS REVIEWED

The following is a list of materials informing this review:

- Gonzalez, D., DRISK REMS Review, dated July 1, 2016.

3 DRISK EVALUATION OF THE CHANTIX REMS

3.1 CURRENTLY APPROVED REMS

The Chantix REMS was approved on October 19, 2009. The goal of the REMS was "to inform patients about the serious risks associated with the use of Chantix, including the potential risk of serious neuropsychiatric symptoms in patients taking Chantix". The REMS elements include a MG and a timetable for submission of assessments (18 months, 3- and 7-years after the approval of the REMS).

3.2 ANALYSIS OF SAFETY INFORMATION

The neuropsychiatric safety of Chantix was evaluated in a randomized, double-blind, active and placebo-controlled study that included patients with a history of psychiatric disorder (N=4074) and subjects without a history of psychiatric disorder (N=3984). In the non-psychiatric cohort, Chantix was not associated with an increased incidence of the composite endpoint comprised of the following neuropsychiatric adverse events: severe events of anxiety, depression, feeling abnormal, hostility, and moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic. In the psychiatric cohort, there were more events reported in each treatment group compared with the non-psychiatric cohort, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: Risk Differences (RDs) (95%CI) vs placebo were 1.59% (-0.42, 3.59) for Chantix, 1.78% (-0.24, 3.81) for bupropion and 0.37% (-1.53, 2.26) for transdermal nicotine.

On September 14, 2016, the Agency held a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss varenicline and the completed postmarketing-requirement randomized, placebo controlled trial of the neuropsychiatric effect of varenicline, bupropion, and nicotine replacement therapy, along with relevant published observational studies to determine whether the findings support changes to the product labeling. Of the 19 AC panel members, 10 voted to remove the boxed warning regarding serious neuropsychiatric adverse events from the Chantix labeling, 4 voted to modify wording to reflect the higher neuropsychiatric risk associated with those with a psychiatric history and 5 voted to keep the boxed warning.

4 DISCUSSION

The Agency has re-evaluated the risk of neuropsychiatric adverse events based on the data from the PMR study and has determined the seriousness of the risk is less than previously determined. Therefore, the risk will be removed from the boxed warning, but will remain in the warning and precaution section of the product label. Based on the new safety information, DRISK's recommendation is to remove the requirement for a MG only REMS. The REMS is no longer necessary to ensure the benefits outweigh the risks for Chantix. The MG will continue to inform patients about serious risk of neuropsychiatric adverse events associated with Chantix and will be retained as part of labeling.

5 CONCLUSION AND RECOMMENDATIONS

Based on the available safety data, DRISK believes that a REMS is no longer necessary to ensure that the benefits of Chantix outweigh the risks.

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/s/

SANGEETA N TANDON
11/10/2016

KIMBERLY LEHRFELD
11/10/2016
on behalf of Cynthia LaCivita

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-040

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021928/S-040

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Pfizer, Inc.
235 E. 42nd Street
New York, NY 10017

Attention: Lilya I. Donohew, PhD
Senior Director, Worldwide Regulatory Affairs

Dear Dr. Donohew:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021928

SUPPLEMENT NUMBER: S-040

PRODUCT NAME: Chantix (varenicline) Tablets; 0.5 mg and 1 mg

DATE OF SUBMISSION: February 18, 2016

DATE OF RECEIPT: February 18, 2016

This supplemental application proposes changes to the Package Insert based on clinical trial data from the study titled, "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" and modifications to the approved risk evaluation and mitigation strategy (REMS) for Chantix which includes revisions to the Medication Guide.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 18, 2016, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be December 18, 2016.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, PhD, RAC
Sr. Regulatory Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

AYANNA S AUGUSTUS
03/01/2016