CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s020

Trade Name: CHANTIX

Generic or Proper Name: varenicline tartrate

Sponsor: Pfizer, Inc.

Approval Date: 07/22/2011

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-020

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928/ S-019/S-020/S-021

SUPPLEMENTS APPROVAL

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

Attention: Lilya I. Donohew, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Donohew:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 22, 2010, received September 23, 2010, 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 acknowledge receipt of your amendments dated October 7, November 10 and 12, and December 6, 2010, January 6, February 2 and 25, March 4 (2), May, 6, 17, 20, and 24, June 6, 8, and 20, July 18 and 22, 2011, and your risk evaluation and mitigation strategy (REMS) assessment dated November 3, 2010.

These supplemental new drug applications propose a modification to the approved REMS and the following labeling revisions to the Package Insert:

S-019: the safety and efficacy of Chantix in smokers with cardiovascular disease (CVD), and revisions to the Medication Guide that include the possible side effects of Chantix

S-020: the safety and efficacy of Chantix in smokers with chronic obstructive pulmonary disease (COPD)

S-021: the safety and efficacy of Chantix when used according to an alternative set of directions for setting a quit date, and revisions to the Medication Guide that include new information on how to take Chantix

We have completed our review of these supplemental applications, as amended. They are 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 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 numbers and annual report dates.

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your applications, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Chantix was approved on May 10, 2006, we have become aware of the possibility of an increased risk of certain cardiovascular adverse events in patients taking Chantix (varenicline) based on the review of the randomized, double-blind, placebo-controlled clinical trial designed to assess the efficacy and safety of Chantix for smoking cessation in patients with stable, documented cardiovascular disease, and a review of the Integrated Summary of Safety. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of cardiovascular events.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1804 Conduct a meta-analysis evaluating the incidence of cardiovascular adverse events in Chantix-treated patients compared to control patients in Pfizer-sponsored randomized clinical trials. The study must include an analysis of all serious adverse events with adjudication and an analysis of all adverse events without adjudication.

The timetable you submitted on July 18, 2011, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	August 15, 2011
Final Protocol Submission:	October 1, 2011
Study Completion:	January 15, 2012
Final Report Submission:	February 15, 2012

Submit the protocol to your IND 058994, with a cross-reference letter to this NDA. Submit the final report to your NDA. Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of each submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Chantix was originally approved on October 19, 2009, and a REMS modification was approved on April 22, 2010. 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 revisions to the Medication Guide that include new information on how to take Chantix and the possible side effects of Chantix.

Your proposed modified REMS, submitted on June 6, 2011, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on October 19, 2009. There are no changes to the REMS assessment plan described in our October 19, 2009 letter.

We remind you that assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product.

Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021928 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021928
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021928
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the

revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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, Regulatory Health Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Package Insert
Medication Guide
REMS

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

/s/

BOB A RAPPAPORT
07/22/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

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
Initial U.S. Approval: 2006

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS
See full prescribing information for complete boxed warning.

- **Serious neuropsychiatric events have been reported in patients taking CHANTIX. (5.1 and 6.2)**
- **Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, 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 while taking CHANTIX or shortly after discontinuing CHANTIX. (5.1 and 6.2)**
- **Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (5.1 and 6.2)**

----------RECENT MAJOR CHANGES----------
Dosage and Administration
Alternative Instructions for Setting a Quit Date (2.1) 7/2011
Warnings and Precautions
Cardiovascular Events (5.4) 7/2011

----------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)
- Renal impairment: Reduce the dose in patients with severe renal impairment (estimated creatinine clearance <30 mL/min). (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----------
- **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. (5.2 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. (5.3 and 6.2)
- **Cardiovascular events:** In a trial of patients with stable cardiovascular disease (CVD) certain cardiovascular events were reported more frequently in patients treated with CHANTIX. Patients with CVD should be instructed to notify their health care providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction. (5.4 and 6.1)
- **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. (5.5)
- **Nausea:** Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.6)

----------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: Pharmacokinetics or pharmacodynamics of certain drugs may be altered due to smoking cessation with CHANTIX, necessitating dose adjustment. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- Pediatric Use: Safety and effectiveness not established (8.4)
- Renal Impairment: Dosage adjustment is required for severe renal impairment. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, 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. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. ***[see Warnings and Precautions (5.1) and Adverse Reactions 6.2)]***

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 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.

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt 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 <30 mL/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 a day. 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) and 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 Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX *[see Boxed Warning and Adverse Reactions (6.2)]*. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the

symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

5.2 Angioedema and Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX *[see Adverse Reactions (6.2), and Patient Counseling Information (17.10)]*. 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.

5.3 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.

5.4 Cardiovascular Events

In a controlled clinical trial of CHANTIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, certain cardiovascular events were reported more frequently in patients treated with CHANTIX than in patients treated with placebo *[see Clinical Trials Experience (6.1)]*. These included treatment-emergent events (on-treatment or 30 days after treatment) of angina pectoris (13 patients in the varenicline arm vs. 7 in the placebo arm), and the serious cardiovascular events of nonfatal MI (4 vs. 1) and nonfatal stroke (2 vs. 0). During non-treatment follow up to 52 weeks, serious cardiovascular events included nonfatal myocardial infarction (3 vs. 2), need for coronary revascularization (7 vs. 2), hospitalization for angina pectoris (6 vs. 4), transient ischemic attack (1 vs. 0), new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (4 vs. 2). Serious cardiovascular events occurring over the 52 weeks of the study (treatment emergent and non-treatment emergent) were adjudicated by an independent blinded committee. 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 health care 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.

5.5 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.

5.6 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 symptoms and suicidality *[see Boxed Warning and Warnings and Precautions (5.1)*
- Angioedema and hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- Serious skin reactions *[see Warnings and Precautions (5.3)]*
- Accidental injury *[see Warnings and Precautions (5.5)]*

In the placebo-controlled 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 (5.6)]*.

Table 1 shows the adverse events for CHANTIX and placebo in the 12-week fixed dose 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 1: 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 Nutrit. 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 trials was similar to those described in Table 1, 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 clinical trials. 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, arrhythmia, bradycardia, myocardial infarction, palpitations, tachycardia, ventricular extrasystoles. *Rare* acute coronary syndrome, atrial fibrillation, cardiac flutter, cor pulmonale, coronary artery disease.

Ear and Labyrinth Disorders. *Infrequent* tinnitus, vertigo. *Rare* deafness, Meniere's disease.

Endocrine Disorders. *Infrequent* thyroid gland disorders.

Eye Disorders. *Infrequent* conjunctivitis, dry eye, eye irritation, eye pain, vision blurred, visual disturbance. *Rare* acquired night blindness, blindness transient, cataract subcapsular, ocular vascular disorder, photophobia, vitreous floaters.

Gastrointestinal Disorders. *Frequent* diarrhea. *Infrequent* dysphagia, enterocolitis, eructation, esophagitis, gastritis, gastrointestinal hemorrhage, mouth ulceration. *Rare* gastric ulcer, intestinal obstruction, pancreatitis acute.

General Disorders and Administration Site Conditions. *Frequent* chest pain, edema, influenza-like illness. *Infrequent* chest discomfort, chills, pyrexia.

Hepatobiliary Disorders. *Infrequent* gall bladder disorder.

Investigations. *Frequent* liver function test abnormal, weight increased. *Infrequent* electrocardiogram abnormal, muscle enzyme increased, urine analysis abnormal.

Metabolism and Nutrition Disorders. *Infrequent* diabetes mellitus, hyperlipidemia, hypokalemia. *Rare* hypoglycemia.

Musculoskeletal and Connective Tissue Disorders. *Frequent*: arthralgia, back pain, muscle cramp, musculoskeletal pain, myalgia. *Infrequent* arthritis, osteoporosis. *Rare* myositis.

Nervous System Disorders. *Frequent* disturbance in attention, dizziness, sensory disturbance. *Infrequent* amnesia, migraine, parosmia, psychomotor hyperactivity, restless legs syndrome, syncope, tremor. *Rare* balance disorder, cerebrovascular accident, convulsion, dysarthria, facial palsy, mental impairment, multiple sclerosis, nystagmus, psychomotor skills impaired, transient ischemic attack, visual field defect.

Psychiatric Disorders. *Infrequent* disorientation, dissociation, libido decreased, mood swings, thinking abnormal. *Rare* bradyphrenia, euphoric mood.

Renal and Urinary Disorders. *Frequent* polyuria. *Infrequent* nephrolithiasis, nocturia, urethral syndrome, urine abnormality. *Rare* renal failure acute, urinary retention.

Reproductive System and Breast Disorders. *Rare* sexual dysfunction. *Frequent* menstrual disorder. *Infrequent* erectile dysfunction.

Respiratory, Thoracic and Mediastinal Disorders. *Frequent* epistaxis, respiratory disorders. *Infrequent* asthma. *Rare* pleurisy, pulmonary embolism.

Skin and Subcutaneous Tissue Disorders. *Frequent* hyperhidrosis. *Infrequent* acne, dry skin, eczema, erythema, psoriasis, urticaria. *Rare* photosensitivity reaction.

Vascular Disorders. *Frequent* hot flush. *Infrequent* thrombosis.

CHANTIX has also been studied in a trial conducted in patients with stable cardiovascular disease, a trial conducted in patients with chronic obstructive pulmonary disease (COPD) and 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").

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 (1.1% 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.

Adverse events in the trial of patients with COPD and in the alternative quit date instruction trial were quantitatively and qualitatively similar to those observed in premarketing studies.

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 Boxed Warning, Warnings and Precautions (5.1)]*. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking.

There have been reports of hypersensitivity reactions, including angioedema *[see Warnings and Precautions (5.2)]*.

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX *[see Warnings and Precautions (5.3)]*.

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.

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

Pregnancy Category C.

There are no adequate and well-controlled studies of CHANTIX use in pregnant women. In animal studies, CHANTIX caused decreased fetal weights, increased auditory startle response, and decreased fertility in offspring. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive and developmental toxicity studies, pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. These exposures were 36 (rats) and 50 (rabbits) times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 1 mg twice daily. While no fetal structural abnormalities occurred in either species, reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD based on AUC). Fetal weight reduction did not occur at animal 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. These resulted in exposures up to 36 times the human exposure (based on AUC) at the MRHD of 1 mg twice daily. Decreased fertility and increased auditory startle response occurred in offspring.

8.3 Nursing Mothers

It is not known whether CHANTIX is excreted in human milk. In animal studies varenicline was excreted in milk of lactating animals. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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 yrs) 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) and 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 1000 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

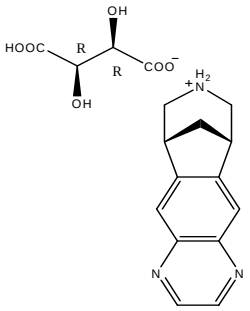
In case of overdose, standard supportive measures should be instituted as required.

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 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 1mg 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, >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.

12.3 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. *[see Dosage and Administration (2.2), and Use in Specific Populations (8.6)]*. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis *[see Overdosage (10)]*.

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 yrs) for 7 consecutive days was similar to that of younger subjects.

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. When 22 pediatric patients aged 12 to 17 years (inclusive) received a single 0.5 mg or 1 mg dose of varenicline, the pharmacokinetics of varenicline were approximately dose-proportional between the 0.5 mg and 1 mg doses. Systemic exposure, as assessed by AUC (0-∞), and renal clearance of varenicline were comparable to those of an adult population.

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

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 [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.

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 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 maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily 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 maximum recommended human daily exposure based on AUC at 1 mg twice daily). 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 (36 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily). 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 maximum recommended human daily 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.

Three additional studies were conducted in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease *[see Clinical Studies (14.4)]*, and in patients instructed to select their quit date within days 8 and 35 of treatment *[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

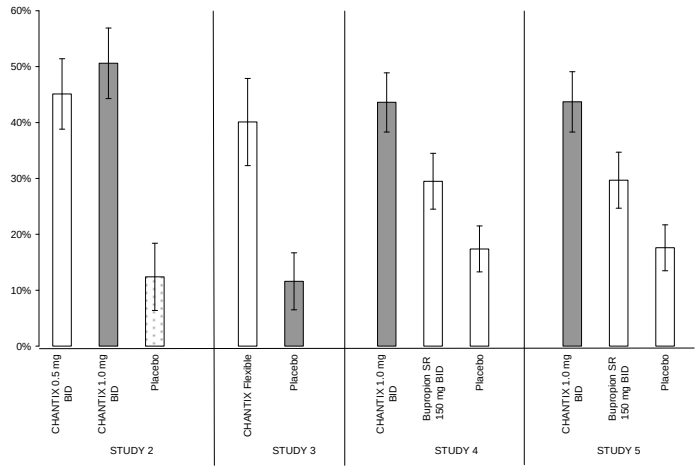


Table 2: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	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 3).

Figure 2: Continuous Abstinence, Weeks 9 through 52

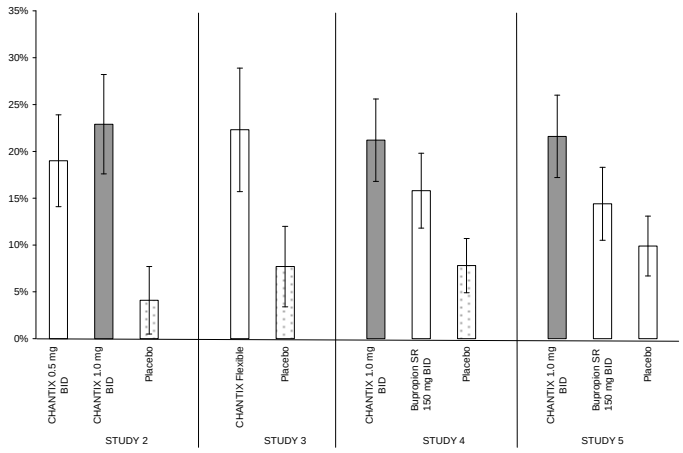


Table 3: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies

	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%)

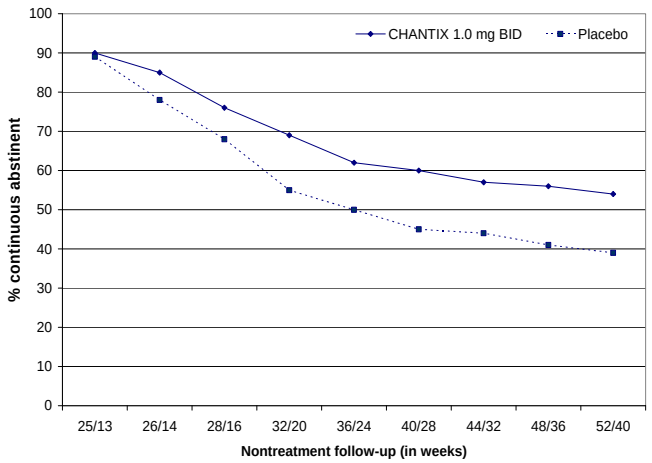
BID = twice daily

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 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 ≥ 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 4: 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

14.5 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%).

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 Month PAK (First month of therapy): Pack includes 1 card of 0.5 mg x 11 tablets and 3 cards of 1 mg x 14 tablets	NDC 0069-0471-97
	Continuing Month PAK (Continuing months of therapy): Pack includes 4 cards of 1 mg x 14 tablets	NDC 0069-0469-97
	Starting Month Box: 0.5 mg x 11 tablets and 1 mg x 42 tablets	NDC 0069-0471-02
	Continuing Month Box : 1 mg x 56 tablets	NDC 0069-0469-12
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 Medication Guide

17.1 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)]*.

17.2 How To Take

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

17.3 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)]*.

17.4 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)]*.

17.5 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)]*.

17.6 Counseling and Support

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

17.7 Neuropsychiatric Symptoms

Inform patients that some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. If patients develop agitation, hostility, depressed mood, or changes in behavior

or thinking that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to discontinue CHANTIX and report these symptoms to their healthcare provider immediately *[see Boxed Warning, Warnings and Precautions (5.1), Adverse Reactions (6.2)]*.

17.8 History of Psychiatric Illness

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

17.9 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.

17.10 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 (5.2), and Adverse Reactions (6.2)]*.

17.11 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 (5.3), and Adverse Reactions (6.2)]*.

17.12 Patients with Cardiovascular Disease

Patients with cardiovascular disease should be instructed to notify their health care providers of symptoms of new or worsening cardiovascular events and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction. *[see Warnings and Precautions (5.4), and Adverse Reactions (6.1)]*.

17.13 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 (5.5)]*.

17.14 Vivid, Unusual, or Strange Dreams

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

17.15 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 *[see Use in Specific Populations (8.1 and 8.3)]*.

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LAB- 0327- 14.0

MEDICATION GUIDE

CHANTIX® (CHANT-iks)

(varenicline) Tablets

Read the Medication Guide that comes with CHANTIX before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your condition or treatment.

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

Some people have had changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions while using CHANTIX to help them quit smoking. Some people had these symptoms when they began taking CHANTIX, and others developed them after several weeks of treatment, or after stopping CHANTIX.

If you, your family, or caregiver notice agitation, hostility, depression or changes in behavior or thinking that are not typical for you, or you develop any of the following symptoms, stop taking CHANTIX and call your doctor right away:

- thoughts about suicide or dying, or attempts to commit suicide
- new or worse depression, anxiety, or panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused

- other unusual changes in behavior or mood

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, and increased appetite or 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.

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

See "**What are the possible side effects of CHANTIX?**"

Some people can have allergic reactions to CHANTIX. Some of these allergic reactions can be life-threatening and include: swelling of the face, mouth (tongue, lips), and throat that can cause trouble breathing. If you have these symptoms, stop taking CHANTIX and get medical attention right away.

Some people can have serious skin reactions while taking CHANTIX. These can include rash, swelling, redness, and peeling of the skin. Some of these reactions can become life-threatening. If you have a rash with peeling skin or blisters in your mouth, stop taking CHANTIX and see your doctor right away.

What is CHANTIX?

CHANTIX is a prescription medicine to help adults 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.

CHANTIX is not recommended for people under 18 years of age.

CHANTIX has not been studied with other treatments for stopping smoking.

Who should not take CHANTIX?

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

- swelling of the face, mouth, and throat that can cause trouble breathing.
- rash, swelling, redness, and peeling of the skin.

What should I tell my doctor before taking CHANTIX?

Before you take CHANTIX, tell your doctor if you:

- have ever had depression or other mental health problems. See "What is the most important information I should know about CHANTIX?"
- have kidney problems or get kidney dialysis. Your doctor may prescribe a lower dose of CHANTIX for you.
- Have heart or blood vessel problems
- have any allergies. See the end of this Medication Guide for a complete list of ingredients in CHANTIX.
- have any other medical conditions
- are pregnant or plan to become pregnant. Ask your doctor for help to stop smoking before you get pregnant because smoking during pregnancy puts you and your baby at risk for problems during pregnancy. CHANTIX has not been studied in pregnant women. It is not known if CHANTIX will harm your unborn baby.

- are breastfeeding. CHANTIX has not been studied in breastfeeding women. It is not known if CHANTIX passes into breast milk. You and your doctor should talk about the best way to feed your baby if you take CHANTIX.

Tell your doctor about all your other medicines, including prescription and nonprescription medicines, vitamins and herbal supplements. Especially, tell your doctor if you take:

- insulin
- asthma medicines
- blood thinners

When you stop smoking, there may be a change in how these and other medicines work for you.

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

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

How should I take CHANTIX?

- There are 2 ways that you can use CHANTIX to help you quit smoking. Talk to your doctor about the following 2 ways to use CHANTIX:

    1. Choose a **quit date** when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your **quit date**. This lets CHANTIX build up in your body. You can keep smoking during this time. 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.

    OR

    2. You can also start taking CHANTIX before you choose a **quit date**. Pick a date to quit smoking that is between days 8 and 35 of treatment. 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.

- Take CHANTIX exactly as prescribed by your doctor.

    1. Take CHANTIX after eating and with a full glass (8 ounces) of water.
    2. Most people will take CHANTIX for up to 12 weeks. If you have completely quit smoking by 12 weeks, your doctor may prescribe CHANTIX for another 12 weeks to help you stay cigarette-free.

- 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.

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

- This dosing schedule may not be right for everyone. Talk to your doctor if you are having side effects such as nausea, strange dreams, or sleep problems. Your doctor may want to reduce your dose.

- If you miss a dose of CHANTIX, take it as soon as you remember. If it is close to the time for your next dose, wait. Just take your next dose at your regular dose.

What should I avoid while taking CHANTIX?

Use caution driving or operating machinery until you know how CHANTIX may affect you. Some people who use CHANTIX may feel sleepy, dizzy, or have trouble concentrating, that can make it hard to drive or perform other activities safely.

What are the possible side effects of CHANTIX?

Serious side effects of CHANTIX may include:

- **New or worse mental health problems, which have been reported in some patients.** See "What is the most important information I should know about CHANTIX?"
- **New or worse heart or blood vessel (cardiovascular) problems** in people who already have cardiovascular problems. Tell your doctor 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:

  - chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
  - pain or discomfort in one or both arms, back, neck, jaw or stomach
  - shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort
- The most common side effects of CHANTIX include:
    - nausea
    - sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
    - constipation
    - gas
    - vomiting

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

These are not all the side effects of CHANTIX. Ask your doctor 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, 59 to 86°F (15 to 30°C).
- Safely dispose of CHANTIX that is out of date or no longer needed.
- **Keep CHANTIX and all medicines out of the reach of children.**

General information about 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.**

This Medication Guide summarizes the most important information about CHANTIX. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CHANTIX that is written for healthcare professionals.

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

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 (for both 0.5 mg and 1 mg)

LAB-0328-10.0

Revised July 2011

This Medication Guide has been approved by the U.S. Food and Drug Administration.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

REMS

NDA 21-928
Chantix® (Varenicline) Tablets
Nicotinic Receptor Partial Agonist
Aid to Smoking Cessation

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
212-733-23-23

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is 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.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Chantix (varenicline) prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

Pfizer will submit REMS Assessments to FDA 18 months, 3 years, and 7 years following the initial REMS approval of October 19, 2009. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Pfizer Inc will submit each assessment so that it will be received by the FDA on or before the due date.

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

/s/

BOB A RAPPAPORT
07/22/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA , ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

Date	July 22, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA # **Supplement #**	21-928 S-019, S-020, S-021
Applicant Name	Pfizer
Date of Submission	September 22, 2010
PDUFA Goal Date	July 22, 2011
Proprietary Name / **Established (USAN) Name**	Chantix Varenicline tartrate
Dosage Forms / Strength	0.5 mg and 1 mg immediate-release tablets
Proposed Indication	Aid to smoking cessation (approved) Supplements propose to add new language to clinical studies section without change to indication
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Rachel Skeete, M.D., M.H.S.; Pamela Horn, M.D.
CDTL	Celia J. Winchell, M.D.
Statistical Review	Kate Meaker, M.S.; Dionne Price, Ph.D.
DDMAC	Kathleen Klemm; L. Shenee' Tombs, Pharm. D.
Project Management	Ayanna Augustus, Ph.D., Parinda Jani
OSE/DRISK	Mary Dempsey, B.S.; Sharon R. Mills, B.S.N., R.N. C.C.R.P.; Claudia B. Karwoski, Pharm.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DRISK=Division of Risk Management

1. Introduction

The original application for Chantix for the indication of "…as an aid to smoking cessation" was approved in May of 2006. Pfizer has submitted three efficacy supplements intended to support the addition of new language to the Clinical Studies section of the product labeling. The supplements each report on the results of a single clinical trial. Two of the trials were in specific patient populations, one in subjects with Chronic Obstructive Pulmonary Disease (COPD) and one in subjects with Cardiovascular Disease (CVD). These two patient populations had been, for the most part, poorly represented in the clinical studies submitted in the original application for Chantix. The third trial assessed an alternative set of instructions for setting a quit date, studied in the same patient population as the original trials. In addition, an updated Integrated Summary of Safety (ISS) was submitted at the Division's request, to look for new safety signals and to assess safety signals seen in the post-marketing period.

2. Background

The initial application contained 30 completed (24 Phase 1 and 8 Phase 2/3) and 3 ongoing clinical studies. The following summary of the efficacy and safety data from that application has been reproduced from page 4 of Dr. Winchell's review:

> 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…
>
> In the original NDA submission, the overall exposure to varenicline was adequate to characterize the safety profile and met ICH requirements. 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.

A number of safety concerns have been specifically addressed in these applications and in the clinical reviews. During the review of the original application, a concern regarding cardiovascular events was raised by the primary reviewer, Dr. Josefberg. However, additional review by Dr. Winchell did not establish a clear safety signal. The pre-marketing dataset was coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology, but few Standardized MedDRA Queries (SMQ) were available at that time. Therefore, the primary reviewer, using an ad-hoc review strategy, found 18 "Cardiac SAE Cases" in the Chantix arm that did not have a clear alternative explanation, in a population of 3940 exposed patients (0.43%) vs. 4 out of 1209 placebo-treated patients (0.33%). Corrected for exposure time, this represented 1.90 cases per 100 patient-exposure-years (PEY) in Chantix vs. 1.63 per 100 PEY in placebo. However, an independent search and adjudication by Dr. Winchell, with my assistance, and using a different post-treatment window, identified 17 possibly-related cases (0.43%, 1.79 per 100 PEY) in the Chantix arm and 5 (0.41%, 1.96 per 100 PEY) in the placebo arm. Because of the lack of a clear signal between these two analyses, the team did not conclude that Chantix increased cardiac risk and did not include labeling language identifying cardiac risk.

Based on post-marketing reporting, certain safety signals are under review by the Division and by our colleagues in the Office of Surveillance and Epidemiology (OSE). These signals have included neuropsychiatric events, cardiovascular events, cerebrovascular events, accidental injuries, serious skin reactions and allergic phenomena, blindness and visual impairment, and convulsions. Some of these events were noted by external drug safety monitoring organizations and reported to the Agency; and some neuropsychiatric events, in particular aggressive behavior, depression and suicide, were reported in the lay press. A recent review of post-marketing AERS reports by OSE identified cases of cardiovascular and cerebrovascular events that appeared to be associated with Chantix use and language was added to the post-marketing section of the product labeling describing them. Other labeling changes have included the addition of language resulting from Pfizer's own identification of reports of difficulties with driving and operating machinery, confirmed by OSE's review of cases of accidental injuries, and the addition of language describing events of serious skin reactions and allergic phenomena identified in another OSE review. The OSE review of blindness and visual impairment did not identify clear cases that would warrant changes to the labeling. A formal OSE review of cases of seizure has not been performed. Convulsions are already included in the product labeling and review of the pooled clinical trial data and new clinical trial data during this review cycle did not raise new concerns or warrant changes to labeling.

The following summary of post-marketing evaluations and actions related to the neuropsychiatric signal has been reproduced from page 5 of Dr. Winchell's review:

> Approximately one year after the approval of Chantix, the FDA learned that the European Medications Authority had identified a signal for suicidal behavior in their pharmacovigilance

related to Chantix. Further information submitted by Pfizer, as well as press and consumer reports, identified a number of cases of patients reporting a variety of unusual experiences, very commonly in the setting of initiating or up-titrating varenicline. The case reports often involved ill-defined neuropsychiatric symptoms encompassing affective, cognitive, perceptual, and behavioral domains, many of which do not fall readily into a known diagnostic category and are not consistently coded to any particular set of MedDRA terms. Most concerning were reports of depression, suicide attempts, suicide, aggressive behavior, and psychosis. However, there are difficulties teasing out the role of varenicline from the role of pre-existing psychiatric illness, the role of nicotine withdrawal, or other explanations. Therefore, although the labeling has been amended to include a boxed warning regarding neuropsychiatric symptoms and a Risk Evaluation and Mitigation Strategy (REMS) with MedGuide addressing this risk, the causal relationship remains unclear and a large post-marketing study is being conducted by Pfizer (in cooperation with Glaxo SmithKline, to evaluate similar events reported in association with Zyban). This study is to enroll patients both with and without psychiatric diagnoses, and to prospectively solicit reports of a range of neuropsychiatric events of interest.

Notably, the database of placebo-controlled trials did not point to a drug-related psychiatric phenomenon at the time of the original NDA, although it is noted that both the original studies and the three studies submitted in these supplements did not enroll patients with current psychiatric conditions. A prescription-event monitoring study in the UK[1], an "experimental medicine" study conducted by Pfizer, observing treatment-emergent psychiatric symptoms in patients using varenicline in an observed setting[2], a cohort study using the UK General Practice Research Database[3], and preliminary results from a recently-completed study of electronic medical records databases at the VA also have not linked Chantix to a higher risk of psychiatric symptoms, suicide or psychiatric hospitalization.

The post-marketing study of neuropsychiatric events is scheduled to begin enrolling subjects in February of 2012, with a final study report due to the Agency in 2017. Based on the review team's analysis of the CVD study submitted in Supplement 019 (see Section 8 below), we have requested that Pfizer add CVD endpoints to the neuropsychiatric study and discussions regarding the methodology to incorporate those endpoints are ongoing. In addition, Pfizer will be required to perform a meta-analysis of all available data to determine the cardiovascular risk-benefit profile in Chantix in patients with and without cardiovascular disease. This meta-analysis will take advantage of advances in the safety review of MedDRA-coded data such as standardized search strategies which will help us identify all possible cases, and will evaluate different post-treatment time windows. The study results from this meta-analysis will be available within the next year, thus allowing us to make a preliminary assessment of the cardiovascular risk-benefit while awaiting the results of the outcome study.

3. CMC

No new CMC data was submitted in these applications.

[1] Drug Safety 2009; 32 (6): 499-507
[2] Biol Psychiatry 2011;69:1075–1082
[3] BMJ 2009;339:b3805

4. Nonclinical Pharmacology/Toxicology

No new pharmacology or toxicology data was submitted in these applications.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics data was submitted in these applications.

6. Clinical Microbiology

No clinical microbiology data were necessary for these applications.

7. Clinical/Statistical-Efficacy

I will briefly summarize the efficacy data. The reader is referred to Dr. Winchell's review and the reviews by Dr. Skeete, Dr. Horn and Ms. Meaker for additional detail.

Supplement 019

Study A3051049 (CVD Study) was a 12-week, randomized, double-blind, placebo-controlled, multicenter trial that compared Chantix vs. placebo for smoking cessation by end of treatment and continuous abstinence for 40 weeks after treatment in subjects with CVD. Eligible subjects were required to have documented, stable CVD and were 35 to 75 years of age. The following examples of eligible and ineligible CVD diagnoses have been reproduced from pages 10 and 11 of Dr. Winchell's review:

- ***Coronary Artery Disease*** demonstrated by:
  - Angina pectoris and evidence of abnormal myocardial perfusion or myocardial ischemia by stress testing or myocardial perfusion imaging or angina pectoris with positive coronary angiography. Test results or physician report had to be provided.
  - Myocardial infarction documented by hospital summaries, procedure reports, laboratory reports, etc.
  - Coronary revascularization documented by physician or procedure report.
- ***Peripheral Vascular Disease*** demonstrated by:
  - Stable peripheral vascular disease (arterial) documented by history and physical exam (ankle-brachial index-ABI <0.9 but >0.5), ultrasonography, arteriography. Subjects with asymptomatic carotid disease documented by imaging studies may have been included.
  - Peripheral revascularization documented by procedure report.
- ***Cerebrovascular Disease***
  - For example, TIA or stroke without significant neurological impairment documented by neurological evaluation, procedure report.

Patients were not eligible if they had

- ***Congestive Heart Failure of New York Heart Association Class III or IV***
- ***Unstable cardiovascular disease or a cardiovascular event in the prior two months***. Examples included

- coronary artery bypass graft (CABG)
- percutaneous transluminal coronary angioplasty (PTCA),
- severe or unstable angina
- serious (life threatening) arrhythmia
- clinically significant cardiac conduction abnormalities (>10 AV block)

- ***Peripheral Vascular Disease resulting in amputation or with ankle-brachial index ≤0.5***
- ***Uncontrolled hypertension or systolic BP > 160 or diastolic BP > 95*** *at Screening or Baseline visit*

The primary endpoint was the 4-week continuous quit rate (CQR) from Weeks 9 through 12, based on reported cigarette or other nicotine product use, along with confirmed exhaled CO less than or equal to 10 ppm. Two secondary endpoints that were intended to support label claims were continuous abstinence from end of treatment through Week 52 and long-term quit rate, defined as subjects who were CO confirmed responders for Weeks 9 through 12 and who reported no more than 6 days of smoking during the 40-week post-treatment period. A step-down procedure was used for the analysis of the primary and secondary endpoints in order to preserve the Type I error rate of 0.05. The following table, reproduced from page 18 of Dr. Winchell's review, summarizes the results of this study:

Reviewer's Efficacy Analysis Results (Study 49)

Exclude 3 subjects with no CVD	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
	N=350	N=350		
Continuous Quit Rate Weeks 9-12	165 47% (42%, 52%)	50 14% (11%, 18%)	6.02 (4.11, 8.82)	<.0001
Continuous Abstinence Weeks 9-52	68 19% (15%, 24%)	26 7% (5%, 10%)	3.11 (1.91, 5.05)	<.0001
Long Term Quit Rate: Week 52	78 22% (18%, 27%)	34 10% (7%, 13%)	2.76 (1.77, 4.29)	<.0001

Source: SAS datasets

Supplement 020

Study A3051054 (COPD Study) was a 12-week, randomized, double-blind, placebo-controlled, multicenter trial that compared Chantix vs. placebo for smoking cessation by end of treatment and continuous abstinence for 40 weeks after treatment in subjects with COPD. The primary endpoint was the 4-week CQR from Weeks 9 through 12, based on reported cigarette or other nicotine product use, along with confirmed exhaled CO less than or equal to 10 ppm. Two secondary endpoints that were intended to support label claims were continuous abstinence from end of treatment through Week 52 and long-term quit rate, defined as subjects who were CO confirmed responders for Weeks 9 through 12 and who reported no more than 6 days of smoking during the 40-week post-treatment period. A step-down procedure was used for the analysis of the primary and secondary

endpoints in order to preserve the Type I error rate of 0.05. The following table summarizes the results of this study[4]:

Reviewer's Efficacy Analysis Results (Study 54)

Exclude 39 subjects not meeting criteria for COPD	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
	N=223	N=237		
Continuous Quit Rate Weeks 9-12	91 41% (34%, 47%)	22 9% (6%, 13%)	7.38 (4.35, 12.54)	<.0001
Continuous Abstinence Weeks 9-52	42 19% (14%, 24%)	14 6% (3%, 9%)	3.94 (2.06, 7.53)	<.0001
Long Term Quit Rate: Week 52	47 21% (16%, 26%)	17 7% (4%, 10%)	3.63 (2.00, 6.62)	<.0001

Source: SAS datasets

Supplement 021

Study A3051095 (referred to as "Flexible Quit Date" or "FQD Study" in the primary and CDTL reviews, and "Alternative Instructions for Setting a Quit Date" in product labeling) was a 12-week, randomized, double-blind, placebo-controlled, multicenter trial that compared Chantix vs. placebo for smoking cessation by end of treatment and continuous abstinence for 12 weeks after treatment. The approved labeling was based upon studies in which the subjects were to choose a target quit date (TQD) and then initiate treatment with Chantix one week before that TQD. In this study, the patients were instructed to begin taking Chantix before setting a TQD, and then set a TQD between days 8 and 35 of treatment. This study was intended to support the inclusion in the label of an alternative set of directions for choosing a quit date.

The primary endpoint was the 4-week CQR from Weeks 9 through 12, based on reported cigarette or other nicotine product use, along with confirmed exhaled CO less than or equal to 10 ppm. One secondary endpoint that was intended to support a label claim was continuous abstinence from end of treatment through Week 24. A step-down procedure was used for the analysis of the primary and secondary endpoints in order to preserve the Type I error rate of 0.05. The following table, reproduced from page 34 of Dr. Winchell's review, summarizes the results of this study:

[4] After the primary review and CDTL were filed, it was noted that two patients who were excluded from both the numerator and denominator due to protocol violations should instead have been included in the denominator and re-adjudicated as non-responders. The numbers in this table have been corrected to reflect this change.

Reviewer's Efficacy Analysis Results (Study 95)

Adjustments to mITT Dataset		Varenicline	Placebo	Odds Ratio (95% CI)	p-value
Applicant's mITT dataset		486	165		
Exclude subjects who quit prior to start of treatment		-3	0		
Include subjects who were randomized and non-responder		+5	+1		
		N=488	N=166		
Continuous Quit Rate Weeks 9-12	n % (95% CI)	259 53% (49%, 58%)	32 19% (13%, 25%)	5.97 (3.77, 9.46)	<.0001
Continuous Abstinence Weeks 9-24	n % (95% CI)	169 35% (30%, 39%)	21 13% (8%, 18%)	4.43 (2.61, 7.51)	<.0001
Time to First Quit Attempt (Days)	# uncensored % uncensored Median Days	389/483 (81%) 17	121/165 (73%) 24	na	na

Source: SAS datasets

I concur with the clinical and statistical review teams that these three clinical trials have provided adequate data to support inclusion of the results in the Clinical Studies section of the product label.

8. Safety

The following table, reproduced from page 39 of Dr. Winchell's review, summarizes the exposure in the pooled studies explored in the updated ISS:

Table 1: Exposure in Pooled Studies

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N=1983**	**Pbo N=1209**	**Var N=4483**	**Pbo N=2892**	**Var N=353**	**Pbo N=350**	**Var N=248**	**Pbo N=251**	**Var N=486**	**Pbo N=165**
Duration of Treatment (Days)[a]	number of subjects									
Unknown	13	10	13	10	0	0	0	0	0	0
1-3	17	6	26	11	1	0	2	2	1	0
4-7	33	15	52	23	6	2	3	2	4	2
8–14	103	99	158	145	8	9	6	7	9	4
15–28	161	140	244	198	14	16	8	13	19	8
29–60	470	235	602	358	27	26	15	27	19	18
61-90[b]	975	593	3065	1939	288	266	194	178	426	131
≥91[b]	211	111	323	208	9	31	20	22	8	2
Median Days (Range)	83.0 1-413	83.0 1-379	84.0 1-413	84.0 1-379	84.0 2–106	85.0 5–104	84.0 1–103	84.0 1–114	83.0 3-106	83.0 5-94
Subject-Days Exposure[c]	166,838	92,791	360,743	222,023	26,515	26,737	19,022	18,575	37,403	12,115

Source: ISS Table 3

Var=varenicline; Pbo=placebo;. CV=cardiovascular; COPD=chronic obstructive pulmonary disease

[a] Duration of treatment is calculated from the first and last days that a subject received study medication, regardless of missed doses or temporary discontinuation from treatment.

[b] Because of the 3-day window allowed for scheduling clinic visits, a subject could be on drug for longer than the protocol specified treatment period, ie, >84 days in a 12-week treatment study.

[c] Drug exposure is based on the actual days when subjects received treatment.

Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037

2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115

Source: Section 5.3.5.3 Table A2.a1, A2.a2, A2.d, A2.e, A2.f, A8.1.a1, A8.1.a2, A8.1.d, A8.1.e, A8.1.f

There were no deaths in the FQD Study. In the COPD Study, there were three deaths, two in the Chantix arm. One was due to a motor vehicle accident at least 12 weeks after the end of treatment. The other was a sudden cardiac death that occurred 2 weeks after the completion of treatment in a subject with a history of coronary artery disease. In the CVD Study, there were seven deaths, two in the Chantix arm. One was due to pancreatic cancer and the other was a fatal myocardial infarction which occurred during the post-treatment period. However, this subject had started off-study use of Chantix approximately 10 days before the event. The only additional death noted in the updated ISS occurred in a Phase 2 study conducted in Japan that had not been unblinded at the time of the original NDA submission. This was a death due to a traffic accident that occurred 99 days post-treatment. The following table, reproduced from page 41 of Dr. Winchell's review, was constructed by Dr. Horn and summarizes the overall crude mortality rates and mortality by patient exposure days:

Table 2: Mortality (Pooled Data)

Treatment Group	Patients[5]	Deaths	Crude Mortality	Subject-Days Exposure[6]	Mortality per subject-days exposure
Varenicline	4483	8	0.00178	360,743	2.21×10^{-5}
Placebo	2892	7	0.00242	222,023	3.15×10^{-5}

The following summary of the SAEs in the three efficacy studies has been reproduced from pages 41 through 43 of Dr. Winchell's review:

FQD Study

There were six (1.2%) treatment-emergent non-fatal serious adverse events in the varenicline group and one (0.6%) in the placebo group that occurred within 28 days of the last dose of the trial drug. One serious adverse event was judged to be treatment-related by the Applicant in each group. Events of interest include two patients in the varenicline arm who reported worsening of vascular disease and required surgery. However, due to the 3:1 randomization (more subjects in the varenicline group) and the higher rate of vascular disease at baseline in the varenicline group, these events are difficult to interpret taken alone. Also of note, only one SAE of a psychiatric nature was reported (depressive symptoms and suicidal thoughts), in a placebo-treated patient.

COPD Study

There were eight non-fatal serious adverse events in the varenicline group and twelve in the placebo group that occurred within 28 days of the last dose of the trial drug. These events were notable for three cardiovascular events in the varenicline group (MI, CHF followed by CVA, worsening angina pectoris) and three in the placebo group (MI, CVA, abnormal EKG with chest pain, admitted to rule out acute coronary syndrome). There were no SAEs of a psychiatric nature.

CVD Study

In the CVD study, 80 treatment-emergent SAEs (on-treatment or within 28 days of last dose) were reported in 51 varenicline-treated patients (14.4%) and 72 treatment-emergent SAEs were reported in 45 placebo-treated patients (12.9%). These numbers are taken from Table 11 on p. 47 of the ISS report and differ from those in Dr. Skeete's review, which were taken from the body of the study report for the individual study. A request for clarification of this discrepancy confirmed that the ISS numbers are correct.

The protocol called for certain SAEs of special interest to be blindly adjudicated by an expert committee. Dr. Skeete's review emphasized those events that were confirmed as cardiac SAEs by the adjudication committee. However, she also tabulated the other events and noted no SAEs of a psychiatric nature.

The cardiovascular event adjudication committee reviewed deaths and serious cardiovascular events to confirm causality, in the case of death, and diagnosis of the events.

The following cardiovascular events were reviewed and adjudicated by the committee:

1. Nonfatal myocardial infarction
2. Any hospital admission for chest pain
3. Hospitalization for angina pectoris
4. Need for coronary revascularization

[5] Taken from Table 3 of ISS
[6] Taken from Table 3 of ISS

5. Resuscitated cardiac arrest
6. Hospitalization for congestive heart failure
7. Fatal, nonfatal stroke or TIA
8. Any diagnosis of PVD in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD
9. Death from any cause

These events were adjudicated using a standard events manual under blinded conditions. The Applicant noted (in response to an Information Request) that a comprehensive approach taken with respect to adjudication ensured that all cardiovascular events were provided for adjudication. These included events occurring in the treatment and posttreatment phase regardless of whether they occurred outside of the reporting period.

Study investigators were informed of the types of events (list above) that were to be forwarded for adjudication by the independent blinded event committee. Investigators were responsible for forwarding the events to the committee. During review of the supplement it was found that 4 cardiovascular events that met criteria for adjudication were not sent to the adjudication committee by investigators at 4 clinical sites. In Pfizer's table below, these events were added in as if they had been adjudicated and confirmed by the committee.

	Varenicline (N=353) n (%)		Placebo (N=350) n (%)	
Number of subjects having at least 1 CV event	**26**	**(7.4)**	**23**	**(6.6)**
Summary by type of event	**Investigator[#]**	**Adjudicated***	**Investigator[##]**	**Adjudicated***
Nonfatal myocardial infarction	9 (2.5)	7 (2.0)	3 (0.9)	3 (0.9)
Need for coronary revascularization	9 (2.5)	8 (2.3)	4 (1.1)	3 (0.9)
Hospitalization for angina pectoris	13 (3.7)	8 (2.3)	9 (2.6)	8 (2.3)
Hospitalization for congestive heart failure	2 (0.6)	0	2 (0.6)	2 (0.6)
Nonfatal stroke	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
Transient ischemic attack	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
New diagnosis of peripheral vascular disease (PVD) or admission for a procedure for the treatment of PVD	7 (2.0)	5 (1.4)	4 (1.1)	3 (0.9)
Cardiovascular death	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Noncardiovascular death	1 (0.3)	1 (0.3)	3 (0.9)	3 (0.9)

Source: Table 13.6.6.4
* Number of subjects as per the CV Event Adjudication Committee
[#] Includes subjects (b) (6) (Need for coronary revascularization) and (b) (6) (Hospitalization for angina pectoris) who were identified to have CV events that qualified for, but were not submitted for adjudication.
[##] Includes subjects (b) (6) (New Diagnosis of Peripheral Vascular Disease [PVD] or Admission for a Procedure for the Treatment PVD) and (b) (6) (Need for coronary revascularization) who were identified to have CV events that qualified for, but were not submitted for adjudication
Abbreviations: N/n=number of subjects; CV=cardiovascular
Subjects with multiple CV events of the same type are counted only once per each row.

Source: Pfizer's Corrected Table 17, May 18 submission.

As illustrated, certain events were more common in the varenicline-treated group than the placebo-treated group. These included non-fatal MI, need for coronary revascularization, non-fatal stroke, new

diagnosis of PVD or admission for PVD procedure. As will be discussed below, this finding is also consistent with analyses of all events (serious and non-serious) in the Standardized MedDRA Query (SMQ) for Ischemic Heart Disease.

From the pooled ISS data, the sponsor tabulated the SAEs by Preferred Term in the following table reproduced from page 47 of Dr. Winchell's review:

SAEs in Cardiac Disorders SOC (Pooled Data)

Section 5.3.5.3 Varenicline Integrated Summary of Safety
Table A20.a1 Summary of All Causality SAE Cases by System Organ Class
All Phase 2-4 placebo-controlled studies completed as of December 2, 2010
Number(%)of Patients

	Varenicline (N=4483) n(%)		Placebo (N=2892) n(%)	
System Organ Class and MedDRA (v13.1) preferred term				
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1		1	
Anaemia	1		1	
CARDIAC DISORDERS	37	(0.8)	23	(0.8)
Angina pectoris	7	(0.2)	2	(0.1)
Myocardial infarction	7	(0.2)	2	(0.1)
Acute myocardial infarction	5	(0.1)	4	(0.1)
Coronary artery disease	4	(0.1)	2	(0.1)
Angina unstable	3	(0.1)	2	(0.1)
Acute coronary syndrome	2		2	(0.1)
Atrial fibrillation	2		4	(0.1)
Tachycardia	2		0	
Arrhythmia	1		0	
Arteriospasm coronary	1		0	
Atrial flutter	1		0	
Bradycardia	1		0	
Cardiac arrest	1		0	
Extrasystoles	1		0	
Mitral valve stenosis	1		0	
Sick sinus syndrome	1		0	
Sinus bradycardia	1		0	
Supraventricular tachycardia	1		1	
Ventricular fibrillation	1		0	
Cardiac failure	0		2	(0.1)

Source: ISS Table A20.A1

Dr. Horn reviewed the SAEs in the Cardiac Disorders System Organ Class (SOC) and tabulated them by High Level Term (HLT). By combining the like terms in the HLT-level analysis, we are able to focus on the different types of events within the SOC without obscuring potential signals due to splitting of the events into numerous sub-terms. Dr. Horn's table has been reproduced below from page 48 of Dr. Winchell's review:

Selected Cardiac SAEs (pooled data)

HLT PT	Varenicline n (%) N= 4483	Placebo n (%) N= 2892
Coronary artery disorders NEC coronary artery disease	4 (0.1)	2 (0.1)
Ischemic coronary artery disorders angina pectoris myocardial infarction acute myocardial infarction angina unstable acute coronary syndrome arteriospasm coronary	25 (0.6)	12 (0.4)
Ventricular arrhythmias and cardiac arrest ventricular fibrillation cardiac arrest	2 (0.04)	0 (0)

Source: Reviewer-generated using data reported in Table A20 of Applicant's ISS. Dr. Horn's Table 27

I concur with the clinical review team's conclusion that the pooled data is suggestive of a higher rate of events of an ischemic nature in the Chantix-treated subjects and that it is consistent with the findings in the CVD study. While the signal is more apparent in the CVD study than in the pooled population data, it is not possible from these analyses to determine whether it is actually limited to patients with a prior history of cardiovascular disease.

As Dr. Winchell notes on page 48 of her review, "…SAEs of a psychiatric nature were not more common in the varenicline-treated populations, and no new SAEs of a psychiatric nature were reported in varenicline-treated patients in three new studies."

In the FQD study, the events for which the rates of discontinuations for AEs in the Chantix arm were greater than the rates of discontinuations for AEs in the placebo arm included nausea, other gastrointestinal signs and symptoms, and sleep disturbances. The rates of discontinuations for neuropsychiatric events were 0.6% in the Chantix arm and 4.2% in the placebo arm. There was, however, one report each in the Chantix arm for the following AEs that required dose reduction or temporary discontinuation: affect lability, agitation, depersonalization, and dissociation.

In the COPD study, 6% of subjects in the placebo arm and 5% of subjects in the Chantix arm discontinued due to treatment-emergent AEs. These events were primarily nausea and vomiting. One patient in the Chantix arm discontinued due to a neuropsychiatric event, i.e., anxiety. However, agitation requiring dose reduction or temporary discontinuation was also reported for two Chantix-treated subjects.

In the CVD study, 4% of subjects in the placebo arm and 8% of subjects in the Chantix arm discontinued due to treatment-emergent AEs, while 2% in the placebo arm and 11% in the Chantix arm required dose reduction or temporary discontinuation. Again, these events were primarily nausea and vomiting. However agitation resulted in discontinuation in one Chantix-

treated subject and in dose reduction or temporary discontinuation in two Chantix-treated subjects.

In the pooled safety data, the primary reason for discontinuations for AEs was nausea. The only other events reported at greater than or equal to 1% were insomnia, depression and depressed mood.

From pages 50 and 51 of Dr. Winchell's review:

> In general, the common adverse event profile in the new studies was similar to that established in the original NDA.
>
> The notable exception is that, in the CVD population, the HLGT Cardiac Disorders was reported in 5.1% of varenicline-treated patients and 2.9% of placebo-treated patients, meeting the criteria which were used to construct the common AEs tabulation. Specifically, the Preferred Term angina was reported in 3.7% in the varenicline arm vs. 2% in placebo. In the HLGT General system disorders NEC, the PT chest discomfort was reported in 1.1% in the varenicline arm vs. 0 in placebo.

AEs of Special Interest

Neuropsychiatric events

The following summary has been reproduced from pages 53 through 55 of Dr. Winchell's review:

> ***Individual New Study Populations***
>
> The reviewers also examined the adverse event data from the individual studies separately. In the FQD study, events of interest related to mood and behavior occurred more commonly in placebo-treated than varenicline-treated patients. In the COPD study, these events occurred with equal frequency in both arms, and only placebo-treated patients experienced events that met the criteria for being an event of interest in the post-marketing study[7], including a patient experiencing depression and suicidal ideation, a patient with severe anxiety, and a patient with moderate agitation. In the CVD study, Dr. Skeete identified slightly more treatment-emergent events coded to "Mood disturbances NEC" in the varenicline group (3% vs. 1% in placebo) and "Depressed mood disorders and disturbances" (3% vs 2% in placebo). However, when she looked further at these events, she found that only placebo-treated patients experienced events that met the criteria for being an event of interest in the post-marketing study. Three placebo-treated

[7] The primary endpoint for this trial is the proportion of patients experiencing events in a cluster of neuropsychiatric events that comprise what is being termed the neuropsychiatric adverse event endpoint. The neuropsychatric adverse event endpoint is defined as:

The occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of:

- Agitation
- Aggression
- Delusions
- Hallucinations
- Homicidal Ideation
- Mania
- Panic
- Paranoia
- Psychosis
- Suicidal Ideation, Suicidal Behavior, or Completed Suicide

subjects experienced an adverse event of anxiety that was assessed as severe and an additional placebo-treated subject experienced an adverse event of aggression which was coded as moderate.

Integrated Population

Pfizer's findings for each of the SMQs are illustrated in the following table:

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
SMQ	number (%) of subjects									
Depression and Suicide/self-injury (narrow)										
Subjects with an event	76 (3.8)	29 (2.4)	134 (3.0)	80 (2.8)	12 (3.4)	8 (2.3)	7 (2.8)	7 (2.8)	12 (2.5)	13 (7.9)
Subjects discontinued due to an event	15 (0.8)	5 (0.4)	23 (0.5)	17 (0.6)	4 (1.1)	0 (0)	0 (0)	4 (1.6)	2 (0.4)	5 (3.0)
Suicide/self-injury (narrow)										
Subjects with an event	1 (0.1)	2 (0.2)	4 (0.1)	5 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	2 (1.2)
Subjects discontinued due to an event	0 (0)	0 (0)	1 (<0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.6)
Hostility/Agression (narrow)										
Subjects with an event	10 (0.5)	7 (0.6)	16 (0.4)	14 (0.5)	0 (0)	1 (0.3)	1 (0.4)	1 (0.4)	3 (0.6)	1 (0.6)
Subjects discontinued due to an event	4 (0.2)	1 (0.1)	(5 (0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	0 (0)
Psychosis and psychotic disorders (narrow)										
Subjects with an event	4 (0.2)	1 (0.1)	4 (0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subjects discontinued due to an event	3 (0.2)	1 (0.1)	3 (0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease
Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
Source (Table and Legend): Applicant's ISS report: p. 56

Pfizer additionally provided data on the events identified by the neuropsychiatric SMQs that were also considered serious, that is neuropsychiatric events that were SAEs. These included:

- Acute psychosis (1 [<0.1%] varenicline)
- Depressed mood (1 [<0.1%] varenicline)
- Depression (2 [0.1%] varenicline)
- Schizophrenia, paranoid type (1 [<0.1%] placebo),
- Suicidal ideation (2 [0.1%] varenicline, 1 [<0.1%] placebo)
- Suicide attempt (1 [<0.1%] placebo)

Using the numbers of subjects exposed to varenicline and placebo in the 2010 Pooled cohort as the denominator, rates of SAEs identified by these SMQs were the same for the two treatment arms, (0.1%,

each). Neuropsychiatric events considered SAEs occurred infrequently in the Chantix clinical trials and occurred at the same rates in both treatment arms.

These analyses do not provide further insight into the drug-relatedness of the post-marketing reports of neuropsychiatric symptoms in patients taking Chantix. The new studies, which were initiated shortly after the NDA was approved, used similar psychiatric exclusion criteria to the original studies and did not actively solicit reports of neuropsychiatric events.

Cardiovascular events

The following summary has been reproduced from pages 55 through 58 of Dr. Winchell's review:

> ***New Study Populations***
>
> Three fatal cardiovascular cases were included in the new studies--one MI (10 days after re-starting off-study varenicline treatment during the follow-up period) and one cardiac arrest on post-treatment Day 15 in varenicline-treated patients, and one MI on post-treatment Day 79 in a placebo-treated patient. Both fatal myocardial infarctions occurred in the CVD study; the cardiac arrest occurred in the COPD study.[8]
>
> Non-fatal cardiovascular SAEs were reported in three varenicline-treated patients in the FQD study (one worsening carotid artery stenosis requiring endarterectomy on Day 43, one worsening of peripheral arterial occlusive disease requiring surgery on Day 111, and one case of atrial flutter occurring >28 days after treatment ended, on Day 147). No SAEs of a cardiac nature were reported in placebo patients. (This study had 3:1 randomization.)
>
> In the COPD study (randomized 1:1), five non-fatal cardiovascular SAEs were reported in varenicline-treated patients (3 on-treatment, 2 >28 days post-treatment) vs. two in placebo-treated patients (on treatment).
>
> In the CVD study (randomized 1:1), 31 patients in the varenicline group had SAEs of a cardiovascular nature that were referred for adjudication to the blinded committee. In the placebo group, 21 patients had events of this nature. (The placebo group also had two non-cardiovascular deaths and the varenicline group had one non-cardiovascular death, which were per protocol referred for adjudication as well.) Several patients had more than one event (e.g., admitted for angina pectoris, coronary revascularization procedure).
>
> In the CVD study, as noted above, there were enough reports of angina pectoris and chest discomfort for these events to be considered common AEs. Events in the HLGT Coronary Artery Disorders were reported in 5.1% of varenicline-treated patients vs. 2.9% of placebo-treated, consisting mostly of PT angina pectoris (3.7% vs 2.0%). Events coded to PT Chest discomfort (in HLGT General system disorders NEC) were reported in 1.1% of varenicline-treated patients (vs 0 in placebo).
>
> Therefore, across all three new study populations, cardiac events were more common in varenicline-treated than placebo-treated patients. However, there were very few events in the non-CVD studies and conclusions in these populations are difficult.

[8] There was an additional fatality on post-treatment day 29 (Study Day 113) in the placebo group of the CVD study that involved acute myocardial infarction, cardiogenic shock, acute renal failure and gastrointestinal hemorrhage that may or may not have been a primary cardiac event.

Integrated Population

In the pre-marketing safety database, patients generally were excluded from participation if they had any history of clinically significant cardiovascular disease, clinically significantly abnormal screening or baseline ECGs; significant arrhythmias; or poorly controlled hypertension (usually subjects were excluded for screening or baseline SBP > 150 mm Hg or DBP > 95 mm Hg). Some Phase 3 protocols, on the other hand, were amended to allow enrollment of subjects with stable, documented, cardiovascular disease (stable for ≥ 6 months).

For subjects in the studies comprising the ISS pooled safety database, the Applicant provided data on risk factors for cardiovascular disease other than smoking history (which all subjects have and is summarized separately) for the completed placebo-controlled Phase 2–4 studies[9]. For studies other than the CVD study, about 40% of subjects in either treatment arm met the criteria for having CV risk factors other than smoking history.

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
Subjects with CV risk factors	number (%) of subjects									
Absent	1184 (59.7)	733 (60.6)	2410 (53.8)	1544 (53.4)	0 (0)	1[a] (0.3)	103 (41.5)	127 (50.6)	303 (62.3)	95 (57.6)
Present	799 (40.3)	476 (39.4)	2073 (46.2)	1348 (46.6)	353 (100)	349 (99.7)	145 (58.5)	124 (49.4)	183 (37.7)	70 (42.4)

Pfizer tabulated adverse events by SOC, HLGT, and preferred term in the sub-populations with and without cardiac risk factors in ISS Table A25.2.1.a1. Inspection of the rates of AEs in relevant SOC/HLGTs, comparing the two subpopulations, revealed that events of a cardiovascular nature were more common in patients with CVD risk factors, but it did not appear that there were events for which drug-relatedness was apparent in only one or the other sub-population.

In the overall pooled datasets, adverse events in the Coronary artery disorders HLGT in the studies included in the ISS were observed with greater frequency in the varenicline arm in all cohorts. Note that common adverse event findings from the CVD study are wholly overlapping with adverse events identified by the Ischemic Heart Disease SMQ.

[9] APPLICANT'S DEFINED CRITERIA FOR CVD RISK FACTORS OTHER THAN SMOKING

- BMI > 30
- A medical condition included in the Cardiac Disorders or Vascular Disorders System Organ Class
- Medical Conditions included in the following HLGTs:
  - Cardiac and vascular disorders congenital
  - Cardiac therapeutic procedures
  - Vascular therapeutic procedures
  - Central nervous system vascular disorders (this HLGT was not included in the criteria used for the 2005 NDA[9])
- Medical Conditions included in the following HLTs:
  - Diabetes mellitus (excluding hyperglycemia)
  - Diabetic complications cardiovascular
  - Elevated cholesterol
  - Elevated cholesterol with elevated triglycerides
  - Elevated triglycerides
  - Hyperlipidemias NEC (not elsewhere classified)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
SOC HLGT	number (%) of subjects									
Cardiac Disorders										
Coronary artery disorders	7 (0.4)	3 (0.2)	36 (0.8)	14 (0.5)	18 (5.1)	10 (2.9)	3 (1.2)	1 (0.4)	5 (1.0)	0 (0)

SOURCE: ISS, Table 14. Commonly Reported All Causality HLGTs (≥5% in any Treatment Group) by SOC, Completed Placebo-Controlled Phase 2-4 Studies; ISS, page 51 *(note: only the Cardiac Disorders SOC segment of the table is shown).*

Cardiovascular AEs were also analyzed using the Ischemic heart disease (narrow) SMQ. The results are shown in the table below (Pfizer's ISS Table 21):

Table 21. Adverse Events (All Causalities) in the Ischemic Heart Disease (Narrow) SMQ; Completed Placebo-Controlled Phase 2-4 Studies

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number Subjects[a]	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
PT	number (%) of subjects									
Number subjects with events	8 (0.4)	3 (0.2)	37 (0.8)	14 (0.5)	18 (5.1)	10 (2.9)	3 (1.2)	1 (0.4)	5 (1.0)	0 (0)
Number of subjects discontinued	4 (0.2)	1 (0.1)	9 (0.2)	2 (0.1)	3 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)
Acute coronary syndrome	1 (0.1)	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Acute myocardial infarction	1 (0.1)	1 (0.1)	5 (0.1)	3 (0.1)	2 (0.6)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.2)	0 (0)
Angina pectoris	2 (0.1)	0 (0)	22 (0.5)	7 (0.2)	13 (3.7)	7 (2.0)	2 (0.8)	0 (0)	4 (0.8)	0 (0)
Angina unstable	1 (0.1)	0 (0)	4 (0.1)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coronary artery disease	1 (0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial infarction	1 (0.1)	0 (0)	2 (<0.1)	1 (<0.1)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial ischemia	0 (0)	1 (0.1)	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coronary angioplasty	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Percutaneous coronary intervention	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease
Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051105
Source: Section 5.3.5.3 Tables A26.5.1.a1, A26.5.1.a2, A26.5.1.d, A26.5.1.e, A26.5.1.f

APPEARS THIS WAY ON ORIGINAL

Considering the findings from the various elements of this review of cardiovascular events collectively, there are a small but, increased number of events, primarily coronary heart disease events,

observed in subjects exposed to varenicline. In current labeling, there is no information regarding ischemic cardiac events; the label will be revised to reflect these new findings from the review of pooled safety data from Phase 2–4 studies, as well as findings from review of cardiovascular events in the CVD study independently.

I concur with the clinical review team that there is a limited, but concerning signal for cardiovascular events seen both in the CVD Study and in the updated pooled safety data. I also agree that no other new safety concerns or additional insights regarding the adverse event signals from the post-marketing data are apparent in the data submitted in these supplemental applications.

9. Advisory Committee Meeting

The review team determined that it would not be productive to take these applications to an advisory committee meeting as they concurred, in general, with the Applicant's conclusions regarding the efficacy data, and the safety concerns raised by the CVD study will require additional study before a clear understanding of the risk can be established.

10. Pediatrics

No new pediatric information was required or submitted for these applications. Pfizer is currently completing pediatric studies as defined in a Pediatric Written Request.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues for these applications.

12. Labeling

The Agency and the Applicant have reached agreement on the product labeling. The following summary of the key labeling concerns has been reproduced from pages 63 and 64 of Dr. Winchell's review:

These supplements proposed adding information to the Clinical Studies section, describing the three new studies and their efficacy results. In the adverse event section, Pfizer proposed adding the following language: (b) (4)

Additionally, Pfizer proposed adding information to the Dosing and Administration section of the labeling that described the alternate instructions for setting a quit day as (b) (4)

Based on the findings of Dr. Skeete's review, the review team proposed adding a new section to the Warnings and Precautions describing the cardiovascular adverse events in the CVD study. Information pertinent to these findings were also added to the patient counseling section and to the MedGuide. Notably, the language in the warning includes a statement regarding benefit, similar to that seen in the boxed warning about neuropsychiatric events. Smoking cessation contributes importantly to reduction in cardiac risk; Chantix-treated patients were about three times more likely than placebo-treated patients to maintain abstinence to Week 52.

Review by the Division of Drug Marketing, Advertising, and Communications (DDMAC) identified a concern about the use of the word "flexible" in labeling. Dr. Horn had previously objected to the characterization of the change in instructions as a (b) (4)," because the "approach to quitting" is not materially different from before. The DDMAC team pointed out that the new instructions were not more "flexible" than before, because the Target Quit Date has always been patient-selected; it is simply a matter of whether Chantix is initiated before or after the TQD is identified. Therefore, references to (b) (4) were changed in labeling to (b) (4) for setting a quit date."

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The Applicant has provided adequate evidence of the efficacy of Chantix in patients with COPD and/or CVD who continue to smoke. They have also provided sufficient data to support the alternative directions for choosing a quit date. Language regarding these findings has been added to the product labeling.

  The only new safety finding noted in these applications was the higher incidence of cardiovascular events in the Chantix-treated subjects in the CVD Study and in the Chantix-exposed subjects in the updated pooled ISS data. As noted above, we are requiring Pfizer to add cardiovascular endpoints to their neuropsychiatric outcomes study and to undertake a thorough, patient-level meta-analysis of all of the available cardiovascular adverse event data. In the interim, we have included language regarding these findings in the Warnings section of the product labeling and we will be issuing an updated Drug Safety Communication to alert patients and prescribers to this labeling change.

  The neuropsychiatric, cardiovascular and other safety signals do raise concerns that must be addressed. However, at this time we do not have conclusive evidence of any safety concern that would warrant additional restrictions on the use of Chantix. It remains clearly effective as a smoking cessation tool, even in

patients whose smoking habit is deeply ingrained as evidenced by the fact that they continue to smoke in spite of having cardiovascular and/or pulmonary disease. Smoking in and of itself carries an extremely high risk of developing cardiovascular disease, not to mention multiple types of malignancies and COPD. At this time, the use of Chantix to assist patients with overcoming their addiction to cigarettes provides a benefit that far outweighs even the risks associated with the drug that have been clearly established, let alone those that remain uncertain. As we obtain more definitive data about the cardiovascular, neuropsychiatric and other potential risks, we will readdress the risk-benefit balance and use any and all tools to provide appropriate risk mitigation as necessary.

- Postmarketing Risk Evaluation and Management Strategies

  Chantix already has an approved MedGuide-only REMS. Language was added to the MedGuide with this application to note the cardiovascular symptoms for which patients should seek immediate medical intervention.

- Postmarketing Study Requirements

  The Applicant will be required to conduct a meta-analysis evaluating the incidence of cardiovascular adverse events in Chantix-treated patients compared to control patients in Pfizer-sponsored randomized clinical trials. The study must include an analysis of all serious adverse events with adjudication and an analysis of all adverse events without adjudication.

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/s/

BOB A RAPPAPORT
07/22/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

OFFICER/EMPLOYEE LIST

Employee List for Chantix NDA 021928/S-019, S-020, S-021

Augustus, Ayanna
Dempsy, Mary
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Price, Dionne
Raghavachari, Ramesh
Rappaport, Bob
Vidra, James D

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	6/7/11
From	Celia Winchell, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	21-928 S-019 S-020 S-021
Applicant	Pfizer
Date of Submission	9/22/2010
PDUFA Goal Date	7/23/2011
Proprietary Name / Established (USAN) names	CHANTIX (varenicline tartrate) tablet, film coated
Dosage forms / Strength	Oral Tablet
Proposed Indication(s)	Aid to smoking cessation treatment (approved) Supplements propose to add new language to clinical studies section without change to indication
Recommended:	*Approval*

Cross Discipline Team Leader Review Template

1 Introduction

This memo will serve as the supervisory review for three simultaneously-submitted efficacy supplements for Pfizer's NDA 21-928, varenicline tartrate, an aid to smoking cessation treatment marketed as Chantix. Each supplement was supported by a single new, randomized, placebo-controlled efficacy trial and sought to add a description of the efficacy results to the Clinical Studies section of labeling. These trials included two in new populations—patients with Chronic Obstructive Pulmonary Disease (COPD) and patients with Cardiovascular Disease (CVD)—using the currently labeled instructions, and one providing for an alternative set of instructions for setting a quit date, studied in the same general, otherwise healthy population included in the original trials submitted for marketing approval.

An updated Integrated Summary of Safety, including trials conducted since the 2005 data lock of the original NDA, was also reviewed to determine whether new safety signals or new information about established safety signals were identified. In this review, I will give greater attention to two specific safety concerns, namely, neuropsychiatric symptoms and cardiovascular events.

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 results of two trials designated as pivotal, Study A3051028 ("Study 28") and A3051036 ("Study 36") are shown in the table below alongside the results of the new trials.

In the original NDA submission, the overall exposure to varenicline was adequate to characterize the safety profile and met ICH requirements. 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.

2.2 Special Concerns in This Review

Two of the new studies involve populations not previously included in the original safety database, namely patients with COPD and patients with more recent histories of cardiovascular disease. Conventional wisdom holds that patients who continue to smoke despite these types of illnesses, which are both caused and exacerbated by ongoing smoking, may be particularly recalcitrant smokers, and the establishment of efficacy of varenicline in these patients is useful information for clinicians. Furthermore, because varenicline does have the potential for cardiovascular effects similar to those of nicotine, the specific evaluation of its safety in patients with cardiovascular disease is also of interest. Furthermore, the addition of these three new studies as well as other studies completed by Pfizer since the 2005 database lock of the original NDA (some for registration elsewhere in the world) presents the opportunity to re-visit the overall safety profile using a larger safety database of controlled trials.

Several specific safety concerns received special attention in the review of these applications. These included issues raised during the initial review for which a signal was not apparent in the original database, and several issues identified postmarketing.

Specifically, these were:

1. Neuropsychiatric events
2. Cardiovascular events
3. Cerebrovascular accidents
4. Accidental injury
5. Serious skin reactions and allergic phenomenon
6. Blindness/visual impairment
7. Convulsions

Neuropsychiatric events:
Approximately one year after the approval of Chantix, the FDA learned that the European Medications Authority had identified a signal for suicidal behavior in their pharmacovigilance related to Chantix. Further information submitted by Pfizer, as well as press and consumer reports, identified a number of cases of patients reporting a variety of unusual experiences, very commonly in the setting of initiating or up-titrating varenicline. The case reports often involved ill-defined neuropsychiatric symptoms encompassing affective, cognitive, perceptual, and behavioral domains, many of which do not fall readily into a known diagnostic category and are not consistently coded to any particular set of MedDRA terms. Most concerning were reports of depression, suicide attempts, suicide, aggressive behavior, and psychosis. However, there are difficulties teasing out the role of varenicline from the role of pre-existing psychiatric illness, the role of nicotine withdrawal, or other explanations. Therefore, although the labeling has been amended to include a boxed warning regarding neuropsychiatric symptoms and a Risk Evaluation and Mitigation Strategy (REMS) with MedGuide addressing this risk, the causal relationship remains unclear and a large post-marketing study is being conducted by Pfizer (in cooperation with Glaxo SmithKline, to evaluate similar events reported in association with Zyban). This study is to enroll patients both with and without psychiatric diagnoses, and to prospectively solicit reports of a range of neuropsychiatric events of interest.

Notably, the database of placebo-controlled trials did not point to a drug-related psychiatric phenomenon at the time of the original NDA, although it is noted that both the original studies and the three studies submitted in these supplements did not enroll patients with current psychiatric conditions. A prescription-event monitoring study in the UK[1], an "experimental medicine" study conducted by Pfizer, observing treatment-emergent psychiatric symptoms in patients using varenicline in an observed setting[2], a cohort study using the UK General Practice Research Database[3], and preliminary results from a recently-completed study of electronic medical records databases at the VA also have not linked Chantix to a higher risk of psychiatric symptoms, suicide or psychiatric hospitalization.

[1] Drug Safety 2009; 32 (6): 499-507
[2] BIOL PSYCHIATRY 2011;69:1075–1082
[3] BMJ 2009;339:b3805

Cardiovascular events and Cerebrovascular events:
One safety concern raised by the primary medical officer in the original NDA review was the possibility of cardiac effects, either pro-arrhythmic or pro-ischemic. However, a case-by-case review did not reveal an excess of either type of case among varenicline-treated patients. Although all patients had risk factors for cardiovascular disease due to their status as smokers, the studied population did not include patients with current cardiovascular conditions.

A recent review of post-marketing AERS reports by the Office of Surveillance and Epidemiology (OSE) identified cases of cardiovascular and cerebrovascular events in association with Chantix, and language was added to the post-marketing section of labeling describing these reports.

Accidental Injury:
Post-marketing cases of accidental injuries reported in patients using Chantix prompted Pfizer to submit a labeling supplement in 2007. A review of AERS cases by OSE also identified cases in which patients reported subjective impairment in driving ability that the patient felt could have resulted in injury, but did not. Language regarding these types of events was added to labeling. Concerns about the potential for Chantix to impair ability to drive was also raised by authors at the Institute for Safe Medical Practices (ISMP), and Chantix has been disallowed for airline pilots by the FAA in 2008.

Serious Skin Reactions and Allergic Phenomenon:
Events involving serious skin reactions and allergic phenomenon were identified by OSE and changes were made to the labeling in 2009 to add warnings about these events.

Blindness and visual impairment:
Based on pre-clinical evidence that varenicline could concentrate in melanized tissues, such as the iris, events involving vision received scrutiny in the original NDA review, but no concerns were identified. However, datamining by ISMP also pointed to concerns about visual effects of Chantix. A review by OSE did not recommend labeling changes.

Convulsions:
This event type was also identified as a concern via datamining by ISMP.

For each of the above concerns, the reviewers evaluated the safety datasets from the individual new trials, as well as Pfizer's ISS incorporating these three trials as well as other trials completed since 2005, to determine whether any further evidence of drug-relatedness could be identified.

3 CMC/Device

There were no new CMC issues raised by these supplements.

4 Nonclinical Pharmacology/Toxicology

No new non-clinical issues were raised by these supplements.

5 Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics information was included in these supplements. Under separate cover, the results of a pediatric pharmacokinetic and tolerability study were submitted, which will be addressed in a separate supplement.

The text below, adapted from the approved labeling, summarizes the clinical pharmacology of Chantix:

Varenicline binds with high affinity and selectivity at $\alpha 4 \beta 2$ 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 $\alpha 4 \beta 2$ 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- Efficacy

Originally submitted as one supplement and administratively split into multiple supplements, this submission contained three new efficacy trials and sought to add a description of the efficacy results from each trial to the Clinical Studies section of labeling. These trials included two in new populations—patients with Chronic Obstructive Pulmonary Disease (COPD) and patients with Cardiovascular Disease (CVD)—using the currently labeled instructions, and one providing for an alternative set of instructions for setting a quit date, studied in the same general, otherwise healthy population included in the original trials submitted for marketing approval. All three trials demonstrated efficacy of Chantix, both in increasing the proportions of patients achieving a month of abstinence at the end of treatment, and in increasing the proportions of patients sustaining abstinence to the end of the year (40 weeks post-treatment follow-up). This confirms that Chantix is effective in two populations often thought to be particularly recalcitrant smokers (those who continue smoking after a diagnosis of COPD or CVD), and that Chantix treatment can be initiated either before the patient has set a quit day (new directions), or after (current directions). It is noted, however, that there is no apparent increased treatment effect when comparing the continuous abstinence rates to the rates of patients reporting 6 or fewer days of smoking (the "long-term quit rate," or LTQR). The LTQR is an endpoint that is intended to capture patients who lapse, but do not relapse. It appears that Chantix does not exert its effect through this mechanism.

The table below summarizes the efficacy findings from these three studies and places them beside the findings from the original pivotal trials submitted in support of the NDA for reference. More detailed descriptions of each study and the results are below.

	CVD study		COPD study		FQD study		Study 28		Study 36	
	Chantix	Placebo	Chantix	Placebo	Chantix	Placebo	Chantix	Placebo	Chantix	Placebo
N	350	350	164	165	488	166	349	344	343	340
Continuous Quit Rate Weeks 9-12	47%	14%	41%	9%	53%	19%	44%	17%	44%	18%
Continuous Abstinence Weeks 9-24					35%	13%				
Continuous Abstinence Weeks 9-52	19%	7%	19%	6%			21%	8%	22%	10%
Long-Term Quit Rate Weeks 9-52*	22%	10%	21%	7%			26%	10%	25%	13%

all comparisons vs. placebo: p<.0001

*LTQR is defined as patients who were abstinent during weeks 9-12 and had no more than 6 days of smoking during the non-treatment follow-up.

7.1 Supplement 19: Study in Patients with Cardiovascular Disease

This submission provided the results of Study A3051049, referred to here as Study 49 or the CVD study. It is a 12-week, randomized, double-blind, placebo-controlled multicenter study. The primary objective of this study was to compare 12 weeks of treatment with varenicline to placebo for smoking cessation by end of treatment and continuous abstinence for 40 weeks after treatment. In this submission, the applicant requests that the information from this clinical study be added to the Clinical Studies section of the label. There is no change to the indication statement requested.

The efficacy results were reviewed by Dr. Rachel Skeete (medical officer) and Katherine Meaker (biostatistics reviewer). The reviewer's confirmed the applicant's conclusion that Chantix was more effective than placebo, as measured by CO-confirmed quit rates at weeks 9-12 and weeks 9-52. Excerpts from their reviews, below, provide relevant details.

7.1.1 Study Design

Protocol A3051049

"A 12-Week, Double-Blind, Placebo-Controlled, Multicenter Study with a 40 Week Follow Up Evaluating the Safety and Efficacy of Varenicline Tartrate 1 mg BID for Smoking Cessation in Subjects with Cardiovascular Disease"

Conducted 20 FEBRUARY 2006 to 18 AUGUST 2008 at 39 clinical trial sites in the U.S., and Europe, South America, and Asia. Approximately 90% of the patients were enrolled outside the US.

This was a randomized, double blind, placebo-controlled, parallel group clinical trial. The duration of active treatment specified in the protocol was 12 weeks of varenicline 1 mg BID or placebo and subjects were to be followed in the non-treatment phase for an additional 40 weeks. Blinded trial medication was discontinued at the Week 12 visit and each subject's smoking status was to be followed through the non-treatment period to Week 52.

Eligible patients were current smokers (at least 10 cigarettes per day during the previous 12 months), aged 35-75, who were motivated to quit smoking. They had to have documented stable cardiovascular disease diagnosed at least two months prior to the screening visit. Patients whose only diagnosis was hypertension were not eligible. Examples of eligible diagnoses included:

- ***Coronary Artery Disease*** demonstrated by:
    - Angina pectoris and evidence of abnormal myocardial perfusion or myocardial ischemia by stress testing or myocardial perfusion imaging or angina pectoris with positive coronary angiography. Test results or physician report had to be provided.
    - Myocardial infarction documented by hospital summaries, procedure reports, laboratory reports, etc.
    - Coronary revascularization documented by physician or procedure report.
- ***Peripheral Vascular Disease*** demonstrated by:

  - Stable peripheral vascular disease (arterial) documented by history and physical exam (ankle-brachial index-ABI <0.9 but >0.5), ultrasonography, arteriography. Subjects with asymptomatic carotid disease documented by imaging studies may have been included.
  - Peripheral revascularization documented by procedure report.
- ***Cerebrovascular Disease***
  - For example, TIA or stroke without significant neurological impairment documented by neurological evaluation, procedure report.

Patients were not eligible if they had

- ***Congestive Heart Failure of New York Heart Association Class III or IV***
- ***Unstable cardiovascular disease or a cardiovascular event in the prior two months***. Examples included
  - coronary artery bypass graft (CABG)
  - percutaneous transluminal coronary angioplasty (PTCA),
  - severe or unstable angina
  - serious (life threatening) arrhythmia
  - clinically significant cardiac conduction abnormalities (>10 AV block)
- ***Peripheral Vascular Disease resulting in amputation or with ankle-brachial index ≤5***
- ***Uncontrolled hypertension or systolic BP > 160 or diastolic BP > 95*** *at Screening or Baseline visit*

Patients were also excluded if they had made a serious (but failed) quit attempt in the previous 3 months or had used any marketed or experimental smoking cessation product[4].

Other selected medical criteria for exclusion were:

- Current or past year diagnosis of or treatment for depression
- Past or present anxiety disorder, panic disorder, psychosis or bipolar disorder
- History of drug (except nicotine) or alcohol abuse or dependence in previous 12 months; positive urine drug screen[5]
- Moderate or severe chronic obstructive pulmonary disease (COPD) or previous hospitalization for COPD
- Clinically significant neurological deficits related to cerebrovascular or other diseases.
- Clinically significant endocrine disorders, hepatic or renal impairment, clinically significant lab abnormalities.
- History of cancer (cured basal cell or squamous cell carcinoma of the skin were allowed)
- Diabetics with an HbA1c > 9
- Body mass index (BMI) < 15 or > 38. Weight < 45.5 kg (100 pounds)

[4] Marketed smoking cessation drugs were prohibited for prior 1 month and included nicotine and (b) (4) as well as off-label use of clonidine and (b) (4). Experimental medications were prohibited for prior 1 year.
[5] For drugs of abuse, without medical indication

- Need for or use of medications during the study that could interfere with the evaluation of the study drug[6]

Patients were randomly assigned at a 1:1 ratio, within center to treatment with varenicline or placebo. Patients were treated with varenicline according to the approved treatment regimen: 1 week run-in titration (0.5 mg BID for 3 days; 1.0 mg BID for 4 days), then 11 weeks at the 1 mg BID dosing. Patients were followed for 40 weeks after treatment (52 weeks total) to assess continued abstinence from smoking. Use of nicotine replacement therapy or other nicotine-containing products was prohibited during the study.

After initial screening, patients were instructed to select a target quit date prior to starting study drug. The target quit date would coincide with the Week 1 visit, after one week on study treatment. Clinic visits were scheduled weekly during the 12-week treatment period and at Weeks 13, 16, 24, 32, 40, 48, and 52 during the non-treatment period. Phone contact was scheduled at Weeks 14, 20, 28, 36, and 44. Use of cigarettes or other nicotine-containing products was measured using the Nicotine Use Inventory (NUI) at all clinic visits or phone contacts throughout the 52-week study. Exhaled carbon monoxide (CO) was measured at each clinic visit.

All participants were to receive up to 10 minutes of smoking cessation counseling in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines[7] or similar local guidelines, at each clinic visit and telephone contact starting with the Baseline visit.

The primary and secondary endpoints were defined based on the NUI and exhaled CO measures. The primary endpoint was the 4-week continuous quit rate (CQR) from Weeks 9-12, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO $\leq$ 10 ppm. Two secondary endpoints were predefined with the intended goal of inclusion of the results in the label. These were continuous abstinence (CA) at Week 52, defined as abstinence from smoking, reported in the NUI, from the end of treatment through Week 52 and long term quit rate (LTQR) defined as subjects who were CO-confirmed responders for Weeks 9-12 and who reported no more than 6 days of smoking during the 40-week non-treatment period (Weeks 13-52).

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[6] Prohibited concomitant medications included:

- Antidepressants
- Antipsychotic agents
- Benzodiazepines
- Mood stabilizers
- Naltrexone
- Nicotine replacement therapy and other aids to smoking cessation
- Over-the-counter and prescribed stimulants and anorectic agents
- Steroids
- Theophylline
- Clonidine
- Any investigational drug

[7] 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.

If any CO measurement at a particular timepoint was > 10 ppm, the subject was considered a smoker at that timepoint. Missed exhaled CO measurements were imputed as negative "therefore not disqualifying the subject as a responder" according to the protocol (section 4.1.1). The wording on the nicotine use inventory asks about use "since last contact", so any missed measurements on the NUI were to be imputed back from the next recorded measurement. Any subjects who discontinued from the study were coded as smokers (non-responders) from the time of discontinuation through the end of the study. Subjects were allowed to discontinue treatment but continue in the study, in which case the efficacy outcomes were determined by observed data.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized and received at least one dose of study treatment.

7.1.2 Population

Planned enrollment was approximately 700 subjects with mild to moderate COPD randomized 1:1 to each of two treatment arms. Of 858 smokers screened, 714 subjects were randomized, but 11 of these did not initiate treatment. A total of 703 (353 varenicline and 350 placebo) were treated with at least one dose of study medication.

Demographics

Patient characteristics are shown in the tables below (from Dr. Skeete's review).

Baseline Demographic Characteristics

Number (%) of Subjects	Varenicline (N=353)	Placebo (N=350)
Gender		
Male	266 (75.4)	287 (82.0)
Female	87 (24.6)	63 (18.0)
Age (years)		
< 55	132 (37.4)	152 (43.4)
55 – 65	159 (45.0)	145 (41.4)
>65	62 (17.6)	53 (15.1)
Mean	57.0	56.0
SD	8.6	8.4
Min – Max	34 – 76	35 – 75
Race		
White	284 (80.5)	282 (80.6)
Black	3 (0.8)	2 (0.6)
Asian	30 (8.5)	30 (8.6)
Other	36 (10.2)	36 (10.3)
Weight (kg)		
Mean	79.7	81.7
SD	15.3	15.2
Min – Max	47.0 – 122.0	45.0 – 137.0
Body Mass Index (kg/m^2)		
Mean	27.5	27.9
SD	4.4	4.4
Min – Max	18.3 – 42.5	17.0 – 39.3
Height (cm)		
Mean	169.9	171.0
SD	8.9	7.9
Min – Max	145.0 – 196.0	147.0 – 191.0

SOURCE: Reproduced from Full Clinical Study Report, A3051049, p. 50 (values verified by Dr. Skeete)

Smoking History	Varenicline (N=353)	Placebo (N=350)
Number of years subject smoked		
Mean	40.0	39.1
Range	5.0-63.0	12.0-60.0
Average number of cigarettes per day over last month		
Mean	22.2	22.9
Range	10.0-60.0	10.0-80.0
Previous serious quit attempts [n (%)]		
None	50 (14.2)	48 (13.7)
One	86 (24.4)	101 (28.9)
Two	75 (21.2)	42 (12.0)
3 or more	142 (40.2)	159 (45.4)
Longest period of abstinence in past year (days)		
Mean	15.7	17.8
Range	0.0-240.0	0.0-210.0
Fagerstrom test for nicotine dependence score[a]		
Mean (SD)	5.6 (2.1)	5.7 (2.0)

SOURCE: Clinical Study Report, A3051049, p. 52

Compared to the population studied in the pre-marketing pivotal trials, these patients were older (mean age 56-57, vs. 43-44 in pre-marketing trials), and had a longer smoking history (mean 39-40 years vs. 24-27). However, they had had longer periods of abstinence over the past year, perhaps indicating a greater readiness and motivation to quit.

Patient's cardiovascular diagnoses are shown in the table below. Diagnoses were similarly distributed across treatment groups, with a plurality of participants having a history of myocardial infarction.

System Organ Class Selected MedDRA Preferred Terms	Varenicline (N=353)		Placebo (N=350)	
	Past n (%)	Present n (%)	Past n (%)	Present n (%)
Cardiac Disorders	**220 (62.3)**	**108 (30.6)**	**228 (65.1)**	**101 (28.9)**
Angina pectoris	114 (32.3)	74 (21.0)	97 (27.7)	71 (20.3)
Cardiac failure congestive	3 (0.8)	13 (3.7)	5 (1.4)	9 (2.6)
Myocardial infarction	155 (43.9)	6 (1.7)	171 (48.9)	12 (3.4)
Nervous System Disorders	**38 (10.8)**	**28 (7.9)**	**47 (13.4)**	**19 (5.4)**
Cerebrovascular Accident	16 (4.5)	0	24 (6.9)	0
Transient Ischemic Attack	20 (5.7)	0	21 (6.0)	0
Vascular Disorders	**25 (7.1)**	**217 (61.5)**	**26 (7.4)**	**222 (63.4)**
Aortic aneurysm	0	0	1 (0.3)	1 (0.3)
Hypertension	14 (4.0)	181 (51.3)	12 (3.4)	185 (52.9)
Peripheral Vascular Disorder	9 (2.5)	73 (20.7)	13 (3.7)	79 (22.6)

Applicant's Table 9
(note: Pfizer was not able to clarify why some patients were described as having a "present" history of myocardial infarction.)

One patient had no history of cardiovascular disease, two had no history of coronary artery, peripheral vascular, or cerebrovascular disease, but had a history arrhythmia or conduction disturbances. These patients were not removed from the analysis because it is unlikely their inclusion would influence interpretation of the results.

Patient Disposition

The number of subjects who completed treatment was 293 (83%) in the varenicline group and 286 (82%) in the placebo group. Subjects who discontinued treatment could remain in the trial, thus not all subjects listed under "discontinued treatment" discontinued the trial. In the varenicline group, 302 (86%) completed the entire study (to the final follow-up visit), vs. 289 (83%) in the placebo group.

Reasons for discontinuation and duration of exposure are shown in the tables below. Patients with an exposure time of >90 days are those whose final visit was outside the scheduled window.

Patient Disposition

Number (%) of Subjects	Varenicline	Placebo
Screened: 858		
Assigned to study treatment: 714		
Treated	353	350
Completed Treatment	293 (83.0)	286 (81.7)
Discontinued Treatment	60 (17.0)	64 (18.3)
Completed Study	302 (85.6)	289 (82.6)
Discontinued Study	51 (14.4)	61 (17.4)
Subject Died	2 (0.6)	5 (1.4)
Related to study drug	7 (2.0)	7 (2.0)
Adverse event	7 (2.0)	5 (1.4)[a]
Lack of efficacy	0	2 (0.6)
Not related to study drug	42 (11.9)	49 (14.0)
Adverse event	1 (0.3)	0
Lost to follow-up	14 (4.0)	10 (2.9)
Other	5 (1.4)	5 (1.4)
Subject no longer willing to participate in study	22 (6.2)	34 (9.7)

[a] original footnote explains that one subject gave both related and unrelated AEs as reasons for discontinuation.
SOURCE: A3051049 Full Clinical Study Report, p. 48.

Duration of Treatment

Number of Subjects	Varenicline	Placebo
Duration Category (days)		
≤1	0	0
2-7	7	2
8-14	8	9
15-28	14	16
29-60	27	26
61-90	288	266
≥91	9	31
Median Duration	84.0	85.0
Range	2-106	5-104

Study report, page 53

Study Conduct

Dr. Skeete identified a number of protocol violations, including 3 patients (noted above) who did not meet criteria for entry based on cardiovascular history. Two of these three patients had cardiac arrhythmias, which were not listed as entry criteria, but constitute cardiovascular disease. These three patients were not excluded from the safety analysis.

Additionally, a number of patients used prohibited medications, including smoking cessation medications. Dr. Skeete identified 15 subjects on placebo compared with 5 on varenicline who used a smoking cessation aid during the treatment phase of the study. As three times as many

placebo subjects as varenicline subjects used smoking cessation aids during the treatment phase, the prohibited medication use findings are anticipated to bias the results against varenicline. Dr. Skeete also noted that some patients used off-study varenicline during the follow-up phase. These patients had already been adjudicated as smokers during the active phase, so do not affect interpretation of the efficacy results. However, the use of varenicline is noted in some AE narratives describing events taking place in the follow-up phase, rendering these events treatment-emergent although they did not occur during the treatment phase or within the 30 days thereafter. Notably, 17 (5%) of the placebo group, as well as 20 (6%) of the varenicline group, were exposed to varenicline during the post-treatment phase of the study.

7.1.3 Statistical Methodologies

The primary endpoint was the 4-week continuous quit rate (CQR) from Weeks 9-12, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO $\leq$ 10 ppm. Two secondary endpoints were predefined with the intended goal of inclusion of the results in the label. These were continuous abstinence (CA) at Week 52, defined as abstinence from smoking, reported in the NUI, from the end of treatment through Week 52 and long term quit rate (LTQR) defined as subjects who were CO-confirmed responders for Weeks 9-12 and who reported no more than 6 days of smoking during the 40-week non-treatment period (Weeks 13-52). Other secondary endpoints were considered exploratory only.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized and received at least one dose of study treatment.

The efficacy endpoints were tested using a logistic regression model with terms for treatment group and center. In order to preserve the Type I family-wise error rate of 0.05, a step-down procedure was used for the analysis of the primary and two secondary endpoints. The order of testing was 1) the CQR for weeks 9-12; 2) CA through Week 52; and 3) the LTQR through Week 52. Each comparison was tested at α=0.05.

7.1.4 Results and Conclusions

Per Dr. Meaker's review, on all three primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). Results, excluding the three patients who did not meet criteria for CVD are shown in the table below (Ms. Meaker's Table 4). The only difference from Pfizer's analysis is that Pfizer calculated the CA through Week 52 to be 20%, and the LTQR to be 22%.

Reviewer's Efficacy Analysis Results (Study 49)

Exclude 3 subjects with no CVD	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
	N=350	N=350		
Continuous Quit Rate Weeks 9-12	165 47% (42%, 52%)	50 14% (11%, 18%)	6.02 (4.11, 8.82)	<.0001
Continuous Abstinence Weeks 9-52	68 19% (15%, 24%)	26 7% (5%, 10%)	3.11 (1.91, 5.05)	<.0001
Long Term Quit Rate: Week 52	78 22% (18%, 27%)	34 10% (7%, 13%)	2.76 (1.77, 4.29)	<.0001

Source: SAS datasets

Another concern raised in reporting the results involved the imputation of missing exhaled-CO measures. As described in the protocol, missing exhaled-CO data was imputed as negative, the equivalent of having a score < 10 ppm. This would not disqualify a subject as a responder for the continuous quit rate or continuous abstinence endpoints. However, subjects who discontinued were assumed to be smokers from the time they left the study, so those subjects were coded as non-responders.

Using the original observation data set, Ms. Meaker determined that there were only a few instances in each treatment group with a missing exhaled-CO measure at a timepoint that would have potentially changed the coding of the responder outcome. Even if these were recoded as non-responders, there was no impact on the results or conclusions.

Ms. Meaker performed exploratory analyses for the primary endpoint by age groups, gender, race, region (US vs. Europe) and center. Results for age, gender and race are found in Table 5 in her review. The results for region and individual centers are shown in Table 6 and 7 of Ms. Meaker's review. The varenicline treatment group consistently showed a higher continuous quit rate than the placebo group

7.2 Supplement 20: Study in Patients with Chronic Obstructive Pulmonary Disease

This submission provided the results of Study A3051054, referred to here as Study 54 or the COPD study. It is a 12-week, randomized, double-blind, placebo-controlled multicenter study. The primary objective of this study was to compare 12 weeks of treatment with varenicline to placebo for smoking cessation by end of treatment and continuous abstinence for 40 weeks after treatment. In this submission, the applicant requests that the information from this clinical study be added to the Clinical Studies section of the label. There is no change to the indication statement requested.

The efficacy results were reviewed by Dr. Pamela Horn (medical officer) and Katherine Meaker (biostatistics reviewer). The reviewer's confirmed the applicant's conclusion that Chantix was more effective than placebo, as measured by CO-confirmed quit rates at weeks 9-12 and weeks 9-52. Excerpts from their reviews, below, provide relevant details.

7.2.1 Study Design

Protocol A3051054

"A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial with 40-Week Follow-Up Evaluating the Safety and Efficacy of Varenicline Tartrate for Smoking Cessation in Patients with Mild-To-Moderate Chronic Obstructive Pulmonary Disease"

Conducted 02 MAY 2006 to 30 APRIL 2009 at 27 clinical trial sites in the U.S., France, Italy, and Spain.

This was a randomized, double blind, placebo-controlled, parallel group clinical trial. The duration of active treatment specified in the protocol was 12 weeks of varenicline 1 mg BID or placebo and subjects were to be followed in the non-treatment phase for an additional 40 weeks. Blinded trial medication was discontinued at the Week 12 visit and each subject's smoking status was to be followed through the non-treatment period to Week 52.

Eligible patients were current smokers (at least 10 cigarettes per day during the previous 12 months), at least 35 years of age, who were motivated to quit smoking. They had to have clinical diagnosis of mild-to-moderate chronic obstructive pulmonary disease[8], confirmed by forced expiratory volume (FEV_1) and forced vital capacity (FVC) testing[9], within 30 days of screening. Patients were not eligible if they had been treated or hospitalized for COPD exacerbation during the 4-week period prior to screening. Patients were also excluded if they had made a serious quit attempt or had used any marketed or experimental smoking cessation product in the previous 3 months. Other selected medical criteria for exclusion were:

- Pregnancy

[8] As defined by the 2003 Global Initiative for Chronic Obstructive Lung Diseases criteria

[9] [FEV_1/FVC] < 70% at the Screening visit or within thirty days of the Screening visit; $FEV_1 \leq 50\%$ of predicted normal value after the administration of a short-acting bronchodilator at Screening visit or within thirty days of the Screening visit.

- Treatment for depression in previous 12 months
- Past or present panic disorder, psychosis or bipolar disorder
- History of drug (except nicotine) or alcohol abuse or dependence in previous 12 months; positive urine drug screen[10]
- Abnormal ECGs at screening
- Clinically significant cardiovascular events in the previous 6 months
- Uncontrolled hypertension
- Neurological disorders or cerebrovascular events (e.g., stroke, transient ischemic attack, etc) in the previous 6 months
- Clinically significant endocrine disorders, hepatic or renal impairment, clinically significant lab abnormalities.
- Active malignancy (other than basal cell carcinoma), or a history of malignancy (unless surgically removed with no evidence of recurrence for at least 5 years)
- Need for or use of medications during the study that could interfere with the evaluation of the study drug[11]

Patients were randomly assigned at a 1:1 ratio, within center to treatment with varenicline or placebo. Patients were treated with varenicline according to the approved treatment regimen: 1 week run-in titration (0.5 mg BID for 3 days; 1.0 mg BID for 4 days), then 11 weeks at the 1 mg BID dosing. Patients were followed for 40 weeks after treatment (52 weeks total) to assess continued abstinence from smoking. Use of nicotine replacement therapy or other nicotine-containing products was prohibited during the study.

After initial screening, patients were instructed to select a target quit date prior to starting study drug. The target quit date would coincide with the Week 1 visit, after one week on study treatment. Clinic visits were scheduled weekly during the 12-week treatment period and at Weeks 13, 16, 24, 32, 40, 48, and 52 during the non-treatment period. Phone contact was scheduled at Weeks 14, 20, 28, 36, and 44. Use of cigarettes or other nicotine-containing products was measured using the Nicotine Use Inventory (NUI) at all clinic visits or phone contacts throughout the 52-week study. Exhaled carbon monoxide (CO) was measured at each clinic visit.

[10] Presumably for drugs of abuse (protocol did not specify).

[11] Prohibited concomitant medications included:

- Antidepressants
- Antipsychotic agents
- Mood stabilizers
- Naltrexone
- Nicotine replacement therapy and other aids to smoking cessation
- Over-the-counter and prescribed stimulants and anorectic agents
- Steroids
- Theophylline
- Any investigational drug

Up to ten minutes of brief counseling regarding smoking cessation was to be provided at the end of each clinic visit, in accordance with AHRQ guidelines.

The primary and secondary endpoints were defined based on the NUI and exhaled CO measures. The primary endpoint was the 4-week continuous quit rate (CQR) from Weeks 9-12, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO ≤ 10 ppm. Two secondary endpoints were predefined with the intended goal of inclusion of the results in the label. These were continuous abstinence (CA) at Week 52, defined as abstinence from smoking, reported in the NUI, from the end of treatment through Week 52 and long term quit rate (LTQR) defined as subjects who were CO-confirmed responders for Weeks 9-12 and who reported no more than 6 days of smoking during the 40-week non-treatment period (Weeks 13-52).

If any CO measurement at a particular timepoint was > 10 ppm, the subject was considered a smoker at that timepoint. Missed exhaled CO measurements were imputed as negative "therefore not disqualifying the subject as a responder" according to the protocol (section 4.1.1). The wording on the nicotine use inventory asks about use "since last contact", so any missed measurements on the NUI were to be imputed back from the next recorded measurement. Any subjects who discontinued from the study were coded as smokers (non-responders) from the time of discontinuation through the end of the study. Subjects were allowed to discontinue treatment but continue in the study, in which case the efficacy outcomes were determined by observed data.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized and received at least one dose of study treatment.

7.2.2 Population

Planned enrollment was approximately 500 subjects with mild to moderate COPD randomized 1:1 to each of two treatment arms. Of 1010 smokers screened, 250 subjects were assigned to varenicline treatment and 254 subjects to placebo treatment. Two subjects and three subjects that were randomized to varenicline and placebo respectively did not initiate treatment. Upon review, it was determined that 39 enrolled participants did not meet the protocol-specified criteria for COPD. The clinical and statistical reviewers excluded these subjects from some analyses.

Demographics

Patient characteristics are shown in the table below (Dr. Horn's Table 9).

Demographic and Baseline Characteristics

		Varenicline (N=248)	Placebo (N=251)
Gender	n		
	Male	155	156
	Female	93	95
Age	n (%)		
	< 35	0	1 (0.4)
	35-44	24 (9.7)	20 (8.0)
	45-54	70 (28.2)	77 (30.7)
	55-65	112 (45.2)	107 (42.6)
	>65	42 (16.9)	46 (18.3)
	Mean ± SD	57.2 ± 9.1	57.1 ± 9.0
	Range	35-83	37-77
Race	n (%)		
	White	203 (81.9)	211 (84.1)
	Black	15 (6.0)	10 (4.0)
	Other	30 (12.1)	30 (12.0)
Mean number of years smoked		40.4	40.6
Mean number of cigarettes per day past month		25.3	23.6
Mean Fagerstrom test score		6.2±2.2	5.9±2.1
Mean longest period abstinence (days)		6.5	6.6

N= number of subjects in the respective treatment group, n = number of subjects with respective characteristic, SD = standard deviation
Source: Applicant's Clinical Study Report, Tables 8 and 10, dataset DEMOG

Dr. Horn noted that, compared to the participants in the pre-marketing pivotal trials, patients in this study had a higher mean age (age 57 in this trial vs. age 43-44 in pivotal trials), lengthier and heavier smoking history, and higher scores on the Fagerstrom Test of Nicotine Dependence. This is consistent with the general observation that patients with COPD who continue to smoke are considered particularly "hard-core" smokers.

Patient Disposition

The number of subjects who completed treatment was 207 (83.5%) in the varenicline group and 193 (76.9%) in the placebo group. Subjects who discontinued treatment could remain in the trial, thus not all subjects listed under "discontinued treatment" discontinued the trial. Specifically, 88% of the varenicline group completed the treatment period and 71% completed the entire study (to the final follow-up visit), vs. 78% completing the treatment period and 62.5% completing the entire study in the placebo group.

Reasons for discontinuation and duration of exposure are shown in the tables below from Dr. Horn's review.

Patient Disposition

Number (%) of subjects	Varenicline		Placebo	
Screened: 1010				
Assigned to study treatment	250		254	
Treated	248		251	
Completed treatment	207	(83.5)	193	(76.9)
Discontinued treatment[a]	41	(16.5)	58	(23.1)
Related to study drug	11	(4.4)	11	(4.4)
Adverse event	11	(4.4)	8	(3.2)
Lack of efficacy	0		3	(1.2)
Not related to study drug	30	(12.1)	47	(18.7)
Adverse event	1	(0.4)	6	(2.4)
Lost to follow up	10	(4.0)	10	(4.0)
Subject not willing to participate in study	13	(5.2)	25	(10.0)
Other	6	(2.4)	6	(2.4)
Completed study	176	(71.0)	157	(62.5)
Discontinued study[b]	72	(29.0)	94	(37.5)
Subject died[c]	2	(0.8)	1	(0.4)
Related to study drug	4	(1.6)	10	(4.0)
Adverse event	4	(1.6)	7	(2.8)
Lack of efficacy	0		3	(1.2)
Not related to study drug	66	(26.6)	83	(33.1)
Adverse event	1	(0.4)	4	(1.6)
Lost to follow up	29	(11.7)	31	(12.4)
Subject not willing to participate in study	31	(12.5)	43	(17.1)
Other	5	(2.0)	5	(2.0)
Analyzed for efficacy				
All subjects	248	(100.0)	251	(100.0)
Evaluable subjects	239	(96.4)	240	(95.6)
Completer subjects	210	(84.7)	196	(78.1)
Analyzed for safety				
Adverse events	248	(100.0)	251	(100.0)
Laboratory data[d]	222	(89.5)	211	(84.1)

[a] Subjects could discontinue from treatment and remain in the study.
[b] Discontinuations from the study could occur during the treatment period or during the post-therapy follow-up period.
[c] Deaths occurred in the non-treatment period and were not assessed as related to study drug.
[d] Laboratory data were analyzed for those subjects who had at least 1 non-missing post-baseline laboratory value.

Duration of Treatment

Number of subjects	Varenicline (N = 248)	Placebo (N = 251)
Duration category (days)		
≤1	2	2
2 – 7	3	2
8 – 14	6	7
15 – 28	8	13
29 – 60	15	27
61 – 90	194	178
≥91	20	22
Median duration	84.0	84.0
Range	1 – 103	1 – 114

N = number of subjects in the respective treatment group.

Study Conduct

Dr. Horn identified a number of protocol violations, including 39 patients (25 varenicline and 14 placebo) who did not have a post-bronchodilator FEV_1/FVC ratio < 0.7 at screening or baseline and did not meet the criterion for COPD diagnosis, 36 subjects (18 varenicline and 18 placebo) whose post- bronchodilator FEV_1/FVC ratio placed them in the severe COPD category. Patients who did not meet the criteria for COPD were excluded from the reviewers' analyses, because it was not felt that these patients' experiences were relevant to conclusions about efficacy and safety in patients with COPD, but those whose COPD was in the severe category were included. These exclusions did not lead to different conclusions about efficacy or safety compared to the applicant's analyses, which included these patients.

Additionally, a number of patients used one or more prohibited medications during the trial. One-hundred seven subjects (47 varenicline, 60 placebo) used one or more prohibited smoking cessation medications, including 14 subjects (5 varenicline, 9 placebo) who used prohibited medication during the treatment period. Of these 14 patients, 12 were already classified as non-responders for the efficacy endpoint, so the violations would not affect the interpretation of the trial. The efficacy data has been analyzed by the statistical reviewer without the two subjects who were classified as quitters who used smoking cessation medications during the first 12 weeks. This did not lead to different conclusions compared to the applicant's analysis. The subjects who used prohibited medications during the non-treatment period were already adjudicated as non-responders and do not need to be removed from the analysis.

Approximately 50 patients were enrolled who were using prohibited psychotropic medications. Because of concerns about the safety of Chantix in patients with psychiatric illness, Dr. Horn explored the experience of this subgroup separately but did not otherwise remove them from the analyses of study results.

7.2.3 Statistical Methodologies

The Statistical review was performed by Katherine Meaker, M.S., Biostatistics Reviewer, and Dionne Price, Ph.D., Biostatistics team leader. Much of the text below was provided by the Biostatistics review team.

The primary endpoint was the 4-week continuous quit rate (CQR) from Weeks 9-12, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO ≤ 10 ppm. Two secondary endpoints were predefined with the intended goal of inclusion of the results in the label. These were continuous abstinence (CA) at Week 52, defined as abstinence from smoking, reported in the NUI, from the end of treatment through Week 52 and long term quit rate (LTQR) defined as subjects who were CO-confirmed responders for Weeks 9-12 and who reported no more than 6 days of smoking during the 40-week non-treatment period (Weeks 13-52). Other secondary endpoints were considered exploratory only.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized and received at least one dose of study treatment.

The efficacy endpoints were tested using a logistic regression model with terms for treatment group and center. In order to preserve the Type I family-wise error rate of 0.05, a step-down procedure was used for the analysis of the primary and two secondary endpoints. The order of testing was 1) the CQR for weeks 9-12; 2) CA through Week 52; and 3) the LTQR through Week 52. Each comparison was tested at α=0.05.

7.2.4 Results and Conclusions

Per Dr. Meaker's review, on all three primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). Results, excluding the patients who did not meet criteria for COPD are shown in the table below (Ms. Meaker's Table 4). The only difference from Pfizer's analysis is that Pfizer calculated a CQR of 42% in the varenicline arm.

Reviewer's Efficacy Analysis Results (Study 54)

Exclude 41 subjects with prohibited protocol violations (39 no COPD; 2 NRT use)	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
	N=221	N=237		
Continuous Quit Rate Weeks 9-12	91 41% (35%, 48%)	22 9% (6%, 13%)	7.49 (4411, 12.71)	<.0001
Continuous Abstinence Weeks 9-52	42 19% (14%, 24%)	14 6% (3%, 9%)	4.00 (2.09, 7.66)	<.0001
Long Term Quit Rate: Week 52	47 21% (16%, 27%)	17 7% (4%, 10%)	3.69 (2.03, 6.73)	<.0001

Source: SAS datasets

Ms. Meaker performed exploratory analyses for the primary endpoint by age groups, gender, race, region (US vs. Europe) and center. Results for age, gender and race are found in Table 5 in her review. She noted that none of the non-Caucasian subjects in the placebo arm were responders. The results for region and individual centers are shown in Table 6 and 7 of Ms. Meaker's review. The CQR in the varenicline arm was similar in the US, Italy and Spain, although the placebo CQR was lowest in the US. In France, both treatment arms had a lower responder rate than in the other countries. The varenicline treatment group consistently showed a higher continuous quit rate than the placebo group.

Because of concerns about neuropsychiatric adverse effects, and the lack of efficacy information in patients with psychiatric illness, the reviewers performed a subgroup analysis in the subset of 50 patients who were protocol violations based on being diagnosed with depression within the past 12 months prior to screening and/or were on prohibited medications such as benzodiazepines, antidepressants, or mood stabilizers. Ms. Meaker notes that the following are descriptive statistics only. Notably, the varenicline group again shows a higher quit rate at both time points compared to the placebo group.

Efficacy Outcomes for Patients Diagnosed with Depression and/or Prescribed Related Medications

	Varenicline	Placebo
	N=27	N=23
Continuous Quit Rate Weeks 9-12	8 (30%)	2 (9%)
Continuous Abstinence Weeks 9-52	3 (11%)	0
Long Term Quit Rate Week 52	3 (11%)	1 (4%)

Source: SAS datasets

7.3 Supplement 21: Study of Alternate Directions for Setting a Quit Date

This submission provided the results of Study A3051095, referred to here as Study 95 or the Flexible Quit Date, or FQD, study. It is a 12-week, randomized, double-blind, placebo-controlled multicenter study. The primary objective of this study was to compare 12 weeks of treatment with varenicline to placebo for smoking cessation by end of treatment and continuous abstinence for 12 weeks after treatment. In this study, rather than choosing a target quit date (TQD) and then initiating Chantix one week before the TQD, as in previous studies and in labeling, the patients were instructed to begin taking Chantix before setting a TQD, and to set a quit date between days 8 and 35 of treatment. In this submission, the applicant requests that the results of the study be added to the Clinical Studies section, and that the Dosing and Administration section of the label be changed to include the following instructions (new text underlined):

> Begin CHANTIX dosing one week before the date set by the patient to stop smoking. Alternatively, (b) (4): the patient can begin CHANTIX dosing then quit smoking between 8 and 35 days of treatment.

There is no change to the indication statement requested.

The efficacy results were reviewed by Dr. Pamela Horn (medical officer) and Katherine Meaker (biostatistics reviewer). The reviewer's confirmed the applicant's conclusion that Chantix was more effective than placebo, as measured by CO-confirmed quit rates at weeks 9-12 and weeks 9-24. Excerpts from their reviews, below, provide relevant details.

7.3.1 Study Design

Protocol A3051095

"Phase 4, Prospective Multi-National, Randomized, Double-blind, Placebo-controlled Study to Evaluate Smoking Cessation with Varenicline Tartrate Compared with Placebo in the Setting of Patient Self-selected (Flexible) Quit Date"

Conducted September 26, 2008 to December 10, 2009 at 33 clinical trial sites in 14 countries.

This was a 3:1 randomized, double blind, placebo-controlled, parallel group study. The duration of active treatment specified in the protocol was 12 weeks of varenicline 1 mg BID or placebo and subjects were to be followed in the non-treatment phase for an additional 12 weeks. Blinded study medication was discontinued at the Week 12 visit and each subject's smoking status was to be followed through the non-treatment period to Week 24. Subjects were to select a quit date to occur between Day 8 (the first day of 1 mg BID dosing) and the Week 5 visit date.

Eligible patients were current smokers (at least 10 cigarettes per day during the previous 12 months), aged 18-75, who were motivated to quit smoking and had not had a continuous period of abstinence of over 3 months in the previous year. Patients were also excluded if they had used any marketed smoking cessation product in the previous 3 months.

Other selected medical criteria for exclusion were:

- Pregnancy
- Treatment for depression in previous 12 months
- Past or present panic disorder, psychosis or bipolar disorder
- History of suicidal ideation or suicidal behavior in the previous 5 years
- History of drug (except nicotine) or alcohol abuse or dependence in previous 12 months; positive urine drug screen[12]
- Abnormal ECGs at screening
- Clinically significant cardiovascular events in the previous 6 months
- Uncontrolled hypertension
- COPD
- Neurological disorders or cerebrovascular events (e.g., stroke, transient ischemic attack, etc) in the previous 6 months
- Clinically significant endocrine disorders, hepatic or renal impairment, clinically significant lab abnormalities.
- History of cancer (other than successfully treated basal cell or squamous cell carcinoma)
- Need for or use of medications during the study that could interfere with the evaluation of the study drug[13]

Patients were randomly assigned at a 3:1 ratio, within center. Patients were treated with varenicline according to the approved treatment regimen: 1 week run-in titration (0.5 mg BID for 3 days; 1.0 mg BID for 4 days), then 11 weeks at the 1 mg BID dosing. Patients were followed for 12 weeks after treatment (24 weeks total) to assess continued abstinence from smoking. Use of nicotine replacement therapy or other nicotine-containing products was prohibited during the study.

The dosing instructions for this differed from the other clinical studies conducted for Chantix in that patients were instructed to start dosing with study treatment, then select a date to quit

[12] Presumably for drugs of abuse (protocol did not specify).

[13] Prohibited concomitant medications included:

- Antidepressants
- Antipsychotic agents
- Benzodiazepines
- Mood stabilizers
- Naltrexone
- Nicotine replacement therapy and other aids to smoking cessation
- Over-the-counter and prescribed stimulants and anorectic agents
- Steroids
- Theophylline
- Any investigational drug

smoking. Previously, patients were instructed to pick a target quit date, and start treatment 1 week prior to that date.

After initial screening, patients were randomized and began study treatment. Site personnel were to dispense study drug for the first week of treatment and provide dosing instructions. Subjects were to receive a "Plan and Quit Questionnaire," which asked them about quit attempts and plans to quit. This questionnaire was to be used to collect data on subject's quitting plans and quit attempts. Clinic visits were scheduled weekly during the 12-week treatment period, and at Weeks 13, 16, 20, and 24 during the non-treatment period. Phone contact was scheduled at Weeks 14, 18, and 22. Patients were asked about their intent to quit smoking at each clinic visit. Use of cigarettes or other nicotine-containing products was measured using the Nicotine Use Inventory (NUI) at all clinic visits or phone contacts throughout the 24 week study. Exhaled carbon monoxide (CO) was measured at each clinic visit.
Up to ten minutes of brief counseling regarding smoking cessation was to be provided at the end of each clinic visit, in accordance with AHRQ guidelines.

The primary and secondary endpoints were defined based on the NUI and exhaled CO measures. The primary endpoint was the 4-week continuous quit rate (CQR) from Weeks 9-12, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO $\leq$ 10 ppm. One secondary endpoint was predefined with the intended goal of inclusion of the results in the label. That was continuous abstinence (CA) at Week 24, defined as abstinence from smoking, reported in the NUI, from the end of treatment through Week 24. Other secondary endpoints were considered exploratory only.

If any CO measurement at a particular timepoint was > 10 ppm the subject was considered a smoker at that timepoint. Missed exhaled CO measurements were imputed as negative "therefore not disqualifying the subject as a responder" according to the statistical analysis plan (section 6.1.1). The wording on the nicotine use inventory asks about use "since last contact", so any missed measurements on the NUI were to be imputed back from the next recorded measurement. Any subjects who discontinued from the study were coded as smokers (non-responders) from the time of discontinuation through the end of the study. Subjects were allowed to discontinue treatment but continue in the study, in which case the efficacy outcomes were determined by observed data.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized and received at least one dose of study treatment.

7.3.2 Population

Planned enrollment was 652 patients randomized 3:1 to varenicline or placebo. Of 831 potential subjects screened, 659 were enrolled in the study, 493 subjects assigned to varenicline treatment and 166 subjects assigned to placebo treatment. Of these, 7 in the

varenicline group and 1 in the placebo group did not receive the study treatment, leaving 486 in the varenicline group and 165 in the placebo group[14].

Demographics

Patient characteristics are shown in the table below (Dr. Horn's Table 9).

Demographic and Baseline Characteristics

		Varenicline (N=486)	Placebo (N=165)
Gender	n (%)		
	Male	293 (60.3)	99 (60.0)
	Female	193 (39.7)	66 (40.0)
Age	n (%)		
	18-44	248 (51.0)	93 (56.4)
	45-64	209 (43.0)	64 (38.8)
	>65	29 (6.0)	8 (4.8)
	Mean ± SD	43.9 ± 12.55	43.2 ± 12.22
	Range	18-75	18-72
Race	n (%)		
	White	331 (68.1)	112 (67.9)
	Asian	103 (21.2)	36 (21.8)
	Black	31 (6.4)	8 (4.8)
	Other	21 (4.3)	9 (5.5)
Mean number of years smoked		26.0	24.6
Mean number of cigarettes per day past month		21.3	21.4
Mean Fagerstrom test score		5.6±2.2	5.4±2.1
Mean longest period abstinence (days)		4.4	4.7

N= number of subjects in the respective treatment group, n = number of subjects with respective characteristic, SD = standard deviation
Source: Clinical Reviewer based on Clinical Study Report Tables 11 and 12

Dr. Horn noted that, compared to the participants in the pre-marketing pivotal trials, patients in this study had a slightly shorter average "Longest period of abstinence" than the subjects in the trials submitted in the initial NDA (Studies A1036 and A1028), possibly indicating a more nicotine-dependent population. The subjects in the three trials did not differ significantly in the other smoking history parameters.

Patient Disposition

The number of subjects who completed treatment was 425 (87%) in the varenicline group and 141 (79%) in the placebo group. Subjects who discontinued treatment could remain in the trial, thus not all subjects listed under "discontinued treatment" discontinued the trial. Specifically, 91% of the varenicline group completed the treatment period and 87% completed

[14] Reasons for not receiving treatment: 5 subjects "Subject no longer willing to participate in study", 2 subjects "Lost to follow-up", 1 subject "Does not meet entrance criteria"

the entire study (to the final follow-up visit), vs. 86% completing the treatment period and 86% completing the entire study in the placebo group.

Reasons for discontinuation and duration of exposure are shown in the tables below from Dr. Horn's review.

Patient Disposition

Number (%) of subjects	Varenicline	Placebo
Screened: 831		
Assigned to study treatment	493	166
Treated	486	165
Completed study	425 (87.4)	141 (85.5)
Discontinued study	61 (12.6)	24 (14.5)
Completed study treatment period [a]	442 (90.9)	142 (86.1)
Discontinued study in treatment period	44 (9.1)	23 (13.9)
Completed treatment [b]	425 (87.4)	131 (79.4)
Discontinued treatment [c]	61 (12.6)	34 (20.6)
Related to study drug	24 (4.9)	14 (8.5)
Adverse event	23 (4.7)	11 (6.7)
Lack of efficacy	1 (0.2)	3 (1.8)
Not related to study drug	37 (7.6)	20 (12.1)
Adverse event	1 (0.2)	2 (1.2)
Lost to follow up	9 (1.9)	10 (6.1)
Subject no longer willing to participate in study	18 (3.7)	6 (3.6)
Other	9 (1.9)	2 (1.2)
Discontinued treatment, but stayed in study [d]	17 (3.5)	11 (6.7)
Completed follow-up period	0	10 (6.1)
Discontinued study in follow-up period	17 (3.5)	1 (0.6)
Not related to study drug	17 (3.5)	1 (0.6)
Lost to follow up	8 (1.6)	0
Subject no longer willing to participate in study	7 (1.4)	1 (0.6)
Other	2 (0.4)	0

[a] Refers to subjects who remained in the study until Week 12 regardless of treatment exposure.
[b] Refers to subjects who took study medication up to Week 12.
[c] Discontinuations from the study could occur during the treatment period or during the post-therapy follow-up period, i.e. subjects discontinuing treatment were not necessarily also discontinuing the study.
[d] Subjects could discontinue from treatment and remain in the study.

Duration of Treatment

	Varenicline N = 486 n (%)	Placebo N = 165 n (%)
Duration category (days)		
2 – 7	5 (1.0)	2 (1.2)
8 – 14	9 (1.9)	4 (2.4)
15 – 28	19 (3.9)	8 (4.8)
29 – 60	19 (3.9)	18 (10.9)
61 – 90 [a]	426 (87.7)	131 (79.4)
≥91 [a]	8 (1.6)	2 (1.2)
Median duration	83.0	83.0
Range	3 - 106	5 - 94

[a] Dosing for more than the planned 84 days occurred if subjects missed visits and the rescheduling of the visits beyond the +/- 3 days led to an extension of the dosing period.

Duration was defined as the total number of dosing days from first to, and including, last day of each study treatment.

N = number of subjects in the respective treatment group, n = number of subjects in the respective category.

Study Conduct

Dr. Horn identified several issues relating to study conduct, including one center (1032, Korea) where Pfizer reported concerns about the reliability of the data. These concerns were not specified, but, as noted below, one subject received the wrong treatment medication. Only 18 subjects were randomized at that center, and a sensitivity analysis with and without the site did not affect the results. At Site 1032, 4 of 14 (29%) of the varenicline-treated patients and 1 of 4 (25%) of the placebo-treated patients were classified as quitters.

Several patients did not meet criteria for study entry. These included 7 patients (all in the varenicline group) who were abstinent from smoking at the baseline visit. Four of these patients relapsed, quit again, and were responders for the primary efficacy endpoint. Three were continuously abstinent to Week 5 or beyond and were responders for the primary efficacy endpoint. These three patients were all in the varenicline group and are excluded from the Statistical Reviewer's efficacy analysis, because the abstinence cannot be attributed to the study drug.

One patient in each treatment group used a prohibited smoking cessation medication during the treatment period; neither was a responder on the primary efficacy endpoint.

One patient assigned to varenicline received 5 days of placebo two patients assigned to placebo received varenicline (one for a single day, and one for 5 days). These subjects were

left in the analysis populations as planned, due to the short durations of the misallocations. If these misallocations had any effect of the efficacy data, they would most likely decrease the ability to find a difference between the two groups. With respect to safety, no adverse events (besides the misallocation) were reported for the subject who received 5 days of varenicline. The subject who received one dose of varenicline reported four mild adverse events during the treatment period and it is unknown how they related temporally to the dose of varenicline. The safety analysis was not adjusted for this case due to the short duration of the misallocation and lack of moderate, severe, or serious adverse event reports in this subject.

7.3.3 Statistical Methodologies

The Statistical review was performed by Katherine Meaker, M.S., Biostatistics Reviewer, and Dionne Price, Ph.D., Biostatistics team leader. Much of the text below was provided by the Biostatistics review team.

The primary endpoint was the 4-week continuous quit rate (CQR) from weeks 9-12, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO $\leq$ 10 ppm. One secondary endpoint was predefined with the intended goal of inclusion of the results in the label. This was continuous abstinence (CA) at week 24, defined as abstinence from smoking, reported in the NUI, from the end of treatment through week 24. Other secondary endpoints were considered exploratory only.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized and received at least one dose of study treatment.

The efficacy endpoints were tested using a logistic regression model with terms for treatment group and center. In order to preserve the Type I family-wise error rate of 0.05, a step-down procedure was used for the analysis of the primary and secondary endpoints. The order of testing was 1) the CQR for weeks 9-12; and 2) CA through week 24. Each comparison was tested at α=0.05.

7.3.4 Results and Conclusions

Per Dr. Meaker's review, on both the primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). Results, excluding 3 subjects (all in the varenicline group) who had stopped smoking prior to starting treatment and remained abstinent through Week 5, and adding six other subjects (5 varenicline arm; 1 placebo arm) who were randomized not included in Pfizer's analyses due to lack of dosing information, are shown in the table below (Ms. Meaker's Table 4). The only difference from Pfizer's analysis is that Pfizer calculated a CQR of 54% in the varenicline arm.

Reviewer's Efficacy Analysis Results (Study 95)

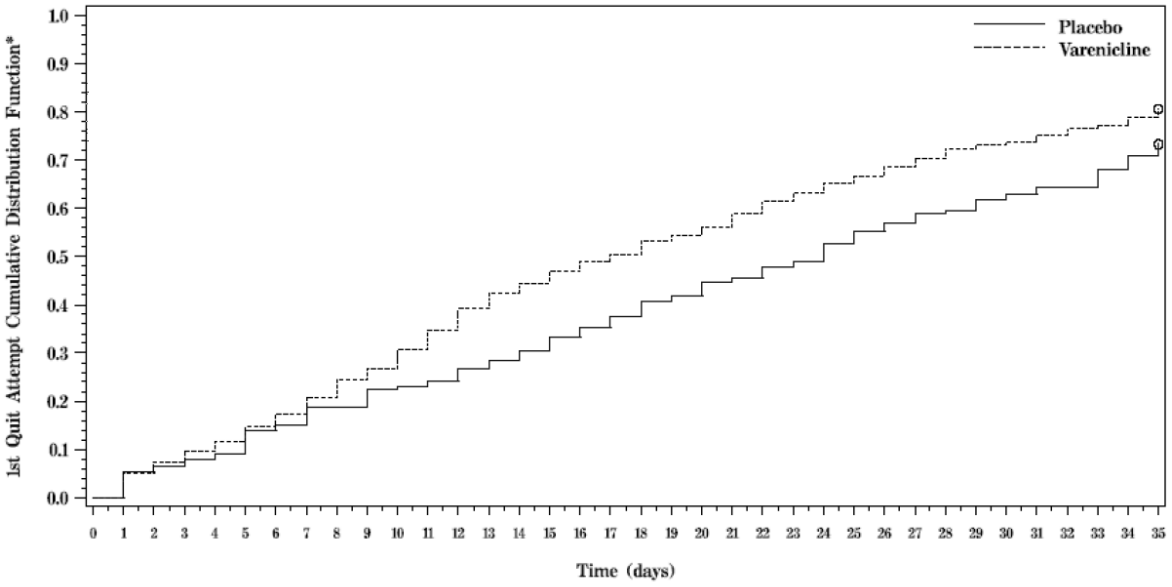
Adjustments to mITT Dataset		Varenicline	Placebo	Odds Ratio (95% CI)	p-value
Applicant's mITT dataset Exclude subjects who quit prior to start of treatment Include subjects who were randomized and non-responder		486 -3 +5	165 0 +1		
		N=488	N=166		
Continuous Quit Rate Weeks 9-12	n % (95% CI)	259 53% (49%, 58%)	32 19% (13%, 25%)	5.97 (3.77, 9.46)	<.0001
Continuous Abstinence Weeks 9-24	n % (95% CI)	169 35% (30%, 39%)	21 13% (8%, 18%)	4.43 (2.61, 7.51)	<.0001
Time to First Quit Attempt (Days)	# uncensored % uncensored Median Days	389/483 (81%) 17	121/165 (73%) 24	na	na

Source: SAS datasets

Although Pfizer did not seek a claim relating to the time to quit attempt, some data were presented in the submission. The mechanism of action of Chantix involves both an agonist effect (to quell withdrawal symptoms after a quit attempt is made) and an antagonist effect, resulting from blocking the effects of nicotine. In theory, the antagonist effect would translate into interference with the subjective effects of smoking that may maintain the behavior, which, in turn, would promote readiness to quit. A patient who begins taking Chantix without a particular quit date in mind might find smoking to be less reinforcing while on Chantix, and might feel ready to quit.

In this study, many patients in both treatment arms did not make a quit attempt at all. However, there appears to be some suggestion that, among those who did, the first quit attempt was earlier in the Chantix-treated group. This is illustrated in the figure below, from Pfizer's clinical study report, Figure 4, page 76.

Applicant's Time to First Quit Attempt



Ms. Meaker performed exploratory analyses for the primary endpoint by age groups, gender, race, region (US vs. non-US) and center. Results for age, gender and race are found in Table 5 and results for region and individual centers are shown in Table 6 and 7 of her review. Both treatment arms had lower responder rates in the US than in the non-US countries.
The varenicline treatment group consistently showed a higher continuous quit rate than the placebo group.

Because of concerns about neuropsychiatric adverse effects, and the lack of efficacy information in patients with psychiatric illness, the reviewers performed a subgroup analysis in the subset of 19 patients who were protocol violations based on being diagnosed with a history of anxiety, panic attacks, psychosis, and/or suicidal ideation at screening. Ms. Meaker notes that the following are descriptive statistics only. Notably, the varenicline group again shows a higher quit rate at both time points compared to the placebo group.

Efficacy Outcomes for Patients Diagnosed with Excluded Psychiatric Diagnoses

	Varenicline	Placebo
	N=16	N=3
Continuous Quit Rate Weeks 9-12	6 (38%)	0
Continuous Abstinence Weeks 9-24	6 (38%)	0
Long Term Quit Rate Week 24	6 (38%)	0

Source: SAS datasets

8 Safety

The initial submission contained only the safety results of the individual studies that were the subject of each application. However, at Agency request, Pfizer submitted an Integrated Summary of Safety (ISS) which provided information on adverse events observed in the pool of placebo-controlled clinical trials to date, juxtaposing this against the findings in the pre-marketing safety database.

The safety reviews of the individual studies were performed by the reviewers of the individual applications (CVD study: Dr. Skeete; COPD study and FQD study: Dr. Horn). The ISS was reviewed collaboratively by both reviewers. Emphasis in the safety reviews was on certain issues which have been a focus of concern since Chantix was approved. These include warnings/precautions already listed in labeling, as well as certain issues which have been considered for inclusion in labeling, but for which the safety signal was not sufficiently clear to warrant labeling change. Specifically, the events of interest were:

1. Neuropsychiatric events
2. Cardiovascular events
3. Cerebrovascular accidents
4. Accidental injury
5. Serious skin reactions and allergic phenomenon
6. Blindness/visual impairment
7. Convulsions

Briefly, Dr. Horn's review did not identify any new population-specific safety concerns in the COPD study, and her review of the FQD study (which enrolled a population similar to that in the pre-marketing studies) also did not identify new safety issues. Dr. Skeete's review of the study in the CVD population, however, identified a higher rate of certain cardiovascular adverse events of interest in the Chantix-treated arm compared to the placebo arm. This finding, along with other explorations in the ISS database relevant to the cardiac safety issue, will be discussed below.

Apart from the cardiovascular findings (see below), review of the individual studies and the ISS did not identify findings warranting labeling changes.

8.1 Populations

The ISS includes data from all completed Phase 2-4 studies of similar design. The studies not included in the original NDA include the three individual studies reviewed in these supplements, as well as a number of additional studies such as those conducted for registration in other global regions. Excluded from the ISS is the pre-marketing study 1035, which involved a randomized withdrawal design, because all participants in both the varenicline and placebo arms, were exposed to varenicline for an initial 12-week run-in.

The studies included and the population exposure are shown in tables below. In the data presentations below, the original pre-marketing data (minus Study 1035) is designated "2005 pooled studies," and the full ISS population, including studies conducted since the NDA was submitted, are designated "2010 pooled studies." The 2010 pooled studies cohort includes the

participants in the CV study, the COPD study, and the FQD study, but these are also shown individually to facilitate review of these supplements.

Below is a table taken from the Applicant's ISS summarizing the studies pooled:

Study	Design	Duration	Treatment Groups	No. of Subjects[a]
2005 POOLED STUDIES COHORT				
PHASE 3 STUDIES				
A3051028 Zyban comparison	R, PG, DB, PC and active comparator	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	349 329 344 Total: 1022
A3051036 Zyban comparison	R, PG, DB, PC and active comparator	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	343 340 340 Total: 1023
PHASE 2 STUDIES				
Study	**Design**	**Duration**	**Treatment Groups**	**No. of Subjects[a]**
A3051002 Dose-ranging	R, PG, DB, PC and active-control	Varenicline: 6 weeks treatment plus 1 week placebo; Zyban: 7 weeks treatment nontreatment follow-up to Week 52	Varenicline 0.3 mg QD Varenicline 1 mg QD Varenicline 1 mg BID Zyban 150 mg BID Placebo	126 126 125 126 123 Total: 626
A3051007 titration (nontreatment follow-up in Study **A3051018**)	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline 0.5 mg NT Varenicline 0.5 mg T Varenicline 1 mg NT Varenicline 1 mg T Placebo	124 129 124 129 121 Total: 627
A3051016 Flexible dosing (nontreatment follow-up in Study **A3051019**)	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline flexible dosing 0.5 to 2 mg daily Placebo	157 155 Total: 312
A3051037 Long-term safety	R, PG, DB, PC	52 weeks treatment	Varenicline, 1 mg BID Placebo	251 126 Total: 377

Study	Design	Duration	Treatment Groups	No. of Subjects[a]
ADDITIONAL STUDIES INCLUDED IN 2010 POOLED STUDIES COHORT				
PHASE 4 STUDIES				
A3051080 Multinational sites in Africa, Mid-East, S. America	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	390 198 Total: 588
A3051095[b] Flexible quit date	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 40	Varenicline, 1 mg BID: Placebo	486 165 Total: 651
A3051104 Smokeless tobacco	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 26	Varenicline, 1 mg BID: Placebo	213 218 Total: 431
A3051115 Assessment of neuropsychiatric symptoms in quitting smokers	R, PG; DB, PC	12 weeks treatment, plus 30 day nontreatment follow-up	Varenicline, 1 mg BID: Placebo	55 55 Total: 110
PHASE 3 STUDIES				
A3051045 Taiwan and Korea	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	126 124 Total: 250
A3051049[b] CV disease	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	353 350 Total: 703
A3051054[b] COPD	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	248 251 Total: 499
A3051055 Multinational Asian sites	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	165 168 Total: 333
PHASE 2 STUDIES				
A3051046_48[c] Japan	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline 0.25 mg BID Varenicline 0.5 mg BID Varenicline 1 mg BID Placebo	153 155 156 154 Total: 618

DB: Double-blind; PC: placebo-controlled; PG: parallel group; R: randomized; QD: once a day; BID: twice a day; NT, Not Titrated, T, Titrated;

[a] No. of Subjects = subjects randomized and treated by treatment group and in total; All studies enrolled smokers with the exception of A3051104 which enrolled smokeless tobacco users.

[b] study included in 2010 Pooled cohort and analyzed as a cohort on its own.

[c] A3051048 was an extension of A3051046.

The overall extent of exposure summarized in the ISS is presented below:

Table 1: Exposure in Pooled Studies

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N=1983**	**Pbo N=1209**	**Var N=4483**	**Pbo N=2892**	**Var N=353**	**Pbo N=350**	**Var N=248**	**Pbo N=251**	**Var N=486**	**Pbo N=165**
Duration of Treatment (Days)[a]	number of subjects									
Unknown	13	10	13	10	0	0	0	0	0	0
1-3	17	6	26	11	1	0	2	2	1	0
4-7	33	15	52	23	6	2	3	2	4	2
8–14	103	99	158	145	8	9	6	7	9	4
15–28	161	140	244	198	14	16	8	13	19	8
29–60	470	235	602	358	27	26	15	27	19	18
61-90[b]	975	593	3065	1939	288	266	194	178	426	131
≥91[b]	211	111	323	208	9	31	20	22	8	2
Median Days (Range)	83.0 1-413	83.0 1-379	84.0 1-413	84.0 1-379	84.0 2–106	85.0 5–104	84.0 1–103	84.0 1–114	83.0 3-106	83.0 5-94
Subject-Days Exposure[c]	166,838	92,791	360,743	222,023	26,515	26,737	19,022	18,575	37,403	12,115

Source: ISS Table 3

Var=varenicline; Pbo=placebo;. CV=cardiovascular; COPD=chronic obstructive pulmonary disease

[a] Duration of treatment is calculated from the first and last days that a subject received study medication, regardless of missed doses or temporary discontinuation from treatment.

[b] Because of the 3-day window allowed for scheduling clinic visits, a subject could be on drug for longer than the protocol specified treatment period, ie, >84 days in a 12-week treatment study.

[c] Drug exposure is based on the actual days when subjects received treatment.

Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115

Source: Section 5.3.5.3 Table A2.a1, A2.a2, A2.d, A2.e, A2.f, A8.1.a1, A8.1.a2, A8.1.d, A8.1.e, A8.1.f

8.2 Major Safety Results

8.2.1 Deaths

8.2.1.1 Individual New Study Populations

There were no deaths in the FQD study.

In the COPD study, there were three deaths (2 varenicline, 1 placebo). The death in the placebo group was attributed to amyotrophic lateral sclerosis. In the varenicline group, one death was due to a motor vehicle accident on Day 168 (at least 12 weeks after the end of treatment). The other was judged to be sudden cardiac death and occurred two weeks after the completion of treatment with varenicline in a subject with a history of coronary artery disease.

In the CVD study, there were seven deaths reported, two in the varenicline arm and five in the placebo arm. The deaths in the varenicline arm included one attributed to pancreatic cancer on Day 301, which does not seem related to varenicline, and a fatal myocardial infarction which occurred during the post-

treatment period, but in a patient who had begun off-study varenicline approximately 10 days before the event.

In the placebo arm, one death occurred during the treatment period and was coded as diabetic coma. During the follow-up period, there were two fatal myocardial infarctions as well as a death due to malignancy and one coded as septic shock.

Therefore, in these three new studies which were reviewed in detail, there appeared to be two cardiac deaths in varenicline-treated patients either on-treatment or shortly after discontinuation. No other possibly drug-related fatal events were reported; notably there were no deaths due to suicide or other neuropsychiatric events.

8.2.1.2 Integrated Population

In the table below, Dr. Horn has tabulated all of the deaths in the pooled Phase 2-4 population. Pfizer reported that no deaths occurred in the Phase 1 studies. Deaths not previously reviewed in the original NDA include one event in Study A1046 which had not been unblinded at the time of original review, and the deaths described above in the COPD study (denoted 1054 in the patient numbers below) and the CVD study (1049); no new deaths were reported in the other studies added to the ISS database since 2005.

Deaths (Pooled Data)

	Patient ID	Age/Race/Sex	Treatment Day	Cause (per Investigator)
Varenicline				
Reviewed in initial NDA	(b) (6)	61/W/M	Day 196 (post-therapy Day 27)	Suicide (+ h/o MDD with suicidality)
	(b) (6)	71/W/M	Day 188 (post-therapy Day 19)	Massive pericardial exudate, Cardiac Arrest, Lung cancer, Lymph metastasis, Pneumonia
	(b) (6)	29/W/M	Day 218 (post-therapy Day 197)	Rectal sarcoma, Discontinued when diagnosed
Not reviewed in initial NDA	(b) (6)	31/A/M	Day 181 (post-therapy Day 99)	Accidental death (Death due to road traffic accident)
	(b) (6)	63/W/M	Day 239 (post-therapy Day 155; however, off-study varenicline had been started 10 days before event)	Acute myocardial infarction
	(b) (6)	76/W/M	Day 301 (post-therapy Day 64)	Pancreatic carcinoma
	(b) (6)	69/W/M	Day 99 (post-therapy Day 15)	Cardiac arrest
	(b) (6)	62/W/M	Day 168 (post-therapy day 93)	Road traffic accident
Placebo				
Reviewed in initial NDA	(b) (6)	64/W/M	Day 352 (post-therapy Day 239)	Death unexplained (fall, collapse of lung, elbow fracture)
Not reviewed in initial NDA	(b) (6)	62/W/M	Day 116 (post-therapy Day 31)	Septic shock
	(b) (6)	63/W/M	Day 36 (post-therapy Day 12)	Hypovolaemia, pneumonia, diabetic coma
	(b) (6)	73/A/M	Day 115 (post-therapy Day	Renal failure, GI bleeding,

			28)	ventricular tachycardia, acute myocardial infarction, cardiogenic shock
	(b) (6)	60/A/M	Day 361 (post-therapy Day 183)	Transitional cell carcinoma
	(b) (6)	51/O/M	Day 162 (post-therapy Day 79)	Acute myocardial infarction
	(b) (6)	51/W/M	Day 397 (post-therapy Day 314)	Amyotrophic lateral sclerosis

The overall crude mortality rate and mortality by patient exposure days is summarized in the table below constructed by Dr. Horn using the number of patients exposed and the subject-days exposure data as reported in the Applicant's ISS. These rates do not indicate that varenicline increases mortality.

Table 2: Mortality (Pooled Data)

Treatment Group	Patients[15]	Deaths	Crude Mortality	Subject-Days Exposure[16]	Mortality per subject-days exposure
Varenicline	4483	8	0.00178	360,743	2.21×10^{-5}
Placebo	2892	7	0.00242	222,023	3.15×10^{-5}

8.2.2 Serious Adverse Events

8.2.2.1 Individual New Study Populations

FQD Study

There were six (1.2%) treatment-emergent non-fatal serious adverse events in the varenicline group and one (0.6%) in the placebo group that occurred within 28 days of the last dose of the trial drug. One serious adverse event was judged to be treatment-related by the Applicant in each group. Events of interest include two patients in the varenicline arm who reported worsening of vascular disease and required surgery. However, due to the 3:1 randomization (more subjects in the varenicline group) and the higher rate of vascular disease at baseline in the varenicline group, these events are difficult to interpret taken alone. Also of note, only one SAE of a psychiatric nature was reported (depressive symptoms and suicidal thoughts), in a placebo-treated patient.

COPD Study

There were eight non-fatal serious adverse events in the varenicline group and twelve in the placebo group that occurred within 28 days of the last dose of the trial drug. These events were notable for three cardiovascular events in the varenicline group (MI, CHF followed by CVA, worsening angina pectoris) and three in the placebo group (MI, CVA, abnormal EKG

[15] Taken from Table 3 of ISS
[16] Taken from Table 3 of ISS

with chest pain, admitted to rule out acute coronary syndrome). There were no SAEs of a psychiatric nature.

CVD Study

In the CVD study, 80 treatment-emergent SAEs (on-treatment or within 28 days of last dose) were reported in 51 varenicline-treated patients (14.4%) and 72 treatment-emergent SAEs were reported in 45 placebo-treated patients (12.9%). These numbers are taken from Table 11 on p. 47 of the ISS report and differ from those in Dr. Skeete's review, which were taken from the body of the study report for the individual study. A request for clarification of this discrepancy confirmed that the ISS numbers are correct.

The protocol called for certain SAEs of special interest to be blindly adjudicated by an expert committee. Dr. Skeete's review emphasized those events that were confirmed as cardiac SAEs by the adjudication committee. However, she also tabulated the other events and noted no SAEs of a psychiatric nature.

The cardiovascular event adjudication committee reviewed deaths and serious cardiovascular events to confirm causality, in the case of death, and diagnosis of the events.

The following cardiovascular events were reviewed and adjudicated by the committee:

1. Nonfatal myocardial infarction
2. Any hospital admission for chest pain
3. Hospitalization for angina pectoris
4. Need for coronary revascularization
5. Resuscitated cardiac arrest
6. Hospitalization for congestive heart failure
7. Fatal, nonfatal stroke or TIA
8. Any diagnosis of PVD in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD
9. Death from any cause

These events were adjudicated using a standard events manual under blinded conditions.
The applicant noted (in response to an Information Request) that a comprehensive approach taken with respect to adjudication ensured that all cardiovascular events were provided for adjudication. These included events occurring in the treatment and posttreatment phase regardless of whether they occurred outside of the reporting period.

Study investigators were informed of the types of events (list above) that were to be forwarded for adjudication by the independent blinded event committee. Investigators were responsible for forwarding the events to the committee. During review of the supplement it was found that 4 cardiovascular events that met criteria for adjudication were not sent to the adjudication committee by investigators at 4 clinical sites. In Pfizer's table below, these events were added in as if they had been adjudicated and confirmed by the committee.

	Varenicline (N=353) n (%)		Placebo (N=350) n (%)	
Number of subjects having at least 1 CV event	**26**	**(7.4)**	**23**	**(6.6)**
Summary by type of event	**Investigator[#]**	**Adjudicated***	**Investigator[##]**	**Adjudicated***
Nonfatal myocardial infarction	9 (2.5)	7 (2.0)	3 (0.9)	3 (0.9)
Need for coronary revascularization	9 (2.5)	8 (2.3)	4 (1.1)	3 (0.9)
Hospitalization for angina pectoris	13 (3.7)	8 (2.3)	9 (2.6)	8 (2.3)
Hospitalization for congestive heart failure	2 (0.6)	0	2 (0.6)	2 (0.6)
Nonfatal stroke	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
Transient ischemic attack	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
New diagnosis of peripheral vascular disease (PVD) or admission for a procedure for the treatment of PVD	7 (2.0)	5 (1.4)	4 (1.1)	3 (0.9)
Cardiovascular death	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Noncardiovascular death	1 (0.3)	1 (0.3)	3 (0.9)	3 (0.9)

Source: Table 13.6.6.4
* Number of subjects as per the CV Event Adjudication Committee
[#] Includes subjects (b) (6) (Need for coronary revascularization) and (b) (6) (Hospitalization for angina pectoris) who were identified to have CV events that qualified for, but were not submitted for adjudication.
[##] Includes subjects (b) (6) (New Diagnosis of Peripheral Vascular Disease [PVD] or Admission for a Procedure for the Treatment PVD) and (b) (6) (Need for coronary revascularization) who were identified to have CV events that qualified for, but were not submitted for adjudication
Abbreviations: N/n=number of subjects; CV=cardiovascular
Subjects with multiple CV events of the same type are counted only once per each row.

Source: Pfizer's Corrected Table 17, May 18 submission.

As illustrated, certain events were more common in the varenicline-treated group than the placebo-treated group. These included non-fatal MI, need for coronary revascularization, non-fatal stroke, new diagnosis of PVD or admission for PVD procedure. As will be discussed below, this finding is also consistent with analyses of all events (serious and non-serious) in the Standardized MedDRA Query (SMQ) for Ischemic Heart Disease.

8.2.2.2 Integrated Population

The table below, constructed from Pfizer's Table 11 on page 47 of the ISS, illustrates the number of patients reporting SAEs and the total number of SAEs across the various populations. This table lists only events reported after the start of treatment or within 28[17] days after the last dose.

[17] Also reported as within 30 days in other data presentations; the numbers of events are the same.

Serious Adverse Events in Phase 2-4 Studies*

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		FQD Study	
	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo
N	1983	1209	4483	2892	353	350	248	251	486	165
Number (%) of subjects with at least one event, all causality	47 (2.4)	19 (1.6)	144 (3.2)	90 (3.1)	51 (14.4)	45 (12.9)	8 (3.2)	11 (4.4)	10 (2.1)	2 (1.2)
total number of SAEs, All causality	69	24	209	129	80	72	8	12	12	2

* Includes fatal and nonfatal SAEs reported after the start of treatment and within 28 days after

Pfizer summarized the all Serious Adverse Events reported in Phase 2-4 placebo-controlled studies by System Organ Class in the table below.

Table 3: Serious Adverse Events (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
SOC	number (%) of subjects									
Blood & lymphatic system disorders	0 (0)	0 (0)	1 (<0.1)	1 (<0.1)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac Disorders	12 (0.6)	4 (0.3)	37 (0.8)	23 (0.8)	19 (5.4)	17 (4.9)	3 (1.2)	1 (0.4)	1 (0.2)	0 (0)
Ear & labyrinth disorders	1 (0.1)	0 (0)	2 (<0.1)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Endocrine Disorders	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eye disorders	3 (0.2)	0 (0)	3 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal Disorders	5 (0.3)	0 (0)	9 (0.2)	8 (0.3)	1 (0.3)	5 (1.4)	0 (0)	0 (0)	1 (0.2)	1 (0.6)
General disorders & administration site conditions	5 (0.3)	3 (0.2)	11 (0.2)	10 (0.3)	5 (1.4)	6 (1.7)	0 (0)	1 (0.4)	0 (0)	0 (0)
Hepatobiliary disorders	2 (0.1)	0 (0)	4 (0.1)	2 (0.1)	1 (0.3)	1 (0.3)	0 (0)	1 (0.4)	0 (0)	0 (0)
Immune system disorders	0 (0)	1 (0.1)	1 (<0.1)	2 (0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Infections & infestations	5 (0.3)	3 (0.2)	18 (0.4)	14 (0.5)	6 (1.7)	6 (1.7)	1 (0.4)	3 (1.2)	1 (0.2)	0 (0)
Injury, poisoning & procedural complications	1 (0.1)	3 (0.2)	8 (0.2)	11 (0.4)	3 (0.8)	3 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	1 (0.1)	0 (0)	2 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolism & nutrition disorders	3 (0.2)	0 (0)	5 (0.1)	2 (0.1)	2 (0.6)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal & connective tissue disorders	3 (0.2)	0 (0)	8 (0.2)	5 (0.2)	1 (0.3)	3 (0.9)	1 (0.4)	1 (0.4)	2 (0.4)	0 (0)
Neoplasms benign, malignant & unspecified	4 (0.2)	1 (0.1)	12 (0.3)	9 (0.3)	5 (1.4)	4 (1.1)	0 (0)	2 (0.8)	1 (0.2)	0 (0)
Nervous system disorders	6 (0.3)	1 (0.1)	17 (0.4)	8 (0.3)	6 (1.7)	5 (1.4)	1 (0.4)	1 (0.4)	2 (0.4)	0 (0)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
SOC	number (%) of subjects									
Pregnancy, puerperium & perinatal conditions	1 (0.1)	0 (0)	3 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	2 (0.1)	2 (0.2)	6 (0.1)	4 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.6)
Renal & urinary disorders	0 (0)	0 (0)	2 (<0.1)	1 (<0.1)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	1 (0.2)	0 (0)
Reproductive system & breast disorders	0 (0)	1 (0.1)	2 (<0.1)	1 (<0.1)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic & mediastinal disorders	0 (0)	2 (0.2)	8 (0.2)	5 (0.2)	4 (1.1)	2 (0.6)	1 (0.4)	1 (0.4)	0 (0)	0 (0)
Skin & subcutaneous disorders	0 (0)	0 (0)	2 (<0.1)	0 (0)	1 (0.3)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Surgical & medical procedures	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	3 (0.2)	1 (0.1)	13 (0.3)	5 (0.2)	9 (2.5)	4 (1.1)	0 (0)	0 (0)	1 (0.2)	0 (0)

Source: ISS Table 29

Dr. Horn looked more closely at SAEs in the SOC Cardiac Disorders.
The tables below show Pfizer's tabulation by Preferred Term, followed by Dr. Horn's tabulation by High Level Term (HLT). Combining like terms into HLT-level analysis makes it possible to focus on the different types of AEs within the SOC without splitting the events into numerous sub-terms, obscuring potential signals.

SAEs in Cardiac Disorders SOC (Pooled Data)

Section 5.3.5.3 Varenicline Integrated Summary of Safety
Table A20.a1 Summary of All Causality SAE Cases by System Organ Class
All Phase 2-4 placebo-controlled studies completed as of December 2, 2010
Number(%)of Patients

System Organ Class and MedDRA (v13.1) preferred term	Varenicline (N=4483) n(%)		Placebo (N=2892) n(%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1		1	
Anaemia	1		1	
CARDIAC DISORDERS	37	(0.8)	23	(0.8)
Angina pectoris	7	(0.2)	2	(0.1)
Myocardial infarction	7	(0.2)	2	(0.1)
Acute myocardial infarction	5	(0.1)	4	(0.1)
Coronary artery disease	4	(0.1)	2	(0.1)
Angina unstable	3	(0.1)	2	(0.1)
Acute coronary syndrome	2		2	(0.1)
Atrial fibrillation	2		4	(0.1)
Tachycardia	2		0	
Arrhythmia	1		0	
Arteriospasm coronary	1		0	
Atrial flutter	1		0	
Bradycardia	1		0	
Cardiac arrest	1		0	
Extrasystoles	1		0	
Mitral valve stenosis	1		0	
Sick sinus syndrome	1		0	
Sinus bradycardia	1		0	
Supraventricular tachycardia	1		1	
Ventricular fibrillation	1		0	
Cardiac failure	0		2	(0.1)

Source: ISS Table A20.A1

Selected Cardiac SAEs (pooled data)

HLT PT	Varenicline n (%) N= 4483	Placebo n (%) N= 2892
Coronary artery disorders NEC coronary artery disease	4 (0.1)	2 (0.1)
Ischemic coronary artery disorders angina pectoris myocardial infarction acute myocardial infarction angina unstable acute coronary syndrome arteriospasm coronary	25 (0.6)	12 (0.4)
Ventricular arrhythmias and cardiac arrest ventricular fibrillation cardiac arrest	2 (0.04)	0 (0)

Source: Reviewer-generated using data reported in Table A20 of Applicant's ISS. Dr. Horn's Table 27

This analysis suggests a higher rate of SAEs, particularly of an ischemic nature, in the varenicline-treated subjects.

This analysis of the pooled data is consistent with the findings in the population in the CVD study; however, it is not clear whether the increased risk is limited to patients with prior diagnoses of cardiovascular disease. The signal is more apparent in that subgroup.

Notably, SAEs of a psychiatric nature were not more common in the varenicline-treated populations, and no new SAEs of a psychiatric nature were reported in varenicline-treated patients in three new studies.

8.2.3 Adverse Events Leading to Discontinuation

8.2.3.1 Individual New Study Populations

FQD Study

In the varenicline group, 24 (5%) of patients discontinued treatment due to treatment-emergent adverse events vs. 13 (8% of the placebo group). This is lower than the 13% of varenicline-treated and 9% of placebo-treated patients that discontinued treatment due to TEAEs in the pivotal trials submitted to the original NDA. Subjects in the varenicline group were more likely to discontinue treatment due to nausea, other gastrointestinal signs and symptoms and sleep disturbances. These findings are consistent with the known adverse event profile. There were also study participants in both arms who discontinued due to psychiatric adverse events of concern, including varenicline group: aggression (1 subject), major depression (1 subject), depression (1 subject); placebo group: suicidal ideation (1 subject), depression (2 subjects), and depressed mood (2 subjects), anxiety (1 subject), and obsessive-compulsive disorder (1 subject). The rate of discontinuation due to this type of event was 0.6% in the varenicline arm vs. 4.2% in the placebo arm.

Additionally, 53 patients (11%) in the varenicline group and 5 patients (3%) in the placebo group required a dose reduction or temporary discontinuation due to treatment-emergent AEs. Nausea and insomnia were the most common reasons, but there were also reports in the varenicline arm (1 each) of affect lability, agitation, depersonalization, and dissociation, which are characteristic of some of the post-marketing reports of a diffuse, difficult-to-characterize neuropsychiatric syndrome.

COPD Study

In the COPD study, 13 patients (5%) in the varenicline group discontinued the treatment due to treatment-emergent AEs, of whom 11 (4%) were assessed as having had treatment-related AEs resulting in discontinuation. In the placebo group, 14 patients (6%) discontinued the treatment due to treatment-emergent AEs, of whom 8 (3%) were judged to have treatment-related events. Reasons for discontinuation primarily related to nausea and vomiting, consistent with the known adverse event profile. Psychiatric events of anger, depression, and suicidal ideation were reported only in the placebo group. On patient in the varenicline group discontinued due to anxiety.

Additionally, 22 patients (9%) in the varenicline group and 11 (4%) in the placebo group required dose reduction or temporary discontinuation due to treatment-emergent AEs. Of these, 16 (7%) in the varenicline group and 5(2.%) in the placebo group were assessed as having treatment-related events leading to dose reduction or temporary discontinuation. The most common reasons were nausea and vomiting. However, agitation was also reported in 2 varenicline and one placebo patient.

CVD Study

In the CVD study, per Table 13.6.3.1 in the Study Report, 29 patients (8%) in the varenicline arm permanently discontinued study drug and 37 (11%) required dose reduction or temporary discontinuation, vs. 15 (4%) (permanent) and 8 (2%) (reduced/temporary) in the placebo arm. The most common reasons, again, were nausea/vomiting. Psychiatric reasons for discontinuation were reported primarily in the placebo group (adjustment disorder, anger, depression (2), depressive symptom, suicidal ideation, agitation), although anxiety was reported in conjunction with discontinuation in 1 varenicline patient, and agitation was cited in conjunction with dose reduction/temporary discontinuation in 2 varenicline patients.

8.2.3.2 Integrated Population

In the Phase 2-4 studies, nausea was the single most reported AE resulting in discontinuation. The only other events reported at ≥1% were Psychiatric events, consisting primarily of insomnia, but also including depression and depressed mood.

Adverse Events Resulting in Permanent Discontinuation of Study Treatment (All Causality, ≥ 1% in any Treatment Group) by SOC, Completed Placebo-Controlled Phase 2-4 Studies

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number Subjects	Var N= 1983	Pbo N= 1209	Var N= 4483	Pbo N= 2892	Var N= 353	Pbo N= 350	Var N= 248	Pbo N= 251	Var N= 486	Pbo N= 165
Number (%) Subjects	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal Disorders	95 (4.8)	20 (1.7)	156 (3.5)	34 (1.2)	14 (3.9)	5 (1.4)	9 (3.6)	2 (0.8)	8 (1.6)	0 (0)
Nausea	59 (3.0)	5 (0.4)	96 (2.1)	10 (0.3)	10 (2.8)	3 (0.9)	5 (2.0)	1 (0.4)	5 (1.0)	0 (0)
Psychiatric disorders	75 (3.8)	34 (2.8)	104 (2.3)	58 (2.0)	8 (2.3)	4 (1.1)	1 (0.4)	5 (2.0)	7 (1.4)	7 (4.2)
Depressed mood	5 (0.3)	0 (0)	9 (0.2)	3 (0.1)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.2)
Depression	10 (0.5)	5 (0.4)	13 (0.3)	11 (0.4)	2 (0.6)	0 (0)	0 (0)	2 (0.8)	1 (0.2)	2 (1.2)
Insomnia	25 (1.3)	11 (0.9)	30 (0.7)	14 (0.5)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	2 (0.4)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease
Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
SOURCE (Table and Legend): Applicant's ISS p. 74–75.

In Phase 1 studies, discontinuations due to skin-related events were also seen, but these were in studies involving co-administration of varenicline with other drugs such as nicotine patch.

8.2.4 Common Adverse Events

In current labeling, common treatment emergent adverse events are provided for MedDRA High Level Group Terms (HLGT) reported in > 5% of patients in the Chantix 1 mg twice daily group, and more commonly than in the placebo group, along with the subordinate Preferred Terms (PT) reported in at least 1% of subjects on 1 mg BID of Chantix and occurring at least 0.5% more commonly in the Chantix arm than placebo. In general, the common adverse event profile in the new studies was similar to that established in the original NDA.

The notable exception is that, in the CVD population, the HLGT Cardiac Disorders was reported in 5.1% of varenicline-treated patients and 2.9% of placebo-treated patients, meeting the criteria which were used to construct the common AEs tabulation. Specifically, the Preferred Term angina was reported in 3.7% in the varenicline arm vs. 2% in placebo. In the HLGT General system disorders NEC, the PT chest discomfort was reported in 1.1% in the

varenicline arm vs. 0 in placebo. The label does not have information describing these as common events and will be revised to reflect these new findings.

The AE table currently in labeling is shown below for reference.

Table 1: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (≥ 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 Nutrit. 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

8.2.5 AEs of Special Interest

8.2.5.1 Neuropsychiatric events

As noted above, based on events identified through post-marketing pharmacovigilance, the following language was added to labeling (including a boxed warning and a MedGuide).

"Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established."

In order to better characterize the neuropsychiatric risk, and to understand whether patients with pre-existing psychiatric illnesses are or are not more vulnerable to treatment-emergent psychiatric symptoms, Pfizer was asked to conduct a post-marketing clinical trial. This trial is being undertaken in cooperation with Glaxo SmithKline, who markets Zyban (bupropion), another, chemically unrelated, smoking cessation product with similar post-marketing event reports.

For these supplements, Pfizer was asked to re-examine the pooled clinical trial database using Standard MedDRA Queries (SMQs) relevant to the neuropsychiatric events, namely depression and suicide/self-injury, hostility/aggression, and psychosis and psychotic disorders. There is a consistently higher occurrence of treatment-emergent adverse events in the SOC Psychiatric Disorders in varenicline-treated patients vs. placebo-treated patients, but it must be noted that this is driven primarily by the very common and well-established treatment-related adverse events of insomnia and abnormal dreams. Both of these are known nicotinic effects and are not the focus of concern of the neuropsychiatric event study. Therefore, attention is given to analyses at a level below the SOC in the MedDRA hierarchy and to SMQs which aggregate similar terms across various levels and SOCs.

8.2.5.1.1 Individual New Study Populations

The reviewers also examined the adverse event data from the individual studies separately. In the FQD study, events of interest related to mood and behavior occurred more commonly in placebo-treated than varenicline-treated patients. In the COPD study, these events occurred with equal frequency in both arms, and only placebo-treated patients experienced events that met the criteria for being an event of interest in the post-marketing study[18], including a patient experiencing depression and suicidal ideation, a patient with severe anxiety, and a patient with moderate agitation. In the CVD study, Dr. Skeete identified slightly more treatment-emergent events coded to "Mood disturbances NEC" in the varenicline group (3% vs. 1% in placebo) and "Depressed mood disorders and disturbances" (3% vs 2% in placebo). However, when she looked further at these events, she found that only placebo-treated patients experienced events that met the criteria for being an event of interest in the post-marketing study. Three placebo-treated subjects experienced an adverse event of anxiety that was assessed as severe and an additional placebo-treated subject experienced an adverse event of aggression which was coded as moderate.

8.2.5.1.2 Integrated Population

Pfizer's findings for each of the SMQs are illustrated in the following table:

[18] The primary endpoint for this trial is the proportion of patients experiencing events in a cluster of neuropsychiatric events that comprise what is being termed the neuropsychiatric adverse event endpoint. The neuropsychatric adverse event endpoint is defined as:

The occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of:

- Agitation
- Aggression
- Delusions
- Hallucinations
- Homicidal Ideation
- Mania
- Panic
- Paranoia
- Psychosis
- Suicidal Ideation, Suicidal Behavior, or Completed Suicide

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
SMQ	number (%) of subjects									
Depression and Suicide/self-injury (narrow)										
Subjects with an event	76 (3.8)	29 (2.4)	134 (3.0)	80 (2.8)	12 (3.4)	8 (2.3)	7 (2.8)	7 (2.8)	12 (2.5)	13 (7.9)
Subjects discontinued due to an event	15 (0.8)	5 (0.4)	23 (0.5)	17 (0.6)	4 (1.1)	0 (0)	0 (0)	4 (1.6)	2 (0.4)	5 (3.0)
Suicide/self-injury (narrow)										
Subjects with an event	1 (0.1)	2 (0.2)	4 (0.1)	5 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	2 (1.2)
Subjects discontinued due to an event	0 (0)	0 (0)	1 (<0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.6)
Hostility/Agression (narrow)										
Subjects with an event	10 (0.5)	7 (0.6)	16 (0.4)	14 (0.5)	0 (0)	1 (0.3)	1 (0.4)	1 (0.4)	3 (0.6)	1 (0.6)
Subjects discontinued due to an event	4 (0.2)	1 (0.1)	(5 (0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	0 (0)
Psychosis and psychotic disorders (narrow)										
Subjects with an event	4 (0.2)	1 (0.1)	4 (0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subjects discontinued due to an event	3 (0.2)	1 (0.1)	3 (0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease
Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
Source (Table and Legend): Applicant's ISS report: p. 56

Pfizer additionally provided data on the events identified by the neuropsychiatric SMQs that were also considered serious, that is neuropsychiatric events that were SAEs. These included:

- Acute psychosis (1 [<0.1%] varenicline)
- Depressed mood (1 [<0.1%] varenicline)
- Depression (2 [0.1%] varenicline)
- Schizophrenia, paranoid type (1 [<0.1%] placebo),
- Suicidal ideation (2 [0.1%] varenicline, 1 [<0.1%] placebo)
- Suicide attempt (1 [<0.1%] placebo)

Using the numbers of subjects exposed to varenicline and placebo in the 2010 Pooled cohort as the denominator, rates of SAEs identified by these SMQs were the same for the two treatment arms, (0.1%, each). Neuropsychiatric events considered SAEs occurred infrequently in the Chantix clinical trials and occurred at the same rates in both treatment arms.

These analyses do not provide further insight into the drug-relatedness of the post-marketing reports of neuropsychiatric symptoms in patients taking Chantix. The new studies, which were intiated shortly after the NDA was approved, used similar psychiatric exclusion criteria to the original studies and did not actively solicit reports of neuropsychiatric events.

8.2.5.2 Cardiovascular events

Cardiovascular events were identified as a possible concern during the original NDA review, although in-depth analysis did not reveal an excess of events in the varenicline-treated patients compared to placebo-treated patients. Post-marketing cases with timing suggestive of drug-relatedness were identified in an OSE review, and information about myocardial infarction and stroke were included in the post-marketing section of labeling in 2010. The reviewers looked at the individual study reports and at Pfizer's analysis of the ISS.

8.2.5.2.1 New Study Populations

Three fatal cardiovascular cases were included in the new studies--one MI (10 days after re-starting off-study varenicline treatment during the follow-up period) and one cardiac arrest on post-treatment Day 15 in varenicline-treated patients, and one MI on post-treatment Day 79 in a placebo-treated patient. Both fatal myocardial infarctions occurred in the CVD study; the cardiac arrest occurred in the COPD study.

Non-fatal cardiovascular SAEs were reported in three varenicline-treated patients in the FQD study (one worsening carotid artery stenosis requiring endarterectomy on Day 43, one worsening of peripheral arterial occlusive disease requiring surgery on Day 111, and one case of atrial flutter occurring >28 days after treatment ended, on Day 147). No SAEs of a cardiac nature were reported in placebo patients. (This study had 3:1 randomization.)

In the COPD study (randomized 1:1), five non-fatal cardiovascular SAEs were reported in varenicline-treated patients (3 on-treatment, 2 >28 days post-treatment) vs. two in placebo-treated patients (on treatment).

In the CVD study (randomized 1:1), 31 patients in the varenicline group had SAEs of a cardiovascular nature that were referred for adjudication to the blinded committee. In the placebo group, 21 patients had events of this nature. (The placebo group also had two non-cardiovascular deaths, which were per protocol referred for adjudication as well.) Several patients had more than one event (e.g., admitted for angina pectoris, coronary revascularization procedure).

In the CVD study, as noted above, there were enough reports of angina pectoris and chest discomfort for these events to be considered common AEs. Events in the HLGT Coronary Artery Disorders were reported in 5.1% of varenicline-treated patients vs. 2.9% of placebo-treated, consisting mostly of PT angina pectoris (3.7% vs 2.0%). Events coded to PT Chest discomfort (in HLGT General system disorders NEC) were reported in 1.1% of varenicline-treated patients (vs 0 in placebo).

Therefore, across all three new study populations, cardiac events were more common in varenicline-treated than placebo-treated patients. However, there were very few events in the non-CVD studies and conclusions in these populations are difficult.

8.2.5.2.2 Integrated Population

In the pre-marketing safety database, patients generally were excluded from participation if they had any history of clinically significant cardiovascular disease, clinically significantly abnormal screening or baseline ECGs significant arrhythmias; or poorly controlled hypertension (usually subjects were excluded for screening or baseline SBP > 150 mm Hg or DBP > 95 mm Hg). Some Phase 3 protocols, on the other hand, were amended to allow enrollment of subjects with stable, documented, cardiovascular disease (stable for ≥ 6 months).

For subjects in the studies comprising the ISS pooled safety database, the applicant provided data on risk factors for cardiovascular disease other than smoking history (which all subjects have and is summarized separately) for the completed placebo-controlled Phase 2–4 studies[19]. For studies other than the CVD study, about 40% of subjects in either treatment arm met the criteria for having CV risk factors other than smoking history.

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
Subjects with CV risk factors	number (%) of subjects									
Absent	1184 (59.7)	733 (60.6)	2410 (53.8)	1544 (53.4)	0 (0)	1[a] (0.3)	103 (41.5)	127 (50.6)	303 (62.3)	95 (57.6)
Present	799 (40.3)	476 (39.4)	2073 (46.2)	1348 (46.6)	353 (100)	349 (99.7)	145 (58.5)	124 (49.4)	183 (37.7)	70 (42.4)

Pfizer tabulated adverse events by SOC, HLGT, and preferred term in the sub-populations with and without cardiac risk factors in ISS Table A25.2.1.a1. Inspection of the rates of AEs in relevant SOC/HLGTs, comparing the two subpopulations, revealed that events of a

[19] APPLICANT'S DEFINED CRITERIA FOR CVD RISK FACTORS OTHER THAN SMOKING

- BMI > 30
- A medical condition included in the Cardiac Disorders or Vascular Disorders System Organ Class
- Medical Conditions included in the following HLGTs:
  - Cardiac and vascular disorders congenital
  - Cardiac therapeutic procedures
  - Vascular therapeutic procedures
  - Central nervous system vascular disorders (this HLGT was not included in the criteria used for the 2005 NDA[19])
- Medical Conditions included in the following HLTs:
  - Diabetes mellitus (excluding hyperglycemia)
  - Diabetic complications cardiovascular
  - Elevated cholesterol
  - Elevated cholesterol with elevated triglycerides
  - Elevated triglycerides
  - Hyperlipidemias NEC (not elsewhere classified)

cardiovascular nature were more common in patients with CVD risk factors, but it did not appear that there were events for which drug-relatedness was apparent in only one or the other sub-population.

In the overall pooled datasets, adverse events in the Coronary artery disorders HLGT in the studies included in the ISS were observed with greater frequency in the varenicline arm in all cohorts. Note that common adverse event findings from the CVD study are wholly overlapping with adverse events identified by the Ischemic Heart Disease SMQ.

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
SOC HLGT	number (%) of subjects									
Cardiac Disorders										
Coronary artery disorders	7 (0.4)	3 (0.2)	36 (0.8)	14 (0.5)	18 (5.1)	10 (2.9)	3 (1.2)	1 (0.4)	5 (1.0)	0 (0)

SOURCE: ISS, Table 14. Commonly Reported All Causality HLGTs (≥5% in any Treatment Group) by SOC, Completed Placebo-Controlled Phase 2-4 Studies; ISS, page 51 *(note: only the Cardiac Disorders SOC segment of the table is shown).*

Cardiovascular AEs were also analyzed using the Ischemic heart disease (narrow) SMQ. The results are shown in the table below (Pfizer's ISS Table 21):

Table 21. Adverse Events (All Causalities) in the Ischemic Heart Disease (Narrow) SMQ; Completed Placebo-Controlled Phase 2-4 Studies

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number Subjects[a]	Var N= 1983	Pbo N= 1209	Var N= 4483	Pbo N= 2892	Var N= 353	Pbo N= 350	Var N= 248	Pbo N= 251	Var N= 486	Pbo N= 165
PT	number (%) of subjects									
Number subjects with events	8 (0.4)	3 (0.2)	37 (0.8)	14 (0.5)	18 (5.1)	10 (2.9)	3 (1.2)	1 (0.4)	5 (1.0)	0 (0)
Number of subjects discontinued	4 (0.2)	1 (0.1)	9 (0.2)	2 (0.1)	3 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)
Acute coronary syndrome	1 (0.1)	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Acute myocardial infarction	1 (0.1)	1 (0.1)	5 (0.1)	3 (0.1)	2 (0.6)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.2)	0 (0)
Angina pectoris	2 (0.1)	0 (0)	22 (0.5)	7 (0.2)	13 (3.7)	7 (2.0)	2 (0.8)	0 (0)	4 (0.8)	0 (0)
Angina unstable	1 (0.1)	0 (0)	4 (0.1)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coronary artery disease	1 (0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial infarction	1 (0.1)	0 (0)	2 (<0.1)	1 (<0.1)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial ischemia	0 (0)	1 (0.1)	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coronary angioplasty	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Percutaneous coronary intervention	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease
Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051105
Source: Section 5.3.5.3 Tables A26.5.1.a1, A26.5.1.a2, A26.5.1.d, A26.5.1.e, A26.5.1.f

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Considering the findings from the various elements of this review of cardiovascular events collectively, there are a small but, increased number of events, primarily coronary heart disease events, observed in subjects exposed to varenicline. In current labeling, there is no information regarding ischemic cardiac events; the label will be revised to reflect these new findings from the review of pooled safety data from Phase 2–4 studies, as well as findings from review of cardiovascular events in the CVD study independently.

8.2.5.3 Cerebrovascular accidents

In analyzing cerebrovascular events, the applicant used the Cerebrovascular disorders Standardized MedDRA Query (SMQ) and the Central Nervous System Hemorrhages and Cerebrovascular Accidents SMQ. Again, the narrow subsets of these SMQs were used for these searches. The applicant found that results from these two SMQs were completely overlapping and hence the findings are presented for both in a single summary. The applicant's findings are presented in the following table from Dr. Skeete's review.

Cerebrovascular events (Pooled data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
PTs	number (%) of subjects									
CNS Haemorrhages &Cerebrovascular accidents (narrow) & Cerebrovascular disorders (narrow)										
Number subjects with events	2 (0.1)	0 (0)	6 (0.1)	2 (0.1)	2 (0.6)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.2)	0 (0)
Number subjects discontinued	1 (0.1)	0 (0)	2 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Carotid artery stenosis	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Cerebrovascular accident	1 (0.1)	0 (0)	4 (0.1)	0 (0)	2 (0.6)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Ischemic stroke	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)
Transient ischemic attack	1 (0.1)	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037 2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
SOURCE (Table and Legend): Applicant's ISS report, p. 63

Cerebrovascular events identified by these SMQs were rare. Again, across all cohorts, <1% of subjects in any treatment arm reported a cerebrovascular event. In the cardiovascular disease study, there was a slight increase in numbers of events seen in the varenicline arm over that seen in the placebo arm. Among the other cohorts, the proportions of subjects experiencing events were essentially the same in the two treatment arms. There were no clear trends seen in the types of events experienced by subjects in these studies (i.e., individual preferred terms (PTs). Therefore, labeling changes based on these events are not warranted.

8.2.5.4 Accidental injury

Following the approval of varenicline, there were post-marketing reports of accidental injury, including traffic accidents and near-miss traffic incidents. Some patients have also reported difficulty concentrating, somnolence, and dizziness that resulted in impairment or raised concern for potential impairment in driving or operating machinery. The label was modified to include a warning about these reports in 7/09. The Applicant analyzed the data for possible effects of varenicline on risk for accidental injury using the Accidents and Injuries Standardized MedDRA Query (SMQ). The table below summarizes the results.

Table 4: All-Causality Adverse Events in the Accidents and Injuries SMQ by HLGT (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
SMQ HLGT	number (%) of subjects									
Accidents and injuries (narrow)										
Number of subjects w/events	117 (5.9)	45 (3.7)	181 (4.0)	99 (3.4)	7 (2.0)	8 (2.3)	8 (3.2)	6 (2.4)	11 (2.3)	6 (3.6)
Number of subjects discontinued	0 (0)	2 (0.2)	2 (,0.1)	4 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint injuries	39 (2.0)	12 (1.0)	55 (1.2)	32 (1.1)	3 (0.8)	3 (0.9)	2 (0.8)	4 (1.6)	3 (0.6)	2 (1.2)
Injuries NEC	75 (3.8)	34 (2.8)	119 (2.7)	71 (2.5)	5 (1.4)	6 (1.7)	6 (2.4)	1 (0.4)	7 (1.4)	5 (3.0)
Injuries by physical agents	11 (0.6)	3 (0.2)	18 (0.4)	6 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	0 (0)
Headaches	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: ISS Table 19

The preferred term "road traffic accident" is contained within the Injuries by physical agents HLGT. There were comparable rates of road traffic accidents in the varenicline and placebo group (0.1% and 0.2%) respectively.

Because of the concern that this search strategy would not identify those cases in which the patient complained of subjective impairment in driving which did not result in an accident or injury ("near-misses), Pfizer was asked to search for any event coded to the MedDRA term "impaired driving ability." No events coded to this PT were identified. In addition to conducting this search, Pfizer also looked for text strings which could be associated with such incidents, such as "car", "vehic", "driv", "motor", "near miss", "near-miss", "road", "accident", "traffic", "green light", "red light", "DUI", "pull over." Terms containing these substrings were then manually reviewed to identify events that represented potential near miss incidents or reported concerns regarding the ability to drive. No relevant events were identified.

8.2.5.5 Serious skin reactions and allergic phenomenon

There were post-marketing reports of skin reactions including Steven's-Johnson syndrome and erythema multiforme in patients using Chantix. The label was modified to include a warning about these reports in 7/09. The Applicant analyzed the data from all Phase 2-4 placebo-controlled studies using the angioedema, anaphylactic reaction, and serious cutaneous adverse reactions SMQs. No severe cutaneous adverse reactions or anaphylactic reactions were identified in varenicline-treated patients. Terms in the SMQ for angioedema were reported in 34 (0.8%) of the varenicline-treated patients in the 2010 pool and 18 (0.6%) of the placebo-treated patients, wich urticaria and facial swelling the most commonly-reported terms. Across all cohorts, these terms were consistently reported in a higher percentage of varenicline-treated than placebo-treated patients. The label already includes a warning about allergic reactions including angioedema.

8.2.5.6 Blindness/visual impairment

Pre-clinical data showed that varenicline had the potential to concentrate in pigmented tissues such as the iris, but no evidence of eye involvement was seen in the original NDA. Reports of visual impairment were identified as a concern via datamining of AERS data by researchers external to FDA. A review of AERS cases by the Office of Surveillance and Epidemiology (OSE) did not recommend a labeling change related to this type of event. Pfizer used the HLGT Vision Disorders to identify relevant AEs in the ISS database. No cases in this SMQ were reported in the three new studies discussed in these supplements. In the 2010 pooled Phase 2-4 data, events in this SMQ were reported in 49 (1.1%) of varenicline-treated and 25 (0.9%) of placebo-treated patients. By far the most commonly-reported term was "vision blurred" (29 (0.6%) varenicline, 19 (0.7%) placebo). Labeling change does not seem warranted based on this review.

8.2.5.7 Convulsions

Convulsions were also a safety concern identified by datamining by external researchers. A very small number of cases was identified in the AERS database by OSE and no labeling change has been pursued. Convulsions were a rare event observed in the clinical trials reviewed in the initial NDA and are included in labeling under Section 6.1 Adverse Reactions, Clinical Trials Experience. One event coded "complex partial seizure," was reported in the CVD study and one coded "epilepsy" was reported in the FQD study, both in varenicline-treated patients. Pfizer used the SMQ for Convulsions (narrow) to identify events in the 2010 pooled Phase 2-4 data. This search identified 8 (0.2%) varenicline-treated and 2 (0.1%) placebo-treated patients. However, 5 of the events in the varenicline arm and both of the events in the placebo arm were coded to the PT "dreamy state." A well-recognized side effect of varenicline is vivid or unusual dreams; events describing this phenomenon could also be coded to this term. The Applicant reported that four of the "dreamy state" adverse events in the varenicline group and both events in the placebo group were due to "having several dreams per night." Excluding the "dreamy state" events, convulsions occurred in 0.05% of varenicline-treated subjects in the studies reviewed in the original NDA and 0.07% of varenicline-treated subjects in the most recently pooled data, leaving three cases, all in the varenicline arm.

One patient (with no history of a seizure disorder) had a grand mal convulsion while taking 1 mg varenicline twice a day. No laboratory or imaging abnormalities were detected and the subject permanently discontinued varenicline and reportedly recovered from the convulsion the same day. This event was reviewed in the original NDA and at that time, the reviewer considered it to be possibly causally related. The other two cases (complex partial seizures, epilepsy) in the new studies occurred in patients with seizure disorders.

8.2.6 Vital Signs and Laboratory Assessments

No new information pointing to an effect of Chantix on vital signs or laboratory assessments was identified. Weight gain was more common in patients treated with Chantix, as noted in the original NDA.

8.2.7 Use in Pregnancy

No systematic clinical studies on the use of varenicline in pregnant or lactating women have been conducted. At the time of NDA approval, Pfizer was asked to conduct a pregnancy cohort study to better understand the risks of Chantix in pregnancy. In this study, information on 5 years of births is being assembled from the national register systems of Denmark and Sweden.

By protocol, women of childbearing potential could be included in clinical studies if they were not pregnant, not nursing, and were practicing effective contraception. Subjects also agreed to avoid pregnancy through 30 days after the last dose of study drug. However, Pfizer's search of their database of placebo-controlled clinical studies of varenicline through 02 December 2010 identified a total of 14 women treated with varenicline and 4 women treated with placebo who were reported to have become pregnant either during or after cessation of treatment in these studies.

Of the 14 varenicline-treated women, 11 became pregnant while taking study drug and three became pregnant >30 days after the last dose,

Of the 11 pregnancies on-treatment, there were 2 term pregnancies, 5 elective terminations, 3 spontaneous abortions, and 1 unknown outcome. Therefore, of the 5 non-terminated pregnancies with known outcome, 3 had an adverse outcome.

Of the 4 placebo-treated women who became pregnant (all on-treatment), there were 3 healthy term pregnancies and one elective termination.

The Maternal Health Team has been asked to evaluate this information, as well as any other available information, and recommend what further actions may be needed to understand the effect of Chantix in pregnancy. Their recommendations will be conveyed to Pfizer under separate cover and are not included in the evaluations of these supplements.

8.3 Safety Summary

Review of the individual studies and of the updated ISS confirmed the known adverse event profile of Chantix. It also identified a higher rate of cardiovascular events, particularly ischemic events, in patients treated with Chantix compared to those treated with placebo. This imbalance is most apparent in the study conducted in patients with pre-existing cardiovascular disease, where the numbers of such events were higher in both treatment arms than in studies in the general population. Because of very small numbers of events, it is difficult to draw conclusions about the risk in the general population.

Explorations of the updated ISS did not provide any new information regarding drug-relatedness of certain adverse events which have been identified as concerns via post-marketing surveillance, including neuropsychiatric events, accidental injuries and impaired driving, cerebrovascular accidents, convulsions, and visual impairment. There have been a small number of pregnancies in patients in clinical trials, and the outcomes suggest a possible adverse effect in pregnancy (more spontaneous abortions). The Maternal Health Team will

evaluate this further and make recommendations outside the context of the reviews of these applications.

9 Advisory Committee Meeting

No Advisory Committee meeting was held.

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

Financial disclosures included with these applications revealed a number of investigators receiving substantial financial compensation. However, analysis of the efficacy data with all potentially conflicted sites removed did not change the conclusions.

12 Labeling

These supplements proposed adding information to the Clinical Studies section, describing the three new studies and their efficacy results. In the adverse event section, Pfizer proposed adding the following language: (b) (4)

Additionally, Pfizer proposed adding information to the Dosing and Administration section of the labeling that described the alternate instructions for setting a quit day as (b) (4)

Based on the findings of Dr. Skeete's review, the review team proposed adding a new section to the Warnings and Precautions describing the cardiovascular adverse events in the CVD study. Information pertinent to these findings were also added to the patient counseling section and to the MedGuide. Notably, the language in the warning includes a statement regarding benefit, similar to that seen in the boxed warning about neuropsychiatric events. Smoking cessation contributes importantly to reduction in cardiac risk; Chantix-treated patients were about three times more likely than placebo-treated patients to maintain abstinence to Week 52.

Review by the Division of Drug Marketing, Advertising, and Communications (DDMAC) identified a concern about the use of the word "flexible" in labeling. Dr. Horn had previously

objected to the characterization of the change in instructions as a [redacted] because the "approach to quitting" is not materially different from before. The DDMAC team pointed out that the new instructions were not more "flexible" than before, because the Target Quit Date has always been patient-selected; it is simply a matter of whether Chantix is initiated before or after the TQD is identified. Therefore, references to [redacted] were changed in labeling to "[redacted] for setting a quit date."

13 Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend approval of all three supplements.

13.2 Risk Benefit Assessment

Chantix is clearly effective in helping smokers stop smoking; this effect is now confirmed in two populations often thought to be treatment-resistant: patients who smoke despite diagnoses with COPD or cardiovascular disease. Chantix can be used effectively according to an alternate set of directions, providing for treatment initiation before the patient sets a quit date. The effect is durable, with a quit rate superior to placebo both at the end of treatment and at the end of follow-up, with patients more likely to sustain a year of abstinence if they are treated with Chantix as compared to placebo. The health benefits of a year of abstinence are well-established.

There do not appear to be new risks associated with the use of Chantix in patients with COPD. There do not appear to be new risks associated with initiating Chantix before the patient sets a quit date, and this alternate set of directions does not seem to impair the efficacy. Therefore, Supplements 20 and 21 should be approved.

The key issue related to risk/benefit assessment pertains to patients with cardiovascular disease, as studied in Supplement 19. In this population, there appears to be an increased risk of cardiovascular events, including serious events in patients treated with Chantix. However, the likelihood of quitting smoking is significantly increased in patients treated with Chantix.

Expressed in terms of Number Needed to Treat (NNT) vs Number Needed to Harm (NNH)[20], it is necessary to treat 8 CVD patients with varenicline for 12 weeks to expect 1 of them to quit smoking through 52 weeks. It is necessary to treat 73 CVD patients with varenicline to expect one additional cardiovascular event through 52 weeks. This suggests a favorable risk/benefit ratio, if we assume that non-smoker status confers multiple health benefits. However, it would be helpful to know more specifically about the health benefits of abstinence from weeks 9-52 for the patients who quit smoking.

[20] Calculated at my request by Ms. Meaker, using the number of patients with at least one adjudicated cardiovascular event.

Although I recommend that Supplement 19 also be approved, I recommend that Pfizer be required to conduct a formal meta-analysis of all available clinical trial data (their own, and any data generated by individual investigators which may be obtained) to determine the rates of cardiovascular adverse events in patients treated with Chantix compared to those treated with placebo, taking into account the smoking status where possible.

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

The labeling and MedGuide should advise patients with cardiovascular disease to inform their physicians of this health history, and to seek medical attention for new or worsening cardiovascular symptoms.

13.4 Recommendation for other Postmarketing Requirements and Commitments

As noted above, Pfizer should be required to conduct a meta-analysis of all available data to determine the cardiovascular risk/benefit profile of Chantix in patients with and without cardiovascular disease.

Because Chantix is approved and already being used in this population, this study need not be conducted prior to approval of the supplement.

13.5 Recommended Comments to Applicant

Specific language pertaining to the need for a meta-analysis will be composed in consultation with OSE and is not available at the time of this writing.

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

/s/

CELIA J WINCHELL
06/08/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21928
Priority or Standard	Standard
Submit Date(s)	September 22, 2010
Received Date(s)	September 23, 2010
PDUFA Goal Date	July 23, 2011
Division / Office	DAAAP
Reviewer Name(s)	Pamela Horn, M.D.
Review Completion Date	
Established Name	varenicline
Trade Name	Chantix
Therapeutic Class	
Applicant	Pfizer
Formulation(s)	Oral
Dosing Regimen	1 mg bid
Indication(s)	Safety and efficacy
Intended Population(s)	In smokers with COPD

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the review of the clinical data, this reviewer recommends approval of this supplemental application, which proposes to include information on the efficacy and safety of the use of Chantix in patients with mild-to-moderate COPD.

- The Applicant submitted the results of a single clinical trial in the population of interest in support of this application. I have determined that the trial was designed and conducted in a reasonably adequate and well-controlled fashion that is sufficient to rely upon for a determination of efficacy and safety.
- The data reviewed in this single trial of patients with mild-to-moderate COPD indicate that Chantix is effective as an aid to smoking cessation as evidenced by continuous abstinence that was both statistically significantly higher than placebo and provide evidence of a clinically meaningful benefit in this population.
- Based on my review of the safety data in this trial, the risks in this population are not appreciably increased over previously studied populations.

1.2 Risk Benefit Assessment

Chantix has several safety concerns. These concerns are balanced by the consistent and substantial efficacy demonstrated in multiple trials in various populations, including the population currently under review.

Benefits:

- Chantix efficacy was established in several previous trials in general populations, and confirmed in a COPD population with one adequate and well-controlled clinical trial. Successful, maintained cessation of smoking has significant, well-established health benefits.
- Smoking cessation is believed to modify the course of chronic obstructive pulmonary disease making the benefits of a product effective in aiding smoking cessation additionally compelling for this population.
- There were no safety signals identified in this review that are unique to this population.

Risks:

- There are concerns about severe and serious neuropsychiatric events associated with Chantix. In the review of the pooled data from all controlled trials, there was similar incidence of neuropsychiatric events between treatment arms.[1] In the trial in the COPD population (trial A1054), there were more severe neuropsychiatric events in the placebo group compared to the varenicline group.

[1] For details of the pooled analysis and conclusions, see section 7.3.5

This safety issue is being further explored in a postmarketing trial and is presented prominently in the current labeling. In this reviewer's opinion, the known risks of these rare events do not outweigh the substantial evidence of efficacy in aiding patients in smoking cessation when the well-established health risks of smoking are taken into consideration.

- There is evidence from the review of the pooled data from all controlled trials that Chantix is associated with a small increase in incidence of ischemic cardiac events over placebo. Dr. Skeete has recommended that the information from the pooled safety data from Phase 2-4 studies, as well as findings from the sub-population of subjects with cardiovascular disease, be included in labeling. Smoking is an independent risk factor for acute myocardial infarction (Odds ratio 2.87[2]). This well-established risk, combined with the demonstrable efficacy Chantix provides in helping patients to stop smoking, outweighs the possible increase in risk conferred by varenicline.

Overall, the risk-benefit profile of Chantix in this population is favorable and similar to the profile for the larger general population who may use this medication.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I have identified no further safety issues in the review of this application that warrant additional postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

I do not recommend any additional postmarket requirements or commitments based on the review of this supplemental application.

2 Introduction and Regulatory Background

2.1 Product Information

NDA 21,928 was submitted by Pfizer on 11/11/05 and approved on 5/10/06. 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.

In the drug-interaction studies reviewed in the initial NDA application, there were no clinically meaningful drug-drug interactions identified. Maximum plasma concentrations

[2] Yusuf, et al, The Lancet, 2004

occur 3-4 hours after oral administration and steady state conditions are reached within 4 days. The elimination half-life is approximately 24 hours. Varenicline is eliminated renally and 92% is excreted in the urine unchanged.

2.2 Tables of Currently Available Treatments for Proposed Indications

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

Other available smoking cessation treatments include:

Table 1: Currently Available Smoking Cessation Treatments

Bupropion
Nicotine
• Transdermal (patch)
• Gum
• Lozenge
• Oral inhaler
• Nasal spray

2.3 Availability of Proposed Active Ingredient in the United States

Varenicline is currently marketed in the United States only in Chantix tablets.

2.6 Other Relevant Background Information

Varenicline has undergone eleven labeling revisions since approval. These are summarized in the table below:

Table 2: Labeling Changes

Date	Supplement number	Changes Made
11/20/07	003	Psychiatric adverse effects related to sleep, mood, attention, and alertness
1/31/08	007	Warnings re: neuropsychiatric symptoms
5/16/08	008	Medication guide added to labeling
7/1/09	012 and 013	Accidental Injury and Angioedema/Hypersensitivity Reaction Precautions
10/19/09	011	Revised REMS
2/4/10	015	Carton/container packaging change
4/22/10	014 and 017	Conversion of package insert into PLR format and REMS modification
12/17/10	023	Postmarketing reports of MI and CVA
2/17/11	018	New two week professional sample package

Source: Clinical Reviewer

The key safety concerns that have emerged since approval have been neuropsychiatric symptoms, accidental injury, angioedema, hypersensitivity reactions, cardiovascular events, cerebrovascular events, visual impairment, and convulsions.

Three additional supplemental NDAs were submitted concurrently to the supplemental application reviewed here:

- Supplement 021: The results of Clinical trial A1095 were submitted in support of the efficacy of Chantix using a flexible quit date paradigm.
- Supplement 019: The results of Clinical trial A1049 were submitted in support of the safety and efficacy of Chantix in patients with cardiovascular disease.

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All data and documents in this application were electronically submitted following the guidances for electronic submission. The documents were organized in eCTD format. The datasets were not in SDTM format. Additional case report forms and patient narratives not in the initial application were requested to clarify the circumstances of treatment discontinuation and coding rationale for patients who discontinued due to adverse events or experienced adverse events of special interest. The Applicant submitted an Integrated Summary of Safety as an amendment to the application following a request by the review team.

3.2 Compliance with Good Clinical Practices

The Applicant stated that the clinical trial was conducted under Good Clinical Practice in the study report.

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454 “Certification: Financial Interests and Arrangements of Clinical Investigator”, attached with a list of 121 of the 132 investigators of the submitted clinical trial, certifying that they had no financial interests or arrangements to disclose.

Of the 132 Clinical Investigators in this clinical trial, the remaining 11 had Financial Interests required to be disclosed under 21 CFR part 54 and submitted Form FDA 3455 “Disclosure: Financial Interests and Arrangements of Clinical Investigators”. All the Clinical Investigators in this clinical trial marked the checkbox classifying the disclosure as:

> "Any significant payments of other sorts made on or after February 2, 1999 from the Applicant of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria"

Of thirty-six Principal Investigators, six submitted financial disclosures. Of the twenty-seven clinical trial centers, nine had Clinical Investigators who submitted financial disclosures. Most of the disclosures totaled between $27,000 and $54,000. Sites 1016, 1018, 1020 and 1021 had disclosures totaling between $84,300 and $621,191 and were all U.S. sites. Analyses were performed on the efficacy data excluding clinical trial sites where Investigators received more than $24,999.00 and only on clinical trial sites where Investigators received more than $24,999.00 to assess for the possibility of bias in the results based on financial interests (See Section 6.1.10). No differences in efficacy results were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new data was submitted to or reviewed by the other review disciplines. See section 2.1 for relevant clinical pharmacology background information.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A single clinical trial was submitted in support of efficacy for this application. The results of trials A1049 (patients with cardiovascular disease) and A1095 (flexible quit date paradigm), in addition to clinical trial A1054 provide new safety information relevant to this supplemental application.

Table 3: Tables of Studies/Trials

Clinical trial	Relevance
Clinical trials contributing to Efficacy Review	
A3051054	Contains efficacy data in the COPD population
Clinical trials contributing to Safety Review	
A3051054	Contains safety data for COPD population
A3051049 (CV population)	Contains safety data for subjects exposed to varenicline **not** reviewed in the initial NDA application
A3051095 (Flexible Quit Date)	
A3051080 (multi-national)	
A3051104 (smokeless tobacco)	
A3051115 (neuropsychiatric symptoms	
A3051045 (Taiwan and Korea)	
A3051055 (Asian sites)	
A3051046_48 (Japan)	
A3051028 (Pivotal P3)	Contains safety data for subjects exposed to varenicline reviewed in the initial NDA application
A3051036 (Pivotal P3)	
A3051002 (dose ranging)	
A3051007 (titration)	
A3051016 (flex dosing)	
A3051037 (long-term safety)	

5.2 Review Strategy

The single clinical trial was reviewed individually for efficacy. The safety review was based on the single clinical trial as well as an Integrated Summary of Safety. The review also focused on the following key safety concerns: neuropsychiatric symptoms, accidental injury, cardiovascular and cerebrovascular events, serious skin reactions, hypersensitivity reactions, visual impairment, and convulsions.

Deleted Sections

- Sub-section 2.4 Important Safety Issues with Consideration to Related Drugs was deleted because this is the only drug in its class.
- Sub-section 2.5 Summary of Presubmission Regulatory Activity Related to Submission was deleted because no meetings were held and no advice was solicited or provided to the Applicant related to this submission.
- Sub-sections 4.1, 4.2, 4.3 and 4.4 were deleted from Section 4 because no new data was submitted related to other review disciplines.

- Sub-section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations was deleted because dosing recommendations were made in the initial NDA review and no new pertinent information was submitted in this application.
- Sub-section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects was deleted because these issues are not pertinent to the current application.
- Sub-section 9.1 was deleted because no literature review was provided or conducted during the review of this application.
- Sub-section 9.3 was deleted because no Advisory Committee meeting was held.

See Section 7, Summary of Safety for a listing of deleted sections of the Safety Review.

This application was reviewed by a single reviewer with the exception of the review of the ISS, which was partly reviewed by Dr. Rachel Skeete.

The protocol, conduct and demographic results of Clinical trial A3051054 will be reviewed in sub-section 5.3 and the efficacy data for clinical trial A3051054 will be reviewed in section 6 Review of Efficacy. The safety data from clinical trial A3041054 and the integrated safety data from all relevant trials will be reviewed in section 7 Review of Safety.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol A3051054
"A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial with 40-Week Follow-Up Evaluating the Safety and Efficacy of Varenicline Tartrate for Smoking Cessation in Patients with Mild-To-Moderate Chronic Obstructive Pulmonary Disease"
Conducted 02 MAY 2006 to 30 APRIL 2009

Below is a summary of clinical trial centers and principal investigators by country from the clinical study report:

Table 4: Clinical trial centers and Investigators

Center	Principal Investigator	Location	Country
1004	Dr. Francis Couturaud	CHU de la Cavale Blanche, Medecine Interne et Pneumologie, Brest	France
1005	Dr. Bernard Pigearias	Cabinet Medical, Nice	
1006	Dr. Frederique Aubourg	Hopital Cochin Explorations Fonctionelles et Respiratoires, Paris	
1030	Dr. Xavier Quantin, (Pascal Chanez, previous PI)	Hopital Arnaud de Villeneuve, Service des Maladies Respiratoires, Montpellier	
1007	Prof. Leonardo M. Fabbri	Universitaria di Modena, Modena	Italy
1008	Prof. Stefano Nardini	Unita' Locale Socio Sanitaria, Veneto	
1009	Dr. Simonetta Monti	Istituto di Fisiologia Clinica, Pisa	
1001	Josep Maria Ramon	L'hospitalet del llobregat, Barcelona	Spain
1002	Manuel Agustin Sojo, (Juan Antonio Riesco, previous PI)	Hospital San Pedro de Alcantara, Caceres	
1003	Carlos Jimenez	Instituto de salud publica, Madrid	
1010	Dr. Christina T. Holt (Dr. Lisa W. Miller, Dr. Susan Swartz, Previous PIs)	Maine Medical Center, Portland, ME	United States
1011	Dr. Mark Dransfield (Dr. Lynn B. Gerald, Previous PI)	UAB Lung Health Center, Birmingham, AL	
1012	Dr. James Francis Donohue	UNC at Chapel Hill, Div of Pulm and Crit Care Med, Chapel Hill, NC	
1013	Dr. David H. Gonzales	OHSU, Smoking Cessation Center, Portland, OR	
1014	Dr. Nicola Alexander Hanania	Ben Taub General Hospital, Houston, TX	
1015	Dr. James Taylor Hays III	Mayo Clinic, Rochester, MN	
1016	Dr. Sandra Beth Weibel (Dr. Frank Thos Leone, previous PI)	Thomas Jefferson University, Comprehensive Center for Tobacco Research and Treatment, Philadelphia, PA	
1017	Dr. Barry Jay Make	National Jewish Medical and Research Center, Denver, CO	
1018	Dr. Donald P. Tashkin	UCLA David Geffen School of Medicine, Los Angeles, CA	
1019	Dr. Eugene R. Bleecker	Cloverdale Clinical Research and Wake Forest University Health Sciences, Winston-Salem, NC	
1020	Dr. Cheryl Ann Oncken	U. Conn Health Ctr, Dept Psychiatry, Farmington, CT	
1021	Dr. Stephen Israel Rennard	U Nebraska Med Ctr, Omaha, NE	
1023	Dr. Howard I. Schwartz	Miami Research Assoc, Miami, FL	
1024	Dr. Michael P. Miller	Clin Res Assoc, Nashville, TN	
1025	Dr. Matthew G. Davis (Dr. Mervyn U. Weerasinghe, Previous PI)	Rochester Clin Research, Rochester, NY	
1029	Dr. S. David Miller	Northeast Med Research, North Dartmouth, MA	
1031	Dr. Craig Fred LaForce	North Carolina Clin Research, Chapel Hill, NC	

Source: Clinical Reviewer based on Applicant's Clinical Study Report p.1 and Appendix A4

Twenty-seven clinical trial sites randomized subjects in four countries, the U.S. and three European countries. The majority of the patients were enrolled in the United States.

Protocol

Objective/Rationale
The purpose of the clinical trial was to compare the efficacy of varenicline 1 mg bid to placebo for smoking cessation in subjects with mild to moderate chronic obstructive pulmonary disease (COPD) after 12 weeks of treatment and to evaluate continuous abstinence for 40 weeks after the treatment period.

The safety objective was to gather safety data in subjects with COPD for 12 weeks of treatment followed by 40 weeks of non-treatment follow-up.

Overall Design
This was a randomized, double blind, placebo-controlled, parallel group clinical trial. The duration of active treatment specified in the protocol was 12 weeks of varenicline 1 mg BID or placebo and subjects were to be followed in the non-treatment phase for an additional 40 weeks. Blinded trial medication was discontinued at the Week 12 visit and each subject's smoking status was to be followed through the non-treatment period to Week 52.

Population and Procedures

Inclusion/Exclusion Criteria
Planned enrollment was approximately 500 subjects with mild to moderate COPD randomized 1:1 to each of two treatment arms

To be eligible, subjects were to be required to meet the following criteria:
- Male or female current cigarette smokers 35 years of age or older who had mild to moderate COPD (as defined by the 2003 Global Initiative for Chronic Obstructive Lung Diseases criteria) and were motivated to stop smoking. See the Appendix for the severity classification table.
- Smoking an average of at least 10 cigarettes per day during the past year and over the month prior to the Screening visit
- Forced expiratory volume in 1 second/ forced vital capacity [FEV_1/FVC] of less than 70% at the Screening visit or within thirty days of the Screening visit.
- FEV_1 less than or equal to 50% of predicted normal value after the administration of a short-acting bronchodilator at Screening visit or within thirty days of the Screening visit.

Subjects were to be excluded for:
- Making a serious attempt to quit smoking in the past 3 months

- Using a nicotine replacement product, bupropion, clonidine, nortriptyline within the previous 3 months, or participating in a study with an experimental or marketed drug for smoking cessation within the previous 3 months
- Not agreeing to abstain completely from using non-cigarette tobacco products (including pipe tobacco, cigars, snuff, chewing tobacco, etc) or marijuana during study participation
- Receiving treatment for depression in the past twelve months
- Having a past or present history of panic disorder, psychosis or bipolar disorder
- Having a history of drug (except nicotine) or alcohol abuse or dependence within the past 12 months
- Having a positive urine drug screen[3]
- Being a female who had a positive serum pregnancy test at screening
- Being a female of child bearing potential and not agreeing to use 1 of the following birth control methods: An oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive (e.g., Norplant), or an injectable contraceptive (e.g., Depo-Provera) for at least 1 month prior to entering the study and continue its use through at least 30 days after the last dose of study drug; or a barrier method of contraception, e.g., condom and/or diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study drug; or abstinence.
- Intending to donate blood or blood components while receiving experimental drug or within 1 month of the completion of study treatment
- Requiring other medications during the study that could interfere with the evaluation of the study drug (e.g., nicotine replacement therapy, bupropion, clonidine, nortriptyline, or other medications used for smoking cessation including over-the-counter or herbal remedies)
- Having clinically significant abnormal ECGs at screening or clinically significant cardiovascular events in the past 6 months, such as: myocardial infarction, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), severe or unstable angina, serious arrhythmia, or clinically significant cardiac conduction abnormalities
- Having uncontrolled hypertension with a systolic blood pressure (BP) greater than 160 mmHg or a diastolic BP greater than 95 mmHg at screening or baseline
- Having clinically significant neurological disorders or cerebrovascular events (e.g., stroke, transient ischemic attack, etc) in the past 6 months
- Having clinically significant endocrine disorders
- Having any condition possibly affecting drug absorption such as clinically significant gastrointestinal disorders with evidence of malabsorption which could be due to extensive gastrointestinal resection, injury, or inflammation

[3] The Applicant's protocol did not specify which drugs were screened; it is likely that the test screened for drugs of abuse.

- Having clinically significant hepatic or renal impairment or other clinically significant abnormal laboratory test values:
    - Subjects with severe abnormalities of renal function (estimated creatinine clearance <30 mL/min);
    - Subjects with serum glutamic-oxaloacetic transaminase (SGOT; aspartate aminotransferase, [AST]) or serum glutamic-pyruvic transaminase (SGPT; alanine aminotransferase, [ALT]) greater than 1.5 times the upper limit of normal (ULN) or total bilirubin greater than 1.1 times the ULN.
- Having an active malignancy of any type, or a history of malignancy. (Subjects who had a history of basal cell carcinoma that had been successfully treated were allowed. Subjects with a history of other malignancies which had been surgically removed and who had no evidence of recurrence for at least 5 years before enrollment in the study were also allowed.)
- Taking a concomitant medication that was prohibited
- Using systemic (intravenous [IV], intramuscular [IM], or oral) corticosteroids during the 4 weeks period prior to screening
- Being treated or hospitalized for COPD exacerbation during the 4-week period prior to screening

Prohibited concomitant medications included:

- Antidepressants, including bupropion (Wellbutrin®), citalopram (Celexa®), fluoxetine (Prozac®), mirtazepine (Remeron®), nefazodone (Serzone®), paroxetine (Paxil®), sertraline (Zoloft®), trazodone, tricyclic antidepressants, monoamine oxidase inhibitors and venlafaxine (Effexor®)
- Antipsychotic agents, including clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), risperidone (Risperdal®), and ziprasidone (Geodon®)
- Benzodiazepines, including alprazolam (Xanax®), diazepam (Valium®), and lorazepam (Ativan®)
- Mood stabilizers, including carbamazepine (Tegretol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), lithium, and valproate (Depakene® or Depakote®)
- Naltrexone
- Nicotine replacement therapy and other aids to smoking cessation
- Over-the-counter and prescribed stimulants and anorectic agents
- Steroids, including systemic anabolic steroids, mineralocorticoids and continuous systemic glucocorticosteroid use greater than 2 weeks (Inhaled glucocorticosteroid use was permitted)
- Theophylline
- Any investigational drug

Procedures

The protocol called for an initial screening visit to occur seven to ten days prior to baseline/randomization during which medical screening procedures were undertaken. A subsequent “baseline” visit was to be scheduled and would be cancelled if results of

laboratory tests did not confirm eligibility. At the time of screening, subjects were to select a target quit date (TQD) to coincide with the Week 1 visit, which was required to be scheduled to occur 8 days after the baseline visit, so that subjects would have a full 7 days of treatment prior to the TQD.

At the baseline visit, assessments as illustrated in the time-and-events table [see Schedule of Visits and Assessments below] were to be performed. Subjects were assigned to treatment using a call-in system. Site personnel were to dispense trial drug for the first week of treatment and provide dosing instructions.

Dosing
Eligible subjects were to be randomized to treatment with varenicline or placebo. To maintain blinding, placebo pills have the same appearance as the respective varenicline pills.

Both varenicline and its matching placebo were to be dispensed to the subjects in bottles from room temperature storage at each scheduled visit between screening and Week 12. Supplies of varenicline were 0.5 mg tablets for the first week and 1 mg tablets for the remaining 11 weeks of the clinical trial treatment period.

Dosing during the treatment period was to be as follows:

- Trial Day 1: Treatment was to begin on the day after the baseline visit.
- Trial Days 1-3: The subjects were to be instructed to take one tablet in the morning for the first 3 days of the dosing period.
- Trial Days 4-7: The dosing was then to increase for the next 4 days to two tablets per day; one in the morning and one in the evening.
- Trial Day 8: Subjects were to have increased their dose to two tablets in the morning and one tablet in the evening (0.5 mg tablets). This day should coincide with the Week 1 visit; subjects were to have received the bottle of 1 mg tablets.
- Trial Days 9-84: Subjects were to begin taking the 1 mg tablets and were to take one tablet in the morning and one in the evening from Trial Day 9 through Week 12.

Dosing instructions called for administration with 240 ml of water and subjects were advised to eat prior to dosing. Subjects were instructed that there were to be at least 8 hours between the morning and evening dosing. Subjects were to return medication bottles at each visit and a dosage record was to be recorded.

Schedule of Visits and Assessments
Subjects were to return for visits to the clinic after the baseline visit over the following 12 weeks at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12. The subjects were instructed to attempt to quit on the target quit date at the Week 1 visit (8 days after the baseline visit). The quit attempt was to occur in the morning prior to the clinic visit that day, so that the subject's last cigarette prior to the quit attempt would be before midnight the night prior

to the Week 1 visit. Subjects were to be called 3 days after the target quit date (TQD+3) to be reminded of clinical trial participation and to receive support for the smoking cessation attempt. These contacts were to be up to 5 minutes in length and counseling was to follow AHRQ guidelines.

At each visit, subjects were to have the following assessments:

- Asked about cigarette and other nicotine use since the last trial visit and in the past 7 days (using the Nicotine Use Inventory).
- End-expiratory exhaled carbon monoxide was to be measured.
- Subjects are to have filled out the Clinical COPD Questionnaire (CCQ).
- Concomitant medications and any adverse events were to be recorded. Subjects were to be questioned about adverse events.
- Other subjective effects and safety measures were undertaken as per the time-and-events schedule below.

At the Week 12 visit (or early termination), subjects were to have the following additional assessments:

- Physical examination
- Weight measurement
- ECG
- Spirometry
- Blood and urine sample collection.

Following completion of the Week 12 visit, subjects were to continue in the non-treatment follow-up phase of the protocol. Subjects discontinuing trial drug prior to the Week 12 visit would be permitted to continue trial participation as long as they complete the remaining scheduled visits through Week 12.

The following time-and-events table illustrates the planned schedule of assessments during the treatment period (from Applicant's protocol):

Table 5: Schedule of Activities
Schedule of Activities
Screening – Week 12 Visit (Treatment Phase)

Procedure	Screen	BL	Wk 1	TQD +3	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	ET_{12}[a]
Informed consent[b]	X															
Medical history	X															
Physical examination[c]	X														X	X
Blood Pressure, Pulse rate	X	X	X				X				X				X	X
Temperature, Height	X															
Weight	X	X													X	X
Fagerström Test	X															
Exhaled CO		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Nicotine Use Inventory			X		X	X	X	X	X	X	X	X	X	X	X	X
Spirometry	X	X													X	X
CCQ		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Smoking diary			X		X	X										
Adverse events		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drugs[e]		X	X		X	X	X	X	X	X	X	X	X	X		
All subjects stop smoking			X													
Dosing record			X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X														X	X
Blood chemistry	X														X	X
CBC with differential	X														X	X
HbA1c	X														X	X
Serum pregnancy test[d]	X														X	X
Serum c-reactive protein, plasma fibrinogen		X													X	X
Serum cotinine	X															
Genotyping sample[f]		X														
Urinalysis	X														X	X
Urine drug screen[g]	X															
Counseling (AHRQ guidelines)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Brief telephone contact				X												

[a] if ET is before the Week 12 visit;
[b] must be signed prior to any protocol procedures being performed;
[c] either screening or BL;
[d] all females unless surgically sterilized or at least 2 years postmenopausal;
[e] At BL Visit, dispense the 0.5 mg titration bottle (or placebo to match); At Weeks 1-11 Visits, dispense 1mg bottles (or placebo to match);
[f] Optional; separate consent form required;
[g] may be performed at other visits at investigator's discretion

AHRQ = Agency for Healthcare Research and Quality
BL = Baseline;
CO = Exhaled Carbon Monoxide;
ET = Early Termination;
TQD +3 = Target Quit Day +3 days

Source: Applicant's Clinical Study Report Appendix A p.485

Non-treatment Follow-up (Weeks 13 through 52)

Subjects were to return for visits to the clinic at Week 13, 16, 24, 32, 40, 48 and 52. At each visit, subjects were to have the following assessments:

- Nicotine Use Inventory (collected information about cigarette and other tobacco use since the last contact and over the previous 7 days)
- CCQ
- End-expiratory exhaled carbon monoxide (nonsmoking status would be considered confirmed with a measurement ≤ 10 ppm).
- Vital signs
- Concomitant medications used as an aid to smoking cessation were to be recorded.

At Weeks 24 and 52 (or early termination) subjects were to have spirometry and weight measurements.

At the Week 52 (or early termination) visit, subjects were to have:

- Physical exam
- ECG
- Blood drawn for the measurement of hematology, blood chemistry, fibrinogen, C-reactive protein and HbA1c.

Up to ten minutes of brief counseling regarding smoking cessation was to be provided at the end of each clinic visit, in accordance with AHRQ guidelines.

Additionally, the Nicotine Use Inventory was to be administered by telephone at Weeks 14, 20, 28, 36, and 44 and subjects were to be asked about adverse events and concomitant medications used as an aid to smoking cessation, and provided with up to 10 minutes of counseling.

The following time-and-events table illustrates the planned schedule of assessments (from Applicant's protocol):

Table 6: Time and Events Table

Week 13 Visit – Week 52 Visit (Nontreatment Follow-Up)

Procedure	Wk 13	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	ET_{52}
Clinic visit	X		X		X		X		X		X	X	X
Phone contact		X		X		X		X		X			
Physical examination												X	X
Blood pressure, Pulse rate	X		X		X		X		X		X	X	X
Weight					X							X	X
Exhaled CO	X		X		X		X		X		X	X	X
Nicotine Use Inventory	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry					X							X	X
CCQ	X		X		X		X		X		X	X	X
Blood chemistry												X	X
CBC with differential												X	X
HbA1c												X	X
Urinalysis												X	X
C-reactive protein, plasma fibrinogen												X	X
Electrocardiogram												X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Counseling (AHRQ)	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: Applicant's Clinical Study Report, Appendix A, p. 486

Evaluations/Endpoints

The pre-specified primary endpoint was the 4-week Continuous Quit Rate (CQR) for 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. Subjects who withdrew before the trial completion were considered non-responders for the remainder of the trial, regardless of smoking status at the time of discontinuation. If a subject missed a visit during weeks 9 through 12, a subject was to be considered a responder if the subject:

> "Responds that they have not smoked or used nicotine products 'since the last visit' at the visit after the missing visit or visits. Missing CO measurements will be imputed as negative (i.e., imputed as <10 ppm), therefore not disqualifying the subject as a responder."

Key secondary endpoints identified in the protocol included:

• Continuous Abstinence (CA) Rate from Week 9 through Week 52: The proportion of subjects who maintained complete abstinence from cigarette smoking and other tobacco use from Weeks 9 through 52

• Long-term Quit Rate (LTQR) at Week 52: The proportion of subjects who remained abstinent from Weeks 9 through 12 and have no more 6 days of smoking during the non-treatment phase

Other secondary endpoints identified included:

- CA rate from Week 9 through Week 24
- LTQR through Week 24
- 7-day point-prevalence of smoking cessation at Weeks 12, 24, and 52[4]
- 4-week point-prevalence of smoking cessation at Week 52[5]
- Change from baseline in spirometry measurements at weeks 12, 24, and 52
- The CCQ total scores and subscale scores at Weeks 12, 24 and 52
- Number of cigarettes smoked per day during the first 3 weeks of the treatment phase.

Statistical Plan

The protocol-specified intent of the primary analysis is to evaluate the alternative hypothesis that varenicline is superior to placebo for smoking cessation after 12 weeks of treatment and reject the null hypothesis. The primary analysis population (Modified Intent-to-Treat) was to be all subjects who took at least one dose of randomized trial medication. Subjects who discontinued the trial were assumed to be non-responders. The trial was powered at ≥ 81% to detect differences in the primary as well as the two key secondary endpoints. A step-down procedure was to be employed within the analysis of both primary and key secondary endpoints, in order to control for type I error within each endpoint.

Results

Trial Conduct/Outcome

Subject Characteristics

Of 1010 smokers screened, 250 subjects were assigned to varenicline treatment and 254 subjects to placebo treatment. Two subjects and three subjects that were randomized to varenicline and placebo respectively did not initiate treatment. Upon review, it was determined that 39 enrolled participants did not meet the protocol-specified criteria for COPD. The clinical and statistical reviewers excluded these subjects from some analyses as noted in the sections below.

[4] Number of subjects who at the given visit reported no smoking and no use of nicotine-containing products (treatment phase) or tobacco products (non-treatment phase) in the last 7 days and who did not have CO > 10 ppm on that day

[5] Number of subjects who at the given visit reported no smoking and no use of nicotine-containing products (treatment phase) or tobacco products (non-treatment phase) in the last weeks and who did not have CO > 10 ppm on that day

There were 27 Centers in four countries that randomized subjects. The PIs, locations, and enrollment of the centers are summarized in the table below.

Table 7: Enrollment by center

Country	Location	Principal Investigator	Center	Number enrolled	Total enrolled per country
France	CHU de la Cavale Blanche, Medecine Interne et Pneumologie, Brest	Dr. Francis Couturaud	1004	25	91
	Cabinet Medical, Nice	Dr. Bernard Pigearias	1005	38	
	Hopital Cochin Explorations Fonctionelles et Respiratoires, Paris	Dr. Frederique Aubourg	1006	15	
	Hopital Arnaud de Villeneuve, Service des Maladies Respiratoires, Montpellier	Dr. Xavier Quantin, (Pascal Chanez, previous PI)	1030	13	
Italy	Universitaria di Modena, Modena	Prof. Leonardo M. Fabbri	1007	15	32
	Unita Locale Socio Sanitaria, Veneto	Prof. Stefano Nardini	1008	2	
	Istituto di Fisiologia Clinica, Pisa	Dr. Simonetta Monti	1009	15	
Spain	L'hospitalet del llobregat, Barcelona	Josep Maria Ramon	1001	18	56
	Hospital San Pedro de Alcantara, Caceres	Manuel Agustin Sojo, (Juan Antonio Riesco, previous PI)	1002	19	
	Instituto de salud publica, Madrid	Carlos Jimenez	1003	19	
United States	Maine Medical Center, Portland, ME	Dr. Christina T. Holt (Dr. Lisa W. Miller, Dr. Susan Swartz, Previous PIs)	1010	28	325
	UAB Lung Health Center, Birmingham, AL	Dr. Mark Dransfield (Dr. Lynn B. Gerald, Previous PI)	1011	15	
	UNC at Chapel Hill, Div of Pulm and Crit Care Med, Chapel Hill, NC	Dr. James Francis Donohue	1012	10	
	OHSU, Smoking Cessation Center, Portland, OR	Dr. David H. Gonzales	1013	25	
	Ben Taub General Hospital, Houston, TX	Dr. Nicola Alexander Hanania	1014	14	
	Mayo Clinic, Rochester, MN	Dr. James Taylor Hays III	1015	37	
	Thomas Jefferson University, Comprehensive Center for Tobacco Research and Treatment, Philadelphia, PA	Dr. Sandra Beth Weibel (Dr. Frank Thos Leone, previous PI)	1016	6	
	National Jewish Medical and Research Center, Denver, CO	Dr. Barry Jay Make	1017	20	
	UCLA David Geffen School of Medicine, Los Angeles, CA	Dr. Donald P. Tashkin	1018	20	
	Cloverdale Clinical Research and Wake Forest University Health Sciences, Winston-Salem, NC	Dr. Eugene R. Bleecker	1019	20	
	U. Conn Health Ctr, Dept Psychiatry, Farmington, CT	Dr. Cheryl Ann Oncken	1020	12	
	U Nebraska Med Ctr, Omaha, NE	Dr. Stephen Israel Rennard	1021	44	
	Miami Research Assoc, Miami, FL	Dr. Howard I. Schwartz	1023	6	
	Clin Res Assoc, Nashville, TN	Dr. Michael P. Miller	1024	18	
	Rochester Clin Research, Rochester, NY	Dr. Matthew G. Davis (Dr. Mervyn U. Weerasinghe, Previous PI)	1025	34	
	Northeast Med Research, North Dartmouth, MA	Dr. S. David Miller	1029	3	
	North Carolina Clin Research, Chapel Hill, NC	Dr. Craig Fred LaForce	1031	13	
			Total		504

Source: Clinical Reviewer based on Applicant's Clinical Study Report p. 1, Appendix A4 and dataset "DEMOG"

Subject Disposition

A total of 504 subjects were randomized in a 1:1 ratio. Of the 250 subjects assigned to varenicline, 248 received the treatment. As shown in the table below, of the 254 subjects assigned to the placebo group, 251 received the treatment. The number of subjects who completed treatment was 207 (83.5%) in the varenicline group and 193 (76.9%) in the placebo group. These completion rates are higher than the completion rates in the two pivotal trials submitted in support of the initial NDA application. Treatment discontinuations who were lost to follow-up were imputed as non-responders. Subjects who discontinued treatment could remain in the trial, thus not all subjects listed under “discontinued treatment” discontinued the trial.

Table 8: Subject Disposition

Number (%) of subjects	Varenicline		Placebo	
Screened: 1010				
Assigned to study treatment	250		254	
Treated	248		251	
Completed treatment	207	(83.5)	193	(76.9)
Discontinued treatment[a]	41	(16.5)	58	(23.1)
Related to study drug	11	(4.4)	11	(4.4)
Adverse event	11	(4.4)	8	(3.2)
Lack of efficacy	0		3	(1.2)
Not related to study drug	30	(12.1)	47	(18.7)
Adverse event	1	(0.4)	6	(2.4)
Lost to follow up	10	(4.0)	10	(4.0)
Subject not willing to participate in study	13	(5.2)	25	(10.0)
Other	6	(2.4)	6	(2.4)
Completed study	176	(71.0)	157	(62.5)
Discontinued study[b]	72	(29.0)	94	(37.5)
Subject died[c]	2	(0.8)	1	(0.4)
Related to study drug	4	(1.6)	10	(4.0)
Adverse event	4	(1.6)	7	(2.8)
Lack of efficacy	0		3	(1.2)
Not related to study drug	66	(26.6)	83	(33.1)
Adverse event	1	(0.4)	4	(1.6)
Lost to follow up	29	(11.7)	31	(12.4)
Subject not willing to participate in study	31	(12.5)	43	(17.1)
Other	5	(2.0)	5	(2.0)
Analyzed for efficacy				
All subjects	248	(100.0)	251	(100.0)
Evaluable subjects	239	(96.4)	240	(95.6)
Completer subjects	210	(84.7)	196	(78.1)
Analyzed for safety				
Adverse events	248	(100.0)	251	(100.0)
Laboratory data[d]	222	(89.5)	211	(84.1)

[a] Subjects could discontinue from treatment and remain in the study.
[b] Discontinuations from the study could occur during the treatment period or during the post-therapy follow-up period.
[c] Deaths occurred in the non-treatment period and were not assessed as related to study drug.
[d] Laboratory data were analyzed for those subjects who had at least 1 non-missing post-baseline laboratory value.

Source: Applicant's Clinical Study Report Table 6

Fifty-four subjects (22%) in the placebo group compared to thirty subjects (12%) in the varenicline group discontinued the trial during the treatment period. The higher percentage of trial discontinuations in the placebo group had the potential to bias the trial in favor of varenicline on the primary efficacy endpoint since subjects who

discontinued the trial during the treatment period (i.e. did not have data for weeks 9 through 12) were imputed a negative outcome. However, there is data for these subjects prior to dropout indicating that imputation of a negative outcome is appropriate. Of the subjects who dropped out of the trial during the treatment period, three had data at the week 9 visit (2 placebo and 1 varenicline) and seven (3 placebo and 4 varenicline) had an early termination visit. All subjects reported smoking at the early termination visit. One subject had confirmed abstinence at the week 9 visit but had relapsed by the early termination visit. Of the other two subjects with data at week 9, both were in the placebo group and reported smoking. One subject in the varenicline group had evidence of abstinence at weeks 2-5. It is reasonable to impute a negative outcome to these subjects because none of the subjects in the placebo group and only two in the varenicline group had evidence of abstinence at any of the visits prior to dropout and success rates in smoking cessation are low in general. Therefore, these dropouts do not appear to have biased the study.

Lack of efficacy was given as the reason for trial discontinuation in 1.2% of subjects in the placebo group and none in the varenicline group. This does not account for the 10% between group difference in trial discontinuation rates during the treatment period. It is possible that subjects who were coded as “not willing to participate in the study” actually dropped out for lack of efficacy, especially since the placebo group had higher rates of these types of dropouts than the varenicline group. A review of the raw data revealed that two subjects in the placebo group who discontinued during the treatment phase were coded as “subject no longer willing to participate in study” but gave responses that indicated that they should have been coded as “insufficient clinical response.”

Discontinuations from treatment due to adverse events were higher in the varenicline group (11 subjects (4.4%) than the placebo group (8 subjects (3.2%)). Treatment discontinuations judged unrelated to trial drug occurred in 30 subjects (12.1%) in the varenicline group and 47 subjects (18.7%) in the placebo group.

Trial discontinuations over the entire trial (to week 52) were higher in the placebo group (29% in the varenicline group and 37.5% in the placebo group).

Demographics

The table below illustrates demographic and baseline characteristics of the two treatment groups. There were a greater proportion of subjects over 65 years of age in the placebo group compared to the varenicline group but the oldest subject (age 83) was in the varenicline group. The mean age of subjects was 57.1 in the varenicline group and 57.1 in the placebo group. The varenicline group did not vary from the placebo group in a way that would suggest bias with respect to smoking history.

Table 9: Demographic and Baseline Characteristics

		Varenicline (N=248)	Placebo (N=251)
Gender	n		
	Male	155	156
	Female	93	95
Age	n (%)		
	< 35	0	1 (0.4)
	35-44	24 (9.7)	20 (8.0)
	45-54	70 (28.2)	77 (30.7)
	55-65	112 (45.2)	107 (42.6)
	>65	42 (16.9)	46 (18.3)
	Mean ± SD	57.2 ± 9.1	57.1 ± 9.0
	Range	35-83	37-77
Race	n (%)		
	White	203 (81.9)	211 (84.1)
	Black	15 (6.0)	10 (4.0)
	Other	30 (12.1)	30 (12.0)
Mean number of years smoked		40.4	40.6
Mean number of cigarettes per day past month		25.3	23.6
Mean Fagerstrom test score		6.2±2.2	5.9±2.1
Mean longest period abstinence (days)		6.5	6.6

N= number of subjects in the respective treatment group, n = number of subjects with respective characteristic, SD = standard deviation
Source: Applicant's Clinical Study Report, Tables 8 and 10, dataset DEMOG

The most notable differences between this population and populations studied previously are higher mean age (age 57 in this trial vs. age 43-44 in pivotal trials), lengthier and heavier smoking history (see table below) and higher medical comorbidity. As noted above, 39 subjects did not meet inclusion criteria for COPD. Exclusion of subjects that did not meet inclusion criteria for COPD did not change the mean age of subjects in either group (varenicline group mean age 57.2, placebo group mean age 57.5). The average Fagerstrom test scores (excluding the subjects that did not meet inclusion criteria for COPD) was 6.1 for the varenicline group and 6.1 for the placebo group.

Table 10: Smoking History by Trial (includes all treatment arms)

	Trial A1054	Trial A1036	Trial A1028
Number of years smoked	40.4-40.6	24-27	24-25
Number of cigs per day past month	23.6-25.6	22-23	21-22
Fagerstrom test score	5.9-6.2	5.2-5.4	5.2-5.4
Longest period abstinence (days)	6.5-6.62	6.3-8	5-5.8

Source: Clinical Reviewer based on Chantix label and table 10 of Applicant's Clinical Study Report

Dosing Information
The median duration of exposure was 84 days in both treatment groups. This is identical to the two pivotal trials from the initial NDA. The table below is taken from Pfizer's final study report.

Table 11: Duration of Treatment (All Subjects)

Number of subjects	**Varenicline (N = 248)**	**Placebo (N = 251)**
Duration category (days)		
≤1	2	2
2 – 7	3	2
8 – 14	6	7
15 – 28	8	13
29 – 60	15	27
61 – 90	194	178
≥91	20	22
Median duration	84.0	84.0
Range	1 – 103	1 – 114

N = number of subjects in the respective treatment group.

Source: Applicant's Clinical Study Report

Protocol Violations

Pfizer reported protocol deviations for subjects that entered the trial but did not meet all the entrance criteria as well as subjects who deviated from the protocol during the trial.

Thirty-nine subjects (25 varenicline and 14 placebo) did not have a post-bronchodilator FEV_1/FVC ratio < 0.7 at screening or baseline and did not meet the criterion for COPD diagnosis. Pfizer analyzed the efficacy data including these 39 subjects. They also did a post-hoc analysis of efficacy excluding these subjects. This deviation affects the

relevance of this trial to the proposed labeling change and this review discusses the efficacy and safety in the subset of subjects that met the criteria for COPD.

Thirty-six subjects (18 varenicline and 18 placebo) had a post- bronchodilator FEV_1/FVC ratio that placed them in the severe COPD category. This protocol deviation provides additional information about varenicline in a population with severe COPD and does not raise concern for bias or relevance for the labeling claims.

One-hundred seven subjects (47 varenicline, 60 placebo) used one or more prohibited smoking cessation medications. Pfizer provided a summary of the subjects. Fourteen subjects (5 varenicline, 9 placebo) used prohibited medication during the treatment period. Of these fourteen subjects, two were classified as responders. The efficacy data has been analyzed by the statistical reviewer without these two subjects. None of the subjects who used prohibited medications during the non-treatment period were responders and do not need to be removed from the analysis.

There were 8 subjects taking mood stabilizers/ anticonvulsants, 22 subjects taking benzodiazepines, one subject taking an antipsychotic, 20 subjects taking anti-depressants, and 6 subjects with a diagnosis of depression. These subjects represent a subpopulation with a comorbid psychiatric diagnosis or concomitant medication with a psychiatric indication (though it is unknown whether the medication was being used to treat a psychiatric condition in these subjects). Due to the lack of safety data in this subpopulation, the safety experience of these subjects is of interest (see section 7.7).

6 Review of Efficacy

Efficacy Summary

The efficacy of varenicline in the COPD population was evaluated in one placebo-controlled trial. The primary efficacy endpoint was a binary endpoint where subjects were considered responders if they were abstinent for weeks 9 through 12 of the treatment period inclusive[6]. This is the same primary efficacy endpoint used in the initial NDA. Based on the data from subjects who met inclusion criteria for COPD, we can be 95% confident that patients with mild to moderate COPD are 4.5 to 13 times more likely to be abstinent during weeks 9 through 12 of treatment when taking varenicline compared to placebo. The Applicant also proposes to include the continuous abstinence rates from weeks 9 through 52, which were also superior to placebo in the label. This secondary endpoint is included in the label for the trials reviewed in the initial NDA. These results are consistent with the results seen in the initial trials of varenicline with the exception of lower placebo response rates in this trial.

[6] Subjects were 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 as reported on the Nicotine Use Inventory and confirmed with end-expiratory exhaled CO measurements ≤ 10 ppm

The results demonstrate significant efficacy over placebo for varenicline in this population. The secondary endpoint of continuous abstinence at one year is important supportive information that suggests that the effects of treatment success with varenicline during the treatment period translate into a longer-lasting benefit that will have clinically significant health benefits for patients.

6.1 Indication

There is no new indication proposed in this application. The Applicant proposes to include the results of this trial in the Clinical Studies section of labeling, as evidence of efficacy as an aid to smoking cessation treatment in patients with COPD.

6.1.1 Methods

See Section 5.3

6.1.2 Demographics

See Section 5.3

6.1.3 Subject Disposition

See Section 5.3

6.1.4 Analysis of Primary Endpoint(s)

Applicant's analysis
The first table below shows the results calculated by Pfizer for the primary endpoint (4-week Continuous Quit Rate for weeks 9-12) in the current trial for all subjects and for only the subjects who met the COPD diagnostic inclusion criterion. The second table summarizes the reviewer's analysis of the 4-week CQR[7] primary efficacy endpoint of three trials reviewed in the initial NDA where subjects received varenicline 1 mg bid.

Table 12: Applicant's Primary Efficacy Evaluation Trial A3051054

Population	Varenicline n (%)	Placebo n (%)	Odds Ratio (95% CI) versus placebo	p-value
All subjects	105 (42)	22 (9)	8.4 (5.0, 14.1)	<0.0001
Subjects with COPD	93 (42)	22 (9)	7.7 (4.5, 13.0)	<0.0001

Source: Clinical Reviewer adapted from Table 12 and p. 173 of the Applicant's Clinical Study Report

[7] Same primary endpoint as the study currently under review

Table 13: Primary Efficacy Endpoint from Trials reviewed in initial NDA application

Trial	Varenicline (%)	Placebo (%)	Odds Ratio (95% CI) versus placebo
A3051028	44	17	3.9 (2.7, 5.5)
A3051036	44	18	3.8 (2.7, 5.4)
A3051007	51	12	7.8 (4.3, 14.3)

Source: Clinical Reviewer adapted from p. 15 of NDA 21928-s000 Medical Review

Differences in the varenicline and placebo groups in the Evaluable and Completer populations were also statistically significant and support the results of the All Subjects analysis.

The Applicant also evaluated the treatment by center interaction and concluded that there was no significant interaction.

Reviewer's Analysis
The results were audited by Dr. Katherine Meaker, Statistical Reviewer.

As in the trials in the initial NDA, the primary efficacy endpoint was the continuous quit rate from weeks 9 through 12 following a two-month "grace period." The choice of two months is not fully justified. In the original NDA, the statistical reviewer analyzed the data with grace periods of as short as two weeks and the main conclusions were unchanged.

Dr. Meaker analyzed the primary efficacy endpoint excluding the 39 subjects who did not meet the inclusion criteria for COPD and 2 subjects who used prohibited medications and were classified as responders in the Applicant's analysis.

Table 14: Reviewer's analysis of Primary Efficacy Endpoint

	Varenicline (%) N=221	Placebo (%) N=237	P-value
CQR Wks 9-12	41.2	9.3	<0.0001

Sources: Dr. Meaker's analysis

Exclusion of these subjects did not significantly change the results. Varenicline demonstrates efficacy over placebo in this population.

6.1.5 Analysis of Secondary Endpoints(s)

The table below summarizes the Applicant's analysis of the pre-specified key secondary endpoints

Table 15: Applicant's analysis of key secondary efficacy endpoints

Endpoint	Varenicline N=248 n (%)	Placebo N=251 n (%)	Odds Ratio (95% CI) versus placebo	p-value
CA Weeks 9-52[8]	46 (19)	14 (6)	4.0 (2.1, 7.7)	< 0.0001
LTQR Week 52[9]	53 (21)	17 (7)	3.9 (2.2, 7.1)	< 0.0001

Source: Clinical Reviewer adapted from Table 12 of the Applicant's Clinical Study Report

Dr. Meaker analyzed these key secondary endpoints excluding the 39 subjects who did not meet the inclusion criteria for COPD and 2 subjects who used prohibited medications and were classified as responders in the Applicant's analysis.

Table 16: Reviewer's Analysis of key secondary efficacy endpoints

Endpoint	Varenicline N=221 (%)	Placebo N=237 (%)	p-value
CA Weeks 9-52	19	6	< 0.0001
LTQR Week 52	21	7	< 0.0001

Sources: Dr. Meaker's analysis

Exclusion of these subjects did not alter the results significantly.

The Applicant also reported results for the other pre-specified secondary efficacy endpoints for abstinence. The "point prevalence" endpoints are defined as the prevalence of abstinence (from cigarettes and nicotine-containing products during the treatment phase and from cigarettes but not nicotine replacement therapies during the non-treatment follow-up phase) based on answering "no" to the "last 7 days" or "last 4 weeks" questions on the Nicotine Use Inventory at the time point being used (week 12 visit, week 24 visit or week 52 visit). Subjects with a CO > 10 ppm on the time point being used were not considered responders.

[8] Continuous abstinence defined as all subjects who remained abstinent from the period defining the primary endpoint through the time point being summarized (Week 52)
[9] Responders for Long Term Quit Rate were responders on the primary efficacy endpoint and had no more than 6 days of smoking during weeks 12 through the time point being summarized (week 52)

Table 17: Other secondary efficacy endpoint analyses

Endpoint	Varenicline N=248 n (%)	Placebo N=251 n (%)	Odds Ratio (95% CI) versus placebo	p-value
CA Weeks 9-24[10]	64 (26)	18 (7)	4.9 (2.8, 8.7)	< 0.0001
LTQR Week 24[11]	70 (28)	19 (8)	5.2 (3.0, 9.0)	< 0.0001
7 day PP week 12	119 (48)	31 (12)	7.0 (4.4, 11.1)	< 0.0001
7 day PP week 24	74 (30)	34 (14)	2.9 (1.8, 4.5)	< 0.0001
7 day PP week 52	65 (26)	36 (14)	2.2 (1.4, 3.5)	0.0008
4 wk PP wk 52	65 (26)	33 (13)	2.5 (1.5, 4.0)	0.0002

Source: Clinical Reviewer adapted from p.65-69 of the Applicant's Clinical Study Report

The use and reporting of point prevalence endpoints and analyses is generally viewed as less informative than continuous abstinence rates because the data are coming from a single time point and represent only a small sample of the data collected over the entire trial. Abstinence for a period of one week is not known to confer a clinical benefit.

These results support the finding of efficacy in the primary efficacy endpoint.

6.1.6 Other Endpoints

The Applicant collected spirometry measurements, administered the Clinical COPD Questionnaire (CCQ) at several time-points, and measured number of cigarettes smoked in the first three weeks of the active treatment period. While there were statistically significant differences between groups that favored varenicline, the clinical significance of these findings is unknown and the Applicant has not proposed to make labeling claims based on these findings.

6.1.7 Subpopulations

Because of the association between varenicline and neuropsychiatric adverse events and the high rate of nicotine dependence in patients with psychiatric comorbidity, the statistical reviewer described the efficacy data in the subpopulation of subjects who were recorded as having a psychiatric diagnosis or a concomitant medication known to be used in the treatment of psychiatric conditions. The following table is taken from Dr. Meaker's review:

[10] Continuous abstinence defined as all subjects who remained abstinent from the period defining the primary endpoint through the time point being summarized (Week 24)
[11] Responders for Long Term Quit Rate were responders on the primary efficacy endpoint and had no more than 6 days of smoking during weeks 12 through the time point being summarized (week 24)

Table 18: Efficacy Outcomes for Patients Diagnosed with Depression and/or Prescribed Related Medications

	Varenicline	Placebo
	N=27	N=23
CQR 9_12	8 (30%)	2 (9%)
CA 9_52	3 (11%)	0
Long Term Quit Rate Week 52	3 (11%)	1 (4%)

Source: SAS datasets

Varenicline also appeared to be more effective than placebo in this subset of subjects. However, as Dr. Meaker notes in her review, the above table merely represents descriptive statistics, and it is not appropriate to make a statistical comparison in this subset. See Dr. Meaker's review for details.

6.1.10 Additional Efficacy Issues/Analyses

Treatment by center interaction

The Applicant used an expanded logistic regression model containing the treatment by center interaction for the primary efficacy endpoint and found no significant interaction. The Applicant concluded that the results could be generalized across centers.

Because approximately 36% of the subjects in this trial were at sites outside the U.S., the statistical reviewer examined the efficacy rates based on subjects' geographic region. The statistical reviewer found no effect on response rates based on region. See Dr. Meaker's review for further details.

Exploration of imputed CO measurements

The imputation of some missing CO measurements as negative (as described in Section 5.3) could have led to subjects who were smoking during the week of the missed measurement to be inappropriately counted as responders. The statistical reviewer examined the data on subjects with missing CO values during weeks 9 through 12, and determined that recoding them as non-responders did not affect the efficacy results. See Dr. Meaker's review for further details.

7 Review of Safety

Safety Summary

At the time of this review, there is significant additional safety information that was not available at the time of the initial NDA review. At the Reviewers' request, the Applicant analyzed the safety data from all phase 2-4 placebo-controlled studies or trials available up to December 2010, combining previously reviewed data with newer data to create a larger database. The data from trial A1054 was reviewed individually and compared to the pooled data. No new safety concerns were identified that were unique to the COPD population. In the pooled data, the commonly observed adverse events are consistent with what was observed in the initial trials and what is currently reflected in labeling.

The pooled data was also examined to further characterize serious, rare adverse events that are currently included in either the Warnings and Precautions section (Section 5) or the Adverse Reactions, Clinical Trials Experience section (Section 6.1) of the label (see Section 7.3.5 of this review). These events include:

- Neuropsychiatric events: At present, the varenicline label carries a boxed warning concerning neuropsychiatric events and a postmarketing trial is required of the applicant to assess these events in subjects with and without a diagnosis of a neuropsychiatric disorder. From the totality of evidence related to neuropsychiatric events generated from the pooled safety database, neuropsychiatric events were infrequent and the overall incidence was similar between treatment arms. Neuropsychiatric SAEs occurred at the same rates. Taken together, the findings from the pooled safety data do not indicate that a revised course of action with respect to neuropsychiatric events is required at this juncture.
- Cardiovascular events: The labeling was modified to reflect postmarketing cardiovascular events in varenicline-treated subjects in 12/2010. Considering the findings from the various elements of this review of cardiovascular events collectively, there is a small but increased number of primarily coronary heart disease events, observed in subjects exposed to varenicline. In current labeling, there is no information regarding ischemic cardiac events in clinical trials; the label will be revised to reflect these new findings from the review of pooled safety data from Phase 2–4 studies, as well as findings from review of cardiovascular events in the CVD study independently. See Dr. Skeete's NDA 21928-s19 review for detailed labeling recommendations.
- Cerebrovascular events: The labeling was modified to reflect postmarketing cerebrovascular events in varenicline-treated subjects in 12/2010. Cerebrovascular events identified in the pooled safety data were rare. There were no clear trends seen in the types of events experienced by subjects in these studies. Therefore, labeling changes based on these events are not warranted.
- Accidental injury: The results of the analyses reviewed provide no further evidence that the risk of accidental injury is increased in patients taking varenicline.
- Serious skin reactions and allergic phenomena: Based on the results of the analyses of the pooled data reviewed below, there have been infrequent cases of allergic phenomena and no reported cases of severe or serious reactions in the clinical trial data. These results support current labeling.
- Blindness and visual impairment: The results of the analyses reviewed confirm the infrequent occurrence of visual disturbances in both the varenicline and placebo groups with similar frequency and are insufficient to conclude or exclude a causal relationship between varenicline and the risk of blindness or visual impairment. The results support the current labeling, which includes visual impairment and blindness related terms as infrequent or rare events of unknown causality.

- Convulsions: There have been cases of convulsions in subjects taking varenicline in the clinical trials. Most of these cases occurred in subjects with a history of a seizure disorder. The data reviewed in this supplement are insufficient to make a determination of causality due to the rarity of events and supports the current labeling of convulsions as a rare adverse event.

While there are safety concerns with varenicline, based on the available data, these concerns do not outweigh the benefits of the drug, as discussed above in Section 1.

Deleted Sections

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The applicant submitted one trial in this supplemental application. The review team additionally requested an Integrated Summary of Safety of all completed, controlled trials to review the pooled safety data that existed at the time of the initial NDA application combined with the data that has been collected in trials since that time. This pooled safety data was to be juxtaposed to the data from the COPD population (trial A1054) to allow comparison of the safety experience overall to the safety experience in the COPD population.

Below is a table taken from the Applicant's ISS summarizing the studies pooled:

Table 19: Pooled Studies

Study	Design	Duration	Treatment Groups	No. of Subjects[a]
2005 POOLED STUDIES COHORT				
PHASE 3 STUDIES				
A3051028 Zyban comparison	R, PG, DB, PC and active comparator	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	349 329 344 Total: 1022
A3051036 Zyban comparison	R, PG, DB, PC and active comparator	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	343 340 340 Total: 1023
PHASE 2 STUDIES				

Study	Design	Duration	Treatment Groups	No. of Subjects[a]
A3051002 Dose-ranging	R, PG, DB, PC and active-control	Varenicline: 6 weeks treatment plus 1 week placebo; Zyban: 7 weeks treatment nontreatment follow-up to Week 52	Varenicline 0.3 mg QD Varenicline 1 mg QD Varenicline 1 mg BID Zyban 150 mg BID Placebo	126 126 125 126 123 Total: 626
A3051007 titration (nontreatment follow-up in Study **A3051018**)	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline 0.5 mg NT Varenicline 0.5 mg T Varenicline 1 mg NT Varenicline 1 mg T Placebo	124 129 124 129 121 Total: 627
A3051016 Flexible dosing (nontreatment follow-up in Study **A3051019**)	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline flexible dosing 0.5 to 2 mg daily Placebo	157 155 Total: 312
A3051037 Long-term safety	R, PG, DB, PC	52 weeks treatment	Varenicline, 1 mg BID Placebo	251 126 Total: 377
ADDITIONAL STUDIES INCLUDED IN 2010 POOLED STUDIES COHORT				
PHASE 4 STUDIES				
A3051080 Multinational sites in Africa, Mid-East, S. America	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	390 198 Total: 588
A3051095[b] Flexible quit date	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 40	Varenicline, 1 mg BID: Placebo	486 165 Total: 651
A3051104 Smokeless tobacco	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 26	Varenicline, 1 mg BID: Placebo	213 218 Total: 431
A3051115 Assessment of neuropsychiatric symptoms in quitting smokers	R, PG; DB, PC	12 weeks treatment, plus 30 day nontreatment follow-up	Varenicline, 1 mg BID: Placebo	55 55 Total: 110
PHASE 3 STUDIES				
A3051045 Taiwan and Korea	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	126 124 Total: 250
A3051049[b] CV disease	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	353 350 Total: 703
A3051054[b] COPD	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	248 251 Total: 499

Study	Design	Duration	Treatment Groups	No. of Subjects[a]
A3051055 Multinational Asian sites	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	165 168 Total: 333
PHASE 2 STUDIES				
A3051046_48[c] Japan	R, PG; DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline 0.25 mg BID Varenicline 0.5 mg BID Varenicline 1 mg BID Placebo	153 155 156 154 Total: 618

Source: ISS Table 1

The Applicant did not include a study of maintenance treatment (Study A1035) in the pooling because its design varied significantly from the other studies (it had a 12-week open label run-in phase prior to the double-blinded placebo-controlled phase). The subjects randomized to the double-blind phase received varenicline for 24 weeks total and thus provide longer term safety data than the other trials. However, most of the adverse events of special interest that were analyzed in this ISS appear to occur early in treatment. Therefore, the results of the subsequent analyses should still provide useful information.

7.1.2 Categorization of Adverse Events

For trial A1054, the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 was used to classify treatment-emergent adverse events by Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT), and System Organ Class (SOC). Coding of adverse events appeared to be appropriate except where re-coding was noted in subsequent sections of the review.

For the ISS, the Applicant reported that the analyses were conducted by converting all the data to MedDRA version 13.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The studies pooled in the ISS were of similar design. In the tables provided by the Applicant, the heading “2005 Pooled Studies” refers to studies or trials that were submitted for review in the original NDA 21928-s000 review. The heading “2010 Pooled Studies” refers to all Phase 2-4 placebo-controlled studies or trials to date. The “CV study” heading refers to Trial A1049, the “COPD study” heading refers to Trial A1054, and the “Flexible Quit Date” heading refers to Trial A1095. Most studies exposed subjects for 12 weeks as shown in Table 18 above.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Trial A1054

Two-hundred-forty-eight subjects were exposed to varenicline in this clinical trial. Of these, twenty-five subjects did not meet the criteria for COPD and thus were not in the target population of the clinical trial. This leaves 223 subjects with COPD that were exposed to varenicline as the safety population of interest for the proposed labeling claims. The subjects were exposed to the labeled dose for twelve weeks, consistent with the intended use of the product, and were followed for a total of 52 weeks, allowing for adequate observation time. The exposure, doses, and durations were adequate to assess safety in this population.

Pooled Data

The overall extent of exposure summarized in the ISS is presented below:

Table 20: Exposure in Pooled Studies

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N=1983**	**Pbo N=1209**	**Var N=4483**	**Pbo N=2892**	**Var N=353**	**Pbo N=350**	**Var N=248**	**Pbo N=251**	**Var N=486**	**Pbo N=165**
Duration of Treatment (Days)[a]	number of subjects									
Unknown	13	10	13	10	0	0	0	0	0	0
1-3	17	6	26	11	1	0	2	2	1	0
4-7	33	15	52	23	6	2	3	2	4	2
8–14	103	99	158	145	8	9	6	7	9	4
15–28	161	140	244	198	14	16	8	13	19	8
29–60	470	235	602	358	27	26	15	27	19	18
61-90[b]	975	593	3065	1939	288	266	194	178	426	131
≥91[b]	211	111	323	208	9	31	20	22	8	2
Median Days (Range)	83.0 1-413	83.0 1-379	84.0 1-413	84.0 1-379	84.0 2–106	85.0 5–104	84.0 1–103	84.0 1–114	83.0 3-106	83.0 5-94
Subject-Days Exposure[c]	166,838	92,791	360,743	222,023	26,515	26,737	19,022	18,575	37,403	12,115

a Duration of treatment is calculated from the first and last days that a subject received study medication, regardless of missed doses or temporary discontinuation from treatment.
b Because of the 3-day window allowed for scheduling clinic visits, a subject could be on drug for longer than the protocol specified treatment period, ie, >84 days in a 12-week treatment study.
c Drug exposure is based on the actual days when subjects received treatment.

Source: ISS Table 3

The Applicant provided a table comparing the demographics in Trial A1054 to the studies included in the initial NDA (2005 Pooled Studies) and all studies (2010 Pooled Studies) which has been reproduced below:

Table 21: Demographics for Completed Placebo-Controlled Phase 2-4 Studies

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo
Total number of Subjects	N= 1983	N= 1209	N= 4483	N= 2892	N= 353	N= 350	N= 248	N= 251	N= 486	N= 165
	number (%) of subjects									
Gender										
Males	999 (50.4)	656 (54.3)	2779 (62.0)	1963 (67.9)	266 (75.4)	287 (82.0)	155 (62.5)	156 (62.2)	293 (60.3)	99 (60.0)
Females	984 (49.6)	553 (45.7)	1704 (38.0)	929 (32.1)	87 (24.6)	63 (18.0)	93 (37.5)	95 (37.8)	193 (39.7)	66 (40.0)
Age (years):										
<18	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
18-44	1027 (51.8)	678 (56.1)	2219 (49.5)	1403 (48.5)	32 (9.1)	36 (10.3)	24 (9.7)	21 (8.4)	248 (51.0)	93 (56.4)
45-64	909 (45.8)	499 (41.3)	2031 (45.3)	1309 (45.3)	250 (70.8)	255 (72.9)	170 (68.5)	174 (69.3)	209 (43.0)	64 (38.8)
≥65	47 (2.4)	32 (2.6)	233 (5.2)	180 (6.2)	71 (20.1)	59 (16.9)	54 (21.8)	56 (22.3)	29 (6.0)	8 (4.8)
Mean ±SD	43.6 ±11.5	42.9 ±11.5	44.6 ±12.3	45.2 ±12.5	57.0 ±8.6	56.0 ±8.4	57.2 ±9.1	57.1 ±9.0	43.9 ±12.6	43.2 ±12.2
Range	18-75	18-75	18-83	18-77	34-76	35-75	35-83	34-77	18-75	18-72

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo
Race										
White	1685 (85.0)	998 (82.5)	2876 (64.2)	1921 (66.4)	284 (80.5)	282 (80.6)	203 (81.9)	211 (84.1)	331 (68.1)	112 (67.9)
Black	176 (8.9)	129 (10.7)	261 (5.8)	178 (6.2)	3 (0.8)	2 (0.6)	15 (6.0)	10 (4.0)	31 (6.4)	8 (4.8)
Asian	29 (1.5)	20 (1.7)	945 (21.1)	541 (18.7)	30 (8.5)	30 (8.6)	0 (0)	0 (0)	103 (21.2)	36 (21.8)
Other[a]	93 (4.7)	62 (5.1)	401 (8.9)	252 (8.7)	36 (10.2)	36 (10.3)	30 (12.1)	30 (12.0)	21 (4.3)	9 (5.5)
Weight (kg)										
Number subjects with data	1977 (99.7)	1206 (99.8)	4310 (96.1)	2716 (93.9)	352 (99.7)	349 (99.7)	248 (100)	251 (100)	486 (100)	165 (100)
Mean±SD	78.6 ±16.8	78.8 ±16.2	76.7 ±16.5	78.3 ±16.2	79.7 ±15.3	81.7 ±15.2	77.9 ±19.4	77.1 ±17.6	76.5 ±15.7	78.5 ±17.1
Height (cm)										
Number subjects with data	1981 (99.9)	1207 (99.8)	4103 (91.5)	2503 (86.5)	353 (100)	349 (99.7)	248 (100)	251 (100)	486 (100)	165 (100)
Mean±SD	171 ±9.7	171.5 ±9.8	170.1 ±9.3	170.9 ±9.3	169.9 ±(8.9)	171.0 ±(7.9)	170.0 ±9.4	170.4 ±9.7	170.5 ±9.0	171.0 ±9.2
BMI (kg/m^2)										
Number subjects with data	1977 (99.7)	1206 (99.8)	4098 (91.4)	2502 (86.5)	352 (99.7)	349 (99.7)	248 (100)	251 (100)	486 (100)	165 (100)
Mean±SD	26.8 ±4.7	26.7 ±4.4	26.2 ±4.7	26.5 ±4.5	27.5 ±4.4	27.9 ±4.4	26.8 ±5.7	26.5 ±5.2	26.2 ±4.3	26.7 ±4.7

Source: Table 4 ISS

As previously noted, the COPD population has a higher mean age than the pooled studies. This population also has a higher proportion of white subjects than the 2010 pooled data, and is similar in proportion to the 2005 pooled data. This is in large part due to the increase in the proportion of studies conducted in Asia since the 2005 pool.

The Applicant also provided tables comparing past and present medical conditions. In the COPD trial (Trial A1054) there were slightly more subjects with a cardiac disorder in both the varenicline and placebo groups than in the 2010 pool and nearly twice the percentage of subjects as the 2005 pool (original NDA). Trial A1054 also had the highest percentage of subjects with a recorded psychiatric disorder in both the varenicline and placebo groups. See Table 57 in the Appendix for details.

7.2.4 Routine Clinical Testing

The safety monitoring plan in Trial A1054 included physical exam, vital signs, 12-lead ECG, hematology, chemistry, glycosylated hemoglobin, biochemical markers of inflammation (CRP and fibrinogen), urinalysis, and treatment-emergent adverse events. This appears adequate for this population and is similar to the routine clinical testing that was conducted in the trials included in the ISS.

7.3 Major Safety Results

The safety analyses provided by the Applicant were done on the 248 varenicline-treated subjects and 251 placebo-treated subjects. Safety results in Trial A1054 were reviewed in all subjects treated as well as the subset of subjects who met the inclusion criteria for any severity of COPD (223 subjects in the varenicline group and 237 in the placebo group). No additional safety signals emerged in the review of all subjects treated. The results of reviewer-generated analyses are presented for subjects meeting criteria for COPD along with the results from the review of the Integrated Summary of Safety.

7.3.1 Deaths

Trial A1054

There were three deaths reported in this clinical trial; two in the varenicline group and one in the placebo group. One death in the varenicline group was judged to be sudden cardiac death and occurred two weeks after the completion of treatment with varenicline in a subject with a history of coronary artery disease. No conclusions about a relationship to varenicline can be made based on this one cardiovascular-related death. Cardiovascular risk is discussed further in section 7.3.5. The other death in the varenicline group was due to a motor vehicle accident on Day 168 (at least 12 weeks after the end of treatment) and does not appear to be associated with varenicline. The death in the placebo group was due to amyotrophic lateral sclerosis (ALS).

Pooled Data

The following is a table summarizing all deaths that have occurred in completed placebo-controlled Phase 2-4 studies. The Applicant reported that there were no deaths in the Phase 1 studies. The ISS did not include the deaths that were reviewed as part of the original NDA application. These deaths were reviewed by Dr. Josefberg and the information in the table below for deaths designated “Reviewed in initial NDA” is reproduced from his review. The remainder of the table is reproduced from the ISS.

Table 22: Deaths (Pooled Data)

	Patient ID	Age/Race/Sex	Treatment Day	Cause (per Investigator)
Varenicline				
Reviewed in initial NDA	(b) (6)	61/W/M	Day 196 (post-therapy Day 27)	Suicide (+ h/o MDD with suicidality)
	(b) (6)	71/W/M	Day 188 (post-therapy Day 19)	Massive pericardial exudate, Cardiac Arrest, Lung cancer, Lymph metastasis, Pneumonia
	(b) (6)	29/W/M	Day 218 (post-therapy Day 197)	Rectal sarcoma, Discontinued when diagnosed
Not reviewed in initial NDA	(b) (6)	31/A/M	Day 181 (post-therapy Day 99)	Accidental death (Death due to road traffic accident)
	(b) (6)	63/W/M	Day 239 (post-therapy Day 155)[12]	Acute myocardial infarction
	(b) (6)	76/W/M	Day 301 (post-therapy Day 64)	Pancreatic carcinoma
	(b) (6)	69/W/M	Day 99 (post-therapy Day 15)	Cardiac arrest
	(b) (6)	62/W/M	Day 168 (post-therapy day 93)	Road traffic accident
Placebo				
Reviewed in initial NDA	(b) (6)	64/W/M	Day 352 (post-therapy Day 239)	Death unexplained (fall, collapse of lung, elbow fracture)
Not reviewed in initial NDA	(b) (6)	62/W/M	Day 116 (post-therapy Day 31)	Septic shock
	(b) (6)	63/W/M	Day 36 (post-therapy Day 12)	Hypovolaemia, pneumonia, diabetic coma
	(b) (6)	73/A/M	Day 115 (post-therapy Day 28)	Renal failure, GI bleeding, ventricular tachycardia, acute myocardial infarction, cardiogenic shock
	(b) (6)	60/A/M	Day 361 (post-therapy Day 183)	Transitional cell carcinoma
	(b) (6)	51/O/M	Day 162 (post-therapy Day 79)	Acute myocardial infarction
	(b) (6)	51/W/M	Day 397 (post-therapy Day 314)	Amyotrophic lateral sclerosis

The deaths from Trial A1049 (denoted by 1049 as the first four digits in the patient ID) have been reviewed by Dr. Skeete as part of s-NDA 21928-019. The pancreatic cancer death does not appear to be causally related to varenicline. The acute myocardial infarction death occurred shortly after the patient re-started varenicline and a causal relationship cannot be ruled out. See section 7.3.5 for further discussion of

[12] Varenicline was restarted 10 days prior to the death

cardiovascular adverse events. The deaths from Trial A1054 (denoted by 1054 as the first four digits in the patient ID) have been reviewed above. There was one other death in the varenicline group from Trial A1046 that was noted in the initial NDA review. At the time of the NDA 21928-s000 review, the study was still blinded. The narrative was reviewed and this death does not appear to have been associated with varenicline.

In all completed Phase 2-4 placebo-controlled trials there have been 8 deaths in the varenicline group (out of 4483 subjects treated as presented in Table 22 below) and 7 deaths in the placebo group (out of 2892 treated as presented in Table 22 below). None of the deaths occurred during the treatment period, but one death occurred while the patient was taking varenicline (prescribed outside of the study protocol). The overall crude mortality rate and mortality by patient exposure days is summarized in the table below. The number of patients exposed and the subject-days exposure data comes from the Applicant's ISS. These rates do not indicate that varenicline increases mortality.

Table 23: Mortality (Pooled Data)

Treatment Group	Patients[13]	Deaths	Crude Mortality	Subject-Days Exposure[14]	Mortality per subject-days exposure
Varenicline	4483	8	0.00178	360,743	2.21×10^{-5}
Placebo	2892	7	0.00242	222,023	3.15×10^{-5}

Source: Reviewer-generated with exceptions noted above

Three of the deaths in the varenicline group and two of the deaths in the placebo group occurred within 28 days of the end of treatment. In the varenicline group, these deaths consisted of a suicide and two cardiac arrests (one of which was associated with lung cancer with metastases, pneumonia, and pericardial exudate). In the placebo group, they consisted of one subject who had pneumonia, hypovolemia, and diabetic shock and one subject who had GI bleeding, renal failure, ventricular tachycardia, cardiogenic shock, and myocardial infarction. The suicide occurred in a subject with documentation of a prior major depressive episode with suicidality that was reportedly ongoing during the trial. One of the myocardial infarctions occurred in a subject with a history of coronary artery disease and should be considered along with the rest of the safety data pertinent to cardiovascular risk. The other myocardial infarction was in the context of significant medical comorbidity, which makes the event more difficult to interpret.

The data reviewed does not indicate that varenicline increases the risk of mortality in the mild-to-moderate COPD population, nor is there new data indicating that the risk of mortality is increased in those who have used varenicline in the Applicant's controlled clinical trials. However, there were more cardiovascular-related deaths in the varenicline group within 28 days of treatment discontinuation (2 in the varenicline group

[13] Taken from Table 3 of ISS
[14] Taken from Table 3 of ISS

vs. 1 in the placebo group). Only two acute myocardial infarctions occurred within 28 days of the treatment period in the absence of life-threatening acute co-morbidity and both were in the varenicline group. See section 7.3.5 for further discussion of cardiovascular adverse events.

7.3.2 Nonfatal Serious Adverse Events

Trial A1054

There were eight non-fatal serious adverse events in the varenicline group and twelve in the placebo group that occurred within 28 days of the last dose of the trial drug. Narratives and CRFs were reviewed for all events in Trial A1054. All events are summarized in the table below.

Table 24: Serious Adverse Events (Trial A1054)

Varenicline			Placebo		
Subject	Description	Onset (Trial Day)	Subject	Description	Onset (Trial Day)
(b) (6) 60 yo M	Acute myocardial infarction resulting in hospitalization, treatment discontinued	39	(b) (6) 71 yo M	Acute myocardial infarction and ventricular fibrillation requiring hospitalization, treatment discontinued	38
(b) (6) 64 yo F	Congestive heart failure followed by cerebrovascular accident and hospitalization resulting in trial and treatment discontinuation	27, 37	(b) (6) 52 yo F	Cerebrovascular accident (transient aphasia) resulting in brief hospitalization resulting in temporary medication discontinuation	27
(b) (6) 77 yo M	Worsening angina pectoris resulting in 2-day hospitalization. The subject stopped treatment the day after release from hospital	4	(b) (6) 57 yo M	Abnormality on routine EKG, subsequently had chest pain and anxiety and was hospitalized to rule out acute coronary syndrome	84
(b) (6) 43 yo F	Cellulitis with fever, myalgia and vomiting resulting in hospitalization, IV antibiotics and temporary medication discontinuation	55	(b) (6) 52 yo F	Hospitalized for four days with acute bronchitis with chest pain, fever and purulent sputum, trial drug continued	5
(b) (6) 38 yo F	Back pain resulting in hospitalization	37	(b) (6) 52 yo F	Hospitalized with bilateral shoulder pain, further episodes accompanied by dyspnea, trial drug discontinued	49
(b) (6) 64yo M	Hospitalized for a plantar keratoderma	27	(b) (6) 61 yo M	Hospitalized for cholelithiasis and underwent surgery	7
(b) (6) 46 yo F	Dysphonia several months prior to trial enrollment and surgery for vocal cord polyp while in trial	-5	(b) (6) 51 yo M	Hospitalized for 4 days for COPD exacerbation, continued trial drug	88
			(b) (6) 65 yo M	Patient had chest pain and was diagnosed with lung cancer by biopsy after MRI showed mass	12
			(b) (6) 60 yo M	Subject underwent surgery for lung cancer	70
			(b) (6) 76 yo M	Hospitalized for pneumonia	23
			(b) (6) 56 yo M	Acute appendicitis, underwent appendectomy	40
SAEs > 28 days post dose					
(b) (6) 59 yo M	Left ventricular dysfunction and congestive heart failure, complicated by pre-existing aortic valve stenosis	151, 155	(b) (6) 51 yo M	Diagnosed with ALS, Pneumonia, palpitations and chest pain	170, 303, 358
(b) (6) 68 yo F	Laryngeal Cancer, discontinued trial	169	(b) (6) 51 yo F	COPD exacerbation	223
(b) (6) 62 yo M	COPD exacerbation and pneumonia	237			
(b) (6) 49 yo F	Atypical chest pain	292			

Source: Clinical Reviewer based on Applicant's Clinical Study Report, Table 28, Applicant-provided narratives and ADVERS dataset

All SAEs resolved with the exception of two SAEs in the placebo group: musculoskeletal pain where the outcome was unknown and lung neoplasm malignant where the outcome was "not recovered."

Subject (b) (6) in the placebo group had aphasia that lasted ten minutes and subsequently resolved. The subject was diagnosed with a cerebrovascular accident. Based on the limited information given about the event, it may have been more accurately described as a transient ischemic attack (TIA). The adjudication of this event as a TIA versus a CVA will not affect the interpretation of the safety data from this individual clinical trial.

Below is a summary of the SAEs from this clinical trial. The additional SAE not included in the Applicant's table from the varenicline group is included.

Table 25: Summary of SAEs (Trial A1054)

	Varenicline N=223	Placebo N=237
SAEs (# subjects)	8 (7)	12 (11)
SAEs > 28 d after last dose of treatment (# subjects)	5 (4)	4 (2)

Source: Applicant-provided case report forms and SAE narratives

One subject who had bronchitis had severe COPD rather than mild or moderate COPD. The subject with cellulitis and the subject with vocal chord polyp did not meet the criteria for COPD. Exclusion of these subjects does not alter interpretation of the SAEs reported.

The data on SAEs from this clinical trial taken alone raise no new safety signals for varenicline in the COPD population. COPD exacerbations and respiratory infections meeting criteria for a serious adverse event were not more common in the varenicline group. See section 7.3.5 for further discussion of cardiovascular adverse events.

Pooled data

There were 144 SAEs (3.2%) in the varenicline group and 90 (3.1%) in the placebo group, indicating that there was a similar incidence of SAEs in the varenicline and placebo groups overall.

The Applicant summarized the all Serious Adverse Events reported in Phase 2-4 placebo-controlled studies by System Organ Class in the table below.

Table 26: Serious Adverse Events (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
SOC	number (%) of subjects									
Blood & lymphatic system disorders	0 (0)	0 (0)	1 (<0.1)	1 (<0.1)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac Disorders	12 (0.6)	4 (0.3)	37 (0.8)	23 (0.8)	19 (5.4)	17 (4.9)	3 (1.2)	1 (0.4)	1 (0.2)	0 (0)
Ear & labyrinth disorders	1 (0.1)	0 (0)	2 (<0.1)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Endocrine Disorders	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eye disorders	3 (0.2)	0 (0)	3 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal Disorders	5 (0.3)	0 (0)	9 (0.2)	8 (0.3)	1 (0.3)	5 (1.4)	0 (0)	0 (0)	1 (0.2)	1 (0.6)
General disorders & administration site conditions	5 (0.3)	3 (0.2)	11 (0.2)	10 (0.3)	5 (1.4)	6 (1.7)	0 (0)	1 (0.4)	0 (0)	0 (0)
Hepatobiliary disorders	2 (0.1)	0 (0)	4 (0.1)	2 (0.1)	1 (0.3)	1 (0.3)	0 (0)	1 (0.4)	0 (0)	0 (0)
Immune system disorders	0 (0)	1 (0.1)	1 (<0.1)	2 (0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Infections & infestations	5 (0.3)	3 (0.2)	18 (0.4)	14 (0.5)	6 (1.7)	6 (1.7)	1 (0.4)	3 (1.2)	1 (0.2)	0 (0)
Injury, poisoning & procedural complications	1 (0.1)	3 (0.2)	8 (0.2)	11 (0.4)	3 (0.8)	3 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	1 (0.1)	0 (0)	2 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolism & nutrition disorders	3 (0.2)	0 (0)	5 (0.1)	2 (0.1)	2 (0.6)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal & connective tissue disorders	3 (0.2)	0 (0)	8 (0.2)	5 (0.2)	1 (0.3)	3 (0.9)	1 (0.4)	1 (0.4)	2 (0.4)	0 (0)
Neoplasms benign, malignant & unspecified	4 (0.2)	1 (0.1)	12 (0.3)	9 (0.3)	5 (1.4)	4 (1.1)	0 (0)	2 (0.8)	1 (0.2)	0 (0)
Nervous system disorders	6 (0.3)	1 (0.1)	17 (0.4)	8 (0.3)	6 (1.7)	5 (1.4)	1 (0.4)	1 (0.4)	2 (0.4)	0 (0)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
SOC	number (%) of subjects									
Pregnancy, puerperium & perinatal conditions	1 (0.1)	0 (0)	3 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	2 (0.1)	2 (0.2)	6 (0.1)	4 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.6)
Renal & urinary disorders	0 (0)	0 (0)	2 (<0.1)	1 (<0.1)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	1 (0.2)	0 (0)
Reproductive system & breast disorders	0 (0)	1 (0.1)	2 (<0.1)	1 (<0.1)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic & mediastinal disorders	0 (0)	2 (0.2)	8 (0.2)	5 (0.2)	4 (1.1)	2 (0.6)	1 (0.4)	1 (0.4)	0 (0)	0 (0)
Skin & subcutaneous disorders	0 (0)	0 (0)	2 (<0.1)	0 (0)	1 (0.3)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Surgical & medical procedures	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	3 (0.2)	1 (0.1)	13 (0.3)	5 (0.2)	9 (2.5)	4 (1.1)	0 (0)	0 (0)	1 (0.2)	0 (0)

Source: ISS Table 29

Cardiac disorders SAEs

There were a higher percentage of subjects with SAEs in the Cardiac Disorders SOC in the varenicline group in the COPD study than in the 2010 pooled studies (1.2% compared to 0.8%). There were also a higher percentage of subjects with SAEs in the Cardiac Disorders SOC in the varenicline group than the placebo group in the 2005 pooled studies. In the 2010 pool, there were higher percentages of serious adverse events with the preferred terms “angina pectoris” (0.2% varenicline, 0.1% placebo) and “myocardial infarction” (0.2% varenicline, 0.1% placebo) in the varenicline group than in the placebo group. There was the same percentage of SAEs coded as acute myocardial infarction in each group. There were an additional two events coded as acute coronary syndrome and one additional event coded as cardiac arrest in the varenicline group compared to two additional events in the placebo group. See the table below for all preferred terms reported in the Cardiac Disorders SOC.

Table 27: SAEs in Cardiac Disorders SOC (Pooled Data)

Section 5.3.5.3 Varenicline Integrated Summary of Safety
Table A20.a1 Summary of All Causality SAE Cases by System Organ Class
All Phase 2-4 placebo-controlled studies completed as of December 2, 2010
Number(%)of Patients

System Organ Class and MedDRA (v13.1) preferred term	Varenicline (N=4483) n(%)		Placebo (N=2892) n(%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1		1	
Anaemia	1		1	
CARDIAC DISORDERS	37	(0.8)	23	(0.8)
Angina pectoris	7	(0.2)	2	(0.1)
Myocardial infarction	7	(0.2)	2	(0.1)
Acute myocardial infarction	5	(0.1)	4	(0.1)
Coronary artery disease	4	(0.1)	2	(0.1)
Angina unstable	3	(0.1)	2	(0.1)
Acute coronary syndrome	2		2	(0.1)
Atrial fibrillation	2		4	(0.1)
Tachycardia	2		0	
Arrhythmia	1		0	
Arteriospasm coronary	1		0	
Atrial flutter	1		0	
Bradycardia	1		0	
Cardiac arrest	1		0	
Extrasystoles	1		0	
Mitral valve stenosis	1		0	
Sick sinus syndrome	1		0	
Sinus bradycardia	1		0	
Supraventricular tachycardia	1		1	
Ventricular fibrillation	1		0	
Cardiac failure	0		2	(0.1)

Source: ISS Table A20.A1

The Cardiac Disorders SOC includes a wide variety of cardiac-related adverse event terms including various arrhythmias. In order to examine adverse event terms specifically related to ischemic cardiac events and avoid splitting of similar terms, this reviewer generated the following table summarizing the relevant HLTs.

Table 28: Selected Cardiac SAEs (pooled data)

HLT PT	Varenicline n (%) N= 4483	Placebo n (%) N= 2892
Coronary artery disorders NEC coronary artery disease	4 (0.1)	2 (0.1)
Ischemic coronary artery disorders angina pectoris myocardial infarction acute myocardial infarction angina unstable acute coronary syndrome arteriospasm coronary	25 (0.6)	12 (0.4)
Ventricular arrhythmias and cardiac arrest ventricular fibrillation cardiac arrest	2 (0.04)	0 (0)

Source: Reviewer-generated using data reported in Table A20 of Applicant's ISS.

Events in the Ischemic coronary artery disorders HLT were more frequent in the varenicline group. See section 7.3.5 for further discussion of cardiovascular adverse events.

Vascular Disorders SAEs

No serious adverse events were reported in the Vascular Disorders SOC in the COPD study. There were more SAEs in the Vascular Disorders SOC in the varenicline group (0.3%) than in the placebo group (0.2%) A table of the preferred terms of SAEs reported in the Vascular Disorders SOC can be found in the Appendix. These results are of unclear significance, as higher rates of vascular related SAEs were not consistently seen across trials. For further discussion of cardiovascular and cerebrovascular events, see section 7.3.5.

The percentages of serious adverse events in the COPD study were otherwise similar to the percentages in the 2005 and 2010 pools and the percentages in the 2010 pools were similar to the percentages in the 2005 pool.

7.3.3 Dropouts and/or Discontinuations

Trial A1054

Overall, 4% (9/223) of varenicline-treated subjects and 3% (8/237) of placebo-treated subjects discontinued treatment due to adverse events compared to 14% and 9% respectively in the trials reviewed in the original NDA (2005 pool) and 9% and 6% respectively in all pooled studies (2010 pool).

The table below was provided by the Applicant to summarize treatment and clinical trial discontinuations due to adverse events. The table beneath it includes re-adjudication of a number of the discontinuations.

Table 29: Discontinuations Due to Adverse Events (Trial A1054)

Discontinuations from Treatment and from Study

Subject ID	MedDRA v12.0 preferred term	Onset (Day)[a]	Outcome	Causality	SAE
Varenicline					
(b) (6)	Nausea	4	Resolved	Study drug	No
(b) (6)	Nausea	12	Resolved	Study drug	No
(b) (6)	Upper respiratory tract infection	2	Resolved	Other	No
(b) (6)	Nausea	29	Resolved	Study drug	No
(b) (6)	Vomiting	18	Resolved	Study drug	No
Placebo					
(b) (6)	Vertigo	1	Resolved	Study drug	No
(b) (6)	Muscle spasms	12	Resolved	Study drug	No
(b) (6)	Musculoskeletal pain	49	Unknown	Other	Yes
(b) (6)	Tremor	20	Still present	Study drug	No
(b) (6)	Suicidal ideation	43	Resolved	Study drug	No
(b) (6)	Lung neoplasm malignant	14	Still present	Disease under study	Yes
(b) (6)	Acute myocardial infarction	38	Resolved	Other	Yes
(b) (6)	Anger	50	Unknown	Study drug	No
	Depressive symptom	50	Still present	Study drug	No
(b) (6)	Depression	9	Still present	Other	No
(b) (6)	Adjustment disorder	44	Still present	Study drug	No
(b) (6)	Dizziness	5	Resolved	Study drug	No

Discontinuations from Treatment yet Remained in the Study

Subject ID	MedDRA v12.0 preferred term	Onset (Day)[a]	Outcome	Causality	SAE
Varenicline					
(b) (6)	Vomiting	67	Resolved	Study drug	No
(b) (6)	Anxiety	55	Resolved	Study drug	No
(b) (6)	Abdominal pain	56	Resolved	Study drug	No
(b) (6)	Nausea	11	Resolved	Study drug	No
(b) (6)	Nausea	8	Resolved	Study drug	No
Placebo					
(b) (6)	Depression	32	Still present	Other	No
(b) (6)	Nausea	17	Resolved	Study drug	No

[a] Day relative to start of study treatment. First day of study treatment = Day 1.
MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.
Source: Applicant's Clinical Study Report, Table 28

Table 30: Discontinuations due to Adverse Events with re-adjudications (Trial A1054)

	Varenicline	Placebo
D/C treatment	~~Abdominal pain~~[15]	Adjustment disorder
	Anxiety	Anger, depressive symptom
	~~URTI~~ Blurred vision, dizziness, irritability, drowsiness and decreased concentration[16]	Dizziness
	Nausea[17]	Muscle spasms
	Nausea	Nausea
	Nausea	Suicidal ideation
	Nausea	Tremor
	Nausea	Vertigo
	Vomiting	Acute MI
	Vomiting	Depression
	Acute MI	Depression
	~~Nausea~~ CVA[18]	Lung neoplasm
		Musculoskeletal pain
D/C treatment and clinical trial	~~URTI~~ Blurred vision, dizziness, irritability, drowsiness and decreased concentration[2]	Adjustment disorder
	Nausea	Anger, depressive symptom
	Nausea	Dizziness
	Nausea	Muscle spasms
	Vomiting	Suicidal ideation
	~~Nausea~~ CVA[4]	Tremor
		Vertigo
		Acute MI
		Depression
		Lung neoplasm
		Musculoskeletal pain

Source: Clinical Reviewer based on case report forms and narratives provided by Applicant

[15] Subject (b) (6) did not meet the Inclusion criteria for COPD diagnosis and should not be included in the safety population

[16] According to the case report form, Subject (b) (6) discontinued the treatment and study due to blurred vision, dizziness, irritability, drowsiness and decreased concentration. The onset of symptoms was temporally related to an increase in varenicline and the initiation of a codeine-containing formulation of Robitussin (for URI). The resolution of symptoms was temporally related to the cessation of both varenicline and Robitussin-AC.

[17] Several other adverse events were recorded at the study visit where nausea was recorded for Subject (b) (6) including: flatulence, dry mouth, constipation, polyuria, abdominal cramping, diarrhea, change in taste, change in depth perception, dizziness, increased sweating, heartburn, headache and agitation

[18] According to the narrative submitted by the Applicant, the subject had a dose reduction from 2 mg of varenicline per day to 1 mg of varenicline per day due to the congestive heart failure exacerbation on May 6th, stopped taking the study drug temporarily due to nausea on May 10th, took a final single dose of varenicline on May 18th and discontinued both the study drug and participation in the study on May 22nd, 2007. Since treatment and study discontinuation occurred after the CVA and during the hospitalization for the CVA, the appropriate coding for discontinuation from treatment and study should be CVA with causality coded as "other."

Subjects in the varenicline group were more likely to discontinue treatment due to nausea and vomiting. No between-group differences were identified in discontinuations due to other types of adverse events.

Subjects who discontinued treatment due to adverse events and were in the placebo group were more likely to drop out of the clinical trial as summarized below:

Table 31: Treatment Dropouts by Study Dropout (Trial A1054)

	Number of dropouts from varenicline arm (%) N=9	Number of dropouts from placebo arm (%) N=13
Discontinued Treatment/Remained in Clinical trial	4 (44)	2 (15)
Discontinued Treatment and Clinical trial	5 (56)	11 (85)

Source: Clinical Reviewer based on Applicant's Table 28, narratives and case report forms

This is not of particular concern when reviewing the safety of varenicline, since subjects that were in the varenicline group were more likely to have follow-up data collected after discontinuation than those in the placebo group. However, 4.6% (11/237) of subjects in the placebo group dropped out of the clinical trial due to adverse events compared to only 2.2% (5/223) in the varenicline group. This difference may be a result of the difference in efficacy between the two groups; subjects who are not receiving a benefit from the trial treatment may be less willing to remain in the clinical trial.

There were no outliers in the total number of dropouts by clinical trial center; the maximum number of dropouts in any one center for any reason during the treatment period was seven.

Subjects coded as "no longer willing to participate" in the varenicline group were cross-referenced with reports of adverse events and no pattern or temporal relationship between adverse event reports and treatment discontinuations was identified.

Pooled studies

The Applicant presented adverse events that led to discontinuation in 1% or greater of either treatment group. Nausea and insomnia were consistently more frequent adverse events leading to discontinuation in the varenicline group than the placebo group and are expected adverse effects of varenicline. In the largest pool (2010 pool), depressed mood was a more frequent adverse event leading to discontinuation in the varenicline group and depression was a more frequent adverse event leading to discontinuation in the placebo group. The data on discontinuations from the pooled studies does not appear to indicate a causal relationship between varenicline, depressed mood, and

depression. For further discussion of neuropsychiatric adverse events, see section 7.3.5.

Table 32: Adverse Events Resulting in Permanent Discontinuation (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
Number (%) Subjects	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal Disorders	95 (4.8)	20 (1.7)	156 (3.5)	34 (1.2)	14 (3.9)	5 (1.4)	9 (3.6)	2 (0.8)	8 (1.6)	0 (0)
Nausea	59 (3.0)	5 (0.4)	96 (2.1)	10 (0.3)	10 (2.8)	3 (0.9)	5 (2.0)	1 (0.4)	5 (1.0)	0 (0)
Psychiatric disorders	75 (3.8)	34 (2.8)	104 (2.3)	58 (2.0)	8 (2.3)	4 (1.1)	1 (0.4)	5 (2.0)	7 (1.4)	7 (4.2)
Depressed mood	5 (0.3)	0 (0)	9 (0.2)	3 (0.1)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.2)
Depression	10 (0.5)	5 (0.4)	13 (0.3)	11 (0.4)	2 (0.6)	0 (0)	0 (0)	2 (0.8)	1 (0.2)	2 (1.2)
Insomnia	25 (1.3)	11 (0.9)	30 (0.7)	14 (0.5)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	2 (0.4)	0 (0)

Source: ISS p. 74-5

Dose Reductions and Temporary Discontinuations in Trial A1054

The table below summarizes dose reductions and temporary Discontinuations due to Treatment-Emergent Adverse Events that occurred in total and that occurred in the Gastrointestinal, Psychiatric, and Cardiac Disorders System Organ Classes.

Table 33: Dose Reductions or Temporary Discontinuations Due to Treatment-Emergent Adverse Events (Trial A1054)

SOC	Varenicline N=223 (%)	Placebo N=237 (%)
Gastrointestinal TEAEs	11 (5)	5 (2)
Psychiatric TEAEs	4 (2)	2 (1)
Cardiac TEAEs	3 (1)	1 (0.4)
All TEAEs	21 (9)*	11 (5)

* One subject reported did not meet inclusion criteria for COPD and is excluded from the table

Source: Clinical Reviewer adapted from Table 25 of Clinical Study Report

Eleven of the subjects in the varenicline group had a gastrointestinal symptom that led to a dose reduction or temporary discontinuation compared to only five in the placebo group. The higher incidence of dose reductions and temporary discontinuations due to gastrointestinal symptoms in the varenicline group is expected based on the adverse event profile of varenicline.

In the Psychiatric Disorders SOC, there were two TEAEs of agitation in the varenicline group compared to one in the placebo group and two TEAEs of insomnia in the varenicline group compared to one in the placebo group. Agitation is an event of interest that is being further evaluated in the aforementioned phase 4 safety trial. Insomnia is a known common adverse effect of varenicline from the original NDA application.

There were more dose reductions and temporary discontinuations due to adverse events in the "Cardiac Disorders System Organ Class" in the varenicline group than the placebo group. There was one event of Premature Ventricular Contractions in each group as well as an "acute myocardial infarction" and a "cardiac failure congestive" in the varenicline group. No meaningful conclusion can be drawn about the higher number of adverse events that fall into the "Cardiac Disorders" System Organ Class due to the small number of events. See section 7.3.5 for further discussion of cardiovascular adverse events.

7.3.4 Significant Adverse Events

There were no adverse events or laboratory abnormalities other than those discussed in Sections 7.3.2, 7.3.3 and 7.3.5 that were identified as significant, based on the ICH E3 guidance for industry E3 Structure and Content of Clinical Study Reports.

There were 38 adverse events coded as severe in the placebo group and 29 adverse events coded as severe in the varenicline group. Severe adverse events were summarized and reviewed at the System Organ Class and Preferred Term level and no patterns of interest emerged.

7.3.5 Submission Specific Primary Safety Concerns

The first two portions of this section review the data on neuropsychiatric adverse events and COPD-related adverse events from trial A1054 alone. The remainder of the section is devoted to the review of the pooled Phase 2-4 data from the Integrated Summary of Safety. There is an excerpted review of neuropsychiatric events, cardiovascular events, and cerebrovascular events by Dr. Skeete, followed by this reviewer's review of accidental injury, serious skin reactions and allergic phenomenon, blindness and visual impairment, and convulsions,

Neuropsychiatric Adverse Events in Trial A1054

The following is a summary of the neuropsychiatric treatment-related and all-causality TEAEs in the safety population that are being evaluated in the Applicant's post-marketing safety study.

Table 34: Neuropsychiatric AEs (Trial A1054)

HLGT	PT	Varenicline N=223	Placebo N=237
Anxiety disorders and symptoms	Anxiety	6	7
	Agitation	2	2
	Nervousness	2	2
	Stress	1	0
Total		**11 (4.9%)**	**11 (4.6%)**
Depressed mood disorders and disturbances	Depression	6	5
	Depressed mood	1	0
	Depressive symptom	0	1
	Dysthymic disorder	0	1
Total		**7 (3.1%)**	**7 (3%)**
Mood disorders and disturbances	Mood altered	1	0
	Anger	0	1
Personality disorders and disturbances in behavior	Aggression	1	0
Suicidal and self-injurious behaviors NEC	Suicidal ideation	0	1
Subjects with any event of interest		**17 (7.6%)**	**17 (7.2%)**

Source: Clinical Reviewer based on ADVERS dataset

There were 3 severe events and 18 moderate severity events. Of these, all three severe events and one of the moderate severity events would meet the severity criteria for inclusion in the primary safety endpoint of the post-marketing study and all occurred in the placebo group. The table below summarizes these events.

Table 35: Neuropsychiatric Events by Severity (Trial A1054)

Severity	Preferred Term	Varenicline	Placebo	Treatment related
Severe				
	Suicidal Ideation		X*	Yes
	Depression		X*	Yes
	Anxiety		X	Yes
Moderate				
	Agitation		X	Yes

* occurred in the same subject

Source: Clinical Reviewer based on ADVERS dataset

The percentages of subjects with the neuropsychiatric events of interest were similar between treatment groups in this clinical trial. Severe events were more common in the

placebo group. No evidence of increases in neuropsychiatric events in the varenicline-treated group in the COPD population has emerged based on this clinical trial.

COPD-related Adverse Events in Trial A1054

Treatment-emergent COPD exacerbations and related disorders attributed to COPD were infrequent and higher in the varenicline group than the placebo group. Two of the events were classified as serious and severe and were both in the placebo group. COPD exacerbation rates vary widely in individuals with COPD, but rates in the placebo arms of clinical trials have been found to be between 1 to 2 exacerbations per year per patient, on average[19]. Due to the infrequency of the events, and the relatively brief treatment period of 12 weeks, a larger sample size would need to be studied to draw conclusions about the rates of events in this population. However, the number of events that were observed during this trial is not unexpected, based on what is known about baseline rates. Based on what is known about varenicline, there is not a high suspicion that varenicline would affect respiratory function or the COPD disease process.

Table 36: COPD-related Adverse Events per Subject (Trial A1054)

Preferred Term	# TEAEs varenicline group N=223	# TEAEs placebo group N=237
Chronic obstructive pulmonary disease	6	3
Bronchitis	0	1
Dyspnoea	1	0
Musculoskeletal pain (pain in/ weight on shoulders)	0	1
Total	7	5

Source: Clinical Reviewer derived from Applicant provided dataset ADVERS subjects removed who did not have COPD based on Appendix B12.2 p. 1444 of Applicant's Clinical Study Report

[19] Keene et al Statistical Analysis of exacerbation rates in COPD: TRISTAN and ISOLDE revisited Eur Respir J 2008; 32: 17–24

Special Safety Concerns evaluated in the ISS

The following introduction is adapted from Dr. Skeete's S-019 review:

For the Integrated Summary of Safety, the applicant was asked to provide in depth adverse event analyses for several event groups considered events of interest for the purposes of this review; events of interest generally included labeled safety warnings of events identified through postmarketing pharmacovigilance, events identified through postmarketing data mining for which no labeling changes have been made to date, and events of particular relevance to the new populations studied in the efficacy supplements. The applicant was also informed that Standardized MedDRA Queries (SMQs) should be used in the analyses where available. The event groups included the following:

1. Neuropsychiatric events
2. Cardiovascular events
3. Cerebrovascular accidents
4. Accidental injury
5. Serious skin reactions and allergic phenomenon
6. Blindness/visual impairment
7. Convulsions

In fulfilling these requests, the applicant conducted additional AE analyses for each of these event groups using safety data from the Phase 2–4 studies. The applicant also analyzed the safety data using a number of SMQs and opted to limit these SMQ searches to the narrow subset of terms for each of the individual SMQs.

The ISS supports the four efficacy supplements that were submitted simultaneously by the applicant, supplements 019–(b) (4) The supplements were reviewed by two reviewers – the current reviewer, who reviewed this COPD supplement, as well as supplement 021, with information on a flexible quit date approach to smoking cessation with Chantix, and Dr. Skeete, who reviewed supplement 019, the CVD study and supplement (b) (4) new claims supported by a new patient-reported outcome dossier. In the same way, the ISS was also reviewed by both reviewers, who each reviewed separate sections of the ISS report. To present the review of the ISS in its entirety as part of the review of the COPD supplement (S-020), the portions reviewed by Dr. Skeete are excerpted and presented in the relevant sections of this review and so indicated.

Neuropsychiatric Events (from Dr. Skeete's review)

Chantix carries a boxed warning concerning neuropsychiatric events. Thus, at the request of the Agency, the applicant placed special emphasis on analyses of these adverse events in the Integrated Summary of Safety (ISS) report. In turn, special attention was given to review of the analyses of these events included in the report. Again, these analyses were based on safety data from the Phase 2–4 studies in the Chantix clinical trial database. It should also be noted that in

Chantix clinical trials, subjects were generally excluded for neuropsychiatric conditions when considered unstable.

In evaluating neuropsychiatric events, the applicant reviewed data from the ISS safety database to identify frequently reported adverse events categorized within the Nervous System Disorders and Psychiatric Disorders System Organ Classes (SOC). Additionally, relevant Standardized MedDRA Queries (SMQs) were performed to search the data in the ISS safety database, with queries limited to the narrow subsets of the individual SMQs. The following SMQs were used by the applicant to identify neuropsychiatric events:

- Depression and suicide/self injury
    - Suicide/self-injury (sub-category of Depression and Suicide/Self Injury SMQ)
- Hostility/Aggression
- Psychosis and psychotic disorders

Results from the applicant's ad-hoc search of data for neuropsychiatric adverse event terms in the ISS safety database and the applicant's search using neuropsychiatric-related SMQs follow. Results from the applicant's search using the applicant-developed search strategy are presented first, followed by, there results of the applicant's search for these terms using the SMQs.

Applicant's Review of Neuropsychiatric Event Terms in the Pooled Safety Database (P 2–4 Studies)

As seen in [Table 47: Commonly Reported Adverse Events by SOC and PT in Completed Placebo-Controlled Phase 2-4 Studies], adverse events in the Nervous System Disorders and Psychiatric Disorders SOCs were among the most frequently reported adverse events in all studies in the pooled cohorts. Within these SOCs, adverse events reported in ≥5% of subjects in any arm included abnormal dreams, dizziness, dysgeusia, headache and insomnia. Consistent with the known varenicline safety profile, abnormal dreams, dysgeusia, headache and insomnia were observed more commonly in the varenicline arm as compared with placebo for all cohorts. A higher rate of reporting of adverse events coded as dizziness was evident for subjects on varenicline in the CVD study, perhaps, consistent with a cerebrovascular etiology. In short, based on the applicant's review of these safety data, adverse events in the Psychiatric and Nervous System Disorders SOCs were observed frequently in patients on varenicline; however, neuropsychiatric events described in the boxed warning were not commonly observed in the clinical trial database.

Standardized MedDRA Queries (SMQs) for Neuropsychiatric Events

Adverse events of depression, suicidality, hostility and aggression and psychoses were not commonly observed within the Psychiatric Disorders and Nervous System Disorders SOCs. Nonetheless, these events were observed in postmarketing surveillance, prompting updates to the varenicline label in the form of a boxed warning, as well as a requirement for the applicant to conduct a postmarketing trial to better understand the relationship between use of Chantix and occurrence of these neuropsychiatric events. As such, in an attempt to perform a more elaborate search of these events in the safety database, related SMQs were used in the analyses of these

events to identify any of these observed events in this larger (as compared with the original NDA) ISS safety database.

The applicant's findings for each of the SMQs are illustrated in the following table:

Table 37: SMQs for Neuropsychiatric Events (Pooled data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
SMQ	number (%) of subjects									
Depression and Suicide/self-injury (narrow)										
Subjects with an event	76 (3.8)	29 (2.4)	134 (3.0)	80 (2.8)	12 (3.4)	8 (2.3)	7 (2.8)	7 (2.8)	12 (2.5)	13 (7.9)
Subjects discontinued due to an event	15 (0.8)	5 (0.4)	23 (0.5)	17 (0.6)	4 (1.1)	0 (0)	0 (0)	4 (1.6)	2 (0.4)	5 (3.0)
Suicide/self-injury (narrow)										
Subjects with an event	1 (0.1)	2 (0.2)	4 (0.1)	5 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	2 (1.2)
Subjects discontinued due to an event	0 (0)	0 (0)	1 (<0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.6)
Hostility/Agression (narrow)										
Subjects with an event	10 (0.5)	7 (0.6)	16 (0.4)	14 (0.5)	0 (0)	1 (0.3)	1 (0.4)	1 (0.4)	3 (0.6)	1 (0.6)
Subjects discontinued due to an event	4 (0.2)	1 (0.1)	(5 (0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	0 (0)
Psychosis and psychotic disorders (narrow)										
Subjects with an event	4 (0.2)	1 (0.1)	4 (0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subjects discontinued due to an event	3 (0.2)	1 (0.1)	3 (0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease
Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
Source (Table and Legend): Applicant's ISS report: p. 56

Depression and Suicide/Self Injury SMQ

For the Depression and Suicide/Self Injury SMQ, the frequency with which these events occurred was identical for both arms in the COPD study while the rate was much higher in the placebo arm of the flexible quit date study. For all other cohorts, more events in this SMQ were observed in the varenicline arms; however, none of these differences were marked. The reason for the variation across cohorts is uncertain, and could represent imbalances in rates of baseline neuropsychiatric history. For the depression and suicide/self injury SMQ, the most frequently reported adverse events were depression and depressed mood.

On the other hand, when suicidality alone was considered in the Suicide/Self Injury SMQ sub-category, there were no events in the CVD study and while differences once again were not marked, reporting of events related to suicidality was consistently higher in the placebo arm of the cohorts. For this sub-category of Suicide/Self Injury, the majority of the events were suicidal ideations. There was also one suicide attempt made by a subject on placebo and an intentional

overdose by a subject on varenicline.

Hostility/Aggression SMQ

Adverse events in the Hostility/Aggression SMQ were generally reported with the same frequency in the varenicline and placebo arms. In cohorts where differences were seen between treatment arms, events were reported somewhat more commonly in the placebo arm (2005 Pooled Studies and 2010 Pooled Studies cohorts). In contrast, treatment discontinuations because of the events typically were more common in the varenicline arm, which suggests that while the events were less frequent in this treatment group, they may have been more severe. That being said, findings from this SMQ must be interpreted in light of the very low numbers of events identified; in all treatment arms, <1% of subjects had adverse events identified by the Hostility/Aggression SMQ. Three preferred terms were identified for the subjects in the ISS safety database, namely aggression, anger, and hostility.

Psychosis and Psychotic Disorders

For the final SMQ performed, only six subjects in all clinical trials were identified. These events were rare and occurred with similar frequency in both arms. In varenicline-treated patients, these included adverse events of hallucination, tactile hallucination and visual hallucination (n=1, each) and an adverse event of acute psychosis in another subject. Among placebo-treated subjects, one subject had a visual hallucination while another had schizophrenia, paranoid type as an adverse event.

Serious Adverse Events – Events Identified by the Neuropsychiatric-related SMQs that were SAEs:

The applicant additionally provided data on the events identified by the neuropsychiatric SMQs that were also considered serious, that is neuropsychiatric events that were SAEs. These included:

- Acute psychosis (1 [<0.1%] varenicline)
- Depressed mood (1 [<0.1%] varenicline)
- Depression (2 [0.1%] varenicline)
- Schizophrenia, paranoid type (1 [<0.1%] placebo),
- Suicidal ideation (2 [0.1%] varenicline, 1 [<0.1%] placebo)
- Suicide attempt (1 [<0.1%] placebo)

Using the numbers of subjects exposed to varenicline and placebo in the 2010 Pooled cohort as the denominator, rates of SAEs identified by these SMQs were the same for the two treatment arms, (0.1%, each). Neuropsychiatric events considered SAEs occurred infrequently in the Chantix clinical trials and occurred at the same rates in both treatment arms.

In sum, from the totality of evidence related to neuropsychiatric events generated from the pooled safety database, neuropsychiatric events were infrequent and the overall incidence was similar between treatment arms. Neuropsychiatric SAEs occurred at the same rates. At present,

the varenicline label carries a boxed warning concerning neuropsychiatric events and a postmarketing study is required of the applicant to assess these events in subjects with and without a diagnosis of a neuropsychiatric disorder. Taken together, these findings from the pooled safety data do not indicate that a revised course of action with respect to neuropsychiatric events is required at this juncture.

Cardiovascular Events (from Dr. Skeete's review)

Review of cardiovascular events included: 1) examination of baseline cardiovascular medical history for subjects in the 2010 pooled cohorts; 2) comparison of cardiovascular-related events and risk factors in subjects considered to be with and without cardiovascular risk factors (other than smoking) at baseline; 3) examination of adverse event terms identified by analyses using the Ischemic Heart Disease Standardized MedDRA Query (SMQ); and 4) comparison of adverse event terms that were identified by the Ischemic Heart Disease SMQ that also met the definition of a serious adverse event (SAE).

Cardiovascular Medical History for Subjects in Studies Comprising the ISS

In the pre-marketing safety database, patients generally were excluded from participation if they had any history of clinically significant cardiovascular disease, clinically significantly abnormal screening or baseline ECGs significant arrhythmias; or poorly controlled hypertension (usually subjects were excluded for screening or baseline SBP > 150 mm Hg or DBP > 95 mm Hg). Some Phase 3 protocols, on the other hand, were amended to allow enrollment of subjects with stable, documented, cardiovascular disease (stable for ≥ 6 months).

For subjects in the studies comprising the ISS pooled safety database, the applicant provided data on risk factors for cardiovascular disease other than smoking history (which all subjects have and is summarized separately) for the completed placebo-controlled Phase 2–4 studies. In general, key modifiable risk factors for cardiac disease include smoking, diabetes, hyperlipidemia, hypertension, obesity and overweight as well as physical inactivity.

In operationalizing presence of cardiovascular risk factors, the applicant classified subjects with a past or present medical history meeting any of the following criteria as having an additional cardiovascular disease risk factor besides smoking.

APPLICANT'S DEFINED CRITERIA FOR CVD RISK FACTORS OTHER THAN SMOKING

- BMI > 30
- A medical condition included in the Cardiac Disorders or Vascular Disorders System Organ Class
- Medical Conditions included in the following HLGTs:
    - Cardiac and vascular disorders congenital
    - Cardiac therapeutic procedures
    - Vascular therapeutic procedures

  - Central nervous system vascular disorders (this HLGT was not included in the criteria used for the 2005 NDA[20])
- Medical Conditions included in the following HLTs:
  - Diabetes mellitus (excluding hyperglycemia)
  - Diabetic complications cardiovascular
  - Elevated cholesterol
  - Elevated cholesterol with elevated triglycerides
  - Elevated triglycerides
  - Hyperlipidemias NEC (not elsewhere classified)

Based on these criteria, the applicant's overall findings for CVD risk factors for subjects in the Phase 2–4 studies are presented in the following table:

Table 38: CVD risk factors (Pooled data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var 1983**	**Pbo 1209**	**Var 4483**	**Pbo 2892**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
Subjects with CV risk factors	number (%) of subjects									
Absent	1184 (59.7)	733 (60.6)	2410 (53.8)	1544 (53.4)	0 (0)	1[a] (0.3)	103 (41.5)	127 (50.6)	303 (62.3)	95 (57.6)
Present	799 (40.3)	476 (39.4)	2073 (46.2)	1348 (46.6)	353 (100)	349 (99.7)	145 (58.5)	124 (49.4)	183 (37.7)	70 (42.4)

Var = varenicline; Pbo = placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036, A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
a One placebo subject had a past history of "retinal artery occlusion." This is considered a form of stroke, but the term is captured under SOC Eye disorders and was not captured using the stated criteria defining CV risk factors used for this table.
SOURCE (Table and Legend): ISS Report, page 45.

Across the various pooled cohorts, the proportion of subjects with cardiovascular disease risk factors other than smoking is comparable overall between treatment arms, with a few exceptions. As history of stable cardiovascular disease was a required eligibility criterion for the CVD study, all subjects were expected to have a CVD risk factor present and do have at least one CVD risk factor present as demonstrated in the table. On the other hand, there is an apparent imbalance between the two arms in the COPD study with approximately 60% in the varenicline arm as opposed to about 50% in the placebo arm of this study. The reverse is true for the flexible quit date study where slightly more subjects in the placebo arm have CV risk factors.

[20] Pfizer noted that in reviewing the criteria used in the 2005 NDA to determine whether a subject had a cardiovascular risk factor(s) other than cigarette smoking, it was noted that the criteria did not include cerebrovascular events, such as PTs including carotid artery stenosis, cerebrovascular accident, ischemic stroke, and transient ischemic attack. These PTs code into the HLGT central nervous system vascular disorders. Therefore, the Integrated Summary of Safety used the 2005 criteria and expanded to include the HLGT central nervous system vascular disorders.

For Chantix clinical trials conducted in the more general study populations of adult smokers (2005 Pooled Studies, 2010 Pooled Studies, Flex Quit Date study), about 40% of subjects in either treatment arm met the criteria for having CV risk factors other than smoking history. This is slightly higher in the 2010 Pooled Studies, likely reflecting inclusion of the CVD and COPD studies in these numbers as well as subjects with medical conditions in the Central Nervous System Vascular disorders HLGT which, as documented above, were not included in the criteria used for the 2005 NDA.

Treatment-Emergent Adverse Events (TEAEs) by Presence or Absence of Risk Factors for Cardiac Disease

The applicant performed an analysis of treatment-emergent adverse events comparing the subset of varenicline- and placebo-treated patients with no cardiovascular disease risk factors and also performed an analysis which compared the subset of varenicline- and placebo-treated patients with cardiovascular disease risk factors present.

In reviewing these safety data, the emphasis was on adverse events representing cardiovascular disease or risk factors for CVD in each of the treatment arms within each subpopulation defined by the presence or absence of a cardiovascular disease risk factor. Because these adverse events were infrequent, only those adverse events that occurred in at least 1% of subjects in the varenicline group and more commonly in the varenicline group were examined in these subpopulations defined by the presence or absence of a cardiac risk factor. These could have occurred at the level of pertinent system organ classes (SOC) (including Cardiac Disorders SOC and Nervous System Disorders SOC), or at the level of relevant High Level Group Terms (HLGTs) and Preferred Terms (PTs). Finally, in reviewing the data on these subpopulations, safety data from the 2010 pooled cohort were the focus for the review. Again, the 2010 Pooled cohort included 4483 varenicline-treated subjects and 2892 placebo-treated subjects.

CV risk factor absent

Cardiac Disorders SOC
In this subpopulation with no cardiovascular risk factors (other than smoking), TEAEs in the cardiac disorders SOC were infrequent overall, but, somewhat more common in the varenicline arm (1.6% in the varenicline arm vs. 1% in the placebo arm). Within this SOC, there were no HLGTs or PTs for which adverse events occurred in at least 1% of subjects in either treatment arm.

Investigations SOC
Within the Investigations SOC, adverse events relating to blood pressure and ECG changes, metabolic derangements and weight changes could provide some insight on whether varenicline impacts antecedents to cardiovascular disease. The only adverse events occurring in ≥1% of varenicline-treated subjects were those related to weight. Weight increases were experienced more commonly in the varenicline arm than the placebo arm (varenicline n= 42, 1.7%, placebo n = 22, 1.4%). In this vein, adverse events of increased appetite too were nearly twice more

common in the varenicline arm than the placebo arm (varenicline, n=101, 4.2% vs. n = 34, 2.2% in placebo).

Nervous System Disorders SOC
Adverse events in the Nervous System SOC were also examined because cerebrovascular disorders are included in this SOC. While there were numerous events observed in both arms within this SOC (varenicline n = 701, 29.1%; placebo n = 386, 25%), adverse events at neither the HLGT level nor the PT level occurred in > 1% of varenicline-treated subjects and more commonly than observed in placebo.

Vascular Disorders SOC
Within the Vascular Disorders SOC, more subjects in the varenicline arm reported events than placebo (n=45, 1.9% vs. n=25, 1.6%, respectively). The only HLGT or PT which met the criteria for review was the Vascular Disorders NEC HLGT for which 1.1% of varenicline-treated subjects reported adverse events compared with 0.7% on placebo. While this HLGT includes Preferred Terms of peripheral vascular disorder and aortic disorder, the numbers seen at the HLGT level were actually driven by the PTs, flushing and hot flush.

CV risk factor present

Cardiac Disorders SOC
In this subset of subjects with CV risk factors (other than smoking) present at baseline, TEAEs in the Cardiac Disorders SOC were more common overall than in the no CVD risk factor subgroup and more common in the varenicline arm (3.6% in the varenicline arm vs. 2.7% in the placebo arm). Within this SOC, adverse events in the Cardiac Arrhythmias and Coronary Artery Disorders HLGTs were more common in the varenicline arm and were observed in at least 1% of varenicline-treated subjects. Within the Cardiac Arrhythmias HLGT, 1.4% of varenicline-treated subjects had an adverse event in this HLGT as compared with 0.7% on placebo, but, there was no consistent pattern among the individual preferred terms within this HLGT, with respect to excess events. Of the subjects in the varenicline group, 1.4% had adverse events in the Coronary Artery Disorders HLGT vs. 1% in the placebo arm. The majority of these adverse events for subjects on varenicline were events coded as angina (angina pectoris, 0.8% and angina unstable 0.1%). Adverse events coded to the preferred term chest pain (General Disorders SOC) were also more common in the varenicline group 1.5% vs. 1.3% in the placebo arm. Viewed in aggregate, AEs of chest pain and angina appear to be occurring with greater frequency in the varenicline group, though overall these events were rarely reported.

Investigations SOC
Within the Investigations SOC, only the Cardiac and Vascular Investigations (excl enzyme tests) HLGT met strict criterion specified for review, with 1.4% subjects in the varenicline vs.1.3% of the placebo group having AEs in this HLGT, but, these rates are more or less the same between

the two treatment groups. Within this category, blood pressure increases[21] occurred in 0.8% of subjects on varenicline and 0.7% in placebo. Weight increases were again more common in the varenicline group (1.6%) than placebo (0.6%), as were adverse events of increased appetite (n=55, 2.7% in varenicline vs. n=22, 1.6% in placebo).

Nervous System Disorders SOC

The same pattern observed for the subpopulation with absent CV risk factors with respect to the Nervous System Disorders SOC was seen for subjects with cardiovascular risk factors. That is, many subjects had adverse events in this SOC, but, in both arms, cerebrovascular events in the CNS vascular disorders HLGT were observed in <1% of subjects. That is, events in the Nervous System Disorders SOC were driven by events that were not cardiovascular events or risk factors.

Vascular Disorders SOC

Adverse events in the Vascular Disorders SOC occurred with similar frequency in the varenicline and placebo arms (3.5% vs. 3.3%, respectively. There were also no adverse events at the HLGT or PT levels occurring in ≥1% of varenicline-treated subjects and more than in placebo. While 1.6% of varenicline-treated subjects had an adverse event of hypertension, 1.7% of subjects in the placebo group did also. These findings differ from the increased blood pressure findings described that were adverse events in the Investigations SOC, but, may represent subjects newly meeting criteria for hypertension as opposed to having a sporadic elevated blood pressure reading.

REVIEWER COMMENT: In comparing these subgroups defined by the presence or absence of cardiac risk factors other than smoking, while ischemic myocardial events are, on the whole, uncommon, they occur with greater frequency in the subgroup with CV risk factors, as anticipated. Among subjects with CV risk factors, subjects on varenicline experienced these events more commonly. These do not appear to be explained by an impact of varenicline on modifiable cardiovascular risk factors, e.g., hypertension or hyperlipidemia. Notably, weight changes and increased appetite were observed more commonly in varenicline-treated subjects. This pattern was consistent for the subgroups defined by the presence or absence of cardiac risk factors other than smoking. It is conceivable that untoward weight changes and changes in appetite that can occur in the setting of smoking cessation could contribute to the cardiovascular disease findings.

Ischemic Heart Disease SMQ

The applicant analyzed cardiovascular events using the narrow subset of the Ischemic Heart Disease SMQ. The applicant's findings are summarized in the following table.

[21] Preferred terms blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased were combined and reviewed in aggregate.

Table 39: Ischemic Heart Disease SMQ (Pooled data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number Subjects[a]	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
PT	number (%) of subjects									
Number subjects with events	8 (0.4)	3 (0.2)	37 (0.8)	14 (0.5)	18 (5.1)	10 (2.9)	3 (1.2)	1 (0.4)	5 (1.0)	0 (0)
Number of subjects discontinued	4 (0.2)	1 (0.1)	9 (0.2)	2 (0.1)	3 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)
Acute coronary syndrome	1 (0.1)	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Acute myocardial infarction	1 (0.1)	1 (0.1)	5 (0.1)	3 (0.1)	2 (0.6)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.2)	0 (0)
Angina pectoris	2 (0.1)	0 (0)	22 (0.5)	7 (0.2)	13 (3.7)	7 (2.0)	2 (0.8)	0 (0)	4 (0.8)	0 (0)
Angina unstable	1 (0.1)	0 (0)	4 (0.1)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coronary artery disease	1 (0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial infarction	1 (0.1)	0 (0)	2 (<0.1)	1 (<0.1)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial ischemia	0 (0)	1 (0.1)	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coronary angioplasty	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Percutaneous coronary intervention	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease
Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037 2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
Source (Table and Legend): Applicant's ISS report: p. 62

Consistent with the findings in the CVD study when the CVD study was reviewed independently, adverse events identified by the Ischemic Heart Disease SMQ were observed with greater frequency in the varenicline arm in the CVD study, and this imbalance, though minor, was consistent across all cohorts.

For all cohorts, regardless of baseline cardiovascular disease medical history findings, more subjects in the varenicline arm had adverse events identified by the Ischemic Heart Disease SMQ. Recall from the medical history data, that cardiovascular risk factors were similar between the varenicline and placebo arms for all cohorts, save for the COPD and flexible quit date studies, yet, the imbalance in observed events in the narrow ischemic heart disease SMQ exists for all cohorts. The differences seen in the COPD study may in part reflect the unequal baseline risk for cardiovascular disease where more subjects in the varenicline arm had risk factors for CVD. On the other hand, although there were slightly more subjects in the placebo arm of the Flexible Quit Date Study with risk factors for CV disease, no subjects on placebo had events identified by the Ischemic Heart Disease SMQ whereas subjects in the varenicline arm did have

events identified by this SMQ, however infrequent. The findings from the ischemic heart disease SMQ appear to be driven by reports of angina and to a lesser extent, myocardial infarction.

Serious Adverse Events – Events Identified by the Ischemic Heart Disease SMQ that were SAEs:

The applicant provided additional data on ischemic heart disease SMQ events that were reported as SAEs, underscoring that some of the events were reported post-therapy and not recorded as AEs in the study database. As summarized by the applicant, Ischaemic heart disease SMQ events reported as SAEs included:

- Acute coronary syndrome (2 [<0.1%] varenicline, 2 [0.1%] placebo)
- Acute myocardial infarction (5 [0.1%] varenicline, 4 [0.1%] placebo)
- Angina pectoris (7 [0.2%] varenicline, 2 [0.1%] placebo)
- Angina unstable (3 [0.1%] varenicline, 2 [0.1%] placebo)
- Coronary artery disease (4 [0.1%] varenicline, 2 [0.1%] placebo)
- Myocardial infarction (7 [0.2%] varenicline, 2 [0.1%] placebo).

Events identified by the Ischemic Heart Disease SMQ that are also serious adverse events (SAEs) are infrequent overall in the two treatment arms. Using the numbers of subjects exposed to varenicline and placebo in the 2010 Pooled cohort as the denominator, rates of SAEs identified by these SMQs were nearly the same for the two treatment arms though, 0.1% higher in the varenicline arm (n=28, 0.6%) than in the placebo arm (n=14, 0.5%).

Considering the findings from the various elements of this review of cardiovascular events collectively, there is a small but, increased number of events, primarily coronary heart disease events observed in subjects exposed to varenicline. In current labeling, there is no information regarding ischemic cardiac events; the label will be revised to reflect these new findings from the review of pooled safety data from Phase 2–4 studies, as well as findings from review of cardiovascular events in the CVD study independently.

Cerebrovascular Events (from Dr. Skeete's review)

In analyzing cerebrovascular events, the applicant used the Cerebrovascular disorders Standardized MedDRA Query (SMQ) and the Central Nervous System Hemorrhages and Cerebrovascular Accidents SMQ. Again, the narrow subsets of these SMQs were used for these searches. The applicant found that results from these two SMQs were completely overlapping and hence the findings are presented for both in a single summary. The applicant's findings are presented in the following table.

Table 40: Cerebrovascular events (Pooled data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
PTs	number (%) of subjects									
CNS Haemorrhages &Cerebrovascular accidents (narrow) & Cerebrovascular disorders (narrow)										
Number subjects with events	2 (0.1)	0 (0)	6 (0.1)	2 (0.1)	2 (0.6)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.2)	0 (0)
Number subjects discontinued	1 (0.1)	0 (0)	2 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Carotid artery stenosis	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Cerebrovascular accident	1 (0.1)	0 (0)	4 (0.1)	0 (0)	2 (0.6)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Ischemic stroke	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)
Transient ischemic attack	1 (0.1)	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Var=varenicline; Pbo=placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037 2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
SOURCE (Table and Legend): Applicant's ISS report, p. 63

Cerebrovascular events identified by these SMQs were rare. Again, across all cohorts, <1% of subjects in any treatment arm reported a cerebrovascular event. In the cardiovascular disease study, there was a slight increase in numbers of events seen in the varenicline arm over that seen in the placebo arm. Among the other cohorts, the proportions of subjects experiencing events were essentially the same in the two treatment arms. There were no clear trends seen in the types of events experienced by subjects in these studies (i.e., individual preferred terms (PTs). Therefore, labeling changes based on these events are not warranted.

Accidental Injury

Following the approval of varenicline, there were post-marketing reports of accidental injury, including traffic accidents and near-miss traffic incidents. Some patients have also reported difficulty concentrating, somnolence, and dizziness that resulted in impairment or raised concern for potential impairment in driving or operating machinery. The label was modified to include a warning about these reports in 7/09. The Applicant analyzed the data for possible effects of varenicline on risk for accidental injury using the Accidents and Injuries Standardized MedDRA Query (SMQ). The table below summarizes the results.

Table 41: All-Causality Adverse Events in the Accidents and Injuries SMQ by HLGT (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
SMQ HLGT	number (%) of subjects									
Accidents and injuries (narrow)										
Number of subjects w/events	117 (5.9)	45 (3.7)	181 (4.0)	99 (3.4)	7 (2.0)	8 (2.3)	8 (3.2)	6 (2.4)	11 (2.3)	6 (3.6)
Number of subjects discontinued	0 (0)	2 (0.2)	2 (,0.1)	4 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint injuries	39 (2.0)	12 (1.0)	55 (1.2)	32 (1.1)	3 (0.8)	3 (0.9)	2 (0.8)	4 (1.6)	3 (0.6)	2 (1.2)
Injuries NEC	75 (3.8)	34 (2.8)	119 (2.7)	71 (2.5)	5 (1.4)	6 (1.7)	6 (2.4)	1 (0.4)	7 (1.4)	5 (3.0)
Injuries by physical agents	11 (0.6)	3 (0.2)	18 (0.4)	6 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	0 (0)
Headaches	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: ISS Table 19

The preferred term “road traffic accident” is contained within the Injuries by physical agents HLGT. There were comparable rates of road traffic accidents in the varenicline and placebo group (0.1% and 0.2%) respectively. Based on this data, varenicline does not appear to increase the incidence of accidental injuries in patients taking it in general, nor in the COPD population. While this analysis does not provide sufficient evidence to rule out an effect of varenicline on risk of accidental injury, it neither increases the suspicion for a causal relationship, nor raises any further concerns.

Serious Skin Reactions and Allergic Phenomenon

There were post-marketing reports of skin reactions including Steven’s-Johnson syndrome and erythema multiforme in patients using Chantix. The label was modified to include a warning about these reports in 7/09. The Applicant analyzed the data from all Phase 2-4 placebo-controlled studies using the Angioedema, anaphylactic reaction,

and serious cutaneous adverse reactions SMQs. The results are summarized in the table below[22].

Table 42: All Causality Adverse Events Related to Skin Reactions and Allergic Phenomenon (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
SMQ PT	number (%) of subjects									
Angioedema (narrow)	17 (0.9)	9 (0.7)	34 (0.8)	18 (0.6)	3 (0.8)	2 (0.6)	2 (0.8)	1 (0.4)	4 (0.8)	0 (0)
Eye swelling	0 (0)	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)	1 (0.3)	1 (0.4)	0 (0)	0 (0)	0 (0)
Eyelid oedema	0 (0)	2 (0.2)	1 (<0.1)	3 (0.1)	0 (0)	1 (0.3)	1 (0.4)	0 (0)	0 (0)	0 (0)
Gingival swelling	3 (0.2)	1 (0.1)	3 (0.1)	3 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lip swelling	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Swollen tongue	2 (0.1)	0 (0)	3 (0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Face oedema	1 (0.1)	0 (0)	4 (0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Allergic oedema	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Angioedema	0 (0)	0 (0)	2 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Pharyngeal oedema	2 (0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urticaria	6 (0.3)	3 (0.2)	12 (0.3)	7 (0.2)	1 (0.3)	0 (0)	0 (0)	1 (0.4)	1 (0.2)	0 (0)
Swelling face	5 (0.3)	2 (0.2)	7 (0.2)	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Anaphylactic reactions (narrow)	0 (0)	0 (0)	34 (0.8)	18 (0.6)	3 (0.8)	2 (0.6)	2 (0.8)	1 (0.4)	4 (0.8)	0 (0)
Circulatory collapse	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Severe cutaneous adverse reactions (narrow)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: ISS Table 20

[22] The Applicant provided source tables for ISS Table 20 (reproduced as Table 32 in this review) in the ISS. Source Table A26.10.1 identified only one adverse event in the Anaphylactic Reactions SMQ: circulatory collapse in the placebo group. The numbers in the "Anaphylactic reactions" row in Table 32 (ISS Table 20) appear to be erroneously duplicated from the "Angioedema" row in all but the "2005 Pooled Studies" column and should be identical to the numbers in the "Circulatory collapse" row.

The most frequent preferred terms in the SMQs were “urticaria” and “swelling face” and both were more commonly observed in the varenicline group. These reactions were infrequent and may be causally related to varenicline. No severe or serious skin reactions were identified. These data are supportive of the currently labeled section on allergic reactions in the medication guide, which discusses swelling of the face, mouth and throat, and do not prompt further action.

Blindness and Visual Impairment

During the clinical trials reviewed in the initial NDA there were infrequent reports of visual disturbance and rare reports of transient blindness and acquired night blindness, which were included in labeling under section 6.1 Adverse Reactions, Clinical Trials Experience. The Office of Surveillance and Epidemiology performed a review of the postmarketing data, the clinical trial data, and the available literature, and concluded on 6/10/10 that the current label appeared adequate to communicate the risk of serious vision disorders. The Applicant analyzed the new data available along with the previously reviewed data for the possible effects of varenicline on eye disorders and summarized the HLGT Vision Disorders as well as the preferred terms within the HLGT. The following table is from the Applicant’s ISS.

Table 43: All-Causality Adverse Events in the HLGT Vision Disorders (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
HLGT PT	number (%) of subjects									
Vision Disorders	31 (1.6)	12 (1.0)	49 (1.1)	25 (0.9)	4 (1.1)	6 (1.7)	4 (1.6)	2 (0.8)	2 (0.4)	1 (0.6)
Accommodation disorder	0 (0)	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Altered visual depth perception	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Blindness transient	2 (0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypermetropia	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Metamorphopsia	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myopia	1 (0.1)	0 (0)	2 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Night blindness	1 (0.1)	0 (0)	2 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Scotoma	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vision blurred	17 (0.9)	9 (0.7)	29 (0.6)	19 (0.7)	2 (0.6)	5 (1.4)	3 (1.2)	2 (0.8)	2 (0.4)	0 (0)
Visual acuity reduced	2 (0.1)	0 (0)	3 (0.1)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Visual impairment	7 (0.4)	2 (0.2)	9 (0.2)	4 (0.1)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)

Source: ISS Table 18

The results of the 2010 pooled analysis support the results from the 2005 pooled analysis reviewed in the original NDA. The most commonly reported adverse event, vision blurred, was reported at approximately the same incidence between the varenicline and placebo groups. Visual impairment was more frequently reported in the varenicline group, though in small numbers in both groups. The interpretation of the above table is complicated by the small number of events as well as the larger number of subjects in the varenicline group compared to the placebo group. The only serious visual adverse event noted in the above table was a case of transient blindness in the varenicline group, which was reviewed in the original NDA[23]. There was an additional event of "night blindness" reported in the varenicline group as well as one additional event in each group of "visual acuity reduced" since the original NDA review. There have been no additional reports of "blindness transient" since the original NDA review in the controlled trial data.

[23] Two additional serious adverse events of "cataracts subcapsular" occurred in the varenicline group, which fall under the "Anterior eye structural change, deposit, and degeneration" HLGT and are, not included in Table 37. Both were reviewed as part of the original NDA.

These data neither confirm nor exclude an effect of varenicline on the risk of blindness or visual impairment in general or in the COPD population and continue to represent infrequent events of unclear significance. The current labeling appropriately includes "vision blurred", "visual disturbance," "acquired night blindness", "blindness transient," and "cataract subcapsular" as treatment-emergent events reported during clinical trials.

Convulsions

Convulsions were a rare event observed in the clinical trials reviewed in the initial NDA and are included in labeling under Section 6.1 Adverse Reactions, Clinical Trials Experience. The Applicant analyzed the data for all Phase 2-4 placebo-controlled studies using the Convulsions SMQ. The results are summarized in the table below.

Table 44: All-Causality Adverse Events Related to Convulsions (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	Var N= 1983	Pbo N= 1209	Var N= 4483	Pbo N= 2892	Var N= 353	Pbo N= 350	Var N= 248	Pbo N= 251	Var N= 486	Pbo N= 165
SMQ PT	number (%) of subjects									
Convulsions (narrow)	1 (0.1)	0 (0)	8 (0.2)	2 (0.1)	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Complex partial seizures	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Convulsion	1 (0.1)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dreamy state	0 (0)	0 (0)	5 (0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Epilepsy	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)

Source: ISS Table 23

There were no adverse events coded as convulsions, complex partial seizures, or epilepsy in the placebo group and there were three in the varenicline group. The Applicant reported that four of the "dreamy state" adverse events in the varenicline group and both events in the placebo group were due to "having several dreams per night." Excluding the "dreamy state" events, convulsions occurred in 0.05% of varenicline-treated subjects in the studies reviewed in the original NDA and 0.07% of varenicline-treated subjects in the most recently pooled data.

The case of complex partial seizures and grand mal convulsion (convulsion above) were coded as serious adverse events. The subject who had the grand mal convulsion (patient ID (b) (6)) was taking 1 mg varenicline twice a day, had no history of a seizure disorder, and was hospitalized. No laboratory or imaging abnormalities were detected and the subject permanently discontinued varenicline and reportedly recovered from the convulsion the same day. This event was reviewed in the original NDA and at that time, the reviewer considered it to be possibly causally related. The

case of complex partial seizures occurred in a subject (patient ID 104910251021) in the CV study. The subject had a history of seizure disorder upon entry into the study and was taking levetiracetam. Based on the Applicant-provided narrative, it is unclear whether there was a worsening of the pre-existing seizure disorder while on varenicline, but it is possible that this was the case. The seizures continued to be poorly controlled on levetiracetam and the subject was hospitalized for further evaluation approximately five months after completion of the full course of varenicline treatment. At last follow-up, the subject had recently been switched to oxcarbazepine and the seizures were ongoing nearly eight months after completion of the course of varenicline therapy.

The case of epilepsy was in the flexible quit date study. This subject (patient ID 109510401024) had an epileptic seizure while taking varenicline coded as moderate in severity in the context of pre-existing epilepsy and a recent dose-reduction in his anti-epileptic medication. Previous decreases of anti-epileptic medication had reportedly "caused fits" in the past. This additional history of a temporal relationship between the decrease in anti-epileptic medication and the seizure makes it less likely that varenicline was a causal agent in the seizure.

Based on this analysis, convulsions were rare in patients who received varenicline and there is a possible causal relationship. Due to the very small number of cases, there is not sufficient controlled data to determine with any level of confidence whether the higher number of events in the varenicline group is due to chance or to a true difference between the varenicline group and placebo group. Two of the three subjects who had convulsions had a history of a seizure disorder. It is possible that varenicline exacerbated the seizure disorder in these patients, though there is not sufficient evidence to conclude that this was the case. Convulsions are currently in the varenicline label and should remain in the label as a rare, potential adverse event.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Trial A1054

The Applicant defined the safety population as all subjects who received treatment and reported all-cause treatment-emergent adverse events by system organ class as well as treatment-emergent adverse events that occurred in 2% or more of either treatment arm by preferred term.

Below is a table of all-cause treatment-emergent adverse events per subject in the subset of subjects who had some degree of COPD based on the protocol-defined spirometry assessments. The thirty-nine subjects who did not meet the protocol-defined spirometry criterion for COPD have been removed from the safety population.

Table 45: TEAEs by System Organ Class (Trial A1054)

System Organ Class	n varenicline N= 223	% varenicline (n/N)	n placebo N=237	% placebo (n/N)
Gastrointestinal disorders	91	41%	51	22%
Infections and infestations	75	34%	69	29%
Psychiatric disorders	56	25%	33	14%
Nervous system disorders	33	15%	37	16%
Respiratory, thoracic and mediastinal disorders	27	12%	25	11%
Musculoskeletal and connective tissue disorders	25	11%	23	10%
General disorders and administration site conditions	22	10%	17	7%
Investigations	16	7%	7	3%
Metabolism and nutrition disorders	12	5%	5	2%

Source: Clinical Reviewer derived from Applicant provided dataset ADVERS subjects removed who did not have COPD based on Appendix B12.2 p. 1444 of Applicant's Clinical Study Report

The table below summarizes the treatment-emergent adverse events by preferred term that occurred in 5% or more of subjects in either treatment group. Preferred Terms are preceded in the table by their System Organ Class.

Table 46: TEAEs by Preferred Term occurring in 5% or more of either treatment group (Trial A1054)

System Organ Class Preferred Term	varenicline N= 223	% varenicline	placebo N= 237	% placebo
Gastrointestinal Disorders				
Nausea	60	27%	18	8%
Flatulence	15	7%	12	5%
Vomiting	15	7%	6	3%
Dry mouth	11	5%	4	2%
Psychiatric Disorders				
Abnormal dreams	25	11%	6	3%
Insomnia	23	10%	13	5%
Infections and Infestations				
Upper respiratory tract infection	22	10%	19	8%
Nasopharyngitis	9	4%	12	5%
Nervous System Disorders				
Headache	18	8%	18	8%

The adverse events that occurred in 5% or greater in the varenicline group and occurred approximately twice as often in the varenicline group as in the placebo group are:

- Nausea
- Abnormal dreams
- Insomnia
- Vomiting
- Dry mouth

These adverse events are all included in the common treatment-emergent adverse events table in the current product labeling.

Pooled Studies
The Applicant provided a table of commonly reported adverse events (shown below)

Table 47: Commonly Reported Adverse Events by SOC and PT in Completed Placebo-Controlled Phase 2-4 Studies (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
SOC PT	number (%) of subjects									
Gastrointestinal Disorders										
Constipation	118 (6.0)	27 (2.2)	235 (5.2)	68 (2.4)	18 (5.1)	5 (1.4)	9 (3.6)	4 (1.6)	13 (2.7)	3 (1.8)
Flatulence	130 (6.6)	34 (2.8)	196 (4.4)	69 (2.4)	8 (2.3)	7 (2.0)	17 (6.9)	12 (4.8)	7 (1.4)	0 (0)
Nausea	572 (28.8)	104 (8.6)	1221 (27.2)	241 (8.3)	98 (27.8)	26 (7.4)	66 (26.6)	17 (6.8)	136 (28.0)	15 (9.1)
Vomiting	59 (3.0)	8 (0.7)	146 (3.3)	25 (0.9)	24 (6.8)	3 (0.9)	15 (6.0)	2 (0.8)	15 (3.1)	1 (0.6)
General Disorders and Administration Site Conditions										
Fatigue	86 (4.3)	40 (3.3)	176 (3.9)	77 (2.7)	18 (5.1)	8 (2.3)	9 (3.6)	0 (0)	19 (3.9)	3 (1.8)
Nervous System Disorders										
Headache	217 (10.9)	116 (9.6)	444 (9.9)	227 (7.8)	36 (10.2)	28 (8.0)	16 (6.5)	12 (4.8)	42 (8.6)	15 (9.1)
Dizziness	101 (5.1)	56 (4.6)	182 (4.1)	127 (4.4)	17 (4.8)	10 (2.9)	4 (1.6)	6 (2.4)	7 (1.4)	7 (4.2)
Dysgeusia	155 (7.8)	45 (3.7)	194 (4.3)	72 (2.5)	16 (4.5)	7 (2.0)	7 (2.8)	6 (2.4)	2 (0.4)	0 (0)
Psychiatric Disorders										
Abnormal dreams	240 (12.1)	56 (4.6)	395 (8.8)	84 (2.9)	28 (7.9)	6 (1.7)	23 (9.3)	6 (2.4)	61 (12.6)	5 (3.0)
Insomnia	248 (14.3)	117 (9.7)	480 (10.7)	184 (6.4)	34 (9.6)	17 (4.9)	21 (8.5)	8 (3.2)	40 (8.2)	5 (3.0)

Source: ISS Table 24

The common adverse event experience overall is similar to that of the COPD population.

The data from Trial A1054 was examined in more detail for the following SOCs: Gastrointestinal disorders, Infections and Infestations, Psychiatric Disorders and "Other SOCs."

Gastrointestinal disorders

At the SOC level, "Gastrointestinal disorders" was the most frequently observed adverse event and was more frequent in the varenicline group.

The "Gastrointestinal disorders" SOC can be broken down to the HLGT, HLT, and PT level. The corresponding High level group terms reported in 5% or more of subjects and Preferred terms reported in 2% or more of subjects in either treatment arm are summarized below.

Table 48: Gastrointestinal Disorders TEAEs (Trial A1054)

MedDRA level	Term	n varenicline N= 223	% varenicline (n/N)	n placebo N=237	% placebo (n/N)
High Level Group Terms					
	Gastrointestinal signs and symptoms	77	35%	35	15%
	Gastrointestinal motility and defaecation conditions	19	9%	15	6%
	Salivary gland conditions	12	5%	4	2%
Preferred Terms					
	Nausea	60	27%	18	8%
	Flatulence	15	7%	12	5%
	Vomiting	15	7%	6	3%
	Dry Mouth	11	5%	4	2%
	Constipation	10	4%	5	2%
	Dyspepsia	9	4%	1	0%
	Gastrooesophageal reflux disease	6	3%	4	2%
	Abdominal pain	6	3%	2	1%
	Abdominal pain upper	5	2%	0	0%
	Diarrhoea	5	2%	8	3%

Source: Clinical Reviewer derived from Applicant provided dataset ADVERS subjects removed who did not have COPD based on Appendix B12.2 p. 1444 of Applicant's Clinical Study Report

Nausea was the most frequently observed adverse event and was observed in 27% of subjects (compared to 40% in the original NDA). All high level group terms and preferred terms in the "Gastrointestinal Disorders" SOC occurred more frequently in the varenicline group. The most frequent adverse event in the HLGT "Salivary gland conditions" was dry mouth, which occurred more frequently in the varenicline group and was also observed in the original NDA trials. These findings are consistent with results

from the Applicant's analysis of the safety population (which includes subjects that did not meet criteria for COPD).

Infections and Infestations

Treatment-emergent infections were more frequently observed in the varenicline group than in the placebo group.

Infections at the SOC level were reported in 34% of the varenicline group and in 29% of the placebo group. The table below summarizes infections at the HLT level on a per subject basis (a subject with the same HLT recorded multiple times is counted only once).[24] At the HLT level, most of the infections were slightly more common in the varenicline group and no clear signals emerged. The average exposure to treatment was 47.06 years in the varenicline group and 48.03 years in the placebo group. The rates of infections per person-time exposure were also higher in the varenicline group (see the table below).

There is no clear evidence that the small differences in frequency of infections between treatment groups represent a drug effect. Even if the differences were due to a drug effect, these small differences in a wide range of infections do not appear to represent a clinically important safety finding.

[24] Note that some subjects had more than one adverse event coded to different HLTs, but were counted only once in the Infections and Infestations SOC count, because both HLTs fell under this SOC.

Table 49: Infections by HLT (Trial A1054)

Infections	# subjects varenicline	% subjects varenicline N=223	Rate per 100 patient exposure years	# subjects placebo	% subjects placebo N=237	Rate per 100 patient exposure years
Infections and infestations	75	34%	159	69	29%	144
Upper respiratory tract infections	43	19.3%	91	41	17.3%	85
Lower respiratory tract and lung infections	11	4.9%	23	10	4.2%	21
Abdominal and gastrointestinal infections	5	2.2%	11	4	1.7%	8
Dental and oral soft tissue infections	5	2.2%	11	3	1.3%	6
Urinary tract infections	5	2.2%	11	1	0.4%	2
Influenza viral infections	4	1.8%	8	3	1.3%	8
Viral infections NEC	4	1.8%	8	3	1.3%	6
Ear infections	3	1.3%	6	2	0.8%	4
Herpes viral infections	2	0.9%	4	2	0.8%	4
Skin structures and soft tissue infections	2	0.9%	4	4	1.7%	8
Bacterial infections NEC	1	0.4%	2	0	0.0%	0
Candida infections	1	0.4%	2	0	0.0%	0
Eye and eyelid infections	1	0.4%	2	0	0.0%	0
Infections NEC	1	0.4%	2	3	1.3%	6

Source: Applicant-provided table 2 “Most Frequent All-Causality Treatment-Emergent HLGT or HLT and Preferred Term”

Psychiatric Disorders

The higher occurrence of TEAEs in the “Psychiatric Disorders” SOC map to “Sleep disorders and Disturbances” at the HLGT level (21% of subjects in the varenicline group compared to 8% of subjects in the placebo group). The table below summarizes the Preferred terms included under the “Psychiatric Disorders” SOC. For further discussion of psychiatric adverse events, see Section 7.3.5 “Submission Specific Primary Safety Concerns.”

Table 50: Preferred Terms reported in 2% or more of subjects (Trial A1054)

Preferred Term	n varenicline N= 223	% varenicline (n/N)	n placebo N=237	% placebo (n/N)
Abnormal dreams	25	11%	6	3%
Insomnia	23	10%	13	5%
Anxiety	6	3%	7	3%
Depression	6	3%	5	2%
Nightmare	5	2%	1	0%

Source: Clinical Reviewer derived from Applicant provided dataset ADVERS subjects removed who did not have COPD based on Appendix B12.2 p. 1444 of Applicant’s Clinical Study Report

Other SOCs

The table below correlates the "General Disorders," "Investigations," and "Metabolism and nutrition" SOCs to the related HLGT and to the most frequently reported adverse events at the Preferred term level. The counts of adverse events and percentages are calculated for the Preferred term.

Table 51: TEAEs in Other SOCs (Trial A1054)

SOC	HLGT	PT	n varenicline N= 223	% varenicline (n/N)	n placebo N=237	% placebo (n/N)
General disorders and administration site conditions	General system disorders NEC	Fatigue	10	4%	2	1%
Investigations	Physical Examination Topics	Weight increased	9	4%	1	0%
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Decreased appetite	5	2%	0	0%

Source: Clinical Reviewer derived from Applicant provided dataset ADVERS subjects removed who did not have COPD based on Appendix B12.2 p. 1444 of Applicant's Clinical Study Report

Fatigue, increased weight, and decreased appetite were also observed in two percent or more of varenicline-treated subjects in the trials reviewed in the original NDA.

No significant differences emerged in comparing the all-subjects-treated safety population used by the Applicant to the COPD-only safety population used in the above analyses.

There were no significant differences in the common adverse events reported in this trial for the COPD population from what is already contained in the product labeling.

7.4.2 Laboratory Findings

Trial A1054

There were no notable differences in incidences of laboratory abnormalities reported as adverse events. There were 199 subjects in the varenicline group and 199 subjects in the placebo group with evaluable laboratory data (the 39 subjects who did not meet inclusion criteria for COPD were excluded). Of the subjects with normal baseline values, 44% in the varenicline group and 37% in the placebo group had laboratory abnormalities. The varenicline group had more elevations in triglycerides (12% varenicline, 7% placebo) and qualitative blood/hemoglobin in urine. The placebo group had more elevated RBCs in urine.

There were no large changes in median laboratory values and no notable differences between treatment groups.

7.4.3 Vital Signs

There were no notable differences in incidences of vital sign abnormalities reported as adverse events. There were no notable differences in vital sign parameters between treatment groups.

7.4.4 Electrocardiograms (ECGs)

There were no notable differences in ECG parameters between treatment groups.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were included in this application.

7.5 Other Safety Explorations

7.5.3 Drug-Demographic Interactions

Pooled Data

The Applicant analyzed adverse events and discontinuation from treatment due to an adverse event by age group, gender, and race.
Age

The Applicant summarized adverse events and discontinuations from treatment due to adverse events by age group.

Table 52: Adverse Events and Treatment Discontinuations by Age (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo
AGE < 45 YEARS										
Total Number of Subjects	1027 (100)	678 (100)	2219 (100)	1403 (100)	32 (100)	36 (100)	24 (100)	21 (100)	248 (100)	93 (100)
Any adverse event	866 (84.3)	518 (76.4)	1781 (80.3)	995 (70.9)	20 (62.5)	22 (61.1)	16 (66.7)	14 (66.7)	164 (66.1)	49 (52.7)
Discontinuation from treatment due to adverse event	114 (11.1)	57 (8.4)	165 (7.4)	84 (6.0)	2 (6.3)	0 (0)	2 (8.3)	3 (14.3)	12 (4.8)	7 (7.5)
AGE 45 - 64 YEARS										
Total Number of Subjects	909 (100)	499 (100)	2031 (100)	1309 (100)	250 (100)	255 (100)	170 (100)	174 (100)	209 (100)	64 (100)
Any adverse event	781 (85.9)	388 (77.8)	1633 (80.4)	900 (68.8)	207 (82.8)	163 (63.9)	126 (74.1)	115 (66.1)	162 (77.5)	37 (57.8)
Discontinuation from treatment due to adverse event	140 (15.4)	50 (10.0)	208 (10.2)	83 (6.3)	23 (9.2)	8 (3.1)	8 (4.7)	8 (4.6)	8 (3.8)	6 (9.4)
AGE ≥ 65 YEARS										
Total Number Subjects	47	32	233	180	71	59	54	56	29	8
Any adverse event	41 (87.2)	24 (75.0)	189 (81.1)	117 (65.0)	61 (85.9)	42 (71.2)	41 (75.9)	35 (62.5)	22 (75.9)	3 (37.5)
Discontinuation from treatment due to adverse event	15 (31.9)	3 (9.4)	33 (14.2)	15 (8.3)	9 (12.7)	8 (13.6)	3 (5.6)	3 (5.4)	4 (13.8)	0 (0)

Source: ISS Table 36

There were no notable differences between age groups in frequency of subjects experiencing any adverse event in the 2010 pool, but subjects in the COPD study did have an increase in adverse event incidence in the varenicline group with increasing age. Additionally, the frequency of subjects discontinuing from treatment due to an adverse event went up with increasing age in the 2010 pool in the varenicline group more than in the placebo group, but this trend was not present in the COPD study. In the largest pools (both the 2005 pool and the 2010 pool) the similar incidence of adverse events between age groups paired with the increase in discontinuations could indicate that while all age groups experience adverse events in approximately the same frequency, the adverse events were more severe or less tolerable with increasing age, leading to increased treatment discontinuation in the older subjects.

Gender

The Applicant summarized adverse events and discontinuations from treatment due to adverse events by gender.

Table 53: Adverse Events and Treatment Discontinuations by Gender (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo
MALE										
Total Number of Subjects	999	656	2779	1963	266	287	155	156	293	99
Any adverse event	814 (81.5)	494 (75.3)	2131 (76.7)	1313 (66.9)	207 (77.8)	179 (62.4)	112 (72.3)	97 (62.2)	188 (64.2)	47 (47.5)
Discontinuation from treatment due to adverse event	109 (10.9)	54 (8.2)	193 (6.9)	106 (5.4)	24 (9.0)	12 (4.2)	5 (3.2)	8 (5.1)	12 (4.1)	6 (6.1)
FEMALE										
Total Number of Subjects	984 (100)	553 (100)	1704 (100)	929 (100)	87 (100)	63 (100)	93 (100)	95 (100)	193 (100)	66 (100)
Any adverse event	874 (88.8)	436 (78.8)	1472 (86.4)	699 (75.2)	81 (93.1)	48 (76.2)	71 (76.3)	67 (70.5)	160 (82.9)	42 (63.6)
Discontinuation from treatment due to adverse event	160 (16.3)	56 (10.1)	213 (12.5)	76 (8.2)	10 (11.5)	4 (6.3)	8 (8.6)	6 (6.3)	12 (6.2)	7 (10.6)

Source: ISS Table 37

Females were consistently more likely to have had any adverse event and to discontinue treatment due to an adverse event in both the varenicline and placebo groups. The higher incidence in adverse events in both the varenicline and placebo groups in females indicates that the gender difference is not likely to be related to varenicline. In the 2005 and 2010 pools, there is a larger difference between the varenicline and placebo groups in discontinuations due to adverse events in females than in males. This could indicate that the adverse events experienced by females were more severe or less tolerable than those experienced by males, but there are also other potential biases or behavioral factors that could account for this difference.

Race

Table 54: Adverse Events and Treatment Discontinuations by Race (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
	Var n (%)	Pbo n (%)	Var n (%)	Pbo n (%)	Var n (%)	Pbo n (%)	Var n (%)	Pbo n (%)	Var n (%)	Pbo n (%)
RACIAL GROUP: WHITE										
Total Number of Subjects	1685 (100)	998 (100)	2876 (100)	1921 (100)	284 (100)	282 (100)	203 (100)	211 (100)	331 (100)	112 (100)
Any adverse event	1461 (86.7)	776 (77.8)	2424 (84.3)	1375 (71.6)	235 (82.7)	193 (68.4)	152 (74.9)	135 (64.0)	269 (81.3)	70 (62.5)
Discontinuation from treatment due to adverse event	247 (14.7)	90 (9.0)	340 (11.8)	140 (7.3)	29 (10.2)	11 (3.9)	10 (4.9)	10 (4.7)	20 (6.0)	10 (8.9)
RACIAL GROUP: BLACK										
Total Number of Subjects	176 (100)	129 (100)	261 (100)	178 (100)	3 (100)	2 (100)	15 (100)	10 (100)	31 (100)	8 (100)
Any adverse event	129 (73.3)	97 (75.2)	179 (68.6)	129 (72.5)	3 (100)	1 (50.0)	9 (60.0)	9 (90.0)	14 (45.2)	3 (37.5)
Discontinuation from treatment due to adverse event	16 (9.1)	13 (10.1)	17 (6.5)	15 (8.4)	0 (0)	0 (0)	0 (0)	1 (10.0)	1 (3.2)	1 (12.5)
RACIAL GROUP: ASIAN										
Total Number of Subjects	29 (100)	20 (100)	945 (100)	541 (100)	30 (100)	30 (100)	0 (0)	0 (0)	103 (100)	36 (100)
Any adverse event	23 (79.3)	14 (70.0)	725 (76.7)	363 (67.1)	19 (63.3)	16 (53.3)	0 (0)	0 (0)	57 (55.3)	14 (38.9)
Discontinuation from treatment due to adverse event	2 (6.9)	1 (5.0)	30 (3.2)	13 (2.4)	1 (3.3)	3 (10.0)	0 (0)	0 (0)	2 (1.9)	1 (2.8)
RACIAL GROUP: OTHER										
Total Number of Subjects	93 (100)	62 (100)	401 (100)	252 (100)	36 (100)	36 (100)	30 (100)	30 (100)	21 (100)	9 (100)
Any adverse event	75 (80.6)	43 (69.4)	275 (68.6)	145 (57.5)	31 (86.1)	17 (47.2)	22 (73.3)	20 (66.7)	8 (38.1)	2 (22.2)
Discontinuation from treatment due to adverse event	4 (4.3)	6 (9.7)	19 (4.7)	14 (5.6)	4 (11.1)	2 (5.6)	3 (10.0)	3 (10.0)	1 (4.8)	1 (11.1)

Source: ISS Table 38

In general, the highest incidence of adverse events and discontinuations from treatment were in the varenicline group in white subjects.

7.5.4 Drug-Disease Interactions

The COPD population in this clinical trial has essentially the same safety experience with varenicline as the non-COPD population.

7.5.5 Drug-Drug Interactions

One subject reported several adverse events while taking codeine containing Robitussin concurrently with Chantix. There is no expected interaction between the two based on what is known about their pharmacokinetics and pharmacodynamics.

7.6 Additional Safety Explorations

7.6.2 Human Reproduction and Pregnancy Data

The Applicant included a section in the ISS summarizing available data to inform use of varenicline in pregnancy and lactation. The Applicant is currently conducting a prospective population-based study to measure outcomes when varenicline is used in pregnancy. The section provided additional information on cases of pregnancy from the Applicant's safety database, which is currently being reviewed in conjunction with the Maternal Health Team, and any action taken based on this review will be implemented separately from the action taken on this supplemental application.

7.7 Additional Submissions / Safety Issues

Protocol Deviations for psychiatric diagnoses and psychoactive concomitant medications in Trials A1054, A1049, and A1095

In general, the sub-population of subjects who were noted to have a protocol deviation for a psychiatric diagnosis or for taking a psychoactive concomitant medication reported more common adverse events. There were 71 patients in the varenicline group and 53 patients in the placebo group in trials A1049, A1054 and A1095. Non-psychiatric adverse events, like nausea and vomiting, and sleep disturbances were reported more frequently in the varenicline group when compared to the general study populations but were not reported more frequently in the placebo group. Depression was reported more frequently in both the varenicline and placebo groups when compared to the total safety populations in these trials. Anxiety was reported more frequently in the varenicline group in this subpopulation than in the total safety populations for the three trials. Below is a table of adverse events observed in 5% or more of either treatment group in this sub-population. This exploratory analysis of the safety data should be interpreted with caution because 1) this study was not designed to evaluate the safety of varenicline in subjects with psychiatric diagnoses and 2) the capture of subjects with psychiatric diagnoses based on protocol deviation data may be incomplete or inaccurate. This is especially true in the case of deviations for psychoactive medications, which are sometimes prescribed for non-psychiatric indications and may or may not mean that the patient taking them has a psychiatric diagnosis. However, it appears that subjects who had a protocol deviation suggestive of a psychiatric diagnosis were more likely to experience or more likely to report gastrointestinal and sleep-related adverse events than all subjects in the safety population. Additionally, in

this sample, subjects were slightly more likely to report anxiety in the varenicline group and were more likely to report depression in both groups than subjects in the total safety population.

TEAEs that occurred in subjects with a psychiatric diagnosis or concomitant treatment with a psychoactive medication protocol deviation are shown in the table below:

Table 55: AEs in Subjects with a Psychiatric diagnosis or concomitant psychoactive medication (Trials A1049, A1054, and A1095)

TEAE	n varenicline	% varenicline (N=71)	n placebo	% placebo (N=53)
Nausea	30	42%	6	11%
Insomnia	14	20%	2	4%
Dyspepsia	9	13%	1	2%
Headache	9	13%	7	13%
Vomiting	8	11%	0	0%
Abnormal dreams	6	8%	1	2%
Diarrhoea	6	8%	4	8%
Dizziness	6	8%	1	2%
Flatulence	6	8%	3	6%
Anxiety	5	7%	2	4%
Constipation	5	7%	2	4%
Depression	5	7%	5	9%
Dry mouth	5	7%	1	2%
Nasopharyngitis	5	7%	2	4%
Irritability	4	6%	1	2%
Back pain	3	4%	3	6%
Fatigue	3	4%	3	6%
Bronchitis	2	3%	3	6%
Influenza	2	3%	5	9%
Upper respiratory tract infection	2	3%	8	15%

Source: Clinical Reviewer based on ADVERS datasets from Trials A1049, A1054 and A1095

8 Postmarket Experience

The applicant provided an analysis of post-marketing safety data in the Summary of Clinical Safety and the Safety Update. The most frequently reported events were in the Psychiatric Disorders SOC. The proportion of serious events in this SOC has increased since the submission of the supplemental applications currently under review and serious cases exceeded nonserious cases in the Safety Update period. Adverse events reported in 2% or more of the cases included a wide range of neuropsychiatric symptoms. For further discussion of neuropsychiatric adverse events, see Section 7.3.5.

The Applicant summarized the post-marketing cases where COPD was specified in the patients' medical history. These patients were older, had a higher proportion of serious

events, had a higher proportion of solicited cases, and had higher proportions of cases that reported concomitant and co-suspect medications. In contrast to the overall dataset, the following events were reported in 2% or greater of the COPD history cases in the period up to supplement submission and the Safety Update period: Dyspnea, COPD exacerbation and pneumonia. A higher frequency of these events is expected in a COPD population. In the Safety Update period, cerebrovascular accident and rash also occurred in 2.17% of reports and did not occur in 2% or greater of the total cases during that same period. Interpretation of these findings will be of limited utility given the small number of cases (138 with COPD history) identified in a large, uncontrolled database. (For example, decreased blood potassium also occurred in 2.17% of patients with COPD history during this period and could be due to chance or related to other comorbidities, but is unlikely to be related to varenicline). For further discussion of cerebrovascular events and serious skin reactions, see Section 7.3.5.

9 Appendices

Table 56: COPD Severity Classification

Appendix 1. Classification of Severity of COPD*

	Stage	Characteristics
0:	At Risk	- normal spirometry - chronic symptoms (cough, sputum production)
I:	Mild COPD	- $FEV_1/FVC < 70\%$ - $FEV_1 \geq 80\%$ predicted - with or without chronic symptoms (cough, sputum production)
II:	Moderate COPD	- $FEV_1/FVC < 70\%$ - $50\% \leq FEV_1 < 80\%$ predicted -with or without chronic symptoms (cough, sputum production)
III:	Severe COPD	- $FEV_1/FVC < 70\%$ - $30\% \leq FEV_1 < 50\%$ predicted - with or without chronic symptoms (cough, sputum production)
IV:	Very Severe COPD	- $FEV_1/FVC < 70\%$ - $FEV_1 \leq 30\%$ predicted, or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

Classification based on postbronchodilator FEV_1

FEV1 – forced expiratory volume in one second **FVC** – forced vital capacity

Respiratory Failure – arterial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level

* Reproduced from the Global Initiative for Chronic Obstructive Pulmonary Disease, based on an April 1998 meeting of the National Heart, Lung, and Blood Institute and the World Health Organization and updated in 2003

Source: Applicant's Final Study Protocol, p. 43

Table 57: Most Frequently Reported Past or Present Medical Conditions (5% or greater in Any Treatment Group) (Pooled Data)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
SOC PT	number (%) of subjects									
Present Medical Conditions										
Cardiac disorders	70 (3.5)	32 (2.6)	214 (4.8)	178 (6.2)	108 (30.6)	101 (28.9)	15 (6.0)	16 (6.4)	9 (1.9)	10 (6.1)
Angina pectoris	4 (0.2)	5 (0.4)	79 (1.8)	79 (2.7)	74 (21.0)	71 (20.3)	1 (0.4)	2 (0.8)	0 (0)	0 (0)
Gastrointestinal disorders	391 (19.7)	261 (21.6)	689 (15.4)	472 (16.3)	60 (17.0)	58 (16.6)	62 (25.0)	59 (23.5)	57 (11.7)	18 (10.9)
Dyspepsia	174 (8.8)	120 (9.9)	219 (4.9)	155 (5.4)	3 (0.8)	2 (0.6)	17 (6.9)	23 (9.2)	17 (3.5)	3 (1.8)
GERD	83 (4.2)	52 (4.3)	173 (3.9)	115 (4.0)	30 (8.5)	27 (7.7)	24 (9.7)	23 (9.2)	15 (3.1)	5 (3.0)
Immune system disorders	503 (25.4)	301 (24.9)	759 (16.9)	449 (15.5)	37 (10.5)	23 (6.6)	26 (10.5)	31 (12.4)	45 (9.3)	12 (7.3)
Drug hypersensitivity	103 (5.2)	78 (6.5)	148 (3.3)	109 (3.8)	18 (5.1)	9 (2.6)	17 (6.9)	16 (6.4)	0 (0)	0 (0)
Seasonal allergies	295 (14.9)	197 (16.3)	455 (10.1)	272 (9.4)	16 (4.5)	4 (1.1)	10 (4.0)	13 (5.2)	33 (6.8)	8 (4.8)
Investigations	111 (5.6)	73 (6.0)	183 (4.1)	115 (4.0)	13 (3.7)	10 (2.9)	33 (13.3)	20 (8.0)	13 (2.7)	6 (3.6)
Blood cholesterol increased	9 (0.5)	12 (1.0)	36 (0.8)	21 (0.7)	3 (0.8)	1 (0.3)	16 (6.5)	6 (2.4)	6 (1.2)	2 (1.2)
Metabolic/ nutritional disorders	253 (12.8)	165 (13.6)	757 (16.9)	581 (20.1)	194 (55.0)	212 (60.6)	62 (25.0)	57 (22.7)	75 (15.4)	35 (21.2)
Dyslipedaemia	1 (0.1)	0 (0)	73 (1.6)	53 (1.8)	15 (4.2)	19 (5.4)	4 (1.6)	5 (2.0)	10 (2.1)	9 (5.5)
Hypercholesterolaemia	65 (3.3)	50 (4.1)	234 (5.2)	218 (7.5)	88 (24.9)	103 (29.4)	32 (12.9)	33 (13.1	28 (5.8)	12 (7.3)
Hyperlipidaemia	147 (7.4)	79 (6.5)	289 (6.4)	183 (6.3)	56 (15.9)	66 (18.9)	9 (3.6)	6 (2.4)	20 (4.1)	5 (3.0)
Type 2 diabetes mellitus	16 (0.8)	10 (0.8)	82 (1.8)	85 (2.9)	38 (10.8)	52 (14.9)	5 (2.0)	5 (2.0)	7 (1.4)	3 (1.8)
Musculoskeletal/ connective tissue disorders	616 (31.1)	341 (28.2)	877 (19.6)	512 (17.7)	55 (15.6)	46 (13.1)	62 (25.0)	54 (21.5)	73 (15.0)	24 (14.5)
Back pain	166 (8.4)	96 (7.9)	239 (5.3)	135 (4.7)	12 (3.4)	10 (2.9)	14 (5.6)	11 (4.4)	25 (5.1)	5 (3.0)
Osteoarthritis	102 (5.1)	57 (4.7)	155 (3.5)	85 (2.9)	12 (3.4)	11 (3.1)	14 (5.6)	10 (4.0)	12 (2.5)	3 (1.8)
Nervous system disorders	628 (31.7)	409 (33.8)	845 (18.8)	531 (18.4)	28 (7.9)	19 (5.4)	52 (21.0)	45 (17.9)	56 (11.5)	21 (12.7)
Headache	413 (20.8)	280 (23.2)	499 (11.1)	326 (11.3)	9 (2.5)	7 (2.0)	18 (7.3)	16 (6.4)	23 (4.7)	7 (4.2)
Psychiatric disorders	137 (6.9)	81 (6.7)	243 (5.4)	156 (5.4)	14 (4.0)	15 (4.3)	34 (13.7)	33 (13.1)	20 (4.1)	5 (3.0)
Insomnia	84 (4.2)	47 (3.9)	146 (3.3)	94 (3.3)	9 (2.5)	8 (2.3)	12 (4.8)	16 (6.4)	14 (2.9)	3 (1.8)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	**Var N= 1983**	**Pbo N= 1209**	**Var N= 4483**	**Pbo N= 2892**	**Var N= 353**	**Pbo N= 350**	**Var N= 248**	**Pbo N= 251**	**Var N= 486**	**Pbo N= 165**
SOC PT	number (%) of subjects									
Respiratory/ thoracic/mediastinal disorders	293 (14.8)	207 (17.1)	764 (17.0)	618 (21.4)	58 (16.4)	54 (15.4)	248 (100)	251 (100)	55 (11.3)	23 (13.9)
COPD	27 (1.4)	22 (1.8)	327 (7.3)	310 (10.7)	36 (10.2)	26 (7.4)	246 (99.2)	251 (100)	9 (1.9)	2 (1.2)
Cough	42 (2.1)	26 (2.2)	74 (1.7)	45 (1.6)	5 (1.4)	5 (1.4)	15 (6.0)	6 (2.4)	7 (1.4)	2 (1.2)
Vascular disorders	171 (8.6)	119 (9.8)	709 (15.8)	521 (18.0)	217 (61.5)	222 (63.4)	77 (31.0)	60 (23.9)	82 (16.9)	25 (15.2)
Hypertension	150 (7.6)	97 (8.0)	613 (13.7)	440 (15.2)	181 (51.3)	185 (52.9)	67 (27.0)	50 (19.9)	70 (14.4)	19 (11.5)
Peripheral vascular disorder	12 (0.6)	7 (0.6)	97 (2.2)	89 (3.1)	73 (20.7)	79 (22.6)	1 (0.4)	3 (1.2)	2 (0.4)	0 (0)
Past medical conditions										
Cardiac disorders	59 (3.0)	30 (2.5)	317 (7.1)	282 (9.8)	220 (62.3)	228 (65.1)	17 (6.9)	12 (4.8)	6 (1.2)	3 (1.8)
Angina pectoris	10 (0.5)	5 (0.4)	128 (2.9)	104 (3.6)	114 (32.3)	97 (27.7)	2 (0.8)	1 (0.4)	0 (0)	0 (0
Myocardial infarction	23 (1.2)	8 (0.7)	190 (4.2)	186 (6.4)	155 (43.9)	171 (48.9)	4 (1.6)	5 (2.0)	4 (0.8)	1 (0.6)
Gastrointestinal disorders	215 (10.8)	132 (10.9)	407 (9.1)	297 (10.3)	50 (14.2)	56 (16.0)	24 (9.7)	18 (7.2)	21 (4.3)	13 (7.9)
Peptic ulcer	36 (1.8)	15 (1.2)	62 (1.4)	49 (1.7)	20 (5.7)	26 (7.4)	1 (0.4)	0 (0)	2 (0.4)	1 (0.6)
Infections/ infestations	441 (22.2)	246 (20.3)	647 (14.4)	379 (13.1)	16 (4.5)	12 (3.4)	33 (13.3)	42 (16.7)	50 (10.3)	16 (9.7)
Pneumonia	49 (2.5)	39 (3.2)	82 (1.8)	61 (2.1)	3 (0.8)	1 (0.3)	14 (5.6)	13 (5.2)	9 (1.9)	3 (1.8)
Nervous system disorders	111 (5.6)	60 (5.0)	208 (4.6)	151 (5.2)	38 (10.8)	47 (13.4)	18 (7.3)	14 (5.6)	22 (4.5)	8 (4.8)
Cerebrovascular accident	4 (0.2)	0 (0)	26 (0.6)	28 (1.0)	16 (4.5)	24 (6.9)	3 (1.2)	3 (1.2)	2 (0.4)	0 (0)
Transient ischemic attack	3 (0.2)	5 (0.4)	26 (0.6)	28 (1.0)	20 (5.7)	21 (6.0)	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.6)
Psychiatric disorders	306 (15.4)	170 (14.1)	431 (9.6)	269 (9.3)	27 (7.6)	23 (6.6)	32 (12.9)	44 (17.5)	49 (10.1)	15 (9.1)
Depression	112 (5.6)	70 (5.8)	179 (4.0)	121 (4.2)	11 (3.1)	12 (3.4)	15 (6.0)	21 (8.4)	33 (6.8)	11 (6.7)
Surgical and medical procedures	524 (26.4)	369 (30.5)	934 (20.8)	779 (26.9)	216 (61.2)	233 (66.6)	80 (32.3)	82 (32.7)	7 (1.4)	2 (1.2)
Coronary revascularisation	0 (0)	0 (0)	163 (3.6)	176 (6.1)	160 (45.3)	176 (50.3)	0 (0)	0 (0)	0 (0)	0 (0)
Female sterilisation	103 (5.2)	71 (5.9)	111 (2.5)	85 (2.9)	0 (0)	3 (0.9)	1 (0.4)	7 (2.8)	1 (0.2)	0 (0)
Hysterectomy	72 (3.6)	47 (3.9)	110 (2.5)	69 (2.4)	6 (1.7)	6 (1.7)	18 (7.3)	12 (4.8)	1 (0.2)	0 (0)

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects	Var N= 1983	Pbo N= 1209	Var N= 4483	Pbo N= 2892	Var N= 353	Pbo N= 350	Var N= 248	Pbo N= 251	Var N= 486	Pbo N= 165
SOC PT	number (%) of subjects									
Peripheral revascularisation	0 (0)	0 (0)	35 (0.8)	36 (1.2)	33 (9.3)	36 (10.3)	0 (0)	0 (0)	0 (0)	0 (0)

Source: ISS Table 7

Table 58: All causality SAE Cases in the Vascular Disorders SOC (Pooled Data)

	Varenicline (N=4483) n(%)		Placebo (N=2892) n(%)	
System Organ Class and MedDRA (v13.1) preferred term				
VASCULAR DISORDERS	13	(0.3)	5	(0.2)
Hypotension	2		0	
Peripheral arterial occlusive disease	2		0	
Peripheral ischaemia	2		0	
Aortic aneurysm	1		0	
Arterial occlusive disease	1		1	
Arterial stenosis	1		0	
Arteriosclerosis	1		0	
Deep vein thrombosis	1		1	
Haematoma	1		0	
Iliac artery occlusion	1		0	
Peripheral vascular disorder	1		1	
Thrombosis	1		0	
Circulatory collapse	0		1	
Femoral artery occlusion	0		1	
Intermittent claudication	0		1	

Source: ISS Table A20.A1

9.2 Labeling Recommendations

The Applicant made changes relevant to this supplement in the following sections: 6.1 Clinical Trials Experience, 14 Clinical Studies. The Applicant also added a new section, 14.4 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease. In section 14.4, I recommend that the label be changed to reflect (b) (4)

[redacted]

See Dr. Skeete's NDA 21928-s19 review for labeling recommendations regarding cardiovascular events.

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

/s/

PAMELA J HORN
05/20/2011

CELIA J WINCHELL
05/20/2011
Concur. See also my CDTL review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

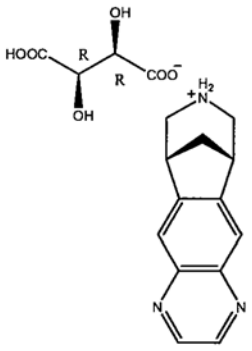
NDA 021928/S-020

CHEMISTRY REVIEW(S)

Chemistry Review # 1	1. Division HFD-820	2. NDA Number **21-928** *Approved May 10, 2006*
3. Name and Address of Applicant Pfizer Inc		**4. Supplement** **Number** **Date** S-19, 20, 21, (b) (4) 22 Sept 2010
5. Name of Drug Chantix ®	**6. Nonproprietary Name** *Varenicline tartrate (CP-526,555-18)*	
7. Efficacy Supplement Provides for: *Usage in chronic obstructive pulmonary disease (COPD), or cardiovascular disease (CVD) for smoking cessation indication*		**8. Amendment(s)** *3/4/2011*
9. Pharmacological Category *Nicotinic receptor partial agonist (Aid to smoking cessation treatment)*	**10. How Dispensed** Rx	**11. Related Documents** *IND 58,994*
12. Dosage Form *Tablet, oral (film coated)*	**13. Strength** *Eq 0.5mg and 1 mg base*	

14. Chemical Name and Structure CAS# 375815-87-5

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 $C_{13}H_{13}N_3 \bullet C_4H_6O_6$. 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 tablets 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 1mg 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.

(b) (4)

[redacted]

15. Comments

No CMC documentation included in module 3 by reviewing listed EDR file amendments 223 and 230 dated Sept 2010, with PDUFA due date 22 July 2011.

Chemistry, Manufacturing and Controls
The currently approved Chantix label dated April 2010 remains an accurate reflection of the properties of varenicline. No new CMC information is provided with this submission; therefore no documents are included for Module 3.

COA for the clinical supplies (chronic obstructive pulmonary disease (COPD), or cardiovascular disease (CVD) for smoking cessation indication) were requested on 2/23/2011, and they were provided on 3/4/2011 to justify compliance with quality for use in clinical studies (EDR file sequence no 245) to recommend an AP action from CMC point of view.

Reference is made to the approved NDA #21-928 for Chantix (varenicline) Tablets and to the Efficacy Supplements S-019, S-020, S-021, (b) (4), submitted on September 22, 2010. We also reference the following Information Request, dated February 23-24, 2011, for studies 1028, 1036, 1049, 1054, 1095:

- Provide Certificates of Analysis (COA) for Chantix tablet batches used for clinical study protocols
- Provide COA for varenicline tartrate batches used to compound Chantix tablet batches
- Provide summary of stability data for Chantix tablet batches used for the clinical studies
- Provide a written statement that Environmental Assessment is not required for the incremental increase in demand.

We hereby provide these data.

Application Number	Submission Sequence	Approximate Size of Submission	Index of Media Units
021928	0245	10MB	Gateway

FDA QUERY 1

Provide Certificates of Analysis (COA) for Chantix tablet batches used for clinical study protocols A3051028, A3051036, A3051049, A3051054, and A3051095.

RESPONSE

Below is a table containing details regarding lot numbers used in the clinical study protocols requested. Certificates of Analysis (CoAs) are provided for these lots.

Clinical Protocol	**Varenicline Tartrate 0.5 mg Tablets**	**Varenicline Tartrate 1.0 mg Tablets**	**Placebo for Varenicline Tartrate 0.5 mg Tablets**	**Placebo for Varenicline Tartrate 1.0 mg Tablets**
A3051028	920098-3000052-G2 920098-3002092-G2	None	ED-O-306-902 N03014	None
A3051036	920098-3000052-G2 920098-3002092-G2	None	ED-O-306-902 N03014	None
A3051049	963128-3000064 963128-3003016	963138-3001064 963138-3003016	959428-3000044	959438-3000044 959903-3000125
A3051054	963128-3000064 963128-3003016	963138-3002064 963138-3003016 963138-3004086	959428-3000044 959893-3000125	959438-3000044 959903-3000125 959903-3001076
A3051095	963153-3000117	963163-3000117	959893-3000125	959903-3001076 .

Evaluation: *Adequate to support the quality of clinical study materials by reference to COA. Drug product lots had met the specifications for appearance, identity, assay, related substances, dissolution, disintegration, water content, etc., and they were approved for use in clinical supplies.*

FDA QUERY 2

Provide COA for Varenicline Tartrate batches used to compound Chantix tablet batches for these clinical studies.

RESPONSE

Below is a table containing details regarding the ingoing API lot numbers used in the drug product batches for the clinical study protocols requested. Certificates of Analysis (CoAs) are provided for these lots. Note that the lot numbers provided in the table below represent the lot numbers as assigned at the drug product manufacturing site. In the event that the lot number from the API manufacturing site is found on the CoA, that number is noted below the table.

Clinical Protocol	Varenicline Tartrate 0.5 mg Tablets	Varenicline Tartrate 1.0 mg Tablets	Ingoing API Lot for Varenicline Tartrate 0.5 mg Tablets [a]	Ingoing API Lot for Varenicline Tartrate 1.0 mg Tablets [a]
A3051028	920098-3000052-G2 920098-3002092-G2	None	801190-3003052 801190-3004062	None
A3051036	920098-3000052-G2 920098-3002092-G2	None	801190-3003052 801190-3004062	None
A3051049	963128-3000064 963128-3003016	963138-3001064 963138-3003016	801195-3000054 801195-3004115	801195-3001054 801195-3004115
A3051054	963128-3000064 963128-3003016	963138-3002064 963138-3003016 963138-3004086	801195-3000054 801195-3004115	801195-3002054 801195-3004115 801195-3004115
A3051095	963153-3000117	963163-3000117	806850-3000066	806850-3000066

[a] These lot numbers reflect the numbers assigned at the drug product manufacturing site. The link to the drug substance manufacturing site is outlined below.

API lot number assigned by drug product manufacturing site	API lot number assigned by drug substance manufacturing site
801190 3003052	54526-9-7B
801190 3004062	54526-23-9B
801195 3000054	04944002
801195 3001054	04944003
801195 3002054	04944004

Evaluation: *Adequate to support the quality of API used to compound clinical study materials by reference to COA. API lots had met the specifications for identity, assay, related substances, residual organic solvents, particle size, etc., and they were approved for use in clinical supplies. The primary degradant,* (b) (4) *, was reported at very low levels (qualification threshold is 0.5%).*

FDA QUERY 3

Provide summary of stability data for Chantix tablet batches used for clinical studies.

RESPONSE

The clinical drug product Section P.8.1 Stability Summary and Conclusion is provided as requested.

Evaluation: *Adequate to support the quality of clinical study materials for clinical study duration by reference to stability summary.*

FDA QUERY 4

A written statement that EA is not required for the incremental increase in demand.

RESPONSE

The Environmental Assessment for Chantix, Varenicline Tartrate, 0.5 mg and 1.0 mg Tablets is provided as an attachment.

Evaluation: *Adequate based on demand forecasting for smoking cessation indication in special population groups (COPD and CVD) based on categorical exclusion claim.*

Stability summary certification was presented on 3/4/2011 for clinical study material stored in ambient conditions and packaged in (b) (4) *bottles with induction seal child resistant closure. Stability studies were initiated in Aug 2004 to support IND studies, and the stability summary certification data has demonstrated the use period of 18 months for API used for clinical test materials. 963128 for 0.5 mg formulation material and 963138 for 1mg formulation material was used for tracking.*

Tablet Strength	Batch Number	Storage Condition	Time Period
0.5 mg	963128-3000064	40°C/75% RH	6 Months
		30°C/65% RH	42 Months
1.0 mg	963138-3000064	40°C/75% RH	6 Months
		30°C/65% RH	42 Months

A review of the varenicline tartrate 0.5 mg film-coated tablets stability data through 42 months at 30°C/65% RH permits the following conclusions.

- Appearance: Tablets stored through 42 months at 30°C/65% RH showed no change in appearance when compared to product description.
- Assay: No significant loss of potency was observed in any of the samples stored through 42 months. Average potency values obtained ranged from (b) (4) of label claim as compared to an initial value of (b) (4)
- Dissolution Rate: The dissolution results through 42 months met specifications for (b) (4) dissolution testing.
- Disintegration: Rapid disintegration (less than 2 minutes) was observed for samples stored through 42 months.
- Purity Evaluation: The HPLC purity evaluation demonstrated good stability for samples stored through 42 months. All stability samples tested to date meet the drug product purity specifications.
  - Specified Degradants:
    - (b) (4) The maximum level of (b) (4)% for tablets stored through 42 months at 30°C/65% RH compared to (b) (4) observed at 24 months. An increasing trend was observed in the level of this degradant however; results at 42 months meet the current specification.
  - Unspecified Degradants: An impurity at (b) (4) was observed at (b) (4) for samples stored at 30°C/65%RH for 42 months, remaining unchanged from the (b) (4) observed at 24 months. In addition, an impurity at (b) (4) was observed at 24 and 42 months with a maximum level of (b) (4). No other unspecified degradants have been observed above the limit of quantitation (b) (4).
- Water Content: Stability samples were also evaluated for water. The amount of water observed in samples stored through 42 months has not significantly changed.
- Thickness and Hardness: Tablets stored through 42 months at 30°C/65%RH showed no sig (b) (4) ant changes in thickness and hardness properties. Ranges of (b) (4) for thickness, and (b) (4) for hardness were observed. Both thickness and hardness properties are being monitored for information only purposes.

The primary degradant for film coated tablets is (b) (4) *that was reported as high as* (b) (4) *at 42 months storage at 30C/65%RH. However,* (b) (4) *levels reported in the original NDA are significantly at lower levels, as per DARRTS entry by Drs. Ravi Harpanhalli, Stephen Miller, Ying Wang, and Chi Wan Chen dated 5/9/2006 page 152-153 of 199. The reported* (b) (4) *between API and primary degradant* (b) (4) *and the reported qualification threshold is* (b) (4). *However, 30C/65%RH storage condition is considered as accelerated storage condition for tracking primary degradant* (b) (4) *given the recommended CRT storage condition. In this context, I believe in tracking* (b) (4) *levels in marketed drug product lots for future consult with OND/tox group.*

A review of the varenicline tartrate 1.0 mg film-coated tablets stability data through 42 months at 30°C/65%RH months permits the following conclusions.

- Appearance: Tablet appearance when stored through 42 months at 30°C/65%RH are all "meets test" when compared to product description.
- Assay: No significant loss of potency was observed in any of the samples stored through 42 months. Average potency values obtained ranged from (b) (4) of label claim as compared to an initial value of 97.6%.
- Dissolution Rate: The dissolution results through 42 months met specifications for USP Stage 1 dissolution testing.
- Disintegration: Rapid disintegration (less than 2 minutes) was observed for samples stored through 42 months.
- Purity Evaluation: The HPLC purity evaluation demonstrated good stability for samples stored through 42 months. All stability samples tested to date meet the drug product purity specifications.
  - Specified Degradants:
    - (b) (4). The highest level (b) (4) for tablets stored through 42 months at 30°C/65%RH.
  - Unspecified Degradants: The highest level of an unspecified degradant was observed at (b) (4) for samples stored at 30°C/65%RH for 42 months.
- Water Content: Stability samples were also evaluated for water. The amount of water observed in samples stored through 42 months has not significantly changed.
- Thickness and Hardness: Tablets stored through 42 months at 30°C/65%RH showed no significant changes in thickness and hardness properties. Ranges of (b) (4) for thickness, and (b) (4) for hardness were observed. Both thickness and hardness properties are being monitored for information only purposes.

COA for the clinical study materials were provided under Regional Information 3.2.R section with in EDR file sequence no 0245 dated 3/4/2011.

Pharmaceutical Sciences Groton Laboratories
Global Research & Development
Dosage Form Release Document

CERTIFICATE OF ANALYSIS

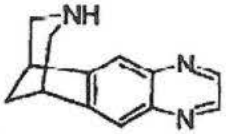
Product/Dosage Form:	Varenicline Tartrate Film Coated Tablets
Potency:	1.0 mg
Pfizer Lot Number:	04-018040
Formulation Number:	963138
Active Component Lot Number:	04944004 (L. Island) 801195-3002054 (Freiburg)
Manufacturer:	Pfizer, Freiburg
Manufacturers Lot Number:	963138-3002064
Date of Manufacture:	June 23, 2004
Use:	Clinical Studies

TEST	SPECIFICATION	TEST RESULT
Identity (by Appearance-Visual)	Modified capsular biconvex, debossed "Pfizer" on one side "VRC 1.0" on the other, light blue film-coated tablet	Meets Test
Identity (TLC)	Meets Test	Meets Test
Identity (HPLC)	Meets Test	Meets Test
Assay (HPLC)	Average of 3 composite tablet assays:	
mg/tablet	(b) (4) mg/tablet	(b) (4) mg/ tablet
% label claim	(b) (4) of Label Claim)	(b) (4)
Uniformity of Dosage Unit (By Content Uniformity)	Meets USP(b) requirements	Meets USP requirements (b) (4) mg/tablet (b) (4) (b)% RSD
Dissolution	5 min: Report Value 10 min: Report Value 15 min: Report Value 30 (b) (4) at 30 minutes	(b) (4)
Disintegration	Six tablets disintegrate within (b) minutes (water medium at 37°C)	Meets Test
Water (KF)	(b) (4) Maximum	(b) (4)
Degradation Products (HPLC)		
Unspecified:	(b) (4) maximum for each degradant	(b) (4)
Total:	NMT (b) (4)	

Pfizer Manufacturing Deutschland GmbH Betriebsstaette Freiburg Quality Assurance	CERTIFICATE OF ANALYSIS	Mat-No: 801195 AP-No: 801190D03
PRODUCT:	CP-526,555-18 EX L.ISLAND	
Lot (internal): 8011953002	Lot (external): 04944004	
Mfg.date: 05/17/04	Exp.date: 04/2005	
Test	**Specification**	**Result**
Characters:	white to off-white to slightly yellow solid	conforms
Identification(IR):	according	conforms
Identification (HPLC):	according	conforms
CP-526.555 Assayed Potency; or Assigned Potency:	Result is taken from Pfizer Drug Subtance Test Note	conforms (b) (4)
Assay CP-526.555 (HPLC):	(b) (4) on an anhydrous, solvent-free basis	(b) (4)
Tartaric Acid Content:	(b) (4) on an anhydrous, solvent-free basis	(b) (4)
Water:	max. (b) (4)	(b) (4)
Residue on Ignition:	max. (b) (4)	(b) (4)
Heavy Metals:	max. (b) (4)	conforms (b) (4)
Residual Solvents		
Methanol:	max. (b) (4)	(b) (4)
Toluene:	max. (b) (4)	conforms < (b) (4)
Methylene chloride:	max. (b) (4)	conforms < (b) (4)
Purity (HPLC):		

CE-157,254:	max [(b)(4)]	conforms < [(b)(4)]
Unspecified, identified		
Method 1 (V 27.0):	max [(b)(4)] % for each	conforms < [(b)(4)]
Method 2 (T 18.62):	max [(b)(4)] % for each	conforms < [(b)(4)]
Unspecified, unidentified		
Method 1 (V 27.0):	max. [(b)(4)] % for each	conforms < [(b)(4)]
Method 2 (T 18.62):	max. [(b)(4)] % for each	conforms < [(b)(4)]
Total impurities:	max. [(b)(4)] %	conforms < [(b)(4)]
Particle size:		
VMD:	max [(b)(4)] micron	conforms
D(v,0.9):	max micron	conforms

MOLECULAR STRUCTURE:



$.C_4O_6H_6$

Date Mfg	11/30/01
Batch Size	567 G
Source	[(b)(4)]
Milling	[(b)(4)]

NAME: 7,8,9,10-Tetrahydro-6H-6,10-methano-1,4,8-triazacyclohepta[b]naphthalene L-tartrate

MOLECULAR FORMULA: $C_{13}H_{13}N_3.C_4H_6O_6$

MOLECULAR WEIGHT: 361.36

DISPOSITION: APPROVED **USE(S):** Clinical Studies

ASSAYED POTENCY: [(b)(4)] "As Is"

Assay

(HPLC) G TP [(b)(4)] [(b)(4)] CP-526,555-18 on an anhydrous, solvent-free basis [(b)(4)]

Tartaric Acid Content G TP [(b)(4)] [(b)(4)] on an anhydrous, solvent-free basis (Theory is [(b)(4)] [(b)(4)]

Purity (HPLC)			
Unspecified:	[redacted]	[redacted] Maximum for each impurity	None detected [1]
Total Impurities:		Maximum for each impurity Maximum	[redacted] 0%
[1] None detected implies that no impurities were detected greater than or equal to LOQ.			LOQ = [redacted]
Identity (by Appearance-Visual)	[redacted]	White to off-white to slightly yellow powder essentially free from any visible foreign matter	Meet Test
Identity			
(IR)	[redacted]	Infrared absorption spectrum of the sample in [redacted] by [redacted] is essentially identical to that of the working standard of CP-526,555-18	Meet Test
(HPLC)	[redacted]	Sample chromatogram exhibits a major peak with the same retention time as that of the working standard of CP-526,555-18	Meet Test
TGA (Heating rate 10°C/min)		[redacted]	
Melting Point <USP	[redacted]	[redacted]	
X-Ray Diffraction Pattern		Reference pattern [redacted] is consistent with sample pattern [redacted] (Meets Test)	
Particle Size (Malvern)		[redacted]	
GC Solvents [redacted]):		[redacted]	
Water	[redacted]	[redacted]	[redacted]
Residue on Ignition	[redacted]		
[redacted]	[redacted]		
Residual Solvents Methanol	[redacted]		

COA for the clinical supplies used for specified clinical protocols assures compliance with the agency approved specifications for the drug product and drug substance, and that there are no genotoxic impurities. This NDA is a team review case, where API was reviewed by Stephen Miller and drug product was reviewed by Ying Wang, and it is a CMC pilot NDA for QBD where tablets are mfg by [redacted] process, and approved on May 10, 2006. This NDA PharmTox review by Drs. Mamata De and Daniel Mellon dated 5/8/2006 (247 pages) has made no reference to [redacted], the primary degradant for film coated tablets.

16. Conclusions and Recommendations

NDA 21-928/S-19 to (b) (4) is recommended for approval action from CMC point of view.

17. Name	**Signature**	**Date**
Dr. Pramoda Maturu, Ph.D, Senior Regulatory Review Chemist		
Dr. James Vidra, PhD, Branch Chief		

File: NDA 21928s19 (b) (4) Verenicine_24Feb11

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

/s/

PRAMODA K MATURU
04/04/2011

JAMES D VIDRA
04/05/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 21928 / S-020
Drug Name:	Chantix (varenicline)
Indication(s):	Smoking Cessation in Patients with Chronic Obstructive Pulmonary Disease (COPD)
Applicant:	Pfizer, Inc.
Date(s):	Submission Stamp Date September 23, 2010
	PDUFA Date: July 23, 2011
	Primary Review Completion Due Date: May 23, 2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Dionne Price, Ph.D. - Team Leader
Medical Division:	Division of Division of Anesthesia and Analgesia Products (DAAP)
Clinical Team:	Pamela Horn, M.D. – Clinical Reviewer
	Celia Winchell, M.D. – Clinical Team Leader
Project Manager:	Ayanna Augustus, Ph.D.

Keywords: clinical studies

Table of Contents

1. EXECUTIVE SUMMARY

Chantix (varenicline tablet) is currently approved as an aid to smoking cessation. This application requests adding results from a single study in subjects with chronic obstructive pulmonary disease to the Clinical Studies section of the label. Based on my evaluation of the study, I conclude that there is evidence that Chantix is an effective aid to smoking cessation in patients with chronic obstructive pulmonary disease.

Study 54 was a randomized, double-blind, multicenter study comparing varenicline to placebo in patients trying to quit smoking. The study design, dosing regimen, efficacy endpoints, and analyses were essentially the same as the Phase 3 studies used to support the initial application in 2005. The key difference was that patients had to have documented mild-to-moderate chronic obstructive pulmonary disease, confirmed within 30 days of screening.

Efficacy was assessed using a Nicotine Use Inventory and end-expiratory exhaled carbon monoxide (exhaled CO) monitoring. The primary and secondary endpoints were defined based on those measures. The primary endpoint was the 4-week continuous quit rate (CQR) from Weeks 9-12, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO $\leq$ 10 ppm. Two secondary endpoints were predefined with the intended goal of inclusion of the results in the label. These were continuous abstinence (CA) at Week 52, defined as abstinence from smoking, reported in the NUI, from the end of treatment through Week 52 and long term quit rate (LTQR) defined as subjects who were CO-confirmed responders for Weeks 9-12, and who reported no more than 6 days of smoking during the 40-week non-treatment period (Weeks 13-52). Other secondary endpoints were considered exploratory only.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized and received at least one dose of study treatment. Five patients were randomized but not treated. A total of 499 patients were included in the mITT analysis data set.

The efficacy endpoints were tested using a logistic regression model with terms for treatment group and center. In order to preserve the Type I family-wise error rate of 0.05, a step-down procedure was used for the analysis of the primary and two secondary endpoints. The order of testing was 1) the CQR for weeks 9-12; 2) CA through Week 52; and 3) the LTQR through Week 52. Each comparison was tested at α=0.05.

On all three endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). The results, which are presented in Tables 3 and 4, provide sufficient evidence to support the inclusion of this study in the Clinical Studies section of the label for aid in smoking cessation in subjects with mild-to-moderate chronic obstructive pulmonary disease.

2. INTRODUCTION

2.1 Overview

Chantix (varenicline tartrate) tablets were originally approved in 2006 indicated as an aid to smoking cessation treatment. Chantix is a nicotinic receptor partial agonist. The applicant has conducted a prospective, well-controlled, randomized clinical study in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD) who are attempting to quit smoking. In this submission, the applicant requests that the information from this clinical study be added to the Clinical Studies section of the label. There is no change to the indication statement requested.

The single study to be reviewed here is Study A3051054, referred to here as Study 54. It is a 12-week, randomized, double-blind, placebo-controlled multicenter study. The primary objective of this study was to compare 12 weeks of treatment with varenicline to placebo for smoking cessation by end of treatment and continuous abstinence for 40 weeks after treatment. The study was conducted according to the protocol. There were no major statistical issues in this study.

2.2 Data Sources

The full submission was organized in electronic common technical document DTD version 3.2. All data was supplied by the applicant to the CDER electronic data room (edr) in SAS transport format. All necessary documentation, formats, and links were provided as well. The data and final study report for the electronic submission were archived under the network path location: \\Cdsesub1\evsprod\NDA021928\0223.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant provided data sufficient to confirm all relevant results from the study report. The tables were clearly identified, and links to supporting output or information in the Appendices were provided.

3.2 Evaluation of Efficacy

Study Design and Endpoints

Study 54 is a 12-week, randomized, double-blind, placebo-controlled multicenter study. It was conducted in 27 centers in the United States and Europe. Patients were current smokers (at least 10 cigarettes per day during the previous 12 months), at least 35 years of age, who were motivated to quit smoking. They had to have clinical diagnosis of mild-to-moderate chronic obstructive pulmonary disease, confirmed by forced expiratory volume (FEV_1) and forced vital capacity (FVC) testing, within 30 days of screening. Patients were excluded if currently suffering depression or with a history of psychosis, anxiety disorder, panic disorder, or bipolar disease.

There are two treatment arms: varenicline and placebo. Patients were randomly assigned at a 1:1 ratio, within center. Patients were treated with varenicline according to the approved treatment regimen: 1 week run-in titration (0.5 mg BID for 3 days; 1.0 mg BID for 4 days), then 11 weeks at the 1 mg BID dosing. Patients were followed for 40 weeks after treatment (52 weeks total) to assess continued abstinence from smoking. Use of nicotine replacement therapy or other nicotine-containing products was prohibited during the study.

After initial screening, patients were instructed to select a target quit date prior to starting study drug. The target quit date would coincide with the Week 1 visit, after one week on study treatment. Clinic visits were scheduled weekly during the 12-week treatment period and at Weeks 13, 16, 24, 32, 40, 48, and 52 during the non-treatment period. Phone contact was scheduled at Weeks 14, 20, 28, 36, and 44. Use of cigarettes or other nicotine-containing products was measured using the Nicotine Use Inventory (NUI) at all clinic visits or phone contacts throughout the 52-week study. Exhaled carbon monoxide (CO) was measured at each clinic visit.

The primary and secondary endpoints were defined based on the NUI and exhaled CO measures. The primary endpoint was the 4-week continuous quit rate (CQR) from Weeks 9-12, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO $\leq$ 10 ppm. Two secondary endpoints were predefined with the intended goal of inclusion of the results in the label. These were continuous abstinence (CA) at Week 52, defined as abstinence from smoking, reported in the NUI, from the end of treatment through Week 52 and long term quit rate (LTQR) defined as subjects who were CO-confirmed responders for Weeks 9-12 and who reported no more than 6 days of smoking during the 40-week non-treatment period (Weeks 13-52). Other secondary endpoints were considered exploratory only.

If any CO measurement at a particular timepoint was > 10 ppm, the subject was considered a smoker at that timepoint. Missed exhaled CO measurements were imputed as negative "therefore not disqualifying the subject as a responder" according to the protocol (section 4.1.1). The wording on the nicotine use inventory asks about use "since last contact", so any missed measurements on the NUI were to be imputed back from the next recorded measurement. Any subjects who discontinued from the study were coded as smokers (non-responders) from the time

of discontinuation through the end of the study. Subjects were allowed to discontinue treatment but continue in the study, in which case the efficacy outcomes were determined by observed data.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized and received at least one dose of study treatment.

Patient Disposition, Demographic and Baseline Characteristics

There were 499 subjects randomized who received study treatment. There were 5 others who were randomized after screening but who did not receive study treatment. In the Appendices to the Study Report, the Applicant indicated the reasons for these subjects not receiving treatment (primarily no longer willing to participate, or protocol violation). As shown in Table 1, more subjects discontinued from the placebo arm than the varenicline treatment arm, with the main difference being subjects who were no longer willing to participate. Subjects were allowed to discontinue treatment but continue in the study.

Table 1: Patient Disposition

	Varenicline	**Placebo**
Randomized	250	254
Received Study Treatment (mITT)	248 (100%)	251 (100%)
Discontinued Treatment	41 (17%)	58 (23%)
Discontinued Study	72 (29%)	94 (38%)
Reason for Discontinuation:		
Adverse Event	17 (7%)	25 (10%)
Lack of Efficacy	0	6 (2%)
Lost to Follow-up	39 (16%)	41 (16%)
Subject no longer willing to participate	44 (18%)	68 (27%)
Death	2 (1%)	1 (<1%)
Other	11 (4%)	11 (4%)
Completed Treatment	207 (84%)	193 (77%)
Completed Study	176 (71%)	157 (63%)

Source: Clinical Study Report Table 6

Baseline Demographics

The two treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 2.

Table 2: Demographic Characteristics

	Varenicline (N=248)	**Placebo (N=251)**
Age (years)		
Mean (SD)	57 (9)	57 (9)
Range	34-83	34-77
Age group:		
34-65 yrs	206 (83%)	205 (82%)
>65 yrs	42 (17%)	46 (18%)
Gender		
Female	93 (38%)	95 (38%)
Male	155 (63%)	156 (62%)
Race		
Caucasian	203 (82%)	211 (84%)
Black	15 (6%)	10 (4%)
Other	30 (12%)	30 (12%)
Weight (kg)		
Mean (SD)	78 (19)	77 (18)
Range	46-147	43-162
Body Mass Index (kg/m^2)		
Mean (SD)	27 (6)	27 (5)
Range	17-45	16-49

Sources: Clinical Study Report Table 8

Statistical Methodologies

The efficacy endpoints were tested using a logistic regression model with terms for treatment group and center. In order to preserve the Type I family-wise error rate of 0.05, a step-down procedure was used for the analysis of the primary and two secondary endpoints. The order of testing was 1) the CQR for weeks 9-12; 2) CA through Week 52; and 3) the LTQR through Week 52. Each comparison was tested at α=0.05.

Results and Conclusions

On all three primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). The applicant's results are presented in Table 3. I was able to replicate the applicant's efficacy analysis results.

Table 3: Applicant's Efficacy Analysis Results (Study 54)

mITT	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
	N=248	N=251		
Continuous Quit Rate Weeks 9-12	105 42% (36%, 48%)	22 9% (5%, 12%)	8.40 (4.99, 14.14)	<.0001
Continuous Abstinence Weeks 9-52	46 19% (14%, 23%)	14 6% (3%, 8%)	4.04 (2.13, 7.67)	<.0001
Long Term Quit Rate: Week 52	53 21% (16%, 26%)	17 7% (4%, 10%)	3.92 (2.18, 7.07)	<.0001

Source: Clinical Study Report Table 12.

There were 39 subjects who were identified as being protocol deviations for not having chronic obstructive pulmonary disease at screening. Two other subjects used prohibited nicotine replacement therapy (NRT) during the treatment period. Dr. Horn, the clinical reviewer, requested that I provide the efficacy results without those 41 patients (see Table 4). Excluding those patients did not change the results or the conclusions. Study 54 provides sufficient evidence to support the inclusion of these results in the Clinical Studies section of the label for aid in smoking cessation in subjects with chronic obstructive pulmonary disease.

Table 4: Reviewer's Efficacy Analysis Results (Study 54)

Exclude 41 subjects with prohibited protocol violations (39 no COPD; 2 NRT use)	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
	N=221	N=237		
Continuous Quit Rate Weeks 9-12	91 41% (35%, 48%)	22 9% (6%, 13%)	7.49 (4411, 12.71)	<.0001
Continuous Abstinence Weeks 9-52	42 19% (14%, 24%)	14 6% (3%, 9%)	4.00 (2.09, 7.66)	<.0001
Long Term Quit Rate: Week 52	47 21% (16%, 27%)	17 7% (4%, 10%)	3.69 (2.03, 6.73)	<.0001

Source: SAS datasets

Another concern raised in reporting the results involved the imputation of missing exhaled-CO measures. As described in the protocol, missing exhaled-CO data was imputed as negative, the equivalent of having a score < 10 ppm. This would not disqualify a subject as a responder for the continuous quit rate or continuous abstinence endpoints. However, subjects who discontinued were assumed to be smokers from the time they left the study, so those subjects were coded as non-responders.

I used the original observation data set, and looked at subjects in either group who were coded as responders (positive outcome) but had any missing exhaled-CO measures over time. There were only a few instances in each treatment group with a missing exhaled-CO measure at a timepoint that would have potentially changed the coding of the responder outcome. Even if these were recoded as non-responders there was no impact on the results or conclusions.

3.3 Evaluation of Safety

Dr. Horn completed the safety review for this study. She did not request any additional safety analyses.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

I reviewed exploratory analyses for the primary endpoint by age groups, gender, race, region (US vs. Europe) and center. There were a few notable differences in the responder rates for the treatments across most of these subgroups.

Results for age, gender and race are shown in Table 5. One unusual result was that none of the non-Caucasian subjects in the placebo arm were responders. The results for region and individual centers are shown in Table 6 and 7. In France, both treatment arms had a lower responder rate than in the other countries.

These are descriptive analyses only and are not intended for inferential purposes. The varenicline treatment group consistently showed a higher continuous quit rate than the placebo group.

Table 5: Subgroup Analyses: Age, Gender, And Race – Reviewer's Results

Primary Endpoint: Continuous Quit Rate Weeks 9-12		
Exclude 3 subjects with no CVD	**Varenicline N=248**	**Placebo N=251**
Age group		
≤ 65 years	78/206 (38%)	18/205 (9%)
> 65 years	27/42 (64%)	4/46 (9%)
Gender		
Female	34/93 (37%)	8/95 (8%)
Male	71/155 (46%)	14/156 (9%)
Race		
Caucasian	92/203 (45%)	22/211 (10%)
Non-Caucasian	13/45 (29%)	0/40 (0%)

Source: SAS datasets

Table 6: Subgroup Analyses by Region

Primary Endpoint: Continuous Quit Rate Weeks 9-12	**Varenicline**	**Placebo**
US	73/161 (45%)	10/162 (6%)
Europe	32/87 (37%)	12/89 (13%)
France	12/45 (27%)	3/45 (7%)
Italy	7/15 (47%)	3/16 (19%)
Spain	13/27 (48%)	6/28 (21%)
Total	105/248 (42%)	22/251 (9%)

Source: SAS datasets

Table 7: Subgroup Analyses by Center

Primary Endpoint: Continuous Quit Rate Weeks 9-12		Varenicline N=248	Placebo N=251
Center #	**Location**		
1001	Spain	4/8 (50%)	1/9 (11%)
1002	Spain	4/9 (44%)	2/10 (20%)
1003	Spain	5/10 (50%)	3/9 (33%)
1004	France	3/13 (23%)	3/12 (25%)
1005	France	3/19 (16%)	0/19 (0%)
1006	France	3/7 (43%)	0/8 (0%)
1007	Italy	3/6 (50%)	1/8 (13%)
1008	Italy	0/1 (0%)	0/1 (0%)
1009	Italy	4/8 (50%)	2/7 (29%)
1010	US	8/14 (57%)	0/14 (0%)
1011	US	2/7 (29%)	0/7 (0%)
1012	US	3/6 (50%)	0/4 (0%)
1013	US	5/13 (38%)	0/12 (0%)
1014	US	2/7 (29%)	0/7 (0%)
1015	US	12/18 (67%)	4/19 (21%)
1016	US	0/4 (0%)	0/2 (0%)
1017	US	6/10 (60%)	1/10 (10%)
1018	US	3/9 (33%)	0/10 (0%)
1019	US	4/10 (40%)	0/10 (10%)
1020	US	3/6 (50%)	2/6 (33%)
1021	US	10/22 (45%)	2/22 (9%)
1023	US	1/3 (33%)	0/3 (0%)
1024	US	3/8 (38%)	0/10 (0%)
1025	US	8/16 (50%)	1/18 (6%)
1027	US	0/0	0/0
1028	US	0/0	0/0
1029	US	1/2 (50%)	0/1 (0%)
1030	France	3/6 (50%)	0/6 (0%)
1031	US	2/6 (33%)	0/7 (0%)
Total		105/248 (42%)	22/251 (9%)

Source: SAS datasets

4.2 Other Special/Subgroup Populations

Dr. Horn identified 9 centers which had higher than desired financial interests with the applicant, Pfizer, Inc. She requested that I do a subgroup analysis excluding those centers, which had enrolled a total of 170 subjects (34% of total enrollment). The results are shown in Table 8 below. The results and conclusions were not impacted by excluding those centers.

Table 8: Efficacy Analyses Excluding Centers with Financial Interests

Drop Centers with Potential Financial Conflicts	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
	N=164	N=165		
Continuous Quit Rate Weeks 9-12	71 43% (36%, 51%)	14 8% (4%, 13%)	8.23 (4.39, 15.44)	<.0001
Continuous Abstinence Weeks 9-52	35 21% (15%, 28%)	10 6% (2%, 10%)	4.20 (2.01, 8.82)	<.0001
Long Term Quit Rate: Week 52	41 25% (18%, 32%)	12 7% (3%, 11%)	4.25 (2.14, 8.44)	<.0001

Excludes Centers 1001, 1002, 1007, 1011, 1013, 1016, 1018, 1020, and 1021.

Dr. Horn identified 50 patients who were protocol violations based on being diagnosed with depression within the past 12 months prior to screening and/or were on prohibited medications such as benzodiazepines, antidepressants, or mood stabilizers. She requested that I provide descriptive statistics of the efficacy outcomes for those subjects. The results are shown in Table 9 below. It is not appropriate to make between group comparisons for these subsets.

Table 9: Efficacy Outcomes for Patients Diagnosed with Depression and/or Prescribed Related Medications

	Varenicline	Placebo
	N=27	N=23
Continuous Quit Rate Weeks 9-12	8 (30%)	2 (9%)
Continuous Abstinence Weeks 9-52	3 (11%)	0
Long Term Quit Rate Week 52	3 (11%)	1 (4%)

Source: SAS datasets

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no statistical issues identified during the review. The studies were conducted as planned, and any protocol amendments did not impact the analysis or interpretation of the results. Dropouts were slightly higher in the placebo group, but subjects who discontinued from the study were coded as smokers (non-responders) from that point on, and missing data was handled appropriately. Excluding subjects from centers which had large financial involvement with Pfizer did not impact the results or conclusions.

The applicant proposed the results of Study 54 be added to the label in the Clinical Studies section, with no change to the actual indication statement. The study description matches the style of the previous studies in the existing label and is appropriate. The applicant included the response rates for the Continuous Quit Rate Weeks 9-12 and Continuous Abstinence for Week 9-52 for each treatment group, with confidence intervals, and no p-values. The applicant's values are for the mITT population results (see Table 3). Dr. Horn would prefer the label reflect the results from my reanalysis (b) (4). There is little difference in the rates for the two analyses.

5.2 Conclusions and Recommendations

The goal of this single study was to show superiority of varenicline over placebo as an aid to smoking cessation in subjects with mild-to-moderate chronic obstructive pulmonary disease who desired to quit smoking. Based on my review of this study, I conclude there is sufficient evidence of efficacy to support adding these results to the clinical study section of the currently approved label for varenicline.

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification
Specify for each trial:

Protocol Number (s): A3051054
Protocol Title (optional): A 12-week, Double-blind, Placebo-controlled, Multicenter Study with a 40-Week Follow-up Evaluating Safety and Efficacy of Varenicline Tartrate 1 mg BID for Smoking Cessation in Subjects with Mild-to-Moderate Chronic Obstructive Pulmonary Disease
Phase: 3
Control: Placebo
Blinding: Double-Blind
Number of Centers: 27
Region(s) (Country): US, France, Italy, Spain
Duration: 12 Weeks on treatment; 40 week follow-up
Treatment Arms: Placebo/**Varenicline Tablets**
Treatment Schedule: 1 mg BID
Randomization: Yes
Ratio: 1:1
Method of Randomization: block randomization with investigative site as the stratification variable
Primary Endpoint: 4-week continuous quit rate (CQR) for weeks 9-12 of treatment
Primary Analysis Population: All subjects who were randomized who took at least one dose of randomized study medication; referred to as the All Subjects data set in study reports.
Statistical Design: Superiority
Adaptive Design: No
Primary Statistical Methodology: Logistic Regression
Interim Analysis: No
DSMB: Yes
Sample Size: 500 (250 per trmt arm)
Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes
Statistic = Pearson Chi-Square
Power= at least 81%
Δ= placebo rate 0.18; varenicline rate 0.38; odds ratio 2.79
α = .05 2-sided

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? Yes
- Did the Applicant perform **Sensitivity Analyses**? Yes

- How were the **Missing Data** handled? All drop-outs were assumed to be smoking (trmt failure)
- Was there a **Multiplicity** involved?

  If yes,

  Multiple Arms (Yes/No)? No

  Multiple Endpoints (Yes/No)? One Primary and two pre-specified "key secondary"
  to be included in the label. Study was powered for all three endpoints.

  Which method was used to control for type I error? Hierarchical

Multiple Secondary Endpoints: Are they being included in the label? If yes, method to control for type 1 error. One Primary and two pre-specified "key secondary"
to be included in the label. Study was powered for all three endpoints.

Which method was used to control for type I error? Hierarchical

- **Were Subgroup Analyses Performed (Yes/No)**? Yes
- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No
- Overall, was the study positive (Yes/No)? Yes

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/s/

KATHERINE B MEAKER
05/23/2011

DIONNE L PRICE
05/23/2011
Concur with overall conclusions.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 21928/SE8/ Supplements 019, 020 and 021
Name of Drug: Chantix (varenicline) tablet; 0.5 mg and 1 mg
Applicant: Pfizer, Inc.

Labeling Reviewed

Submission Date: September 22, 2010 (original) and July 22, 2011
Receipt Date: September 23, 2010 (original) and July 22, 2011

Background and Summary Description: Pfizer submitted labeling supplements with clinical data (SE8) which propose the following labeling revisions to the package insert:

S-019: the safety and efficacy of Chantix (varenicline) in smokers with cardiovascular disease (CVD), and revisions to the Medication Guide that include the possible side effects of Chantix (varenicline)

S-020: the safety and efficacy of Chantix (varenicline) in smokers with chronic obstructive pulmonary disease (COPD)

S-021: the safety and efficacy of varenicline in a more individualized quit date setting paradigm, and revisions to the Medication Guide that include new information on how to take Chantix (varenicline)

The revised labeling submitted by the sponsor via email on July 18, 2011 was compared to labeling approved on December 17, 2010, SLR-023.

Review

Please note that the sponsor's proposed omissions are indicated by strikeovers, inclusions by underlined text.

HIGHLIGHTS OF PRESCRIBING INFORMATION:

(b) (4)

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

(b) (4)

Recommendations

These supplements are recommended for approval.

Ayanna Augustus, Ph.D.	July 20, 2011
Regulatory Project Manager	Date
Parinda Jani	July 22, 2011
Chief, Project Management Staff	Date

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/s/

AYANNA S AUGUSTUS
07/22/2011

PARINDA JANI
07/22/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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MATERNAL HEALTH TEAM (MHT) REVIEW

Date: 6-9-2011 **Date Consulted:** 3-8-2011

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team

Through: Karen B. Feibus, M.D.
Medical Team Leader, Maternal Health Team

Through: Lisa Mathis, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Anesthesia, Analgesia, and Addiction Products

Drug: Chantix (varenicline), NDA 21928/S-19-(b) (4) IND 58, 994 (Postmarketing commitment-Pregnancy cohort study)

Subject: Pregnancy safety data

Sponsor: Pfizer

Materials Reviewed:

- Sponsor's submissions:
  - Integrated Summary of Safety- Pregnancy data (03-04-2011)
  - Interim Report of Pregnancy Cohort Study (04-14-2011): Summary of pregnancy data from clinical trials, postmarketing safety database, a British prescription study, and the published literature

- PubMed literature review:
  - Varenicline exposure during pregnancy and pregnancy outcomes
  - Antidepressant exposure during pregnancy and spontaneous abortion

Consult Questions:

1. Please review the material in section 2.4.4.4 of the ISS and determine if any changes to the postmarketing program of evaluation of Chantix for safety in pregnant women are indicated in light of this information.

2. Please review sponsor's April 14th 2011 submission.

EXECUTIVE SUMMARY

The cumulative varenicline pregnancy safety data, which include data from the first year of the Swedish and Danish databases, the sponsor's pre and postmarketing safety database, and a small British prescription database study, are very limited. The data are too limited to provide any conclusions regarding the safety of varenicline. At the present time, the data do not present any safety signals that would warrant requesting postmarketing studies in addition to the current ongoing pregnancy database study that was agreed upon as a postmarketing commitment at the time of Chantix® approval.

INTRODUCTION

On September 22, 2010, Pfizer submitted (b) (4) efficacy supplements for Chantix, which provide clinical data on the safety and efficacy in patients with cardiovascular disease, chronic obstructive pulmonary disease, a new quit paradigm, and patient reported outcome dossier for smoking satisfaction and psychological reward. On March 4, 2011, the sponsor submitted an Integrated Summary of Safety (ISS) in response to the Division of Anesthesia, Analgesia, and Addiction Products' (DAAAP) request for an ISS using the overall safety data from all completed placebo-controlled studies, juxtaposed with data from each of the new studies submitted in the efficacy supplements. DAAAP requested that the Pediatric and Maternal Health Staff's Maternal Health Team (MHT) review the pregnancy exposure data in the ISS and determine if any changes to the current post-marketing commitment are needed.

The current post-marketing commitment (PMC) regarding pregnancy is a prospective epidemiologic cohort study using data from national registries in Sweden and Denmark in pregnant women who are exposed to varenicline. On April 14, 2011, the sponsor submitted additional data, which include an interim report of the pregnancy cohort study, a summary of pregnancy data from clinical trials, the sponsor's post-marketing safety database, a small British prescription study, and the published literature. This review provides MHT's review of the Chantix pregnancy exposure data and provides recommendations regarding future data collection. Please see MHT reviews by Karen Feibus, MD (March 6, 2011) and Richardae Araojo, Pharm D, MS (March 17, 2010) regarding recommendations for the varenicline pregnancy cohort study.

BACKGROUND

Overview of study drug

Chantix® (varenicline) is a partial agonist at $\alpha_4\beta_2$ nicotinic acetylcholine (ACh) receptors that prevents nicotine receptor binding and nicotine-mediated stimulation of the mesolimbic dopamine system, which is thought to underlie the reward and behavioral reinforcement associated with smoking dependence. FDA approved Chantix® as an aid to smoking cessation in May 2006. Other FDA approved smoking cessation drug products include bupropion and nicotine replacement therapies.

Based on findings in nonclinical reproductive toxicology studies, varenicline is labeled Pregnancy Category C. Nonclinical studies in animals did not show any teratogenic effects, but treatment of pregnant rabbits with 50 times the human dose of varenicline resulted in reduced fetal weights. This effect was not seen at 23 times the human dose. In addition, treatment of pregnant rats with 36 times the human dose of varenicline resulted in decreased fertility and increased auditory startle response in offspring. Labeling in the United States has category C language that says that Chantix® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Smoking in Pregnancy

Despite widespread educational efforts about the harmful maternal and fetal effects of maternal smoking, approximately 20% of pregnant women in the United States smoke cigarettes. Smoking during pregnancy is associated with spontaneous abortion, placental abruption, preterm premature rupture of membranes, and low birth weight[1]. In addition, data support an association between prenatal cigarette smoke exposure and an increased risk of SIDS, pulmonary infections, cognitive deficits and behavioral problems in infancy and childhood[2].

Published Data

There are no reports in the medical literature regarding exposure to varenicline during pregnancy.

REVIEW OF DATA

Sponsor's submissions

Integrated Summary of Safety

The sponsor's Integrated Summary of Safety (ISS), dated March 4, 2011, includes pregnancies that occurred in completed placebo-controlled clinical studies of varenicline through December 2, 2010. Of the 14 varenicline-exposed women, five carried their pregnancy to term and had healthy babies, five elected to terminate their pregnancy, and three experienced spontaneous abortion. The outcome of the remaining pregnancy was unknown.

[1] ACOG Committee Opinion 2005 Number 315 Smoking Cessation During Pregnancy
[2] Crawford J. Smoking Cessation in Pregnancy:Why, How, and What next. Clin ObGyn 51(2):419-435.

Normal Outcomes

Cases [redacted] and [redacted] had pregnancies that resulted in normal pregnancy outcomes at term. In these cases, varenicline exposure in utero varied between two and approximately less than six weeks of gestation. In the remaining three cases [redacted] and [redacted], the women became pregnant more than 30 days after cessation of varenicline treatment.

Reviewer comment:

The three pregnancies that occurred more than 30 days after cessation of varenicline treatment should not be considered "exposed," as the half life of varenicline is 24 hours and would have been cleared by this time.

Elective Terminations

Five varenicline-treated women elected to terminate their pregnancy. In four of these cases ([redacted], [redacted], [redacted], and [redacted], varenicline exposure in utero varied between two and approximately less than 12 weeks. In the remaining case [redacted], duration of exposure in utero could not be determined.

Miscarriages

Three varenicline-treated women experienced a miscarriage. Case [redacted] was a 30 year old Caucasian female who was exposed to varenicline for "approximately less than 12 days following conception". Ten days later she experienced a spontaneous abortion. The sponsor attributed this case to a possible chromosomal abnormality and assessed this case as unrelated to drug exposure.

Reviewer comment

Although a chromosomal abnormality is the most common cause of spontaneous abortion, it is not possible to confirm that this is the etiology of the pregnancy loss unless there is pathological confirmation. This case should not be excluded as a possible drug associated effect.

Case [redacted] was a 32 year old mixed race female who became pregnant five days after initiation of varenicline treatment and was exposed for the first three weeks of pregnancy. Nine days later she had a curettage for management of a spontaneous abortion. The sponsor's assessment was that a contributory role of the study drug could not be ruled out.

Case [redacted] was a 25 year old mixed race female who was exposed for the first six weeks of pregnancy. She experienced a spontaneous abortion six weeks later. The sponsor assessed this case as being unrelated to varenicline treatment.

Reviewer comment

Because there is no temporal relationship between drug exposure and the spontaneous abortion in case [redacted] MHT concurs that this was probably not drug related.

ISS Summary of Varenicline exposed pregnancy outcomes n=14

Normal, full term	5
Spontaneous abortion	3
Elective termination	5
Unknown	1

Reviewer comments regarding ISS Pregnancy Data:

1. *The data are insufficient to allow an assessment of the safety of varenicline exposure during pregnancy. Because the data are so limited, there is no safety signal at the present time that would warrant an additional FDAAA (FDA Amendments Act) triggered post-marketing requirement (PMR) from the sponsor.*

2. *Based on a discussion with Office of Surveillance and Epidemiology, Division of Epidemiology reviewer Dr. Cynthia Kornegay, there are insufficient varenicline pregnancy exposures in the Department of Defense database to sufficiently power a database study evaluating outcomes following varenicline exposure during pregnancy.*

April 14, 2011 Sponsor's Summary of Pregnancy Data

Report On First Interim Data For Varenicline Pregnancy Cohort Study

The report on the first interim look is based on all Danish and Swedish births during the first calendar year of the study period, which includes all births during the period from May 2007 through December 2007 (i.e., the 2007 cohort) – followed through the end of 2008. The 2007 birth cohort consisted of 53,471 births, of which 11 were exposed to varenicline in utero ("exposed" cohort), 6,079 were exposed to maternal smoking, but not varenicline, in utero ("unexposed" cohort), and the remaining 47,381 infants were unexposed to varenicline and maternal smoking ("reference" cohort). Among the births in the exposed cohort, there were two major malformations and no occurrences of any secondary endpoints (stillbirth, low birth weight, preterm delivery, premature rupture of membranes (PROM) and sudden infant death syndrome (SIDS)). Major malformations occurred among 208 live births in the unexposed cohort and 1,769 in the reference cohort, yielding prevalences of 3.5% and 3.7%, respectively. Both of the major malformations in the exposed cohort occurred among births in Sweden.

One malformation in the varenicline exposed cohort was a congenital anomaly of the hip, unspecified (ICD-10: Q65.9), diagnosed at day 3 of life, when a secondary diagnosis of talipes calcaneovalgus (ICD-10: Q66.4) was also made. The infant was born full term with normal birth weight. The mother was between 20 and 25 years old at delivery with normal pre-pregnancy body mass index. Before pregnancy the mother had been admitted to the hospital for postconcussional syndrome and acute intoxication due to alcohol intake. She was considered to have been exposed to varenicline during pregnancy because she was dispensed a 28 day prescription that began 13 days prior to the estimated conception date. The mother also filled prescriptions for metoclopramide during the first and second trimester, and prescriptions for

lansoprazole and bupropion such that the number of days supplied extended from six months prior to conception until the month of conception.

The other major malformation case in the exposed cohort was an infant diagnosed with Down's syndrome, unspecified (ICD-10: Q90.9) at one month of life. This infant was born full term with normal birth weight. The mother was between 25 and 30 years old at delivery with normal pre-pregnancy body mass index and had no hospitalizations for relevant comorbidities. The mother was considered to have been exposed to varenicline during pregnancy because she was dispensed a 28 day prescription that began the day before the estimated conception date.

Reviewer comments

No conclusions can be drawn from these data, as the number of varenicline exposures is small (n=11), and the two malformations are not similar and are not consistent with any pattern. Also, Down's syndrome usually occurs due to nondysjunction during the meiosis phase of cell division and is not a drug associated event.

Modified Prescription Event Monitoring Study

The sponsor conducted a study to examine the safety and use of varenicline prescribed in general practice in England as a treatment for smoking cessation in adults. The investigators used the method of modified prescription event monitoring (M-PEM), a method of postmarketing surveillance, to identify an observational cohort of patients. Data from dispensed National Health Service (NHS) prescriptions for varenicline written by general practitioners (GPs) in England between December 2006 and March 2007 were supplied in confidence by the NHS Business Services Authority (NHSBSA) Prescription Pricing Division for England. GPs were sent questionnaires regarding the patients for whom they prescribed varenicline. There were 35 pregnancies reported from the entire cohort during the study period. There were four terminations, five spontaneous abortions, and five unknown/unspecifed outcomes. Among the 21 live births, there were two reported abnormalities.

The first reported abnormality occurred in a 27 year old female who started varenicline prior to her last menstrual period; the duration of exposure was unknown. The patient had a normal vaginal delivery at 37 weeks gestation, and the infant was noted to have respiratory distress, and a pneumothorax. The patient had taken the following medications during her pregnancy: metronidazole, azithromycin, diclofenac sodium, levothyroxine, cyclizine, beclomethasone and (b) (4) inhalers and buprenorphine.

The second reported abnormality occurred in a 34 year old female who started and stopped varenicline prior to her last menstrual period; the GP reported that "the patient had probably never started varenicline". The infant was reported to have supraventricular tachycardia. The mother had taken "some alcohol" during her pregnancy and was prescribed digoxin parentally.

Reviewer comments

These data are limited by the small number of exposures and by potential confounders, such as exposure to multiple other medications. Therefore, it is not possible to draw any conclusions about whether varenicline exposure contributed to the adverse pregnancy

outcomes. The second case appears not to have been exposed to varenicline during pregnancy.

Sponsor's Postmarketing Safety Database

The sponsor's postmarketing safety database, which covers the period from May 10, 2006-December 31, 2010, includes 306 pregnancies with the following outcomes:

- 36 normal full term live births
- 31 spontaneous abortions
- 13 terminations
- 2 infant deaths
- 9 congenital anomalies (see table 1 below)
- Remaining cases with unknown outcomes.

Table 1
Congenital Anomalies Following In utero Exposure to Varenicline (Sponsor's Post-marketing Safety Database)

Case Number, Age	Outcome	Varenicline Exposure History, Concomitant Medications, Medical History	Reviewer Comments
(b) (6) 33	Fetal demise at 16 weeks, Cleft palate, Ambiguous genitalia, Missing middle finger in each hand, Low set ears	1 week of exposure to varenicline in the first trimester	Genetic studies not available. Cannot determine if drug associated outcomes.
(b) (6) 32	Pyelocaliectasis in a full term baby	First trimester exposure, unknown duration	Cannot rule out drug effect
(b) (6) Unknown	Neonatal death; The baby was born "with lots of problems and unspecified syndrome"	Unknown	The information is vague and not helpful
(b) (6) 40 -50 years	Unspecified anomaly	The patient reported contraceptive failure while taking an unspecified contraceptive and varenicline	No information provided therefore this is not helpful
(b) (6) 42	Trisomy 18;Termination at 25 weeks gestation	2 week exposure in the first trimester	This is a random genetic occurrence therefore not drug associated
(b) (6) Unknown	Small for gestational age	First trimester exposure of unknown duration. History of fetal growth restriction in all 3 prior pregnancies. Concomitant lamotrigine and quetiapine exposure.	Drug effect less likely due to confounding by previous pregnancies complicated by fetal growth restriction
(b) (6) Unknown	Spontaneous abortion	Exposure through semen	Drug effect not likely

Case Number, Age	Outcome	Varenicline Exposure History, Concomitant Medications, Medical History	Reviewer Comments
(b) (6) 21	Cleft palate	2 week exposure in the first trimester. Bipolar disease, ADHD, past alcoholism. Concomitant zolpidem, lamotrigine, gabapentin, amphetamine, dextroamphetamine	Confounded by exposure to lamotrigine, which is associated with an increased risk for oral clefts.
(b) (6) 25	Infant death due to osteogenesis imperfecta	Unknown exposure information	This is a genetic disorder therefore not drug associated

Reviewer comments

The cases listed in table 1 are limited by the small number of cases and also by the lack of detailed information in some cases, which makes interpretation impossible. There are two cases of cleft palate; however, one case is confounded by concomitant exposure to lamotrigine, which is known to increase the risk for this outcome. The remaining data do not represent any pattern of findings. In summary, the sponsor's postmarketing safety database provides very limited data regarding use in pregnancy.

DISCUSSION AND CONCLUSIONS

The data from varenicline exposures that occurred during clinical trials are insufficient (n=14) to allow an assessment of the safety of varenicline exposure during pregnancy. No conclusions can be drawn from the first interim data report from the Danish and Swedish database study, as the number of varenicline exposures is small (n=11). Data from the sponsor's pre and postmarketing safety databases and a small British prescription database study are also very limited. The medical literature does not have any reports on varenicline exposure during pregnancy. In summary, the cumulative safety data regarding varenicline exposure during pregnancy are limited and do not present a safety signal at the present time that would warrant an additional FDAAA triggered post-marketing requirement (PMR) from the sponsor.

An unanswered question that remains is how to capture data on pregnancy loss and fetal death up to 22 and 28 weeks, which is a limitation of the current Danish and Swedish database study being conducted as a PMC. Another unanswered question is whether varenicline increases the risk for adverse pregnancy outcomes that some studies suggest may be associated with selective serotonin reuptake inhibitors (SSRIs), such as certain cardiovascular malformations, persistent pulmonary hypertension of the newborn (PPHN), and newly emerging data on an increased risk of miscarriage[3,4]. These questions may be difficult to address at the present time due to the low

[3] Einarson A, Choi J, Einarson TR, Koren G. Rates of spontaneous and therapeutic abortions following use of antidepressants during pregnancy:results from a large prospective database. J Obstet Gynaecol Can. 2009 May;31(5):452-6.

[4] Broy P, et al. Gestational exposure to antidepressants and the risk of spontaneous abortion: A review. Current Drug Delivery 2010, 7, 76-93.

usage of varenicline by pregnant women and the challenge of obtaining larger sample sizes to adequately power a study. According to the OSE- Division of Epidemiology (OSE-DEpi) there are insufficient varenicline pregnancy exposures in the Department of Defense database to sufficiently power a study evaluating outcomes following varenicline exposure during pregnancy. It may be helpful to obtain input from OSE-DEpi regarding whether large population based epidemiologic studies using the United Kingdom General Practice Research Database (GPRD), Medications in Pregnancy Risk Evaluation Program (MEPREP), or other databases could assist in answering some of the unanswered questions.

RECOMMENDATIONS

1. Consult the Office of Surveillance and Epidemiology, Division of Epidemiology to provide suggestions about feasible approaches to evaluate the potential association between varenicline use during pregnancy and the risk for:
    - miscarriage and pregnancy loss (due to the limitations of the current Danish and Swedish database study being conducted as a PMC)
    - cardiovascular malformations
    - PPHN

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/s/

LEYLA SAHIN
06/09/2011

Karen B FEIBUS
06/09/2011
I concur with the information and recommendations presented in this review.

LISA L MATHIS
06/10/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: May 23, 2011

To: Ayanna Augustus, Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products (DAAP)

From: Kathleen Klemm, Regulatory Review Officer
L. Shenee' Toombs, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, DTC Group Leader
Mathilda Fienkeng, Regulatory Review Officer
DDMAC

Subject: NDA 021928/S-019, S-020, S-021 (b) (4)
DDMAC labeling comments for CHANTIX (varenicline) Tablets (Chantix)

In response to DAAP's January 21, 2011, consult request, DDMAC has reviewed the draft package insert (PI) and Medication Guide for Chantix and offers the following comments.

DDMAC's comments on the PI and Medication Guide are based on the proposed draft marked-up labeling titled, "Substantially revised PI emailed by Ayanna Augustus on May 6, 2011 proposed label 05 11.doc". DDMAC's comments are provided directly on the document attached below.

Thank you for the opportunity to comment on these proposed materials. If you have any questions regarding the PI, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Shenee' Toombs at 301.796.4174 or Latoya.Toombs@fda.hhs.gov.

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/s/

KATHLEEN KLEMM
05/23/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-020

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021928/S-019, S-020, S-021, (b) (4)

PRIOR APPROVAL SUPPLEMENTS

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

Attention: Lilya I. Donohew, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Donohew:

We have received your September 22, 2010, Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021928

SUPPLEMENT NUMBER: S-019, S-020, S-021, (b) (4)

PRODUCT NAME: Chantix (varenicline) Tablets 0.5 mg and 1 mg

DATE OF SUBMISSION: September 22, 2010

DATE OF RECEIPT: September 23, 2010

These supplemental applications propose for the following labeling revisions to the Package Insert:

S-019: the safety and efficacy of varenicline in smokers with cardiovascular disease (CVD)

S-020: the safety and efficacy of varenicline in smokers with chronic obstructive pulmonary disease(COPD)

S-021: the safety and efficacy of varenicline in a more individualized quit date setting paradigm

(b) (4)

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on November 22, 2010, in accordance with 21 CFR 314.101(a).

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 under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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).

Cite the application numbers listed above at the top of the first page of all submissions to these applications. 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 and Analgesia 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, contact me, at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

AYANNA S AUGUSTUS
10/15/2010