CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s019

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-019

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**x**
Other Action Letters	
Labeling	**x**
REMS	**x**
Summary Review	**x**
Officer/Employee List	**x**
Office Director Memo	
Cross Discipline Team Leader Review	**x**
Medical Review(s)	**x**
Chemistry Review(s)	**x**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	**x**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	**x**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**x**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-019

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-019

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

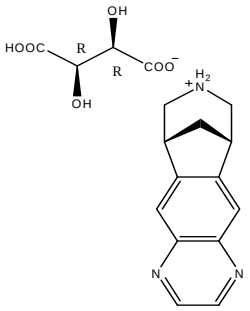
In case of overdose, standard supportive measures should be instituted as required.

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

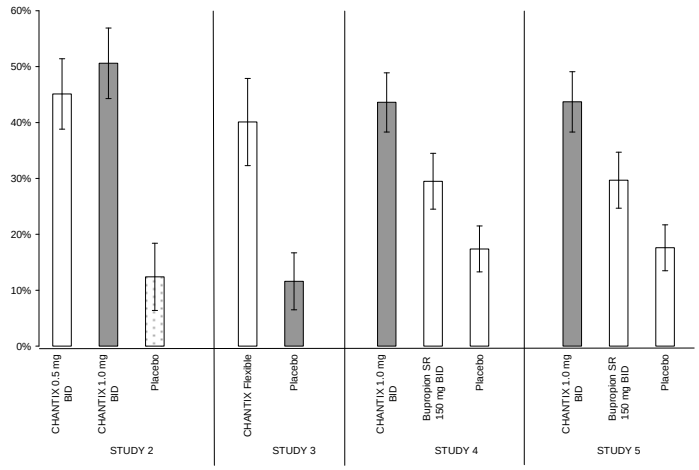


Table 2: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	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

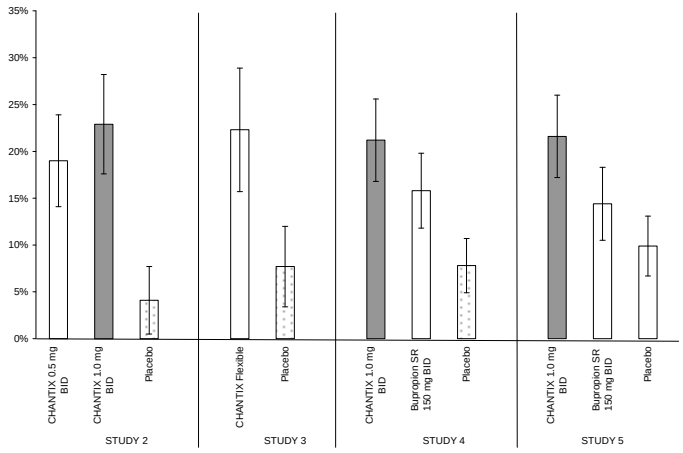


Table 3: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies

	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%)

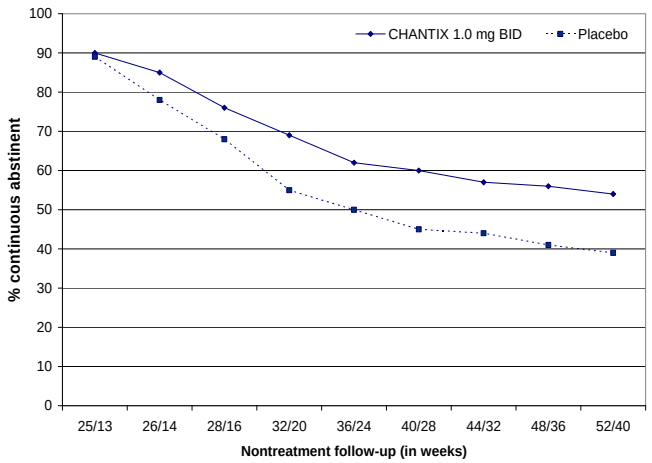
BID = twice daily

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)]*.

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

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-019

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-019

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, A3051101, A3051106
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.

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-019

OFFICER/EMPLOYEE LIST

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

Augustus, Ayanna
Dempsy, Mary
Horn, Pamela
Mills, Sharon
Price, Dionne
Raghavachari, Ramesh
Rappaport, Bob
Vidra, James D

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-019

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).

---

[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)

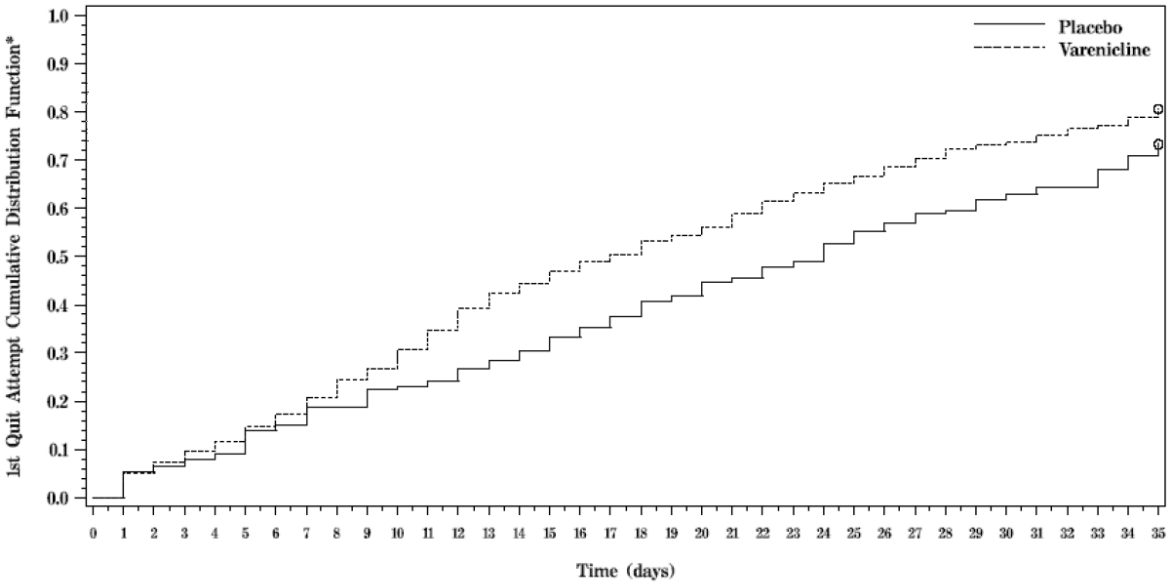
Adjustments to mITT Dataset		Varenicline	Placebo	Odds Ratio (95% CI)	p-value
Applicant's mITT dataset Exclude subjects who quit prior to start of treatment Include subjects who were randomized and non-responder		486 -3 +5	165 0 +1		
		N=488	N=166		
Continuous Quit Rate Weeks 9-12	n % (95% CI)	259 53% (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

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.

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-019

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21928/S-019
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 / OND
Reviewer Name(s)	Rachel Skeete MD, MHS
Review Completion Date	May 23, 2011
Established Name	Varenicline
(Proposed) Trade Name	Chantix®
Therapeutic Class	Partial agonist selective for the α4β2 nicotinic acetylcholine receptor subtypes
Applicant	Pfizer
Formulation(s)	Oral tablet
Dosing Regimen	1 mg BID PO following titration
Indication(s)	Aid to Smoking Cessation
Intended Population(s)	Smokers with Cardiovascular Disease

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 21928/S-019, which supports labeling claims for use of Chantix® in smokers with cardiovascular disease, is recommended for approval based on review of the information submitted in this supplemental new drug application (NDA).

1.2 Risk Benefit Assessment

Chantix® (varenicline) is a partial agonist at the α4β2 nicotinic receptor that was approved in May 2006 as an aid to smoking cessation. Pfizer submitted the present efficacy supplement to support new labeling claims regarding the safety and efficacy of use of Chantix in subjects with cardiovascular disease. The application provides safety and efficacy data to support use of Chantix in subjects with cardiovascular disease. Risk-benefit assessment involved weighing the safety findings in smokers with cardiovascular disease against both the efficacy findings in this population, and the well-understood benefits of smoking cessation in the setting of cardiovascular disease, and a host of other diseases and conditions.

The efficacy of Chantix in this population was demonstrated in a single, adequate, and well-controlled study, which the applicant conducted as a Phase 4 marketing study. In this 52-week study, smokers with stable cardiovascular disease (other than or in addition to hypertension and diagnosed at least 2 months prior to Screening) received 12 weeks of Chantix (1 week titration period followed by 1 mg BID[1] of Chantix for 11 more weeks). Subjects received smoking cessation counseling in conjunction with therapy. The primary efficacy endpoint was the 4-week Continuous Quit Rate (CQR) for Weeks 9 through 12 and was obtained through reports of cigarette or other nicotine use, since the last study visit, confirmed by measurement of end-expiratory exhaled carbon monoxide (CO) ≤10 ppm. A statistically significantly higher 4-week CQR was demonstrated in the varenicline arm compared with the placebo arm (varenicline, 47% vs. placebo, 14%, $p<0.0001$). Varenicline-treated patients also had higher rates of continuous abstinence from Week 9 through Week 52 of the study.

The applicant's submission included safety data from the population of smokers with cardiovascular disease in the single, adequate and well-controlled study supporting safety and efficacy in this population. These safety data were supplemented with data from an Integrated Summary of Safety (ISS), submitted at Agency request. The ISS summarized safety findings from completed Phase 1–4 placebo-controlled clinical trials in the Chantix clinical trial database. Review of the safety data demonstrated a small but increased risk in cardiovascular events, including nonfatal myocardial infarction and angina, in the varenicline arm of the cardiovascular disease study. In other populations of smokers evaluated in Chantix clinical trials, events were observed in less than 1% of subjects in either treatment arm. Health care providers will be informed of this risk and these events through labeling.

Because CO-confirmed abstinence (CQR for Weeks 9 through 12) was demonstrated in 47% of subjects on Chantix as compared with 14% on placebo in the cardiovascular disease study and

[1] BID – two times per day

because the health benefits of smoking in general, and in this population in particular, are immediate and substantial, the label is being updated to warn of this risk in order that patients and provider can make informed risk-benefit assessments on an individual patient basis.

Further, smoking is a major and independent modifiable risk factor for cardiovascular disease and smoking cessation is of particular importance in this population and other populations of smokers. Smoking cessation after MI reduces the risk of cardiovascular morbidity and mortality by 36 to 50 percent. In general, when smokers quit, the risk for a myocardial infarction drops sharply after just one year. Risk of stroke declines after two years of smoking cessation and can fall to about the same as a nonsmoker's after five years.[2]

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A MedGuide-only Risk Evaluation and Mitigation Strategy (REMS) related to neuropsychiatric events has already been approved. The MedGuide will be updated to include information about cardiovascular events. Review of the efficacy supplement has not identified additional safety issues that warrant additional postmarket REMS at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

No Postmarket Requirements and Commitments are recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Chantix® (varenicline tartrate) is a first-in-class, new molecular entity (NME) approved as an aid to smoking cessation. Varenicline is a partial nicotinic receptor agonist, selective for the α4β2 nicotinic acetylcholine receptor subtype. Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid.

Chantix is supplied as an immediate release film-coated tablet in two strengths. These include:

1) 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. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; and
2) 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 1mg CHANTIX tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base.

The inactive ingredients in varenicline tablets include 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.

[2] U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

Chantix® (varenicline)

- Trade name: Chantix®
- Drug established name: varenicline tartrate
- 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)
- Drug class: partial α4β2 nicotinic receptor agonist
- Proposed indication: Chantix is currently indicated for use in adult smokers in general; the present supplement proposes inclusion of information specific to safety and efficacy in adult smokers with cardiovascular disease
- Dose: 1 mg by mouth twice daily
    - 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

    - Chantix should be taken after eating and with a full glass of water.
    - 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.
- Intended Population(s): smokers with cardiovascular disease
- Age groups: Adults
    - Studies in children and adolescent smokers with cardiovascular disease are considered impossible or highly impracticable because the types of cardiovascular disease in question are anticipated to occur primarily in the adult population.

2.2 Tables of Currently Available Treatments for Proposed Indications

DRUGS USED AS AIDS TO SMOKING CESSATION			
Generic/Chemical Name	**Trade Name**	**Sponsor(s)**	**Dosage form(s)**
Nicotine polacrilex	Nicorette gum, chewing (OTC; also generic)	GlaxoSmithKline Consumer Healthcare LP	• Oral gum pieces
Nicotine polacrilex	Commit Lozenge (OTC; also generic)	GlaxoSmithKline Consumer Healthcare LP	• Lozenges – buccal delivery system
Nicotine patch	Habitrol (also generic)	Novartis	• Transdermal • Film, extended release
Nicotine patch	Nicoderm CQ (also generic)	Sanofi Aventis	• Transdermal • Film, extended release
Nicotine inhalant	Nicotrol	Pfizer/Pharmacia and	• Cartridge with

DRUGS USED AS AIDS TO SMOKING CESSATION			
Generic/Chemical Name	**Trade Name**	**Sponsor(s)**	**Dosage form(s)**
		Upjohn	mouthpieces – buccal delivery system
Nicotine nasal spray	Nicotrol	Pfizer/Pharmacia and Upjohn	• Solution with metered spray pump
Buproprion	Zyban	GlaxoSmithKline	• Oral tablets

2.3 Availability of Proposed Active Ingredient in the United States

Varenicline is currently marketed in the United States only in Chantix tablets. The applicant, Pfizer, holds patents on several steps in the varenicline manufacturing process. No other domestic varenicline sources are known.

2.4 Important Safety Issues With Consideration to Related Drugs

No other α4β2 nicotinic agonist medications have been approved for use in the United States or elsewhere. At least one structurally and pharmacologically similar drug, (b) (4)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There were no pre-submission meetings held or discussions related to this efficacy supplement.

The applicant did submit a Request for Advisory Comments to the Division of Drug Marketing, Advertising and Communications (DDMAC). The applicant had requested review of a Professional Detail Aid that the applicant was supporting with data from the clinical study which forms the basis of this efficacy supplement.

On review of the professional detail aid, the applicant was informed that varenicline appears to be more efficacious than placebo in this population; however, subjects in the varenicline arm appeared to experience more cardiovascular disease-related adverse events including angina and dyspnea.

2.6 Other Relevant Background Information

The applicant concurrently submitted three efficacy supplements that contain efficacy and safety data; the supplements are numbered S-019 to S-021.

This supplement (S-019) seeks to add information about efficacy and safety of Chantix in patients with cardiovascular disease. In the pre-marketing safety database, patients generally were excluded from participation if they had any history of clinically significant cardiovascular disease, (examples included myocardial infarction, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), severe or unstable angina, serious arrhythmia, and clinically significant conduction abnormalities); clinically significantly abnormal screening or baseline ECGs; or poorly controlled hypertension (usually subjects excluded for screening or baseline SBP > 150 mm Hg or DBP > 90 mm Hg). Some Phase 3 protocols were amended to allow enrollment of subjects with stable, documented, cardiovascular disease (stable for ≥ 6 months). Key differences for the cardiovascular disease study, from the usual entry criteria, were that subjects with stable, documented cardiovascular disease diagnosed up to 2 months prior to study entry were enrolled, and subjects with diabetes were allowed to enroll as long as their hemoglobin A1c (HbA1c) was not greater than 9%.

Efficacy supplements S-020 and S-021 are the two other supplemental NDAs containing new efficacy and safety data that were submitted concurrently with S-019, the supplemental application under review here. Supplement 020 provides data in support of the efficacy and safety of Chantix in patients with chronic obstructive pulmonary disease (COPD). Supplement 021 provides data supporting an alternative approach to setting a quit date. An ISS, submitted at Agency, request supports all three supplements. The efficacy supplements were reviewed by two reviewers and review of the ISS was divided between the two reviewers.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Inspection of the case report forms and line listings by the reviewer revealed no concerns about data quality or integrity. The submission was well-organized and did not present any major barriers to review. When needed, clinical information requests were sent to the applicant in order to clarify information in the submission and to provide new information to help the review. Datasets, overall, were in a format that allowed for the reviewer to evaluate and reproduce findings.

3.2 Compliance with Good Clinical Practices

According to the applicant, the clinical trial in smokers with cardiovascular disease was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) guidelines as is as required by and described in 21 Code of Federal Regulations parts 50, 54, 56, 312 subpart D, and 314. The applicant additionally indicates that all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

3.3 Financial Disclosures

The applicant's submission included the completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455). The applicant indicated that the

majority of the study investigators are certified as having no Financial Arrangement as defined in 21 CFR 54.2. The applicant has also stated that a total of 8 investigators did not respond or could not be reached by their due diligence effort.

For each of the investigators who submitted financial disclosure information and were not certified as having no Financial Arrangement as defined in 21 CFR 54.2, the applicant provided information on the financial arrangements or financial interests that require disclosure as part of Form FDA 3455. Specifically, the applicant provided information on "any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria."

In sum, not all the investigators could be certified because they either had financial arrangements as defined in 21 CFR 54.2 or did not respond or could not be reached by the applicant's due diligence effort. The sites for these investigators are provided in the following table.

1001	1002	1011	1012	1014
1015	1022	1023	1025	1030
1033	1035	1038	1042	

Because of a concern that potential conflict of interest among these investigators could skew results in favor of the applicant, Dr. Katherine Meaker, the primary statistical reviewer, was asked to perform the primary efficacy analysis excluding all data from the sites included in the table above, for which there were investigators who had financial arrangements with the applicant that required disclosure or who did not respond or could not be reached by the applicant's due diligence effort. Subjects in these sites represented approximately 35% of the total number of subjects. When the analyses were repeated excluding these data, there was still a significant difference in the primary endpoint and key secondary endpoints in favor of varenicline.

Again, the applicant certified that for all other investigators: 1) it had not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) the investigators had no proprietary interest in the product or significant equity in the sponsor; and 3) the investigators had not received significant payments of other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Only clinical safety and efficacy data were submitted and reviewed by the Clinical and Statistical reviewers. No other data relevant to other review disciplines were submitted.

4.1 Chemistry Manufacturing and Controls

No new CMC information was included in this submission.

4.2 Clinical Microbiology

No new clinical microbiology information was included in this submission.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was included in this submission.

4.4 Clinical Pharmacology

No new clinical pharmacology information was included in this submission. However, key aspects of the clinical pharmacology of varenicline taken from the Clinical Pharmacology section, Section 12, of the current label, are provided.

4.4.1 Mechanism of Action

The mechanism of action section as detailed in current labeling is excerpted here.

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

4.4.2 Pharmacodynamics

The pharmacodynamic properties are summarized in the label as described in the following excerpt.

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

4.4.3 Pharmacokinetics

Varenicline pharmacokinetics are summarized in the label as follows.

Absorption/Distribution: Maximum plasma concentrations of varenicline occur typically within 3–4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic

availability was ~90%. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

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

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

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

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) 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) 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; therefore, a dose adjustment of Chantix would not be required.

Use with Other Drugs for Smoking Cessation:

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

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

5 Sources of Clinical Data

Sources of clinical data for this efficacy supplement include the adequate and well-controlled study in smokers with cardiovascular disease, namely Study A3051049, the Integrated Summary of Safety, and postmarketing surveillance data.

Efficacy
- Study A3051049

Study A3051049 is the pivotal and sole efficacy trial conducted and included in this submission in support of efficacy.

Safety
- Study A3051049
- Integrated Summary of Safety (ISS)

Study A3051049 is the sole safety trial conducted and included in this submission in support of safety. In an effort to perform a more complete evaluation of the safety experience in the A3051049 population and the other populations of smokers exposed to Chantix in the clinical trials, an Integrated Summary of Safety (ISS) report, submitted at Agency request, was also reviewed. The ISS report then is intended to complement the safety data from Study A3051049 to provide a fuller picture of the safety experience with Chantix.

The ISS comprises safety findings from completed placebo-controlled Chantix clinical trials that used the immediate-release (IR) formulation and supports the submitted efficacy supplements,

S-019 to S-021. The objective in examining the ISS for this review of safety was to compare and contrast findings among the different populations of smokers and to aggregate safety data across all studies.

The ISS database includes data from Phase 1 through 4 completed placebo-controlled studies for which there was a completed study report on or prior to December 2, 2010, the applicant's chosen cut-off date for inclusion of data in the ISS. In the ISS report, the applicant chose to report on these data by grouping the studies into Phase 1 studies and Phase 2–4 studies.

For the Phase 1 studies, a single pooled cohort of 16 completed placebo-controlled studies was used for the analysis, while five cohorts were used in the analysis of the Phase 2–4 studies. The Phase 2–4 studies cohorts included 2 pooled cohorts and 3 individual study cohorts. One Phase 3 study, Study A3051035, was not included in the ISS because of its unique design; this maintenance study included a 12-week open label, run-in phase prior to the double-blind, placebo-controlled treatment phase. The individual studies in the cohort of Phase 1 studies and the cohorts used in the Phase 2–4 studies are summarized in the following tables and described in more detail in Section 5.3.

Postmarketing Surveillance Data

The applicant performed a postmarketing safety analysis based on postmarketing adverse event reports contained in its safety database. The postmarketing adverse events reports include cases of AEs reported spontaneously to the sponsor, cases reported from health authorities, cases published in the medical literature, and cases reported from Pfizer-sponsored marketing programs (solicited cases) regardless of causal association.

5.1 Tables of Studies/Clinical Trials

The study/clinical trial that is the source of clinical efficacy data for this submission is summarized in the following table, Table 1.

The studies/clinical trials that are the sources of clinical safety data for this submission are summarized in Table 2 and Table 3.

Table 1 Summary of Chantix Clinical Trials Reviewed for this Efficacy Supplement

EFFICACY					
Study No.	**Design/Status**	**Population**	**Location**	**Regimen**	**Duration**
A3051049	Phase 3b, multicenter, randomized, double-blind, placebo-controlled 52-week trial, comprising a 12-week treatment phase, followed by a 40-week nontreatment phase in smokers with stable cardiovascular disease.	N=703 smokers with stable cardiovascular disease • Chantix n=353 o Mean age = 57.0 yrs (range: 34 – 76) o Gender: 24.6% female • Placebo: n=350 o Mean age = 56.0 yrs (range: 35 – 75) o Gender: 18 % female	39 centers in Multiple Countries: o United States o the Netherlands o Brazil o Australia o Canada o Denmark o Argentina o the United Kingdom o Czech Republic o Greece o Germany o Taiwan o Mexico o Republic of Korea o France	Chantix (1 week titration followed by 11 weeks of 1 mg orally twice daily dosing) or placebo for 12 weeks	52 weeks

Table 2 Phase 1 Studies included in the Integrated Summary of Safety

Study	Design	Dosage/ Regimen/ Duration	Comparator	No. of Subjects[a]
Studies included in 2005 NDA submission				
Absorption, Distribution, Metabolism, and Excretion Studies				
305-001 First in Human SD & MD	R, PG, DB, PC	SD: 0.01, 0.03, 0.1, 0.3, 1, 3 or 10 mg (OPC) MD: 1 mg QD, 2 mg QD; 3 mg QD, 1 mg BID SD/MD 14 days	Placebo	102 SD 44 MD Smokers and non-smokers
Special Populations				
A3051009 Elderly (≥ 65 yrs), PK	R, DB, PC, PG	1 mg QD, 1 mg BID 7 days	Placebo	24
A3051027 SD Japanese	R, DB, PC, XO	0.25, 0.5, 1.0, 2.0 mg SD	Placebo	14
A3051029 SD PK Adolescents (12-17 yrs)	R, ISBSO, PC, PG	0.5 mg SD 1 mg SD Placebo SD	Placebo	27
A3051039 Abuse liability in recreational drug users	R, DB,PC, XO	1 mg SD 3 mg SD	Amphetamine 15 mg, 30 mg SD Placebo SD	45
A3051041 MD Japanese	R, DB, PC, PG	0.5, 1.0 mg BID 14 days	Placebo	24
Drug Interaction Potential				
A3051031 Digoxin PK Interaction	R, ISBSO, PC, 2-way XO	Digoxin (as Lanoxicaps®) 0.2 mg QD + 1 mg BID varenicline x 14 days	Digoxin 0.2 mg QD + placebo	18
A3051032 Warfarin PK/PD interaction	R, ISBSO, PC, 2-way XO	Warfarin 25 mg SD + 1 mg BID varenicline x 14 days	Warfarin 25 mg SD + placebo	24
A3051033 NRT PK/PD(safety) interaction	R, DB, PC, 2-way XO	NRT Patch 21 mg/24 hr + 1 mg BID varenicline x 14 days	NRT Patch 21 mg + placebo	24
A3051034 Zyban PK/PD (safety) interaction	R, ISBSO, PC, 2-way XO	Zyban 150 mg BID + 1 mg BID varenicline x 14 days	Zyban 150 mg BID + Placebo	46
Pharmacodynamic Studies				
A3051005 Relief of craving	R, DB, PC, XO	SD	Placebo	40

Study	Design	Dosage/ Regimen/ Duration	Comparator	No. of Subjects[a]
A3051014 Titration, improved tolerability	R, DB, PG, PC	Varenicline for 3 weeks, titrated during Week 1 to 1.5 mg BID (titration) Varenicline 1 mg BID for 2 weeks, then placebo for 1 week (no titration) Placebo for 2 weeks, then Varenicline 1.5 mg BID for 1 week (positive control) 21 days	Placebo	120
CR Formulation Studies including IR				
A3051012-IR[b]	R, DB, PC, XO	2 mg IR, 2 mg CR, 3 mg CR, 4 mg CR	None	18 (17 included in pooled Phase 1 cohort)
A3051013-IR[b]	R, SB, PG, PC	IR 1 mg BID, 1.5 mg BID CR, 3 mg QD CR, 2 mg BID CR, 4 mg QD CR, placebo	Placebo	120 (40 included in pooled Phase 1 cohort)
New studies not included in 2005 NDA submission				
A3051070 Multiple dose PK in adolescent smokers	R, DB, PG, PC	0.5 mg QD, 0.5 mg BID, 1mg BID, placebo	Placebo	72
A3051106 PK and pro-cognitive effects in healthy, elderly, nonsmokers; under various titration schemes	R, ISBSO, PG, PC	0.5 mg BID, 1 mg QD, 1 mg BID, placebo	Placebo	50

SD: single-dose; MD: multiple-dose; OPC: oral powder for constitution; R: randomized; SB: single-blind; DB: double-blind; ISBSO: investigator and subject blind, sponsor open; PC: placebo-controlled; PG: parallel group; XO: crossover design; QD: once a day; BID: twice a day; NRT: nicotine replacement therapy; , IR: immediate release, CR: controlled release, PD: pharmacodynamics, PK: pharmacokinetics;.

[a] No. Subjects = unique subjects randomized and treated. Note that subjects in XO design studies may have received more than 1 study drug. All studies used volunteer adult smokers without significant medical conditions, except where noted.

[b] Routine safety data from the IR and placebo arms of this study were included in the pooled Phase 1 study cohort. Routine safety data from the CR arms of this study were not included.

SOURCE (Table and Legend): ISS Report, pp. 27–28

Table 3 Phase 2 - 4 Studies included in the Integrated Summary of Safety

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				
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

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.

SOURCE (Table and Legend): ISS Report, pp. 11–13

5.2 Review Strategy

Efficacy

The objective of the efficacy review was to determine if the efficacy claims regarding smokers with cardiovascular disease were supported by the data in the submission. Efficacy data were reviewed primarily by the Statistics Reviewer, Katherine Meaker, and findings were jointly interpreted by the Statistics and Clinical Reviewers. For efficacy, the placebo-controlled trial, Study A3051049, was the focal study for the efficacy review.

Safety

Review of safety for this efficacy supplement entailed review of safety information from the single trial in support of this supplement, A3051049, as well as an Integrated Summary of Safety report summarizing the safety experience with Chantix for completed placebo-controlled Chantix clinical trials that used the immediate-release (IR) formulation. Safety data from A3051049 were reviewed individually to examine the safety experience of Chantix in smokers with cardiovascular disease. These data were also supplemented with safety findings from the ISS for comparative purposes. The expanded safety database was evaluated through review of the ISS to reexamine the overall safety experience of Chantix in the expanded safety population.

5.3 Discussion of Individual Studies/Clinical Trials

The pivotal efficacy trial in support of this submission is Study A3051049, which is the phase 3b trial entitled "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." Study A3051049 is summarized in detail in the review of efficacy. (See Section 6.1.1 Methods)

Studies reviewed for safety, in addition to Study A3051049, were those included in a cohort of Phase 1 studies and 5 cohorts of Phase 2–4 studies, as summarized in the ISS. Studies included in the ISS were completed placebo-controlled (PC) studies in the varenicline smoking cessation clinical program that were conducted with the immediate release (IR) formulation. Once again, studies that had a completed study report on or prior to December 2, 2010, the cut-off date, qualified for inclusion.

Phase 1 studies
For the Phase 1 studies, the analysis included a single pooled cohort of 16 completed PC studies: 305-001, A3051005, A3051009, A3051012 (IR and placebo arms only), A3051013 (IR and placebo arms only), A3051014, A3051027, A3051029, A3051031, A3051032, A3051033, A3051034, A3051039, A3051041, A3051070, and A3051106. These studies enrolled a total of 731 unique subjects. These studies are summarized in Section 5.1, Tables of Studies/Clinical Trials.

Phase 2–4 studies
Five cohorts were included in the Phase 2–4 study analysis; there were 2 pooled cohorts and 3 individual studies. However, one Phase 3 completed PC study that met criteria for inclusion in the ISS was not included because of its unique design; this maintenance study, Study A3051035, included a 12-week open label run-in phase prior to the double-blind, placebo-controlled phase. Also, some of the studies included a Zyban comparator arm. For these studies, data were presented for varenicline- and placebo- treated subjects only; data from the Zyban treatment group in A3051002, A3051028, and A3051036 were not included except in descriptions of the studies (tabular and narrative), pregnancy data, and death listings.

The five cohorts included: 1) a reference cohort; 2) an all completed Phase 2–4 placebo-controlled studies cohort; 3) Study A3051049, which forms the basis of this efficacy supplement; 4) Study A3051054; and 5) Study A3051095.

1. The reference cohort included completed, PC Phase 2–3 studies reported in the 2005 NDA: A3051002, A3051007, A3051016, A3051028, A3051036, and A3051037. These 6 studies included a total of 1983 varenicline-treated subjects and 1209 placebo-treated subjects. Throughout the ISS, this cohort is referred to as the ***2005 Pooled Studies cohort***.

2. All completed Phase 2–4 placebo-controlled studies: this cohort includes all completed PC Phase 2–4 studies (except Study A3051035, the maintenance study) as of the December 2, 2010 cut-off date (accordingly, 2005 Pooled Studies cohort inclusive): A3051002, A3051007, A3051016, A3051028, A3051036, A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, and

A3051115. These 15 studies included a total of 4483 varenicline-treated subjects and 2892 placebo-treated subjects. Throughout the ISS, this cohort is referred to as the ***2010 Pooled Studies cohort***.

3. A3051049 forms the basis for this efficacy supplement and has been described in detail throughout this review. Throughout the ISS, this cohort is referred to as the ***CV Study cohort***.

4. A3051054 enrolled subjects with mild-to-moderate chronic obstructive pulmonary disease (COPD) and included a total of 248 varenicline-treated subjects and 251 placebo-treated subjects. Of note, 39 subjects enrolled in the study did not meet the protocol-defined criteria for mild-to-moderate COPD (25 subjects in the varenicline arm; 14 subjects in the placebo arm). Throughout the ISS, this cohort is referred to as the ***COPD Study cohort***.

5. A3051095 enrolled a general population of healthy smokers and included a total of 486 varenicline-treated subjects and 165 placebo-treated subjects. Throughout the ISS, this cohort is referred to as the ***Flexible Quit Date Study cohort***.

6 Review of Efficacy

Efficacy Summary

A single placebo-controlled efficacy trial, conducted in multiple countries worldwide showed that patients defined as having stable cardiovascular disease diagnosed 2 months prior to Screening, and treated with Chantix were more likely to cease smoking during the last four weeks of treatment. Smoking status was determined by self-report verified by exhaled carbon monoxide levels. Varenicline-treated subjects were also more likely to be abstinent from smoking during the last four weeks of treatment through Week 52 of the non-treatment phase.

6.1 Indication

This efficacy supplement is being submitted to market Chantix in the US as safe and effective in smokers with stable cardiovascular disease. Specifically, the applicant seeks to revise the current Chantix label to include the following:

> "Chantix was evaluated in a randomized, double-blind, placebo-controlled study of 703 subjects with stable, documented cardiovascular disease (other than hypertension) that had been diagnosed for more than 2 months. Subjects aged 35 to 75 years were randomized to Chantix 1 mg BID or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. In this study 353 subjects received Chantix treatment and 350 received placebo. 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%)."

6.1.1 Methods

The applicant, Pfizer, conducted a single, Phase 3b study, Study A3051049, that is intended to serve as the pivotal trial for assessment of the efficacy and safety of Chantix as an aid to smoking cessation in smokers with cardiovascular disease.

A summary of the A3051049 study protocol follows.

PROTOCOL A3051049

Title: 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

Protocol Finalized:	August 18, 2005
Final Amendment (Amendment 4):	March 8, 2007
Study Initiated (First Subject Visit):	February 20, 2006
Study Completed (Last Subject Visit):	August 18, 2008
Final Signoff Date:	December 22, 2008

Investigators/Location:

The study was conducted in 39 centers in the United States, the Netherlands, Brazil, Australia, Canada, Denmark, Argentina, the United Kingdom, Czech Republic, Greece, Germany, Taiwan, Mexico, Republic of Korea, and France:

Country	Center	Principal Investigator	Country	Center	Principal Investigator
United States	1001	Ellen Dornelas	Greece	1023	Christina Gratsiou
United States	1002	Douglas Jorenby	Greece	1024	Evdokia Adamopoulou
Netherlands	1003	Ernst Lammers	United States	1025	Nancy Rigotti
Netherlands	1004	Paul I van Spiegel	Germany	1026	Isabelle Schenkenberger
Brazil	1005	Jacqueline Scholz Issa	Taiwan	1027	Chi-Tau Kuo
Brazil	1006	Jose Miguel Chatkin	Taiwan	1028	Chen-Huan Chen
Australia	1007	Matthew Peters	United Kingdom	1029	Wilfred Winston Yeo*
Australia	1008	Robert Bell	United Kingdom	1030	Peter Vowden
Canada	1009	Claude Gagne	Mexico	1031	Justine Regalado Pineda
Canada Canada	1010 1011	Benoit Gervais Andrew Pipe	Germany Korea,	1032 1033	Anil Batra Seung-Woon Rha

Country	Center	Principal Investigator	Country	Center	Principal Investigator
			Republic of		
Canada	1012	Robert John Petrella	Korea, Republic of	1034	Se-Joong Rim
Denmark	1014	Philip Toennsen	France	1035	Beatrice Le Maitre
Denmark	1015	Ronald Dahl	France	1036	Franck Paganelli
Argentina	1017	Veronica Irene Schoj	France	1037	Michel Pierre Galinier
Argentina	1018	Ana Maria Tambussi	Germany	1038	Stefan Andreas
United Kingdom	1019	Paul Dominic MacIntyre	Mexico	1039	Rodolfo Posadas
Czech Republic	1020	Iva Tomaskova	United Kingdom	1040	Philip Howard
Czech Republic	1021	Era Kralikova	Korea, Republic of	1041	Byung-Hee Oh
United Kingdom	1022	Bryan Williams	Korea, Republic of	1042	Ki-Hoon Han

*Recruited, but, did not enroll any subjects
SOURCE: Reproduced from Sponsor's protocol, p. 1

CLINICAL STUDY

Objective/Rationale:
The primary objective of the study was to compare 12 weeks of treatment with varenicline 1 mg BID to placebo for smoking cessation in subjects with cardiovascular disease and to evaluate continuous abstinence from smoking 40 weeks after the treatment period.

The safety objective was to gather safety data in subjects with cardiovascular disease for 12 weeks of treatment with varenicline 1 mg BID or placebo followed by a 40 week non-treatment follow-up period.

Overall Design:
This was a randomized, double-blind, placebo-controlled, multicenter study designed to assess the efficacy and safety of varenicline 1 mg BID in comparison to placebo for smoking cessation in subjects with stable cardiovascular disease. Subjects were randomized in a 1:1 ratio to receive either varenicline (1 week titration followed by 11 weeks of 1 mg BID dosing) or placebo. The study consisted of a 12-week treatment period that was followed by a 40-week non-treatment period. Subjects received smoking cessation counseling throughout the study.

Study Duration: Total study duration was 52 weeks which included a 12-week treatment period followed by a 40-week non-treatment period.

Study Population: Planned enrollment was approximately 700 subjects randomized 1:1 to receive either varenicline or placebo.

To be eligible, subjects were required to meet the following criteria:

Inclusion Criteria:

- Male or female cigarette smokers, between the ages of 35 and 75 years, inclusive, who were motivated to stop smoking
- Smoked an average of at least 10 cigarettes per day during the past year and during the month prior to the Screening visit
- Stable, documented cardiovascular disease other than hypertension diagnosed >2 months prior to the Screening visit. Examples 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.
- For female subjects, surgical sterilization or at least 2 years postmenopausal, or using medically acceptable contraception
- Able to be outpatients and be assessed in a clinic setting
- One subject per household

Exclusion Criteria:

- Serious quit attempt in the past 3 months but failed
- Currently suffering with depression, or diagnosed with depression or treated with an anti-depressant for depression within prior 12 months
- Past or present history of psychosis, anxiety disorder, panic disorder, or bipolar disorder
- Moderate or severe chronic obstructive pulmonary disease (COPD) or previous hospitalization for COPD
- NYHA Class III or IV congestive heart failure
- Unstable cardiovascular disease or cardiovascular events in the past 2 months.
    - Examples included coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), severe or unstable angina, serious (life threatening) arrhythmia, and clinically significant cardiac conduction abnormalities (>10 AV block)
- Uncontrolled hypertension or systolic BP > 160 or diastolic BP > 95 at Screening or Baseline visit
- Clinically significant neurological deficits related to cerebrovascular or other diseases, for example, stroke
- Peripheral vascular disease (PVD) that resulted in amputation or where the ankle-brachial index was ≤0.5
- Clinically significant endocrine disorders or gastrointestinal diseases that are uncontrolled, including uncontrolled hyperthyroidism, and active peptic ulcer disease
- Clinically significant hepatic or renal impairment or other clinically significant abnormal laboratory test values:

  - AST/ALT > 1.5 x ULN or total bilirubin > 1.1 x ULN
  - Severe abnormalities of renal function (estimated creatinine clearance by Cockcroft-Gault equation <30 mL/min)
- History of cancer (cured basal cell or squamous cell carcinoma of the skin were allowed)
- History of drug (except nicotine) or alcohol abuse or dependence within the past 12 months
- Positive urine drug screen for drugs of potential abuse and no medical indication for use of the drug
- Body mass index (BMI) < 15 or > 38. Weight < 45.5 kg (100 pounds)
- Previous enrollment in a study that included varenicline
- Treatment with another investigational drug within 30 days or 5 half-lives (whichever is longer) before the Baseline visit or within 30 days of completion of another study
- Prohibited concomitant medications
- Requirement for other medications during the study that might interfere with the evaluation of the study drug (for example, nicotine replacement therapy, bupropion, clonidine, nortriptyline, or other medications used for smoking cessation including over the counter herbal remedies)
- Use of a nicotine replacement product, bupropion, clonidine, or nortriptyline within the previous month
- Participation in a study with an experimental drug for smoking cessation within the past year
- Refusal to completely abstain from using non-cigarette tobacco products (including, for example, pipe tobacco, cigars, snuff, chewing tobacco, etc.) or marijuana during study participation
- Plans to donate blood or blood components while receiving study drug or within 1 month of the completion of the study treatment
- Inability and/or unlikely to comprehend and follow the study protocol, including subjects unable and/or unwilling to participate in the non-treatment follow-up
- Unlikely to commit to a year-long study
- Diabetics with an HbA1c > 9

Study Conduct

Screening
An initial screening visit was to take place 3–14 days prior to the Baseline/randomization visit. Screening procedures were to include informed consent, demography, medical history, smoking history, concomitant medications, the Fagerström Test for Nicotine Dependence, height, weight, temperature, blood pressure and heart rate, physical examination, ECG, blood samples for hematology, blood chemistry, cotinine, serum pregnancy test, HbA1c, urine dipstick (urine specimen may have been sent if the dipstick was positive), and drug screen.

Baseline/Randomization
Following screening, subjects were to attend a Baseline/randomization visit where subjects were randomized to varenicline or placebo. Randomization was to occur using a block randomization procedure with investigative site as the stratification variable. Investigators were to obtain subject randomization numbers and treatment group assignments through a central web-based or telephone call-in drug management system or through instruction from the sponsor. At Baseline/randomization, study drug was to be dispensed for the first week and dosing was to begin the following day.

Treatment Period
The 12-week treatment period began with the Baseline/randomization visit. During this period, subjects were to receive either varenicline or placebo beginning with a one week titration over the first week followed by 11 weeks of BID dosing. All subjects were to have set a target quit

date (TQD) to coincide with the Week 1 visit, which occurred at the end of the first week of the treatment phase. All subjects were to have been instructed to quit smoking at midnight preceding the day of the Week 1 visit. Subjects returned for weekly clinic visits during the treatment period.

Non-treatment follow-up
Blinded study medication was to be discontinued at the Week 12 visit and subjects' smoking status was to be followed through the non-treatment period to Week 52. During the non-treatment follow-up, subjects were to have returned for visits at Weeks 13, 16, 24, 32, 40, 48 and 52, and were to be contacted by phone at Weeks 14, 20, 28, 36 and 44.

Dosing, administration and supply of study drug
Tablets (blinded varenicline or placebo) were supplied in bottles containing sufficient tablets for one week. Varenicline was to be supplied as 0.5 mg tablets for the first week and 1.0 mg tablets for the remaining 11 weeks of the study treatment period. Medication had to be stored at all times at room temperature (15–30° C) at each site.

Study drug was to have been dispensed to subjects by qualified site study staff at each scheduled visit from the Baseline visit to the Week 11 visit. Subjects were to be given the Week 1 bottle (containing 0.5 mg varenicline or placebo tablets) at the Baseline visit. Thereafter, at each visit through Visit 11 subjects were to receive one bottle (containing 1 mg varenicline or placebo tablets). Subjects were also to be instructed to store the study drug at room temperature.

Study drug was to be administered according to the dosing chart below. As described, subjects were to receive the Week 1 bottle at the Baseline visit and treatment was to begin the day after. For the first 3 days of the Week 1 dosing period, subjects were to take 1 tablet per day in the morning. For the next 4 days, this was to increase to 2 tablets per day, 1 tablet in the morning and 1 tablet in the evening. On study Day 8, which was to coincide with the Week 1 visit, subjects were to increase their dose to 2 tablets in the morning from the current bottle and 1 tablet in the evening from the bottle dispensed at the Week 1 visit. At the Week 1 visit and subsequent visits, subjects were to have been given the respective Week 2–12 bottles and were to take 2 tablets daily, one in the morning and one in the evening. All subjects were to take the morning dose of study drug on the day of the Week 1 visit.

Treatment group	Study Days 1 to 3	Study Days 4 to 7	Study Day 8	Week 2 – Week 12
Blinded varenicline (or placebo)	One 0.5 mg tablet daily in the morning	One 0.5 mg table in the morning and one 0.5 mg tablet in the evening	Two 0.5 mg tablets in the morning and one 1.0 mg tablet in the evening (from bottle dispensed at Week 1 Visit)	One 1.0 mg tablet in the morning and one 1.0 mg tablet in the evening
.	Week 1 bottle			Week 2–12 bottles

Source: Sponsor's final protocol p. 18

Dosing was to occur with 240 ml (8 ounces) of water and it was recommended that subjects ate prior to dosing. There were to have been 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 completed. Subjects were to have been instructed not to discard any study drug bottles.

Smoking Cessation Counseling
All subjects were to receive up to 10 minutes of smoking cessation counseling in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines[3] or similar local guidelines, at each clinic visit and telephone contact starting with the Baseline visit.

Assessments and Procedures

The following efficacy and safety assessments and procedures were to have occurred throughout the study according to the schedule as outlined in the Time and Events table below.

Efficacy Assessments

- Nicotine Use Inventory – Efficacy data on smoking cessation was assessed using the Nicotine Use Inventory (NUI). The NUI was used to collect information on cigarette or other nicotine use during the study. The NUI was to be completed at all post-randomization clinical visits and telephone contacts except the TQD+3 telephone contact. The specific wording of the NUI questions may have varied according to the visit. (See Appendix).
- End-Expiratory Exhaled Carbon Monoxide (Exhaled CO) – To confirm the efficacy reported in the NUI, an end-expiratory exhaled carbon monoxide (exhaled CO) was to have been measured at each clinic visit. An exhaled CO ≤10 ppm was required to claim successful smoking cessation.
- Other – The number of cigarettes smoked per day was to be collected during the first 3 weeks of the study and recorded in the case report form (CRF).

Safety Assessments

- Physical Examination – Performed at Screening and at Weeks 12 and 52 visits or early termination visit before the end of Week 12 (ET_{12}) or Week 52 (ET_{52}).
- Body Weight, Height and Waist Circumference – Height measured at Baseline; Weight measured at Baseline, Weeks 1, 4, 8, 12, ET_{12}, 13, 24, 40 and 52 visits or ET_{52} visit; Waist circumference at Baseline, Weeks 4, 8, and 12.
- Blood Pressure and Heart Rate, and Temperature – Recorded at Screening, Baseline and Weeks 1, 4, 8, 12, ET_{12}, 13, 24, 40, 52, ET_{52}. All blood pressure measurements were to be taken in the dominant arm and initially recorded in both of the subject's arms unless a concomitant condition favored the use of a particular arm. The arm with the higher average systolic reading average was the dominant arm and was then to be used for blood pressure determinations throughout the study. Blood pressure and heart rate measurements were to be determined after the subject had been seated for 3 minutes and then repeated 2 minutes later. Two measurements were to be taken in each position and the two values were to be recorded in the case report form. In addition, blood pressures and heart rates should have

[3] 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.

been determined immediately upon and 60 seconds after standing at all clinic evaluations. Temperature was to have been measured at the Screening visit.

- ECG – Obtained at Screening, Week 12 and at the Week 52 visit or ET_{12} or ET_{52} visit. All electrocardiogram tracings were to have had interval measurements and interpretation completed by a central electrocardiogram reader, unless otherwise specified. The time of last dose of study medication, prior to the ECG was to be recorded at Week 12 or ET12 visit.
- Laboratory Testing – Blood safety tests listed in the table below (hematology and chemistry) were to have been performed at Screening (within 3–14 days prior to randomization), Week 12, and at the Week 52 visit or ET_{12}, ET_{52} visit.

Test Panel	Tests
Hematology	Hemoglobin, Hematocrit, RBC count, WBC count and differential, Platelet count
Chemistry	Total Protein, Albumin, Total bilirubin, AST, ALT, Alkaline Phosphatase, LDH, BUN, Creatinine, Glucose, Cholesterol, Triglycerides, Sodium, Potassium, Chloride, Bicarbonate, Calcium, Phosphorous

Source: Applicant's protocol p. 25

  - Urinalysis was to have been done by dipstick at the Screening visit (within 3–14 days prior to randomization) and if necessary, microscopy may have been performed by the central laboratory to confirm findings.
  - Urine drug screening was to have been done at the Screening visit (within 3–14 days prior to randomization) and may have been performed at other visits at the investigator's discretion.
    - Serum cotinine was to be measured at the Screening visit.
  - A serum pregnancy test (β-hCG) was to be done at the Screening visit (within 3–14 days prior to randomization) for women of child bearing potential. If IRB/EC or local laws required, an additional pregnancy test may have been done.
  - HbA1c was to be done at the Screening visit for all diabetic subjects. It was to be done at the Baseline visit for all other subjects. It was to have been repeated at the Week 12 and Week 52 visit or ET_{12}, ET_{52} visit for all subjects.
  - In addition, at the Baseline, Weeks 12 and 52 visits or ET_{12} or ET_{52} visit a lipid profile, and urine albumin/creatinine ratio was to have been collected.
  - Additional laboratory tests or more frequent testing may have been performed, as clinically indicated.

- Inflammatory Markers – C-Reactive Protein and serum fibrinogen were to be measured at the Baseline and Weeks 12 and 52 visits or ET12 or ET52 visit.
- Adverse Events – All observed or volunteered adverse events (serious and non-serious) regardless of treatment group or suspected causal relationship to the investigational product(s) were to have been recorded on the CRF from the time the subject had taken at least one dose of trial treatment through the last subject visit. Non-serious adverse events were reportable from the time the subject provided informed consent through and including 14 calendar days after the last administration of the investigational product. They were to be reported on the adverse event page(s) of the CRF. In addition, any adverse event the investigator determined to be study drug-related was to be collected through the Week 52 visit. SAEs were to have been reported through the Week 52 visit.

Assessments: Treatment Phase **Screening Visit - Week 12 Visit**

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 ET12a
Informed consentb	X														
Medical history	X														
Physical examination	X														X
Temperature, Height, Weight	X														
Heart Rate, Blood Pressure, Weight	X	X	X				X				X				X
Waist Measurement		X					X				X				X
End-expiratory exhaled Carbon Monoxide		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
Fagerström Test (FTND)	X														
Smoking Log Dispensed		X	X		X										
All adverse events		X	X		X	X	X	X	X	X	X	X	X	X	X
Dispense study drugs		Xc	Xc		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
Concomitant Medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X														X
Serum cotinine	X														
Blood chemistry; CBC with differential	X (fasting or non-fasting)														X (fasting)
C-Reactive Protein, lipid profile, fibrinogen		X													X
Genotyping Sampled		X													
HgbA1c	Xe	Xf													X
Serum pregnancy testg	X														
Urinalysis (dipstick)	X														
Urine albumin/creatinine ratio		X													X
Urine drug screenh	X														
Counseling (AHRQ guidelines)		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] at BL Visit, dispense the 0.5 mg titration bottle (or placebo to match); At Week 1-11 Visits, dispense 1mg BID bottles (or placebo to match)
[d] optional; separate consent form required [e] diabetic subjects only [f] all subjects except diabetics
[g] all females unless surgically sterilized or at least 2 years postmenopausal; If IRB/EC or local laws require, an additional pregnancy test may be done
[h] may be performed at other visits at investigator's discretion or similar local guidelines
AHRQ = Agency for Healthcare Research and Quality or similar local guidelines BL = Baseline ET = Early Termination

Week 13 Visit - Week 52 Visit (Non-treatment 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	ET52[a]
Clinic Visit	X		X		X		X		X		X	X	X
Phone Contact		X		X		X		X		X			
Heart Rate, Blood Pressure, Weight	X				X				X			X	X
Waist Measurement					X				X			X	X
Physical Examination												X	X
Electrocardiogram												X	X
Fasting blood chemistry; CBC with differential; C-Reactive Protein, lipid profile, fibrinogen, urine albumin/creatinine ratio												X	X
HgbA1c												X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
All adverse events	X	X											
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
End-expiratory exhaled Carbon Monoxide	X		X		X		X		X		X	X	X
Nicotine Use Inventory	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

[a] if ET is before the Week 52 visit

SAFETY CONSIDERATIONS

Concomitant Medications

*The episodic or chronic use of the following medications was **prohibited** during the study:*

- any investigational drug
- antidepressants used for the treatment of depression, including bupropion (Wellbutrin®), citalopram (Celexa®), fluoxetine (Prozac®), mirtazepine (Remeron®), nefazodone (Serzone®), paroxetine (Paxil®), sertraline (Zoloft®), trazodone, tricyclic antidepressants, MAO inhibitors, and venlafaxine (Effexor®)
- antipsychotic agents, including clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), risperidone (Risperdal®), and ziprasidone (Geodon®)
- benzodiazepines used for the treatment of anxiety, including alprazolam (Xanax®), diazepam (Valium®), and lorazepam (Ativan®)
- mood stabilizers used for the treatment of affective disorders, mania/depression or bipolar affective disorder, 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, glucocorticoids, and mineralocorticoids (inhaled steroid use was permitted)
- theophylline
- clonidine

Withdrawal and Discontinuation Criteria

Subjects could have been withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject did not return for a scheduled visit, every effort was to be made to contact the subject. In any circumstance, every effort should have been made to document subject outcome, if possible. The investigator was to inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

If the subject withdrew from the trial and also withdrew consent for disclosure of future information, no further evaluations should have been performed and no additional data should have been collected. The applicant indicated that it could retain and continue to use any data collected before such withdrawal of consent.

Relapse to smoking was not a basis for withdrawing a subject from the study. Subjects who relapsed to smoking were to be encouraged to make further quit attempts and to continue their participation in the protocol-specified visits and procedures.

Data Safety Monitoring Committee

An independent data safety monitoring committee (DSMC) was to assess unblinded safety data. The DSMC was to periodically review safety summaries throughout the study. The content of the safety summaries, the DSMC roles and responsibilities, and the general procedures, including communications, would be defined and documented in the data monitoring plan prior to the start of the study.

Cardiovascular Event Adjudication Committee

The following cardiovascular events were to be reviewed and adjudicated by an independent event committee to confirm the diagnosis of the events:

- nonfatal myocardial infarction
- any hospital admission for chest pain
- hospitalization for angina pectoris
- need for coronary revascularization
- resuscitated cardiac arrest
- hospitalization for congestive heart failure
- fatal, nonfatal stroke or transient ischemic attacks (TIA)
- any diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD
- death from any cause

These events were to be adjudicated using a standard events manual under blinded conditions. The safety data adjudicated by the event committee was to be summarized by treatment group.

STATISTICAL METHODS

The applicant described the following data analysis/statistical methods for the study:

> Efficacy Analysis
> The primary inference of this study was to evaluate the hypothesis that varenicline is superior to placebo for the 4-week Continuous Quit Rate (CQR) for Weeks 9 through 12. The primary endpoint of 4-week CQR for Weeks 9 through 12 was to be obtained through reports of cigarette or other nicotine use since the last study visit confirmed by measurement of end-expiratory exhaled CO ≤10 ppm. If any CO measurement at a particular timepoint was >10 ppm, the subject was considered a smoker at that timepoint.
>
> Furthermore, to address the primary objective of this study to compare between treatment groups for abstinence from smoking during the non-treatment follow-up period through Week 52, the following 2 key secondary endpoints were used:
> 1. The Continuous Abstinence (CA) rate from Week 9 through Week 52[4]
> 2. The Long-Term Quit Rate (LTQR) from Week 9 through Week 52[5]

[4] The proportion of subjects who maintained complete abstinence from cigarette smoking (not even a puff) and other tobacco use for Weeks 9 – 52. Abstinence was confirmed via expired CO at clinic visits.
[5] The proportion of subjects who have successfully quit during the treatment phase of the study and who have had no more than 6 days of smoking during the non-treatment phase of the study.

Other secondary efficacy endpoints to compare between treatment groups for abstinence from smoking during the non-treatment follow-up period through Week 52 included:

- CA rate from Week 9 through Week 24
- LTQR from Week 9 through Week 24
- 7-day point prevalence of smoking cessation at Weeks 12, 24, and 52
- 4-week point prevalence of smoking cessation at Week 52

REVIEWER COMMENT: Measures of abstinence, in this case, CA and LTQR measures are considered acceptable for the purposes of efficacy ascertainment. Measures of point prevalence and analyses of these measures on the other hand are of uncertain clinical benefit and meaningfulness, and are not reviewed or evaluated in making a determination of efficacy of this smoking cessation aid in this population.

These efficacy endpoints were to be based on subject self-report (NUI), confirmed by end-expiratory exhaled CO measurements at clinic visits.

To assess whether varenicline reduced the amount of smoking more than placebo during the first 3 weeks of the treatment period of the study, the number of cigarettes smoked daily were collected during this period using smoking diaries.

Baseline levels and changes from baseline over time in blood markers of inflammation (e.g., CRP and fibrinogen) were to be summarized.

Analysis of Primary and Secondary Endpoints

The primary analysis population (Modified Intent-to-Treat) is all subjects who took at least 1 dose of randomized study medication. Subjects who discontinued the study were assumed to be smokers from the timepoint of discontinuation through the end of the study. In calculating responder rates, subjects who discontinued the study were to be included in the denominator but not in the numerator as responders, regardless of their last smoking status evaluation.

In order to preserve the type I family-wise error rate of 0.05, a step-down procedure was to be used for the analysis of the primary and 2 key secondary endpoints. The hierarchy of comparisons was to be 1) the 4-week CQR for Weeks 9 through 12; 2) CA at Week 52; and 3) the LTQR through Week 52. Statistical significance was to be declared for each hypothesis in the ordered list until a p-value >0.05 was obtained, at which point the hypothesis would be declared to not be statistically significant.

All other statistical testing was to be 2-sided and use a 0.05 level of significance. Nominal p-values were to be reported for secondary analyses, as long as the primary endpoint was met, with no adjustments for the analysis of multiple secondary endpoints.

Sample Size Determination

It was anticipated that 700 subjects randomized to varenicline or placebo in a 1:1 ratio would provide at least 99% power to detect a difference in the primary endpoint between the varenicline and placebo groups, assuming a true placebo 4-week CQR of 0.18 and a varenicline response rate of at least 0.40 (odds ratio of at least 3.04). This sample size was also anticipated to provide at least 84% power to detect a difference in CA from Week 9 through Week 52 assuming a placebo response rate of 0.10 and a varenicline response rate of at least 0.18 (odds ratio of at least 2.00). It was assumed that the power to detect a treatment effect in LTQR at Week 52 was comparable to that for the CA through Week 52.

REVIEWER COMMENT: The applicant did not specify procedures for imputing missing data in the protocol. Methods for imputation of missing data were described in the Summary of Clinical Efficacy:

> *Nicotine Use Inventory Data*
> *In the case of a missed visit or visits during the 4-week period when the CQR was assessed (Weeks 9–12) in the CV [study], a subject was considered a responder if the subject had not smoked or used nicotine products 'since the last visit' or at the visit after the missing visit(s).*
>
> *For CA in the case of missed visit(s) during the nontreatment follow-up period from weeks 13 through 52/24, a subject was considered a responder if the subject met the following criterion: the subject responded that they have not smoked or used nicotine products 'since the last contact' at the visit after the missing visit(s).*
>
> *For the LTQR, if the number of days smoked was missing for a subject visit, the CA responder status of the subject at that visit determined the imputation. If the subject was a responder, the number of days was imputed as 0; if the subject was a non-responder, the number of days was imputed as 7. Therefore, a CA non-responder with a missing number of days smoked was also a LTQR non-responder.*
>
> *CO Data*
> *Missing CO was imputed as negative (i.e., not disqualifying the subject as a responder).*

REVIEWER COMMENT: Imputation of missing CO data as negative, that is, presuming that the subject has not smoked could bias efficacy ascertainment. In addition to corroborating self-report, the CO measurement is also thought to promote veracity of individual self-report. As such, the data were re-analyzed imputing missing CO data as positive and the results from these analyses are presented in Section 6.1.4., Analysis of Primary Endpoint(s) below.

> Interim Analysis
> With the exception of the Data Safety Monitoring Committee reviews of safety data, no interim analyses of the data were planned for this study.

REVIEWER COMMENT: The Applicant's study design overall is consistent with the Division's accepted guidelines on trial design and analytic approach for this indication. From the standpoint of efficacy ascertainment, a grace period of eight weeks, however, is not deemed necessary. Rather, a two-week grace period is considered reasonable to allow patients to be therapeutic on treatment. However, in the original NDA, the statistical reviewer analyzed the data with varying grace periods and found that the main conclusions were unchanged regardless of whether a shorter or longer grace period was used.

KEY PROTOCOL AMENDMENTS

The rationale and specific changes and locations were provided for Protocol Amendment # 4. The protocol as summarized in this section is a review of the protocol as submitted in this final protocol amendment. Previous amendments were made February 8, 2006, April 28, 2006, and January 22, 2007. According to the applicant, the January 2007 amendment, Amendment 3, was never implemented because an exclusion criterion from previous versions was

inadvertently admitted in the final version. Amendment 4 restored that exclusion criterion and carried forward the changes that were made in Amendment 3. Key changes included in that amendment, as described the applicant, were:

- Revisions to inclusion criteria to better define Coronary Artery Disease, Peripheral Vascular, and Cerebrovascular Disease and extend the inclusion criteria to allow a broader group of cardiovascular subjects beyond those with atherosclerotic cardiovascular disease.
- Revisions to exclusion criteria to clarify exclusions for psychiatric conditions, significant neurological deficits and the use of drugs of potential abuse and no medical indication for use of the drug. Deleted the exclusion for patients with pure coronary spasm, a group for whom the question of efficacy and safety is an important one and, therefore, a group that should not be excluded.
- Revisions to prohibited concomitant medications to clarify that it was the use to treat certain conditions, such as depression, rather than the drugs themselves that is prohibited.
- Clarification that the physical examination is to be performed at the Screening visit, not the Baseline visit.
- Required changes in safety information due to revision of AEM01 SOP, 27 Apr 06 (paternal exposure).

REVIEWER COMMENT: The above protocol changes were included in Amendment # 4 which corresponds to the final protocol submitted with this efficacy supplement submission. A protocol amendment was made on April 28, 2006, Amendment 2, and occurred after the initial subject was enrolled. Amendment 2 removed the restriction of a maximum of 24 months for the initial diagnosis of the subject's cardiovascular disease. Overall, these protocol amendments further defined the study population and the group of smokers with cardiovascular disease to whom the data can be extrapolated.

6.1.2 Demographics

Demographic information for the patients in Study A3051049 is described in the following text and detailed in the Demographic Characteristics Table below.

A total of 703 subjects were randomized to treatment with varenicline (N=353) or placebo (N=350). Patients were primarily male and white. Patients ranged in age from 34 to 76 years, with a mean age of 56 years. The study population overall was overweight with a mean body mass index (BMI) of 27.9 kg/m^2 (range: 17.0 to 42.5 kg/m^2).

Baseline characteristics were similar in general between the varenicline and placebo arms for most characteristics. However, the varenicline arm was slightly older and had a slightly lower BMI on average, though the subject with the highest BMI was in the varenicline arm. The placebo arm included fewer male subjects. However, if the gender imbalance biases efficacy results in any way, it is anticipated to bias results in favor of placebo and against varenicline, as women are considered to be more recalcitrant with respect to smoking cessation. Differences in baseline demographic characteristics are small and are not anticipated to materially affect interpretation of efficacy outcomes.

Baseline Demographic Characteristics

Table 4 Baseline Demographic Characteristics - A3051049

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 reviewer)

Smoking History

Review of smoking history data revealed similar baseline smoking history and characteristics in the two arms. The mean age at which subjects began smoking, the total number of years the subjects smoked, the number of cigarettes smoked per day, and the average number of cigarettes smoked per day over the past month were similar on average among the two groups. The placebo group had been smoking at this rate for less time than the varenicline group and in general had more quit attempts.

Table 5 Smoking History - A3051049

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

REVIEWER COMMENT: Differences in smoking history and characteristics at baseline were small and are not anticipated to materially affect interpretation of efficacy outcomes.

6.1.3 Subject Disposition

A total of 714 smokers were randomized (i.e., assigned to study treatment). Eleven (11) subjects were randomized, but not treated. The reasons for subjects being randomized, but not treated included: no longer willing to participate in the study (5 subjects), protocol violation (3 subjects), lost to follow-up (1 subject), and other (2 subjects). A total of 703 subjects were treated with at least 1 dose of study medication (353 varenicline, 350 placebo). A total of 85.6% varenicline and 82.6% placebo subjects completed the study. While there were 714 subjects randomized to treatment, those subjects who were randomized and not treated were not included in the efficacy or safety analyses. Thus, analysis populations consist of those 703 subjects who were assigned to treatment and received at least one dose of study medication. Datasets consist of safety data on these 703 subjects.

Subjects who permanently discontinued treatment due to an adverse event and also discontinued study are represented in the table. Other subjects discontinued treatment but remained in the study and are discussed in more detail in the Safety Review.

Table 6 Subject 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] Subject (b) (6) discontinued the study due to treatment-related malaise and treatment-unrelated emphysema and is only included in the related to study drug row.
SOURCE: A3051049 Full Clinical Study Report, p. 48.

REVIEWER COMMENT: The applicant did not perform further investigation to identify additional details on the reasons for subject discontinuation in cases where subjects were listed as discontinuing because of "lost to follow-up," "subject no longer willing to participate," and "other". Such an investigation could prove useful in determining whether discontinuations in these cases were, in fact, for an underlying safety reason or for reasons of lack of efficacy. From the information that is available, few subjects in either arm are discontinued from study for lack of efficacy.

6.1.4 Analysis of Primary Endpoint(s)

Nicotine Use Inventory
Efficacy data on smoking cessation was assessed using the Nicotine Use Inventory (NUI). The NUI was used to collect information on cigarette or other nicotine use during the study. The NUI was to be completed at all post-randomization clinical visits and telephone contacts except TQD+3 telephone contact. The specific wording of the NUI questions may have varied according to the visit. (See Appendix.)

End-Expiratory Exhaled Carbon Monoxide (Exhaled CO)
In order to confirm the efficacy reported in the NUI, an end-expiratory exhaled carbon monoxide (exhaled carbon monoxide [CO]) was to be measured at each clinic visit. If any CO measurement at a particular time point was >10 ppm, the subject was to be considered a smoker at that time point.

Primary efficacy endpoint: 4-week CQR Weeks 9–12

The primary endpoint of 4-week CQR for Weeks 9 through 12 was to be obtained through reports of cigarette or other nicotine use since the last study visit confirmed by measurement of end-expiratory exhaled CO ≤10 ppm. If any CO measurement at a particular timepoint was >10 ppm, the subject was considered a smoker at that timepoint.

A logistic regression model was fitted to the primary endpoint and included the main effects of treatment group and center as independent variables.

Results from the Primary Analysis of the Primary Endpoint

As noted, analysis populations for this study included only subjects who were randomized and received at least one dose of study medication. Efficacy results are provided for the Modified Intent-to-Treat population or All Subjects population. In the All Subjects population, defined as all subjects who took at least 1 dose of randomized study medication, the CO-confirmed 4-week CQR for the last 4 weeks (i.e., Weeks 9–12) of treatment was significantly higher for the varenicline treatment group (47%) than for the placebo group (14%) (p<0.0001).

For comparison, the 4-week CQR for the general population of smokers studied in the two original Phase 3 clinical trials involving the marketed dose of 1 mg BID and Zyban control was 44% in the varenicline treatment group for both studies as compared with 17% and 18% in the placebo group for the two studies.

An even higher quit rate was observed in the cardiovascular study, suggesting that this may represent a population even more motivated to quit than the general populations of smokers studied in Chantix clinical trials.

4-WEEK CQR WEEKS 9–12 – n (%)		
Varenicline (N=353)	**Placebo (N = 350)**	**p-value**
167 **(47)**	50 **(14)**	<0.0001

The applicant's results above were confirmed by the Statistics Reviewer, Dr. Katherine Meaker. Additionally, 3 subjects in the varenicline arm did not meet the protocol-specified definition of stable cardiovascular disease diagnosed 2 months prior to Screening. Dr. Meaker analyzed the efficacy data excluding these three subjects and the results were unchanged. Also, as mentioned, missing CO data was imputed by the applicant as negative. Dr. Meaker also analyzed the missing CO data, using the more conservative imputation strategy of designating missing CO data as positive, and considering the subject a non-responder, and found that imputing missing data in this fashion had no relevant impact.

The Statistics Reviewer also performed additional sensitivity analyses and the reader is referred to the Statistical Review by Dr. Katherine Meaker for findings from these analyses.

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary efficacy parameters in this trial that are measures of abstinence include the continuous abstinence rate and long-term quit rate measures and are the focus of this section of the review. Other secondary endpoints that the applicant included in this trial were point prevalence measures. Endpoints measuring point prevalence are of unclear clinical benefit and meaningfulness and are not being reviewed or evaluated in the evaluation of efficacy.

The two key secondary efficacy parameters of interest then are Continuous Abstinence (CA) Weeks 9 – 52 and the long-term quit rate (LTQR) Week 52. These secondary efficacy parameters are defined as follows:

CA Weeks 9 – 52	The proportion of subjects who maintained complete abstinence from cigarette smoking (not even a puff) and other tobacco use for Weeks 9 – 52. Abstinence was confirmed via expired CO at clinic visits.
LTQR Week 52	The proportion of subjects who have successfully quit during the treatment phase of the study and who have had no more than 6 days of smoking during the non-treatment phase of the study.

The differences between the varenicline and placebo groups were statistically significant for both the key secondary endpoints of CA Weeks 9 – 52 and LTQR Week 52.

Continuous Abstinence Rate

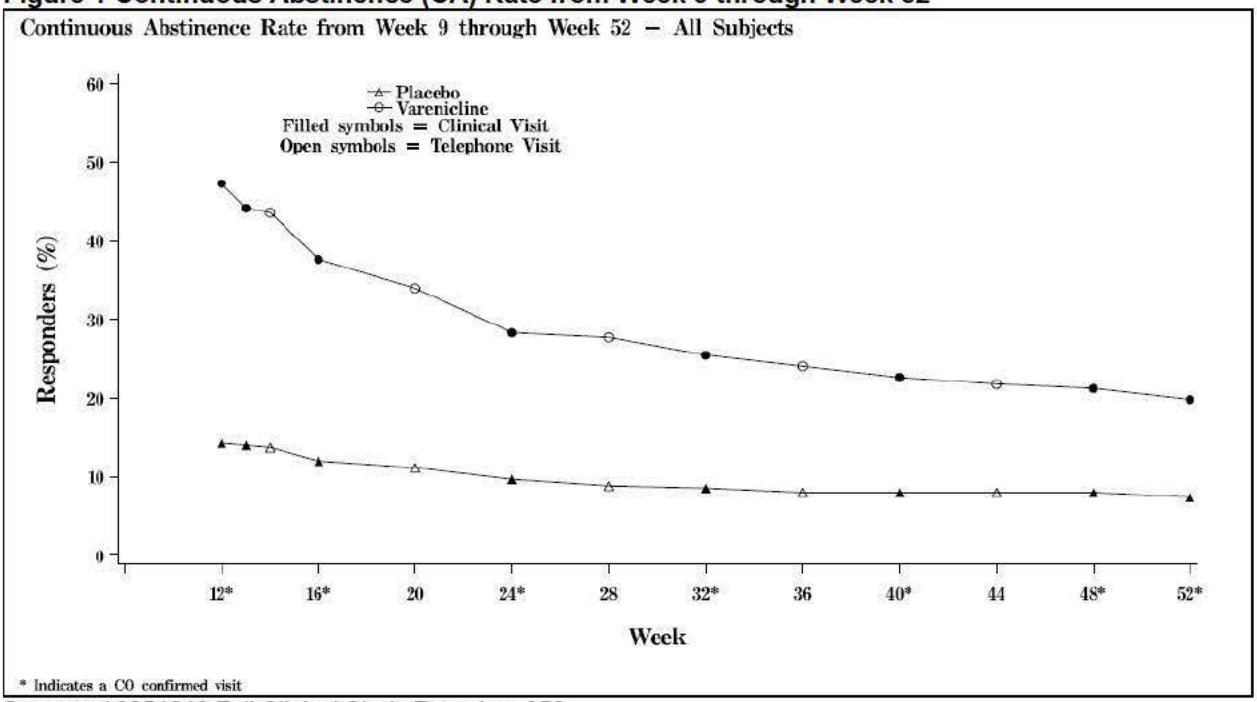
The continuous abstinence (CA) rate Weeks 9 – 52 was significantly higher in the varenicline group compared with the placebo group (19.83% and 7.43%; p<0.0001).

CA WEEKS 9 – 52 – n (%)		
Varenicline (N=353)	**Placebo (N = 350)**	**p-value**
70 **(20)**	26 **(7)**	<0.0001

As mentioned, 3 subjects in the varenicline arm did not meet the protocol-specified definition of stable cardiovascular disease diagnosed 2 months prior to Screening. Dr. Meaker analyzed the efficacy data excluding these three subjects and the results changed minimally. Without these 3 subjects, the rate in the varenicline arm is 19% compared with 20% when the subjects are included.

A graphical display of CA rate from Week 9 through Week 52 is also provided below.

Figure 1 Continuous Abstinence (CA) Rate from Week 9 through Week 52



SOURCE: A3051049 Full Clinical Study Report, p. 952.

Long-Term Quit Rate

The LTQR also was significantly higher for varenicline compared with placebo at Week 52 (22.7% vs. 9.7%, respectively, p<0.0001).

LTQR WEEK 52 – n (%)		
Varenicline (N=353)	**Placebo (N = 350)**	**p-value**
80 **(23)**	34 **(10)**	<0.0001

When Dr. Meaker performed this analysis excluding the three subjects who did not meet the protocol-specified definition of cardiovascular disease, the results changed slightly. Without these 3 subjects, the LTQR in the varenicline arm is 22% compared with 23% when the subjects are included.

> REVIEWER COMMENT: For these two secondary endpoints, only a few additional subjects are added by employing the less conservative LTQR definition, suggesting that varenicline's effectiveness is derived from promoting complete abstinence rather than an effect of preventing lapses from turning to relapses.

6.1.6 Other Endpoints

The applicant also evaluated 7-day point prevalence of abstinence at Weeks 12, 24 and 52 and the 4-day point prevalence of abstinence at Week 52. As discussed earlier, the clinical relevance of these measures is questionable and these measures are not being reviewed for the purposes of making a determination of efficacy.

6.1.7 Subpopulations

The applicant performed analyses of the primary endpoint for subgroups defined by age, Fagerstrom score, and average number of cigarettes smoked per day.

Table 7 Four-Week CQR Weeks 9 through 12 by Selected Baseline Characteristics

CO-confirmed 4-Week Continuous Quit Rate from Week 9 through 12 by selected Baseline Characteristics - All Subjects

		Varenicline	Placebco
Age (Years)			
<55	N	132	152
	Weeks 9-12: n (%)	54 (40.91)	19 (12.50)
	Odds Ratio (95% CI) vs. placebo	7.42 (3.76,14.63)	
	p-value vs. placebo	<0.0001	
55-65	N	159	145
	Weeks 9-12: n (%)	75 (47.17)	20 (13.79)
	Odds Ratio (95% CI) vs. placebo	6.64 (3.65,12.08)	
	p-value vs. placebo	<0.0001	
>65	N	62	53
	Weeks 9-12: n (%)	38 (61.29)	11 (20.75)
	Odds Ratio (95% CI) vs. placebo	**	
	p-value vs. placebo	**	
Fagerstrom Score			
0 - 3	N	58	56
	Weeks 9-12: n (%)	30 (51.72)	10 (17.86)
	Odds Ratio (95% CI) vs. placebo	9.91 (3.30,29.75)	
	p-value vs. placebo	<0.0001	
4 - 6	N	181	162
	Weeks 9-12: n (%)	84 (46.41)	24 (14.81)

n: The number of subjects who, at each visit from Week 9 through 12 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit (on the Nicotine Use Inventory) and who did not have CO > 10ppm at any of these visits.
Odds Ratios and p-values are obtained from a logistic regression model including the main effects of treatment and pooled center.
** Cannot be calculated due to sample size.

CO-confirmed 4-Week Continuous Quit Rate from Week 9 through 12 by selected Baseline Characteristics - All Subjects

		Varenicline	Placebo
4 - 6	Odds Ratio (95% CI) vs. placebo	**	
	p-value vs. placebo	**	
7 - 10	N	113	130
	Weeks 9-12: n (%)	53 (46.90)	16 (12.31)
	Odds Ratio (95% CI) vs. placebo	6.44 (3.32,12.48)	
	p-value vs. placebo	<0.0001	
Ave no. cigarettes/day, past month			
10 - <20	N	123	116
	Weeks 9-12: n (%)	65 (52.85)	22 (18.97)
	Odds Ratio (95% CI) vs. placebo	6.48 (3.33,12.60)	
	p-value vs. placebo	<0.0001	
20 - <30	N	154	143
	Weeks 9-12: n (%)	71 (46.10)	19 (13.29)
	Odds Ratio (95% CI) vs. placebo	7.25 (3.85,13.65)	
	p-value vs. placebo	<0.0001	
>= 30	N	76	91
	Weeks 9-12: n (%)	31 (40.79)	9 (9.89)
	Odds Ratio (95% CI) vs. placebo	**	
	p-value vs. placebo	**	

n: The number of subjects who, at each visit from Week 9 through 12 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit (on the Nicotine Use Inventory) and who did not have CO > 10ppm at any of these visits.
Odds Ratios and p-values are obtained from a logistic regression model including the main effects of treatment and pooled center.
** Cannot be calculated due to sample size.

SOURCE: A3051049 Full Clinical Study Report, p. 950 – 951.

The Continuous Quit Rate (CQR) appears to increase with age for both arms and increase with lower Fagerstrom scores and lower average number of cigarettes smoked. The increases in the CQR are much greater in the varenicline groups and in all subpopulations, the quit rates in the varenicline arm are considerable.

The Statistics Reviewer also performed additional subpopulation analyses and the reader is referred to the Statistical Review by Dr. Katherine Meaker for findings from these analyses.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This efficacy supplement seeks no new dosing recommendations. Chantix is currently marketed as tablets for twice daily oral administration (1 week titration followed by 11 weeks of 1 mg oral twice daily dosing). The objective of this current application is to revise the label to include information on the safety and efficacy of Chantix in subjects with stable cardiovascular disease using the same dosing regimen. The labeled dosing regimen was used in the cardiovascular disease study. Accordingly, this section is not applicable to this application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The A3051049 study, which is the sole study in support of these labeling changes, demonstrated efficacy of Chantix over the last four weeks of the 12-week treatment phase and during the 40-week follow-up non-treatment phase.

6.1.10 Additional Efficacy Issues/Analyses

Protocol Violations

The following categories of protocol deviations were identified from the protocol deviation dataset:

- Age greater than 75 years
- Age less than 35 years
- ALT (SGPT) greater than 1.5 x ULN
- AST (SGOT) greater than 1.5 x ULN
- Body Mass Index at screening greater than 38
- Diastolic BP greater than 95 mmHg at screening or baseline
- Evidence or history of clinically significant allergic reactions to drugs
- History of cancer
- *No Clinically significant cardiovascular disease history at least 2 months prior to Screening visit*
- *Period of abstinence greater than 3 months in the past year*
- *Post-Treatment use of smoking cessation drug*
- *Post-Treatment use of Varenicline*
- *Prohibited medication used during study*
- Subjects who are diabetic and HbA1c >9
- Subjects with a Positive, QNS and SNS urine drug screen at screening visit
- Systolic BP greater than 160 mmHg at screening or baseline
- Total Bilirubin greater than 1.1 x ULN
- *Use of Investigational study drug from other protocol*
- Weight at screening less than 45.5 kg

Categories of protocol deviations that could impact interpretation of efficacy results include:

1. No Clinically significant cardiovascular disease history at least 2 months prior to Screening visit
2. Period of abstinence greater than 3 months in the past year
3. Post-Treatment use of smoking cessation drug
4. Post-Treatment use of Varenicline
5. Prohibited medication used during study
6. Use of Investigational study drug from other protocol

The other categories of protocol deviations are anticipated to impact interpretation of safety results.

The following table summarizes the protocol deviations by treatment arm that could potentially impact interpretation of efficacy results.

Protocol Deviations – n (%)	**Varenicline (N=353)**	**Placebo (N= 350)**
Any protocol deviation anticipated to impact efficacy results interpretation	87 (25)	91 (26)
No Clinically significant cardiovascular disease history	3 (1)	0

Protocol Deviations – n (%)	Varenicline (N=353)	Placebo (N= 350)
at least 2 months prior to Screening visit		
Period of abstinence > 3 months in the past year	15 (4)	18 (5)
Post-Treatment use of smoking cessation drug	5 (1)	10 (3)
Post-Treatment use of Varenicline	20 (6)	17 (5)
Prohibited medication used during study	57 (16)	59 (17)
Use of Investigational study drug from other protocol	1 (<1)	2 (1)

REVIEWER COMMENT: The majority of protocol deviations pertained to use of prohibited medication during study. Depending on the type(s) of medications used, this could impact interpretation of efficacy and/or safety results. Concomitant medications used by subjects in this study were examined to determine whether these included use of other smoking cessation aids during the active phase of study, specifically nicotine products and buproprion, regardless of the indication. Using these search criteria, 15 subjects on placebo compared with 5 on varenicline were found to have been using a smoking cessation aid during 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. Overall the protocol deviations were comparable across treatment arms, with small differences between treatment arms that are not anticipated to materially impact analysis of efficacy findings. In general these small differences are anticipated to bias the results, if at all, in favor of placebo.

7 Review of Safety

Safety Summary

For this Review of Safety, safety data from the following sources were reviewed:

1. Study A3051049 Clinical Trial Data
2. An Integrated Summary of Safety comprising data from Phase 1–4 placebo-controlled trials in the Chantix Clinical Trials Database
3. Postmarketing surveillance data summarized in Section 8

Based on this safety review, the overall safety profile in smokers with stable cardiovascular disease was found to be qualitatively similar to that seen in the general population of smokers. However, while nonfatal cardiovascular events were rare overall in smokers with stable cardiovascular disease, they occurred with greater frequency in the varenicline arm compared with the placebo arm. These events included myocardial infarction, need for coronary revascularization, and new diagnosis of peripheral vascular disease or admission for a procedure for the treatment of peripheral vascular disease.

There were three myocardial infarction events associated with fatal outcomes. Two occurred in placebo-treated patients and one occurred in a varenicline-treated subject.

7.1 Methods

Safety data from Study A3051049, the cardiovascular disease (CVD) study, were reviewed to evaluate the safety of Chantix in this population of smokers with cardiovascular disease. The Integrated Summary of Safety was used to supplement these data and allow for comparisons between the CVD population and the general populations of smokers in Chantix clinical trials.

For the general population of smokers, the safety profile for Chantix is considered to be fairly well-established. The safety profile for the general population was characterized largely from the review of premarketing safety data in the original 2005 Chantix NDA. These premarketing safety data derived from studies that were generally restricted to smokers with no clinically significant or unstable disease. For that reason, this review of safety was directed at comparing and contrasting the safety findings from the CVD study, which is the basis for this efficacy supplement, with that of the safety experience of the subjects in the premarketing safety database without cardiovascular disease to assess potential drug-disease interactions in smokers with cardiovascular disease.

Since approval of Chantix in 2006, based on the 2005 NDA, additional postmarketing trials with varenicline have been completed, expanding the Chantix clinical trial database. Thus, safety comparisons can be made between the CVD study population and the populations in the other completed clinical trials in this expanded Chantix safety database. This review of safety compared and contrasted safety findings from the CVD study and the expanded database in the assessment of potential drug-disease interactions in smokers with CVD.

Additionally, the expanded database allows for a reassessment of the overall safety experience of Chantix. With larger numbers of subjects in this expanded database, safety issues that might not have been evident in the somewhat smaller premarketing database, might be identifiable among this larger group of subjects included in the expanded database. This safety review included a review of the expanded database to assess for potential novel safety findings in the larger database.

Based on knowledge of the major adverse effects associated with varenicline, there are several specific adverse events of interest associated with use of varenicline. The current product label for varenicine contains boxed warnings regarding risk of serious neuropsychiatric events with varenicline treatment. There are additional warnings about angioedema and hypersensitivity reactions, serious skin reactions, accidental injury, and nausea. In reviewing the safety data for this efficacy supplement, emphasis was also placed on determining if a relationship exists between occurrence of these events and varenicline exposure in smokers with cardiovascular disease as well as in subjects in the expanded clinical trial database.

Safety information on subjects in the expanded Chantix clinical trial database derives from the Integrated Summary of Safety, or ISS, report. The ISS supports three efficacy supplements that were submitted simultaneously by the applicant and contain both safety and efficacy data for review, namely supplements 019, 020, and 021. The supplements were reviewed by two reviewers: the current reviewer, who reviewed this CVD supplement, supplement 019, and Dr. Pamela Horn, who reviewed supplement 020, which addresses use of Chantix in a population with COPD and supplement 021, with information on a flexible quit date approach to smoking cessation with Chantix. In the same manner, 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 this review of the CVD supplement (S-019), the portions reviewed by Dr. Horn are excerpted and presented in the relevant sections of this review and so indicated.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study A3051049 is the sole trial conducted and included in this submission in support of safety. In an effort to ensure comprehensive evaluation of the safety experience in this population and other populations of smokers exposed to Chantix in clinical trials, an Integrated Summary of Safety (ISS) report was also reviewed as part of this efficacy supplement review.

The ISS report summarizes safety data from completed Chantix clinical trials that had a completed study report on or prior to December 2, 2010, except as noted previously, Study A3051035, the Phase 3 maintenance study that was not included because of its unique design.

Studies included in the ISS were used to compare and contrast findings among the different populations of smokers and to aggregate safety data across all studied. The safety database includes 16 Phase 1 placebo-controlled trials and five cohorts of Phase 2–4 studies. The five cohorts included the 2005 Pooled Studies cohort (reference cohort), the 2010 Pooled Studies cohort, the CV[6] (or CVD) Study cohort (subjects reviewed in this efficacy supplement), the COPD study cohort, and the Flexible Quit Date Study cohort. The studies comprising the ISS are described in more detail in Section 5.1, Tables of Studies/Clinical Trials.

7.1.2 Categorization of Adverse Events

7.1.2.1 Study A3051049 – Cardiovascular Disease study

For Study A3051049, Adverse Events (AEs) were encoded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0.

For Study A3051049, AEs were categorized based on when they occurred in relationship to the treatment phase of the study. That is, adverse events were described as occurring during the following three time periods:

1. pre-treatment phase – prior to first dose of study
2. treatment phase – first dose of study drug through 28 days following the last dose
3. posttreatment phase – end of the treatment phase through study completion

7.1.2.2 Integrated Summary of Safety

For the studies included in the Integrated Summary of Safety report, all AEs were re-coded using MedDRA Version 13.1, from the original version of MedDRA in effect at the time each individual study was conducted. Tabulations of adverse events in the ISS include only treatment-emergent adverse events, defined as events that began on or after the first day of study treatment (or, if present before baseline, had increased in severity during treatment) and within 30 days after the last dose of study drug.

The applicant provided summaries in tabular form of all-causality, treatment-emergent AEs and of events considered treatment-related by the investigators or sponsor. AEs were summarized

[6] Note that CV and CVD are used interchangeably throughout the review.

by SOC. Additional tables presented adverse events by Preferred Term (PT) grouped by SOC and, in some cases, by High Level Group Term (HLGT) and High Level Term (HLT) also, with incidence and severity. In summaries by severity, subjects were counted only once at the greatest severity experienced. Adverse events for which severity was missing were classified as severe, unless the subject experienced another occurrence of the same event for which a severity was recorded. In this case, the reported severity was summarized. Missing baseline intensities were imputed as mild. Intensities were defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

SOURCE: ISS Report p. 32.

The applicant's approach to assigning a severity classification when data were missing is considered conservative.

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

7.1.3.1 Study A3051049 – Cardiovascular disease study

Study A3051049 was the single trial included in the submission in support of the proposed labeling revisions and, therefore, pooling is not applicable to this single study.

7.1.3.2 Integrated Summary of Safety

For the Integrated Summary of Safety, as noted previously, data were pooled across the Phase 1 trials and across the Phase 2–4 trials (except Study A3051035, the Phase 3 maintenance study, which was not included in the ISS because of its unique design) separately to estimate and compare incidence. Data from 16 Phase 1 trials were pooled and a single cohort comprising these studies was used for the analysis of these data. For the Phase 2–4 studies, there were five cohorts included in the analysis; data were pooled in two of these cohorts. The two pooled cohorts included:

1. The reference cohort including completed, placebo-controlled Phase 2–3 studies reported in the 2005 NDA and referred to as the *2005 Pooled Studies cohort* throughout the ISS.
2. A cohort including all completed placebo-controlled Phase 2–4 studies as of the December 2, 2010 cut-off date (accordingly, the 2005 Pooled Studies cohort is inclusive). Throughout the ISS, this cohort is referred to as the *2010 Pooled Studies cohort*.

Again, the remaining three cohorts defined for the Phase 2–4 studies were the three individual Phase 4 studies which individually form the basis for efficacy supplements S-019 (the supplement under review in this efficacy and safety review), S-020, and S-021. All are included in the 2010 Pooled Studies cohort, but, also analyzed separately to enable comparisons between the Phase 4 studies under review and data from the pooled studies.

Additional detail about the pooled cohorts is provided in Section 5.3, Discussion of Individual Studies/Clinical Trials.

7.2 Adequacy of Safety Assessments

Study A3051049
A total of 353 smokers in the cardiovascular disease study were exposed to at least one dose of Chantix. Safety assessments are considered acceptable for the purposes of safety evaluation in the cardiovascular disease population evaluated in Study A3051049. Standard safety measures have been used in this study and timing of assessments was reasonable; a detailed account of timing of assessments is provided in Section 7.2.4, Routine Clinical Testing.

ISS population
A total of 4483 smokers received at least one dose of Chantix across all completed studies (aside from Study A3051035; see Section 5.3) in the Chantix clinical trial database through the December 2, 2010 cutoff date used for the Integrated Summary of Safety (ISS). The ISS provides data and analyses related to adverse events. Other safety assessments, i.e., laboratory data, vital signs, ECG are not included. Safety data provided in the ISS are considered adequate to allow for a safety assessment based on adverse events across and within the data from pooled and individual studies.

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

7.2.1.1 Exposure

7.2.1.1.1 Exposure in Study A3051049 Subjects
A total of 703 subjects with stable cardiovascular disease participated in this clinical trial designed to assess the safety and efficacy of Chantix in the CVD population. A total of 353 subjects received at least one dose of Chantix. In this study, Chantix (1 week titration followed by 11 weeks of 1 mg oral twice daily dosing) or placebo was administered daily for 12 weeks and, consequently, duration of exposure is determined by number of days on treatment.

The following table summarizes the cumulative exposure to Chantix and placebo for the subjects who participated in study A3051049.

Table 8 Duration of Exposure - A3051049

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

SOURCE: A3051049 Study Report, p. 53

As illustrated by the table, in both arms, the majority of subjects received study drug from between 61 to 90 days. Subjects in this study were intended to receive study drug for 84 days. Of note, although subjects were encouraged to schedule clinic visits on the same day of each week (every 7 days), the applicant indicated that some subjects were not able to comply with this schedule and delays in clinic visits resulted in prolonged treatment periods, accounting for durations of treatment beyond the intended duration of treatment of 84 days. The majority of subjects in both arms were in the duration category containing the intended treatment duration. That is, most fell within the 61 – 90 day category which contains the 84-day intended treatment duration. The number of subjects was similar between the two arms for all categories and for median duration of exposure. Taken together, this allows for evaluation of safety among comparable groups with respect to exposure and exposure at intended durations.

7.2.1.1.2 Exposure in Integrated Summary of Safety Populations

In the Phase 1 studies, which were generally studies of short duration, most varenicline-treated subjects received less than 14 days of treatment and many received only a single day of treatment.

Treatment duration and exposure for all treated subjects in completed Phase 2–4 Studies are summarized in the following table.

Table 9 Treatment Duration and Exposure - Phase 2-4 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

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, i.e., >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 (Table and Legend): Applicant's ISS p. 34.

Again, subjects in the Phase 2–4 studies by and large were intended to receive study drug for 84 days. As was described above for Study A3051049, although subjects were encouraged to schedule clinic visits on the same day of each week (every 7 days) in all studies, the applicant noted that some subjects were not able to comply with this schedule and delays in clinic visits resulted in prolonged treatment periods. This delay accounts in part for durations of treatment beyond the intended duration of treatment of 84 days. Additionally, the high end of the ranges for the 2 pooled cohorts (413 varenicline, 379 placebo) represent subjects from the A3051037 study, the long-term study where subjects were treated for 52 weeks vs. the standard 12 weeks of treatment.

Once again, across the pooled cohorts and individual studies, the majority of subjects in both treatment and placebo arms fell within the duration category containing the typical intended duration of treatment, that is, 84 days. Furthermore, for varenicline and placebo arms, the number of subjects was similar across the arms for all treatment duration categories and for median duration. Taken together, this all allows for evaluation of safety among comparable groups with respect to exposure and exposure at intended durations.

7.2.1.2 Demographics

7.2.1.2.1 Demographic Characteristics in the A3051049 (CVD) Study

Demographic and Other Baseline Characteristics for the subjects in the cardiovascular disease study are summarized in the table below.

Table 10 Demographic Characteristics - A3051049 Study

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

The treatment arms of the CVD study population were broadly similar in terms of race and weight. There were more women in the varenicline arm than the placebo arm. One might think that the risk of cardiovascular events would therefore be lower in the varenicline arm, but it should be noted that all the enrolled patients had pre-existing cardiovascular disease. Moreover, cigarette smoking has been associated with higher relative risk of MI and higher CHD mortality among women than men and the absolute increase in risk from smoking is similar for men and women. Regarding age, the varenicline arm had fewer patients in the <55 age category than the placebo arm and had slightly more subjects over the age of 65. However, overall, these differences are unlikely to affect the interpretation of the results.

7.2.1.2.2 Demographic Characteristics in the Integrated Summary of Safety Populations

Demographic and Other Baseline Characteristics for the subjects in the Phase 1 studies in the ISS populations are summarized in the table below.

Demographic Characteristics – Completed Placebo-Controlled Phase 1 Studies

Table 11 Demographic Characteristics - Phase 1 Studies

Total Number of Subjects	All Subjects N=731	Varenicline <2mg N=282	Varenicline 2mg N=249	Varenicline >2mg N=154	Varenicline +Other[a] N=105	Other Drug[b] N=142	Placebo N=322
	number (%) of subjects						
Gender							
Male	489 (66.9)	187 (66.3)	154 (61.8)	105 (68.2)	73 (69.5)	104 (73.2)	214 (66.5)
Female	242 (33.1)	95 (33.7)	95 (38.2)	49 (31.8)	32 (30.5)	38 (26.8)	108 (33..5)
Age (years):							
<18	99 (13.5)	79 (28.0)	14 (5.6)	0 (0)	0 (0)	0 (0)	20 (6.2)
18-44	475 (65.0)	143 (50.7)	169 (67.9)	132 (85.7)	74 (70.5)	109 (76.8)	243 (75.5)
45-64	83 (11.4)	12 (4.3)	44 (17.7)	22 (14.3)	31 (29.5)	33 (23.2)	41 (12.7)
≥65	74 (10.1)	48 (17.0)	22 (8.8)	0 (0)	0 (0)	0 (0)	18 (5.6)
Mean±SD	34.6±16.3	33.5±19.9	36.8±15.0	34.5±8.8	37.5±9.7	35.8±10.0	34.1±13.8
Range	12-85	12-85	13-80	19-55	18-55	18-55	12-80
Race							
White	472 (64.6)	170 (60.3)	148 (59.4)	75 (48.7)	68 (64.8)	87 (61.3)	192 (59.6)
Black	151 (20.7)	58 (20.6)	73 (29.3)	66 (42.9)	29 (27.6)	35 (24.6)	85 (26.4)
Asian	44 (6.0)	26 (9.2)	20 (8.0)	3 (1.9)	0 (0)	3 (2.1)	18 (5.6)
Other	64 (8.8)	28 (9.9)	8 (3.2)	10 (6.5)	8 (7.6)	17 (12.0)	27 (8.4)
Weight (kg)							
Mean±SD	72.0±12.2	69.0±12.6	73.9±11.5	75.5±10.5	74.6±10.9	74.5±11.0	73.4±12.0
Height (cm)							
Mean±SD	171.4±9.4	169.5±9.7	171.5±9.1	172.3±9.0	172.7.2±8.2	173.2±8.4	172.2±9.4
BMI (kg/m^2)							
Mean±SD	24.5±(3.5)	23.9±3.5	25.1±3.4	25.5±3.3	25.0±3.1	24.8±3.1	24.7±3.5

Protocols included: 305-001, A3051005, A3051009, A3051012-IR, A3051013-IR, A3051014, A3051027, A3051029, A3051031, A3051032, A3051033, A3051034, A3051039, A3051041, A3051070, A3051106
Var = varenicline; Pbo = placebo.
a Other drugs include digoxin, warfarin, NRT patch, Zyban, metformin; varenicline dosed at 1 mg BID.
b Other drugs include digoxin, warfarin, NRT patch, Zyban, metformin, amphetamine.
Note: A single subject is counted only once in any given treatment group, but may be counted in multiple treatment groups.
Doses in Phase 1 studies are total daily doses. Percentages may not add to 100% due to rounding.
SOURCE (Table and Legend): Applicant's ISS p. 37.

Demographic and Other Baseline Characteristics for the subjects in the Phase 2–4 studies in the ISS populations are summarized in the table below.

Demographic Characteristics – Completed Placebo-Controlled Phase 2–4 Studies

Table 12 Demographic Characteristics - 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

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
Var = varenicline; Pbo = placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease; SD =standard deviation; n/a = not applicable.
Percentages may not add to 100% due to rounding.
[a] CRFs for some studies listed racial categories in addition to White, Black, Asian, and Other. Subjects in those additional racial categories are included in this summary as "Other".
SOURCE (Table and Legend): Applicant's ISS p. 35–36.

Compared with the other cohorts evaluated in the ISS, meaning compared with the cohorts of Phase 1 and pooled cohorts of Phase 2–4 studies, the CVD cohort had fewer women and the highest BMIs on average. The CVD cohort was also older on average than the other cohorts, except for the COPD cohort. These dissimilarities between the CVD and the other cohorts are likely representative of a higher burden of cardiovascular disease risk factors (in addition to smoking) anticipated in a population of subjects with cardiovascular disease.

7.2.1.3 Cardiovascular Medical History

7.2.1.3.1 Cardiovascular Medical History in the A3051049 (CVD) Study

Information on selected cardiovascular medical history for the subjects in the CVD study is provided in the table below.

Table 13 Cardiovascular Medical History - CVD Study

System Organ Class Selected MedDRA PT	Varenicline (N=353)		Placebo (N=350)	
	Past	Present	Past	Present
	n (%)	n (%)	n (%)	n (%)
Cardiac Disorders	220 (62)	108 (31)	228 (65)	101 (29)
Angina pectoris	114 (32)	74 (21)	97 (28)	71 (20)
Cardiac failure congestive	3 (<1)	13 (4)	5 (1)	9 (3)
Myocardial infarction	155 (44)	6 (2)	171 (49)	12 (3)
Nervous System Disorders	38 (11)	28 (8)	47 (13)	19 (5)
Cerebrovascular Accident	16 (5)	0	24 (7)	0
Transient Ischemic Attack	20 (6)	0	21 (6)	0
Vascular Disorders	25 (7)	217 (62)	26 (7)	222 (63)
Aortic aneurysm	0	0	1 (<1)	1 (<1)
Hypertension	14 (4)	181 (51)	12 (3)	185 (53)
Peripheral Vascular Disorder	9 (3)	73 (21)	13 (4)	79 (23)

SOURCE: Reproduced from Full Clinical Study Report, A3051049, p. 51

Three subjects on varenicline did not have diagnoses meeting the protocol-specified definition of cardiovascular disease. One subject had no history of cardiovascular disease (Subject 10351018). Two subjects had no history of coronary artery, peripheral vascular or cerebrovascular disease, but had a history arrhythmia or conduction disturbances including atrial fibrillation (Subject (b) (6)) and atrioventricular block and ventricular arrhythmia (Subject (b) (6)). These three subjects were considered when interpreting the safety findings from this study. Although from the demographic findings, the varenicline arm represented a slightly older population of subjects, and there is increased cardiovascular risk with advancing

age, this arm also included three subjects who did not have underlying protocol-specified cardiovascular disease predisposing them to recurrent events.

The most commonly reported selected cardiovascular medical history disorders (reported in >100 subjects in any treatment group) included hypertension (14 varenicline and 12 placebo, past and 181 varenicline and 185 placebo, present), myocardial infarction (155 varenicline and 171 placebo, past and 6 varenicline and 12 placebo, present), and angina pectoris (114 varenicline and 97 placebo, past and 74 varenicline and 71 placebo, present). There are subjects with "present" diagnoses of myocardial infarction in spite of the eligibility criterion that subjects be diagnosed up to 2 months prior to Screening. According to Pfizer, this occurred because "eligibility required a diagnosis more than 2 months prior to the screening visit, however the disease recorded in the cardiovascular medical history could be considered resolved by the investigator (past) or considered on-going by the investigator (present). There was no requirement that all cardiovascular disease history was resolved (meaning coded past) at the time of screening and randomization into the trial, as long as the diagnosis preceded the screening visit by more than two months." Thus, although, one would anticipate that given the study design, all subjects at baseline who had an MI would be considered status post MI, this is the rationale provided for the designation "present" for certain subjects with MI.

7.2.1.3.2 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 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, the applicant provided data on risk factors for cardiovascular disease other than smoking (a risk factor which all subjects in the smoking cessation trials have and which 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.

Subjects with a past or present medical history meeting any of the following criteria were considered to have an additional cardiovascular disease risk factor.

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[7])

[7] 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

- 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 findings for the Phase 2–4 studies are presented 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**
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.

REVIEWER COMMENT: Across the various pooled cohorts, the proportion of subjects with cardiovascular disease risk factors other than smoking is overall comparable between treatment arms. As history of stable cardiovascular disease was a required eligibility criterion for the CV study, all subjects were expected to have a CV risk factor present and do have at least one CV 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 50% in the placebo arm of this study having a CV risk factor. The reverse is true for the flexible quit date study where slightly more subjects in the placebo arm have CV risk factors.

For Chantix clinical trials conducted in the more general populations of 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 CV 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.

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.

7.2.1.4 Smoking History

7.2.1.4.1 Smoking History in the A3051049 (CVD) Study

Smoking history was similar between the two treatment arms as illustrated in the below.

Table 14 Smoking History - A3051049

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)

Clinical Study Report, A3051049, p. 52

7.2.1.4.2 Smoking History in the Integrated Summary of Safety Populations

The applicant provided smoking history data for the subjects in the Phase 2–4 studies in the ISS population. These studies enrolled subjects who smoked an average of ≥ 10 cigarettes per day over the last year and who had no period of abstinence greater than 3 months with the exception of A3051104 which enrolled subjects who used smokeless tobacco.

		2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
Total Number of Subjects		**Var 1983**	**Pbo 1209**	**Var 4270**	**Pbo 2674**	**Var 353**	**Pbo 350**	**Var 248**	**Pbo 251**	**Var 486**	**Pbo 165**
Smoking history		number (%) of subjects									
Total number years	mean	26.0	25.3	26.8	27.7	40.0	39.1	40.4	40.6	26.0	24.6
	range	1-59	0-61	1-67	0-64	5-63	12-60	11-67	18-64	2-57	2-59
	n	1982	1208	4269	2673	353	350	248	251	486	165
Average number cigarettes/day over past month	mean	22.2	22.3	22.6	22.5	22.2	22.9	25.3	23.6	21.3	21.4
	range	8-90	6-80	8-99	6-80	10-60	10-80	10-99	10-60	10-70	7-60
	n	1982	1208	4269	2673	353	350	248	251	486	165
Number lifetime quit attempts[a] (%)	None	17.6	24.1	33.0	39.0	14.2	13.7	17.3	20.3	32.7	36.4
	1	16.9	17.2	21.0	19.1	24.4	28.9	26.6	26.7	30.9	27.3
	2	15.5	14.8	12.6	11.5	21.2	12.0	12.1	9.6	13.4	14.5
	≥3	50.1	43.9	33.4	30.4	40.2	45.4	44.0	43.4	23.0	21.8

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, A3051115 (note Study A3051104, which enrolled smokeless tobacco users, is not included in this table)

Var = varenicline; Pbo = placebo; CV=cardiovascular; COPD=chronic obstructive pulmonary disease.
[a] any method
SOURCE (Table and Legend): Applicant's ISS p. 44.

Subjects in the cardiovascular disease study as well as those in the COPD study had greater total number of years smoking on average compared with the other cohorts which primarily include general populations of smokers (2005 Pooled Studies, 2010 Pooled Studies, Flex Quit Date study). The longer smoking history in the CV and COPD cohorts is consistent with these populations being older overall than the general populations of smokers and with age being a risk factor for these conditions. The prolonged smoking history in the CVD and COPD populations also aligns with current understanding of risk factors in these conditions, where smoking is implicated as a risk factor in these disease processes, i.e., development of disease with longer smoking exposure.

7.2.2 Explorations for Dose Response

In the A3051049 study, subjects received 1 mg twice daily of varenicline (after the 1 week titration) and thus no dose-response relationships with respect to safety could be explored.

7.2.3 Special Animal and/or In Vitro Testing

No studies involving animal and/or in vitro testing were conducted in support of this supplemental application.

7.2.4 Routine Clinical Testing

The safety assessments and timing of assessments for studies in subjects with cardiovascular disease are described below. The assessment chart for this study can be found in the Methods section of the efficacy section of the review, Section 6.1.16.1.1 Methods.

Safety Assessment	Schedule
Adverse Events – observed & volunteered	Non-serious AEs were reported from Informed Consent through 14 calendars after the last administration of study drug. SAEs were reported at any time during the study through the Follow-Up Visit or 28 days after the last dose of study drug, whichever was later. Any SAE occurring at any other time after completion of the study was promptly reported if a causal relationship to the study drug was suspected.
Clinical Laboratory Evaluations • Blood safety tests • Urinalysis • Urine drug screening • Pregnancy Test • HbA1c • Lipid profile and urine Alb/Cr ratio • Inflammatory Markers – CRP & fibrinogen	• Screening, Week 12 and Week 52 (or ET12, ET52) • Screening • Screening • Screening • Screening (diabetics) or Baseline, Wks 12 & 52 (or ET12 ET52) • Baseline, Week 12 and Week 52 (or ET12, ET52) • Baseline, Week 12 and Week 52 (or ET12, ET52)
Vital signs (BP, HR)	Screening, at Baseline, and at Weeks 1, 4, 8, 12, ET12, 13, 24, 40, 52, ET52
ECG	Screening, Week 12, and at the Week 52 visit or ET12 or ET52

Safety Assessment	Schedule
	visit
Physical Exam	Screening, Week 12 and Week 52 (or ET12, ET52)
Body Weight	Baseline and Week 1, 4, 8, 12, ET12, 13, 24, 40, and 52 visits (or ET52 visit)
Waist circumference	Baseline, Weeks 4, 8, and 12

7.2.5 Metabolic, Clearance, and Interaction Workup

Clinical pharmacology data for Chantix were submitted as part of the original Chantix NDA submission and reviewed at that time. See the Clinical Pharmacology section for a description of the findings as summarized in the current Chantix label.

7.3 Major Safety Results

Review of major safety results included a review of deaths, nonfatal serious adverse events, permanent treatment discontinuations, and significant adverse events.

7.3.1 Deaths

7.3.1.1 Deaths in the A3051049 Study

There were seven deaths reported in Study A3051049, two in the varenicline arm and five on placebo.

The following table provides a summary of the deaths that took place in the study. Note that *causality* in this table generated by the applicant refers to causality attributed by the investigator.

Table 15 Listing of Deaths - A3051049 Study

Treatment/Subject No.	Adverse Event (MedDRA Preferred Term)	Day of Death	Causality	Demographics
Varenicline				
(b) (6)	Myocardial infarction	239	Other illness	63 yo, W, male
(b) (6)	Pancreatic cancer	301	Other illness	76 yo, W, male
Placebo				
(b) (6)	Septic shock	116	Other	61 yo, W, male
(b) (6)	Diabetic coma, hypovolemia, pneumonia	36	Other illness	63 yo, W, male
(b) (6)	Acute myocardial infarction, cardiogenic shock, renal failure acute, and gastrointestinal hemorrhage	115	Other illness	73 yo, A, male
(b) (6)	Transitional cell carcinoma	361	Other illness	60 yo, A, male
(b) (6)	Acute myocardial infarction	162	Disease under study	51 yo, O, male

SOURCE: Clinical Study Report, A3051049, p. 65

Of the two varenicline cases with fatal outcome, the myocardial infarction event could be plausibly related to the drug, while, the pancreatic cancer AE seems unlikely to be related given the time course of exposure and outcome within the observation period for this study.

The subject on varenicline with myocardial infarction (ID# (b) (6)) was a 63-year-old male with a history of peripheral vascular disease, hypertension, and COPD who had received varenicline for 79 days during the treatment phase and died of an acute myocardial infarction on study day 239. Although this event occurred during the post-treatment phase, after this subject completed varenicline therapy per protocol, varenicline was later resumed shortly before the subject had a fatal outcome associated with myocardial infarction. The patient had first complained of left upper leg pain during his Week 32 visit, went to the ER about 3 days later because the pain had intensified, and was hospitalized. He was treated with warfarin, varenicline, enoxaparin, and IV heparin drip. Approximately 16 days before the event, the patient underwent left superficial femoral artery and proximal popliteal artery laser atherectomy with further angioplasty and stenting. He was discharged home 2 days later in stable condition on varenicline, which was started approximately ten days before the start of the event (he had been off study drug for about 5 months prior to resuming varenicline therapy). The patient died at home and autopsy was performed and the patient was determined to have had an acute coronary myocardial infarction and coronary artery disease.

> REVIEWER COMMENT: In the varenicline arm there was one death of cardiovascular disease etiology. There were two deaths in the placebo arm that were due to cardiovascular disease in two patients with a history of cardiac disease. The single subject in the varenicline arm had risk factors for cardiovascular disease, including

smoking history and peripheral vascular disease, the subject was post-op from PVD intervention, and the cardiovascular disease-related deaths that occurred in this study were less frequent in the varenicline arm. Despite these alternative explanations, a causal relationship between varenicline exposure and the event and/or interaction between the drug and concomitant meds (including anticoagulant therapy) can not be ruled out given that the patient was exposed to varenicline at the time of the event.

7.3.1.2 Deaths in the ISS population

Deaths in the ISS populations were reviewed by Dr. Pamela Horn. Dr. Horn's summary of the findings with respect to deaths in ISS population is excerpted below.

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 16: 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)[8]	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,

[8] Varenicline was restarted 10 days prior to the death.

				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[9] (denoted by 1049 as the first four digits in the patient ID) have been reviewed [this reviewer] 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. [Refer to the discussion of deaths for Trial A1059 and] See section 7.3.5 for further discussion of cardiovascular adverse events. The deaths from Trial A1054 (denoted by 1054 as the first four digits in the patient ID) have been reviewed [in Dr. Horn's review of Trial A1054]. 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 [the Mortality (Pooled Data) Table] below) and 7 deaths in the placebo group (out of 2892 treated as presented in [the Mortality (Pooled Data) Table] 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 17: Mortality (Pooled Data)

Treatment Group	Patients[10]	Deaths	Crude Mortality	Subject-Days Exposure[11]	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 [Generated by Dr. Horn] 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.

[9] Refers to Study A3051049
[10] Taken from Table 3 of ISS
[11] Taken from Table 3 of ISS

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 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. These findings are interpreted in conjunction with the other safety findings related to cardiovascular adverse events in section 7.3.5.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Nonfatal Serious Adverse Events – Study A3051049

Nonfatal serious adverse events have occurred in 21 (6%) of subjects treated with varenicline and 19 (5%) of subjects on placebo during the treatment phase and in 28 (8%) of subjects on varenicline and 20 (6%) of placebo-treated subjects during the post-treatment phase, according the applicant's analyses. As noted, the treatment phase included the period from the first dose of study drug through 28 days following the last dose.

Pfizer described the methodology used for calculating the nonfatal serious adverse events as follows: SAEs were categorized as "On Treatment or Within 28 Days of Last Treatment" or as "Prior to Treatment or Greater than 28 Days from Last Dose" by comparing the event onset date to the therapy start or stop date. In cases where therapy stop date was not stated, the SAEs were categorized as "On Treatment or Within 28 days of Last Treatment." Subjects were counted in only 1 of the categories, i.e., if a subject had an SAE while on treatment and another SAE >28 days after treatment, they were only counted for the SAE that occurred on treatment.

7.3.2.1.2 Cardiovascular Event Adjudication Committee

In this study, serious adverse events that were cardiovascular SAEs were also reviewed by an independent cardiovascular adjudication event committee. 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.

When study investigators submitted an event for review, they completed the following CV Event Notification Form.

Figure 2 CV Event Notification Form

CV EVENT NOTIFICATION FORM

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

Site ID ____ ____ ____ ____

Subject Initials ___ ___ ___ Subject ID ___ ___ ___ ___ ___ ___ ___ ___

Complete one form for each event Date of Event: __ __ - __ __ __ - __ __ __ __

A. Coronary Revascularization Procedure

❑ Coronary Artery Bypass Graft
❑ PTCA (including atherectomy and stent placement)
❑ Other Coronary Revascularization Procedure

specify: _____

B. Cerebrovascular Event

Type of event (check one)

❑ Non-fatal stroke
❑ Transient ischemic attack (TIA)

C. Peripheral Vascular Disease

Does the subject have a previous diagnosis of PVD?

❑ Yes Date of Diagnosis __ __- __ __ __-__ __ __ __
❑ No

D. ❑ Congestive Heart Failure	**E. ❑ Resuscitated Cardiac Arrest**
F. ❑ Non-Fatal Myocardial Infarction	**G. ❑ Hospitalized Angina**
H. ❑ Death – Cardiovascular	**I. ❑ Death – Other than Cardiovascular Death**

Subject Hospitalized?

❑ Yes	**❑ No**
Date Admitted: __ __ - __ __ __ - __ __ __ __	Date Treated: __ __ - __ __ __ - __ __ __ __
Hospital Name: _____	at Name: _____
Address: _____	Address: _____
_____	_____
Phone: _____	Phone: _____
Physician: _____	Physician: _____

SOURCE: Included in a Response to Information Request

In response to an Information Request, it has come to the attention of the applicant that at least four cases (2 in the varenicline and 2 in the placebo arm) that appeared to qualify for adjudication were not forwarded to the committee.

These subjects included:

- Subject # (b) (6) (varenicline) who was hospitalized for chest pain (the investigator considered the event to be part of a pre-existing medical condition).
- Subject # (b) (6) (varenicline) who had increased tiredness, was evaluated by a cardiologist, advised to have a revascularization procedure and underwent the procedure.
- Subject # (b) (6) (placebo) who had stent occlusion/In-stent re-stenosis and procedure for treatment of PVD.
- Subject # (b) (6) (placebo) who had coronary artery disease/worsening of coronary artery disease, need for revascularization. (This subject was already included in the adjudicated count of subjects with CV events since the subject had other adjudicated events).

The applicant notes that in light of these cases that were not forwarded to the committee, they are looking into their processes for sending events for adjudication and oversight of that process to identify if there are areas for improvement.

As this efficacy supplement supports labeling claims about use of Chantix in persons with cardiovascular disease, the emphasis of the discussion of nonfatal SAEs in this section was placed on cardiovascular events that were adjudicated by the committee.

7.3.2.1.3 Nonfatal SAEs Not Adjudicated by Committee

Notwithstanding the emphasis on adjudicated cardiovascular SAEs, all nonfatal SAE narratives submitted by the applicant were reviewed and a summary of each of the individual narratives can be found in the Appendix of this review. As noted above, most nonfatal SAEs occurred during the posttreatment phase. As a reminder, the active phase includes the time period from the start of treatment through 28 days after the last dose of study drug.

During the treatment or active phase of the study, nonfatal SAEs that occurred in subjects on varenicline and not meeting criteria for adjudication included: a tibia fracture that occurred in the setting of a motorcycle accident (ID# (b) (6)); anasarca and a cardiac arrhythmia (ID# (b) (6)); diabetes mellitus (ID# (b) (6)); testicular torsion (ID# (b) (6)); cervicobrachialgia (ID# (b) (6); complex partial seizures (ID# (b) (6)); cellulitis (ID# (b) (6); gingival bleeding, recession and periodontal destruction (ID# (b) (6)); and jaw cyst (ID# (b) (6)) and syncopal cough (ID: (b) (6). The accidental injury and complex partial seizures could potentially be drug-related, are described in currently labeling, occurred infrequently, and warrant no additional labeling changes. The subject with diabetes mellitus was newly diagnosed and causality was attributed to weight gain associated with smoking cessation. Finally, another subject had an arrhythmia. This was a single occurrence in a single subject during the active phase and while a causal relationship cannot be ruled out, labeling changes regarding this single event do not seem merited. The same can be said for the subject who experienced syncope.

For comparison, during the active phase of treatment, the placebo arm had the following non-adjudicated SAEs: COPD exacerbation in the setting of pneumonia (ID#: (b) (6)), ischemic foot ulcer (ID#: (b) (6) syncope (ID#: (b) (6)), in-stent arterial stenosis (ID# (b) (6),

anemia (ID# (b) (6)), diabetes mellitus and ketoacidosis (ID# (b) (6), circulatory collapse ((b) (6)), chest pain (ID# (b) (6), and inguinal hernia (ID# (b) (6)). A number of these events would appear to have a cardiovascular etiology. The subject with in-stent arterial stenosis, as mentioned above was a case that should have been sent to the adjudication committee, but, was not sent. The episode of syncope occurred in a subject after prolonged exposure to heat and consumption of alcohol; cardiac work-up was negative. The case of circulatory collapse was a subject who had an episode of loss of consciousness 2 days post angioplasty and was found on hospitalization to be hypotensive on Bblockers and diuretics; on a data clarification form, the investigator noted that the event was related to the patient walking home after anesthetic against medical advice. The applicant was queried about this case regarding whether this case was to be forwarded to the committee. The applicant responded that there is no mention of angioplasty in the case report form and therefore no documentation that an angioplasty had in fact occurred. Finally, another subject had chest pain and vomiting, but, was observed and managed in the ER and not hospitalized.

Nonfatal SAEs that occurred in the posttreatment phase in both treatment arms and were not forwarded to the adjudication committee were also reviewed. No consistent pattern was evident for noncardiac events (refer to the Appendix for additional details). Cardiac disorders and vascular disorders not adjudicated by the committee (because they did not meet criteria for review or were cases that the investigator failed to send to committee) were examined in more detail. In the varenicline arm these cases included: arteriospasm coronary (ID# (b) (6)), chest pain (ID# (b) (6), atrial fibrillation, mitral stenosis/regurgitation and atrial fibrillation and sick sinus syndrome, events on 3 separate occasions in a single subject (ID# (b) (6).

In the placebo arm during the nontreatment phase, non-adjudicated cardiac and cardiovascular disorders included: atrial fibrillation (ID# (b) (6), supraventricular tachycardia (ID# (b) (6)), atrial fibrillation (ID# (b) (6)), and femoral artery occlusion (ID# (b) (6)).

Subjects ID# (b) (6) and ID# (b) (6) in the varenicline arm and ID# (b) (6) in the placebo arm were supposed to have been forwarded to the committee, as described above. Review of event narratives, the CRF, and the adverse event dataset, indicate that an additional few cases (in both treatment arms) that met criteria for adjudication may also not have been forwarded to the committee.

7.3.2.1.4 Adjudicated Cardiovascular Events

The following table summarizes the findings from the adjudication committee.

Table 18 Summary of Cardiovascular Events - All Subjects

	Varenicline (N=353)		Placebo (N=350)	
	n	(%)	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	8 (2.3)	8 (2.3)	3 (0.9)	3 (0.9)
Hospitalization for angina pectoris	12 (3.4)	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)	3 (0.9)	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)

Subjects with multiple CV events of the same type are counted only once per each row.
Source: Applicants Full Clinical Study Report, A3050149, p. 61.

The adjudicated cardiovascular events in the table above are also summarized in the following table that includes brief narratives of the events[12]. The numbers of subjects in the above table and the narrative table below may differ slightly because subjects with multiple events of the same type are counted only once, whereas in the narrative table, each separate event is described. Also, if a subject had multiple CV events that were in the setting of a single episode, these were described as a single episode in the narratives. For example, a subject could have had a nonfatal MI and needed coronary revascularization for management of the MI; in this case, both would be described as part of the single episode though they may have been represented as two separate events in the above table. As noted, a table of nonfatal SAEs not adjudicated by the committee is provided in the Appendix. Deaths from any cause were adjudicated by the committee also and have already been discussed in Section 7.3.1, Deaths; thus, the discussion of deaths is not repeated in this section on nonfatal SAEs.

[12] Narratives were constructed from the SAE narratives, case report forms, adverse event dataset, CE adjudication dataset and responses to Information Requests.

Table 19 Nonfatal Adjudicated Cardiovascular Event Narratives

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
NONFATAL MYOCARDIAL INFARCTION			
Varenicline-Treated Subjects (N=353)			
(b) (6)	58 y/o M Varenicline USA	Non-Fatal Myocardial infarction; Hospitalized Angina; Percutaneous Revascularization	• Hospitalized with angina x 3 days Day 147 then NSTEMI diagnosis on Day 149. Numerous lesions on angiogram. Angioplasty on 2 days; 3 stents placed. • Post-treatment phase; Last day of treatment Day 85 • In addition to nonfatal MI, also adjudicated as hospitalization for angina pectoris, and need for coronary revascularization • PMH: MI, angina, HTN, coronary revascularization
(b) (6)	40 y/o M Varenicline USA	Non-Fatal Myocardial infarction; Percutaneous Revascularization	• Acute anterior wall MI Day 193 s/p PTCA/stent of LAD lesion. • Post-treatment phase; Last day of treatment Day 84. • In addition to nonfatal MI, also adjudicated as need for coronary revascularization; See also table of non-adjudicated events. Hospitalized angina not adjudicated. • PMH: angina, MI, coronary revascularization
(b) (6)	53 y/o M Varenicline Netherlands	Non-Fatal Myocardial Infarction	• On EKG at a planned visit, had subendocardial anteroseptal MI. Event Day 55. Had reported CP earlier during soccer training. Coronary angiography with subtotal trauma mid LAD. Determined to have progressive angina pectoris, elevated troponin and strong deviating ECG. Had angioplasty. • Med permanently discontinued due to AE on Day 57 • Stroke
(b) (6)	66 y/o M Varenicline Brazil	Non-Fatal myocardial infarction	• Inferior wall STEMI Day 56. 100% L marginal artery and 80% anterior descending artery lesion. L coronary stent was placed. • Medication temporarily interrupted due to event. • PMH: MI, HTN
(b) (6)	46 y/o M Varenicline Argentina	Non-Fatal Myocardial Infarction; Percutaneous Revascularization	• Acute inferior wall MI Day 296. Coronary angiography with 3VD. Proximal moderate stenosis RCA. Circumflex artery non-significant stenosis proximal region. A lateral branch of this artery significant lesion and considered culprit lesion. Moderate proximal lesion observed on left anterior artery. PTCA/stent of culprit lesion. • Post-treatment phase. Last day of treatment Day 84. • Also adjudicated as need for coronary revascularization. • PMH: MI, coronary revascularization, angina, HTN
(b) (6)	66 y/o M Varenicline United Kingdom	Non-Fatal Myocardial infarction	• Myocardial infarction Day 1 after 1st dose of varenicline. Trop 0.42mcg/L 6–7 days after event, and CK at 201 IU/L • Therapy permanently discontinued Day 8 – pt. was evaluated ~ 7 days after onset of

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
			chest pain, SOB. • PMH: MI
(b) (6)	57 y/o M Varenicline Germany	Non-Fatal Myocardial Infarction	• Acute MI Day 83 of study. Had PTCA/stent of 100% RIVA stenosis. Later echo with well recovered global LV fxn, movement disorder of the myocardial wall in the apex of the heart still visible. • Study drug permanently discontinued. • PMH: Stroke, angina
Placebo-treated subjects (N=350)			
(b) (6)	67 y/o M Placebo USA	Non-Fatal Myocardial Infarction	• Post-op from SBO surgery developed chest pain on Day 240 determined to be 2/2 myocardial ischemia and respiratory distress on Day 249 requiring intubation, and. Had been diagnosed with metastatic lung cancer post-therapy and later developed SBO on Day 240 secondary to adhesions. Had diagnostic laparoscopy/ex-lap. Later developed pneumonia on Day 249. • Post-treatment phase. Last day of treatment Day 85. • PMH: MI, angina, coronary revascularization, stroke, PVD, HTN
(b) (6)	63 y/o M Placebo Australia	Non-Fatal Myocardial Infarction Percutaneous Revascularization	• Acute inferior infarction MI Day 206 s/p stent x 2. • Post-treatment phase. Last day of treatment Day 85. • Also adjudicated as need for coronary revascularization • PMH: angina, coronary revascularization
(b) (6)	56 y/o M Placebo Germany	Non-Fatal Myocardial infarction	• NSTEMI Day 96 due to an in-stent re-stenosis of the RCA. PCI day 97. Echo with compensated reduced EF of 57%. • Within 28 day lag window; Last day of treatment Day 93. • PMH: MI, coronary revascularization
HOSPITALIZATION FOR ANGINA			
Varenicline-treated Patients (N=353)			
(b) (6)	56 y/o M Varenicline USA	Hospitalized Angina	• Angina on Day 104 s/p RCA stent. Had been off clopidogrel, and markedly elevated TSH. • Within 28 day lag window; Last day of treatment Day 84. • PMH: MI, angina, coronary revascularization, HTN
(b) (6)	52 y/o M Varenicline USA	Hospitalized Angina; Percutaneous Revascularization	• Hospital admission for angina Day 200. MI ruled out. (+) Pharmacological stress test. Had cardiac cath & 2 stents placed. • Post-treatment phase. Last day of treatment Day 71. • Also adjudicated as need for coronary revascularization. • PMH: MI, angina, coronary revascularization, HTN
(b) (6)	47 y/o F Varenicline	Hospitalized Angina	• Angina and angiography Day 227 (AE not assessed as SAE because underwent angiography as same day surgery).

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
			• Posttreatment phase. • PMH: angina, coronary revascularization
(b) (6)	62 y/o M Varenicline United Kingdom	Hospitalized Angina Hospitalization for CHF	• Hospitalized following episode of chest pain Day 192; Had ETT and was discharged. • Hospitalized with chest pain Day 195. Trop (-) x 2. Had angiography, with normal L main, LAD occluded in its mid segment; had stenosis at origin from left main. First septal filled reasonably well. Circumflex 2 stents were seen proximally and widely patent, though distal vessel was of significant smaller caliber than stents. RCA occluded and there was a degree of intra-coronary collateralization particularly in the left side. RCA graft patent was not demonstrated. • Event occurred during post-treatment phase. Last day of treatment Day 85. • Subject also had CHF event submitted and adjudicated as Hospitalization for Angina. • PMH: MI, angina, coronary revascularization, PVD, HTN
(b) (6)	61 y/o F Varenicline United Kingdom	Hospitalized Angina	• Chest pain meeting criteria for seriousness on 10/2/07; 10/15/07; 12/3/07; 2/9/08 on case report form; Procedure for 12/3/07 event was coronary angiogram with stent performed. • Event onset for chest pain events given as Day 131 and Day 261. • Medication was discontinued Day 21 due to nausea • PMH: angina, HTN
(b) (6)	58 y/o M Varenicline Germany	Hospitalized Angina	• Hospitalized for unstable angina on Day 125. Cath with (+) development in RCA after stenting. • Within 28 day lag window; Last day of treatment Day 98. • Completed treatment phase prior to event • PMH: angina, coronary revascularization, PVD, peripheral revascularization, HTN
(b) (6)	63 y/o M Varenicline Germany	Hospitalization for Angina Pectoris Percutaneous Revascularization	• Chest pain not relieved by glycerol trinitrate. Went to ER, had elevated CK-MB level 21 U/L (range ≤ 17). Coronary angiography 99% stenosis of circumflex. PTCA/stent. Proximal R. circumflex also dilated. Day 191. • Post-treatment phase. Last day of treatment Day 43. • Also adjudicated as need for coronary revascularization. • PMH: angina pectoris, hypertension, coronary artery disease and dyslipidemia
Placebo-treated Subjects (N=350)			
(b) (6)	61 y/o M Placebo USA	Hospitalized Angina	• Hospitalized for worsening angina Day 181 of the study. Cardiac enzymes (-) x 3 and cardiac cath with no flow limiting lesions. • Post-treatment phase. Last day of treatment Day 84. • PMH: MI, angina, HTN, myocardial infarction, coronary revascularization, PVD, , right CEA, stroke
(b) (6)	55 y/o M Placebo Brazil	Hospitalized Angina	• Unstable angina requiring hospitalization Day 148, medically managed. ECG w/o significant changes, CK-MB 9.12 ng/mL, troponin x 3 < 0.2 ng/dl. Cardiac "catheterism" showed arterial lesions with 4 previous grafts. It was decided for clinic treatment.

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
			• PMH: CABG, angina, HTN
(b) (6)	57 y/o M Placebo Australia	Hospitalized Angina	• Hospitalized for chest pain on Day 77. Troponin (-).Thallium scan performed as outpatient. • No action taken with study drug. • PMH: MI, angina, coronary revascularization
(b) (6)	46 y/o M Placebo Australia	Hospitalized Angina	• Hospitalized with left-sided chest pain on Day 119; angiogram without convincing evidence of ischemia. • Post-treatment; Last day of treatment Day 21. • PMH: MI, angina, coronary revascularization.
(b) (6)	53 y/o M Placebo Australia	Hospitalized Angina	• Hospitalized for "tightness in his throat" Day 110. After evaluation, determined to have non-cardiac chest pain. • Within 28 day lag window; Last day of treatment Day 83. • PMH: MI, A fib and/or flutter, AVR, HTN, TIA
(b) (6)	50 y/o M Placebo USA	Hospitalized Angina Coronary Artery Bypass Graft	• Developed worsening angina Day -2 prior to start of study drug. Had elective cardiac catheterization and later CABG. Study drug was started during hospitalization and held for procedures. • Event of angina occurred before start of study drug. • Also adjudicated as need for coronary revascularization. • PMH: MI, angina, coronary revascularization, HTN
(b) (6)	62 y/o F Placebo Germany	Hospitalized Angina	• ACS Day 48 of study treatment after non-serious accident earlier in the day. Pt. described as being nervous. Elevated CK-MB. Coronary angiography revealed degeneration of one bypass graft (Ramus diagonalis), thought likely to be present for a longer time prior to event. • Study treatment stopped temporarily. • PMH: angina, coronary revascularization, A fib and/or flutter
(b) (6)	65 y/o M Placebo Germany	Hospitalized Angina	• Chest pain not relieved by nitrates when seen by GP on Day 314. Transferred to hospital. Trop (-), ECG normal. Transferred to CP unit. Stress test and angina during test. Coronary angiography revealed no major change when compared to previous diagnostic examination in which a re-stenosis of RCA was treated with PTCA and stent insertion. Present angiography revealed one posterolateral branch of circumflex occluded but dilation of that small vessel was not a therapeutic option. It was decided to add nitrates to his medication. • Post-treatment phase. Last day of treatment Day 90. • PMH: MI, angina, coronary revascularization, HTN
NEED FOR CORONARY REVASCULARIZATION			
Varenicline-treated Patients (N=353)			

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
(b) (6)	68 y/o F Varenicline USA	Coronary Artery Bypass Graft	• Severe atherosclerotic CAD Day 98. Chest tightness and SOB starting 4 days before seeing MD, referred same day and had angiogram. Angiogram - circumflex 75% to 80% ostial stenosis; RCA 80% calcified ostial stenosis, mid LAD 40% stenosis. Had CABG 5 days post cath. Underwent CABG 5 days post cath. Course complicated by COPD exacerbation. Of note, on f/u, subject strongly maintains that she never had h/o CAD or COPD. Hospital D/C summary reports h/o CAD and COPD, but site has no documentation to validate. Because no documentation, PI has determined subject did not have h/o CAD and COPD. • Within 28 day lag window; Last day of treatment Day 85. • PMH: PVD, peripheral revascularization
(b) (6)	59 y/o M Varenicline Brazil	Percutaneous Revascularization	• Worsening angina Day 215, reporter notes diagnosed on cath. Had PTCA/stent. • Post-treatment phase. Last day of treatment Day 84. • PMH: MI, angina, ventricular arrhythmia, HTN
(b) (6)	60 y/o M Varenicline Czech Republic	Percutaneous Revascularization	• Right carotid artery stenosis on Day 143 of therapy. On CRF appears to be R carotid artery stenosis s/p R carotid endarterectomy; however adjudicated as need for coronary revascularization. • Post-treatment phase. Last day of treatment Day 84. • PMH: PVD, peripheral revascularization
Placebo-treated Subjects (N=350)			
(b) (6)	54 y/o M Placebo Argentina	Percutaneous Revascularization	• Acute coronary syndrome Day 233. Experienced worsening angina. Had spect showing transitory perfusion defect in low, front, & lateral area, so scheduled for angioplasty where had stent placed in proximal circumflex. • Post-treatment phase. Last day of treatment Day 78. • PMH: angina
NEW DIAGNOSIS OF PVD OR HOSPITALIZATION FOR TREATMENT OF PVD			
Varenicline-treated Patients (N=353)			
(b) (6)	65 y/o M Varenicline USA	Peripheral Vascular Disease – not a new diagnosis	• L external Iliac artery occlusion Day 287. Elective admission for angioplasty with stent placement. • Post-treatment phase. Last day of treatment Day 85. • PMH: angina, coronary revascularization, PVD, peripheral vascular disease, HTN
(b) (6)	63 y/o M Varenicline USA	Percutaneous revascularization Peripheral Vascular Disease	• Had worsening LLE PVD 5/29/07. Management involved LLE angiogram, cutting balloon and cryoballoon angioplasty • Left upper leg arterial occlusion. Sonogram, CT angiography, angiograms, oxygen, atherectomy, angioplasty, stenting on 11/24/07. Day 213. • Also had event of cardiovascular death sent to committee, adjudicated as CV death • Post-treatment phase. Last day of treatment Day 84.

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
			• PMH : MI, angina, coronary revascularization, Afib, PVD, peripheral revascularization, HTN
(b) (6)	59 y/o M Varenicline Netherlands	Peripheral Vascular Disease – not a new diagnosis	• Diagnosed with AAA without experiencing complaints. Day 205. Resection performed at subject's request approx 4 months later. Event onset Day 205. • Post-treatment phase. Last day of treatment Day 85. • PMH: MI, Afib, HTN
1 (b) (6)	54 y/o M Varenicline Brazil	Peripheral Vascular Disease – not a new diagnosis	• Peripheral ischemia, Critical L leg ischemia Day 245. Had distal femoral popliteal bypass surgery and iliac artery and femoral artery embolectomy left leg. • Procedural complication. Left distal fem-pop bypass occlusion Day 308 and hospitalized to treat the occlusion. Later underwent arterial embolectomy and later a distal femoral popliteal bypass on left leg. • Post-treatment phase. Last day of treatment Day 83. • PMH: MI, angina, coronary revascularization, PVD, HTN
(b) (6)	71 y/o M Varenicline USA	Peripheral Vascular Disease – new diagnosis	• Disabling claudication Day 219. Saw cardiologist and had peripheral arterial testing which revealed B/L arterial occlusive disease, moderate R, mild L. Diagnosed with PVD. Pt. referred and elective intervention scheduled ~ 2.5 months later and patient had angioplasty to R superficial femoral artery. It was reported that "typically procedures are not done unless the pt has disabling pain or is in danger of losing limb." Had been on nortriptyline for leg pain prior to the study, and restarted it thinking it might help with anxiety as his son was dying from cancer. • Post-treatment phase. Last day of treatment Day 84. • PMH: angina, coronary revascularization, HTN, 1st degree AV block/hemiblock
Placebo-treated Subjects (N=350)			
(b) (6)	56 y/o M Placebo Netherlands	Peripheral Vascular Disease – not a new diagnosis	• Right leg claudication Day 27. Had angioplasty. • Treatment Phase, no action taken with drug. Last day of study treatment Day 84 • PMH: PVD, CVA, HTN
(b) (6)	63 y/o M Placebo USA	Peripheral Vascular Disease – not a new diagnosis	• Severe R subclavian artery stenosis Day 163. Patient also been experiencing dyspnea on exertion and, given h/o silent MI, was admitted for elective catheterization and peripheral angiogram. Found to have chronic (pre-existing) occlusions of the RCA and 3rd obtuse marginal coronary branch. Medical management advised. Patient proceeded to peripheral angiogram and had angioplasty/stent of R subclavian artery. • Post-treatment phase. Last day of treatment Day 59. • PMH: MI, angina, PVD, peripheral revascularization, HTN
(b) (6)	59 y/o M Placebo Germany	Peripheral Vascular Disease – not a new diagnosis	• Worsening of PVD 5/15/07. Event onset day given as N/A. ad percutaneous transluminal angioplasty of R leg. Scheduled for and had later fem-pop bypass left leg. • CAD Day 251. Coronary angiography recommended to determine if worsening of CAD exists. On angiogram, two stenoses of the Ramus circumflex were seen and diagnosis of

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
			progression of CAD made. PTCA/stent performed. • Femoral artery occlusion Day 362, 11/25/07. Left femoral artery occlusion. Had embolectomy. • Post-treatment phase. Last day of treatment Day 85. • PMH: MI, angina, coronary revascularization, PVD, peripheral revascularization
NONFATAL STROKE OR TIA			
Varenicline-treated Patients (N=353)			
(b) (6)	67 y/o M Varenicline Denmark	Non-Fatal Stroke	• CVA Day 97. Hospitalized. Recovered with sequelae of weakening in strength on R side. • Within 28 day lag window; Last day of treatment Day 84. • PMH: CVA, coronary revascularization, atrial flutter, CHF, HTN
(b) (6)	58 y/o M Varenicline Germany	Non-Fatal Stroke	• CVA Day 4. Experienced dizziness & vertigo then slipped and fell. Next day contacted study site and referred to hospital where determined to have had stroke. Carotid U/S w/o evidence of stenosis but plaque. Plaque rupture and embolism considered but no definitive proof of this. • Medication permanently discontinued. Last day of treatment Day 5. • PMH: angina, Afib, coronary revascularization, HTN
(b) (6)	61 y/o M Varenicline USA	Transient Ischemic Attack (TIA)	• Hospitalized for TIA Day 209. • Post-treatment phase. Last day of treatment Day 84. • PMH: CVA, MI, angina, coronary revascularization, CHF, PVD, HTN
Placebo-treated Subjects (N=350)			
(b) (6)	61 y/o M Placebo Netherlands	Non-Fatal Stroke	• Hospitalized for CVA with left-sided hemiparesis Day 185. • Post-treatment phase. Last day of treatment Day 85. • PMH: MI, coronary revascularization, ventricular arrhythmia
HOSPITALIZATION FOR CHF			
Placebo-treated Subjects (N=350)			
(b) (6)	66 y/o M Placebo Denmark	Congestive Heart Failure	• Cardiac failure Day 93. Managed with diuresis. • Within 28 day lag window; Last day of treatment Day 84. • PMH: MI, coronary revascularization, HTN
(b) (6)	61 y/o M Placebo United Kingdom	Congestive Heart Failure	• Hospitalized for atrial fibrillation and CHF Day 8. • Blinded therapy permanently discontinued. • CHF Day 56. Blinded therapy already discontinued Day 8. • PMH: MI, angina, ischemic heart disease, Afib, coronary revascularization, HTN
Events Adjudicated as Not Meeting Criteria by Independent Committee *CV Event as Submitted to Committee in Italics*			
Varenicline-treated Patients (N=353)			

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
(b) (6)	40 y/o M Varenicline USA	Hospitalization for angina pectoris* *Hospitalization for angina pectoris*	• Hospitalized with angina, STEMI Day 193 s/p PTCA/stent LAD lesion. CPK 5001 u/l, CK-MB 329 ng/ml, and troponin I 308 mg/ml. See adjudicated MI table above.* • Post-treatment phase; Last day of treatment Day 84. • PMH: angina, MI, coronary revascularization
(b) (6)	59 y/o M Varenicline Brazil	Hospitalized Angina *Hospitalization for angina pectoris*	• Worsening angina Day 215, which reporter notes was diagnosed on "catheterism." Scheduled for and had angioplasty with stent. See above Need for coronary revascularization table. • Post-treatment phase. Last day of treatment Day 84. • PMH: MI, angina, ventricular arrhythmia, HTN
(b) (6)	53 y/o M Varenicline Canada	Nonfatal Myocardial infarction *Nonfatal MI*	• Admitted due to intermittent angina, MI diagnosed. Day 442. ECG & blood work done but, results were not available as of the time of the report(s). • Post-treatment phase. Last day of treatment Day 84. • PMH: coronary revascularization, HTN
(b) (6)	47 y/o M Varenicline United Kingdom	Hospitalized Angina *Hospitalization for Angina Pectoris*	• Hospitalized for chest pain Day 36 after visiting MD 4 days after had pain. ECG and blood tests (-), unchanged and Trop < 0.5mcg/L x 2. Discharged following day, reported to be pain free. • Treatment phase. No action taken with study drug. • PMH: ischemic heart disease, angina, coronary intervention and stenting, mild LV dysfunction
(b) (6)	70 y/o M Varenicline Czech Republic	Peripheral Vascular Disease – New diagnosis *New Diagnosis of Peripheral Vascular Disease (PVD) or Admission for a Procedure for the Treatment PVD*	• Hospitalized with R leg femoropopliteal thrombosis Day 72. Managed medically. Study medication continued in hospital until treatment phase completed. • No action taken with study drug. Last day of treatment Day 80. • PMH: MI
(b) (6)	61 y/o M Varenicline USA	Hospitalization for Congestive Heart Failure *Hospitalization for Congestive Heart Failure*	• Awoke with palpitations Day 113. Saw MD, sent to ER found to be in Afib with RVR, was hypotensive and in mild CHF. Cardioverted after BP lowered more with IV/PO metoprolol and remained in NSR. BNP: 1436 pg/mL thought to be related to Afib since echo with nml EF. Admitted for obs and anticoagulation. • Post-treatment phase. Last day of treatment Day 84. • PMH: PVD, peripheral revascularization, rheumatic mitral stenosis/regurg; HTN, pulm HTN

Subject ID	Demographics/ Treatment Arm	Investigator Term/Submission Term	Comment
(b) (6)	61 y/o M Varenicline USA	Peripheral Vascular Disease – not a new diagnosis *New Diagnosis of Peripheral Vascular Disease (PVD) or Admission for a Procedure for the Treatment PVD*	• Event not in SAE table or CRF.
(b) (6)	61 y/o M Varenicline USA	Hospitalized Angina *Hospitalization for Angina Pectoris*	• Developed severe angina, Day 209, on day of planned discharge for hospitalization for COPD with complicated hospital course. HR 140, BP 130s, placed on IV heparin and nitro drip. Catheterization was unchanged from '04 findings. SVG to diagonal was 100% occluded in past and remains so. Discharged the next day. See also Nonfatal Stroke / TIA table above. • Post-treatment phase. Last day of treatment Day 84. • PMH: COPD, CVA, MI, angina, coronary revascularization, CHF, PVD, HTN
Placebo-treated Subjects (n=350)			
(b) (6)	53 y/o M Placebo Canada	Transient Ischemic Attack (TIA) *Transient Ischemic Attack*	• Palpitations and numbness Day 331. Admitted to hospital with sx subject described as L arm numbness and palpitations. Normal ETT and ECG with NSR with no significant changes. Blood work normal except for increased WBC count. On routine Wk 52 visit, was not experiencing any of the symptoms. • Post-treatment phase. Last day of treatment Day 83. • PMH: MI, A fib and/or flutter, AVR, HTN, TIA
(b) (6)	66 y/o M Placebo United Kingdom	Hospitalized Angina *Hospitalization for angina pectoris*	• Hospitalized for chest pain Day 204. Unspecified investigations took place, which were all negative. • Post-treatment phase. Last day of treatment Day 63; medication had been previously discontinued for non-serious rash on torso. • PMH: MI, angina, coronary revascularization, PVD
Pre-Randomization			
(b) (6)	66 y/o F Pre-randomization Brazil (ultimately randomized to varenicline)	Non-fatal Myocardial Infarction *Nonfatal MI*	• Prinzmetal angina occurring before first dose of study drug. Cath (-) obstruction, only vasospasm. • Event occurred pre-randomization. • PMH: MII, angina, PVD

Table prepared by reviewer from SAE narratives, adjudicated cardiovascular events tables, case report forms, adverse event dataset, CE adjudication dataset and responses to Information Requests.
Subjects are listed under the terms adjudicated by committee; Investigator terms are the investigators diagnosis submitted to committee.

REVIEWER COMMENT: The preceding table summarizes the cardiovascular events occurring during study that were adjudicated by the Cardiovascular Events Adjudication Committee. On examination of these safety data, there is an apparent increased vulnerability to cardiovascular events in this study population of smokers with cardiovascular disease, in particular, for nonfatal myocardial infarction events.

The blinded adjudication committee reviewed events that occurred in both the active and posttreatment phases. The following table summarizes events that occurred during the treatment phase (including the 28-day window following the last dose).

	Varenicline N=353	**Placebo N=350**
Cardiovascular Event - n		
Nonfatal Myocardial Infarction	4	1
Hospitalization for Angina Pectoris	2	5
Need for Coronary Revascularization	1	1
New PVD Diagnosis or hosp for treatment of PVD	0	1
Cerebrovascular Accident	2	0
Hospitalization for CHF	0	2

During the treatment phase, cardiovascular events are again infrequent, however, with respect to nonfatal myocardial infarction and cerebrovascular accidents, there is an excess of events experienced in the varenicline arm. This excess of events, specifically for MI and CVA, is observed even though there were more events in the varenicline arm sent to committee that were not adjudicated as events as compared with placebo and although the varenicline arm included an additional 3 subjects with no protocol-specified diagnoses of cardiovascular disease. Notably, more subjects in the placebo arm were hospitalized for angina.

During the original Chantix NDA review, there was an indication of increased cardiovascular events and conduction disorders in patients treated with varenicline. However, the difference appeared to be explained by imbalances in time on treatment. As noted earlier, in the cardiovascular disease study, treatment exposure was similar in both arms of the study. Current Chantix labeling describes a potential increased risk of cardiovascular disease conditions observed in postmarketing, including myocardial infarction and stroke. This information was added recently in a label update. The label will be revised to include this new clinical trial data which suggests a small but increased risk of nonfatal myocardial infarction in association with varenicline treatment.

7.3.2.2 Nonfatal SAEs in the ISS population

Nonfatal SAEs in the ISS populations were reviewed by Dr. Pamela Horn. Dr. Horn's summary of the findings with respect to nonfatal SAEs in the ISS population is excerpted below.

> 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 20: 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 21: 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

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, [Dr. Horn] generated the following table summarizing the relevant HLTs.

Table 22: 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	25 (0.6)	12 (0.4)

arteriospasm coronary		
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. For further discussion of [cardiovascular-related AEs], see section 7.3.5.

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

Permanent treatment discontinuations are displayed in the following table. Over 80% of subjects in each treatment arm completed the 52-week study, but, not all of these subjects completed the course of treatment. A number of subjects discontinued treatment, but, did not discontinue participation in the study; they continued to attend in-person and telephone visits and continued with assessments per protocol. Because evaluation of treatment discontinuations provides an indication of the types of drug toxicities that make use of the treatment intolerable, the discussion here focuses on all treatment discontinuations due to adverse events. Thus these subjects include those who also discontinued from study as well.

Table 23 TEAEs Resulting in Permanent Treatment Discontinuation Reported in Any Subject in Any Treatment Group

SOC	Varenicline N=353		Placebo N=350		
PT	n	%	n	%	Totals
Gastrointestinal disorders	20	5.7	9	2.6	29
Nausea	10	2.8	3	0.9	13
Diarrhoea	3	0.8	1	0.3	4
Constipation	2	0.6	0	0	2
Gastrooesophageal reflux disease	2	0.6	0	0	2
Vomiting	2	0.6	2	0.6	4
Abdominal pain upper	1	0.3	0	0	1
Abdominal distension	0	0	1	0.3	1

SOC	Varenicline N=353		Placebo N=350		
PT	n	%	n	%	Totals
Dyspepsia	0	0	1	0.3	1
Stomatitis	0	0	1	0.3	1
Psychiatric disorders	12	3.4	4	1.1	16
Abnormal dreams	2	0.6	0	0	2
Depressed mood	2	0.6	0	0	2
Depression	2	0.6	0	0	2
Insomnia	2	0.6	1	0.3	3
Alcoholism	1	0.3	0	0	1
Confusional state	1	0.3	0	0	1
Nightmare	1	0.3	0	0	1
Restlessness	1	0.3	0	0	1
Anxiety	0	0	2	0.6	2
Mood altered	0	0	1	0.3	1
General disorders and administration site conditions	6	1.7	5	1.4	11
Chest pain	2	0.6	2	0.6	4
Fatigue	1	0.3	1	0.3	2
Feeling cold	1	0.3	0	0	1
Malaise	1	0.3	1	0.3	2
Sluggishness	1	0.3	0	0	1
Irritability	0	0	1	0.3	1
Nervous system disorders	7	2	4	1.1	11
Headache	3	0.8	1	0.3	4
Cerebrovascular accident	1	0.3	0	0	1
Dizziness	1	0.3	1	0.3	2
Dysgeusia	1	0.3	0	0	1
Tremor	1	0.3	0	0	1
Disturbance in attention	0	0	2	0.6	2
Cardiac disorders	6	1.7	4	1.1	10
Angina pectoris	2	0.6	0	0	2
Acute myocardial infarction	1	0.3	0	0	1
Arrhythmia	1	0.3	0	0	1
Cardiac failure	1	0.3	0	0	1
Myocardial infarction	1	0.3	0	0	1
Atrial fibrillation	0	0	1	0.3	1
Cardiac failure congestive	0	0	1	0.3	1
Cardiovascular disorder	0	0	1	0.3	1
Palpitations	0	0	1	0.3	1
Respiratory, thoracic and mediastinal disorders	3	0.8	1	0.3	4
Dyspnoea	2	0.6	0	0	2
Dry throat	1	0.3	0	0	1
Emphysema	0	0	1	0.3	1
Skin and subcutaneous tissue disorders	3	0.8	1	0.3	4

SOC	Varenicline N=353		Placebo N=350		
PT	n	%	n	%	Totals
Rash	2	0.6	1	0.3	3
Hyperhidrosis	1	0.3	0	0	1
Metabolism and nutrition disorders	2	0.6	0	0	2
Anorexia	1	0.3	0	0	1
Hypercholesterolaemia	1	0.3	0	0	1
Vascular disorders	2	0.6	0	0	2
Arteriosclerosis	1	0.3	0	0	1
Hypertension	1	0.3	0	0	1
Immune system disorders	1	0.3	0	0	1
Hypersensitivity	1	0.3	0	0	1
Musculoskeletal and connective tissue disorders	1	0.3	0	0	1
Back pain	1	0.3	0	0	1
Eye disorders	0	0	3	0.9	3
Vision blurred	0	0	2	0.6	2
Visual acuity reduced	0	0	1	0.3	1

Table generated by the reviewer from the discontinuations dataset.

The above table includes a listing of any permanent discontinuations in any treatment arm. The applicant also provided an analysis of treatment-emergent adverse events resulting in permanent discontinuations of study drug reported by ≥2 subjects in any treatment group.

Table 24 TEAEs Resulting in Permanent Treatment Discontinuation Reported by ≥2 Subjects in Any Treatment Group

System Organ Class AE Preferred Term[a]	CV Study	
	Varenicline N=353 n (%)	Placebo N=350 n (%)
Cardiac Disorders	**4 (1.1)**	**3 (0.9)**
Angina pectoris	2 (0.6)	0 (0)
Eye Disorders	**0 (0)**	**3 (0.9)**
Vision blurred	0 (0)	2 (0.6)
Gastrointestinal disorders	**14 (4.0)**	**5 (1.4)**
Constipation	2 (0.6)	0 (0)
Diarrhea	3 (0.8)	1 (0.3)
Nausea	10 (2.8)	3 (0.9)
Vomiting	2 (0.6)	2 (0.6)
Gastrooesophageal reflux disease	2 (0.6)	0 (0)
General disorders and administration site conditions	**5 (1.4)**	**5 (1.4)**
Chest pain	2 (0.6)	2 (0.6)
Irritability	0 (0)	1 (0.3)
Nervous system disorders	**7 (2.0)**	**4 (1.1)**
Headache	3 (0.8)	1 (0.3)
Disturbance in attention	0 (0)	2 (0.6)
Psychiatric disorders	**8 (2.3)**	**4 (1.1)**
Anxiety	0 (0)	2 (0.6)
Depressed mood	2 (0.6)	0 (0)
Depression	2 (0.6)	0 (0)
Insomnia	1 (0.3)	1 (0.3)
Respiratory, thoracic, mediastinal disorders	**3 (0.8)**	**1 (0.3)**
Dyspnoea	2 (0.6)	0 (0)
Skin and subcuataneous tissue disorders	**3 (0.8)**	**1 (0.3)**
Rash	2 (0.6)	1 (0.3)

Source: Submitted in Response to Information Request

REVIEWER COMMENT: In this study of smokers with stable cardiovascular disease, adverse events leading to treatment discontinuation are consistent with the known safety profile of varenicline, with a few notable exceptions. The subjects in this study on varenicline were more likely to discontinue due to adverse events of angina (n=2) and myocardial infarction (n=1) than subjects in the placebo arm. Similarly, adverse events of dyspnea were more common in the varenicline arm than placebo arm (n=2 vs. n=0). Adverse events of chest pain leading to treatment discontinuation were observed in the original NDA, while events of myocardial infarction and dyspnea have not been previously observed as adverse events that warranted treatment discontinuation. These new findings in the CVD population represent a departure from the established safety profile of Chantix in previously-studied populations.

Permanent treatment discontinuations in the ISS population

The applicant provided a summary of all adverse events that led to discontinuation of treatment in ≥ 1% of subjects in any treatment group by SOC in the ISS populations for the Phase 1

groups and Phase 2–4 groups. The tables generated by the applicant based on these analyses are provided below.

Phase 1 Studies

Table 25 Adverse Events Resulting in Permanent Discontinuation of Study Treatment (All Causality, > 1% in any Treatment Group) by SOC, Completed Placebo-Controlled Phase 1 Studies

Total Number of Subjects	Varenicline <2mg N=282	Varenicline 2mg N=249	Varenicline >2mg N=154	Varenicline +Other[a] N=105	Other Drug[b] N=142	Placebo N=322
SOC PT	number (%) of subjects					
Gastroinesinal Disorders	0 (0)	2 (0.8)	5 (3.2)	5 (4.8)	0 (0)	0 (0)
Nausea	0 (0)	1 (0.4)	1 (0.6)	3 (2.9)	0 (0)	0 (0)
Vomiting	0 (0)	2 (0.8)	5 (3.2)	2 (1.9)	0 (0)	0 (0)
Investigations	0 (0)	0 (0)	0 (0)	1 (1.0)	3 (2.1)	0 (0)
Alanine aminotransferase increased	0 (0)	0 (0)	0 (0)	1 (1.0)	2 (1.4)	0 (0)
Skin & subcutaneous skin disorders	0 (0)	0 (0)	0 (0)	6 (5.7)	3 (2.1)	0 (0)
Urticaria	0 (0)	0 (0)	0 (0)	2 (1.9)	3 (2.1)	0 (0)

Protocols included: 305-001, A3051005, A3051009, A3051012-IR, A3051013-IR, A3051014, A3051027, A3051029, A3051031, A3051032, A3051033, A3051034, A3051039, A3051041, A3051070, A3051106
Var = varenicline; Pbo = placebo.
[a] Other drugs include digoxin, warfarin, NRT patch, Zyban, metformin; varenicline dosed at 1 mg BID.
[b] Other drugs include digoxin, warfarin, NRT patch, Zyban, metformin, amphetamine.
Note: A single subject is counted only once in any given treatment group, but may be counted in multiple treatment groups.
Doses in Phase 1 studies are total daily doses. Percentages may not add to 100% due to rounding
SOURCE (Table and Legend): Applicant's ISS p. 76.

Phase 2–4 Studies

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)

	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 (%)
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 the Phase 1 studies, permanent discontinuations of treatment in association with varenicline were primarily for adverse events in the Gastrointestinal (GI) disorders system organ class (SOC). GI adverse events, particularly AEs of nausea, are well-known to be associated with varenicline and are already described in labeling. In the Phase 2–4 studies, adverse events in the GI SOC and Psychiatric disorders SOC emerged as AEs leading to permanent treatment discontinuations. As noted, GI adverse events, particularly AEs of nausea, are well-known to be associated with varenicline and are already described in labeling. Of the events in the psychiatric disorders SOC, insomnia is more common and is another labeled common adverse event. In the overall population, meaning the 2010 Pooled cohort, AEs of depressed mood and depression that led to treatment discontinuation were similar between the two arms.

7.3.4 Significant Adverse Events

The Chantix (varenicline) label carries the following safety warnings and precautions:

Boxed Warning	***Neuropsychiatric Symptoms and Suicidality*** 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. 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.
Warnings and Precautions	• ***Angioedema and Hypersensitivity Reactions*** – Clinical signs inc. swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). Infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. • ***Serious Skin Reactions*** – postmarketing reports of rare but serious skin reactions including SJS and erythema multiforme. • ***Accidental Injury*** – postmarketing reports of traffic accidents, near-miss accidents in traffic, or other accidental injuries. In some cases, patients reported somnolence, dizziness, LOC or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. • ***Nausea*** – most common adverse reaction. Generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months.

Because of the labeled safety warnings regarding serious neuropsychiatric events, angioedema and hypersensitivity, serious skin reactions, accidental injury, and nausea, special attention was placed on evaluating these potential risks in this new Chantix clinical trial population of smokers with cardiovascular disease. Adverse events reviewed in this section are also examined again in the following section, Section 7.3.5, Submission Specific Primary Safety Concerns using analyses of aggregate safety data from the Integrated Summary of Safety Report.

7.3.4.1 Neuropsychiatric Events

Again, the label carries a boxed warning regarding serious neuropsychiatric events. As such, safety data from this population were evaluated to determine the number and types of adverse neuropsychiatric events that occurred in the CVD population without regard to level of severity and regardless of whether the event met the regulatory definition of seriousness. The following table summarizes the overall neuropsychiatric adverse event profile of the population in this study.

Table 26 Treatment-Emergent Neuropsychiatric Events - A3051049

Treatment Emergent Neuropsychiatric Events -- n (%)

HLGT		Varenicline N = 353	Placebo N = 350
Anxiety Disorders and symptoms		**12 (3%)**	**16 (5%)**
	Anxiety	8 (2)	13 (4)
	GAD	0	1 (<1)
	Neurosis	1 (<1)	0
	Phobia	0	1 (<1)
	Stress	3 (1)	1 (<1)
Deliria (incl confusion)		**1 (<1)**	**0**
	Confusional State	1 (<1)	0
Depressed mood disorders and disturbances		**11 (3%)**	**8 (2%)**
	Depression	5 (1)	3 (1)
	Depressed mood	5 (1)	4 (1)
	Depressive symptom	0	1 (<1)
	Dysthymic disorder	1 (<1)	0
General system disorders NEC		**6 (2%)**	**9 (3%)**
	Irritability	6 (2%)	9 (3%)
Manic and bipolar mood disorders and disturbances		**1 (<1)**	**0**
	Bipolar disorder		
Mood disturbances and disturbances NEC		**9 (3%)**	**3 (1%)**
	Dysphoria	1 (<1)	0
	Mood swings	1 (<1)	1 (<1)
	Mood altered	1 (<1)	2 (1)

Emotional disorder	1 (<1)	0
Apathy	4 (1)	0
Listless	1 (<1)	0
Personality disorders and disturbances in behaviour	**0**	**1 (<1)**
Aggression	0	1 (<1)

REVIEWER COMMENT: As illustrated in the table, except for adverse events in the Mood Disturbances and Disturbances NEC HLGT that were seen somewhat more commonly among varenicline-treated subjects, neuropsychiatric events occurred at similar rates between the two arms and overall were slightly more common in the placebo arm.

Because of the concerns about serious neuropsychiatric events with varenicline that emerged in the setting of postmarketing surveillance, the applicant, after approval of the original NDA, has been required to conduct a postmarketing requirement (PMR) trial to better assess whether a relationship exists between use of varenicline and occurrence of neuropsychiatric events. The primary endpoint for this trial is a primary *safety* endpoint defined by a cluster of neuropsychiatric events that comprise what is being termed the neuropsychiatric adverse event endpoint. The neuropsychiatric 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

Safety data from the population with cardiovascular disease were reviewed for neuropsychiatric events that met criteria for the neuropsychiatric adverse event endpoint. The findings are presented in the table below:

Treatment-Emergent Neuropsychiatric Events meeting definition for PMR Study NPS AE endpoint	
Severe AEs of anxiety, depression, feeling abnormal, hostility	
PT	**Varenicline Placebo**
Anxiety	3

Depression			
Feeling abnormal			
Hostility			
Moderate or Severe AEs			
PT	**Varenicline**	**Placebo**	
Agitation			
Aggression		1	(moderate)
Delusions			
Hallucinations			
Homicidal Ideation			
Mania			
Panic			
Paranoia			
Psychosis			
Suicidal ideation, Suicidal behavior, Completed suicide			

Reviewer Comment: Notably, no varenicline-treated subjects had AEs that met the definition, and, in fact, only placebo-treated patients met the criteria for an adverse event in the neuropsychiatric endpoint. 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.

7.3.4.2 Angioedema and Hypersensitivity

The following table was generated by an ad-hoc search by the reviewer for terms related to angioedema and hypersensitivity.

Table 27 Angioedema and Hypersensitivity Events

	Varenicline n	Placebo n
Angioedema and urticaria		
Urticaria	1	0
Allergic conditions		
Allergic oedema	1	0
Hypersensitivity	2	1
Eye disorders NEC		
Eye swelling	0	1
Ocular infections, irritations and inflammations		
Eyelid oedema	0	1
Tongue conditions		
Swollen tongue	1	0

Angioedema and hypersensitivity reactions were infrequent overall, none met the regulatory definition for seriousness, and events were assessed as mild or moderate. They occurred with somewhat greater frequency in the varenicline arm than in the placebo arm. Warnings about these reactions already exist in the label. On review of the new data from this trial, where events were few and non-serious, new labeling about these events is not warranted.

7.3.4.3 Serious Skin Reactions

There was a single case of rash that was classified as a serious adverse event. This adverse event occurred in a subject in the varenicline arm long after varenicline treatment had ceased. The event is described in more detail in the SAE table in the Appendix (subject ID # (b) (6). Another subject, subject ID # (b) (6) was classified as having an SAE of hyperhydrosis during the active phase of treatment and similarly is described in more detail in the table of SAEs.

Serious skin reactions are already described in the label. Serious skin reactions described in the label did not occur in the CVD trial. Accordingly, findings from this trial do not warrant labeling revisions regarding serious skin reactions.

7.3.4.4 Accidental Injury

The following table was generated by an ad-hoc search by the reviewer for terms within relevant groupings of adverse events within the MedDRA hierarchy related accidental injury.

The table below summarizes the types of accidental injuries and seriousness of injuries that took place during the treatment phase of the study in the varenicline and placebo arms.

Table 28 Accidental Injury Adverse Events

	Varenicline (N=353)		Placebo (N=350)	
	n	Serious	n	Serious
Bone and joint injuries				
Ankle fracture	0	n/a	1	1
Foot fracture	0	n/a	1	2
Tibia fracture	1	1	0	n/a
Sternal fracture	1	2	0	n/a
Injuries NEC				
Whiplash injury	0	n/a	1	2
Animal scratch	1	2	0	n/a
Fall	0	n/a	1	2
Road traffic accident	1	1	0	n/a
Wound	0	n/a	2	2
Head injury	1	2	0	n/a
Tooth fracture	2	1	0	n/a
Skin laceration	1	2	2	2
Medication errors				
Overdose	0	n/a	1	2

Serious 1 = yes; 2 = no

Once again, injuries were rare in this study and appear to have occurred at similar rates in each of the two arms. Warnings about accidental injury are already included in the label and additional warnings are not warranted based on the findings of this trial.

7.3.5 Submission Specific Primary Safety Concerns

Submission Specific Primary Safety concerns for this review center around the labeled safety warnings for Chantix identified through postmarketing pharmacovigilance, events identified through postmarketing data mining for which no labeling change has been made to date, and events specific to the two new safety populations addressed in the efficacy supplements under review, namely smokers with CVD and COPD. Findings from the review of the primary safety concerns for the CVD population have been described in Section 7.3.4. In this section, findings from the review of the submission-specific primary safety concerns for the ISS population are discussed.

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. As noted, events of interest generally included labeled safety warnings labeled safety warnings of events identified through postmarketing pharmacovigilance, events identified through postmarketing data mining for which no labeling change has been made to date, and events of particular relevance to the new populations studied in the efficacy supplements[13]. The

[13] Efficacy supplements 020 – 021 were submitted concurrently with the efficacy supplement currently under review, that is, Supplement 019, regarding the population of smokers with CVD.

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 (as opposed to broad) subset of terms for each of the individual SMQs.

The ISS supports the three efficacy supplements that were submitted simultaneously by the applicant and include safety and efficacy data, supplements 19, 20, and 21. The supplements were reviewed by two reviewers – the current reviewer, who reviewed this CVD supplement and Dr. Pamela Horn, who reviewed supplement 020, which addresses use of Chantix in a population with COPD and supplement 021, with information on a flexible quit date approach to smoking cessation with Chantix. 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 individual CVD supplement (S-019), the portions reviewed by Dr. Horn are excerpted and presented in the relevant sections and so indicated.

7.3.5.1. Neuropsychiatric Events

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, the 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 will be seen from the relevant excerpt from Dr. Horn's review of the common adverse events for the pooled cohorts (Section 7.4), 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 29 Neuropsychiatric-Related SMQs - Phase 2-4 Studies

	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.

7.3.5.2. Cardiovascular Events

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[14])
- 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)

[14] 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.

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:

	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.

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 varenicine group than placebo 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 (varenicine 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[15] 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

[15] Preferred terms blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased were combined and reviewed in aggregate.

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.

Table 30 Adverse Events in the Ischemic Heart Disease (Narrow) SMQ – 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, 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 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.

7.3.5.3. Cerebrovascular Events

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 31 Cerebrovascular Disorders SMQs - Phase 2-4 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
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): 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.

7.3.5.4 Accidental Injury

Dr. Pamela Horn reviewed adverse events of accidental injury summarized by the applicant in the ISS. Dr. Horn's discussion of these events is excerpted here.

> 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 32: 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.

Notably, the events described in labeling, which included terms coded to the MedDRA term "impaired driving ability," and sometimes describing a subjective sense of impairment in driving ability and "near-miss" accidents, are not completely captured in the Accidental Injury SMQ. Information received from Pfizer, at Agency request, after Dr. Horn had finalized her review, confirmed that there were no cases in the database coded to the term "impaired driving ability." Moreover, a text string search to identify "near misses" also did not identify such events in the ISS database.

7.3.5.5 Serious Skin Reactions and Allergic Phenomenon

Dr. Horn reviewed the information provided by the applicant on Serious Skin Reactions and Allergic Phenomenon. Dr. Horn's analysis of these results is excerpted and presented here.

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[16].

Table 33: 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

[16] The Applicant provided source tables for ISS Table 20 (reproduced as the [All Causality Adverse Events Related to Skin Reactions and Allergic Phenomenon (Pooled Data)]) 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.

7.3.5.6 Blindness/Visual Impairment

Dr. Horn reviewed the data on adverse events related to blindness/visual impairment included by the applicant in the ISS. Dr. Horn's analysis of these events is excerpted here.

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 34: 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[17]. 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.

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

[17] 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 [the above table]. Both were reviewed as part of the original NDA.

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.

7.3.5.7 Convulsions

Convulsions, another special safety concern evaluated in the ISS, were reviewed by Dr. Horn. Dr. Horn's assessment of these events is excerpted here.

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 35: 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 (b) (6)) 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 (b) (6) 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

Supportive safety results included a review of common adverse events occurring in the individual CVD trial and in the ISS populations, and laboratory findings, vital sign data, and electrocardiogram data from the cardiovascular disease trial.

7.4.1 Common Adverse Events

Common Adverse Events – Study A3051049

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. The following common adverse events table summarizes treatment-emergent adverse events in the CVD study meeting these same criteria.

Table 36 Treatment-Emergent AEs by SOC and HLGT > 5% in Varenicline group and more commonly than in Placebo group and Preferred Term > 1% in Varenicline group at a Rate > 0.5% more than Placebo Subjects - A3051049

	Varenicline		Placebo	
	n	(%)	n	(%)
Number (%) of Subjects:				
Evaluable for adverse events	353		350	
With adverse events	288	(81.6)	227	(64.9)
Discontinued due to adverse events	34	(9.6)	16	(4.6)
Number (%) of Subjects with Adverse Events by:				
System Organ Class				
and High Level Group Term				
and MedDRA (v11.0) Preferred Term				
CARDIAC DISORDERS	23	(6.5)	19	(5.4)
Coronary artery disorders	18	(5.1)	10	(2.9)
Angina pectoris	13	(3.7)	7	(2.0)
GASTROINTESTINAL DISORDERS	177	(50.1)	90	(25.7)
Gastrointestinal motility and defaecation conditions	48	(13.6)	28	(8.0)
Constipation	23	(6.5)	7	(2.0)
Diarrhoea	22	(6.2)	18	(5.1)
Gastrooesophageal reflux disease	5	(1.4)	3	(0.9)
Gastrointestinal signs and symptoms	141	(39.9)	65	(18.6)
Abdominal distension	7	(2.0)	3	(0.9)
Abdominal pain upper	15	(4.2)	9	(2.6)
Dyspepsia	19	(5.4)	12	(3.4)
Nausea	104	(29.5)	30	(8.6)
Vomiting	29	(8.2)	4	(1.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	59	(16.7)	40	(11.4)
General system disorders NEC	57	(16.1)	38	(10.9)
Asthenia	4	(1.1)	0	
Chest discomfort	4	(1.1)	0	

	Varenicline		Placebo	
	n	(%)	n	(%)
Number (%) of Subjects with Adverse Events by:				
System Organ Class				
and High Level Group Term				
and MedDRA (v11.0) Preferred Term				
Fatigue	25	(7.1)	14	(4.0)
Oedema peripheral	7	(2.0)	4	(1.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	42	(11.9)	36	(10.3)
Musculoskeletal and connective tissue disorders NEC	26	(7.4)	25	(7.1)
Back pain	14	(4.0)	9	(2.6)
NERVOUS SYSTEM DISORDERS	93	(26.3)	78	(22.3)
Headaches	45	(12.7)	40	(11.4)
Headache	45	(12.7)	39	(11.1)
Neurological disorders NEC	45	(12.7)	35	(10.0)
Dizziness	22	(6.2)	16	(4.6)
Dysgeusia	16	(4.5)	8	(2.3)
PSYCHIATRIC DISORDERS	102	(28.9)	60	(17.1)
Sleep disorders and disturbances	78	(22.1)	34	(9.7)
Abnormal dreams	28	(7.9)	6	(1.7)
Insomnia	42	(11.9)	23	(6.6)
Sleep disorder	12	(3.4)	5	(1.4)

Source: Submitted by the applicant in response to an Information Request.

Reviewer comment: The common treatment-emergent adverse events observed in the CVD population are similar to the overall findings from the populations in the Chantix clinical trial safety database. Notable exceptions are angina and chest discomfort, which both occurred more commonly in subjects treated with Chantix and did not meet the criteria for common adverse event reporting used in current labeling. The label does not have information describing these as common events and will be revised to reflect these new findings.

In the ISS, the applicant provided common adverse event tables including one summarizing commonly reported all causality PTs and another with commonly reported all causality HLGTs observed in ≥ 5% of subjects in either treatment group in the Phase 2–4 studies. Because there are a multitude of preferred terms, many with same or similar meanings, certain signs and symptoms may be occurring with frequency but would not meet the definition of a common event when using a cutoff of ≥5%. Thus in this instance, aggregating terms that represent a similar disease process is more useful for identifying common adverse events, and hence the common adverse events table based on HLGTs is the table of interest and the relevant portions are shown here.

Consistent with the findings in the CVD study, 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 (See Section 7.3.5.2.).

	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)*.

For all cohorts, more subjects in the varenicline arm had adverse events included in the coronary artery disorders HLGT. Recall from the medical history data, that cardiovascular risk factors were similar between the varenicline and placebo arms for all cohorts, except for the COPD and flexible quit date studies, yet, the imbalance in reporting coronary artery disorders exists for all cohorts. The differences seen in the COPD study may reflect the imbalance in history of cardiovascular disorders where more subjects in the varenicline arm had risk factors for CVD. On the other hand, while there were slightly more subjects in the placebo arm with risk factors for CV disease, no subjects on placebo had events in the coronary artery disorders HLGT while subjects in the varenicline arm did have events in this HLGT, however infrequent. Note that the Coronary artery disorders HLGT findings in the common AEs analysis are the same as that identified by the Ischemic Heart disease SMQ.

Adverse events in the Coronary Artery Disorders HLGT were not observed at ≥ 5 % in either the varenicline or placebo arms in the Phase I studies.

Findings from the common adverse event analyses are consistent with findings from the review of the CVD study and ISS data on CV events and support the labeling revisions related to cardiovascular events.

Common Adverse Events (Overall) in the ISS Population
The following is borrowed from Dr. Horn's review of the common adverse events summary in the ISS.

Table 37: 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.

Dr. Horn found that the common adverse event experience in the ISS populations is similar to that of the COPD population. As demonstrated in the above table, the same can be said for the CVD population, except where noted. As noted earlier, overall findings from the common

adverse event analyses are consistent with findings from the review of the CVD study and ISS data on CV events and support the labeling revisions related to cardiovascular events.

7.4.2 Laboratory Findings

Laboratory data submitted by the applicant were reviewed. The applicant analyzed laboratory data for subjects with evaluable data by examining categorical changes in laboratory values for subjects with normal values at baseline, and for all subjects with evaluable data regardless of baseline abnormality. The applicant also analyzed laboratory safety data through an examination of median changes from baseline to last observation, with last observation defined as last observation while on study drug or during the 30-day lag period.

Overall, there were few subjects with clinically abnormal results when analyzed categorically, e.g., no subjects with ALT/AST > 3xULN, regardless of the baseline abnormality. Similarly, median changes in laboratory values from baseline to last observation were small and don't appear to represent clinically meaningful changes. There was also no consistent pattern in the results, although, there is some suggestion that subjects on varenicline had slightly more LDL cholesterol and triglyceride elevations, but, fewer decreases in HDL, when examined categorically. For subjects with normal baseline values, only increases in triglycerides (> 1.3 x ULN) were seen in the varenicline arm. When examining absolute values, median elevations in HDL level (+8) and no median changes were observed for triglycerides and LDL cholesterol for the varenicline arm; the placebo arm experienced no median change in HDL, but, at the median there were decreases in triglycerides and LDL cholesterol.

In short, no consistent pattern was seen to explain the cardiovascular disease findings and these findings are not considered to merit labeling changes.

7.4.3 Vital Signs

Blood pressure and heart rate were measured at the following time points.

Vital signs (BP, HR)	Screening, at Baseline, and at Weeks 1, 4, 8, 12, ET12, 13, 24, 40, 52, ET52

The applicant's analyses of blood pressure and heart rate changes were reviewed to determine whether the drug appeared to have an impact on these physiologic parameters and, in turn, on cardiovascular disease outcomes. Mean blood pressure and heart rate changes at the end of the treatment phase (Week 12) and at the end of the posttreatment follow-up phase were examined for each treatment arm.

Mean blood pressure and heart rate changes were overall small and are not likely to represent a clinically meaningful change. In the placebo arm, there were again, small, but, larger mean decreases than varenicline, and smaller mean increases than varenicline when mean increases were observed in the systolic and diastolic blood pressure. However, hypertension was assessed as an adverse event infrequently, but, more commonly in the placebo arm. This is also being reflected in the label, as it represents clinical judgment regarding changes in blood pressure that are considered to be clinically relevant, that is, BP changes assessed as an

adverse event of hypertension, rather than small numerical changes in blood pressure readings on average.

Waist circumference

The applicant examined mean changes in waist circumference from baseline to Week 12 and Week 52. The results of this analysis are presented in the following table.

Table 38 Mean Change in Waist Circumference from Baseline to Wk 12 and Wk 52

	Varenicline (N=353)		Placebo (N=350)	
Waist Circumference (cm)	Mean Change	SD	Mean Change	SD
Week 12 [a]	1.3	(4.73)	0.3	(3.98)
Week 52 [b]	1.8	(5.87)	1.0	(5.60)

Abbreviations: SD=standard deviation; N=number of subjects
[a] N=298 varenicline; N=282 placebo
[b] N=279 varenicline; N=258 placebo
SOURCE (Table and Legend): Applicant's Full Clinical Study Report, Protocol A3051049, p. 67

Weight (kg)

The applicant also examined mean changes in weight from baseline to Week 12 and Week 52, by stratifying subjects according to their smoking cessation status. These findings are presented in the following table.

Table 39 Mean Change in Weight from Baseline to Wk 12 and Wk 52 by Smoking Cessation Status

	Varenicline		Placebo	
	Cessators[a]	Non-Cessators[b]	Cessators[a]	Non-Cessators[b]
Week 12				
N	161	145	48	243
Mean change (SD)	2.2 (2.7)	1.5 (2.4)	1.7 (2.6)	1.0 (2.4)
Week 52				
N	67	213	26	229
Mean change (SD)	5.2 (4.4)	1.3 (4.2)	3.9 (4.8)	1.0 (4.4)

Abbreviation: SD=standard deviation
[a]Cessators at Week 12 or Week 52 were defined as the number of subjects reporting no smoking from Week 9 through 12 (inclusive) or through 52 (inclusive) as determined by the cigarette use and nicotine-containing products questions on the NUI, and having CO ≤10 ppm for those visits.
[b]Non-cessators at Week 12 or Week 52 were any subjects in the All Subjects population not classified as cessators.
SOURCE (Table and Legend): Applicant's Full Clinical Study Report, Protocol A3051049, p. 69

When smoking cessation status is taken into account, the weight changes are less pronounced between non-cessators in the varenicline and placebo arms, suggesting that the differences seen in the two arms are a function of smoking cessation status, rather than an effect of drug. However, on average, subjects who were cessators on varenicline had larger increases in weight across the two time points. These weight and waist circumference changes likely represent the rare untoward consequences of smoking cessation, that is, decreased appetite suppression, and in turn, weight gain and increased weight circumference. Conceivably, these

differences in waist circumference and weight could contribute to some of the differences seen for cardiovascular events in the two arms.

7.4.4 Electrocardiograms (ECGs)

The applicant examined ECG data for mean changes in HR and PR, QRS, QT and corrected QTc intervals from baseline to Week 12. Results of these analyses are displayed in the following table.

Table 40 Mean Change in ECG Data from Baseline to Wk 12

	Varenicline (N=353)		Placebo (N=350)	
ECG Parameter	**Mean Change**	**SD**	**Mean Change**	**SD**
Heart rate (bpm) [a]	-1.0	(11.37)	-1.4	(10.48)
QT interval (msec) [a]	3.1	(27.11)	5.4	(28.13)
QTcB interval (msec) [a]	0.9	(21.50)	1.1	(21.21)
QTcF interval (msec) [a]	1.7	(19.00)	2.6	(19.97)
PR interval (msec) [b]	-1.0	(13.87)	-0.4	(13.20)
QRS complex (msec) [a]	2.5	(11.18)	1.8	(9.53)

Abbreviations: SD=standard deviation; bpm=beats per minute; msec=milliseconds; N=number of subjects
[a] N=305 varenicline; N=289 placebo
[b] N=301 varenicline; N=277 placebo
QTcB=QT interval/square root (60/heart rate)
QTcF=QT interval/cube root (60/heart rate)
SOURCE (Table and Legend): Applicant's Full Clinical Study Report, Protocol A3051049, p. 70.

The applicant noted the following:

> A total of 2 (0.7%) varenicline and 1 (0.3%) placebo subjects had a postbaseline QTcB interval ≥500 msec. A total of 1 (0.3%) varenicline and no placebo subjects had a postbaseline QTcF interval ≥500 msec.
>
> - Subject (b) (6) (varenicline) had Baseline QTcB of 510 msec and QTcF of 501 msec and had a QTcB of 502 msec on Day 84. The subject had a history of past myocardial infarction and was on the concomitant medication, atenolol.
> - Subject (b) (6) (varenicline) had Baseline QTcB of 501 msec and had a QTcB of 562 msec and QTcF of 535 msec on Day 84. The subject had a history of atrial fibrillation and was on the concomitant medications, amiodarone and bisoprolol.
> - Subject (b) (6) (placebo) had Baseline QTcB of 511 msec and QTcF of 501 msec, respectively and QTcB of 503 msec on Day 84. The subject had a history of diabetes mellitus, past myocardial infarction, and coronary revascularization and was on the concomitant medication, carvedilol.

No clear and consistent pattern was seen for trends in electrocardiogram data related to intervals for the varenicline and placebo groups. Based on findings from the ECG data in this study, changes to the label relating to this ECG data are not considered warranted at this time.

Categorical ECG Changes

Categorical changes in the interpretations of the electrocardiograms (ECGs) were examined by this reviewer using a cursory analysis that compared the overall interpretation at baseline with the overall interpretations at Week 12 and Week 52. ECGs were interpreted by the investigators as: 1) normal; 2) abnormal, not clinically significant and; 3) abnormal, clinically significant. ECGs for which there was no interpretation were not included in the analysis (n=173) and ECGs designated unevaluable were also not included in the analysis. More detailed ECG findings than the normal, abnormal and clinically significant, not clinically significant dichotomies were also captured in the ecg.xpt dataset but, this information was not gathered consistently and analysis of clinical findings was not feasible because of the missing data.

No clear patterns emerged from review of the ECG interpretation data to suggest that relevant shifts in the overall interpretations of the ECGs were apparent.

7.4.5 Special Safety Studies/Clinical Trials

Study A3051049 was the single study conducted to support the proposed labeling revisions. No additional safety studies/clinical trials were performed. Safety data from all completed clinical trials were summarized for the ISS that supports this labeling supplement. Safety data from the ISS has been reviewed and reported throughout the review in the sections to which the data pertains.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

In the Integrated Summary of Safety, the applicant performed additional safety explorations using data available in the Chantix clinical trial database.

7.5.1 Dose Dependency for Adverse Events

Study A3051049, like most studies in the varenicline development program utilized a single dose of varenicline. To evaluate dose dependency of adverse events, the applicant analyzed data from four Phase 2 studies that included multiple varenicline treatment arms. The Phase 2 studies included A3051002, A3051007, A3051016 and A3051046_48 (which includes a new study [extension study], A3051046_48, conducted in Japan since the original 2005 NDA). For the purposes of this analysis, the applicant grouped varenicline doses into 2 categories: <1mg BID and 1 mg BID.

From these analyses, a dose-response relationship was evident for the adverse event of nausea, which occurred in twice as many subjects in the high-dose arm in the Phase 2–4 studies. Less pronounced dose-response relationships were seen for other adverse events in the GI SOC including constipation, flatulence, and dyspepsia, as well as for neuropsychiatric events including irritability, abnormal dreams, insomnia, dizziness, and dysgeusia.

Nausea is a well-known dose limiting toxicity of Chantix and is described as a warning in the label; dose reductions minimize the adverse event of nausea and this is also described in the label. Analysis of dose-response relationships does not reveal new safety information that warrants a labeling change.

7.5.2 Time Dependency for Adverse Events

Safety data were reviewed primarily by examining adverse events that occurred at any time during the treatment phase. There was no further examination based on the days or weeks during the treatment phase.

7.5.3 Drug-Demographic Interactions

To evaluate drug-demographic interactions, the applicant performed adverse event analyses by stratifying each of the cohorts used for analysis of data from the Phase 2–4 studies by age, gender, and race. For the age analysis, cohorts were divided into three age categories: <45, 45 – 64, and ≥ 65. Racial categories included white, black, Asian, and other. For each analysis of potential drug-demographic interactions, the applicant summarized frequently-reported common adverse events, defined in this case as preferred terms (PT) occurring in at least five percent of subjects (PT ≥ 5%) in any treatment group, subjects experiencing any adverse event and subjects who discontinued because of an adverse event. In reviewing these data, emphasis was placed on findings based on the stratified variables for the 2010 Pooled cohort, because it represents the entire ISS population for the Phase 2–4 studies and the CVD cohort, the population that is the focus of this efficacy supplement. Additionally, the review looked specifically at the applicant's summaries of any adverse events and discontinuations for adverse events for patterns, rather than the individual adverse events.

Age
There were no clear trends observed across the age categories for subjects reporting any adverse events.

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo
SOC PT	number (%) of subjects									
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)

The overall incidence of adverse events for the age < 45 category (varenicline, 80.3%; placebo, 70.9%) and the 45–64 category (varenicline, 80.4%; placebo, 68.8%) in the 2010 Cohort was very similar. Subjects who were 65 years of age or older accounted for 5.2% of varenicline-treated subjects in the 2010 Pooled Studies, and 20.1% of varenicline-treated subjects in the CV study. This age category also had similar numbers for the 2010 Pooled Cohort (varenicline, 81.1%; placebo, 65.0%). These data identify no clear drug-age interaction with respect to reporting adverse events.

Small but steady increases in the numbers of subjects who discontinued treatment due to adverse event were observed across the three age categories in the 2010 Pooled cohort and CVD cohort. This might represent more pronounced toxicities with age or less tolerance among providers and patients for continuing treatment once toxicities arise.

From these data, a small drug-age interaction is suggested; however, these data are not enough to warrant changes to the label regarding age.

Gender

Female subjects in the 2010 Pooled cohort and CV Study cohort were more likely to report any adverse event as well as discontinue from treatment due to an adverse event. This pattern was also observed among the other cohorts as well.

	2005 Pooled Studies		2010 Pooled Studies		CV Study		COPD Study		Flexible Quit Date Study	
	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo	Var	Pbo
SOC PT	number (%) of subjects									
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)

Gender differences were pronounced for nausea above all. In the 2010 pooled cohort, female subjects (varenicline, 40.4%; placebo, 14.4%) reported nausea with greater frequency than their male counterparts (varenicline, 21.1%; placebo, 7.3%). Disproportionate reporting of nausea was also seen in the CV study, with female subjects (varenicline, 50.6%; placebo, 11.1%) reporting nausea more commonly than males (varenicline, 22.6%; placebo, 8.0%).

The adverse event of nausea is already described in great detail in the label and this AE affects both male and female patients. Dose reductions offer some alleviation from this adverse event and this is also described in labeling. A label update to reflect increased reports of nausea is not necessary at this time. Although, female subjects are more likely to report adverse events overall, the types of adverse events commonly reported by female and male subjects were similar and these AEs have already been described in the label.

Race

In the cohorts comprising individual studies, that is, the CV study, COPD study, and flexible quit date study, non-white racial groups were less-well represented in the study samples than their white counterparts. Thus, the aggregated data, specifically, the 2010 Pooled Studies cohort, is more appropriate for looking at race-drug interactions.

	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 (%)
SOC PT	number (%) of subjects									
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)

Among varenicline-treated subjects, white subjects were more likely to report adverse events, while black subjects and subjects in the “other” category were least likely to report an adverse event. Asian subjects had intermediate reporting.

Interpretation of data from the ISS population is difficult as these studies were conducted in multiple geographic regions. Analyses of data by race in this sense cannot account for the cultural and regional influences important in an evaluation of race-drug interaction. Thus, findings presented in the ISS with respect to race, render extrapolation to US racial groups difficult.

7.5.4 Drug-Disease Interactions

Drug-disease interactions, particularly, drug-cardiovascular disease interactions have been evaluated and described throughout the protocol.

7.5.5 Drug-Drug Interactions

The applicant noted that no relevant additional drug-drug interaction data are available beyond what was submitted in the original 2005 NDA.

7.6 Additional Safety Evaluations

No new information pertinent to carcinogenicity, pediatric use, overdose, or abuse potential was included in this submission. Those sections have been deleted.

7.6.2 Human Reproduction and Pregnancy Data

Pfizer is currently evaluating the safety of Chantix in pregnancy as part of a post-marketing commitment. The applicant is conducting a prospective population-based cohort study comparing the occurrence of major congenital malformations among infants either exposed or not exposed to varenicline in utero. The ISS report supporting this efficacy supplement submission also contained information about pregnancies identified in the clinical trial database, and it was noted that there were 3 spontaneous abortions occurring among varenicline-treated women who became pregnant either during or after cessation of treatment in Chantix clinical trials. The Pediatric and Maternal Health Staff's Maternal Health Team has been consulted to determine what additional actions might be needed. Evaluation of these safety data relating to pregnancy data will be addressed separately from this efficacy supplement and has been designated a Tracked Safety Issue (TSI).

7.7 Additional Submissions / Safety Issues

A Safety Update (SU) was submitted on March 4, 2011. The SU reviews additional clinical and postmarketing safety data entered in the sponsor's safety database through December 2, 2010, the cutoff date for inclusion of data in the ISS. The clinical safety data consist of data on deaths and nonfatal serious adverse events (SAEs) reported in all completed placebo-controlled clinical studies of varenicline. These clinical data were reviewed by the applicant for the period starting with a unique data cutoff date executed for each individual study through December 2, 2010.

From the analyses of clinical trial data performed for the Safety Update, no new deaths or SAEs were identified. That is, all deaths and SAEs had been reported and reviewed either in the original 2005 NDA, the subsequent 90-Day SU for the original NDA, or in the recent supplemental NDAs S-019 to S-021. Of note, one SAE of Cerebrovascular accident was reported in Study A3051028 for a varenicline-treated subject (Case (b) (6) and was subsequently reviewed in the previous 90-Day SU to the original 2005 Chantix NDA. This SAE was not included in the respective Case Study Report and was a single event listed in the SU Appendix Table summarizing deaths and SAEs identified in the present SU analysis.

Postmarketing data for varenicline submitted with the efficacy supplement summarized available postmarketing data through July 28, 2010. The Safety Update supplements this postmarketing data by extending the review the period. The postmarketing varenicline data (excluding clinical trial cases) were reviewed for the period of July 29, 2010 through December 2, 2010 in the Safety Update. These postmarketing data are discussed in the following section.

Again postmarketing findings from the Safety Update are discussed in the following section.

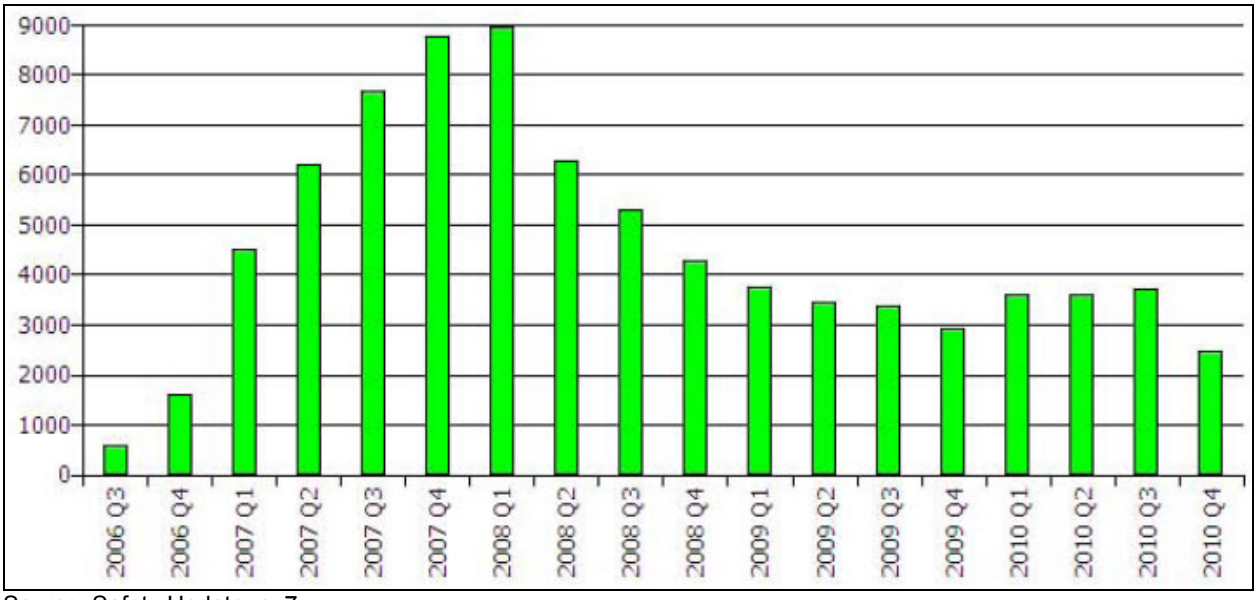
8 Postmarket Experience

Varenicline was first marketed in the United States, and has an International Birth Date of May 10, 2006. Since its initial US launch, Chantix has received marketing authorization in (b) (4) countries. As of the supplemental NDA submission date in September 2010, the applicant reported that Chantix was being marketed in (b) (4) countries. The worldwide cumulative exposure of varenicline is estimated at (b) (4) patient-years through March 31, 2010. These estimates were derived from the (b) (4). The following figure illustrates patient-years of exposure by year and quarter.

The applicant performed a postmarketing safety analysis based on postmarketing adverse event reports contained in its safety database. The postmarketing adverse events reports include cases of AEs reported spontaneously to the sponsor, cases reported from health

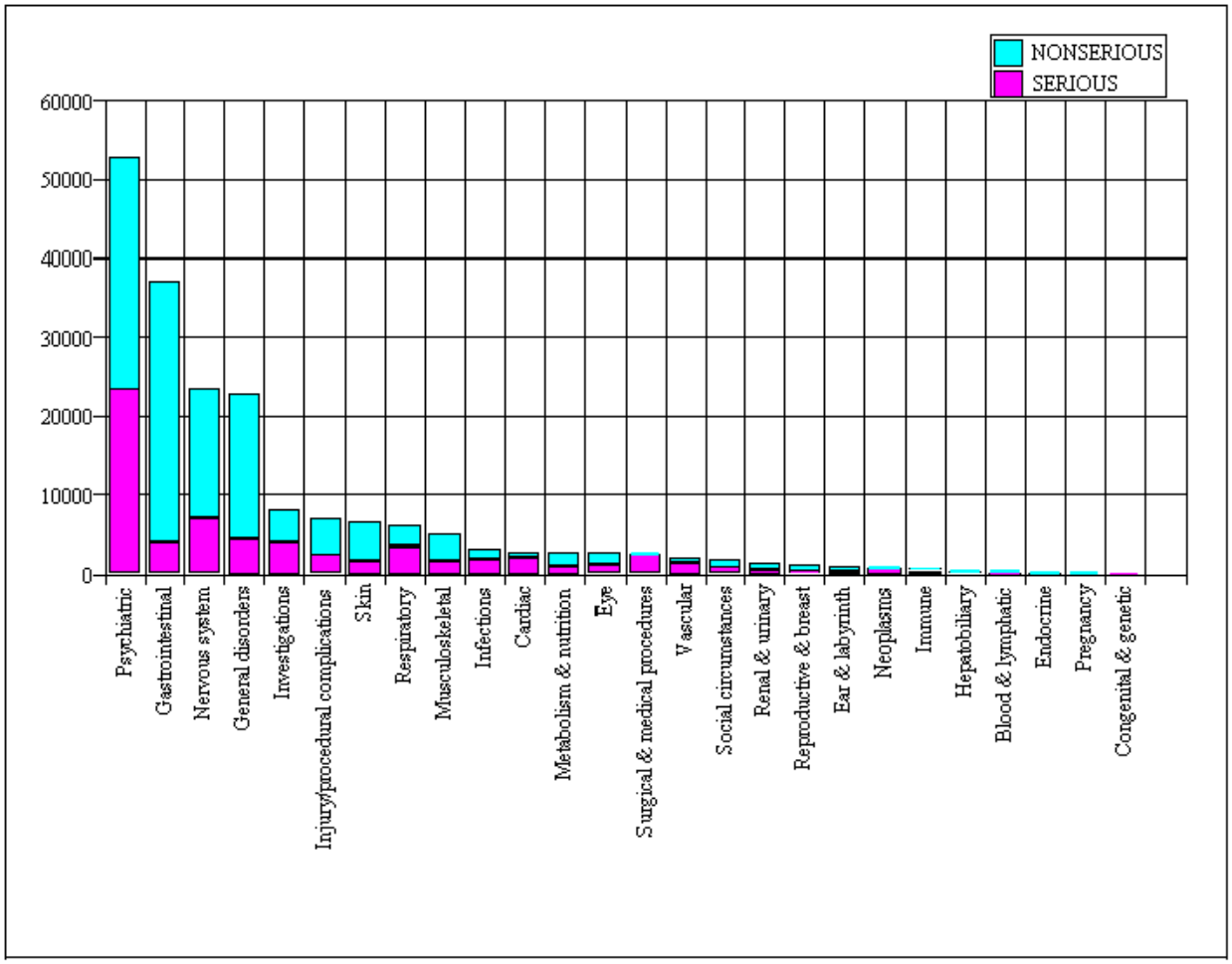
authorities, cases published in the medical literature, and cases reported from Pfizer-sponsored marketing programs (solicited cases) regardless of causal association.

The safety database was searched for varenicline cases other than those from clinical trials reported from the IBD through July 28, 2010 and in the Safety Update (submitted March 2011) this was extended through December 2, 2010. In the same fashion as the figure shown above, the following figure below shows the total number of these cases by year and quarter.



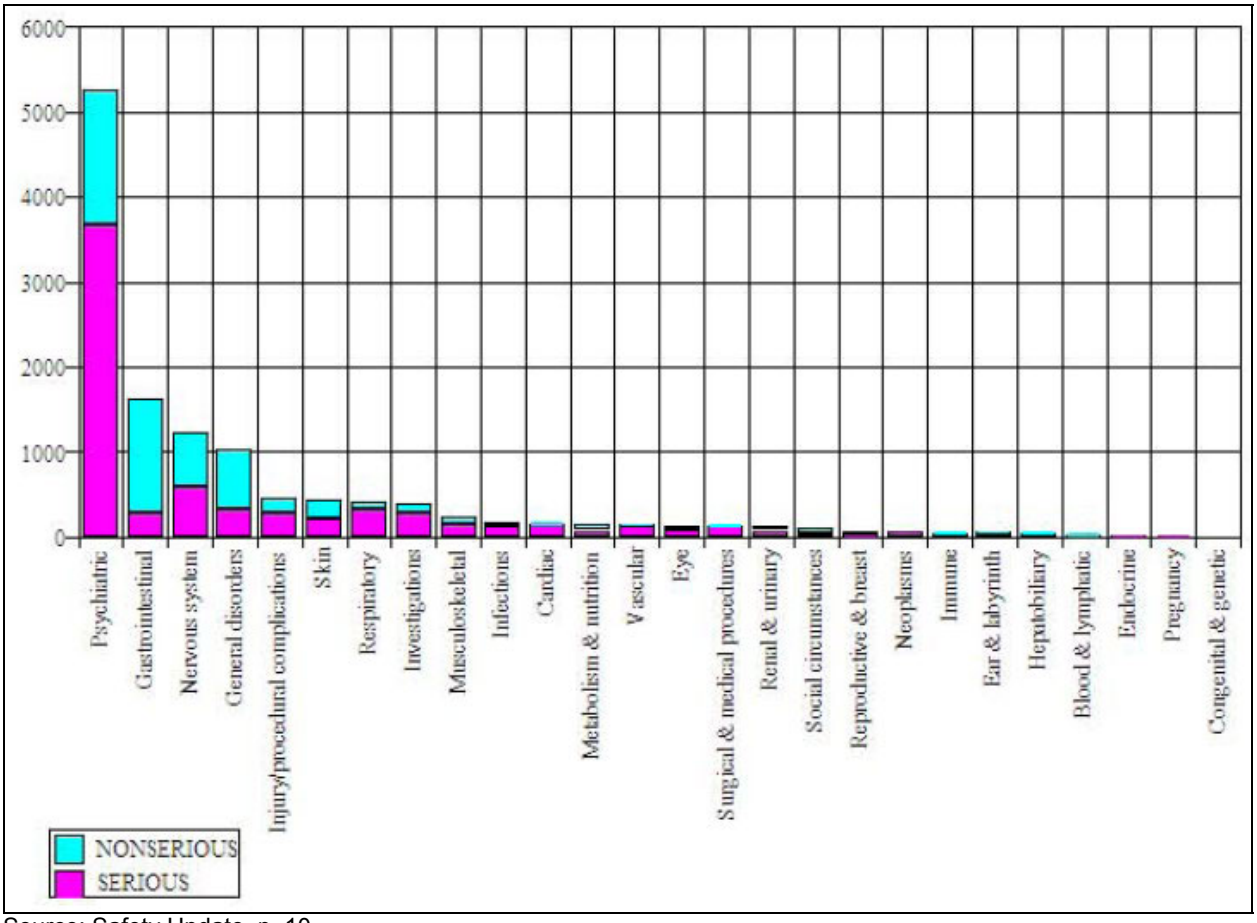
Source: Safety Update, p. 7

The applicant performed an analysis of commonly reported events and provided the results by SOC and specifying whether the events met the criteria for seriousness.



Source: Summary of clinical safety p.70

In the safety update, the sponsor updated this information and provided data from July 29, 2010 to December 2, 2010.



Source: Safety Update, p. 10

Reporting over the two timepoints was similar, but, GI reporting notably decreased. The vast majority of events were in the Psychiatric and Gastrointestinal SOC. By comparison, much fewer cardiac events were reported. Among the cardiac cases, the vast majority were serious. This might represent a reporting bias in that reporters may report events that are cardiac in nature, primarily when they are serious events.

Pfizer further searched the postmarketing database for cases in which cardiovascular disease was reported in the medical history. The search included the most commonly reported conditions in the CV study. The applicant found 1708 cases through this search. The applicant found that the characteristics of the 1708 cases were generally similar to those reported for the all postmarketing population. Notable differences include a higher proportion of patients in the 65-74 year age range (21.8% CV history vs. 7.4% overall population) and a higher proportion of cases classified as serious (64.9% CV history vs. 42.6% overall population). The most frequently reported events (≥ 2%) in the CV history cases were similar both in regard to the specific events and the reporting frequency to those reported in the overall postmarketing dataset, including the frequently reported psychiatric events encoding to the PTs Depression, Abnormal dreams, and Insomnia (all reported at ≥5% in both datasets). Events reported in ≥2% of cases in this dataset and at a rate 3X that of the overall dataset appeared to be related to the compromised cardiovascular status of the patients. These events encoded to the PTs

Myocardial infarction (4.6% CV dataset vs. 0.7% overall dataset), Chest pain (5.0% vs. 1.5%), and Blood glucose increased (3.0% vs. 0.8%)[18].

The applicant also provided an update on findings for cases reporting medical history of selected cardiovascular events as follows.

> This search executed for the period of 29 July 2010 through 02 December 2010 retrieved 109 cases reporting the selected CVD conditions in the patients' medical history. Overall, many of the selected characteristics of these cases were generally comparable with those summarized for the total patient population of the Safety Update (SU). Notable differences included: 1) a higher proportion of patients over 50 years of age in the CVD population (64.2%) versus that in the total population (28.2%); 2) a higher proportion of cases classified as serious in the CVD population (83.5%) versus that in the total population (63.5%); 3) a higher proportion of solicited cases in the CVD population (60.6%) versus that in the total population (34.6%); and 4) the higher proportions of cases reporting concomitant products and cosuspect medications in the CVD population (80.7% and 10.1%, respectively) versus those in the total population (34.3% and 3.9%, respectively). A higher proportion of elderly patients and a higher proportion of cases classified as serious were also noted for the CVD population compared with the total population for the period of IBD through 28 July 2010
>
> The frequent events (≥ 2% of cases) reported for patients with CVD medical history were generally comparable, both in regard to the nature and frequency of events, with those reported for the total population. Consistent with the most frequent psychiatric events reported for the total population shown in Figure 3 of this SU, Depression (18.3%), Suicidal ideation (11.0%), and Anxiety (7.3%) were also the most frequent psychiatric events reported for the CVD population (Appendix SU2). Nausea was reported at a substantially lower frequency for the CVD population (5.5%) as compared with that reported for the total population (14.2%). The only event likely related to impaired CV function reported for patients with CVD medical history was encoded to the PT Blood pressure increased (2.8%), which was not reported among frequent events reported for the total population.[19]

Findings from postmarketing data are consistent overall with the findings from the review of the clinical trial data and with the updates to the label that have been made to the Chantix label based on postmarketing pharmacovigilance and data mining efforts undertaken by external entities. No additional labeling changes are deemed warranted at this point based on this summary of postmarketing surveillance data.

[18] Applicant's summary of postmarketing cases reporting a medical history of cardiovascular disease taken from the Clinical Summary of Safety
[19] Applicant's summary of postmarketing cases reporting a medical history of cardiovascular disease taken from the Safety Update

9 Appendices

9.1 Literature Review/References

No new data from the literature were included in support of this submission.

9.2 Labeling Recommendations

The proposed labeling submitted by the applicant includes revisions to the approved labeling addressing the safety and efficacy of Chantix in patients with cardiovascular disease.

The following are the key labeling changes made on review of the supplement:

- The proposed description of the clinical trial was changed to clarify that subjects were enrolled if they had stable cardiovascular disease diagnosed 2 months prior to Screening; diagnoses of cardiovascular disease were other than or in addition to hypertension
- The applicant's claims of efficacy in smokers with cardiovascular disease have been demonstrated and are included in the label
- Cardiovascular events:
    - Certain events were adjudicated by an independent blinded committee and were observed more frequently in the varenicline arm, though the numbers in both arms were small overall. The applicant did report that more cardiovascular events, specifically angina, were seen in the varenicline population. The label will be revised to reflect the small but increased risk of cardiovascular events in this population in the following sections
    - Warning and Precautions: A new warning related to cardiovascular events is being included in the label
    - Adverse events section: This section will be augmented with findings from the blinded adjudication committee
    - Patient Education: The patient education section will include new information about cardiovascular events

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this efficacy supplement.

Appendix

The following table includes narratives for nonfatal serious adverse events that were not adjudicated by the Cardiovascular Events Adjudication Committee. The table includes narratives for:

1. Nonfatal SAEs – Treatment Phase, Varenicline
2. Nonfatal SAEs – Treatment Phase, Placebo
3. Nonfatal SAEs – Posttreatment Phase, Varenicline
4. Nonfatal SAEs – Posttreatment Phase, Placebo
5. Nonfatal SAEs – Pre-randomization

Nonfatal SAEs – not adjudicated by CE committee

Table 41 Nonfatal SAE Narratives

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
A3051049 Study			
Active Phase, Varenicline			
(b) (6)	48 y/o M Varenicline Brazil	Tibia fracture; Accident	• Motorcycle accident on Day 15. Patient and investigator attribute to a distracted car driver who didn't see the patient. Sustained tibia fracture; immobilized. Pt. discharged same day. • Continued study medication. • PMH: MI, angina, CABG, HTN, , asthma, lumbar pain, headache
(b) (6)	71 y/o M Varenicline Brazil	Generalized oedema, Arrhythmia	• Cardiac arrhythmia and cardiac heart failure decompensation Day 76. • Pt. permanently discontinued study drug because of AEs. • PMH: coronary insufficiency, CHF, PVD, COPD
(b) (6)	60 y/o M Varenicline Canada	Diabetes mellitus	• Diagnosed with diabetes Day 64. Fasting plasma glucose at Screening 102mg/dL (normal range: 70-140). Pt. noticed glucose on finger stick was increasing. Evaluated by family MD and HbA1c was 7.9% and glucose was 10.4mmol/L (normal range: 3.6-7.8). No glucosuria, ketonuria. Was thought to be due to weight gain associated with quitting. • No action taken with the study medication. Last day of study treatment Day 85. • PMH: MI, coronary revascularization, peripheral revascularization, HTN, obesity, hypercholesterolemia
(b) (6)	59 y/o M Varenicline Denmark	Testicular Torsion	• Hospitalization and operation for testicular torsion Day 56. Last day of study treatment Day 53. • PMH: PVD, HTN, hypercholesterolemia
(b) (6)	48 y/o M Varenicline Argentina	Cervico-brachialgia	• Left arm pain Day 3. CV workup (-). SPECT (-). • No action taken with study drug. • PMH: MI, angina, coronary revascularization, PVD, dyslipidemia, DM, obesity, anxiety
(b) (6)	59 y/o F Varenicline USA	Complex partial seizures	• Complex partial seizures Day 4. Saw neurologist in follow-up after about 2 months of treatment and reported almost daily occurrences of what was determined to be complete partial seizures. Hospitalized for testing, monitoring and medication adjustment. • No action was taken with study medication. • PMH: Seizure disorder, PVD, HTN, GERD, DM, hyperlipidemia, COPD
(b) (6)	54 y/o M Varenicline United Kingdom	Cellulitis	• R leg cellulitis at donor site for fem-pop bypass Day 38. • No action taken with study drug. • PMH: history of bilateral problems with recent left graft surgery, PVD, peripheral revascularization (L CFA endarterectomy & distal SFA/POP angioplasty)
(b) (6)	49 y/o M Varenicline	Gingival bleeding,	• Gingival hemorrhage Day 39. Eight teeth extracted and supplied with prosthesis at dentist. Dentist and,

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
	Germany	Gingival recession, Periodontal destruction	in turn, family physician consider that it may be result of study drug because, despite subject's perfect oral hygiene there was a massive tendency for hemorrhages after intake of study medication, as well as the successive rapidly progressing degradation of the periodontium which led to loosening stage III and finally to the loss of teeth. Also, severe tendency for hemorrhage subsided abruptly after the study medication was discontinued and did not redevelop since then. This information was from the subject's insurance company. • Medication discontinued before subject went to dentist. Last day of study treatment given as Day 84. • PMH: MI, HTN, stroke, hypothyroidism, reactive depression, hypercholesterolemia, ligament rupture, wrist fracture, knee injury, back pain
(b) (6)	39 y/o M Varenicline France	Jaw cyst	• Maxillary cyst Day 107. Had maxillary cyst ablation. • Subject completed treatment. • PMH: MI, coronary revascularization, hypercholesterolemia
(b) (6)	67 y/o M Varenicline France	Cough, dyspnea	• Syncopal cough Day 103. • Last day of study treatment Day 91. • PMH: chronic heart failure since Nov2004, past medical history of angina in Aug2000 and ongoing medical history of high blood pressure since Nov2004, chronic obstructive pulmonary disease since Jun2004 and chronic lymphocytic leukemia since 2000
Active Phase, Placebo			
(b) (6)	61 y/o M Placebo Netherlands	Chronic obstructive pulmonary disease, Pneumonia	• COPD exacerbation 2/2 pneumonia Day 107 • Last day of study treatment Day 87. • PMH: MI, coronary revascularization, PVD, peripheral revascularization, COPD, DM, hypercholesterolemia, anemia, pancreatic insufficiency, gastritis
(b) (6)	47 y/o M Placebo Brazil	Infected skin ulcer	• Right foot ischemic ulcer Day 86 of study. Infection resolved with antibiotic therapy and debridement. Event occurred day after treatment study treatment ended. Last day of study treatment Day 85. • PMH: MI, PVD, HTN, COPD, hypercholesterolemia
(b) (6)	49 y/o M Placebo Denmark	Syncope	• Hospitalized Day 4 for syncopal episode that occurred after prolonged exposure to heat, and alcohol consumption. PE, ECG, coronary enzyme and cerebral CT showed no significant signs. Serum ethanol 38 mmol/L. • No action taken with study drug. Subject completed treatment. • PMH: angina, coronary revascularization, TIA, sleep apnea, syncope, hypercholesterolemia
(b) (6)	67 y/o F placebo USA	Atrial fibrillation	• In rapid Afib more frequently, rate not controlled on current meds. Day 85. Hospitalized x 2 for cardioversion, 2nd attempt successful then reversion, continued on amiodarone to see if would spontaneously convert. Pt reported that she converted with only occasional recurrences of Afib on higher dose amio. • Last day of study treatment Day 85.

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
			• PMH: paroxysmal Afib, MI, angina, coronary revascularization, HTN, hypercholesterolemia, occasional intermittent palpitations
(b) (6)	57 y/o M Placebo Germany	In-stent arterial restenosis	• In-stent arterial stenosis Day 15. Had control angiography which was pre-planned prior to study start to assess patency and found to have in-stent restenosis. Later had angioplasty. • No action taken with study drug. Subject completed study treatment. • PMH: CVA, CEA, HTN, DM, "angioplastic, Arteria carotis communis"
(b) (6)	65 y/o F Placebo Germany	Anemia	• Anemia Day 17. Hospitalized for EGD/Colonoscopy after developed anemia and tarry stools. GI w/u (-).On oral anticoagulation for antiphospholipid syndrome and hyperhomocystenemia & concomitant med believed to be causal. • Medication stopped temporarily. Subject completed study treatment. • PMH: PVD, peripheral revascularization, peptic ulcer, hyperthyroidism, COPD, hyperlipoproteinemia
(b) (6)	52 y/o M Placebo Taiwan	Diabetes mellitus Ketoacidosis	• Hospitalized for diabetes mellitus (Glu: 983 mg/dl) with ketoacidosis Day 76. • No action taken with study drug. Last day of study treatment Day 80. • PMH: MI, angina, coronary revascularization, anemia, HTN, hypercholesterolemia, methanol poisoning with cerebellar infarction, acute pancreatitis
(b) (6)	54 y/o M Placebo United Kingdom	Circulatory collapse	• Collapse Day 27and admitted to medical unit for observation. Investigator attributes causality to patient walking home after anesthetic against medical advice. • Medication stopped temporarily. Subject completed study treatment. • PMH: MI, angina, PVD, CHF, HTN, peptic ulcer, jaundice, anemia, renal insufficiency, COPD
(b) (6)	57 y/o M Placebo United Kingdom	Chest pain	• Chest pain and vomiting Day 51 and managed in the accident and emergency department. No hospitalization. Simvastatin dose was increased, "angina med comm." and blood test • Blinded therapy stopped temporarily. Last day of study treatment Day 83. • PMH: MI, PVD, gastritis
(b) (6)	63 y/o M Germany Placebo	Inguinal hernia	• Hospitalized for surgery for inguinal hernia which developed day ~ 2 months after starting blinded therapy. He presented with hernia at scheduled Wk 24 visit. Had developed before this visit. • No action taken with study drug. Subject completed study treatment. • PMH: angina, SVT, coronary revascularization, peptic ulcer, hepatitis, dyslipidemia
(b) (6)	64 y/o M Placebo Germany	Back pain	• Severe back pain Day 108. Monoclonal gammopathy of undetermined significance (MGUS) on biopsy. • Last day of study treatment Day 90. • PMH: MI, angina, coronary revascularization, HTN, dyslipidemia, peptic ulcer, Graves' disease, depression
Post-treatment Phase, Varenicline			
(b) (6)	68 y/o F Varenicline USA	COPD *(See also CV non fatal SAE listing)*	• COPD exacerbation Day 323. Hospitalized for COPD exacerbation in setting of possible infection. ECG with nonspecific changes thought due to strain, improved somewhat on follow-up ECG. FEV1 of 0.8. • Last day of study treatment Day 85.

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
			• PMH: PVD, peripheral revascularization, asthma, peptic ulcer, GERD, anemia, restless leg syndrome, radicular chronic back pain, cholecystitis, Vit B12 deficiency
(b) (6)	64 y/o F Varenicline USA	Clostridium difficile colitis	• C. diff colitis Day 250. Hospitalized for dehydration and managed with antibiotics and IVF then discharged. Re-admitted for prolonged (31Mar08 to 23May08) and complicated hospitalization for clostridium difficile colitis involving multiple surgeries, multiple ICU stays, multiple infections and sepsis. • Last day of study treatment Day 84. • PMH: angina, HTN, CHF, COPD, GERD, anxiety, migraines
(b) (6)	67 y/o M Varenicline Australia	B-cell lymphoma	• B-cell non-Hodgkin's lymphoma Day 206. (Retroperitoneal and bone marrow). Had TURP. • Last day of study treatment Day 82. • PMH: coronary revascularization, R. eye tumor (1941). No reoccurrence, GERD, hypercholesterolemia
(b) (6)	50 y/o M Varenicline Canada	Diabetes mellitus	• DM Day 375. Baseline HbA1c 6.2% (nml 4.5 to 6.0). At Wk 52 visit, A1c 8.4%, pt. considered to have DM. A few days later, pt's fasting blood glucose level 11.6 mmol/L (nml 3.3–6.1). Started on metformin. • Last day of study treatment Day 84. • PMH: PVD, peripheral revascularization, obesity, HTN, hypercholesterolemia, appendectomy
(b) (6)	73 y/o M Varenicline Canada	Lung neoplasm malignant, Pneumothorax	• Lung cancer diagnosis Day 197. Had dyspnea and was hospitalized for pneumothorax Day 201 as a result of the lung biopsy. • Last day of study treatment Day 85. • PMH: stroke, angina, PVD, peripheral revascularization, HTN, bradycardia secondary to Bblocker, COPD, peptic ulcer, anemia
(b) (6)	64 y/o F Placebo Canada	Fall, Ankle fracture, Rotator cuff syndrome	• Fell and fractured ankle Day 110. Had ORIF for ankle fracture. Non-weight bearing for 6 wks and on first step of full weight bearing status subject fell injuring L rotator cuff Day 161 and underwent surgery for L rotator cuff repair. • Last day of study treatment Day 88. • PMH: MI, angina, coronary revascularization, ventricular arrhythmia, hypothyroidism, OA, cholecystectomy, diverticulosis, hyperlipidemia
(b) (6)	63 y/o F Varenicline Denmark	Arteriospasm coronary	• Experienced increasing tiredness and cardiology consultation revealed need for PCI. Hospitalized for PCI. Event onset Day 199. • Last day of study treatment Day 85. • PMH: angina, coronary revascularization, CHF, depression, neck pain, hypercholesterolemia.
(b) (6)	59 y/o F Varenicline Argentina	Biopsy breast	• Hospitalized for breast biopsy Day 167. Histopath: intracanalicular fibroadenoma – diameter 0.4 cm • Last day of study treatment Day 84. • PMH: MI, hypothyroidism, anemia
(b) (6)	62 y/o F Varenicline United Kingdom	Overdose	• Overdose Day 331. Hospitalized for diazepam and lormetazepam OD while intoxicated. Seen by psychiatrist and discharged home the following day having recovered from the event. • Last day of study treatment Day 21. • PMH: ischemic heart disease, angina, HTN

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
(b) (6)	57 y/o M Varenicline United Kingdom	Rash	• Rash Day 219. Predominantly R thigh but with outbreaks on torso and upper limbs. Punch biopsy with toxic erythema possibly drug-related with no evidence of vasculitis. • Last day of study treatment Day 84. • PMH: MI, ischemic heart disease, coronary stent, GERD, hypercholesterolemia
(b) (6)	60 y/o F Varenicline Czech Republic	Bile duct stenosis	• Bile duct stenosis Day 357. Hospitalized, had stent Implantation. • Last day of study treatment Day 97. • PMH: coronary revascularization, stroke, HTN, DM, cholecystectomy, vertebral surgery
(b) (6)	61 y/o M Varenicline United Kingdom	Chest pain	• Hospitalized for observation for episode of chest pain Day 172, discharged recovered the following day. • Last day of study treatment Day 83. • PMH: angina, PTCA/stent '05
(b) (6)	61 y/o M Varenicline USA	Atrial fibrillation	• Awoke with palpitations Day 113, saw MD and sent to ER. Found to be in Afib with RVR, hypotensive and in mild CHF. Cardioverted after BP lowered more with IV/PO metoprolol, remained in NSR. BNP: 1436 pg/mL thought to be related to Afib since echo with nml EF. Admitted for obs and anticoagulation. • Last day of study treatment Day 84. • PMH: PVD, peripheral revascularization, rheumatic mitral stenosis/regurg; HTN, pulm HTN, sleep apnea, hypercholesterolemia
		Mitral stenosis/mitral regurgitation Atrial fibrillation	• Developed dyspnea and found to have mitral valve stenosis and regurgitation and had MVR. Day 222. Later developed rapid Afib Day 228 with sinus pause then cardioverted and remained in NSR. • Last day of study treatment Day 84. • PMH: PVD, peripheral revascularization, rheumatic mitral stenosis/regurg; HTN, pulm HTN, sleep apnea, hypercholesterolemia
		Sick sinus syndrome	• Afib with RVR. Cardioverted. Noted to have 6-sec pause. Pacemaker implanted. SSS Day 236. • Last day of study treatment Day 84. • PMH: PVD, peripheral revascularization, rheumatic mitral stenosis/regurg; HTN, pulm HTN, sleep apnea, hypercholesterolemia
(b) (6)	61 y/o M Varenicline USA	Chronic obstructive pulmonary disease, Angina pectoris	• COPD exacerbation believed to be 2/2 RSV infection Day 182. Event not thought to be cardiac in nature, CXR clear, NT-BNP 402 pg/L. Event was severe and ultimately required intubation, had worsening symptoms not relieved by bipap. Pt transferred to ICU for elective intubation. Developed severe angina Day 196, day of planned discharge, HR 140, BP 130s, placed on IV heparin and nitro drip. Catheterization was unchanged from '04 findings. SVG to diagonal was 100% occluded in past and remains so. Discharged next day. • Last day of study treatment Day 84. • PMH: CVA, MI, angina, coronary revascularization, CHF, PVD, HTN, COPD, asthma, dyslipidemia, nocturnal leg cramps, tussive syncope
		Nephrolithiasis, Shingles	• Three hospitalizations for renal calculi, first Day 224 of the study. S/p cystoscopy and ureteral stent placement, eventually removed, lithotripsy. Large stone removed and multiple smaller calculi awaiting

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
			passage. Kidney stones were not present at baseline. Multiple episodes of pain also and determined to have shingles Day 255 of the study. • Last day of study treatment Day 84. • PMH: CVA, MI, angina, coronary revascularization, CHF, PVD, HTN, COPD, asthma, dyslipidemia, nocturnal leg cramps, tussive syncope
(b) (6)	71 y/o M Varenicline USA	Carotid artery stenosis	• Severe right internal carotid artery disease (Day 281) diagnosed after ultrasound performed after complaints of L arm paresthesis, pt. c/o intermittent numbness and tingling in his hands. Neck CT angio confirmed diagnosis. The parasthesis was determined to be a positional pre-existing (at least 3 years) problem and did not represent a symptom of the stenosis. Since he was not symptomatic from the stenosis, he was anticoagulated and discharged home to await elective scheduling of a carotid endarterectomy. Later had CEA. • PMH: coronary artery disease, hypercholesterolemia and peripheral vascular disease
(b) (6)	71 y/o M Varenicine USA	Anaemia	• Anemia Day 298 believed due to GI bleed in setting of supratherapeutic INR. Pt. transfused. • Last day of study treatment Day 84. • PMH: angina, coronary revascularization, HTN, 1st degree AV block/hemiblock, peptic ulcer, alcohol abuse, hypercholesterolemia.
(b) (6)	76 y/o M Varenicine USA	Haematoma, Hypotension, Pneumonia staphylococcal	• Left hip hematoma Day 179 secondary to fall, anemic on admission. Hypotensive Day 200 due to ongoing problem of diarrhea and vomiting believed from gastroenteritis though source of infxn not identified. ICU stay for aggressive treatment of hypotension and possible infxn. Developed MRSA pneumonia Day 201. Also with dysarthria believed to be due to vocal cord dysfxn with intubation, unsteady gait thought to be related to prolonged hospitalization, and left leg weakness from hematoma. An AAA of 3.3 cm was found on CT and was not considered a separate SAE. • Last day of study treatment Day 84. • PMH: coronary revascularization, PVD, TIA, aortic stenosis, s/p AVR, LBBB, COPD, HTN.
(b) (6)	58 y/o M Varenicline Germany	Lung neoplasm malignant	• Diagnosed with lung cancer. Event onset day given as N/A. During medical follow-up for MI, had abnormal thyroid lab data and evaluation revealed primary lung cancer with thyroid metastasis. • Medication reported to have been permanently discontinued in setting of an MI. Last treatment day for this SAE given and Day 94. • PMH: Stroke, angina, laryngeal CA, asthma, coxarthrosis, migraine
(b) (6)	67 y/o M Varenicline France	Cough, dyspnea	• Hospitalized for cough and dyspnea Day 170. Had dry cough x 2 months since day 103, syncopal cough. Fibroscopy was performed and revealed an important bronchial and tracheal dyskinesia. • Last day of study treatment Day 91. • PMH: angina, CHF, HTN, COPD, CLL
(b) (6)	45 y/o F varenicine Germany	Menorrhagia, Vaginal hemorrhage	• Menorrhagia for number of months (pt couldn't give exact date) thought to be the result of fibroids. Had hysterectomy and was later readmitted Day 274 of the study for vaginal bleeding after sexual intercourse. • Last day of study treatment Day 86.

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
			• PMH: angina, coronary revascularization, HTN, hyperthyroidism, headache, dyslipidemia
(b) (6)	45 y/o F Varenicline Germany	Gastroenteritis norovirus	• Gastroenteritis diagnosed Day 373. Diagnosed with gastroenteritis after febrile with N/V. Had also c/o'd pain in back and R arm, which are same sx she had at time of MI. Several ECGs performed and CK/CK-MB collected which revealed no myocardial ischemia. • Last day of study treatment Day 84. • PMH: MI, angina, ventricular arrhythmia
(b) (6)	63 y/o M Varenicline Germany	Basal cell carcinoma	• BCC Day 160. Nevus present before study enlarged. Biopsied, found to be BCC. BCC later excised. • Last day of study treatment Day 43. • PMH: angina, HTN, coronary artery disease, dyslipidemia, "polyposis col", elevated level of uric acid
Post-treatment Phase, Placebo			
(b) (6)	67 y/o M Placebo USA	Small bowel obstruction Cardiac ischemia Bilateral pneumonia Respiratory distress *(See also CV SAEs table)*	• Diagnosed with metastatic small cell lung cancer post-therapy and later developed SBO on Day 240 secondary to adhesions. Had diagnostic laparoscopy/ex-lap. Postop developed respiratory distress Day 249 requiring intubation, and chest pain determined to be 2/2 myocardial ischemia Day 249. Later developed pneumonia. • Last day of study treatment Day 85. • PMH: MI, angina, coronary revascularization, PVD, peripheral revascularization, stroke, BCC-nose, hypercholesterolemia
		Atrial fibrillation	• Atrial fibrillation developed Day 295. Converted quickly to NSR with digoxin, heparin and metoprolol. • Last day of study treatment Day 85. • PMH: MI, angina, coronary revascularization, PVD, peripheral revascularization, stroke, BCC-nose, hypercholesterolemia
(b) (6)	58 y/o M Placebo Netherlands	Polyp	• Bile bladder polyp Day 333. Hospitalized and underwent pancreaticoduodenectomy for obstruction icterus due to papilar adenoma. • Last day of study treatment Day 86. • PMH: PVD, peripheral revascularization, CODP, skin cancer
(b) (6)	64 y/o F Placebo Brazil	Supraventricular tachycardia	• Developed SVT Day 252. • Last day of study treatment Day 86. • PMH: MI, coronary angioplasty, HTN, jaundice, hepatitis, gastritis, hypothyroidism, headache, dyslipidemia, OA
(b) (6)	59 y/o M Placebo Australia	Scrotal abscess	• Scrotal abscess Day 352. Hospitalized for I&D of left scrotal abscess. • Last day of study treatment Day 85. • PMH: Atrial fibrillation, coronary revascularization
(b) (6)	63 y/o M Placebo Canada	Bile duct cancer	• Cholangiocarcinoma with ganglionic metastasis Day 260. While hospitalized had colonoscopy, gastroscopy, and 2 ERCPs. Had mild pancreatitis post-ERCP. • Last day of study treatment Day 84.

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
			• PMH: angina, coronary revascularization, HTN, hypercholesterolemia
(b) (6)	67 y/o M Placebo Canada	Sciatica, Intervertebral disc protrusion	• Hospitalized for right sciatic pain Day 269, found to have L3 herniated disk Day 271. Managed with analgesic and anti-inflammatory medications. • Last day of study treatment Day 85. • PMH: MI, coronary revascularization, HTN, right knee arthrosis, b/l femoral pulse decreased.
(b) (6)	55 y/o M Placebo Canada	Open fracture, Joint dislocation	• Open fracture, joint dislocation Day 380. R femur compound fracture and R ankle compound dislocation fracture after motorbike accident where pt. thrown into a ditch after hitting a car and subsequently hit by a car. • Last day of study treatment Day 85. • PMH: MI, coronary revascularization, ventricular arrhythmia, depression, alcohol abuse, diverticulitis, laminectomy, colostomy
(b) (6)	64 y/o F Placebo Canada	Fall, Ankle fracture, Rotator cuff syndrome	• Fell and fractured ankle Day 110. Had ORIF for ankle fracture. Non-weight bearing for 6 wks and on first step of full weight bearing status subject fell injuring L rotator cuff Day 161 and underwent surgery for L rotator cuff repair. • Last day of study treatment Day 88. • PMH: MI, angina, coronary revascularization, ventricular arrhythmia, hypothyroidism, OA, cholecystectomy, diverticulosis, hyperlipidemia
(b) (6)	69 y/o M Placebo Denmark	Anaphylactic reaction	• Anaphylactic reaction Day 278. Swollen throat and tongue, progressed rapidly. On perindopril and had several unspecified tests that showed an allergy to perindopril. Perindopril thought most likely cause. • Last day of study treatment Day 85. • PMH: MI, HTN, swollen tongue, syncope intermittent
(b) (6)	49 y/o M Placebo Czech Republic	Vestibular disorder	• Vestibular syndrome with susp. vascular etiology Day 308. U/S showed atherosclerosis w/o stenosis in both carotid bifurcations with nml flow parameters. Compensated patient discharged to home care. • Last day of study treatment Day 94. • PMH: TIA, nephrolithiasis
(b) (6)	56 y/o M Placebo USA	Small bowel obstruction	• Partial SBO Day 261. Managed and resolved with IV fluids. CT scan did not reveal causality. • Last day of study treatment Day 85. • PMH: angina, coronary revascularization, dyslipidemia, basal cell carcinoma
(b) (6)	65 y/o F Placebo Germany	Gastric haemorrhage	• Gastric hemorrhage Day 366. Hospitalized same day after she developed black stools and collapsed. Ulcer and pan gastritis without acute bleeding on EGD. Transfusion and pantoprazole given. Left hospital AMA. Also had SAE of anemia Day 17; had EGD. • Last day of study treatment Day 93. • PMH: PVD, peripheral revascularization. Hyperthyroidism, GERD, COPD, hyperlipoproteinemia
(b) (6)	60 y/o M Placebo Germany	Oropharyngeal cancer stage unspecified	• Oropharyngeal carcinoma. Diagnosed with esophageal carcinoma after lymph node excised, demonstrating a squamous cell carcinoma. CT revealed tumor in oro-pharynx with suspected infiltration of the paravertebral musculature. On endoscopy, primary tumor found to be located in region of oro-pharynx. Event onset day provided as N/A.

Subject ID	Demographics / Treatment Arm	Term of Interest/Preferred Term	Comment
			• Last day of study treatment Day 92. • PMH: Afib and/or flutter, PVD, peripheral revascularization, HTN, hyperlipoproteinemia
(b) (6)	60 y/o M Placebo Korea, Republic of	Transitional cell carcinoma	• Metastatic transitional cell carcinoma Day 267. • Last day of study treatment Day 84. • PMH: angina, coronary revascularization, HTN, DM, benign renal tumor s/p resection
(b) (6)	60 y/o M Placebo Korea, Republic of	Cholelithiasis	• Gallstone disease Day 205 days. Presented to ER, managed outpt. Referred for surgery, declined by pt. with plans for surgery if problem persisted. • Last day of study treatment Day 85. • PMH: cholelithiasis, DM, angina, coronary revascularization, hyperlipidemia, cataract
(b) (6)	60 y/o M Placebo Germany	Femoral artery occlusion	• Femoral artery occlusion Day 362. Developed left leg edema described as 'the subject was not able to put weight on it'. Admitted to hospital with a diagnosis of L femoral artery occlusion. Underwent embolectomy same day and was transferred to ICU. • Last day of study treatment Day 85. • PMH: MI, angina, PVD, peripheral revascularization, peptic ulcer, depressive disorder, hypercholesterolemia, gout
Pre-randomization			
(b) (6)	44 y/o M Pre-randomization	Chest pain	• Experienced chest pain after screening but prior to randomization. Negative cath; negative GI eval. • No study drug dispensed, not randomized. • PMH: angina, hypertension, myocardial infarction, and coronary revascularization
(b) (6)	57 y/o F Pre-randomization	Angina pectoris, Myocardial infarction	• NSTEMI, worsening angina. Coronary angiography with diffuse atheromatic lesions at the coronary arteries with no significant stenosis. • PMH: hypertension, angina, old myocardial infarction and hypothyroidism

Table prepared by reviewer from SAE narratives, adjudicated cardiovascular events tables, case report forms, adverse event dataset, CE adjudication dataset and responses to Information Requests.

Nicotine Use Inventory

Appendix 6. Nicotine Use Inventory

asked at the Week 1 visit through the Week 12 visit

- Has the subject smoked any cigarettes (even a puff) since the last study visit?
- Has the subject used any other nicotine-containing products (eg, nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) since the last study visit?
- Has the subject smoked any cigarettes (even a puff) in the last 7 days?
- Has the subject used any other nicotine-containing products (eg, nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) in the last 7 days?

*asked at the Week 13 visit through the Week 52 visit**

- Has the subject smoked any cigarettes (even a puff) since the last contact?
- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) since the last contact?
- Has the subject smoked any cigarettes (even a puff) in the last 7 days?
- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) in the last 7 days?
- How many days has the subject smoked cigarettes since the last contact?

asked at the Week 52 visit

- Has the subject smoked any cigarettes (even a puff) in the last 4 weeks?
- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) in the last 4 weeks?

* Nicotine replacement therapy and/or other smoking cessation medications must be recorded in the concomitant medicine pages in the case report form.

Source: Clinical Study Report, A3051049 Protocol, p. 1039

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

/s/

RACHEL SKEETE
05/23/2011

CELIA J WINCHELL
05/23/2011
Concur. See also my CDTL memo.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

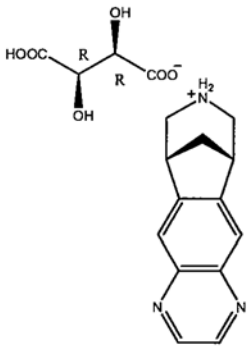
NDA 021928/S-019

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

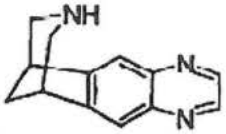
Product/Dosage Form:	Varenicline Tartrate Film Coated Tablets
Potency:	1.0 mg
Pfizer Lot Number:	04-018040
Formulation Number:	963138
Active Component Lot Number:	04944004 (L. Island) 801195-3002054 (Freiburg)
Manufacturer:	Pfizer, Freiburg
Manufacturers Lot Number:	963138-3002064
Date of Manufacture:	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-019

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-019
Drug Name:	Chantix (varenicline)
Indication(s):	Smoking Cessation in Patients with Cardiovascular Disease (CVD)
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:	Rachel Skeete, 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 cardiovascular 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 cardiovascular disease.

The study (Study 49) 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 stable, documented cardiovascular disease, other than hypertension, diagnosed at least two months prior to 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. Eleven patients were randomized but not treated. A total of 703 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 cardiovascular 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 cardiovascular disease (CVD) 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 is Study A3051049, referred to here as Study 49. 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 was provided.

3.2 Evaluation of Efficacy

Study Design and Endpoints

Study 49 was a 12-week, randomized, double-blind, placebo-controlled multicenter study. It was conducted in 39 centers in the United States, South America, Europe and Asia. Patients were current smokers (at least 10 cigarettes per day during the previous 12 months) between the ages of 35 and 75, who were motivated to quit smoking. They had to have stable, documented cardiovascular disease, other than hypertension, diagnosed > 2 months prior to screening. Patients were excluded if currently suffering depression, or with a history of psychosis, anxiety disorder, panic disorder, or bipolar disease.

There were 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 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 703 subjects randomized who received study treatment. There were 11 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) but the actual randomization assignment was not reported. As shown in Table 1, the pattern of and reason for discontinuations were similar across the two groups.

Table 1: Patient Disposition

	Varenicline	**Placebo**
Randomized 714 total		
Received Study Treatment (mITT)	353 (100%)	350 (100%)
Discontinued Treatment	60 (17%)	64 (18%)
Discontinued Study	51 (14%)	61 (17%)
Reason for Discontinuation:		
Adverse Event	8 (2%)	5 (1%)
Lack of Efficacy	0	2 (1%)
Lost to Follow-up	14 (4%)	10 (3%)
Subject no longer willing to participate	22 (6%)	34 (10%)
Death	2 (1%)	5 (1%)
Other	5 (1%)	5 (1%)
Completed Treatment	293 (83%)	286 (82%)
Completed Study	302 (86%)	289 (83%)

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=353)	**Placebo (N=350)**
Age (years)		
Mean (SD)	57 (9)	56 (8)
Range	34-76	34-76
Age group:		
34-65 yrs	291 (82%)	297 (85%)
>65 yrs	62 (18%)	53 (15%)
Gender		
Female	87 (25%)	63 (18%)
Male	266 (75%)	287 (82%)
Race		
Caucasian	284 (81%)	282 (81%)
Black	3 (1%)	2 (1%)
Asian	30 (9%)	30 (9%)
Other	36 (10%)	36 (10%)
Weight (kg)		
Mean (SD)	80 (15)	82 (15)
Range	47-122	45-137

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 the primary and two 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 49)

mITT	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
	N=353	N=350		
Continuous Quit Rate Weeks 9-12	167 47% (42%, 53%)	50 14% (11%, 18%)	6.05 (4.13, 8.86)	<.0001
Continuous Abstinence Weeks 9-52	70 20% (16%, 24%)	26 7% (5%, 10%)	3.19 (1.97, 5.18)	<.0001
Long Term Quit Rate: Week 52	80 23% (18%, 27%)	34 10% (7%, 13%)	2.82 (1.82, 4.38)	<.0001

Source: Clinical Study Report Table 12.

There were three subjects who were identified as being protocol deviations as not having cardiovascular disease at screening. Dr. Skeete, the clinical reviewer, requested that I provide the efficacy results without those three patients (see Table 4). Excluding those patients without CVD did not change the results or the conclusions. Study 49 provides sufficient evidence to support the inclusion of these results the Clinical Studies section of the label for aid in smoking cessation in subjects with cardiovascular disease.

Table 4: 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.

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 Skeete 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. non-US) and center. There were no notable differences in the responder rates for the treatments across any of these subgroups. The varenicline treatment group consistently showed a higher continuous quit rate than the placebo group. Results for age, gender and race are shown in Table 5. The results for region and individual centers are shown in Tables 6 and 7.

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=350**	**Placebo N=350**
Age group		
≤ 65 years	128/289 (44%)	39/297 (13%)
> 65 years	37/61 (61%)	11/53 (21%)
Gender		
Female	40/85 (47%)	6/63 (10%)
Male	125/265 (47%)	44/287 (15%)
Race		
Caucasian	130/282 (46%)	36/282 (13%)
Non-Caucasian	35/68 (51%)	14/68 (21%)

Source: SAS datasets

Table 6: Subgroup Analyses by Region

Primary Endpoint: Continuous Quit Rate Weeks 9-12	**Varenicline**	**Placebo**
US	17/30 (57%)	1/31 (3%)
Non-US	150/323 (46%)	49/319 (15%)
Asia/Australia	28/54 (52%)	6/56 (11%)
Canada	8/41 (20%)	1/40 (3%)
Europe	80/167 (48%)	29/163 (18%)
South/Cent. America	34/61 (56%)	13/60 (22%)
Total	167/353 (47%)	50/350 (14%)

Source: SAS datasets

Table 7: Subgroup Analyses by Center

Primary Endpoint: Continuous Quit Rate Weeks 9-12		Varenicline N=353	Placebo N=350
Center #	**Location**		
1001	US	9/13 (69%)	1/14 (7%)
1002	US	2/3 (67%)	0/4 (0%)
1003	Netherlands	9/18 (50%)	4/19 (21%)
1004	Netherlands	8/10 (80%)	4/9 (44%)
1005	Brazil	7/12 (58%)	0/12 (0%)
1006	Brazil	13/18 (72%)	7/18 (39%)
1007	Australia	8/13 (62%)	0/13 (0%)
1008	Australia	4/12 (33%)	0/13 (0%)
1009	Canada	3/14 (21%)	0/14 (0%)
1010	Canada	2/6 (33%)	1/6 (17%)
1011	Canada	3/15 (20%)	0/14 (0%)
1012	Canada	0/6 (0%)	0/6 (0%)
1014	Denmark	7/13 (54%)	5/13 (38%)
1015	Denmark	4/7 (57%)	0/6 (0%)
1017	Argentina	3/5 (60%)	2/5 (40%)
1018	Argentina	2/4 (50%)	0/3 (0%)
1019	United Kingdom	3/10 (30%)	1/9 (11%)
1020	Czech Republic	7/12 (58%)	3/13 (23%)
1021	Czech Republic	8/13 (62%)	5/13 (38%)
1022	United Kingdom	3/7 (43%)	1/6 (17%)
1023	Greece	2/8 (25%)	0/8 (0%)
1024	Greece	2/3 (67%)	0/3 (0%)
1025	United States	5/13 (38%)	0/13 (0%)
1026	Germany	9/22 (41%)	2/21 (10%)
1027	Taiwan	2/5 (40%)	1/6 (17%)
1028	Taiwan	4/6 (67%)	3/6 (50%)
1029	United Kingdom	0/0	0/0
1030	United Kingdom	4/8 (50%)	1/5 (20%)
1031	Mexico	0/2 (0%)	0/1 (0%)
1032	Germany	2/2 (100%)	0/4 (0%)
1033	Korea, Republic of	3/5 (60%)	0/5 (0%)
1034	Korea, Republic of	4/5 (80%)	1/5 (20%)
1035	France	6/10 (60%)	2/10 (20%)
1036	France	0/1 (0%)	0/2 (0%)
1037	France	2/8 (25%)	1/8 (13%)
1038	Germany	2/10 (20%)	0/8 (0%)
1039	Mexico	9/20 (45%)	4/21 (19%)
1040	United Kingdom	1/3 (33%)	0/6 (0%)
1041	Korea, Republic of	0/2 (0%)	1/3 (33%)
1042	Korea, Republic of	3/6 (50%)	0/5 (0%)
Total		167/353 (47%)	50/350 (14%)

Source: SAS datasets

4.2 Other Special/Subgroup Populations

Dr. Skeete identified 14 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 243 subjects (35% 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=227	N=233		
Continuous Quit Rate Weeks 9-12	113 50% (43%, 56%)	40 17% (12%, 22%)	5.31 (3.39, 8.31)	<.0001
Continuous Abstinence Weeks 9-52	44 19% (14%, 25%)	19 8% (5%, 12%)	2.80 (1.57, 5.00)	0.0005
Long Term Quit Rate: Week 52	51 22% (17%, 28%)	25 11% (7%, 15%)	2.49 (1.47, 4.23)	0.0007

Excludes Centers 1001, 1002, 1011, 1012, 1014, 1015, 1022, 1023, 1025, 1030, 1033, 1035, 1038, and 1042.

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 not a concern, 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 49 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 proposed changes to the label for Study 49 are acceptable.

5.2 Conclusions and Recommendations

The goal of this single study was to show superiority of varenicline over placebo for the aid of smoking cessation in subjects with cardiovascular disease who desired to quit smoking. Based on my review of these studies, I conclude there is sufficient evidence of efficacy to support adding these results to the Clinical Studies section of the currently approved label for varenicline.

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification
Specify for each trial:

Protocol Number (s): A3051049
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 Cardiovascular Disease

Phase: 3
Control: Placebo
Blinding: Double-Blind
Number of Centers: 39
Region(s) (Country): US, Netherlands, Brazil, Australia, Canada, Denmark, Argentina, United Kingdom, Czech Republic, Greece, Germany Taiwan, Mexico, Republic of Korea, France
Duration: 12 Weeks = 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/No
Sample Size: 700 (350 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= 84%
Δ= placebo rate 0.18; varenicline rate 0.40; odds ratio 3.04
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

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

/s/

KATHERINE B MEAKER
05/23/2011

DIONNE L PRICE
05/23/2011
Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-019

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Review of Proposed Methodology and Survey Instruments for the Risk Evaluation and Mitigation Strategy (REMS)

Date:	February 24, 2012
Reviewer:	Brian Gordon, M.A. Social Science Reviewer Division of Risk Management
Team Leader	Robert Shibuya, M.D., Team Leader Division of Risk Management
Drug Name:	Chantix (varenicline)
Application Type/Number:	NDA 21-928
Submission:	December 13, 2011
Applicant/sponsor:	Pfizer
OSE RCM #:	2011-4555
TSI #:	260, 1197

1 INTRODUCTION

This memorandum is in response to a request by the Division of Anesthesia, Analgesia, and Addiction (DAAAP) for the Division of Risk Management (DRISK) to review the revised patient methodology and survey instrument that will be used to assess the effectiveness of the Risk Evaluation and Mitigation Strategy (REMS) for Chantix. Please send these comments to the applicant within two weeks and copy DRISK on the correspondence. Let us know if you would like a meeting to discuss these comments before sending them to the applicant.

2 REVIEW METHODS AND MATERIALS

2.1 MATERIAL REVIEWED

- October 19, 2009, Approval Letter and REMS
- April 13, 2011, DRISK 18-month REMS assessment review [J. Perla]
- July 22, 2011, Approval Letter and REMS
- December 13, 2011, Chantix revised REMS assessment protocol (methodology and survey instruments) for assessment that is due October 2012

2.2 REVIEW METHODS

The social scientist reviewed the applicant's revised patient methodology. The review included an evaluation of the sample size, recruitment methods and materials, data collection methods, inclusion criteria and survey instrument, to determine if the methodology is appropriate to effectively assess patients' knowledge of the risks associated with and safe use of Chantix.

3 CONCLUSIONS AND RECOMMENDATIONS

The applicant revised the REMS assessment survey to include questions about the cardiovascular risk that was added to the Chantix Medication Guide on July 22, 2011. The questions the applicant added are acceptable. We have no additional comments or recommendations about the Chantix REMS assessment surveys.

Please let us know if you have any questions.

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

/s/

BRIAN A GORDON
02/24/2012

ROBERT B SHIBUYA
02/24/2012
I concur.

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

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
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
FAX 301-796-9744

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

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

/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.

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

---

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

/s/

KATHLEEN KLEMM
05/23/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-019

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