CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-928

Medical Review(s)

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

MEMORANDUM

DATE: May 3, 2006

TO: File, NDA 21-928

FROM: Celia Jaffe Winchell, M.D.
Medical Team Leader

RE: Supervisory Review of NDA Safety Review
And Primary Clinical Efficacy Review
Varenicline
Pfizer, Inc.

1 BACKGROUND

NDA 21-928 for varenicline (proposed proprietary names: Champix, [ ], Chantix) was submitted by Pfizer on 11/11/2005. Varenicline, a new chemical entity which acts as a partial agonist at the nicotine receptor, was previously designated CP526-555 and was developed under IND 58,994, opened on 9/14/1999. [

]

however, the drug product proposed for marketing under this NDA is the immediate-release product.

According to Pfizer, varenicline is highly selective partial agonist of the α4β2 nicotinic receptor subtype, which, in animal models, has been shown to be responsible for the reinforcing properties of nicotine. It is expected that a partial agonist of the α4β2 nicotinic receptor should provide relief from craving and withdrawal symptoms and, in addition, through interference with the actions of full agonists (i.e., nicotine), reduce the psychogenic reward associated with smoking.

Pfizer incorporated an active-treatment arm in its early efficacy studies, to establish assay sensitivity. Upon obtaining preliminary evidence that varenicline might be more effective than the active comparator, Zyban (bupropion hydrochloride, marketed by Glaxo Smithkline), Pfizer elected to pursue a strategy of establishing a comparative claim against Zyban in Phase 3. At the time of filing, the Division considered the applicant's report of the results of these studies to support a superiority claim, and determined that the application was eligible for Priority Review status on the basis of varenicline's representing a significant improvement over existing therapies.

This application is based on the available results from 30 completed (24 Phase 1, 8 Phase 2/3) and 3 ongoing clinical studies. The clinical studies of the safety of this product in the smoking cessation indication have been reviewed by Howard Josefberg, M.D. I conducted the efficacy review, along with Joan Buenconsejo, Ph.D., (biostatistics). The application has also been reviewed by Srikanth Nallani, Ph.D., and Jenny Zheng, Ph.D.,(clinical pharmacology and biopharmaceutics), Mamata De, Ph.D. (pharmacology/toxicology), and a chemistry, manufacturing, and controls team consisting of Stephen Miller, Ph.D., Ravi Harapanhalli, Ph.D., and Ying Wang, Ph.D.

This memo serves as the supervisory review of the safety data, and also includes the primary clinical efficacy review. I will briefly review the safety data summarized in the primary clinical review, and provide, where needed, my own analyses of the primary safety data. I will summarize relevant information found in the primary reviews from the other disciplines, document my primary review of the efficacy studies, and make recommendations for action on the NDA.

2 EFFECTIVENESS

2.1 Discussion of Endpoints

The development program for varenicline was initiated and conducted during a time of evolution in the Agency's thinking about the design of smoking cessation trials. Currently, in order to gain approval as an aid to smoking cessation, CDER expects that an NME be demonstrated to be effective as an aid to smoking cessation in two independent trials showing that more smokers achieve abstinence within a pharmacologically-justified grace period, and maintain it through the period of treatment, when treated with active drug than when treated with placebo.

Abstinence should be maintained over the entire treatment period in order to justify the administration of the entire course of treatment. If the effect of the treatment is not expected immediately due to mechanism of action, pharmacokinetics, or other factors, then efficacy ascertainment may take place over a period following a "grace period." However, success should be defined as complete abstinence, suitably biochemically verified over multiple visits, from the end of the grace period to the end of the ascertainment period.

Historically, six-week trials were considered conventional, and the ascertainment window was set at weeks 2-6, somewhat arbitrarily. However, this trial duration was appropriate for nicotine replacement products, which were assumed to treat a self-limiting condition (acute nicotine withdrawal), and more recently, the clinical approach to smoking cessation treatment has been moving toward a viewing the disorder of tobacco dependence as a chronic, relapsing condition, and a longer-term approach to treatment has been more common. Initially, some trials were proposed that employed an efficacy ascertainment window of weeks 2-6 in the midst of a longer period of treatment, in an effort to meet the "agency standard." The Agency articulated the view that relapse during ongoing treatment would not be regarded as treatment success, and advised that a "last four weeks of treatment" window would be more suitable. This was the analytic approach specified in the protocols for the varenicline studies.

However, the Division's thinking has evolved as longer and longer treatment durations have been proposed, sometimes resulting in a grace period of many months and an efficacy ascertainment period of four weeks. Ultimately, the concept of "abstinence throughout treatment following a pharmacologically-justified grace period" was articulated in a White Paper and has been communicated to sponsors of ongoing development programs.

The two-month grace period in the varenicline trials is not fully justified, although the partial agonist properties of varenicline might result in blockade of exogenous nicotine, allowing for an extinction approach to behavior change. On the other hand, its agonist properties would also predict early efficacy as it provides some relief for acute withdrawal symptoms.

Pfizer also identified reasons to expect that a long grace period was unnecessary, noting in one protocol early in development:

> As a partial nicotine agonist, CP-526,555 is likely to have certain advantages in treating nicotine dependence over currently available therapies. The agonist properties of the compound may act in a manner similar to nicotine replacement therapies, substituting for nicotine from cigarettes and possibly reducing craving and withdrawal symptoms. The antagonist properties of the compound at the nicotine receptor may reduce the reward experienced by those smoking over the therapy, thereby reducing the likelihood of a full relapse. Consequently, subjects may achieve abstinence quickly and maintain abstinence over the course of treatment.

Therefore, in order to determine whether the drug's efficacy can be demonstrated using a shorter grace period, I asked Dr. Buenconsejo to analyze the data from the efficacy studies applying various grace periods from as little as two weeks up to the protocol-specified eight weeks. Her analyses reveal that the efficacy of varenicline is apparent even without the prolonged grace period applied in the protocol-specified analysis. They also demonstrate that there were quite a few subjects who required several weeks to initiate abstinence; thus, the antagonist properties of the drug and an extinction mechanism of action may play and important role in varenicline's efficacy.

Currently, many sponsors of drug products intended for use in smoking cessation have chosen to establish the acute efficacy of their product in helping smokers quit, using (at least) two trials involving a relatively short period of treatment (generally 6-12 weeks), and then seek to extend the claim by determining whether a longer treatment period results in a higher abstinence rate than a shorter treatment period. Typically, a randomized-withdrawal design in responders to open-label treatment is employed. Although relapse to smoking is used as an endpoint in such a study, such a study does not support a separate "**relapse prevention**" claim, which would imply that all recent quitters, regardless of method used to quit, would benefit from a course of treatment with the product. It merely establishes a longer duration of efficacy of the cessation treatment, which is a valid claim in and of itself, but is not a relapse prevention claim.

The Division currently requires only a single trial to support this claim for a product which has already been demonstrated to be an effective aid to smoking cessation in two or more adequate and well-controlled, shorter-term trials. However, the science concerning the best approach to analyses of these randomized-withdrawal studies is continuing to evolve. It is important to determine whether a higher relapse rate in subjects randomized to switch to placebo, compared with those who remain on active treatment, represents removal of an effective agent, or whether it simply illustrates that a withdrawal syndrome develops upon discontinuation of the drug, promoting relapse to smoking to relieve these symptoms. In examining the data from Pfizer's randomized withdrawal trial, I asked Dr. Buenconsejo to give attention to the time course of relapse to smoking, to attempt to tease out early relapses (perhaps attributable to withdrawal

symptoms, if these exist) from later ones (much less likely to be due to withdrawal). In the discussions below, I will present the results of her analyses.

2.2 Issues in Efficacy Review

The critical issues in the efficacy review went beyond simply confirming the applicant's findings concerning the efficacy of the dose proposed for marketing, 1 mg b.i.d. Two other important concerns required careful consideration: the appropriateness of the dose recommendation, and the review of the comparative claim against Zyban. These two matters, although considered separately, are ultimately intertwined, because the Phase 3 head-to-head studies conducted to support the comparative claim used only one varenicline dose. In addition, Pfizer proposed inclusion of claims in labeling related to subjective measures of craving, withdrawal, and smoking satisfaction, which required specific review of the appropriateness of the instruments.

2.2.1 Comparative Claim vs. Zyban

In order to support a comparative claim against the only other currently-marketed non-nicotine smoking cessation product, Zyban, Pfizer needed to conduct a trial that fairly represented Zyban's efficacy. In order to do this, it was important that the population be potentially responsive to Zyban, that the dosing of Zyban employ a regimen known to be effective, and that the outcome measures be suitable for detecting Zyban's efficacy as well as varenicline's. My review of the protocols indicates that these conditions were met. Previous users of Zyban were excluded (so that no subject who was a known non-responder to Zyban treatment or known to be Zyban-intolerant could be randomized to Zyban), and the exclusion criteria stipulated conditions that would render the subject unsuitable for Zyban treatment, as described in the Zyban package insert. The dosing regimen followed Zyban labeling (150 mg/day x 3 days, then 150 mg b.i.d). The design incorporated a week of Zyban treatment prior to TQD, as in Zyban efficacy trials, and the efficacy analysis included a grace period more than sufficient to allow subjects to respond to Zyban. (Although the Zyban label recommends initiation of Zyban 1-2 weeks prior to TQD, the pivotal efficacy studies were designed with TQD after one week of treatment.) My conclusion is that these studies, prospectively designed to support a comparative claim, were appropriate in their population, dosing, and analysis methods to support a valid comparison between the treatments.

The last issue to consider in determining the appropriateness of the study was the method used to blind the Zyban administered in the trial, and whether the method could potentially interfere with Zyban's efficacy. The Zyban tablets used in studies A3051002, A3051028 and A3051036 were purchased commercially and blinded by removal of tablet markings (deinking) with an ethanol soaked cloth. Results from dissolution testing showed that the deinking process does not affect the performance of the blinded Zyban tablets.

2.2.2 Dose-Finding Program

Pfizer conducted a thorough Phase 2 program to choose the dose to be studied in the Phase 3 program, and the specific regimen. The initial proof-of-concept efficacy study, Study A3051002, compared three doses of varenicline (0.3 mg q.d., 1 mg q.d., and 1 mg b.i.d., to placebo, and incorporated a Zyban arm but did not seek to support a comparative claim. This shorter-term (6-7 weeks) study gave Pfizer initial evidence that varenicline at 1 mg b.i.d. had efficacy superior to Zyban. In this study, 1 mg b.i.d. also appeared clearly more effective than 1 mg q.d. Studies conducted designed and conducted prior to the conclusion of study A3051002 explored 0.5 mg b.i.d. and 1 mg b.i.d as well as a flexible-dosing regimen in which subjects could self-titrate to effect or tolerability. These two studies (A3051007 and A3051016) could be interpreted to support recommending a dose of 0.5 mg b.i.d.; however, before these were completely analyzed, Pfizer had initiated the Phase 3 program using the 1 mg b.i.d. dose in the comparative studies. Evidence, including dose/response analysis conducted by Drs. Nallani and Zheng, demonstrates that 0.5 mg b.i.d. is an effective dose, although some incremental efficacy is noted at the 1 mg b.i.d. dose, particularly at long-term endpoints. Pfizer proposes that all patients titrate to the 1 mg b.i.d. dose to maximize the likelihood of success.

2.2.3 Subjective Endpoints

Pfizer proposed to make labeling claims based on subjective endpoints assessed during clinical trials using several instruments, specifically the Minnesota Nicotine Withdrawal Scale (MNWS), the Questionnaire on Smoking Urges (QSU-Brief), and the Smoking Effects Inventory (also known as the Modified Cigarette Effects Questionnaire, or mCEQ). (See Appendix for samples and information about these scales.) Prior to submission of the application, Pfizer was advised that the inclusion of claims based on these instruments was subject to review of the validity and reliability of the measures, and were asked to provide materials addressing these issues.

The appropriateness of the instruments used was reviewed by Dr. Jane Scott, of the Study Endpoints and Label Development (SEALD) team. Dr. Scott evaluated information submitted to demonstrate the validity and reliability of these instruments to determine whether specific labeling concepts were adequately measured and concluded the following about the measures used and proposed for inclusion in labeling:

2.2.3.1 Craving

- "Urge to smoke" more accurately describes the items in the MNWS and all but two items in the QSU-Brief. The term "craving" is a value-laden term that is not part of the psychiatric definitions of nicotine withdrawal syndrome in either the DSM-IV or the ICD-10. Inclusion of it in these studies is based on recommendations by a Work Group that has not been confirmed by the larger scientific community.
- There is no information demonstrating that patients in the target population have confirmed the content validity of this instrument to measure what is important to patients regarding the urge to smoke or craving. It is not clear that smokers in the USA who are attempting to quit smoking would describe their desire for a cigarette as "craving" or that the items used measure an intensity of sensation sufficient to be described as craving.

- The empirically derived domain scores for the QSU-brief need to show consistent results to confirm results based on total scores.

2.2.3.2 Symptoms of Withdrawal

- There was no information submitted to demonstrate that the symptoms of withdrawal from the MNWS provide a comprehensive measure of the symptoms of withdrawal that patients with nicotine dependence experience when they quit smoking.
    - The MNWS does not assess all of the symptoms of nicotine withdrawal included in DSM-IV diagnostic criteria. The absence of one of eight defining symptoms of nicotine withdrawal (depressed heart rate) in the MNWS raises questions about the appropriateness of describing results based on the MNWS as "symptoms of withdrawal" in product labeling or advertising.
    - The ICD-10 does not directly parallel DSM-IV and provides a longer list of symptoms associated with nicotine withdrawal for use in diagnosing a tobacco withdrawal state.
    - The symptoms use to support statements about symptoms of withdrawal in this submission reflect recommendations of the Society for Research on Nicotine and Tobacco (SRNT) Work Group on the Assessment of Craving and Withdrawal in Clinical Trials.
- Only the two multiple item domains were targeted as measures of withdrawal. To support claims related to withdrawal, it would be important to show that results for all domains of the MNWS withdrawal measure improve with treatment.

2.2.3.3 Reinforcing Effects of Smoking

- It is not clear that all the reinforcing effects of smoking are reflected in these 12 items. As with the other measures, there is no evidence that patients in the target population confirmed that each domain of the mCEQ captures the most important aspects of the intended concept.
- The use of recall to the last cigarette smoked during the prior week introduces recall bias that undermines the validity of data for assessments completed more than a few hours previously, particularly if the patient has smoked a number of times in the recall period.
- The concept of "satisfaction with smoking" introduces questions about how best to capture satisfaction and whether satisfaction can be understood outside of the context of expectations and the ability of the experience to meet expectations.

2.3 Overview of Efficacy Results

Evidence of efficacy was provided in six controlled clinical trials. Pfizer's efficacy program included a series of dose-finding studies in Phase 2, followed by two similarly-designed short-term Phase 3 studies intended to support a comparative claim against the active-control arm, Zyban. The final efficacy study examined whether an additional 12 weeks of treatment with varenicline increased long-term abstinence rates, using a randomized-withdrawal design in responders to varenicline treatment. All studies provided evidence of efficacy of varenicline.

For the purposes of the NDA review, particular attention was given to the Phase 3 studies involving the dose proposed by Pfizer for marketing, 1 mg b.i.d. (A3051028 and A3051036, the Zyban comparison studies; and A3051035, the "maintenance" study), and to those Phase 2 studies which provided information concerning the efficacy of other dosing regimens given over 12 weeks (studies A3051007 and A3051016).

The applicant's table below briefly summarizes the features of the controlled clinical trials.

Appears This Way
On Original

Phase 2/3 Studies Contributing to Efficacy and Safety Analyses

Protocol Type & Number Country [no of sites]	Study start/stop dates	Design	Treatment Group, Regimen, Number of Subjects[a]		Duration of Treatment/Study
Efficacy: Smoking Cessation					
Phase 2 Studies					
Dose-Ranging A3051002 United States [7]	21 Feb 2000/ 03 Jan 2002	Randomized, Parallel Group, Double-blind, Placebo-controlled, Active controlled	Varenicline 0.3 mg QD 1 mg QD 1 mg BID Zyban[b] Placebo	 N=126 N=126 N=125 N=126 N=123	6 weeks + 1 week placebo 7 weeks 7 weeks Optional nontreatment follow-up to 1 yr from start of treatment
Titration A3051007/1018[d] United States [10]	**A3051007** 26 Sept 2001/ 07 Oct 2002 **A3051018** 21 Dec 2001/ 21 July 2003	Randomized, Parallel Group, Double-blind, Placebo-controlled	Varenicline 1 mg BID NT 1 mg BID T[c] 0.5 mg BID NT 0.5 mg BID T[c] Placebo	 N=124 N=129 N=124 N=129 N=121	12 week treatment period Nontreatment follow-up to 1 yr from start of treatment
Flexible-dose A3051016/1019[d] United States [5]	**A3051016** 26 Dec 2001/ 18 Sept 2002 **A3051019** 19 Mar 2002/ 24 June 2003	Randomized, Parallel Group, Double-blind, Placebo-controlled	Varenicline Flexible dosing (0.5 mg QD to 1mg BID) Placebo	N=157 N=155	12 week treatment period Nontreatment follow-up to 1 yr from start of treatment
Phase 3 Studies					
Zyban Comparator A3051028 United States [19]	19 Jun 2003/ 22 Apr 2005	Randomized, Parallel Group, Double-blind, Placebo-controlled, Active Comparator	Varenicline 1mg BID Zyban[b] 150 mg BID Placebo	N=349 N=329 N=344	12 week treatment period Nontreatment follow-up to 1 yr from start of treatment
Zyban Comparator A3051036 United States [14]	26 Jun 2003/ 21 Mar 2005	Randomized, Parallel Group, Double-blind, Placebo-controlled, Active Comparator	Varenicline 1mg BID Zyban[b] 150 mg BID Placebo	N=343 N=340 N=340	12 week treatment period Nontreatment follow-up to 1 yr from start of treatment
Efficacy: Maintenance of Abstinence Study					
Maintenance A3051035 United States [6] Denmark [3], Sweden [3], Norway [3], Czech Republic [1], United Kingdom [2], Canada [6]	13 Apr 2003/ 3 Mar 2005	Open-label, followed by Randomization to Double-blind Varenicline or Placebo	OL Varenicline 1mg BID DB Varenicline 1 mg BID Placebo	 N=1927 N=602 N=604	OL: 12 week treatment with varenicline DB: Varenicline 1mg BID or placebo for 12 additional weeks Nontreatment follow-up to 1 yr from start of treatment

The table below (from Dr. Buenconsejo's review) summarizes the results of the five studies involving varenicline treatment for 12 weeks or more, showing the proportion of subjects meeting responder criteria (abstinent weeks 8-12). For A3051035, determination of the abstinence rate during weeks 8-12 of the open-label varenicline run-in was not a protocol-specified analysis, but these figures were calculated by Dr. Buenconsejo from the Sponsor's datasets to provide additional confirmation of the findings of the other studies.

Primary Efficacy Criterion – Four-Week Continuous Quit Rate

	Varenicline 0.5 mg b.i.d.	Varenicline 1.0 mg b.i.d.	Varenicline Flexible	Zyban	Placebo
Study A3051028 (%)		44%		30%	17%
OR (95% CI) varenicline vs.				1.9 (1.4, 2.6)	3.9 (2.7, 5.5)
Study A3051036 (%)		44%		30%	18%
OR (95% CI) varenicline vs.				1.9 (1.4, 2.6)	3.8 (2.7, 5.4)
Study A3051035 (%)		51%*			
Study A3051007 (%)	45%	51%			12%
OR (95%) vs. placebo	6.1 (3.3, 11.1)	7.8 (4.3, 14.3)			
Study A3051016 (%)			40%		15%
OR (95%) vs. placebo			5.7 (3.1, 10.4)		

* Post-hoc calculation based on Weeks 8 – 12 data during the open-label phase of Study A1035.

As is obvious from the table above, 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. On this basis, this application was accorded priority review status. Notably, Zyban was also demonstrated to be superior to placebo in all studies in which a Zyban arm was included.

2.4 Population

Inclusion/exclusion criteria were very similar across studies. Adult smokers, with a maximum age of 65 in the Phase 2 studies and 75 in the Phase 3 studies, were eligible to participate if they had been smoking at least 10 cigarettes per day for the prior year, without a significant period of abstinence. In the Phase 3 Zyban comparator studies, participants were not permitted to have a prior history of Zyban treatment. The population was 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 Zyban comparator studies also excluded subjects unsuitable for Zyban treatment, such as subjects with a history of bulimia or seizure disorder, or conditions predisposing to a lowered seizure

threshold. This was very broadly defined so as to exclude anyone using insulin or oral hypoglycemics, as well as subjects using medications such as antipsychotics and antidepressants which lower seizure threshold. The allowable concomitant medications were limited. Details of the inclusion/exclusion criteria for each study can be found in the individual study reviews in the Appendices of this review.

2.5 Design and Endpoints

2.5.1 Smoking Cessation Studies

The main smoking cessation studies 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. Note that, for administrative reasons, Pfizer assigned a new protocol number to the post-treatment follow-up phase in several studies. References to protocol numbers other than those in the table above are, in general, to these post-treatment follow-up "studies."

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 $\leq$ 10 ppm. An additional analysis of interest to the division was the proportion of subjects initiating abstinence by week 3 (2 weeks from TQR) and maintaining abstinence throughout treatment. This two week "grace" period is in keeping with the analytic approach to other nicotine agonist drugs.

Key secondary endpoints identified in the protocol included:
- Continuous Abstinence Rate from Week 9 through Week 52
- Long-term Quit Rate through Week 52(the proportion of subjects who have successfully quit during the treatment phase of the study based on the 4-week CQR from Week 9 through Week 12 and who have had no more than 6 days of smoking during the nontreatment phase)

Other secondary endpoints identified included:
- Continuous Abstinence Rate 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
- Change from baseline in body weight
- Results of the Minnesota Nicotine Withdrawal Scale, the Brief Questionnaire of Smoking Urges, and the Smoking Effects Inventory

2.5.2 Maintenance of Efficacy Study

The maintenance of efficacy study, A3051035, examined whether an additional 12 weeks of dosing with varenicline 1 mg b.i.d. would increase long-term smoking abstinence rates. Enrolled subjects were entered into a 12-week open-label phase during which all subjects were treated with varenicline 1 mg b.i.d. (titrated from 0.5 qd to 1 mg b.i.d. over a week) and attended clinic visits at Weeks 1 through 8, 10 and 12 with a TQD set at the Week 1 visit. Smoking status was assessed at each visit through self-report and exhaled CO. At the Week 12 visit, subjects who were abstinent for the previous 7 days were eligible for re-randomization to either continue on treatment or switch (blindly) to placebo for an additional 12 weeks of treatment. After re-randomization, study visits occurred at Weeks 13, 14, 16, 20 and 24. Smoking status and exhaled CO was obtained at each visit. The study included non-treatment follow-up of smoking status up to Week 52. Subjects attended clinic visits at Weeks 25, 28, 36, 44, and 52 and were contacted via telephone at Weeks 26, 32, 40, and 48.

The primary efficacy criteria are shown below (Pfizer's table from clinical study report):

Primary Endpoint:	
Continuous Abstinence (CA) Rate Weeks 13 to 24	Proportion of subjects abstinent from day of first dose of double-blind medication through Week 24 visit
Key Secondary Endpoints:	
Continuous Abstinence (CA) Rate Weeks 13 to 52	Proportion of subjects abstinent from day of first dose of double-blind medication through Week 52 visit
Long Term Quit Rate at Week 52	Proportion of subjects who maintained abstinence through double-blind treatment (Weeks 13-24), and had ≤6 days of smoking during non-treatment follow-up phase
Other Secondary Endpoints:	
7-Day Point-Prevalence of Abstinence	Proportion of subjects abstaining from smoking during the preceding 7 days; assessed at every contact, analyzed with inferential statistics at Weeks 24 and 52
4-Week Point-Prevalence of Abstinence	Proportion of subjects abstaining from smoking during the last four weeks of the nontreatment follow-up phase (Weeks 49-52)
Time to first cigarette post-randomization	Calculated from the date of first randomized therapy to the date of first cigarette smoked

2.6 Results

The results of the two Phase 2 trials and the three Phase 3 trials reviewed for efficacy are briefly summarized below. For more thorough descriptions of each study, see the Appendices.

2.6.1 Study Title(s): Protocol A3051028: A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study with Follow-up Evaluating the Safety and Efficacy of Varenicline Tartrate (CP-526,555) in Comparison to Zyban® for Smoking Cessation and Protocol A3051036: A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study with Follow-up Evaluating the Safety and Efficacy of Varenicline Tartrate (CP-526,555) in comparison to Zyban® for Smoking Cessation

These studies were identical in design and very similar in results; therefore the results are displayed side-by-side below, as per Dr. Buenconsejo's review.

2.6.1.1 Demographics and Patient Disposition

The demographics of the treatment groups and baseline smoking history and smoking behavior were similar across treatment groups. In both studies, more than half of the participants were male (54%, 58%), and in both studies, the varenicline arm had the lowest proportion of male subjects (50% in study A1028 and 55% in A1036). This is notable because conventional wisdom holds that female smokers may be more difficult to treat; if true, this would potentially bias the study *against* varenicline. Participants had been smoking for an average of approximately 24-27 years (range, 2 – 61), smoked, on average, 22 cigarettes/day (range 10-80), and had a mean Fagerstrom Test of Nicotine Dependence (FTND) score of just over 5. Over 85% of subjects had made a previous serious quit attempt.

Patient disposition is illustrated in the table below, adapted from Dr. Buenconsejo's review:

	Study A1028			Study A1036		
	Varenicline	Zyban	Placebo	Varenicline	Zyban	Placebo
Screened	1483			1413		
Assigned to Treatment	352	329	344	344	342	341
All Subjects (Treated)[a]	349	329	344	343	340	340
Completed the Study	213 (61%)	184 (56%)	187 (54%)	240 (70%)	221 (65%)	204 (60%)
Discontinued Study	136 (39%)	145 (44%)	157 (46%)	103 (30%)	119 (35%)	136 (40%)
During the treatment Phase	90 (26%)	104 (32%)	129 (38%)	83 (24%)	100 (29%)	118 (35%)
Adverse Events	14 (4%)	34 (10%)	24 (7%)	14 (4%)	16 (5%)	13 (4%)
Lack of Efficacy	2	1	4	1	0	3
Protocol Deviations	4	1	6	2	9	4
Pregnancy	0	0	0	1	1	0
Refusal to participate further	23 (7%)	31 (9%)	42 (12%)	28 (8%)	31 (9%)	51 (15%)
Lost to follow-up	43 (12%)	36 (11%)	49 (14%)	33 (10%)	39 (11%)	43 (13%)
Other	4	1	4	4	4	4
During the non-treatment Phase	46 (13%)	41 (13%)	28 (8%)	20 (6%)	19 (6%)	18 (5%)
Subject Died	0	0	1	0	1	0
Adverse Events	0	0	0	0	0	0
Lack of Efficacy	0	0	0	0	0	0
Protocol Deviations	0	1	0	0	2	1
Pregnancy	0	0	0	0	0	0
Refusal to participate further	11	10	5	3	6	4
Lost to follow-up	34	29	22	14	10	12
Other	1	1	0	3	0	1
Protocol Deviations	11 (3%)	13 (4%)	22 (6%)	17 (5%)	16 (5%)	13 (4%)

The most common reasons for discontinuation were "refusal to participate further" and "loss to follow-up." From an efficacy standpoint, treatment failure is imputed to these subjects. There are more subjects in both categories in the placebo arms of each of the studies; this could represent a potential bias. However, relapse to smoking after treatment discontinuation is generally considered to be the rule, rather than the exception, and it seems reasonable to impute treatment failure to these subjects.

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as several subjects who took prohibited medications during the treatment phase. These included a few subjects, distributed across treatment groups, who used nicotine replacement therapy, as well as a number of subjects who used medications unlikely to affect the efficacy outcome or interpretation of the study.

2.6.1.2 Efficacy Results

Dr. Buenconsejo re-calculated abstinence rates using a missing data imputation strategy that differed from Pfizer's. Whereas the Phase 2 program had used a conservative strategy of imputing treatment failure to subjects with missing CO values, or to subjects who missed more than one consecutive treatment visit, the Phase 3 protocols permitted imputation of treatment success as long as the next non-missing value was consistent

with abstinence. In addition, she calculated rates using a shorter "grace period" than the protocol-specified 8 weeks. Pfizer's results and Dr. Buenconsejo's are shown below.

2.6.1.2.1 Abstinence Rates

In the table below (adapted from tables 9 and 10) from Dr. Buenconsejo's review, Pfizer's reported rates of abstinence over weeks 9-12 are shown along with Dr. Buenconsejo's calculated rates. Dr. Buenconsejo recalculated the abstinence rates using the data imputation methods used in Phase 2, rather than the more liberal methods stipulated in the Phase 3 protocols, and found that only four subjects (3 in varenicline and 1 in placebo) did not meet the four-week abstinence criteria when these rules were applied; the overall conclusion did not change.

Primary Efficacy Criterion - Four-Week Abstinence Rates

	Study A1028			Study A1036		
	Varenicline	Placebo	Zyban	Varenicline	Placebo	Zyban
Applicant's results:						
ITT Subjects	N=349	N=344	N=329	N=343	N=340	N=340
Abstinent (%)	155 (44%)	61 (18%)	97 (30%)	151 (44%)	60 (18%)	102 (30%)
Odds ratio		3.9	2.0		3.8	1.9
(varenicline vs.)		(2.7, 5.6)	(1.4, 2.7)		(2.7, 5.5)	(1.4, 2.6)
p-value (varenicline vs.)		<0.0001	<0.0001		<0.0001	<0.0001
Evaluable	N=309	N=302	N=275	N=310	N=304	N=295
Abstinent (%)	152 (49%)	61 (20%)	96 (35%)	151 (49%)	60 (20%)	99 (34%)
Odds ratio		4.1	1.9		4.1	1.9
(varenicline vs.)		(2.9, 6.0)	(1.3, 2.6)		(2.8, 5.8)	(1.4, 2.7)
p-value (varenicline vs.)		<0.0001	0.0004		<0.0001	0.0001
Reviewer's results:						
ITT Subjects	N=349	N=344	N=329	N=343	N=340	N=340
Abstinent (%)	152 (44%)	60 (17%)	97 (30%)	150 (44%)	60 (18%)	101 (30%)
Odds ratio		3.9	1.9		3.8	1.9
(varenicline vs.)		(2.7, 5.5)	(1.4, 2.6)		(2.7, 5.4)	(1.4, 2.6)
p-value (varenicline vs.)		<0.0001	0.0001		<0.0001	0.0001

2.6.1.2.2

Additionally, Dr. Buenconsejo calculated rates of continuous abstinence from the end of a various grace periods following the TQD through the end of treatment and found that varenicline was superior to placebo no matter what grace period was applied. In addition, superiority to Zyban was also noted using any grace period in Study A3051036, and any grace period of 3 weeks or more in Study A3051028, suggesting that the finding of efficacy and the superiority to Zyban were not limited to a single analytic approach to the data. These results are illustrated below in Dr. Buenconsejo's Table 12.

Continuous Abstinence Rate from Weeks 3 through Timepoints – Number (%) of Subjects (Study A3051028 and Study A3051036)

	Varenicline N=349	Placebo N=344	OR Varenicline vs.	p-value	Zyban N=329	OR Varenicline vs.	p-value
			Study A3051028				
Week 3 – 12	102 (29%)	41 (12%)	3.2 (2.1, 4.8)	<0.0001	77 (23%)	1.4 (1.0, 2.0)	0.0800
Week 4 – 12	108 (31%)	45 (13%)	3.1 (2.1, 4.7)	<0.0001	81 (25%)	1.4 (1.0, 2.0)	0.0611
Week 5 – 12	122 (35%)	40 (15%)	3.4 (2.3, 4.9)	<0.0001	85 (26%)	1.6 (1.1, 2.2)	0.0092
Week 6 – 12	127 (36%)	54 (16%)	3.2 (2.2, 4.7)	<0.0001	89 (27%)	1.6 (1.1, 2.2)	0.0091
Week 7 – 12	135 (39%)	56 (16%)	3.4 (2.4, 4.9)	<0.0001	93 (28%)	1.6 (1.2, 2.3)	0.0043
Week 8 – 12	141 (40%)	56 (16%)	3.7 (2.5, 5.3)	<0.0001	95 (29%)	1.7 (1.2, 2.4)	0.0017
Week 9 – 12	152 (44%)	60 (17%)	3.9 (2.7, 5.5)	<0.0001	97 (29%)	1.9 (1.4, 2.6)	0.0001
			Study A3051036				
Week 3 – 12	101 (29%)	38 (11%)	3.5 (2.3, 5.3)	<0.0001	71 (21%)	1.6 (1.1, 2.3)	0.0079
Week 4 – 12	113 (33%)	42 (12%)	3.6 (2.4, 5.4)	<0.0001	79 (23%)	1.7 (1.2, 2.3)	0.0040
Week 5 – 12	121 (35%)	47 (14%)	3.5 (2.4, 5.2)	<0.0001	88 (26%)	1.6 (1.1, 2.2)	0.0063
Week 6 – 12	128 (37%)	49 (14%)	3.8 (2.5, 5.4)	<0.0001	91 (27%)	1.7 (1.2, 2.3)	0.0025
Week 7 – 12	133 (39%)	52 (15%)	3.6 (2.5, 5.3)	<0.0001	95 (28%)	1.7 (1.2, 2.3)	0.0021
Week 8 – 12	140 (41%)	53 (16%)	3.9 (2.7, 5.6)	<0.0001	99 (29%)	1.7 (1.2, 2.4)	0.0010
Week 9 – 12	150 (44%)	60 (18%)	3.8 (2.7, 5.4)	<0.0001	101 (30%)	1.9 (1.4, 2.6)	0.0001

In addition, Pfizer calculated the long-term abstinence rates among study participants. These data show that after 12 weeks of treatment, more subjects who are treated with varenicline (or Zyban) remain abstinent 40 weeks later than subjects who are treated with placebo. However, the relapse rate across groups did not support the idea that a course of treatment with varenicline necessarily renders a successful quitter less vulnerable to relapse than smokers who quit without varenicline. Pfizer also calculated a rate termed the "long term quit rate" (LTQR) which differed from continuous abstinence in that subjects could report up to six days of smoking during the non-treatment follow-up and be deemed "long-term quitters." Although, conceptually, this is unobjectionable, it is not clear that the methods used to capture the smoking histories were detailed enough to allow participants to accurately report anything other than any smoking vs. no smoking. Therefore, the LTQR may not be an accurate reflection of the smoking behavior of participants, but is shown below as an alternative definition of relapse. Notably, this alternative definition does not appear to provide evidence that varenicline treatment has a specific effect that allows former smokers to lapse without relapsing.

The rate of non-relapse at the end of the observation period (week 52) is shown below (table constructed using data from Dr. Buenconsejo's Tables 12, 13, 14, 15 and 16). The percentages shown are the proportion of subjects abstinent during weeks 9-12 who survived to week 52 according to the criteria shown.

	Study A3051028			Study A3051036		
	Varenicline N=343	Placebo N=340	Zyban N=340	Varenicline N=349	Placebo N=344	Zyban N=329
Subjects abstinent at week 12	152	60	97	150	60	101
Subjects continuously abstinent to week 52, N (%)	74 (49%)	27 (45%)	52 (54%)	74 (49%)	34 (57%)	49 (49%)
Number reporting ≤6 days smoking during follow-up, N(%)	88 (57%)	32 (53%)	57 (58%)	86 (57%)	43 (71%)	61 (60%)

2.6.1.2.3 Secondary Endpoints/Subjective Measures

Pfizer also seeks to make claims about the effects of varenicline on various subjective measures of craving, withdrawal, and smoking satisfaction. In the tables below, from Dr. Buenconsejo's review, the scores from the various subjective measures over the first 7 weeks of treatment are displayed, and show numerically small but statistically significant differences between varenicline and placebo on some measures. However, the selection of certain subscales from the MNWS to support a claim of "relief of withdrawal" was noted by Dr. Scott of the SEALD team to be inappropriate. Indeed, rather than relieving some symptoms of withdrawal (insomnia is listed in DSM-IV as a possible symptom of nicotine withdrawal), varenicline appears (based on analysis of the adverse events dataset) to cause insomnia; likewise, varenicline may be associated with increased appetite, another symptom of withdrawal. Therefore, a claim regarding relief of withdrawal seems inappropriate.

Table 1: Secondary Endpoints – All Subjects (Study A1028)

	Average of Weeks 1 - 7		Comparisons vs. Placebo [a]		
	LS Mean (SE)[b]	95% CI	Difference (SE)	95% CI	p-value
Craving					
MNWS Urge to Smoke (Item 1)					
Varenicline	1.1 (0.05)	(1.0, 1.2)	-0.5 (0.06)	(-0.7, -0.4)	<0.0001
Zyban	1.4 (0.05)	(1.3, 1.5)	-0.2 (0.06)		0.0001
Placebo	1.6 (0.05)	(1.6, 1.7)		(-0.4, -0.1)	
QSU-Brief Total Craving Score					
Varenicline	1.7 (0.05)	(1.6, 1.8)	-0.4 (0.06)	(-0.6, -0.3)	<0.0001
Zyban	1.9 (0.05)	(1.8, 2.0)	-0.2 (0.07)		0.0013
Placebo	2.1 (0.05)	(2.0, 2.2)		(-0.3, -0.1)	
Withdrawal					
MNWS Negative Affect (Items 2 – 5)					
Varenicline	0.6 (0.03)	(0.5, 0.7)	-0.2 (0.04)	(-0.3, -0.1)	<0.0001
Zyban	0.6 (0.03)	(0.6, 0.7)	-0.2 (0.04)		0.0002
Placebo	0.8 (0.03)	(0.7, 0.8)		(-0.3, -0.1)	
MNWS Restlessness (Item 6)					
Varenicline	0.7 (0.04)	(0.6, 0.8)	-0.1 (0.05)	(-0.2, -0.0)	0.0095
Zyban	0.7 (0.04)	(0.7, 0.8)	-0.1 (0.05)		0.0841
Placebo	0.8 (0.04)	(0.8, 0.9)		(-0.2, 0.0)	
Reinforcing Effects of Smoking					
SEI/mCEQ Smoking Satisfaction (Item 1, 2 and 12)					
Varenicline	2.4 (0.08)	(2.3, 2.6)	-0.6 (0.1)	(-0.8, 0.4)	<0.0001
Zyban	2.9 (0.08)	(2.7, 3.1)	-0.1 (0.1)	(-0.3, 0.1)	0.1778
Placebo	3.0 (0.07)	(2.9, 3.2)			
SEI/mCEQ Psychological Reward (Questions 4 – 8)					
Varenicline	2.1 (0.06)	(1.9, 2.2)	-0.5 (0.08)	(-0.7, -0.3)	<0.0001
Zyban	2.3 (0.06)	(2.2, 2.4)	-0.2 (0.08)		0.0038
Placebo	2.5 (0.06)	(2.4, 2.7)		(-0.4, -0.1)	

[a] Inferential analyses are based on a repeated-measures model with factors: treatment group, baseline measure, center, visit, and treatment by visit interaction. Model estimates on the average effect and the p-values versus placebo are obtained by contrasting the average of Week 1 through Week 7.

[b] Higher scores indicate greater intensity of symptoms.

Table 2: Secondary Endpoints – All Subjects (Study A1036)

	Average of Weeks 1 - 7		Comparisons vs. Placebo [a]		
	LS Mean (SE)[b]	95% CI	Difference (SE)	95% CI	p-value
	Craving				
MNWS Urge to Smoke (Item 1)					
Varenicline	1.2 (0.04)	(1.2, 1.3)	-0.5 (0.06)	(-0.6, -0.4)	<0.0001
Zyban	1.3 (0.04)	(1.3, 1.4)	-0.4 (0.06)		<0.0001
Placebo	1.7 (0.04)	(1.6, 1.8)		(-0.5, -0.3)	
QSU-Brief Total Craving Score					
Varenicline	1.8 (0.05)	(1.7, 1.9)	-0.4 (0.07)	(-0.6, -0.3)	<0.0001
Zyban	1.9 (0.05)	(1.8, 2.0)	-0.3 (0.07)		<0.0001
Placebo	2.2 (0.05)	(2.1, 2.3)		(-0.5, -0.2)	
	Withdrawal				
MNWS Negative Affect (Items 2 – 5)					
Varenicline	0.6 (0.03)	(0.5, 0.7)	-0.1 (0.04)	(-0.2, -0.1)	0.0011
Zyban	0.6 (0.03)	(0.5, 0.7)	-0.1 (0.04)		0.0014
Placebo	0.7 (0.03)	(0.7, 0.8)		(-0.2, -0.1)	
MNWS Restlessness (Item 6)					
Varenicline	0.8 (0.04)	(0.7, 0.8)	-0.1 (0.05)	(-0.2, 0.0)	0.0539
Zyban	0.8 (0.04)	(0.7, 0.9)	-0.1 (0.05)	(-0.2, 0.0)	0.1619
Placebo	0.9 (0.04)	(0.8, 0.9)			
	Reinforcing Effects of Smoking				
SEI/mCEQ Smoking Satisfaction (Item 1, 2 and 12)					
Varenicline	2.7 (0.07)	(2.6, 2.9)	-0.4 (0.1)	(-0.6, -0.3)	<0.0001
Zyban	2.8 (0.07)	(2.7, 3.0)	-0.3 (0.1)		0.0003
Placebo	3.2 (0.06)	(3.1, 3.3)		(-0.5, -0.2)	
SEI/mCEQ Psychological Reward (Questions 4 – 8)					
Varenicline	2.2 (0.06)	(2.1, 2.3)	-0.3 (0.1)	(-0.5, -0.2)	<0.0001
Zyban	2.3 (0.06)	(2.1, 2.4)	-0.3 (0.1)		0.0003
Placebo	2.5 (0.05)	(2.4, 2.6)		(-0.4, -0.1)	

[a] Inferential analyses are based on a repeated-measures model with factors: treatment group, baseline measure, center, visit, and treatment by visit interaction. Model estimates on the average effect and the p-values versus placebo are obtained by contrasting the average of Week 1 through Week 7.
[b] Higher scores indicate greater intensity of symptoms.

Varenicline's effects on "craving" and "urge to smoke" both appear to be measuring the same construct, probably best described, per Dr. Scott, as "urge to smoke." However, a consistent effect on the instruments and questions measuring this concept appears to be demonstrated.

Dr. Scott observed that the measures of the reinforcing effects of smoking captured all the relevant aspects of smoking reinforcement. She concluded that "reinforcing effects of smoking" is not a clearly-defined concept suitable for labeling.

2.6.1.3 Discussion

The results of these two studies, no matter what analysis is applied, demonstrate that varenicline treatment is associated with a higher proportion of patients achieving abstinence of various durations than is treatment with either placebo or Zyban. However, the most striking feature of the results is their uncanny consistency. The quit rates for all three treatment arms are identical. This is an unusual outcome for a program of smoking cessation studies, wherein even the placebo rate generally fluctuates several percentage points (or more) from one study to the next. For this reason, the review team feared that either inadvertent error (e.g. analyzing and reporting the same set of data twice) or deliberate fraud could have been involved. Therefore, the Division of Scientific Investigations (DSI) was asked to take special pains to ensure that the reported information matched the source documents at each investigated site, and even to go so far as to contact study participants to verify that they did, in fact, exist and had, in fact been participants in the study with the outcomes as documented. The results of these inspection indicate that the results reported from the study sites were consistent with the source documents, and that the study subjects contacted confirmed that they had participated in the study. No indication of fraud was found.

2.6.1.4 Efficacy Conclusion, Study A3051028 and Study A3051036

These studies provide substantial evidence of efficacy of varenicline, 1 mg b.i.d., as an aid to smoking cessation, and substantial evidence that this dose is superior to the labeled dosing regimen of Zyban as an aid to smoking cessation. In addition, the studies provide evidence that varenicline decreases the urge to smoke experienced by smokers in the initial weeks of a quit attempt.

2.6.2 Study Title: Protocol A3051007: A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating the Safety and Efficacy Of Four Dosing Strategies For CP-526,555 (0.5 mg b.i.d., Titrated 0.5 mg b.i.d, 1 mg b.i.d, and Titrated 1 mg b.i.d.) in Smoking Cessation

2.6.2.1 Treatment Arms

This study compared four dosing regimens for varenicline to placebo. The dosages and regimens were selected on the basis of efficacy and tolerability results from Study A3051002, as well as tolerability data from Phase 1 clinical studies. These studies suggested that the maximum tolerated daily dosage was 2.0 mg/day, but that the incidence of nausea and vomiting was lower when that dosage was administered as 2 divided doses (1.0 mg b.i.d.) rather than as a single dose of 2.0 mg. 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.

Study medication was administered for 12 weeks as follows for each dosage group:

Varenicline:

0.5 mg b.i.d. nontitrated:	0.5 mg b.i.d. for 12 weeks
0.5 mg b.i.d. titrated:	0.5 mg QD for 7 days, then 0.5 mg b.i.d. for 11 weeks
1.0 mg b.i.d. nontitrated:	1.0 mg b.i.d. for 12 weeks
1.0 mg b.i.d. titrated:	0.5 mg QD for 3 days, then 0.5 mg b.i.d. for 4 days, then 1.0 mg b.i.d. for 11 weeks
Placebo b.i.d.:	2 placebo tablets b.i.d. for 12 weeks

2.6.2.2 Demographics and Patient Disposition

The demographics of the treatment groups and baseline smoking history and smoking behavior were broadly similar across treatment groups. The proportion of male participants ranged from 44% in the 0.5 mg b.i.d. non-titrated arm to 53% in the placebo and 0.5 mg b.i.d. titrated arms. The mean age of participants was 42-44 years. From 71% (placebo group) to 86% (0.5 mg b.i.d. non-titrated and 1 mg b.i.d. non-titrated groups) were Caucasian. Participants had been smoking for an average of approximately 24-26 years, smoked, on average, 21 cigarettes/day (range 7-80), and had a mean Fagerstrom Test of Nicotine Dependence (FTND) score of 5-6. From 4%-11% of subjects had made no prior serious quit attempts, and 58-62% had made 3 or more.

Patient disposition is illustrated in the table below, adapted from Pfizer's final study report:

	0.5 mg b.i.d. nontitrated N = 124	0.5 mg b.i.d. titrated N = 129	1.0 mg b.i.d. nontitrated N = 124	1.0 mg b.i.d. titrated N = 129	Placebo N = 121
Number Screened: 980					
Assigned to Treatment	129	130	129	130	129
Treated[a]	124	129	124	129	121
Completed Study	96 (77.4)	92 (71.3)	95 (76.6)	100 (77.5)	72 (59.5)
Discontinued Study	28 (22.6)	37 (28.7)	29 (23.4)	29 (22.5)	49 (40.5)
Discontinued Study *Medication*	36 (29.0)	48 (37.2)	40 (32.3)	51 (39.5)	55 (45.5)
Adverse events[a]	9 (7.3)	19[b] (14.7)	18[b] (14.5)	28 (21.7)	22[b] (18.2)
Lack of efficacy	0 (0.0)	2 (1.6)	2 (1.6)	0 (0.0)	4 (3.3)
Subject defaulted[c]	21 (16.9)	25 (19.4)	16 (12.9)	13 (10.1)	23 (19.0)
Other[d]	6 (4.8)	2 (1.6)	4 (3.2)	10 (7.8)	6 (5.0)

[a] Percentages based on number of subjects treated
[b]Includes laboratory abnormalities
[c]Subject defaulted = subject withdrew consent or was lost to follow-up.
[d] "Other" includes the following: protocol violations, subject did not meet entry criteria, non- compliance, and personal reasons.

As shown in the table below, within each varenicline dosage (0.5 mg b.i.d. or 1.0 mg b.i.d.), initial dose titration did not reduce the incidence of study drug discontinuations due to adverse events. Most drug discontinuations due to adverse events occurred more than 14 days after initiation of study medication, after titration was completed. Nausea and insomnia were the adverse events most often leading to discontinuation of varenicline.

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as several subjects who took prohibited medications during the treatment phase. These included a few subjects, distributed across treatment groups, who used nicotine replacement therapy. In addition, Pfizer identified and excluded from the "evaluable" population those patients who did took less than 14 days of study medication in the first 21 days of the study. These subjects are included in the intent-to-treat (ITT) analysis. The number of patients in this group ranged from 7 (5%) of the 1 b.i.d. non-titrated group to 16 (13%) of the placebo group; this could have an impact on study interpretation. However, in Pfizer's own analysis using the evaluable population, all pairwise comparisons against placebo continued to be statistically significant at the $p<.0001$ level.

2.6.2.3 Efficacy Results

Because this was an Phase 2 study, the protocol called for analysis of a quit rate at weeks 4-7 and another at weeks 9-12 because Pfizer had not yet determined the duration of treatment that would be studied in the Phase 3 program. However, as the study has the same basic features as the Phase 3 studies, it is amenable to the same analyses applied to those studies, and in this memo I will summarize only those analyses (as reported in Dr. Buenconsejo's review).

2.6.2.3.1 Abstinence Rate

The table below is adapted from Dr. Buenconsejo's tables 32 and 34.

	Varenicline						Placebo
	0.5 mg b.i.d. (pooled)	0.5 mg b.i.d. Nontitrated	0.5 mg b.i.d. Titrated	1 mg b.i.d. (pooled)	1 mg b.i.d. Nontitrated	1 mg b.i.d. Titrated	
ITT Subjects	N=253	N=124	N=129	N=253	N=124	N=129	N=121
Abstinent (%)	114 (45%)	61 (49%)	53 (41%)	128 (51%)	57 (46%)	71 (55%)	15 (12%)
Odds ratio (95% CI) vs. placebo	6.1 (3.3, 11.1)	7.2 (3.7, 13.8)	5.2 (2.7, 9.9)	7.8 (4.3, 14.3)	6.4 (3.3, 12.4)	9.6 (5.0, 18.4)	
p-value vs. placebo	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Evaluable	N=231	N=113	N=118	N=235	N=114	N=121	N=104
Abstinent (%)	112 (49%)	60 (53%)	52 (44%)	128 (54%)	57 (50%)	71 (59%)	15 (14%)
Odds ratio (95% CI) vs. placebo	5.8 (3.1, 10.7)	6.9 (3.5, 13.5)	4.9 (2.5, 9.5)	7.5 (4.1, 13.9)	6.1 (3.1, 12.0)	9.1 (4.6, 17.8)	
p-value vs. placebo	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

As shown in the table above, all four tested regimens were superior to placebo as aids to smoking cessation. An incremental benefit of 1 mg b.i.d. over 0.5 mg b.i.d. was noted particularly when a titration method was used; however, no benefit of the higher dose was noted in the non-titrated schemes.

Dr. Buenconsejo also calculated rates of continuous abstinence from the end of a various grace periods following the TQD through the end of treatment. As illustrated in the table below, from her review, the effect of varenicline is not dependent on analysis of a specific efficacy window.

Continuous Abstinence Rate from Weeks 3 through Timepoints – (Study A3051007)

	Varenicline 0.5 mg b.i.d. N=253	Varenicline 1.0 mg b.i.d. N=253	Placebo N=121
Week 3 – 12	81 (32%)	83 (33%)	11 (9%)
Week 4 – 12	84 (33%)	96 (38%)	12 (10%)
Week 5 – 12	90 (36%)	108 (43%)	13 (11%)
Week 6 – 12	97 (38%)	115 (45%)	13 (11%)
Week 7 – 12	100 (40%)	117 (46%)	14 (12%)
Week 8 – 12	107 (42%)	123 (49%)	15 (12%)
Week 9 – 12 *	114 (45%)	128 (51%)	15 (12%)

** Primary Efficacy Criterion*

In the non-treatment follow-up (administratively designated protocol A3051018), the proportion of subjects remaining abstinent to the 52 week point (40 weeks post-treatment) was higher in the varenicline-treated than in the placebo-treated groups, with 19% of the 0.5 mg b.i.d. group, 23% of the 1 mg b.i.d. group, and 4% of the placebo group remaining abstinent to the end of follow-up. This represents a non-relapse rate of 42% in the 0.5 mg b.i.d. group, 45% in the 1 mg b.i.d. group, and 33% in the placebo

group. A survival curve reveals that most relapses occurred in the 12 weeks following treatment discontinuation.

2.6.2.4 Discussion

Although dose titration at the initiation of treatment did not reduce the likelihood of premature treatment discontinuation due to adverse events, Pfizer observed that the rate of nausea was reduced when initial dose titration was employed. Based on this observation, a titrated scheme was used in subsequent studies including the Phase 3 program. However, examination of the common AE tables from this study suggests that few specific AEs were affected by the presence or absence of titration (increased appetite and diarrhea are other examples of AEs seen more frequently in the non-titrated groups than the same-dose titrated groups). However, comparing the titrated arms, a number of adverse events were more common in subjects treated with 1 mg b.i.d. compared to those treated with 0.5 mg b.i.d., as shown in the table below from Pfizer's final study report (note: this table employs COSTART, not MedDRA, coding, and shows treatment-emergent adverse events occurring in ≥5% of any varenicline treatment group and at a higher frequency in any varenicline treatment group than with placebo. It is arranged by decreasing frequency among all subjects taking 1.0 mg b.i.d.). Comparisons of particular interest, showing a higher incidence of certain events in the 1 mg b.i.d., titrated arm compared to the 0.5 mg b.i.d., titrated arm are bolded and italicized below (my emphasis):

Most Frequent (≥5%) Treatment-Emergent Adverse Events [Number (%) of Subjects]

COSTART		CP-526,555			Placebo
Preferred Term	0.5 mg b.i.d. nontitrated N = 124	0.5 mg b.i.d. titrated N = 129	1.0 mg b.i.d. nontitrated N = 124	1.0 mg b.i.d. titrated N = 129	N = 121
Nausea	28 (22.6)	***21 (16.3)***	52 (41.9)	***45 (34.9)***	18 (14.9)
Insomnia	42 (33.9)	***27 (20.9)***	27 (21.8)	***48 (37.2)***	14 (11.6)
Headache	34 (27.4)	25 (19.4)	30 (24.2)	29 (22.5)	21 (17.4)
Abnormal dreams	21 (16.9)	***15 (11.6)***	21 (16.9)	***25 (19.4)***	6 (5.0)
Taste perversion	20 (16.1)	***10 (7.8)***	17 (13.7)	***15 (11.6)***	5 (4.1)
Dyspepsia	11 (8.9)	***8 (6.2)***	12 (9.7)	***19 (14.7)***	9 (7.4)
Flatulence	19 (15.3)	11 (8.5)	14 (11.3)	13 (10.1)	7 (5.8)
Constipation	8 (6.5)	***6 (4.7)***	13 (10.5)	***14 (10.9)***	3 (2.5)
Somnolence	7 (5.6)	***7 (5.4)***	13 (10.5)	***12 (9.3)***	2 (1.7)
Thinking abnormal	8 (6.5)	8 (6.2)	11 (8.9)	11 (8.5)	5 (4.1)
Vomiting	4 (3.2)	***1 (0.8)***	8 (6.5)	***12 (9.3)***	3 (2.5)
Increased appetite	10 (8.1)	***5 (3.9)***	11 (8.9)	***8 (6.2)***	2 (1.7)
Asthenia	6 (4.8)	***5 (3.9)***	7 (5.6)	***10 (7.8)***	7 (5.8)
Diarrhea	7 (5.6)	***2 (1.6)***	11 (8.9)	***6 (4.7)***	7 (5.8)
Accidental injury	10 (8.1)	11 (8.5)	7 (5.6)	8 (6.2)	5 (4.1)
Back pain	6 (4.8)	8 (6.2)	10 (8.1)	4 (3.1)	8 (6.6)
Rash	5 (4.0)	***2 (1.6)***	3 (2.4)	***8 (6.2)***	3 (2.5)
Pharyngitis	10 (8.1)	7 (5.4)	7 (5.6)	4 (3.1)	4 (3.3)
Pain	8 (6.5)	5 (3.9)	6 (4.8)	4 (3.1)	5 (4.1)
Myalgia	7 (5.6)	5 (3.9)	2 (1.6)	5 (3.9)	3 (2.5)
Menstrual disorder	4 (5.7)	0	0	1 (1.5)	2 (3.5)

2.6.2.5 Efficacy Conclusion, Study A3051007

This study provides evidence of efficacy of both a 0.5 mg b.i.d. dose of varenicline and a 1 mg b.i.d. dose, using either a titrated or a non-titrated dosing regimen. It also suggests some incremental efficacy may be gained by using the higher dose, but demonstrates a number of dose-related adverse events that should be considered, and supports the use of a titration strategy to reduce the incidence of drug-related nausea.

2.6.3 Study Title: Protocol A3051016 A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating the Safety and Efficacy Of a Flexible-Dosing Strategy For CP-526,555 (0.5 mg To 2.0 mg Total Daily Dose) In Smoking Cessation (and A3051019, post-treatment follow-up)

2.6.3.1 Treatment Arms

The purpose of this study was to assess the efficacy and safety of varenicline, administered in a flexible dosing strategy within the range of 0.5 mg to 2.0 mg daily, for smoking cessation in a population of healthy smokers.

Subjects took 1 tablet (varenicline or placebo) QD for 3 days, then 1 tablet b.i.d. for 4 days. After Day 7, subjects who experienced adverse effects, or wanted to try a lower dosage, could reduce the dosage as long as they took at least 1 tablet (0.5 mg) daily, either in the morning or evening. If subjects wanted to try a higher dosage, they could increase the dosage up to a maximum of 2 tablets b.i.d. (each tablet 0.5 mg; total daily dose 2.0 mg). Subjects adjusted their dosage as often as they wished, within the range of 0.5 mg to 2.0 mg total daily dose (1 to 4 tablets daily). Subjects were instructed to initiate treatment on the evening of the baseline visit and to take the doses morning and evening with 240 mL of water. It was recommended that subjects eat prior to dosing (to potentially improve tolerability of the varenicline).

2.6.3.2 Demographics and Patient Disposition

The demographics of the treatment groups and baseline smoking history and smoking behavior were broadly similar across treatment groups. 50-54% of participants were male, and the mean age in both groups was 42 years. White subjects comprised 93% of the varenicline group and 88% of the placebo group. Participants had been smoking for an average of approximately 25 years, smoked, on average, 20 cigarettes/day (range 5-45), and had a mean Fagerstrom Test of Nicotine Dependence (FTND) score of 5.4. Roughly 11-12% had made no prior quit attempts while 60-61% had made 3 or more.

Patient disposition is illustrated in the table below, adapted from Dr. Buenconsejo's review:

Subject Disposition – Studies A3051016/A3051019

	Varenicline	Placebo
Screened	434	
Treatment Phase (A1016)		
Assigned to Treatment	160	160
All Subjects (Treated)[a]	157	155
Evaluable Population[b]	145 (92%)	138 (89%)
Completed the Study	122 (78%)	110 (71%)
Discontinued Study	35 (22%)	45 (29%)
Discontinued Study *Medication*	48 (31%)	53 (34%)
Discontinuation by Reason:		
Adverse Events[c]	11 (7%)	7 (4%)
Lack of Efficacy	0	7
Subject Defaulted[d]	23	33
Other[e]	14	6
Protocol Deviations	13	24

[a] Treated: All randomized subjects who took at least one dose of study medication
[b] Evaluated: Subset of the All Subjects population who received at least 14 days of study medication in the first 21 days of the study.
[c] Adverse event includes laboratory abnormalities
[d] Subject defaulted = subject withdrew consent or was lost to follow-up
[e] Other includes: protocol violations, subject did not meet entry criteria, noncompliance, and personal reasons.
[f] Completer: Subset of the All Subjects population who were at least 80% compliant with treatment as measured by their receiving a dose for 80% of the planned number of days of 12-week treatment period.
[g] Denominator, N, in the number of subjects treated in Study A1007.

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as a few subjects, distributed across treatment groups, who used nicotine replacement therapy. In addition, Pfizer identified and excluded from the "evaluable" population those patients who did took less than 14 days of study medication in the first 21 days of the study. These subjects are included in the intent-to-treat (ITT) analysis. The number of such patients represented 5% of the varenicline group and 10% of the placebo group; this could have an impact on study interpretation. However, in Pfizer's own analysis using the evaluable population, the comparison against placebo continued to be statistically significant.

2.6.3.3 Dosing

As shown in the table below (Pfizers Table 3.1.3 from the final study report of A3051016), participants in the placebo group were more likely to titrate to the maximum allowable dose than were participants in the varenicline group. This may be explained either by the ongoing upward titration in unsuccessful quitters (more common in the placebo group) or the poorer tolerability of the highest dose in the varenicline group, or a combination of the two. Notably, 62% of the varenicline group (vs 75% of the placebo group) titrated to the maximum dose during the second week of treatment, but in each subsequent treatment week, the number of subjects using the maximum allowable dose fell in the varenicline group. More stability in the proportion of participants using the

maximum allowable dose was seen in the placebo group. This suggests that, given the opportunity to self-titrate, subjects did not choose the 1 mg b.i.d. dose tested in the Phase 3 trials and recommended by Pfizer as the only labeled dose. Nevertheless, the proportion of successful quitters in this study was very consistent with that reported in the studies using the higher dose.

As expected for a titration-to-effect study, an inverted-U curve for efficacy was observed when the treatment effect was considered by self-selected dose (analyzed by Dr. Buenconsejo but not reported in her review). This is attributable to the fact that unsuccessful participants are more likely to titrate to the highest allowable dose than are participants who respond earlier, and cannot be interpreted as evidence of greater efficacy of the low dose over the higher dose.

CP-526,555 Protocol A3051016
Number of Subjects with Modal Daily Dose by Week

Week	(Days)	CP-526,555 0.5 mg	CP-526,555 1.0 mg	CP-526,555 1.5 mg	CP-526,555 2.0 mg	Placebo* 0.5 mg	Placebo* 1.0 mg	Placebo* 1.5 mg	Placebo* 2.0 mg
1	(1 - 7)	33 (21.02)	124 (78.98)	0 (0.00)	0 (0.00)	34 (21.94)	121 (78.06)	0 (0.00)	0 (0.00)
2	(8 - 14)	7 (4.55)	36 (23.38)	14 (9.09)	96 (62.34)	5 (3.38)	22 (14.86)	8 (5.41)	111 (75.00)
3	(15 - 21)	11 (7.43)	45 (30.41)	9 (6.08)	83 (56.08)	3 (2.19)	24 (17.52)	6 (4.38)	103 (75.18)
4	(22 - 28)	12 (8.45)	47 (33.10)	10 (7.04)	72 (50.70)	4 (3.10)	22 (17.05)	7 (5.43)	96 (74.42)
5	(29 - 35)	13 (9.63)	41 (30.37)	7 (5.19)	73 (54.07)	5 (4.03)	24 (19.35)	6 (4.84)	89 (71.77)
6	(36 - 42)	25 (19.08)	36 (27.48)	8 (6.11)	62 (47.33)	8 (6.72)	17 (14.29)	6 (5.04)	88 (73.95)
7	(43 - 49)	25 (19.53)	35 (27.34)	12 (9.38)	56 (43.75)	7 (5.93)	14 (11.86)	6 (5.08)	91 (77.12)
8	(50 - 56)	25 (20.00)	37 (29.60)	12 (9.60)	51 (40.80)	7 (6.14)	22 (19.30)	4 (3.51)	81 (71.05)
9	(57 - 63)	29 (23.59)	36 (29.27)	7 (5.69)	51 (41.46)	7 (6.48)	20 (18.52)	5 (4.63)	76 (70.37)
10	(64 - 70)	31 (25.62)	40 (33.06)	9 (7.44)	40 (33.06)	8 (7.62)	20 (19.05)	4 (3.81)	73 (69.52)
11	(71 - 77)	36 (30.77)	37 (31.62)	8 (6.84)	36 (30.77)	9 (9.65)	22 (21.15)	4 (3.85)	69 (66.35)
12	(78 - 84)	33 (29.46)	39 (34.82)	7 (6.25)	33 (29.46)	8 (7.92)	24 (23.76)	3 (2.97)	66 (65.35)
All Weeks		32 (20.51)	49 (31.41)	6 (3.85)	69 (44.23)	13 (8.44)	34 (22.08)	3 (1.95)	104 (67.53)

*mg equivalence to CP-526,555 as calculated by the number of pills taken multiplied by 0.5

2.6.3.4 Efficacy Results

Like the other Phase 2 studies, this study had a protocol-specified analysis of the quit rate at weeks 4-7 as well as during the last four weeks of treatment. However, like Study A3051007, this study is amenable to the analyses ultimately selected for the Phase 3 studies, and I will summarize only those analyses here.

2.6.3.4.1 Abstinence Rate

Dr. Buenconsejo reported the proportion of subjects abstinent from week 9 through week 12, as shown in the table below adapted from her table 40:

Primary Efficacy Criterion – Four-Week Continuous Quit Rate (Study A1016)

	Weeks 9 – 12	
	Varenicline	Placebo
ITT Subjects	N=157	N=155
Abstinent (%)	63 (40%)	18 (15%)
p-value vs. placebo		<0.0001
Evaluable	N=145	N=138
Abstinent (%)	62 (43%)	18 (13%)
p-value vs. placebo		<0.0001

Dr. Buenconsejo also calculated rates of continuous abstinence from the end of a various grace periods following the TQD through the end of treatment. As illustrated in the table below, from her review, the effect of varenicline is not dependent on analysis of a specific efficacy window.

Continuous Abstinence Rate from Weeks 3 through Timepoints – Number (%) of Subjects (Study A3051016)

	Varenicline N=157	Placebo N=155
Week 3 – 12	45 (29%)	14 (9%)
Week 4 – 12	48 (31%)	16 (10%)
Week 5 – 12	51 (32%)	16 (10%)
Week 6 – 12	56 (36%)	16 (10%)
Week 7 – 12	59 (38%)	17 (11%)
Week 8 – 12	61 (39%)	17 (11%)
Week 9 – 12 *	63 (40%)	18 (12%)

** Primary Efficacy Criterion*

In the non-treatment follow-up (administratively designated protocol A3051019), the proportion of subjects remaining abstinent to the 52 week point (40 weeks post-treatment) was higher in the varenicline-treated than in the placebo-treated groups, with 22% of the varenicline group, and 8% of the placebo group remaining abstinent to the end of follow-up. This represents a non-relapse rate of 55% in the varenicline group 66%

in the placebo group. A survival curve reveals that most relapses occurred in the 12 weeks following treatment discontinuation.

2.6.3.5 Efficacy Conclusion, Study A3051016

This study provides evidence that varenicline, given as a self-titrated regimen with a maximum dose of 1 mg b.i.d., is effective as an aid to smoking cessation. It also suggests that most smokers given the opportunity to self-titrate do not choose the dose proposed by Pfizer for marketing, 1 mg b.i.d.

2.6.4 Study Title: Protocol A3051035: A 52-Week Multicenter Study Evaluating the Safety and Efficacy of Varenicline (CP-526,555) for the Maintenance of Smoking Cessation

2.6.4.1 Demographics and Patient Disposition

The demographics of the treatment groups and baseline smoking history and smoking behavior were similar across treatment groups. Participants were approximately evenly divided between males and females, were, on average, 45 years old and overwhelmingly Caucasian (97%). Participants had been smoking for an average of approximately 28 years, smoked, on average, 21 cigarettes/day, and had a mean Fagerstrom Test of Nicotine Dependence (FTND) score of 5.4. About 83% had made one or more previous quit attempts. The demographics were similar in the open-label run in and in the randomized groups, suggesting that no particular demographic or smoking history characteristic was obviously associated with either success or failure in the treatment phase.

Patient disposition is illustrated in the tables below, modified from Pfizer's final study report:

Subject Disposition [Number (%) of Subjects] - Open- Label Treatment Phase

	Varenicline	
Number screened 2416		
Assigned to treatment	1928	
Treated[a]	1927	
Completed open-label phase	1210	(62.8)
Discontinued from study	717	(37.2)
Discontinuations by reason:		
Adverse events	202	(10.5)
Lack of efficacy	42	(2.2)
Protocol deviation	71	(3.7)
Pregnancy	1	(0.1)
Refusal to participate further	150	(7.8)
Lost to follow-up	132	(6.9)
Other	119	(6.1)

[a] Percentages are based on number of subjects treated.

"Other" reasons reported included, according to the final study report, two subjects whose reasons could be considered adverse events (one with elevated blood pressure and

one with elevated ALT). The table above has been modified to reflect these subjects as discontinuations due to AEs. The remaining discontinuations described as "other" involved 41 subjects who were retrospectively determined to be ineligible for participation, 30 subjects with a variety of "personal reasons" or other reasons for discontinuation, and 63 subjects who are described as not having met double-blind entrance criteria. For some of these subjects, it was noted that the subject was smoking. These subjects (13 in number) have been added to the "lack of efficacy" category above in my modification of the table. Arguably, all 63 should be added, but as re-randomization required other criteria as well (compliance, e.g.), it is not clear whether all of the subjects who did not qualify for re-randomization were treatment failures. In any case, Dr. Buenconsejo's analysis of abstinence rates (below) shed additional light on the efficacy of varenicline in the open-label phase more definitively than the patient disposition. Most notably, this table shows that roughly 10% of subjects discontinued due to adverse events.

As shown in the table below, the resultant population was enriched for subjects able to tolerate varenicline. The discontinuation rate due to adverse events in the ensuing twelve-week, double-blind period was strikingly lower, at slightly over 1%.

Subject Disposition [Number (%) of Subjects] – Double-Blind Phase

		Double-blind Varenicline		Double-blind Placebo	
Randomized	1210	603		607	
Treated[a]	1206	602		604	
Completed study		494	(82.1)	463	(76.7)
Discontinued from study		108	(17.9)	141	(23.3)
Treatment Phase (Weeks 13-24)		47	(7.8)	94	(15.6)
Discontinuations by reason:					
Adverse events		8	(1.3)	8	(1.3)
Lack of efficacy		4	(0.7)	5	(0.8)
Protocol deviation		3	(0.5)	2	(0.3)
Refusal to participate further		19	(3.2)	44	(7.3)
Lost to follow-up		12	(2.0)	31	(5.1)
Other		1	(0.2)	4	(0.7)
Nontreatment Follow-up Phase		61	(10.1)	47	(7.8)
Discontinuations by reason:					
Death		2	(0.3)	0	0
Adverse Events		2	(0.4)	1	(0.2)
Lack of efficacy		0	(0.0)	2	(0.3)
Refusal to participate further		27	(4.5)	19	(3.1)
Lost to follow-up		28	(4.7)	24	(4.0)
Other		2	(0.3)	1	(0.2)

[a]Percentages based on the number of subjects treated.

Significant protocol violations included subjects who used NRT or other smoking cessation pharmacologic aids during the study; all of these were in the placebo arm during the double-blind phase and therefore, if anything, would bias the study against

varenicline. In addition, 3 subjects randomized to varenicline in the double-blind phase did not meet the entry criterion of smoking at least 10 cigarettes/day in the month prior to screening. Pfizer also designated as inevaluable those subjects (approximately 5% of each arm in the double-blind phase) who took fewer than 14 days of study medication in the first 21 days.

2.6.4.2 Efficacy Results

2.6.4.2.1 Abstinence Rate

2.6.4.2.1.1 Initial Abstinence: Open-label Phase

The criteria for randomization into the double-blind phase included only *one* week of abstinence at the end of the open-label phase. Pfizer chose this in order to maximize the number of subjects entering open-label treatment who would be eligible to participate in the double-blind trial. To the extent that the study was intended to be a randomized-withdrawal design in *responders to treatment*, the Division felt that a liberal definition of treatment response, if anything, would bias the study against varenicline if subjects who were not true responders were allowed to participate. However, it was of interest to establish that "true responders" (i.e., patients who achieved four weeks of abstinence at the end of treatment) were evenly distributed between the double-blind arms. Although it was not a protocol-specified analysis, Dr. Buenconsejo calculated the proportion of subjects entering the open-label phase who met the "abstinent weeks 8-12" criterion that defined treatment success in the other 12-week studies. Data were available only from weeks 1-8, 10, and 12, so Dr. Buenconsejo used the data from weeks 8,10, and 12, and considered successful any patient with CO-confirmed abstinence at those three visits. Overall, 51% if the subjects participating in the open-label phase achieved this four-week abstinence criterion. In addition, 64% met the one-week abstinence criterion required for rerandomization.

Of the 1210 subjects randomized to treatment in the double-blind phase, all (per protocol) met the one-week abstinence criterion, while 82% of the varenicline group and 79% of the placebo group also had been abstinent from at least week 8 (four-week abstinence).

2.6.4.2.1.2 Maintenance of Efficacy: Double-blind Phase

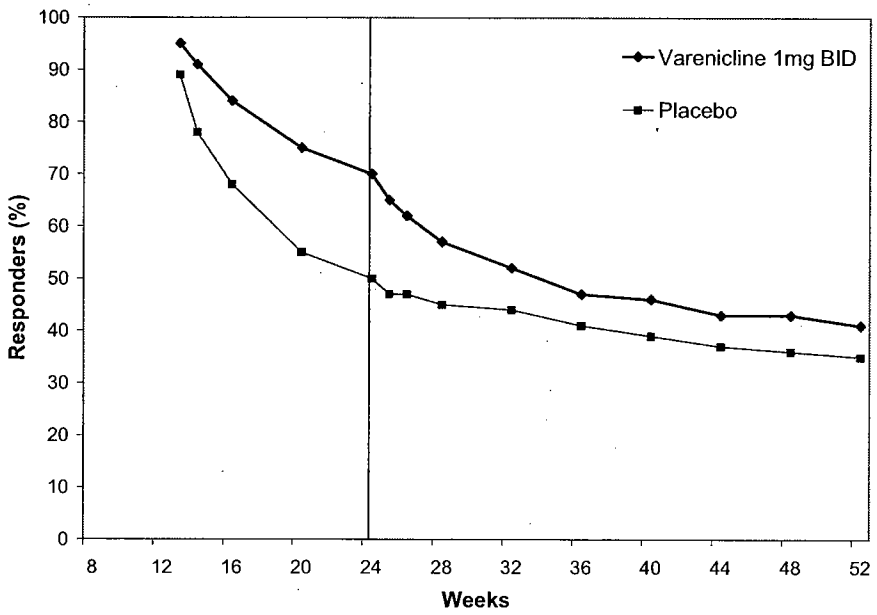
The primary efficacy analysis for this study, per protocol, was the proportion of subjects continuously abstinent from week 13 through week 24 (i.e., throughout the double-blind treatment phase). In addition, Pfizer's objective was also to show that a longer period of treatment with varenicline would improve the long-term abstinence rates, and therefore, smoking behavior post-treatment, to week 52 (28 weeks of post-treatment follow-up) was also analyzed. As in the other Phase 3 studies, a "continuous abstinence" rate was calculated as well as a "long-term quit rate" which allowed no more than 6 days of smoking during the follow-up period. Again, I have doubts about reliance on subject's ability to recall a specific number of days of smoking (vs. any smoking/no smoking, which can be recalled with reliability); therefore, I think the continuous abstinence rate is more informative than the long-term quit rate.

Because of concerns about the method of imputation of missing data, Dr. Buenconsejo applied a more conservative approach and re-calculated the abstinence rates over the week 13-24 and week 13-52 windows. These analyses are shown below in tables adapted from her review (tables 21, 22, and 23).

	Pfizer's analysis		Reviewer Re-analysis	
	Double-Blind Varenicline	Double-Blind Placebo	Double-Blind Varenicline	Double-Blind Placebo
Continuous Abstinence, Weeks 13-24				
ITT Subjects	N=601	N=603	N=601	N=603
Abstinent (%)	425 (71%)	301 (50%)	420 (70%)	301 (50%)
Odds ratio (95% CI) vs. placebo		2.5 (2.0, 3.2)		2.4 (1.9, 3.0)
p-value vs. placebo		<0.0001		<0.0001
Evaluable	N=574	N=574	N=574	N=574
Abstinent (%)	418 (73%)	299 (52%)	415 (72%)	299 (52%)
Odds ratio (95% CI) vs. placebo		2.5 (2.0, 3.2)		2.5 (1.9, 3.2)
p-value vs. placebo		<0.0001		<0.0001
Continuous Abstinence, Weeks 13-53				
ITT Subjects	N=601	N=603	N=601	N=603
Abstinent (%)	265 (44%)	224 (37%)	247 (41%)	214 (35%)
Odds ratio (95% CI) vs. placebo		1.3 (1.1, 1.7)		1.3 (1.0, 1.6)
p-value vs. placebo		0.0123		0.0394
Evaluable	N=574	N=574	N=574	N=574
Abstinent (%)	262 (46%)	223 (39%)	244 (43%)	214 (37%)
Odds ratio (95% CI) vs. placebo		1.3 (1.0, 1.7)		1.3 (1.0, 1.6)
p-value vs. placebo		0.0193		0.0705

The graph below from Dr. Buenconsejo's review, and of her own construction, illustrates the time course of relapse following treatment discontinuation.

Continuous Abstinence Rate from Week 13 to Week 52 – Reviewer's (A3051035)



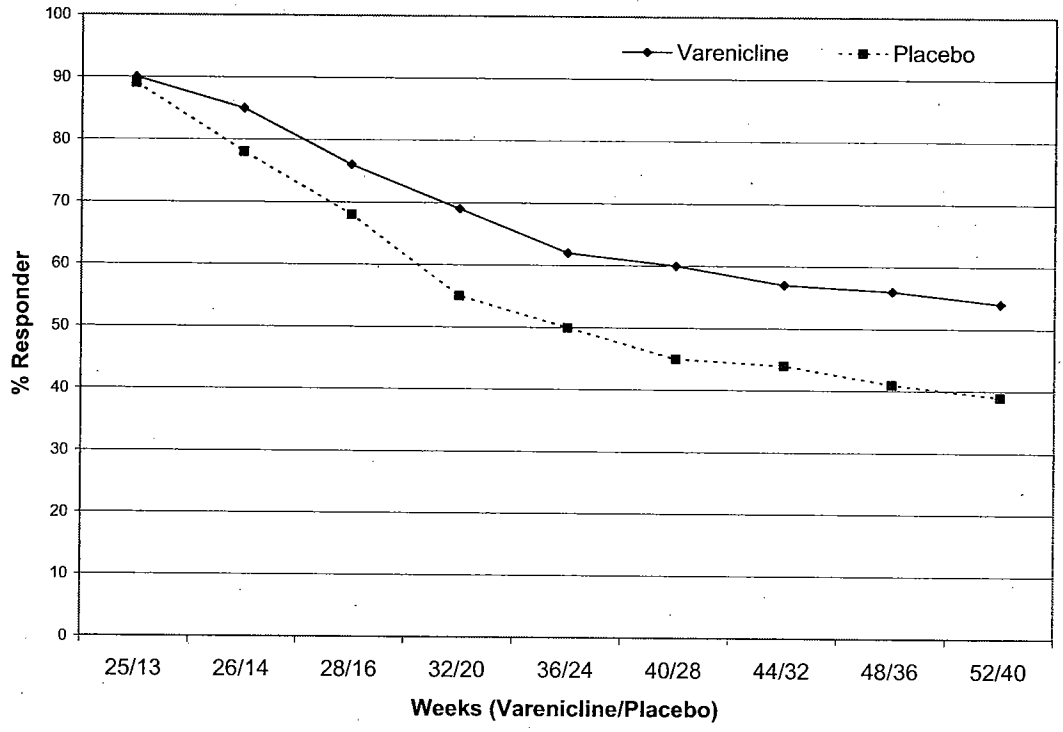
The graph illustrates that ongoing treatment with varenicline helps maintain abstinence achieved with varenicline treatment. Subjects continuing on varenicline have a shallower relapse curve than those switched to placebo. After treatment discontinuation, however, these subjects also have a steep rate of relapse. It is also notable that varenicline reduces, but does not completely prevent relapse. About 30% of subjects relapsed despite ongoing varenicline treatment.

On further review, Dr. Buenconsejo and I determined that the analytic approach taken actually compared 40 weeks of post-treatment follow-up for the placebo group (who had received 3 months of varenicline treatment) to 28 weeks of post-treatment follow-up for the varenicline group (who had received 6 months of varenicline treatment). To explore further whether 6 months of varenicline treatment is really superior to 3 months of varenicline treatment, it would be necessary to compare each group at comparable timepoints measured as *weeks since discontinuation of treatment.* If the 52 week results of superior long-term abstinence in the varenicline group can be explained entirely by the shorter period of post-treatment observation, a true effect of longer term treatment on long-term success would not be demonstrated.

Therefore, Dr. Buenconsejo graphed the proportion of subjects who were abstinent during the last week of varenicline treatment (*study week* 12 for the double-blind placebo group and *study week* 24 for the double-blind varenicline group) who maintained continuous abstinence through each post-treatment follow-up week as shown in the graph below. The x-axis aligns *Study Week 13* (post-treatment follow-up week 1 for the double-blind placebo group) with *Study Week 25* (post-treatment follow-up week 1 for

the varenicline group), and so on. This allows demonstration of the fact that, after *identical periods of post-treatment follow-up*, subjects who took varenicline for six months are more likely than subjects who took varenicline for three months to maintain abstinence for 28 weeks post-treatment. Although both groups show that the first three months after treatment discontinuation are a time when smokers are vulnerable to relapse, the relapse curve for those who had a longer period of varenicline treatment is shallower.

Continuous Abstinence Rate from Week 13/25 to Week 40/52



Pfizer also calculated the LTQR (long-term quit rate). This analysis counted as treatment successes any subjects who reported fewer than 6 days of smoking over the observation period. Any continuously abstinent smoker would also be considered successful in the LTQR calculation, and the rates differ only by those subjects who smoked, but did so only minimally. The LTQR differs minimally from the continuous abstinence rates, suggesting that few subjects smoked in this controlled fashion.

	Continuous Abstinence		LTQR		Difference (Subjects smoking <6 cigarettes)	
	Double-Blind Varenicline N=601	Double-Blind Placebo N=603	Double-Blind Varenicline N=601	Double-Blind Placebo N=603	Double-Blind Varenicline N=601	Double-Blind Placebo N=603
Week 25	389 (65%)	286 (47%)	421 (70%)	297 (49%)	32 (5%)	11 (2%)
Week 26	370 (62%)	281 (47%)	415 (69%)	293 (49%)	45 (7%)	12 (2%)
Week 28	340 (57%)	274 (45%)	394 (66%)	289 (48%)	54 (9%)	15 (2%)
Week 32	311 (52%)	264 (44%)	374 (62%)	288 (48%)	63 (10%)	24 (4%)
Week 36	285 (47%)	246 (41%)	348 (58%)	274 (45%)	63 (10%)	28 (5%)
Week 40	276 (46%)	235 (39%)	332 (55%)	265 (44%)	56 (9%)	30 (5%)
Week 44	259 (43%)	226 (37%)	310 (52%)	259 (43%)	51 (8%)	33 (5%)
Week 48	256 (43%)	220 (36%)	301 (50%)	253 (42%)	45 (7%)	33 (5%)
Week 52	247 (41%)	214 (35%)	287 (48%)	245 (41%)	40 (7%)	31 (5%)

2.6.4.2.2 Secondary Endpoints/Subjective Measures

In this study the MNWS was used to assess experience of craving and withdrawal after treatment with varenicline was discontinued. One week after open-label treatment, mean MNWS subscale scores were higher for subjects in the double-blind placebo group (who had just completed open-label varenicline treatment) than for those in the double-blind varenicline treatment group. At Week 25, one week after discontinuation of double-blind study medication, mean scores on the withdrawal subscales for previously varenicline-treated subjects were slightly higher than placebo treated subjects, suggesting that there may be some withdrawal effects associated with the discontinuation of varenicline.

2.6.4.3 Efficacy Conclusion, Study A3051035

This study provides evidence that the efficacy of varenicline is maintained over a longer period of treatment than tested in the other Phase 3 trials. This study demonstrates that smokers who successfully quit smoking during varenicline treatment are more likely to maintain abstinence if varenicline treatment is continued for three additional months.

2.6.5 Study A3051002 A Seven-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating the Safety and Efficacy of Three Doses of CP-526,555 (0.3 mg QD, 1 mg QD, And 1 mg b.i.d.) in Comparison With Zyban® in Smoking Cessation

This study was Pfizer's initial Phase 2 efficacy study and was not reviewed in detail by Dr. Buenconsejo. However, it provides supportive information about the efficacy of lower doses that are relevant to the determination of the recommendations that should be made in the Dosing and Administration section of the label. Therefore, I will briefly summarize the design and results here.

This was a multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled study. The study comprised a 7-week treatment phase, followed by an optional nontreatment phase that was to continue through 52 weeks from the baseline visit. Subjects who qualified were randomized to one of 3 CP-526,555 dose regimens (0.3 mg QD, 1.0 mg QD, or 1.0 mg b.i.d.); to the active control, Zyban (sustained-release bupropion, 150 mg b.i.d.), or to placebo, with a planned sample size of approximately 125 subjects per treatment group.

Duration of active treatment in this study was 7 weeks for Zyban, as this was the duration of treatment in two of the three pivotal clinical trials that provided substantial evidence of the efficacy of Zyban and led to its approval for marketing as a smoking cessation aid. Dosing of CP-526,555 was limited to 6 weeks, this being the duration of dosing covered by preclinical toxicological data at this stage of clinical development. During the seventh week of dosing, subjects in the CP-526,555 dosage groups received placebo. Subjects who discontinued study medication prematurely could remain in the study, attending the remaining visits and completing all assessments. Beginning on the day of the baseline visit and through the end of the 7-week treatment phase, subjects maintained a daily smoking diary in which they recorded the number of cigarettes smoked each day. Subjects were to take study medication for 1 week before attempting to quit smoking. Thereafter, subjects were to attempt to remain abstinent from smoking and other nicotine use. Subjects attended weekly clinic visits at which efficacy and safety were assessed. After completing the 7-week treatment phase, subjects had the option to participate in the nontreatment phase. During this phase, they were to attend clinic visits at Week 12, Week 24, and Week 52, and were also followed by phone contact every 4 weeks.

Participants were healthy cigarette smokers between the ages of 18 and 65 years, who during the past year had smoked an average of at least 10 cigarettes per day, with no period of abstinence greater than 3 months.

Treatment arms included:

- CP-526,555 (0.3 mg QD, 1.0 mg QD, or 1.0 mg b.i.d.) x 6 weeks, plus one week of placebo
- Zyban (150 mg b.i.d.) x 7 weeks
- Placebo b.i.d. x 7 weeks

During the treatment phase, assessments at each visit included smoking diary collection and oral self-reporting of smoking and other nicotine use (yes, no), confirmed by quantification of exhaled carbon monoxide (CO). In addition, subjects completed the MNWS, QSU-brief, and SEI.

The primary efficacy measure was the 4-week floating-window continuous quit rate (CQR), defined as the proportion of subjects in each treatment group who, based on data from the daily smoking diary, abstained from smoking for a period of at least 28 consecutive days at any time during the treatment period. A secondary measure of abstinence was the 4-week fixed window CQR, defined as the proportion of subjects abstaining from smoking during specified 4-week periods. In this study, 4-week fixed window CQRs were determined for Weeks 4-7 and for Weeks 3-6 based on subject oral self-report of smoking since the last study visit (biochemically confirmed by measures of exhaled CO $\leq$10 ppm). During the nontreatment phase, abstinence was assessed based on rates of continuous abstinence, determined by subject oral self-report (COconfirmed when assessed at clinic visits). Rates were determined for continuous abstinence from the target quit date forward and from Week 4 forward.

2.6.5.1 Demographics and Patient Disposition

Approximately 87% of subjects were white, and the mean age was approximately 42 years (range 18-65 years). Subjects represented a population of smokers who on average had smoked about 20 cigarettes per day for an average of approximately 24 years. More than half of the subjects in each treatment group had made at least 3 prior attempts to quit smoking, and the frequency of prior Zyban use (one or more attempts) ranged from 13% to 21% across treatment groups.

Subject Disposition [Number (%)[a] of Subjects]—Study A3051002

	CP-526,555			Zyban 150	Placebo
	0.3 mg QD	1 mg QD	1 mg b.i.d.	b.i.d.	
Number screened = 1023					
Assigned to treatment	128	128	127	128	127
Treated[a]	126	126	125	126	123
Completed study	65 (51.6)	77 (61.1)	77 (61.6)	68 (54.0)	66 (53.7)
Discontinued study	61 (48.4)	49 (38.9)	48 (38.4)	58 (46.0)	57 (46.3)
Discontinuations by reason: Adverse events[b]	7 (5.6)	6 (4.8)	6 (4.8)	9 (7.1)	5 (4.1)
Lack of efficacy	1 (0.8)	4 (3.2)	2 (1.6)	4 (3.2)	7 (5.7)
Subject defaulted[c]	41 (32.5)	31 (24.6)	31 (24.8)	38 (30.2)	33 (26.8)
Other[d]	12 (9.5)	8 (6.3)	9 (7.2)	7 (5.6)	12 (9.8)

[a]Percentages based on number of subjects treated
[b]Includes laboratory abnormalities
[c]Subject defaulted = subject withdrew consent or was lost to follow-up.
[d]"Other" includes the following: protocol violations, subject did not meet entry criteria, non-compliance, and personal reasons.

2.6.5.2 Efficacy Results

Although the protocol-specified primary analysis was "floating" four-week window, allowing any subject with any four consecutive weeks of abstinence to be considered a success, this is not an analysis the Agency accepts, because it attributes success even to subjects who relapse while on treatment. Therefore, more relevant are the two other analyses of quit rates presented in the final study report, the fixed-window continuous quit rate (CQR) calculated using weeks 3-6 (the last four weeks of varenicline treatment) and weeks 4-7 (the last four weeks of Zyban treatment). The results of these (Pfizer's report) are shown below in a table I prepared using data from the final study report.

Subjects with CO-confirmed Abstinence Through Weeks 3-6 or Weeks 4-7

	Varenicline			Zyban	Placebo
	0.3 mg/day	1 mg/day	1 mg BID		
	N = 126	N = 126	N = 125	N = 126	N = 123
Weeks 3-6	28 (22%)	37 (29%)	45 (36%)	32 (25%)	15 (12%)
p-value vs placebo	.03335	.0007	<.0001	.0060	
Weeks 4-7	32 (25%)	39 (31%)	51 (41%)	36 (29%)	17 (14%)
	.0186	0.0009	<0.0001	0.0033	

2.6.5.3 Efficacy Conclusions

This study provides supportive evidence of efficacy of both the 1 mg b.i.d. proposed by Pfizer as the recommended dose in labeling, and lower doses of varenicline, including 1 mg/day (as a single daily dose) and 0.3 mg/day.

2.7 Overall Efficacy Discussion and Conclusions

These studies provide substantial evidence that varenicline is superior to placebo in helping smokers achieve abstinence. The finding is robust and the odds ratios vs. placebo can be described as impressive. Typical findings in smoking cessation studies show that the active treatment yields a quit rate 1.5 – 2 times that of placebo. Varenicline treatment, in these studies, appears to result in a quit rate over three times that of placebo. In addition, at a dose of 1 mg b.i.d., varenicline is superior to Zyban as well. Because no appropriately-designed study compared Zyban to lower doses of varenicline, it cannot be determined whether lower doses of varenicline are superior to Zyban, but lower doses of varenicline are clearly superior to placebo.

The two Phase 3 trials provide substantial evidence supporting the 1 mg b.i.d. dose. However, because of dose-dependent adverse events, patients may wish to use lower doses. Considering the supportive evidence from Study A3051002 (for 1 mg/day as a single daily dose, and 0.3 mg/day), and Study A3051007 (demonstrating efficacy of 1 mg/day in two divided doses), as well as Study A3051016 (showing that patients can self-titrate to an effective dose below 1 mg b.i.d.), there is both sufficient evidence and sufficient reason for the Dosing and Administration section of the label to recommend

titrated dosing, rather than a fixed 1 mg b.i.d. dose. The titrated regimen was associated with the lowest rate of premature discontinuation of study medication due to adverse events—roughly half that seen with forced-titration regimens. Therefore, a flexible dosing approach could keep more patients on treatment.

The secondary claims regarding varenicline's effects on craving, withdrawal, and smoking satisfaction are less clearly supported. Per Dr. Scott's review, the measures described as "craving" would be better described as capturing "urge to smoke." It does appear that Pfizer has demonstrated an effect of varenicline on various measures of "urge to smoke," and that this could be included in the labeling.

However, the findings on the MNWS that are described as effects on "withdrawal" are equivocal, with only some sub-scales affected by varenicline in a favorable direction. Indeed, some symptoms of withdrawal (e.g. insomnia) seem worsened by varenicline. Therefore, a claim regarding an effect on withdrawal is not warranted.

Dr. Scott's assessment is that the concept of "smoking satisfaction" seems insufficiently defined, and the instruments insufficiently validated. Therefore, claims regarding smoking satisfaction are not suitable for inclusion in labeling.

3 SAFETY

In a safety database of sufficient size and using suitable safety monitoring procedures, varenicline treatment is associated with 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. In the long-term safety study, discontinuations due to adverse events were more common, reported in fully 28% of varenicline-treated subjects, of whom most were considered to have discontinued due to treatment-related AEs (24%). In comparison, 7% of the placebo arm discontinued due to treatment-related AEs and 10% for AEs of all causalities.

Varenicline did not have consistent effects on any laboratory parameters, cardiac conduction parameters, or vital sign measurements.

3.1 Exposure

The overall exposure to varenicline was adequate to characterize the safety profile and met ICH requirements. The overall safety database includes 4690 individuals who were exposed to varenicline and are included in the integrated safety database. To date, 456 subjects have been 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.

The safety data derives primarily from studies of 12 weeks or less. An additional randomized, placebo-controlled long-term study was conducted in order to provide additional long-term safety data to meet ICH requirements. Exposures beyond 12 weeks are attributable to this study, A3051037.

In the tables below, modified from Dr. Josefberg's review, the extent of exposure in the various safety populations (Phase 1, Phase 2/3) is shown.

Dose-by-Duration, Phase-1 Studies (Immediate Release Formulation)

Treatment Duration	Varen < 2-mg/d N=241	Varen 2-mg/d N=309	Varen > 2-mg/d N=112	Varen + Other N=146	Other Active N=141	Placebo Only N=255
≤ 1 day	74	81	24	1	12	102
2-7 days	114	117	80	70	55	74
8-14 days	46	105	8	75	74	72
15-28 days	7	6	0	0	0	7
Total	**241**	**309**	**112**	**146**	**141**	**255**

Exposure in Phase-2/3 Safety Database

Cohort/Database Study Number	0.3mg QD	1mg QD	0.5mg b.i.d.	1mg b.i.d.	Flex Dose	All Varen	Zyban*	PBO	Total
Fixed-dose, Placebo-Controlled									
A3051002 (Dose ranging)	126	126		125			126	123	626
A3051007 (Titration)			253	253				121	627
A3051028 (Zyban-Comparator)				349			329	344	1022
A3051036 (Zyban-Comparator)				343			340	340	1023
FDPC Subtotal	126	126	253						
FDPC Subtotal	←	**505**	→	**1070**		1575	**795**	**928**	**3298**
Other Completed Phase 2/3 Studies									
A3051035 (Maintenance)				1927					1927
A3051037 (Safety)				251				126	377
A3051016 (Flexible dose)					157			155	312
A3051043 (OL in Japan)			30						30
Other Phase 2/3 Subtotal			30	2178	157	2365			
All Phase-2/3 Studies Cohort	126	126	283	3248	157				
All Phase-2/3 Studies Cohort		→		→		**3940**	**795**	**1209**	**5944**

Source: Modified from applicant Table 2.7.4 A2.1 *Zyban dosed at 150-mg b.i.d., after titration

Duration of Exposure, All Completed Phase 2/3 Studies as of 07/05 Database Lock

Treatment Duration[a]	Varenicline N=3940	Zyban® N=795	Placebo N=1209
Unknown[b]	18	16	10
>2 weeks (≥15 days)	3592	676	1079
>6 weeks (≥43 days)	3110	570	855
>11 weeks (≥78 days)	2425	424	663
>12 weeks (≥85 days)	1531	222	426
>20 weeks (≥141 days)	697	0	76
>24 weeks (≥169 days)	456	0	72
>48 weeks (≥337 days)	130	0	57
>52 weeks (≥365 days)	95†	0	43

†An additional 17 subjects treated for exactly 364 days brings this number to 112.

A safety update submitted on 2/9/2006 provided information on SAEs and deaths from an additional 270 participants in ongoing studies, some of whom were on blinded therapy.

3.2 Deaths

Five deaths were reported in the safety database, including three in varenicline-treated subjects, and one each in Zyban-treated and placebo-treated subjects. No deaths reported appear to be clearly associated with varenicline. The overall mortality rate in controlled trials, was 0.316 per 100 patient-exposure-years for varenicline-treated subjects in Phase 2/3, 2.5 in the Zyban-treated subjects, and 1.181 in the placebo-treated subjects.

The safety update included the report of one death on blinded therapy, which did not appear to be related to study drug.

3.3 Serious Adverse Events

The table below from Dr. Josefberg's review shows that the overall incidence of serious adverse events in the controlled studies were similar in varenicline-treated and placebo-treated subjects when time of exposure was taken into account.

SAE Incidence per Patient-Exposure-Year*, Phase-2/3 Trials
Number of Patients Experiencing ≥ One SAE, AND Overall Number of SAEs

	All	Completed	Phase-2/3
	Varenicline	Zyban	Placebo
	All doses	150-mg b.i.d.	
Patients →	**(N=3940)**	**(N=795)**	**(N=1209)**
Pt-Years Exposure	**948.60**	**129.97**	**254.05**
	N	N	N
Pts. with any SAE	82	17	19
Patients with SAEs / Patient-Exposure-Years	0.086	0.131	0.075
Number of SAE Cases	91	17	20
SAE Cases / Patient-Exposure-Years	0.096	0.131	0.079
On-Drug^ SAE Cases	66	11	16
On-Drug SAE Cases / Patient-Exposure-Years	0.070	0.085	0.063

*Patient-exposure-year estimated, SAEs occurring after database lock and in ongoing trials are included
^ On-Drug period covers events up to 7-days after treatment discontinuation
Source: Clinical reviewer

The safety update reported 12 additional cases in either varenicline-treated (3 cases) or blinded-therapy-treated participants; most occurred well after treatment was discontinued no additional safety concerns were raised by these reports.

3.3.1 Cardiac SAES

Serious adverse in the Cardiac System Organ Class (SOC) occurred most commonly, and more commonly in varenicline than placebo treated patients.

Cigarette smoking is associated with a variety of cardiovascular risks; many toxins in cigarette smoke are believed to contribute to smoking-related cardiovascular disease, although nicotine itself has cardiovascular effects that can enhance risks. Nicotine's stimulant effects produce accelerated heart rate, increased myocardial contractility, constriction of some blood vessels, and increased blood pressure. Nicotine can precipitate or aggravate acute coronary ischemic events by increasing myocardial work while simultaneously causing coronary vasoconstriction.

Because many smokers have pre-existing cardiac disease, it is difficult to tease out the effect of a drug such as varenicline which is intended for use in this high-risk population. To examine whether varenicline increased the risk of serious cardiac events, I examined the narratives for all SAEs coded to the System Organ Class "cardiac," as well as events coded to the Preferred Term "chest pain."

In several cases, study subjects underwent cardiac evaluations including angiography. For a few, these studies did not reveal coronary artery disease. However, because the mechanism of action of varenicline, which acts in a manner pharmacologically similar to nicotine, could be vasoconstriction, these were included in the analysis as cardiac SAEs possibly related to study drug.

For some cases, Pfizer's assignment of a day of onset differs from mine. Some events met criteria for seriousness based on subject hospitalization for medical evaluations, such as a cardiac catheterization. When these procedures appeared, based on review of the narrative, to have been scheduled in response to cardiac symptoms reported earlier in treatment, I considered the event to have begun at the time the symptoms were reported. I included all events occurring within a week of completing varenicline treatment.

For the purposes of analysis, I grouped the events by type, separating events of a primarily arrhythmic nature from those of a primarily ischemic nature. In one case, a subject had two events, but the first (bradycardia) was later attributed in retrospect to a subsequent ischemic event; I included this subject only once, as an ischemic event.

After excluding events which did not occur on treatment or shortly after discontinuation, and events with an obvious alternative explanation, I found that there were four subjects with arrhythmic SAEs on varenicline treatment and one on placebo treatment. There were 13 subjects with ischemic SAEs on varenicline and four on placebo. Correcting for either population exposed or patient-years of exposure, I found similar risks in the two treatment arms, as shown in the table below:

	Varenicline	Placebo
Total Exposed	N = 3940	N = 1209
Patient-Years Exposure	948.60	254.05
All Possibly Related Cardiac SAEs	17	5
% of Exposed Subjects	0.43%	0.41%
Events per 100 PEY	1.79	1.96
Possibly Related Arrhythmic SAEs	4	1
% of Exposed Subjects	0.10%	0.08%
Events per 100 PEY	0.42	0.39
Possibly Related Ischemic SAEs	13	4
% of Exposed Subjects	0.33%	0.33%
Events per 100 PEY	1.37	1.57

One case of treatment-emergent angina on study day 77, reported in the safety update could not be assigned to a treatment arm because the treatment assignment had not been unblended. However, considering the worst-case analysis, assigning this subject to the varenicline arm without adjusting the denominators, the number of ischemic events per 100 patient-exposure years would increase to 1.47 in the varenicline arm (still comparable to/lower than the placebo arm) and the number of overall cardiac SAEs per 100 patient-exposure years in the varenicline group would increase to 1.89 (again, still comparable to/lower than the placebo arm).

The table below lists the cases considered in this analysis. They are grouped by similar preferred terms; gray highlighting indicates that the case was *not* included as possibly related in the analysis. Narrative summaries are in an addendum filed separately from this review.

MedDRA Preferred Term	**Subject ID**	**Total Daily Dose**	Study day of event onset/ Treatment stop day	Comment	Included in analysis, or reason for exclusion
Arrhythmias					
Varenicline-treated Subjects					
Atrial fibrillation	A305102810231018 75/W/M	2 mg	84 / 84	Discovered at last study visit	YES
Atrial fibrillation	A305103510301014 73/W/M	2 mg	29 / 28	Subject had only taken study drug once since study day 18	NO (not considered "on treatment")
Cardiac arrest	A305103510241019 71/W/M	2 mg	188 / 169	Occurred in context of terminal lung cancer	NO (not primarily cardiac)
Extrasystoles, Sinus bradycardia	A305103710061019 (a) 74/W/M	2 mg	241 / n/a	Occurred in context of ischemic event (see below)	NO (included among ischemic events only)
Supraventricular tachycardia	A305100750110594 44/W/F	1 mg	51 / 51		YES
Supraventricular tachycardia	A305103510311006 56/W/M	2 mg	172 / 143	History of WPW and similar events	NO (attributable to preexisting illness)
Tachycardia	A305103710061033 44/W/F	2 mg	171 / n/a	Normal cardiac cath & echo	YES
Tachycardia	A305103910011110 20/A/M	3 mg	1 / 1	Clin pharm study participant had tachycardia, fever, nausea, numbness after 1 dose	YES
Ventricular fibrillation	A305101650310148 52/W/M	2 mg	101 / 87	Post-treatment day 14, found unconscious; cath = occlusion, ECG = ischemia	NO (post-treatment day 14; drug has 24 hour half-life)
Placebo-treated Subjects					
Atrial Fibrillation	102810181032 64/W/M	0 mg	85/85	Discovered at last study visit; BL ECG PACs, PVCs	YES

MedDRA Preferred Term	**Subject ID**	**Total Daily Dose**	Study day of event onset/ Treatment stop day	Comment	Included in analysis, or reason for exclusion
Ischemic Events					
Varenicline-Treated Subjects					
Acute coronary syndrome	A305103610051011 50/W/M	2 mg	70 / 70	"Heartburn" w/onset study day 61, eval by 1°MD study day 70 & underwent subsequent angioplasty	YES
Angina unstable	A305100250050100 40/W/M	1 mg	92 / 42	Initial sx occurred 37 days post-tx	NO (post-treatment day 37)
Angina unstable	A305100750280336 48/W/M	1 mg	59 / 59	Exertional chest pain; angiogram = occlusion	YES
Coronary artery disease	A305100850203101 57/NativeAm/M	0.5 mg	19 / 12	Post-tx day 7, chest pain; recurred post-tx day 10 w/ECG changes, cath = CAD	NO (post-treatment day 7)
Coronary artery disease	A305103710011021 58/W/M	2 mg	28 / 191	Presented w/right sided chest pain on day 79, reported experiencing it intermittently since study day 28. Subsequent stress test (day 183), bypass surgery	YES
Coronary artery disease	A305103710061019 (b) 74/W/M	2 mg	259/n/a	Sinus brady (see above) study day 241, admitted for bradycardia, hypotension study day 259, ECG acute ischemia. Subsequent angioplasty day 315.	YES
Coronary artery disease	A305103710061025 60/W/M	2 mg	~305 / n/a	C/O chest pain ~study day 305; cardiac cath study day 362; stent placed post-tx day 1	YES
Myocardial infarction	A305101650310173 54/W/M	1 mg	23 / 50	Stress test on day 23 (?why) +chest pain; spontaneous chest pain day 50, varenicline d/c; MI at time of stent placement on post-tx day 7	YES

MedDRA Preferred Term	**Subject ID**	**Total Daily Dose**	Study day of event onset/ Treatment stop day	Comment	Included in analysis, or reason for exclusion
Myocardial infarction	A305103510171142 59/W/F	2 mg	101 / 169	P-wave changes consistent w/MI noted in study-related ECGs; subject had undergone gyn surgery after ~18 wks on tx; peri-operative MI suspected (asymptomatic)	YES
Myocardial infarction	A305103510291026 45/Creole/M	2 mg	102 / 84		NO (post-tx day 18)
Myocardial infarction	A3051035 10341063 65/H/M	2 mg	158 / 165		YES
Myocardial infarction	A305103710061052 55/W/F	2 mg	7 / 7		YES
Chest pain	A305103610101184 44/B/F	1 mg	78/78	Chest pain w/numbness of left arm and jaw, responsive to NTG, admitted for cardiac w/u, "negative"	YES
Chest pain	A305103610411100 43/B/F	2 mg	68/63	Medication d/c due to vertigo on day 63. Post-therapy day 5, subject developed elevated BP & chest pain.	NO (cardiac origin unclear, pt h/o GERD)
Chest pain	A305103710061009 48/W/M	2 mg	208/365	Retrosternal chest pain w/radiation to neck, SOB, dizziness; hospitalized, cath = CAD. Varenicline continued.	YES
Chest wall pain	A305103710071022 40/W/F	2 mg	47/na	Left-sided chest pain w/radiation to axilla, N/V, study day 47-48, lightheadedness, nausea, syncope day 50, admitted for w/u, normal CK&ECG; varenicline continued w/o recurrence of sx	YES
Non-cardiac chest pain	A305102810051050	2 mg	61/50	Hospitalized for chest pain, negative cardiac w/u. Hx c/w musculoskeletal origin	NO (history suggests musculo-skeletal origin)
Chest pain, non-cardiac	A3051013 100222010 48/W/F	4 mg CR	12/12	Chest pain &left hand numbness, responsive to NTG, normal echo & CK	YES

MedDRA Preferred Term	**Subject ID**	**Total Daily Dose**	Study day of event onset/ Treatment stop day	Comment	Included in analysis, or reason for exclusion
Placebo-treated Subjects					
Myocardial Ischaemia	A305103610081084 74/W/M	0 mg	13/~85	Pre-treatment ECG w/1°AVB; stress test study day 13 (? Reason); elective angioplasty day 29	YES
Coronary artery disease	A305103710101005 56/W/M	0 mg	114/137+?	Angina on day 114; +stress test, angioplasty on day 130, study drug resumed.	YES
Acute myocardial infarction	A305102810031045 55/B/M	0 mg	28/27	Post-tx day 1	YES
Chest pain	A305102810081124 53/B/M	0 mg	78/80	C/o chest pain @wk11 study visit, EKG changed from BL, sent to ER and admitted. ECG, stress test, cath = normal	YES

3.4 Discontinuations

Overall, 13% of varenicline-treated subjects, 14% of Zyban-treated subjects, and 9% of placebo-treated subjects in the completed Phase 2/3 studies prematurely discontinued study medication due to adverse events. The only specific events associated with discontinuation in >1% of any group were nausea, headache, and insomnia. Nausea led to permanent treatment discontinuation in 3% of subjects treated with varenicline, vs. 1% treated with Zyban and 0.4% treated with placebo. In addition, nausea-related discontinuations showed dose-dependence. In the tabulations for the fixed-dose placebo-controlled studies, in which subjects treated with varenicline b.i.d. were tabulated separately from those treated with lower doses, the rate of discontinuations associated with nausea was 1% in subjects treated with doses lower than 1 mg b.i.d. and 3% in those treated with 1 mg b.i.d.. Headache leading to treatment discontinuation was reported with similar frequency across the varenicline, Zyban, and placebo groups (~1%) while insomnia leading to treatment discontinuation was reported in approximately 1% of the varenicline and placebo groups, vs. 2% of the Zyban group.

In the long-term safety study, 28% of varenicline-treated subjects discontinued study treatment due to adverse events (all causality) and 24% for AEs considered treatment-related. In comparison, 7% of the placebo arm discontinued due to treatment-related AEs and 10% for AEs of all causalities. However, the onset of adverse events in this study was generally within the first four weeks of treatment. This suggests that discontinuation may not be attributable to new-onset adverse events observed during long-term treatment, but due to the persistence of bothersome effects such as nausea and abnormal dreams, which may be tolerated during the course of a three-month treatment but which patients are unwilling to endure for significant periods of time.

The table below (Pfizer's table S7, final study report, Study A3051037) illustrates specific AEs associated with premature treatment discontinuation in the long-term study. Unlike the short-term studies, in which only three specific AEs accounted for discontinuation in at least 1% of subjects, several additional treatment-related AEs emerge as potential causes of treatment discontinuation in this longer-term observation.

Adverse Events Most Frequently Contributing to Permanent Discontinuation of Study Medication [Number (%) of Subjects]

	Varenicline N = 251		Placebo N = 126	
	All Causality	Treatment-Related	All Causality	Treatment-Related
Gastrointestinal disorders	36 (14.3)	35 (13.9)	3 (2.4)	2 (1.6)
Nausea	19 (7.6)	19 (7.6)	0	0
Diarrhea	5 (2.0)	5 (2.0)	0	0
GERD	5 (2.0)	4 (1.6)	0	0
Dyspepsia	4 (1.6)	4 (1.6)	0	0
Constipation	2 (0.8)	2 (0.8)	0	0
Flatulence	2 (0.8)	2 (0.8)	1 (0.8)	1 (0.8)
Psychiatric disorders	20 (8.0)	17 (6.8)	3 (2.4)	3 (2.4)
Insomnia	8 (3.2)	7 (2.8)	1 (0.8)	1 (0.8)
Abnormal dreams	6 (2.4)	6 (2.4)	0	0
Depression	5 (2.0)	3 (1.2)	1 (0.8)	1 (0.8)
Agitation	3 (1.2)	3 (1.2)	0	0
Nervous system disorders	9 (3.6)	9 (3.6)	1 (0.8)	1 (0.8)
Headache	4 (1.6)	4 (1.6)	0	0
Somnolence	3 (1.2)	3 (1.2)	0	0
(All other SOCs)				
Chest pain	2 (0.8)	1 (0.4)	0	0
Arthralgia	2 (0.8)	1 (0.4)	1 (0.8)	1 (0.8)
Vision blurred	1 (0.4)	1 (0.4)	2 (1.6)	1 (0.8)

Includes adverse events that contributed to discontinuation of study medication in 2 or more subjects in either treatment group. Treatment discontinuation in a given subject could be attributed to a single adverse event or to multiple events.

This suggests that tolerability issues may limit the chronic use of varenicline. Conversely, the results from StudyA3051035, in which treatment was discontinued at the end of 12 weeks if subjects had not achieved at least one week of abstinence, showed a strikingly lower rate of adverse events and discontinuations in the sub-population that was eligible for re-randomization and continued varenicline treatment for an additional three months. Therefore, there may be a cohort of patients for whom varenicline is effective and well-tolerated who can continue with chronic dosing if needed.

A comparison of premature discontinuation rates attributed to adverse events across studies shows that a flexible-dosing regimen is associated with less treatment dropout than a forced-titration regimen. Note that the flexible-dosing regimen began with forced titration to 0.5 mg b.i.d. over one week, but after that permitted self-titration between 0.5 mg/day and 1 mg b.i.d.. However, this flexibility appears to have conferred improvement in tolerability, even compared to a regimen of titration to 0.5 mg b.i.d. followed by ongoing treatment at that dose. The table below, compiled by Dr. Buenconsejo, shows treatment discontinuations, temporary discontinuations, and dose reductions across studies, indicating improved tolerability of varenicline when a flexible-dosing scheme is used.

Treatment Discontinuations Due to Adverse Events N (%)

	Varenicline 0.5 mg b.i.d. (titrated)	Varenicline 1.0 mg b.i.d. (titrated)	Varenicline Flexible	Placebo
Study 28 (%)		46 (13%) [a]		45 (13%)
Study 36 (%)		40 (12%) [b]		34 (10%)
Study 35 (%) Open-label varenicline phase		309 (16%)		
Study 07 (%)[c]	18 (14%)	28 (22%)		21 (17%)
Study 16 (%)[c]			11 (7%)	7 (5%)

[a] three additional subjects temporarily discontinued study medication due to treatment-related adverse events and later permanently discontinued treatment
[b] three additional subjects temporarily discontinued study medication due to treatment-related adverse events and later permanently discontinued treatment due to adverse events
[c] Adverse event includes laboratory abnormalities

3.5 Significant Adverse Events

3.5.1 Nausea

The most clearly dose-related and treatment-limiting adverse event associated with varenicline treatment is nausea. Nausea was reported by as many as 40% of varenicline-treated subjects (long-term study, A3051037), and 19% of the subject who reported nausea ultimately discontinued varenicline treatment because of it. (Overall discontinuation rate due to nausea in this study was approximately 8%.) In the shorter-term studies, approximately 3% of varenicline-treated subjects prematurely discontinued study medication due to nausea Nausea was generally described as mild or moderate; however its occurrence was obviously treatment-limiting, particularly in longer-term treatment. Dr. Zheng's pharmacometric analysis shows a clear dose-dependency of nausea, and a greater vulnerability to this adverse drug effect in female subjects compared to male subjects. Dose-titration appeared to be beneficial in reducing the proportion of subjects who experienced nausea, as shown in the data from Study A3051007 (below), where both total daily dose and presence/absence of titration contributed to the overall occurrence of nausea.

COSTART			Varenicline		Placebo
Preferred Term	0.5 mg b.i.d. nontitrated N = 124	0.5 mg b.i.d. titrated N = 129	1.0 mg b.i.d. nontitrated N = 124	1.0 mg b.i.d. titrated N = 129	N = 121
Nausea	28 (22.6)	**21 (16.3)**	52 (41.9)	**45 (34.9)**	18 (14.9)

Studies A30510028 and A30510036 used a titrated, 1 mg b.i.d. dosing regimen, and nausea was reported by 29% and 30% of varenicline-treated subjects (respectively) vs. 8% and 10% of placebo-treated, consistent with the results for those treatment arms from Study A305107.

Self-titration was also helpful in preventing this adverse event, with nausea reported in 13% of subjects treated with the flexible dosing regimen in Study A3051016.

3.5.2 Weight Gain

Increased appetite was reported as an adverse event more commonly in varenicline-treated than in placebo-treated subjects in the 12-week controlled trials. This translated into weight gain reported as an AE more commonly in the varenicline-treated than placebo-treated group in the long-term study. In the long-term study, Study A3051037, the median change in body weight from baseline to last observation was 2.09 kg for varenicline- treated subjects (N = 248) and 0.67 kg for subjects in the placebo treatment group (N = 124). A weight increase of >7% from baseline to any time during the study was seen in 27.8% of varenicline-treated subjects (69/248) compared with 8.8% of placebo-treated subjects (11/125). Because weight gain is commonly associated with smoking cessation, it is difficult to tease out an independent effect of varenicline on weight separate from its efficacy as an aid to smoking cessation.

At my request, Pfizer provided additional information showing the prevalence of weight gain in subjects in Study A3051037, classifying the subjects as continuous smokers, continuous non-smokers, or intermittent smokers. The great majority of the subjects were in the third category. As shown below, the likelihood of weight gain is greater as the extent of abstinence increases (never abstinent < intermittently < continuously).

Subjects Gaining ≥7% of Body Weight, Study A3051037

	Varenicline	Placebo
All Subjects	69/248 (28%)	11/125 (9%)
Continuously Abstinent	11/23 (48%)	1/2 (50%)
Intermittently Abstinent	54/153 (35%)	8/23 (35%)
Never Abstinent	4/72 (6%)	2/100 (2%)

Pfizer also provided tabulations of weight change in two of the 12-week studies, Studies A3051028 and A3051036. Because of the shorter duration of observation, Pfizer identified subjects who had gained at least 3% of baseline bodyweight. The results are shown below.

Subjects Gaining ≥3% of Baseline Body Weight, Studies A3051028/A3051036

	Varenicline	Placebo
A3051028: all subjects	170/341 (50%)	126/334 (38%)
Quitters	93/155 (60%)	44/61 (72%)
Non-Quitters	77/186 (41%)	82/273 (30%)
A3051036: all subjects	175/231 (53%)	143/331 (43%)
Quitters	105/151 (70%)	44/60 (73%)
Non-quitters	70/180 (39%)	99/271 (37%)

Again, the difference between varenicline and placebo is evident in the "all subjects" comparison. Varenicline-treated subjects were more likely to gain weight in both studies. However, the likelihood of weight gain is explained primarily by smoking status. Within the subgroups (quitters vs. non-quitters), an effect of varenicline is not apparent. Therefore, the observation of higher prevalence of weight gain among varenicline-treated subjects is probably best explained by the higher prevalence of successful quitters.

3.5.3 Neoplasms

Because of preclinical evidence suggesting that nicotine may serve as a tumor promoter, it is possible that varenicline might have a similar effect. Therefore, particular attention was given to reports of neoplasms. In the "all-completed Phase 2/3 studies" dataset, SAEs coded to the MedDRA SOC "neoplasms" were approximately twice as common in varenicline-treated than in placebo-treated subjects or Zyban-treated subjects, whether corrected for time of exposure or calculated as a percent of subjects exposed. Overall, 12 such events (0.6%; .025/PEY) were reported in varenicline-treated subjects, vs 1 (0.1%; .007/PEY) in bupropion-treated and 2 (0.2%; .008/PEY) in placebo-treated. Examination of the cases reveals that some were diagnosed so soon after beginning therapy that a causative role for varenicline in promoting tumor growth is exceptionally unlikely. When these cases are removed, the incidence of neoplasms is similar in varenicline-treated and Zyban-treated subjects; however, both placebo cases would be removed under this rubric leaving a rate of 0. Nevertheless, there is minimal support for a conclusion that varenicline acts as a tumor promoter.

3.5.4 Eye and Skin Events

Preclinical studies showed that varenicline concentrated in melanized tissues; this creates concern for an effect of varenicline on the retina and skin. No evidence of adverse effects on the eye were observed in animal studies. However, the clinical trials did not incorporate specific monitoring for ophthalmologic effects of varenicline.

Ophthalmologic SAEs included a subject who developed "blurred vision" after approximately 3 months of varenicline treatment, and whose decreasing visual acuity was confirmed on serial exams and whose symptoms were attributed to varenicline. Two varenicline-treated and one placebo-treated subject were diagnosed with cataracts. In one varenicline-treated subject, the cause was believed to be chronic use of ophthalmic topical steroids, while in the other, no alternative explanation was noted. Vision loss attributed to a transient ischemic attack occurred in one varenicline-treated subject.

Another subject developed blurred vision after 6 weeks of treatment with varenicline, requiring corrective lenses. The problem resolved despite ongoing varenicline treatment and was subsequently attributed to a neurological condition not previously diagnosed.

Discontinuations due to blurred vision occurred in 4 varenicline-treated and 2 placebo-treated subjects.
Non-serious skin-related adverse events, mostly various rashes, were more common in varenicline patients as in placebo patients (8% vs. 5%), but less common than in Zyban patients (10%). No specific rash type appeared to predominate.

3.6 Common Adverse Events

Dr. Josefberg examined the rates of common adverse events in the placebo-controlled clinical trials, giving primary attention to the pool of studies identified as the "fixed-dose placebo-controlled Phase 2/3 studies." These studies involved similar populations, safety monitoring methods, and treatment durations (12 weeks, with the exception of the initial Phase 2 study, Study A3051002, which was 6 weeks). Pfizer used the MedDRA dictionary to code adverse events for later studies, and retrospectively re-coded earlier studies into MedDRA to allow for integrated safety review. Because of the high degree of granularity in the MedDRA coding system, we determined that examining the data for common (i.e., 5% or more frequent) *preferred terms* had the potential to miss some important findings, in the event that similar phenomenon had been coded to various similar, but distinct, preferred terms. Therefore, Pfizer was asked to prepare a table using the MedDRA hierarchy to capture more completely the common adverse events seen in the clinical trials. Specifically, a table listing any *High Level Group Term* occurring in at least 5% of any varenicline-treated group was requested, with any HLGT more common in placebo than varenicline-treated groups removed. In addition, to provide greater insight into which specific terms contributed to the HLGT, any specific Preferred Term occurring in at least 1% in any group was listed underneath the HLGT. Therefore, in the table below, the total number for each HLGT is not the sum of the Preferred Terms listed below it, because only those Preferred Terms reported at the 1% rate were included in the table. We also asked Pfizer to add a separate column for the 1 mg/day dose, as the efficacy review strongly suggested that this dose should be recommended in labeling.

In the table below, Dr. Josefberg also combined very similar terms, such as "insomnia," "middle insomnia," and "initial insomnia," to create a clearer picture of the drug's effects. Clearly varenicline-related adverse events include nausea, vomiting, flatulence, constipation, insomnia, abnormal dreams, dysgeusia, and increased appetite.

Most Frequent AE HLGTs (≥ 5% Any Group), with Subordinate PTs (≥ 1% Any Group)
Phase 2/3 Fixed-Dose, Placebo-Controlled Studies

System Organ Class High Level Group Term Preferred Term	VRN 0.5 mg b.i.d. N=253	VRN 1mg b.i.d. N=1070	Zyban 150mg b.i.d. N=795	Placebo N=928
GASTROINTESTINAL				
GI Signs and Symptoms	41 (32.5)	484 (45.2)	168 (21.1)	191 (20.6)
(Nausea and/or Vomiting)	52 (20.6)	373 (34.9)	103 (13.0)	111 (12.0)
Nausea	49 (19.4)	361 (33.7)	92 (11.6)	103 (21.1)
Abdominal pain*	14 (5.5)	78 (7.3)	34 (4.3)	49 (5.3)
Flatulence	29 (11.5)	71 (6.6)	21 (2.6)	25 (2.7)
Dyspepsia	16 (6.3)	58 (5.4)	27 (3.4)	32 (3.4)
Vomiting	5 (2.0)	57 (5.3)	24 (3.0)	15 (1.6)
GI Motility/Defecation Conditions	25 (9.9)	137 (12.8)	88 (11.1)	60 (6.5)
Constipation	14 (5.5)	84 (7.9)	62 (7.8)	26 (2.8)
Diarrhoea	9 (3.6)	45 (4.2)	19 (2.4)	34 (3.7)
Gastroesophageal reflux disease	2 (1.0)	10 (0.9)	6 (0.8)	1 (0.1)
Salivary Gland Conditions	22 (8.6)	61 (5.7)	71 (8.9)	42 (4.5)
Dry Mouth	11 (4.3)	58 (2.4)	70 (8.8)	40 (4.3)
PSYCHIATRIC DISORDERS				
Sleep Disorders/Disturbances	87 (34.3)	338 (31.6)	268 (33.7)	177 (19.1)
Insomnia**	63 (24.9)	208 (19.4)	202 (25.4)	130 (14.0)
Abnormal dreams ±Nightmare	36 (14.2)	151 (14.1)	56 (7.0)	48 (5.2)
Sleep disorder	6 (2.4)	57 (5.3)	46 (5.8)	24 (2.6)
Depressed Mood Disorder/Disturb^	11 (4.3)	29 (2.7)	23 (2.9)	17 (1.8)
INFECTIONS/INFESTATIONS				
Pathogen Class Unspecified	136 (26.9)	230 (21.5)	163 (21.5)	233 (25.1)
URI and/or Nasopharyngitis	99 (2.0)	165 (1.5)	111 (1.4)	187 (2.0)
Sinusitis	10 (2.0)	18 (1.7)	12 (1.5)	19 (2.0)
Tooth Infection	6 (1.2)	5 (0.5)	7 (0.9)	0 (0)
Urinary tract infection	5 (1.0)	3 (0.3)	5 (0.6)	4 (0.4)
Viral Infectious Disorders	36 (7.1)	54 (5.0)	35 (4.4)	48 (5.2)
Influenza	20 (4.0)	31 (2.9)	18 (2.3)	29 (3.1)
Gastroenteritis viral	11 (2.2)	8 (0.7)	4 (0.5)	8 (0.9)
NERVOUS SYSTEM				
Headaches (HLGT)	59 (23.3)	194 (18.1)	117 (14.7)	145 (15.6)
Neurological Disorders NEC	59 (23.3)	196 (18.3)	120 (15.1)	127 (13.1)
Dysgeusia	30 (11.6)	78 (7.3)	49 (6.2)	40 (4.3)
Dizziness	16 (6.3)	72 (6.7)	55 (6.9)	68 (7.3)
Somnolence	9 (3.6)	3 (4.0)	10 (1.3)	24 (2.6)
Lethargy	3 (1.2)	15 (1.4)	6 (0.8)	2 (0.2)
Paraesthesia	2 (0.8)	10 (0.9)	8 (1.0)	7 (0.8)

System Organ Class High Level Group Term Preferred Term	VRN 0.5 mg b.i.d. N=253	VRN 1mg b.i.d. N=1070	Zyban 150mg b.i.d. N=795	Placebo N=928
Mental Impairment Disorders	16 (6.3)	62 (5.8)	43 (5.4)	52 (5.6)
Disturbance in attention	15 (5.9)	54 (5.0)	38 (4.8)	47 (5.1)
GENERAL DISORDERS				
General Disorders NEC	29 (11.5)	122 (11.4)	74 (9.3)	103 (11.1)
Asthenia ± Fatigue ± Malaise	10 (4.0)	77 (7.2)	34 (4.3)	57 (6.1)
Pain	3 (1.2)	14 (1.3)	5 (0.6)	9 (1.0)
Chest pain ± Chest discomfort	5 (1.0)	17 (1.6)	16 (2.0)	15 (1.6)
Thirst	3 (1.2)	8 (0.7)	3 (0.4)	6 (0.6)
Influenza like illness	2 (0.8)	3 (0.3)	1 (0.1)	4 (0.4)
RESPIR/THORACIC/MEDIAST				
Respiratory Disorders NEC	31 (12.3)	98 (9.2)	68 (8.6)	71 (7.7)
Cough	14 (2.8)	26 (2.4)	18 (2.3)	23 (2.5)
Pharyngolaryngeal pain^^	6 (2.4)	32 (3.0)	20 (2.5)	27 (2.9)
Dyspnoea	3 (1.2)	12 (1.1)	2 (0.3)	4 (0.4)
MUSCULOSKEL./CONNECTIVE				
Musculoskel/Connect. Tissue NEC	36 (7.1)	73 (6.8)	44 (5.5)	63 (6.8)
Back pain	22 (4.4)	42 (3.9)	30 (3.8)	33 (3.6)
Joint Disorders	17 ((6.7)	42 (3.9)	28 (3.5)	28 (3.0)
Arthralgia	13 (5.1)	38 (3.6)	23 (2.9)	24 (2.6)
SKIN/SUBCUTANEOUS TISSUE				
Epidermal and Dermal Conditions	22 (8.7)	65 (6.1)	52 (6.5)	35 (3.8)
Rash	5 (2.0)	26 (2.4)	19 (2.4)	17 (1.8)
Pruritis	3 (1.2)	15 (1.4)	13 (1.6)	5 (0.5)
METABOLISM & NUTRITION				
Appetite/General Nutrit. Disorders	18 (7.1)	71 (6.6)	50 (6.3)	35 (3.8)
Increased appetite	15 (5.9)	47 (4.4)	27 (3.4)	21 (2.3)
Decreased appetite ± Anorexia	3 (1.2)	23 (2.1)	23 (2.9)	13 (1.4)

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia, Initial insomnia, Middle insomnia, Early morning awakening
^ HLGT 'Depressed mood disorders/disturbances' includes HLTs 'Depressive disorders'/'Mood alterations w/depressive symptoms
^^ Includes PTs Pharyngolaryngeal pain and Throat irritation
Source: Clinical reviewer from applicant Tables A10.1a, A10.1b, (2.7.4) and AE datasets

Data from the long-term safety study identifies the same treatment-associated adverse event terms as noted above, and also adds weight gain.

3.7 Explorations to Identify Potential Tolerability Differences Across Dosing Regimens

Study A3051007 was conducted specifically to compare four different dosing regimens of varenicline, 0.5 mg b.i.d. with and without initial dose titration, and 1 mg b.i.d. with and without initial dose titration. The results of this study did not suggest that initial dose titration had an appreciable effect on premature discontinuation of study drug. However, in comparing titrated to non-titrated arms within the same total daily dose, an effect of titration was apparent for nausea, diarrhea, and increased appetite. Some other treatment-emergent AEs appeared to be more common in the titrated groups than the non-titrated. In addition, this study also demonstrated that the 0.5 mg b.i.d. dose was more tolerable than the 1 mg b.i.d. dose, with many drug-related adverse events showing a dose-dependency. The table below, from Pfizer's final study report (which uses COSTART terminology) shows treatment-emergent adverse events occurring in at least 5% of any varenicline-treated group, and at a higher frequency than in placebo.

Most Frequent Treatment-Emergent Adverse Events [Number (%) of Subjects]

	CP-526,555				
COSTART Preferred Term	0.5 mg b.i.d. nontitrated N = 124	0.5 mg b.i.d. titrated N = 129	1.0 mg b.i.d. nontitrated N = 124	1.0 mg b.i.d. titrated N = 129	Placebo N = 121
Nausea	28 (22.6)	**21 (16.3)**	52 (41.9)	**45 (34.9)**	18 (14.9)
Insomnia	42 (33.9)	**27 (20.9)**	27 (21.8)	**48 (37.2)**	14 (11.6)
Headache	34 (27.4)	25 (19.4)	30 (24.2)	29 (22.5)	21 (17.4)
Abnormal dreams	21 (16.9)	**15 (11.6)**	21 (16.9)	**25 (19.4)**	6 (5.0)
Taste perversion	20 (16.1)	**10 (7.8)**	17 (13.7)	**15 (11.6)**	5 (4.1)
Dyspepsia	11 (8.9)	**8 (6.2)**	12 (9.7)	**19 (14.7)**	9 (7.4)
Flatulence	19 (15.3)	11 (8.5)	14 (11.3)	13 (10.1)	7 (5.8)
Constipation	8 (6.5)	**6 (4.7)**	13 (10.5)	**14 (10.9)**	3 (2.5)
Somnolence	7 (5.6)	**7 (5.4)**	13 (10.5)	**12 (9.3)**	2 (1.7)
Thinking abnormal	8 (6.5)	8 (6.2)	11 (8.9)	11 (8.5)	5 (4.1)
Vomiting	4 (3.2)	**1 (0.8)**	8 (6.5)	**12 (9.3)**	3 (2.5)
Increased appetite	10 (8.1)	**5 (3.9)**	11 (8.9)	**8 (6.2)**	2 (1.7)
Asthenia	6 (4.8)	**5 (3.9)**	7 (5.6)	**10 (7.8)**	7 (5.8)
Diarrhea	7 (5.6)	**2 (1.6)**	11 (8.9)	**6 (4.7)**	7 (5.8)
Accidental injury	10 (8.1)	11 (8.5)	7 (5.6)	8 (6.2)	5 (4.1)
Back pain	6 (4.8)	8 (6.2)	10 (8.1)	4 (3.1)	8 (6.6)
Rash	5 (4.0)	**2 (1.6)**	3 (2.4)	**8 (6.2)**	3 (2.5)
Pharyngitis	10 (8.1)	7 (5.4)	7 (5.6)	4 (3.1)	4 (3.3)
Pain	8 (6.5)	5 (3.9)	6 (4.8)	4 (3.1)	5 (4.1)
Myalgia	7 (5.6)	5 (3.9)	2 (1.6)	5 (3.9)	3 (2.5)
Menstrual disorder	4 (5.7)	0	0	1 (1.5)	2 (3.5)

.Arranged by decreasing frequency among all subjects taking 1.0 mg b.i.d. CP-526,555.

Based on this study, Pfizer determined that a dose-titration strategy should be recommended. The dose-dependency of several common AEs also supports the notion that patients with trouble tolerating varenicline at the recommended dose should be encouraged to try a lower dose.

3.8 Laboratory Data

Dr. Josefberg examined the descriptive comparisons of laboratory data provided by the Applicant, which included tabulations of mean changes from baseline in various lab parameters, shift tables, and listings of outliers and discontinuations due to laboratory abnormalities. His review focused on results of controlled trials, but included reports of the all-completed studies database when they were not obviously consistent with the FDPC data, and where the additional exposure duration (from the all completed studies data) was thought to be informative.

In the Phase 1 studies, an excess of shifts from normal to abnormal in varenicline-treated patients was observed when all lab results were presented together. Dr. Josefberg's examination of the categorical shift tables showed that most of the increase in shifts to abnormal values could be attributed to urinalysis findings. Many of these cases involved increased urine specific gravity (only). There were, however, considerably higher percentages of subjects with WBCs ≥6/HPF at varenicline doses ≥2-mg/day than at doses <2-mg/day (and placebo). Subjects at the 2-mg/day dose were also more likely to have RBCs ≥6/HPF (25%) compared with placebo and >2-mg/day subjects (6% and 3%, respectively). There were no associated indications of renal effects (e.g. abnormal BUN/Cr), and this observation was not confirmed in the larger Phase 2/3 database. In the Phase 1 studies, there were also higher percentages of subjects whose hemoglobin and hematocrit decreased, and whose monocyte count increased, in the >2-mg/day group than in all other treatment conditions. Eosinophilia occurred more commonly as well in the >2-mg/day and in the 'varenicline + other drug' groups (≈10% vs. 3-5%). As with the urinalysis data, these findings, while concerning, are of unclear clinical relevance and were not confirmed in the Phase 2/3 database.

The incidence of clinical laboratory abnormalities was similar for all Phase-2/3 treatment groups. Laboratory abnormalities were infrequent, with the exception of elevated triglycerides and cholesterol, but these were distributed roughly equally across treatment groups.

There were no large differences between treatment groups in baseline values or median changes from baseline. With respect to categorical shifts in hematology, chemistry and metabolic values for the fixed-dose, placebo-controlled database, no abnormalities appear to have occurred more commonly in varenicline-treated patients. Anemia, monocytosis and eosinophilia do not appear to have occurred more commonly in varenicline-treated patients than in those treated with Zyban or with placebo. Findings for the all completed Phase-2/3 studies database are similar, with elevated monocyte and eosinophil counts (%) found in about 3% of patients in both the varenicline and placebo groups.

Mean changes from baseline in LFTs were similar across treatment groups, and the incidence of treatment-emergent potentially clinically significant abnormalities (PCSA) in AST, ALT, total bilirubin, or alkaline phosphatase showed no consistent pattern of

treatment-relatedness, as shown in the table below, which summarizes categorical changes in LFTs (from baseline to worst value).

Lab Parameter	Criteria	All Phase-2/3 Studies	
		Any Dose N=3758	**Placebo N=1123**
Total Bilirubin	>1.5 x ULN	4/3730 (0.1%)	1/1116 (<0.1%)
AST (SGOT)	>3.0 x ULN	11/3701 (0.3%)	6/1099 (0.5%)
ALT (SGPT)	>3.0 x ULN	9/3594 (0.3%)	1/1074 (<0.1%)
Alkaline Phosph	>3.0 x ULN	0/3675	0/1100
LDH	>3.0 x ULN	1/3669 (<0.1%)	1/1085 (0.1%)
CPK	>2.0 x ULN	6/38 (16%)	4/25 (16%)

Transaminase and bilirubin elevations (> 1.5 X ULN) at baseline precluded Phase-3 participation, thus few patients (in any treatment group) had abnormal baseline AST, ALT, or total bilirubin. The Phase 2/3 protocols included instructions to investigators to report as AEs any laboratory abnormalities that resulted in permanent or temporary treatment discontinuation, or in dose reduction. Investigators were also instructed to discontinue treatment immediately for any subject with marked liver function abnormalities (AST or ALT ≥3X ULN, T. bilirubin ≥2 X ULN or alkaline phosphatase ≥1.5X ULN). The table below illustrates that, while uncommon, discontinuations due to hepatic laboratory abnormalities were more frequent in varenicline-treated than placebo-treated subjects.

Laboratory Test Related Dropouts – Phase 2/3 Fixed-Dose, Placebo-Controlled

Preferred Term	**Varenicline <1-mg b.i.d. N=505**	**Varenicline 1-mg b.i.d. N=1070**	**Zyban 150-mg b.i.d. N=795**	**Placebo N=928**
Blood LDH increased	0 (0)	0 (0)	0 (0)	1 (0.1)
ALT increased	4 (0.8)	4 (0.4)	2 (0.3)	1 (0.1)
AST increased	1 (0.2)	1 (0.1)	0 (0)	3 (0.3)
Hepatic enzyme increased	1 (0.2)	0 (0)	0 (0)	0 (0)
Liver function test abnormal	1 (0.2)	4 (0.4)	0 (0)	1 (0.1)

Dr. Josefberg listed all PCSA hepatic laboratory abnormalities and provided an assessment of relatedness for events in the All-Completed Phase 2/3 population (for example, excluding cases of isolated abnormalities). I have tabulated his findings below. Using only possibly related cases, there does not appear to be a clear excess of abnormalities on varenicline treatment.

	Varenicline <1-mg b.i.d. N=496	**Varenicline 1-mg b.i.d. N=1006**	**Placebo N=851**
Patients with LFT Abnormality			
Total	8 (1.6%)	35 (3.5%)	11 (1.3%)
Related	5 (1.0%)	13 (1.3%)	6 (0.7%)

Creatinine phosphokinase values were not routinely assessed. Both baseline and follow-up CPK values are available for approximately sixty patients (in the all-completed studies database), obtained by investigators or hospitals because of LFT or urinalysis abnormalities (not per protocol). Overall, ten of these patients (six varenicline, four placebo) experienced shifts from normal to >2.0 X ULN, in some cases reaching values exceeding ten times the upper limit of normal. No cases of rhabdomyolysis were reported, nor were any adverse events coded as 'Myopathy' or related terms.

3.9 Vital Signs

No consistent effect of varenicline on blood pressure or pulse was observed.

3.10 ECGs

The Agency agreed to accept this application for review without a thorough QT study (TQT), because the development program was nearing completion prior to finalization of the TQT guidance document. As agreed at the Pre-NDA meeting, Pfizer provided a report of preclinical studies and clinical observations of cardiac QT interval changes observed in different phase 1/2/3 clinical trials in lieu of a TQT study.

This information was reviewed by Drs. Nallani and Zheng, who concluded:

> At concentrations of ~ 100-fold compared to clinically observed plasma levels, varenicline treatment did not result in significant observations in *in vitro* HERG inhibition assay and action potential assay in isolated canine Purkinje fibers. Since dogs did not tolerate the human equivalent doses of varenicline due to vomiting, the effect of single and multiple doses of varenicline on cardiovascular effects were assessed in conscious monkeys at doses upto 1.2 mg/kg/day. There were no significant changes in vital signs or electrocardiograms. Plasma concentrations (C_{max-ss} ~ 155 ng/mL, AUCss 2550 ng.h/mL) observed in these studies are above and beyond those observed clinically.
>
> PK/PD analysis of pooled data from Phase 1 studies looking at the changes in QT interval corrected by a study specific-correction factor over a range of plasma

levels was submitted. Significant QT prolongation signal was not observed in the clinically observed plasma concentration range.

3.11 Drug Abuse, Withdrawal, and Overdose Experience

The abuse potential of varenicline was evaluated in several animal models and in a specific clinical pharmacology study of drug liking. The results of these studies were reviewed by Dr. Katherine Bonson of the Controlled Substances Staff. Dr. Bonson noted that

> In animal behavioral studies, varenicline has behavioral effects that mimic those of nicotine. In rats trained to self-administer nicotine, varenicline is self-administered to the same degree as nicotine. In drug discrimination tests, varenicline produces full generalization to the nicotine cue in rats.
>
> In a human laboratory abuse liability study conducted with non-smoking individuals experienced with stimulants, a single oral dose of 1 mg varenicline produced increases in subjective responses for "good drug effects" and "high" that were statistically significantly greater than placebo but less than those responses produced on the same scales by a single oral dose of amphetamine at 15 and 30 mg. However, in this subject population, only varenicline (1 mg) produced statistically significantly greater increases in "nausea" compared to placebo.
>
> In contrast, in individuals who smoked and used stimulants, 1 mg varenicline did not produce statistically significant increases in the positive or negative subjective measures. In contrast, amphetamine (15 and 30 mg) produced statistically significant increases in positive and negative subjective responses in this subject population.
>
> A 3 mg dose of varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers with a history of stimulant abuse.

Dr. Bonson also noted that

> There is no evidence of withdrawal in the 5 days following discontinuation of varenicline after 14 day administration to rats. Similarly, there are no withdrawal signs in monkeys treated for nine months with varenicline following drug discontinuation.

However, examination of the adverse events reported in the seven days following drug discontinuation (or re-randomization to placebo in Study A3051035) shows that certain adverse events consistent with nicotine withdrawal are reported in a small percentage of subjects upon stopping varenicline, but consistently more frequently than in subjects stopping placebo. In addition, several of the clinical trials included the administration of the MNWS during the week following drug discontinuation. Withdrawal scores in subjects discontinuing varenicline were slightly higher in the week following discontinuation, suggesting that some symptoms of withdrawal can be expected. (see

Appendix.) Dose taper at the end of treatment might be advisable, but was not evaluated specifically in the clinical trials. Further study in Phase 4 to determine whether dose-taper could reduce the rate of post-treatment relapse may be warranted.

4 CHEMISTRY, MANUFACTURING AND CONTROLS ISSUES

[

]

5 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS ISSUES

5.1 General Clinical Pharmacology Issues

Dr. Srikanth Nallani reviewed the clinical PK/PD studies and *in vitro* studies characterizing the absorption, distribution, metabolism, and excretion (ADME) aspects of varenicline. His main conclusions include:

> Varenicline tartarate is the salt of a week organic base with highly soluble and permeable characteristics (Biopharmaceutics Classification System – 1 drug). The immediate release tablet exhibits rapid dissolution characteristics *in vitro* ([ ] dissolution in < 15 minutes). Pharmacokinetics of varenicline are linear and dose-proportional in the range of 0.3 – 2 mg single and multiple doses (QD or b.i.d.). Compared to single dose, Cmax and AUC were ~ 3-fold (accumulation) higher at steady-state. Administration of varenicline with food does not change its bioavailability. Varenicline is absorbed with a Tmax of ~ 3 hours and exhibits very low plasma protein binding (10-20 %). It is secreted into saliva in humans and distribution into brain and melanin-rich tissues was noted in preclinical studies. Varenicline undergoes very little metabolism (<10%) and is excreted predominantly by renal route with a small role for renal hOCT-2 in active secretion. Pharmacokinetics of varenicline are similar irrespective of the time of administration (AM vs PM). The elimination half-life of varenicline is generally 20 hours.
>
> Per Dr. Nallani's review, dose adjustment is not required with respect to the intrinsic factors such as age, gender, race, body weight and hepatic dysfunction. However, adjustment is recommended in subjects with severe and end-stage renal disease.

Pharmacokinetic or pharmacodynamic changes were not noted with the coadministration of multiple doses of varenicline with multiple doses of digoxin, warfarin, or metformin. An increase in exposure to varenicline with coadministration of cimetidine was observed but was of insufficient magnitude to warrant recommending dose adjustment.

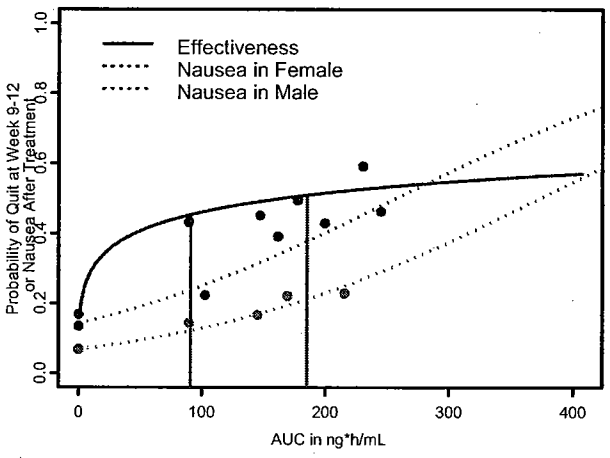
There did not appear to be pharmacokinetic interactions with nicotine or bupropion in co-administration studies; however adverse events and treatment discontinuations due to adverse events were more common with coadministration.

Several bioequivalence studies were performed to bridge the Phase 2a, Phase 2b, Phase 3 and to-be-marketed formulations. The results indicate that the proposed to-be marketed formulation, a film-coated tablet, and the uncoated tablet formulation used in the pivotal clinical trials are bioequivalent.

5.2 Exposure-Response Analyses

Drs. Nallani and Zheng undertook exposure-response analyses of efficacy and tolerability using population PK/PD analyses of Phase 2 Study A3051007 and three Phase 3 clinical studies (A3051028, A3051036 and A3051037). Using nausea as the tolerability endpoint, they also evaluated the dose-response relationship for tolerability. Their analyses confirm a dose-response for both efficacy and safety, but also point out a discrepancy between the incremental efficacy attained by increasing from 0.5 mg b.i.d. to 1 mg b.i.d. and the incremental likelihood of nausea. They also noted that women reported nausea more commonly at each level of exposure. The figure below illustrates this point.

Revised Exposure-Response relationship for the weeks 9-12 CQR and nausea after treatment for combine Phase 2/3 Studies



This analysis confirms the findings in the clinical safety review and provides support for recommending a lower starting dose in labeling.

6 NON-CLINICAL PHARMACOLOGY/TOXICOLOGY ISSUES

Dr. Mamata De reviewed the non-clinical pharmacology and toxicology portion of the review. Her review notes:

Preclinical studies include toxicology studies in rats, dogs, mice and monkeys with duration of single dose to 12 months, 2-year carcinogenicity studies in mice and rats, genotoxic studies, reproductive toxicity studies in rats and rabbits, and special toxicology studies. The major target organs were brain/central nervous system, gastrointestinal tract, and lymphoid system. Decrease in body weight and food consumption was observed in animal studies.

Although the test article was found to be distributed in the melanin containing tissue in the skin and eye, no toxicological manifestation of this pharmacological effect of the compound were noted in any of the chronic toxicity studies. Retinal dysplasia was observed in 1/20 rats in the 6-month study at 30 mg/kg dose (HED=288 mg). At this dose a > 200 fold safety margin exist as compared to the clinical dose based on the body surface area.

A battery of tests indicated that varenicline did not have mutagenic potential. In the 2-year carcinogenicity studies, drug-related neoplastic alterations were limited to hibernoma in male rats. 1/65 male rats showed benign hibernoma at 10 mg/kg dose; 2/65 male rats showed malignant hibernoma at 15 mg/kg dose. This finding is not statistically significant. The 'hibernoma' is a rare tumor finding in rodents.

In reproductive toxicology studies, varenicline reduced the pregnancy rate. No teratologic effect was observed in rats. A decrease in fetal weight was seen in rabbits. Varenicline crossed the placenta and was also noted to be secreted in milk.

7 PROPRIETARY NAME REVIEW

Pfizer's intial proprietary name proposal, Champix, was rejected by the Division of Drug Marketing, Advertising, and Communications (DDMAC) as promotional, due to the connotations of the word "champ." Therefore, Pfizer submitted several alternatives, including [ ] and Chantix. These are under consideration by DDMAC and by DMETS.

8 DISCUSSION

Pfizer has provided convincing evidence of the efficacy of varenicline at the dose proposed in labeling, 1 mg b.i.d., as an aid to smoking cessation. However, the application also contains convincing evidence of the efficacy of a lower dose of varenicline (1 mg/day, as a single dose or divided doses), and strong indications of a dose-response relationship for all the most common drug-related adverse events, and my initial impression was that 1 mg b.i.d. was neither the minimum effective dose nor the optimal dose for varenicline. Pfizer's focus on the 1 mg b.i.d. was assumed to derive

from the fact that evidence for the comparative claim vs. Zyban has only been provided in studies using that dose.

The superiority of the 1 mg b.i.d. dose over the labeled regimen of Zyban for helping smokers attain abstinence was clearly demonstrated in suitably-designed trials. Pfizer should be permitted to present this information and make this claim in labeling. Although the 1 mg b.i.d. dose appears to be only marginally more effective than the 1 mg/day dose, it does offer some incremental efficacy. Furthermore, although it is less well-tolerated than the lower dose, it is nevertheless reasonably tolerable, with discontinuations due to adverse events in the range of 13%. Therefore, it seemed reasonable to recommend that patients titrate to their own level of efficacy and tolerability; in fact, just such a dosing regimen was tested and shown to be superior to placebo. Although most drugs inevitably are used in this fashion clinically, it is rare that a New Drug Application actually contains efficacy data that demonstrates convincingly that a fixed-dose regimen at the low end is effective, that a fixed-dose regimen at the high end is effective and tolerated, *and* that a flexible-dosing, self-titrated scheme is effective. A dosing and administration section calling for a flexible-dosing scheme beginning at 0.5 mg/day, as in the flexible dosing study, seemed appropriate. The proposed section also explicitly states [ ] The data from the post-treatment MNWS scores suggest that there may be some increase in symptoms consistent with withdrawal upon treatment discontinuation. Furthermore, the majority of post-treatment relapse occurs within the first 3 months after treatment discontinuation. Taper may be advisable to limit withdrawal and perhaps to improve rates of non-relapse. On the other hand, chronic dosing does not seem to be well-supported in this application, as longer-term use appears to be associated with a higher rate of discontinuation due to adverse events; mild but bothersome events that persist for months appeared to be treatment limiting for many study participants.

My initial recommendation was that the label would need to differ materially from the language proposed by Pfizer. I proposed a change in the dosing and administration section to titrated dosing as well as significant changes in the presentation of results in the clinical trials section. Pfizer's intent was to illustrate several different depictions of quit rates from the two Phase 3 Zyban-comparator trials. As the Dr. Buenconsejo's review amply illustrates, there are any number of ways of looking at the abstinence rates, and there is no compelling reason to choose the "weeks 9-12" other than its designation as the "primary efficacy endpoint" in the protocol. The designation of a primary efficacy endpoint in a protocol is a statistical necessity to protect against Type I error arising from multiple comparisons; it is not necessarily an endorsement of a particular analysis as the best, most meaningful, most accurate, or most illustrative. There are few precedents in labeling for this therapeutic category. The nicotine replacement products, when labeled for prescription sale, did not illustrate a specific mean abstinence rate per treatment arm; instead the range of rates across centers was shown. The Zyban label presents quit rates from the beginning of the fourth week of treatment (the end of a three-week grace period) through various time points in the study through post-treatment follow-up, giving a mean value and confidence intervals. Pfizer's current proposed presentation, a bar graph, does

not give the opportunity to present confidence intervals or ranges of rates across centers, and could be replaced with a table similar to that in the Zyban label.

Moreover, the studies supporting lower doses of varenicline will need to be presented in labeling as well.

Pfizer also seeks to make several claims about the subjective effects of varenicline on craving, withdrawal, and smoking satisfaction. As noted above, a persuasive case was made for an effect of varenicline on "urge to smoke," using two different instruments. However, the concept of "craving" does not appear to be well-delineated, nor do the results clearly support a claim regarding "craving." The effects on withdrawal are mixed and a claim regarding relief of withdrawal insufficiently supported. The concept of "smoking satisfaction" was felt to be inadequately defined and inappropriate for inclusion in labeling.

Because varenicline is likely to be used extensively, including in women of childbearing potential, and because the effects of nicotine on the developing fetus are a matter of ongoing investigation, a pregnancy registry may be helpful in learning more about the effect of varenicline in pregnancy.

Pfizer proposes to market the drug in a blister-packaging presentation tied to the proposed dosing and administration section. Specifically, the following package configurations are proposed for marketing:

	Description	NDC
Packs		
	First month of therapy: Pack (Includes 1 card - 0.5 mg x 11 tablets and 3 cards - 1 mg x 14 tablets)	NDC 0069-0471-97
	Continuing months of therapy: Pack (Includes 4 cards - 1 mg x 14 tablets)	NDC 0069-0469-97
Bottles		
	0.5 mg - bottle of [redacted]	NDC 0069-0468-[redacted]
	1 mg - bottle of 56	NDC 0069-0469-56

The dosing packs provide the appropriate supply and configuration of tablets for a forced-titration to 1 mg b.i.d. and continued dosing thereafter on 1 mg b.i.d.. However, my initial impression was that this application contained sufficient evidence to support approving a lower dose, and that flexible dosing would be optimal for minimization of adverse events. Therefore, the dosing pack was inconsistent with the dosing and administration section as I initially recommended it should read, and the presentation did not give patients the necessary flexibility to titrate to an individually optimized dose. I initially recommended only the bottles of tablets be approved for marketing.

9 ADDENDUM REGARDING DOSING AND ADMINISTRATION

After presenting Pfizer with our initial proposed revisions to the Clinical Trials and Dosing and Administration sections of the package insert, the Division participated in a teleconference in which Pfizer expressed the belief that the incremental efficacy of the 1 mg b.i.d. dose, in their view, outweighed the risk of increased nausea and premature treatment discontinuation in the population of smokers wishing to quit. Pfizer then submitted several documents outlining their rationale.

Pfizer argued that: "Patients should progress dosing to 1 mg b.i.d. on Day 8 because this dose offers the highest chance of successful smoking cessation. In the area of addiction treatment, the patient who has reached the important decision to make a quit attempt should be given the best opportunity for success. The 1 mg b.i.d. dose of varenicline maximizes efficacy." In support of this contention, Pfizer cited the results from Studies A3051002 (varenicline at 0.3 mg QD, 1 mg QD, 1 mg b.i.d.) and A3051007 (0.5 mg b.i.d. and 1 mg b.i.d.), noting that only subjects taking the 1 mg b.i.d. varenicline dose in Study A3051002 demonstrated a statistically significant increase in continuous abstinence rates at Weeks 4-52 compared with placebo. In Study A3051007, the abstinence rate at Weeks 9-52 was numerically higher for subjects on 1 mg b.i.d compared to subjects on 0.5 mg b.i.d.

Pfizer also provided an analysis by Robert West, an recognized expert on nicotine and tobacco research, calculating the long-term benefit, in years of potential life saved, of small differences in rates of permanent cessation. Dr. West argues that:

> A robust index of effectiveness of a course of treatment is the increase in the proportion of smokers who achieve at least 6 months of continuous abstinence. The reason for adopting this index is that our estimates of health gains from stopping smoking are mostly based on permanent cessation versus continued smoking and 6 months of continuous abstinence gives sufficient information to make reliable estimates of permanent cessation.
>
> Some licensing authorities use a shorter period of abstinence such as 4 weeks but this faces a number of problems. The most serious of these is that estimating permanent cessation rates from 4-week abstinence rates is too imprecise and requires too many assumptions to be made about relapse rates after this point, especially when treatment continues past this point. Another approach is to examine the effect in the last 4 weeks of treatment. Again this suffers from the problem of imprecise estimation of permanent cessation and the possibility that resumption of smoking may merely have been delayed by the treatment rather than prevented.
>
> Considering 6 months of continuous abstinence as the key outcome measure, we can calculate with some degree of confidence how different effect sizes will translate into reductions in premature deaths. ...

The basis for this calculation is as follows:-

It has been found that there is approximately 20% relapse between 6 months and 12 month, approximately 60% of those abstinent for 12 months remain so for at least 8 years and there is no difference in relapse rates after 12 months between treated and untreated abstainers. There is therefore what may be considered a permanent treatment effect on abstinence amounting to 50% of the effect at 6 months. This means that, from 1% of those who achieve 6 months of continuous abstinence we would expect 0.5% to maintain permanent abstinence.

Based on this analysis, Dr. Buenconsejo and I returned to the data from the study which compares 0.5 mg b.i.d. to 1 mg b.i.d. directly, Study A3051007, and looked at the long-term continuous abstinence rates. Because the study incorporated four dosing regimens for varenicline, only two of which are contemplated for marketing (0.5 mg b.i.d titrated and 1 mg b.i.d. titrated), we also looked at the titrated groups separately from the non-titrated groups. All previous efficacy analyses had pooled these groups.

Our initial impression of minimal incremental efficacy in this study was based on the analysis of the Week 9-12 outcome, with titrated and non-titrated arms pooled into one arm per dose. As shown below, when the different doses contemplated for recommendation in labeling (titrated only) are compared, and the long-term outcome is considered, which more accurately predicts the rate of permanent cessation, a more compelling advantage of 1 mg b.i.d. is apparent.

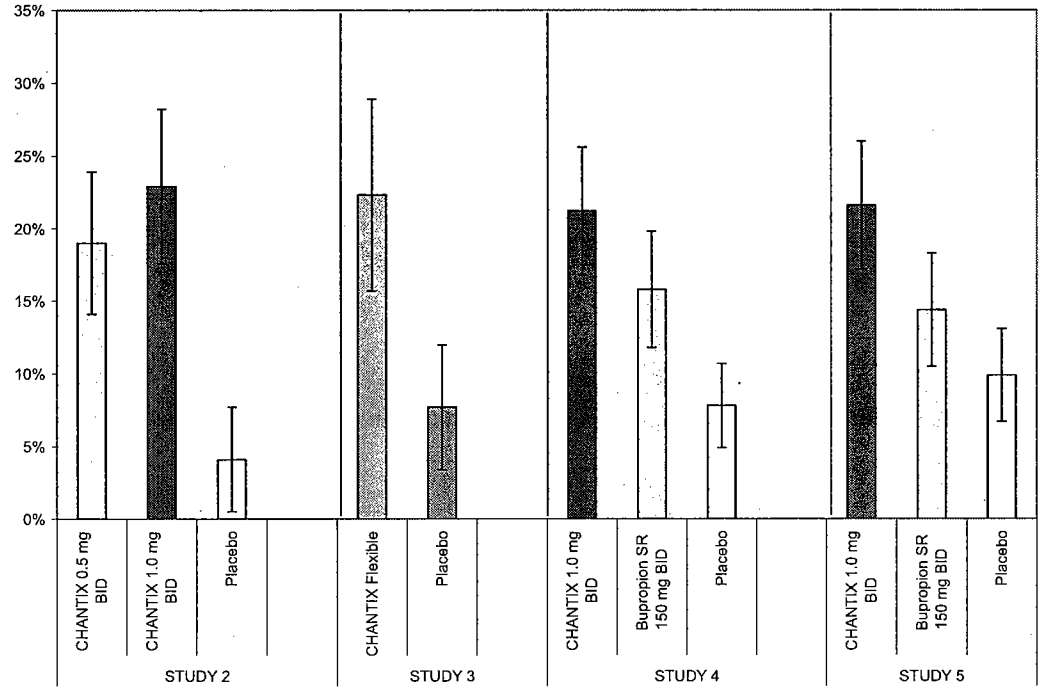
% of subjects abstinent	0.5 mg b.i.d. (all)	0.5 mg b.i.d. (titrated only)	1 mg b.i.d. (all)	1 mg b.i.d. (titrated only)
Weeks 9-12	45%	41%	51%	55%
Weeks 9-52	19%	23%	23%	35%

Additionally, Pfizer argued that varenicline, even at 1 mg b.i.d. is well-tolerated. Overall, approximately 13% of subjects treated with varenicline 1 mg b.i.d in 12-week dosing studies prematurely discontinued treatment due to adverse events. However, we had argued that the dropout rate was only 7% when subjects were allowed to self-titrate. Because tobacco addiction is a behavioral disorder, often a quit attempt is possible only at the specific time the patient is ready and motivated; a patient discontinuing treatment due to intolerable side effects is unlikely to be amenable to another quit attempt right away. That opportunity would be lost for that patient. For this reason, we had argued that self-titration was an optimal strategy.

However, Pfizer points out that, conversely, an attempt that fails due to inadequate dosing would similarly represent a lost opportunity to attain abstinence.

Focusing on the long-term abstinence rates which serve as the most reliable surrogates for permanent cessation of tobacco use (which is, itself, already a surrogate for health benefit), it does appear that the 1 mg b.i.d dose may offer an advantage over the 0.5 mg b.i.d. dose. No direct comparison with the flexible dosing strategy I initially proposed for

inclusion in labeling was undertaken. However, because of the similarity of the trial designs and populations, and the consistency of the placebo rates, some degree of cross-study comparison is possible. The figure below, prepared by Dr. Buenconsejo, illustrates the rates of continuous abstinence from Week 9 through Week 52 in Studies A3051007 (represented as Study 2), A3051016 (Study 3), A3051028 (Study 4), and A3051036 (Study 5).



This data suggest that the flexible dosing strategy remains very promising and that, within the context of the clinical trial, underdosing resulting in failure was not an issue with long-term consequences rendering this method inferior to the forced-titration regimen in terms of long-term abstinence. However, it must be acknowledged that clinical trial participants were provided with sufficient supplies of medication to self-titrate as needed without any financial disincentive to use a higher dose. Patients may well be influenced by factors other than their own subjective response to medication when selecting a dose in "real-world" use. It is generally accepted that the efficacy of self-titrated dosage forms of nicotine replacement is limited by patients' failure to use adequate doses. Whether influenced by a philosophical opposition to taking "too much" medicine or by cost concerns, it is highly likely that patients' behavior may differ from clinical trial participants' in this regard.

Pfizer also speculated that the ability to titrate appropriately would be limited by patients' inability to distinguish between adverse drug effects and the symptoms of nicotine withdrawal. Patients might not know whether to increase or decrease the dose in response to particular symptoms. To the extent that the frequent visits to the trial site

might have provided the study participants with some guidance, this close monitoring is unlikely to be a feature of the real-world use of the product. Although I think that there is enough evidence that certain symptoms (notably nausea and other G.I. effects) are likely to be caused by varenicline, rather than by nicotine withdrawal, it is possible that patients without frequent contact with the prescribing physician may be confused by the titration directions, which were somewhat vague in Study A3051016.

Therefore, although the titration strategy appears to have been the best-tolerated and, in the long run, no less efficacious, it may be difficult to reproduce the conditions of the clinical trial in the general population. Because the risks of lack of efficacy (i.e., a failed quit attempt, probably followed by a period of unwillingness to try again) are more severe than the risks of the adverse effects associated with higher doses of varenicline (GI symptoms, sleep disturbance, etc., not routinely leading to treatment discontinuation), it does appear that a forced-titration to 1 mg b.i.d. is the optimal dose to recommend. However, the label should include language advising clinicians to lower the dose of varenicline for patients who are troubled by typical drug-associated adverse effects, in order to retain patients on-treatment.

In addition, the Clinical Trials section of the label should present the data from all of the efficacy studies, not simply from the three proposed for inclusion by Pfizer (A3051038, A3051036, and A3051035). Furthermore, the behavioral support provided in the clinical trials should be described in labeling, and the need for some behavioral support and educational materials similar to that provided to study participants should be mentioned. The indication statement should reflect this, as it does in the Zyban label, by representing the product as an "aid to smoking cessation treatment," which implies that some other aspect of treatment would be involved along with the medication. Currently, the proposed label simply states that the product is [ ]

10 CONCLUSIONS AND RECOMMENDATIONS

I recommend approval of varenicline, with modifications to the clinical trials, indication, abuse/dependence and dosing/administration sections of the proposed labeling as described.

11 APPENDICES

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On Original

Appears This Way
On Original

11.1 APPENDIX 1: Protocol A3051028

A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study with Follow-up Evaluating the Safety and Efficacy of Varenicline Tartrate (CP-526,555) in Comparison to Zyban® for Smoking Cessation

Conducted June 19 2003-April 22 2005

11.1.1 Protocol

11.1.1.1 Objective/Rationale

The purpose of the study was to compare the efficacy of varenicline 1 mg b.i.d. to placebo and Zyban for smoking cessation after 12 weeks of treatment.

11.1.1.2 Overall Design

The study was a double-blind, placebo-controlled, randomized clinical trial designed to assess the efficacy and safety of varenicline 1 mg b.i.d. in comparison to placebo and Zyban® 150 mg b.i.d. for smoking cessation. The duration of active treatment specified in the protocol was 12 weeks and subjects were to be followed in the nontreatment phase for an additional 40 weeks.

11.1.1.3 Population and Procedures

11.1.1.3.1 Inclusion/Exclusion Criteria

Planned enrollment was approximately 1005 subjects randomized 1:1:1 to each of three treatment arms (335 per arm)

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

- Male or female cigarette smokers between the ages of 18 and 75 years, inclusive, who were motivated to stop smoking.
- For female subjects, surgical sterilization or at least 2 years postmenopausal, or using medically acceptable contraception
- Smoking an average of at least 10 cigarettes per day during the past year and over the month prior to the screening visit, with no period of abstinence greater than 3 months in the past year.
- Able to be outpatients and be assessed in a clinic setting.

Subjects were to be excluded for:

- Pregnancy/nursing
- Serious or unstable disease within the past 6 months
- Prior use of bupropion, Zyban, or Wellbutrin
- Condition rendering subject inappropriate for treatment with Zyban®. Examples include:
    - any history of seizures or conditions that would increase the risk of seizures, including febrile seizures, childhood seizures, and seizures associated with alcohol withdrawal as well as subjects with a history of clinically significant head injury
    - diabetes mellitus requiring insulin or oral hypoglycemics

  - hepatic or renal impairment
  - current or prior diagnosis of anorexia nervosa or bulimia nervosa
  - use of an MAO inhibitor within the past 14 days
- Clinically significant cardiovascular disease in the past 6 months.
  Examples of clinically significant cardiovascular disease would include the following:
  myocardial infarction, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), unstable angina, a serious arrhythmia, or clinically significant ECG conduction abnormalities.
- Uncontrolled hypertension or a screening or baseline systolic blood pressure greater than 150 mm Hg or a diastolic blood pressure greater than 95 mm Hg.
- Severe chronic obstructive pulmonary disease (COPD). Mild and moderate COPD were allowed.
- History of cancer (treated basal cell or squamous cell carcinoma of the skin allowed).
- Evidence or history of clinically significant allergic reactions (seasonal allergies allowed).
- SGOT (AST) or SGPT (ALT) greater than 150% ULN or total bilirubin greater than 110% ULN.
- Body Mass Index (BMI) less than 15 or greater than 38. No subject was to be enrolled with a weight less than 100 pounds.
- Current or past 12 months treatment for depression.
- Current or prior history of panic disorder, psychosis, or bipolar disorder.
- History of drug (except nicotine) or alcohol abuse or dependence within the past 12 months.
- Concomitant treatment with another investigational drug within 30 days of the study baseline visit or with plans to take another investigational drug within 30 days of study completion.
- Previously randomized in a study that has included varenicline tartrate (CP-526,555).
- Intention to donate blood or blood components while receiving experimental drug or within 1 month of the completion of the study.
- Requirement to use other medications during the study that might interfere with the evaluation of the study drug (e.g., nicotine replacement therapy).
- Use of a nicotine replacement product, clonidine, or nortriptyline within the previous month.
- Use of tobacco products other than cigarettes, including pipe tobacco, cigars, snuff, and chew, or marijuana use within the past month and not agreeing to abstain from use of these products during study participation.
- Inability to to comprehend and follow the study protocol, including subjects unable and/or unwilling to participate in the nontreatment follow-up.

Disallowed concomitant medications included:

- antidepressants, including bupropion (Wellbutrin®), citalopram (Celexa®), fluoxetine (Prozac®), mirtazepine (Remeron®), nefazodone (Serzone®),

paroxetine (Paxil®), sertraline (Zoloft®), trazodone, tricyclic antidepressants, and venlafaxine (Effexor®)
- antipsychotic agents, including clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), risperidone (Risperdal®), and ziprasidone (Geodon®)
- benzodiazepines, including alprazolam (Xanax®), diazepam (Valium®), and lorazepam (Ativan®)
- insulin
- mood stabilizers, including carbamazepine (Tegretol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), lithium, and valproate (Depakene® or Depakote®)
- naltrexone
- nicotine replacement therapy and other aids to smoking cessation
- oral hypoglycemic agents
- over-the-counter and prescribed stimulants and anorectic agents
- steroids, including systemic anabolic steroids, glucocorticoids, and mineralocorticoids (inhaled steroid use is permitted)
- theophylline

11.1.1.3.2 Procedures

The protocol called for an initial screening visit, during which medical screening procedures were undertaken. A subsequent "baseline" visit was to occur 3 days – 3 weeks after the screening visit, which would be cancelled if results of laboratory tests did not confirm eligibility. At the time of screening, subjects were to select a target quit date (TQD) to coincide with the Week 1 visit, which was required to be scheduled to occur 8 days after the baseline visit, so that subjects would have a full 7 days of treatment prior to the TQD.

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

11.1.1.3.2.1 Dosing

Eligible subjects were to be randomized to treatment with varenicline, Zyban, or placebo. To maintain blinding, subjects took both medications, of which none or either was active, at each dosing occasion.

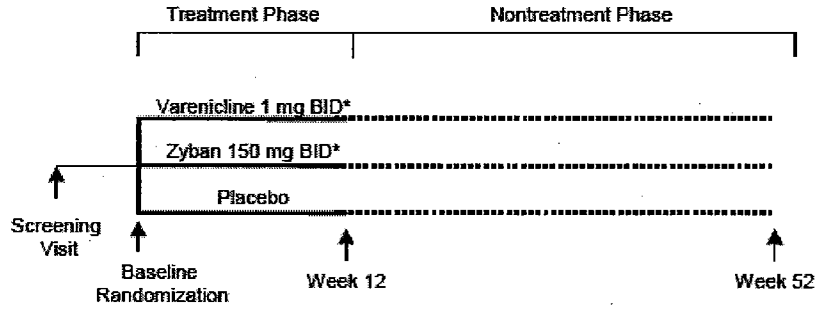
Both varenicline and its matching placebo and blinded Zyban® were to be dispensed to the subjects from room temperature storage at each scheduled visit between screening and Week 12. Supplies of varenicline were in a strength of 0.5 mg tablets and provided in blister cards. Blinded Zyban® was in a strength of 150 mg tablets and provided in blister cards. The Zyban tablets were purchased commercially and blinded by removal of tablet markings (deinking) with an ethanol soaked cloth. Results from dissolution testing showed that the deinking process does not affect the performance of the blinded Zyban tablets.

Treatment was to begin on the day after the baseline visit. The subjects were instructed to take a total of 2 tablets per day for the first 3 days of the dosing period. In the morning, the first blinded varenicline tablet and the first blinded Zyban® tablet on the dosing cards were to be taken. The dosing was then to increase for the next 4 days to 4 tablets per day, 2 in the morning (the first blinded varenicline tablet and the first blinded Zyban® tablet) and 2 in the evening (the second blinded varenicline tablet and the second blinded Zyban® tablet). The dosing was then to increase to 6 tablets per day, 3 in the morning (the first 2 blinded varenicline tablets and the first blinded Zyban® tablet) and 3 in the evening (the second 2 blinded varenicline tablets and the second blinded Zyban® tablet) for the remainder of the study. All subjects were to dose study medication on the day of the Week 1 visit in the morning prior to the visit. Dosing instructions called for administration with 240 ml of water and subjects were advised to eat prior to dosing. Subjects were instructed that there were to be at least 8 hours between the morning and evening dosing. Subjects were to return blister cards at each visit and a dosage record was to be recorded.

11.1.1.3.2.2 Schedule of Visits and Assessments

The overall study schematic is illustrated in the figure below.

Figure 1. Study Design



Treatment Period													Non-treatment Follow-up										
B L	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52
C	C	C	C	C	C	C	C	C	C	C	C	C	C	T	T	C	T	T	C	T	C	T	C

Randomization
Target Quit Date

C: clinic visit; T: telephone contact

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

to be reminded of study participation and to receive support for the smoking cessation attempt. These contacts were to be no longer than 5 minutes and counseling was to follow AHRQ guidelines. In addition, subjects will be asked to complete the Minnesota Nicotine Withdrawal Scale (MNWS) and the Brief Questionnaire of Smoking Urges (QSU) in the morning on day of the TQD+3 contact.

At each visit, subjects were to be asked about cigarette and other nicotine use since the last study visit and in the past 7 days (using the Nicotine Use Inventory). End-expiratory exhaled carbon monoxide was to be measured. All concomitant medications and any adverse events were to be recorded. Other subjective effects and safety measures were undertaken as per the time-and-events schedule below.

The treatment phase was to end after 12 weeks of subject participation. During the Week 12 visit, or at early termination, subjects were to be asked about cigarette and other nicotine use since the last visit and in the past 7 days. End-expiratory exhaled carbon monoxide will be measured and up to 10 minutes of brief counseling regarding smoking cessation will be provided. Safety assessments and subjective measures were to be obtained.

Following completion of the Week 12 visit, subjects were to continue in the nontreatment follow-up phase of the protocol. Subjects who did not complete the Week 12 visit were not eligible to continue. Subjects discontinuing study *drug* prior to the Week 12 visit would be permitted to continue *study* participation as long as they complete the remaining scheduled visits through Week 12.

Nontreatment Follow-up (Weeks 13 through 52)
Subjects were to return for visits to the clinic at Week 13, Week 24, Week 36, Week 44, and Week 52. At each visit, subjects were to be administered a Nicotine Use Inventory (Appendix G), which collected information about cigarette and other tobacco use since the last contact and over the previous 7 days. In addition, subjects were to be asked to report the number of days of cigarette smoking and other tobacco use since the prior contact. End-expiratory exhaled carbon monoxide was to be measured at each clinic visit (nonsmoking status would be considered confirmed with a measurement $\leq$ 10 ppm). Vital signs and weight were to be measured at each clinic visit. Concomitant medications used as an aid to smoking cessation were to be recorded. At the Week 52 (or early termination) visit, subjects were to have blood drawn for the measurement of C-reactive protein.

The MNWS (past week) was to be self-administered at the Week 13 visit, with answers based on symptoms over the prior week (Appendix I). The Smoking Cessation Quality of Life Questionnaire was to be self-administered by subjects at Week 24 and Week 52 (or early termination).

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

Additionally, the Nicotine Use Inventory was to be administered by telephone at Weeks 16, 20, 28, 32, 40, and 48 (+/- 14 days) and subjects were to be asked about concomitant medications used as an aid to smoking cessation, and reminded of their study participation.

11.1.1.3.2.3 Behavioral treatment

Subjects were to be given an educational booklet on smoking cessation to review ("Clearing the Air: How to Quit Smoking...and Quit for Keeps" – National Cancer Institute Publication 95-1647) and provided up to ten minutes of counseling, in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines (Fiore 2000).

The following time-and-events table illustrates the planned schedule of assessments:

A3051028 Study Schedule

Assessment	Screen	BL	Wk 1[a]	TQD+3	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	ET
Medical history, Informed consent	X															
Physical examination[b]	X														X	X
Vital signs (HR, BP), weight	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Temperature		X														
Height	X															
Adverse events		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dosing record			X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Fagerström Test for Nicotine Depend.	X															
Nicotine Use Inventory		X	X		X	X	X	X	X	X	X	X	X	X	X	X
MNWS, QSU-Brief		X	X	Xc	X	X	X	X	X	X					X	X
Smoking Effects Inventory[d]		X	X		X	X	X	X	X	X						X
Smoking Cessat. QoL Questionnaire		X													X	X
Chemistry, CBC, ECG, Pregnancy	X	X			X										X	X
C-reactive protein		X													X	X
Reference serum sample		X														
Serum cotinine	X															
Plasma pharmacokinetic sample					X										X	X
Genotyping sample [e]		X														
Urinalysis (dipstick)	X	X			X										X	X
Urine Drug Screen[f]	X															
Exhaled carbon monoxide		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Counseling (AHRQ guidelines)		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X		X	X	X	X	X	X	X	X	X	X		
Telephone contact (AHRQ guidelines)				X												

[a] must be scheduled 8 days after the baseline visit; [b] either screening or BL; [c] self-administered by subjects in the morning on the TQD+3; [d] also completed daily between baseline and Week 1, only required in subjects who have smoked since prior completion; [e] optional; [f] may be collected at visits in addition to screening at discretion of investigator; BL=baseline; TQD=target quit date; ET=early termination; QoL=Quality of Life; CBC=complete blood count; AHRQ=Agency for Healthcare Research and Quality

Non-treatment follow-up schedule

Procedure	Week 13 (clinic visit)	Weeks 16 and 20 (telephone contact)	Week 24 (clinic visit)	Weeks 28 and 32 (telephone contact)	Week 36 (clinic visit)	Week 40 (telephone contact)	Week 44 (clinic visit)	Week 48 (telephone contact)	Week 52 (clinic visit)	ET
Nicotine Use Inventory	X	X	X	X	X	X	X	X	X	X
Weight, blood pressure, pulse rate	X		X		X		X		X	X
End-expiratory exhaled carbon monoxide	X		X		X		X		X	X
Concomitant medications (as aids to smoking cessation)	X	X	X	X	X	X	X	X	X	X
C-reactive protein									X	X
Minnesota Nicotine Withdrawal Scale (past week)	X									
Smoking Cessation Quality of Life Questionnaire			X						X	X
Counseling (AHRQ guidelines)	X		X		X		X		X	X

ET = early termination

11.1.1.4 Evaluations/Endpoints

The pre-specified primary endpoint was the 4-week Continuous Quit Rate (CQR) for Weeks 9 to 12. Subjects were to be classified as responders if they were able to maintain complete abstinence from cigarette smoking and other nicotine use for the last 4 weeks of treatment with end-expiratory exhaled CO measurements ≤ 10 ppm. Subjects who withdrew before the study completion were considered non-responders for the remainder of the study, regardless of smoking status at the time of discontinuation. However, imputation of missing data within a specific endpoint, resulting from incomplete CRF or eCRF data was computed as follows:

> ... in the case of a missed visit(s) during the evaluation period (Weeks 9 – 12), a subject was considered a responder if the subject indicated that he/she had not smoked or used nicotine products 'since the last visit' at the visit after the missing visit(s). No attempt was made to impute missing data from other weekly interview questions. For Point Prevalence of abstinence at the end of the study (i.e., 4 weeks to Week 52), missing interview questions of whether the subject has 'smoked in the last four weeks' or 'used any other tobacco products in the last four weeks' were not imputed (i.e., subject was considered a non-responder for this endpoint).

Note that this imputation strategy differed from the more conservative approach used in Phase 2, during which subjects missing more than one visit in the four-week period of interest were considered non-responders.

Key secondary endpoints identified in the protocol included:

• Continuous Abstinence Rate from Week 9 through Week 52 (defined as the proportion of subjects who maintained complete abstinence from cigarette smoking ("not even a puff") and other tobacco use for a specified time period, generally from Week 9 (i.e., the beginning of the lapse-free period) through Week 52).

• Long-term Quit Rate through Week 52(the proportion of subjects who have successfully quit during the treatment phase of the study based on the 4-week CQR from Week 9 through Week 12 and who have had no more than 6 days of smoking during the nontreatment phase)

Other secondary endpoints identified included:

• Continuous Abstinence Rate 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
• Change from baseline in body weight
• Results of the Minnesota Nicotine Withdrawal Scale, the Brief Questionnaire of Smoking Urges, and the Smoking Effects Inventory. Specifically:

> Craving was assessed using the Total Score and two subscale scores of the Brief Questionnaire of Smoking Urges (QSU-Brief) supplemented by the Urge to Smoke item (i.e. Item 1) of the Minnesota Nicotine Withdrawal Scale (MNWS).

Withdrawal was assessed using four subscales (Negative Affect, Insomnia, Restlessness, and Increased Appetite) derived from Items 2-9 of the MNWS. Of these, the Negative Affect subscale captures multiple symptoms including depressed mood, irritability, frustration or anger, anxiety, and difficulty concentrating (Items 2-5), and the Insomnia subscale captures both difficulty going to sleep and difficulty staying asleep (Items 8 and 9).

Lastly, reinforcing effects of smoking were assessed using five subscales (Smoking Satisfaction, Psychological Reward, Enjoyment of Respiratory Tract Sensations, Craving Reduction, Aversion) derived from the 12-item Smoking Effects Inventory (also called the Modified Cigarette Evaluation Questionnaire, SEI/ mCEQ). The Smoking Satisfaction subscale is composed of satisfaction, taste, and enjoyment of smoking; the Psychological Reward subscale is composed of feeling more calm, more awake, less irritable, improved concentration, and decreased hunger associated with smoking, and the Aversion subscale is composed of dizziness and nausea upon smoking.

11.1.1.5 Statistical Plan

The protocol-specified primary inference for the study was a comparison of varenicline to placebo and Zyban® for the 4-week CQR for Weeks 9 through 12 of treatment. The secondary objective was to compare abstinence through Week 52. The study was powered to detect differences in the primary as well as key secondary endpoints in comparison to placebo and Zyban®. A step-down procedure was to be employed within the analysis of both primary and key secondary endpoints, in order to control for type I error within each endpoint.

11.1.2 Results

11.1.2.1 Study Conduct/Outcome

11.1.2.1.1 Subject Characteristics

Of 1483 subjects screened, 1025 subjects were selected for enrollment, with 352 randomized to treatment with varenicline, 329 to treatment with Zyban, and 344 to treatment with placebo. Three subjects randomized to varenicline did not initiate treatment.

11.1.2.1.1.1 Enrollment by Center

Enrollment was distributed among centers as listed in the table below:

Center Number	Principal Investigator Center Name and Address	Treatment Group	Rand	Treated N	Responders n	CQR% (n/N)
Study A3051028						
All	**All**	Varenicline	352	349	155	44.4
		Zyban	329	329	97	29.5
		Placebo	344	344	61	17.7
		Total	**1025**	**1022**		
1028-1002	**K. Kovitz/M Friedman** Tulane University Health Sciences Center SL9 1430 Tulane Avenue New Orleans, LA 70112-2699	Varenicline	9	9	2	22.2
		Zyban	10	10	0	0
		Placebo	8	8	0	0
		Total		**27**		
1028-1003	**M. Nides** Los Angeles Clinical Trials Suite 308 2990 South Sepulveda Boulevard Los Angeles, CA 90054	Varenicline	29	29	13	44.8
		Zyban	30	30	10	33.3
		Placebo	30	30	4	13.3
		Total		**89**		
1028-1004	**S. Rennard** University of Nebraska Medical Center 982465 Nebraska Medical Center Omaha, NE 68198-2465	Varenicline	18	18	12	66.7
		Zyban	18	18	2	11.1
		Placebo	20	20	6	30.0
		Total		**56**		
1028-1005	**D. Zimbroff** Pacific Clinical Research Medical Group Suite 200 1317 West Foothill Boulevard Upland, CA 91786	Varenicline	24	24	10	41.7
		Zyban	21	21	5	23.8
		Placebo	24	24	1	4.2
		Total		**69**		
1028-1006	**D. Gonzales** Oregon Health & Science University CR115 3181 Southwest Sam Jackson Park Road Portland, OR 97239-3098	Varenicline	18	18	9	50.0
		Zyban	18	18	7	38.9
		Placebo	18	18	2	11.1
		Total		**54**		
1028-1007	**C. Oncken** University of Connecticut Health Center Internal Medicine 263 Farmington Avenue Farmington, CT 06030-3940	Varenicline	32	32	10	31.3
		Zyban	32	32	12	37.5
		Placebo	31	31	2	6.5
		Total		**95**		
1028-1008	**H. Schwartz** Miami Research Associates, Inc. 7500 SW 87th Ave Suite 202 Miami, FL 33173	Varenicline	31	30	11	36.7
		Zyban	29	29	8	27.6
		Placebo	31	31	9	29.0
		Total		**90**		
1028-1010	**J. Heiser** Pharmacology Research Institute Suite 290 1601 Dove Street Newport Beach, CA 92660	Varenicline	28	28	18	64.3
		Zyban	24	24	12	50.0
		Placebo	26	26	7	26.9
		Total		**78**		
1028-1011	**L. Larsen** Intermountain Clinical Research 150 South 1000 East Salt Lake City, UT 84102	Varenicline	26	26	11	42.3
		Zyban	26	26	4	15.4
		Placebo	26	26	9	34.6
		Total		**78**		
1028-1012	**L. Covey** Social Psychiatry Research Institute Suite 201 3044 Coney Island Avenue Brooklyn, NY 11235	Varenicline	12	11	2	18.2
		Zyban	12	12	4	33.3
		Placebo	11	11	1	9.1
		Total		**34**		

Center Number	Principal Investigator Center Name and Address	Treatment Group	Rand	Treated N	Responders n	CQR% (n/N)
1028-1013	E. Glover Addiction & Psychiatric Medicine Research, West Virginia University RCB Health Sciences Center Suite 1400 Morgantown, WV 26506	Varenicline	13	13	7	53.9
		Zyban	13	13	6	46.2
		Placebo	12	12	1	8.3
		Total		38		
1028-1016	M. Muramoto University of Arizona Health Sciences Center, Department of Family and Community Medicine 1450 North Cherry Avenue Tucson, AZ 85719	Varenicline	4	4	2	50.0
		Zyban	3	3	2	66.7
		Placebo	3	3	1	33.3
		Total		10		
1028-1017	V. Rens Habitat Abatement Clinic Suite 2 1515 Scott Street San Francisco, CA 94143	Varenicline	10	10	4	40.0
		Zyban	10	10	1	10.0
		Placebo	10	10	0	0
		Total		30		
1028-1018	L. Pbert University of Massachusetts Medical School 55 Lake Avenue North Worcester, MA 01655	Varenicline	22	22	11	50.0
		Zyban	21	21	8	38.1
		Placebo	22	22	10	45.5
		Total		65		
1028-1019	A. Talwar North Shore University Hospital, Center for Tobacco Control 225 Community Drive, South Entrance Great Neck, NY 11021	Varenicline	4	4	3	75.0
		Zyban	3	3	2	66.7
		Placebo	2	2	0	0
		Total		9		
1028-1020	J. Geohas Radiant Research, Chicago Suite 2700 515 North State Street Chicago, IL 60610	Varenicline	21	21	10	47.6
		Zyban	16	16	4	25
		Placebo	20	20	2	10
		Total		57		
1028-1021	A. Mangione/B. Packman Radiant Research Incorporated Suite 203 9880 Bustleton Avenue Philadelphia, PA 19115	Varenicline	13	12	6	50.0
		Zyban	12	12	6	50.0
		Placebo	15	15	1	6.7
		Total		39		
1028-1023	M. Throne Radiant Research Incorporated Suite 360 1100 Lake Hearn Drive Atlanta, GA 30342	Varenicline	24	24	8	33.3
		Zyban	23	23	3	13.0
		Placebo	23	23	5	21.7
		Total		70		
1028-1024	J. Pappas Central Kentucky Research Associates, Incorporated 3rd Floor 3475 Richmond Road Lexington, KY 40509	Varenicline	14	14	6	42.9
		Zyban	8	8	1	12.5
		Placebo	12	12	0	0
		Total		34		

11.1.2.1.1.2 Subject Disposition

A total of 1,025 subjects were randomized in a 1:1:1 ratio. Three subjects assigned to treatment (randomized to varenicline) did not take any study drug. Thus, a total of 1,022 subjects, 349 varenicline, 329 Zyban, and 344 placebo, were treated with study drug.

Subject Disposition is shown in the table below, from Pfizer's final study report.

Subject Disposition [Number (%) of Subjects]

	Varenicline	Zyban	Placebo
Number screened = 1483			
Assigned to treatment	352	329	344
Treated[a]	349	329	344
Completed Study[b]	213 (61.0)	184 (55.9)	187 (54.4)
Discontinued Study	136 (39.0)	145 (44.1)	157 (45.6)
During Treatment Phase	90 (25.8)	104 (31.6)	129 (37.5)
Adverse events	14 (4.0)	34 (10.3)	24 (7.0)

Lack of efficacy	2 (0.6)	1 (0.3)	4 (1.2)
Protocol deviation	4 (1.1)	1 (0.3)	6 (1.7)
Refusal to participate further	23 (6.6)	31 (9.4)	42 (12.2)
Lost to follow-up	43 (12.3)	36 (10.9)	49 (14.2)
Other[c]	4 (1.1)	1 (0.3)	4 (1.2)
During Nontreatment Follow-up Phase	46 (13.2)	41 (12.5)	28 (8.1)
Subject died	0 (0.0)	0 (0.0)	1 (0.3)
Protocol deviation	0 (0.0)	1 (0.3)	0 (0.0)
Refusal to participate further	11 (3.2)	10 (3.0)	5 (1.5)
Lost to follow-up	34 (9.7)	29 (8.8)	22 (6.4)
Other[d]	1 (0.3)	1 (0.3)	0(0.0)

[a]Percentages based on number of subjects treated.
[b]Subjects could discontinue study medication but remain in the study.
[c] Other reasons (treatment phase): varenicline – 2 subjects moved out of the area; 1 subject had scheduling difficulties; and one had discontinued smoking prior to baseline
Zyban – 1 subject moved out of the area. placebo – 2 subjects moved out of area; one called up for National Guard service; 1 subject did not wish to stop smoking at this time.
[d] Other reasons (nontreatment phase): varenicline – 1 subject unable to attend visit before study closed by sponsor. Zyban – 1 subject called up for military service.

Subjects could discontinue study medication but remain in the study. Therefore, in the context of subject disposition, "completed the study" refers to the number of subjects who participated in the study for the full 52 weeks, whether or not they completed 12 weeks of dosing during the treatment phase.

The table below, adapted from Pfizer's Table 24, illustrates the distribution of subjects temporarily or permanently discontinuing study *medication* or requiring a dose reduction because of adverse events.

Treatment Discontinuations or Dose Reductions Due to Adverse Events N (%)

	Varenicline N = 349	Zyban N = 329	Placebo N = 344
Treatment discontinuations	30 (9)	50 (15)	31 (9)
Dose reductions or temporary discontinuations	16* (5)	11 (3)	14 (4)

*Three additional subjects temporarily discontinued study medication due to treatment-related adverse events and later permanently discontinued treatment due to adverse events.

During the 12-week treatment phase, across all treatment groups, the most frequent reasons for withdrawal were lost to follow-up, refusal to participate further, and adverse events. Adverse events were the reason for premature *study* discontinuation in 4% of the varenicline group, 10% of the Zyban group, and 7% of the placebo group, and for premature *treatment* discontinuation in 9% of the varenicline group, 15% of the Zyban group, and 9% of the placebo group. From an efficacy standpoint, treatment failure is imputed to subjects not completing the study, including those lost to follow-up and those discontinuing due to refusal to participate. There are more subjects in both of these categories in the placebo arm; this could represent a potential bias. However, relapse to smoking after treatment discontinuation is generally considered to be the rule, rather than the exception, and it seems reasonable to impute treatment failure to these subjects.

11.1.2.1.2 Demographics

The table below illustrates demographic and baseline characteristics of the three treatment groups. Overall, 79% of the subjects were White, 46% of the subjects were female, and the average age was approximately 42 years (range 18-75 years). Smoking history was similar across treatment groups, with subjects representing a population of smokers who on average had smoked for the previous 24 years (range 1-61 years) and had smoked an average of 21 cigarettes per day over the previous month. The varenicline arm had the lowest proportion of male subjects (50% vs. 58% in the Zyban arm and 54% in the placebo arm). This is notable because conventional wisdom holds that female smokers may be more difficult to treat; if true, this would potentially bias the study *against* varenicline.

	Study A1028		
	Varenicline N=349	Zyban N=329	Placebo N=344
Sex (Male), n(%)	175 (50%)	192 (58%)	186 (54%)
Mean Age (SD), y	43 (11)	42 (12)	43 (12)
Range	18 – 75	18 – 75	18 – 73
Race, n(%)			
White	278 (80%)	264 (80%)	262 (76%)
Black	35 (10%)	28 (9%)	49 (14%)
Asian	4 (1%)	5 (2%)	9 (3%)
Other	32 (9%)	32 (10%)	24 (7%)
	N=348	N=329	N=343
Number of years subject smoked			
Mean	24	24	25
Range	2 – 56	2 – 61	1 – 61
Number of cigarettes per day over past month			
Mean	21	21	22
Range	10 – 70	10 – 65	10 – 80
Previous Serious quit attempt			
None	53 (15%)	45 (14%)	55 (16%)
>1	295 (85%)	284 (86%)	288 (84%)
Longest period of abstinence in past year, d			
Mean	5.0	5.8	5.6
Range	0 – 90	0 – 90	0 – 97
Fagerstrom Test for Nicotine Dependence Score			
N	347	329	342
Mean (SD)	5.2 (2.2)	5.2 (2.1)	5.4 (2.0)

11.1.2.1.3

11.1.2.1.4 Dosing Information

The table below (Pfizer's Table 12, A3051028 final study report) illustrates exposure duration and compliance with medication across treatment groups. Groups were similar with respect to mean duration of exposure.

Duration of Treatment – Number (%) of Subjects)

	Varenicline N = 349	Zyban N = 329	Placebo N = 344
Duration (Days) [a]			
≥1 Unknown[b]	349 (100.0) 6 (1.7)	329 (100.0) 9 (2.7)	344 (100.0) 7 (2.0)
>3	343 (98.3)	313 (95.1)	337 (98.0)
>7	341 (97.7)	303 (92.1)	334 (97.1)
>14	318 (91.1)	274 (83.3)	303 (88.1)
>21	298 (85.4)	254 (77.2)	277 (80.5)
>28	290 (83.1)	245 (74.5)	257 (74.7)
>35	281 (80.5)	239 (72.6)	243 (70.6)
>42	274 (78.5)	229 (69.6)	233 (67.7)
>49	269 (77.1)	224 (68.1)	221 (64.2)
>56	260 (74.5)	220 (66.9)	215 (62.5)
>63	251 (71.9)	215 (65.3)	212 (61.6)
>70	245 (70.2)	210 (63.8)	207 (60.2)
>77	240 (68.8)	202 (61.4)	203 (59.0)
>84	110 (31.5)	101 (30.7)	128 (37.2)
>91	4 (1.1)	5 (1.5)	8 (2.3)
Median duration	84.0	84.0	84.0
Range	7 - 102	1 - 107	5 - 107

[a] For each subject, treatment duration is calculated as the total number of days from first day of dosing through the last day of dosing, without deducting for missed doses.
[b] Unknown: subjects lost to follow-up after being dispensed study medication. Subjects are assumed to have taken at least one dose and are included in the All Subjects population.

11.1.2.1.5

11.1.2.1.6 Protocol Violations

Pfizer reported that

> Protocol deviations were identified programmatically by searching the database for randomized subjects who had screening or baseline values falling outside of the ranges specified by inclusion or exclusion criteria (eg, values for age, weight, medical history, smoking history, laboratory parameters, etc). The database was also searched for subjects who used prohibited medications during the study and subjects who were withdrawn from the study due to protocol deviations. In addition, lists of protocol deviations were compiled by site monitors during routine center visits or during remote review of electronic data. All deviations identified by the methods described above were reviewed for clinical significance. Those considered potentially significant are summarized in [the table below, Pfizer's Table 6]. A total of 12, 12, and 22 subjects in the varenicline, Zyban, and placebo groups had significant deviations.

	Varenicline N = 349	Zyban N = 329	Placebo N = 344
Subjects with significant protocol deviations	**12**	**12**	**22**
Subjects with significant protocol deviations (by category)[a]			
Did not meet inclusion/exclusion criteria			
Abstinence from smoking >3 months in the past year	0	0	1
Present drug or alcohol abuse or dependence at Screening	0	0	1
Body Mass Index >38 at Screening	2	1	0
Screening or baseline systolic BP >160 mm Hg or diastolic BP >100 mm Hg	1	0	3
Screening liver function test values greater than 150% ULN	0	1	0
Positive urine drug screen at Screening	1	2	3
Used prohibited concomitant medications			
Used NRT during the treatment phase	2	1	3
Used prohibited medication other than NRT during the treatment phase[b]	6	7	12
Used marijuana during the treatment phase	0	0	1

[a]Subjects may be included in more than one category

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as several subjects who took prohibited medications during the treatment phase. These included a few subjects, distributed across treatment groups, who used nicotine replacement therapy, as well as a number of subjects who used medications unlikely to affect the efficacy outcome or interpretation of the study.

11.1.3 Efficacy Results

11.1.3.1 Abstinence Rates

11.1.3.1.1 Sponsor's Analysis

The table below, constructed from Tables 13 and 14 of Final Study Report shows the results calculated by Pfizer for the major efficacy outcomes analyzed:

Applicant's Efficacy Results, Study A3051028

	Varenicline	Placebo	Zyban
	N=349	N=344	N=329
CQR Weeks 9-12, ITT population			
Abstinent (%)	155 (44%)	61 (18%)	97 (30%)
Odds ratio (varenicline vs.)		3.9	2.0
		(2.7, 5.6)	(1.4, 2.7)
p-value (varenicline vs.)		<0.0001	<0.0001
Continuous Abstinence, weeks 9-24 Abstinent (%)	104 (30%)	36 (11%)	68 (21%)
		3.7	1.7
		(2.5, 5.7)	(1.2, 2.36)
Odds ratio (varenicline vs.)			
p-value		<0.0001	0.0060

(varenicline vs.)			
Continuous Abstinence, weeks 9-52	77 (22%)	29 (8%)	54 (16%)
		3.13 (1.97, 4.97)	1.45 (0.98, 2.14)
		<0.0001	0.0640
LTQR to week 24	119 (34%)	44 (13%)	76 (23%)
Odds ratio (varenicline vs.)		3.63 (2.45, 5.38)	1.75 (1.24, 2.48)
p-value (varenicline vs.)		<0.0001	0.0014
LTQR to week 52	89 (26%)	33 (10%)	59 (18%)
Odds ratio (varenicline vs.)		3.30 (2.13, 5.11)	1.58 (1.09, 2.31)
p-value (varenicline vs.)		<0.0001	0.0161

Note that although not a planned analysis, the Zyban comparison with placebo for the 4 week CQR had an odds ratio (95% CI) = 2.00 (1.39,2.89) with a nominal p value of 0.0002. The results for continuous abstinence to Week 24 showed odds ratio (95%CI) = 2.26 (1.45, 3.52); nominal p-value = 0.0002, and for continuous abstinence to Week 52, odds ratio (95%CI) = 2.16 (1.33, 3.51); nominal p-value = 0.0014.

Results of the analyses for the Evaluable and Completer populations support the robustness of the results for the All Subjects analysis. Other data presentations included seven-day "point prevalence" abstinence rates. These are not presented here because the Division's position has been that seven days of abstinence is too brief to confer any meaningful health benefit or to predict longer-term abstinence; therefore this analysis, although popular with academic researchers, is of little regulatory significance.

11.1.3.1.2 Reviewer's Analysis

Pfizer's results were audited by Dr. Joan Buenconsejo, Statistical Reviewer, who identified a small number of mis-classified subjects, and also applied the more conservative approach to missing data imputation employed in the earlier studies. The results of her analysis, shown below, confirm Pfizer's conclusions that varenicline was superior to both placebo and Zyban with respect to helping smokers achieve abstinence. In addition, Dr. Buenconsejo conducted, at the clinical team's request, several additional analyses using different definitions of treatment success.

By way of background, it should be noted that, historically, six-week trials for smoking cessation treatments have been considered conventional, and the ascertainment window was set at weeks 2-6, somewhat arbitrarily. However, while this trial duration was appropriate for nicotine replacement products, which were assumed to treat a self-limiting condition (acute nicotine withdrawal), more recently, the clinical approach to smoking cessation treatment has been moving toward a viewing the disorder of tobacco dependence as a chronic, relapsing condition, and a longer-term approach to treatment has been more common. Initially, some trials were proposed that employed an efficacy ascertainment window of weeks 2-6 in the midst of a longer period of treatment, in an effort to meet the "agency standard." The Agency articulated the view that relapse during ongoing treatment would not be regarded as treatment success, and advised that a

"last four weeks of treatment" window would be more suitable. This was the analytic approach specified in the protocols for the varenicline studies.

However, the Division's thinking has evolved as longer and longer treatment durations have been proposed, sometimes resulting in a grace period of many months and an efficacy ascertainment period of four weeks. Ultimately, the concept of "abstinence throughout treatment following a pharmacologically-justified grace period" was articulated in a White Paper and has been communicated to sponsors of ongoing development programs.

The two-month grace period in the varenicline trials is not fully justified, although the partial agonist properties of varenicline might result in blockade of exogenous nicotine, allowing for an extinction approach to behavior change. On the other hand, its agonist properties would also predict early efficacy as it provides some relief for acute withdrawal symptoms. Therefore, in order to determine whether the drug's efficacy can be demonstrated using a shorter grace period, Dr. Buenconsejo analyzed the data from the efficacy studies applying various grace periods from as little as two weeks up to the protocol-specified eight weeks.

For the protocol-specified primary analysis, Dr. Buenconsejo's review reveals that only a few subjects required re-adjudication, and the main conclusions were unchanged, as shown in the table below:

CQR, Weeks 9-12, Study A3051028

	Study A1028		
	Varenicline	Placebo	Zyban
Applicant's results:			
ITT Subjects	N=349	N=344	N=329
Abstinent (%)	155 (44%)	61 (18%)	97 (30%)
Odds ratio (varenicline vs.)		3.9	2.0
		(2.7, 5.6)	(1.4, 2.7)
p-value (varenicline vs.)		<0.0001	<0.0001
Reviewer's results:			
ITT Subjects	N=349	N=344	N=329
Abstinent (%)	152 (44%)	60 (17%)	97 (30%)
Odds ratio (varenicline vs.)		3.9	1.9
		(2.7, 5.5)	(1.4, 2.6)
p-value (varenicline vs.)		<0.0001	0.0001

Additionally, Dr. Buenconsejo calculated rates of continuous abstinence from the end of a various grace periods following the TQD through the end of treatment and found that varenicline was superior to placebo no matter what grace period was applied. In addition, superiority to Zyban was also noted using any grace period of 3 weeks or more, suggesting that the finding of efficacy and the superiority to Zyban were not limited to a single analytic approach to the data. These results are illustrated below in Dr. Buenconsejo's Table 12.

	Varenicline N=349	Placebo N=344	OR Varenicline vs.	p-value	Zyban N=329	OR Varenicline vs.	p-value
			Study A3051028				
Week 3 – 12	102 (29%)	41 (12%)	3.2 (2.1, 4.8)	<0.0001	77 (23%)	1.4 (1.0, 2.0)	0.0800
Week 4 – 12	108 (31%)	45 (13%)	3.1 (2.1, 4.7)	<0.0001	81 (25%)	1.4 (1.0, 2.0)	0.0611
Week 5 – 12	122 (35%)	40 (15%)	3.4 (2.3, 4.9)	<0.0001	85 (26%)	1.6 (1.1, 2.2)	0.0092
Week 6 – 12	127 (36%)	54 (16%)	3.2 (2.2, 4.7)	<0.0001	89 (27%)	1.6 (1.1, 2.2)	0.0091
Week 7 – 12	135 (39%)	56 (16%)	3.4 (2.4, 4.9)	<0.0001	93 (28%)	1.6 (1.2, 2.3)	0.0043
Week 8 – 12	141 (40%)	56 (16%)	3.7 (2.5, 5.3)	<0.0001	95 (29%)	1.7 (1.2, 2.4)	0.0017
Week 9 – 12	152 (44%)	60 (17%)	3.9 (2.7, 5.5)	<0.0001	97 (29%)	1.9 (1.4, 2.6)	0.0001

In addition, Pfizer calculated the long-term abstinence rates among study participants. These data show that after 12 weeks of treatment, more subjects who are treated with varenicline (or Zyban) remain abstinent 40 weeks later than subjects who are treated with placebo. However, the relapse rate across groups did not support the idea that a course of treatment with varenicline necessarily renders a successful quitter less vulnerable to relapse than smokers who quit without varenicline. Pfizer also calculated a rate termed the "long term quit rate" (LTQR) which differed from continuous abstinence in that subjects could report up to six days of smoking during the non-treatment follow-up and be deemed "long-term quitters." Although, conceptually, this is unobjectionable, it is not clear that the methods used to capture the smoking histories were detailed enough to allow participants to accurately report anything other than any smoking vs. no smoking. Therefore, the LTQR may not be an accurate reflection of the smoking behavior of participants, but is shown below as an alternative definition of relapse. Notably, this alternative definition does not appear to provide evidence that varenicline treatment has a specific effect that allows former smokers to lapse without relapsing.

The rate of non-relapse at the end of the observation period (week 52) is shown below (table constructed using data from Dr. Buenconsejo's Tables 12, 13, 14, 15 and 16). The percentages shown are the proportion of subjects abstinent during weeks 9-12 who survived to week 52 according to the criteria shown.

Continuous Abstinence and Long-term Quit Rate, Study A3051028

	Varenicline N=343	Placebo N=340	Zyban N=340
Subjects abstinent at week 12	152	60	97
Subjects continuously abstinent to week 52, N (%)	74 (49%)	27 (45%)	52 (54%)
Number reporting ≤6 days smoking during follow-up, N(%)	88 (57%)	32 (53%)	57 (58%)

11.1.3.2 Subjective Measures

Pfizer also seeks to make claims about the effects of varenicline on various subjective measures of craving, withdrawal, and smoking satisfaction.

11.1.3.2.1 Minnesota Nicotine Withdrawal Scale (MNWS): Sponsor's Analysis

Pfizer's Table 19 below shows the results from the Minnesota Nicotine Withdrawal Scale.

	N	LS Mean (SE)	Difference (SE)	95% CI	p-value	Effect Size
Varenicline						
Urge to Smoke	341	1.11 (0.04)	-0.54 (0.06)	(-0.66, -0.42)	<0.0001	-0.67
Negative Affect	341	0.59 (0.03)	-0.19 (0.04)	(-0.27, -0.11)	<0.0001	-0.30
Restlessness	340	0.70 (0.04)	-0.14 (0.05)	(-0.24, -0.03)	0.0095	-0.16
Increased Appetite	341	1.04 (0.05)	0.12 (0.06)	(0.00, 0.24)	0.0422	0.15
Insomnia	341	0.69 (0.04)	0.05 (0.05)	(-0.05, 0.15)	0.3615	0.06
Placebo						
Urge to Smoke	337	1.65 (0.05)				
Negative Affect	337	0.78 (0.03)				
Restlessness	337	0.84 (0.04)				
Increased Appetite	336	0.92 (0.05)				
Insomnia	337	0.64 (0.04)				
Zyban						
Urge to Smoke	318	1.41 (0.05)	-0.24 (0.06)	(-0.36, -0.12)	0.0001	-0.30
Negative Affect	318	0.62 (0.03)	-0.16 (0.04)	(-0.25, -0.08)	0.0002	-0.25
Restlessness	317	0.74 (0.04)	-0.09 (0.05)	(-0.20, 0.01)	0.0841	-0.10
Increased Appetite	318	0.88 (0.05)	-0.04 (0.06)	(-0.16, 0.08)	0.5560	-0.05
Insomnia	318	0.75 (0.04)	0.11 (0.05)	(0.00, 0.21)	0.0481	0.13

Pfizer's conclusions regarding these data were that

> [The] results of the repeated measures analysis showed that varenicline was significantly better than placebo in reducing craving and withdrawal, as measured by the 3 subscales of primary interest: Urge to Smoke, Negative Affect, and Restlessness... at all weekly timepoints from Week 2 through Week 7, scores for all 3 of these subscales were lower for varenicline than for placebo. The subscale score for Increased Appetite was significantly higher for varenicline than for placebo, but there was no significant difference between varenicline and placebo for the Insomnia subscale.

11.1.3.2.2 MNWS: Reviewer's Analysis

The data show numerically small but statistically significant differences between varenicline and placebo on some measures. However, the selection of certain subscales from the MNWS to support a claim of "relief of withdrawal" was noted by Dr. Jane Scott of the Study Endpoints and Label Development Team to be inappropriate. Indeed, rather than relieving some symptoms of withdrawal varenicline appears (based on analysis of the adverse events dataset, as well as a slightly higher score on the MNWS) to cause insomnia, which is considered a symptom of nicotine withdrawal; likewise, varenicline

may be associated with increased appetite, another symptom of withdrawal. Therefore, a claim regarding relief of withdrawal seems inappropriate.

11.1.3.2.3 Craving: Applicant's Analysis

In addition to the effects noted on the "urge to smoke" question on the MNWS, effects were also seen on the Brief Questionnaire of Smoking Urges (QSU-brief). Pfizer notes that "Varenicline was significantly more effective than placebo in reducing craving as measured by the Total Craving Score and the two subscales Factor 1 (characterized by a strong desire and intention to smoke with smoking perceived as pleasurable) and Factor 2 (characterized by an urgent desire to smoke and anticipation of relief from negative affect)."

Results of the MNWS urge to smoke item and the QSU-brief are shown in the table below, constructed by Dr. Buenconsejo.

	Average of Weeks 1 - 7		Comparisons vs. Placebo		
	LS Mean (SE)[b]	95% CI	Difference (SE)	95% CI	p-value
	Craving				
MNWS Urge to Smoke (Item 1)					
Varenicline	1.1 (0.05)	(1.0, 1.2)	-0.5 (0.06)	(-0.7, -0.4)	<0.0001
Zyban	1.4 (0.05)	(1.3, 1.5)	-0.2 (0.06)	(-0.4, -0.1)	0.0001
Placebo	1.6 (0.05)	(1.6, 1.7)			
QSU-Brief Total Craving Score					
Varenicline	1.7 (0.05)	(1.6, 1.8)	-0.4 (0.06)	(-0.6, -0.3)	<0.0001
Zyban	1.9 (0.05)	(1.8, 2.0)	-0.2 (0.07)	(-0.3, -0.1)	0.0013
Placebo	2.1 (0.05)	(2.0, 2.2)			

11.1.3.2.4 Craving: Reviewer's Analysis

The effects on these measures do not appear to be in dispute; however, the use of the term "craving" to describe the phenomenon captured by these instruments is questionable. Dr. Scott noted that the measures of "craving" appear to be capturing effects best described as "urge to smoke." Therefore, although it is not clear that varenicline has an effect on "craving," *per se*, an effect on "urge to smoke" appears to have been demonstrated.

11.1.3.2.5 Smoking Satisfaction: Applicant's Analysis

The Smoking Effects Inventory (SEI) was administered only to those subjects who reported smoking since the previous visit. Pfizer concluded that:

> Varenicline was significantly more effective than placebo in reducing the reinforcing effects of smoking described by 4 of the SEI subscales: Smoking Satisfaction, Psychological Reward, Enjoyment of Respiratory Tract Sensations, and Craving Reduction. For each of these subscales, scores at each weekly timepoint were lower for varenicline than for placebo, and results of the repeated measures analysis of these subscale scores for Week 1 through Week 7 show that the treatment differences were statistically significant. This was particularly the case for Smoking Satisfaction and Psychological Reward, the two subscales of primary interest. For the Aversion subscale, scores were lower for varenicline-treated subjects than for placebo-treated subjects at each weekly timepoint throughWeek 6, although for this subscale, the repeated measures analysis did not show statistically significant treatment difference.

11.1.3.2.6 Smoking Satisfaction: Reviewer's Analysis

Dr. Scott observed that the measures of the reinforcing effects of smoking captured all the relevant aspects of smoking reinforcement. She concluded that "reinforcing effects of smoking" is not a clearly-defined concept suitable for labeling.

11.1.3.2.6.1 Analysis by Subgroups

The table below from Dr. Buenconsejo's review shows the effect of varenicline to be consistent across demographic subgroups.

Weeks 9 – 12 CQR by Age, Gender, Race, and Baseline Smoking Characteristics – Study 28

	Varenicline % (n/N)	Zyban % (n/N)	OR (95% CI)	Placebo % (n/N)	OR (95% CI)
Overall	44 (152/349)	30 (97/329)	1.9 (1.4, 2.6)	17 (60/344)	3.9 (2.7, 5.5)
Gender					
Male	42 (73/175)	30 (58/192)	1.7 (1.1, 2.6)	16 (30/186)	4.1 (2.4, 6.8)
Female	45 (79/174)	28 (39/137)	2.2 (1.3, 3.6)	19 (30/158)	3.7 (2.2, 6.2)
Age					
<45 years	41 (80/195)	25 (49/196)	2.1 (1.3, 3.2)	16 (33/201)	3.7 (2.3, 6.0)
>= 45 years	47 (72/154)	36 (48/133)	1.6 (1.0, 2.7)	19 (27/143)	4.1 (2.3, 7.1)
Race					
White	48 (134/278)	30 (80/264)	2.2 (1.5, 3.1)	18 (48/262)	4.2 (2.8, 6.3)
Black	11 (4/35)	18 (5/28)	0.5 (0.1, 2.5)	14 (7/49)	0.6 (0.1, 2.9)
Others	39 (14/36)	32 (12/37)	2.2 (0.7, 6.8)	15 (5/33)	6.8 (1.7, 27.9)
Fagerstrom Score					
0 – 3	54 (41/76)	48 (34/71)	1.2 (0.6, 2.4)	19 (13/68)	5.8 (2.4, 13.8)
4 – 6	44 (77/177)	26 (42/159)	2.3 (1.4, 3.7)	23 (38/168)	2.7 (1.7, 4.5)
7 – 10	35 (33/94)	21 (21/99)	2.1 (1.1, 4.4)	8 (9/106)	7.7 (3.2, 18.4)
Average No. of Cigarettes/day, past month					
10 - <20	48 (62/128)	32 (35/109)	2.0 (1.1, 3.4)	25 (26/106)	2.9 (1.6, 5.3)
20 - <30	45 (70/157)	31 (49/156)	1.8 (1.1, 3.0)	14 (24/170)	5.5 (3.1, 9.6)
>= 30	32 (20/63)	20 (13/64)	2.1 (0.8, 5.1)	15 (10/67)	3.8 (1.5, 9.7)

11.1.3.2.6.2 Analysis by Center

See table above, in section on Enrollment by Center

11.1.3.3 Conclusions Regarding Efficacy Data in Study

This study provides evidence that varenicline is superior to placebo and to Zyban in helping smokers attain abstinence. In addition, varenicline reduces the "urge to smoke" in smokers attempting to quit.

11.1.3.4 Safety Results: Common AEs

The table below shows the common adverse events observed in this study, as reported by Pfizer in the final study report. Adverse events (MedDRA preferred terms) that occurred in at least 2% of subjects and at a frequency greater than placebo in either the varenicline or Zyban treatment groups are summarized below. Among varenicline-treated subjects,

the most frequently reported gastrointestinal disorders were nausea, dry mouth, flatulence, and constipation; while the most frequent psychiatric disorders were insomnia and abnormal dreams. In the nervous system, the most frequent adverse events in the varenicline treatment group were headache, dizziness, and disturbance in attention.

Most Common Adverse Events Study A3051028 N (%)
Pfizer's Table 25

SOC Adverse Event (MedDRA Preferred Term)	Varenicline N = 349		Zyban N = 329		Placebo N = 344	
Gastrointestinal disorders	175	(50.1)	116	(35.3)	102	(29.7)
Nausea	98	(28.1)	41	(12.5)	29	(8.4)
Dry mouth	23	(6.6)	29	(8.8)	19	(5.5)
Flatulence	20	(5.7)	14	(4.3)	10	(2.9)
Constipation	19	(5.4)	23	(7.0)	13	(3.8)
Dyspepsia	15	(4.3)	7	(2.1)	8	(2.3)
Vomiting	13	(3.7)	16	(4.9)	3	(0.9)
Abdominal pain upper	9	(2.6)	6	(1.8)	7	(2.0)
Psychiatric disorders	121	(34.7)	129	(39.2)	92	(26.7)
Insomnia	49	(14.0)	72	(21.9)	44	(12.8)
Abnormal dreams	36	(10.3)	18	(5.5)	19	(5.5)
Irritability	21	(6.0)	17	(5.2)	20	(5.8)
Sleep disorder	20	(5.7)	13	(4.0)	13	(3.8)
Initial insomnia	8	(2.3)	4	(1.2)	3	(0.9)
Nervous system disorders	110	(31.5)	102	(31.0)	95	(27.6)
Headache	54	(15.5)	47	(14.3)	42	(12.2)
Dizziness	21	(6.0)	19	(5.8)	20	(5.8)
Disturbance in attention	17	(4.9)	16	(4.9)	13	(3.8)
Somnolence	15	(4.3)	3	(0.9)	12	(3.5)
Dysgeusia	13	(3.7)	20	(6.1)	15	(4.4)
Infections and Infestations	88	(25.2)	76	(23.1)	92	(26.7)
Nasopharyngitis	20	(5.7)	17	(5.2)	18	(5.2)
Sinusitis	2	(0.6)	8	(2.4)	6	(1.7)
Musculoskeletal and Connective Tissue Disorders	37	(10.6)	28	(8.5)	32	(9.3)
Arthralgia	10	(2.9)	5	(1.5)	7	(2.0)
Back pain	11	(3.2)	11	(3.3)	8	(2.3)
Respiratory, Thoracic and Mediastinal Disorders	30	(8.6)	38	(11.6)	39	(11.3)
Nasal congestion	5	(1.4)	8	(2.4)	6	(1.7)
Pharyngolaryngeal pain	5	(1.4)	8	(2.4)	7	(2.0)
Skin and Subcutaneous Tissue Disorders	27	(7.7)	36	(10.9)	20	(5.8)
Rash	10	(2.9)	4	(1.2)	6	(1.7)
Urticaria	0	(0.0)	10	(3.0)	2	(0.6)
Metabolism and Nutrition Disorders	**16**	**(4.6)**	**19**	**(5.8)**	**6**	**(1.7)**
Increased appetite	8	(2.3)	10	(3.0)	0	(0.0)

11.2 Appendix 2: Protocol A3051036

A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study with Follow-up Evaluating the Safety and Efficacy of Varenicline Tartrate (CP-526,555) in Comparison to Zyban® for Smoking Cessation

Conducted June 26 2003- March 21 2005

11.2.1 Protocol

11.2.1.1 Objective/Rationale

The purpose of the study was to compare the efficacy of varenicline 1 mg b.i.d. to placebo and Zyban for smoking cessation after 12 weeks of treatment.

11.2.1.2 Overall Design

The study was a double-blind, placebo-controlled, randomized clinical trial designed to assess the efficacy and safety of varenicline 1 mg b.i.d. in comparison to placebo and Zyban® 150 mg b.i.d. for smoking cessation. The duration of active treatment specified in the protocol was 12 weeks and subjects were to be followed in the nontreatment phase for an additional 40 weeks.

11.2.1.3 Population and Procedures

This study was identical in design to Study A3051028, including the population and all study procedures. See above for description of inclusion/exclusion criteria, schedule of assessments, and dosing.

11.2.1.4 Evaluations/Endpoints

The evaluations and endpoints are also identical to Study A3051028. Much of the text in this section is repeated for convenience of the reader, but duplicates material from the section above describing Study A3051028

The pre-specified primary endpoint was the 4-week Continuous Quit Rate (CQR) for Weeks 9 to 12. Subjects were to be classified as responders if they were able to maintain complete abstinence from cigarette smoking and other nicotine use for the last 4 weeks of treatment with end-expiratory exhaled CO measurements $\leq$ 10 ppm. Subjects who withdrew before the study completion were considered non-responders for the remainder of the study, regardless of smoking status at the time of discontinuation. However, imputation of missing data within a specific endpoint, resulting from incomplete CRF or eCRF data was computed as follows:

> ... in the case of a missed visit(s) during the evaluation period (Weeks 9 – 12), a subject was considered a responder if the subject indicated that he/she had not smoked or used nicotine products 'since the last visit' at the visit after the missing visit(s). No attempt was made to impute missing data from other weekly interview questions. For Point Prevalence of abstinence at the end of the study (i.e., 4 weeks to Week 52), missing interview questions of whether the subject has 'smoked in the last four weeks' or 'used any other tobacco products in the last four weeks' were

not imputed (i.e., subject was considered a non-responder for this endpoint).

Note that this imputation strategy differed from the more conservative approach used in Phase 2, during which subjects missing more than one visit in the four-week period of interest were considered non-responders.

Key secondary endpoints identified in the protocol included:
• Continuous Abstinence Rate from Week 9 through Week 52 (defined as the proportion of subjects who maintained complete abstinence from cigarette smoking ("not even a puff") and other tobacco use for a specified time period, generally from Week 9 (i.e., the beginning of the lapse-free period) through Week 52).

• Long-term Quit Rate through Week 52(the proportion of subjects who have successfully quit during the treatment phase of the study based on the 4-week CQR from Week 9 through Week 12 and who have had no more than 6 days of smoking during the nontreatment phase)

Other secondary endpoints identified included:
• Continuous Abstinence Rate 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
• Change from baseline in body weight
• Results of the Minnesota Nicotine Withdrawal Scale, the Brief Questionnaire of Smoking Urges, and the Smoking Effects Inventory. (See details in description of Study A3051028)

11.2.1.5 Statistical Plan
The protocol-specified primary inference for the study was a comparison of varenicline to placebo and Zyban® for the 4-week CQR for Weeks 9 through 12 of treatment. The secondary objective was to compare abstinence through Week 52. The study was powered to detect differences in the primary as well as key secondary endpoints in comparison to placebo and Zyban®. A step-down procedure was to be employed within the analysis of both primary and key secondary endpoints, in order to control for type I error within each endpoint.

11.2.2 Results

11.2.2.1 Study Conduct/Outcome
11.2.2.1.1 Subject Characteristics

Of 1413 subjects screened, 1027 subjects were selected for enrollment. Four subjects did not initiate treatment, therefore the treated population comprised 1023 subjects with 343 randomized to treatment with varenicline, 340 to treatment with Zyban, and 340 to treatment with placebo.

11.2.2.1.1.1 Enrollment by Center

Enrollment was distributed among centers as listed in the table below:

Center Number	Principal Investigator Center Name and Address	Treatment Group	Rand	Treated N	Responders n	CQR% (n/N)
A3051036						
All	**All**	Varenicline	344	343	151	44.0
		Zyban	342	340	102	30.0
		Placebo	341	340	60	17.7
		Total	**1027**	**1023**		
1036-1001	**J. Hays** Mayo Clinic 200 First Street Southwest Rochester, MN 55905	Varenicline	21	21	17	81.0
		Zyban	21	21	7	33.3
		Placebo	20	20	6	30.0
		Total		**62**		
1036-1002	**D. Jorenby** University of Wisconsin Medical School, Center for Tobacco Research and Intervention Suite 200; 1930 Monroe Street Madison, WI 53711-2027	Varenicline	27	27	15	55.6
		Zyban	28	28	8	28.6
		Placebo	28	28	6	21.4
		Total		**83**		
1036-1003	**B. Make** National Jewish Medical and Research Center 1400 Jackson Street Denver, CO 80206	Varenicline	14	14	6	42.9
		Zyban	14	14	7	50.0
		Placebo	13	13	2	15.4
		Total		**41**		
1036-1004	**B Bock/R. Niaura/I Rebocho** The Miriam Hospital, Centers for Behavioral and Preventive Medicine; Coro Building - Suite 500 1 Hoppin Street Providence, RI 02903	Varenicline	11	11	6	54.6
		Zyban	11	11	3	27.3
		Placebo	12	12	1	8.3
		Total		**34**		
1036-1005	**N. Rigotti** Massachusetts General Hospital, Tobacco Research & Treatment Center; 9th Floor 50 Staniford Street Boston, MA 02114	Varenicline	19	19	10	52.6
		Zyban	18	18	11	61.1
		Placebo	18	18	4	22.2
		Total		**55**		
1036-1006	**D. Sachs** Palo Alto Center for Pulmonary Disease Prevention 145 North California Avenue Palo Alto, CA 94301	Varenicline	13	13	9	69.2
		Zyban	13	13	4	30.8
		Placebo	12	12	3	25.0
		Total		**38**		

Center Number	Principal Investigator Center Name and Address	Treatment Group	Rand	Treated N	Responders n	CQR% (n/N)
1036-1007	**S. Swartz** Maine Medical Center Center for Tobacco Independence 315 Park Avenue Portland, ME 04102	Varenicline	11	11	5	45.5
		Zyban	12	12	4	33.3
		Placebo	11	11	1	9.1
		Total		**34**		
1036-1008	**M. Weerasinghe** Rochester Clinical Research, Inc. Suite L20 500 Helendale Rd Rochester, NY 14609	Varenicline	30	30	14	46.7
		Zyban	30	30	7	23.3
		Placebo	30	30	3	10.0
		Total		**90**		
1036-1009	**L. Gilderman** University Clinical Research Incorporated 1150 North University Drive Pembroke Pines, FL 33024	Varenicline	36	36	11	30.6
		Zyban	35	35	8	22.9
		Placebo	36	36	7	19.4
		Total		**107**		
1036-1010	**S. Sharp** Clinical Research Associates, Inc. Suites B+D 2222 State Street Nashville, TN 37203	Varenicline	74	74	27	36.5
		Zyban	73	72	18	25.0
		Placebo	74	74	12	16.2
		Total		**220**		
1036-1011	**S. Goldstein** Medical & Behavioral Health Research, PC 1B 55 Central Park West New York, NY 10023	Varenicline	16	16	1	6.3
		Zyban	18	17	7	41.2
		Placebo	17	17	6	35.3
		Total		**50**		
1036-1012	**A. Christen** Indiana University School of Dentistry Oral Health Research Institute 415 Lansing Street Indianapolis, IN 46202	Varenicline	22	21	5	23.8
		Zyban	20	20	1	5.0
		Placebo	21	20	2	10.0
		Total		**61**		
1036-1013	**C. Merideth** Affiliated Research Institute Suite 350 8989 Rio San Diego Dr. San Diego, CA 92108	Varenicline	22	22	10	45.5
		Zyban	21	21	5	23.8
		Placebo	20	20	2	10.0
		Total		**63**		
1036-1014	**T. Jackson** Center for Tobacco Research and Intervention, Physician's Office Building Suite 506 1218 West Kilbourn Avenue Milwaukee, WI 53201	Varenicline	28	28	15	53.6
		Zyban	28	28	12	42.9
		Placebo	29	29	5	17.2
		Total		**85**		

11.2.2.1.1.2 Subject Disposition

Subject Disposition is shown in the table below, from Pfizer's final study report.

	Varenicline		Zyban		Placebo	
Number screened = 1413						
Assigned to treatment	344		342		341	
Treated[a]	343		340		340	
Completed Study[b]	240	(70.0)	221	(65.0)	204	(60.0)
Discontinued Study	103	(30.0)	119	(35.0)	136	(40.0)
During Treatment Phase	83	(24.2)	100	(29.4)	118	(34.7)
Adverse events	14	(4.1)	16	(4.7)	13	(3.8)
Lack of efficacy	1	(0.3)	0		3	(0.9)
Protocol deviations	2	(0.6)	9	(2.6)	4	(1.2)
Pregnancy	1	(0.3)	1	(0.3)	0	0
Refusal to participate further	28	(8.2)	31	(9.1)	51	(15.0)
Lost to follow-up	33	(9.6)	39	(11.5)	43	(12.6)
Other[c]	4	(1.2)	4	(1.2)	4	(1.2)
During Nontreatment Follow-up Phase	20	(5.8)	19	(5.6)	18	(5.3)
Subject died	0	0	1	(0.3)	0	0
Protocol deviations	0	0	2	(0.6)	1	(0.3)
Refusal to participate further	3	(0.9)	6	(1.8)	4	(1.2)
Lost to follow-up	14	(4.1)	10	(2.9)	12	(3.5)
Other[d]	3	(0.9)	0	0	1	(0.3)

[a]Percentages based on number of subjects treated.
[b]Subjects could discontinue study medication but remain in the study.
[c] varenicline – 2 subjects did not meet entrance criteria, 1 subject moved, and one contracted HIV.
Zyban – 3 subjects moved and one did not meet entrance criteria.
placebo - 1 subject did not meet entrance criteria, 2 had work-related problems, and 1 subject was C
J
[d] Other reasons (nontreatment phase): varenicline – 1 subject refused to sign a revised Informed Consent form and 2 subjects moved. placebo - 1 subject moved.

Subjects could discontinue study medication but remain in the study. Therefore, in the context of subject disposition, "completed the study" refers to the number of subjects who participated in the study for the full 52 weeks, whether or not they completed 12 weeks of dosing during the treatment phase.

The table below, adapted from Pfizer's Table 25, illustrates the distribution of subjects temporarily or permanently discontinuing study *medication* or requiring a dose reduction because of adverse events.

Treatment Discontinuations or Dose Reductions Due to Adverse Events N (%)

	Varenicline N = 343	Zyban N = 340	Placebo N = 340
Treatment discontinuations	36 (11)	43 (13)	25 (7)
Dose reductions or temporary discontinuations	4 (1)	14 (4)	9 (3)

*Three additional subjects temporarily discontinued study medication due to treatment-related adverse events and later permanently discontinued treatment due to adverse events.

During the 12-week treatment phase, across all treatment groups, the most frequent reasons for withdrawal were lost to follow-up, refusal to participate further, and adverse events. Adverse events were the reason for premature *study* discontinuation in 4% of the varenicline group, 5% of the Zyban group, and 4% of the placebo group, and for premature *treatment* discontinuation in 11% of the varenicline group, 13% of the Zyban group, and 7% of the placebo group. From an efficacy standpoint, treatment failure is imputed to subjects not completing the study, including those lost to follow-up and those discontinuing due to refusal to participate. There are more subjects in both of these categories in the placebo arm; this could represent a potential bias. However, relapse to smoking after treatment discontinuation is generally considered to be the rule, rather than the exception, and it seems reasonable to impute treatment failure to these subjects.

11.2.2.1.2 Demographics

The table below illustrates demographic and baseline characteristics of the three treatment groups. Overall, 84% of the subjects were white, 42% of the subjects were female, and the average age was approximately 43 years (range 18-75 years). Smoking history was similar across treatment groups, with subjects representing a population of smokers who on average had smoked for the previous 24 years (range 1-61 years) and had smoked an average of 21 cigarettes per day over the previous month. The varenicline arm had the lowest proportion of male subjects (55% vs. 61% in the Zyban arm and 58% in the placebo arm). This is notable because conventional wisdom holds that female smokers may be more difficult to treat; if true, this would potentially bias the study *against* varenicline.

	Varenicline N=343	Zyban N=340	Placebo N=340
Sex (Male), n(%)	189 (55%)	206 (61%)	198 (58%)
Mean Age (SD), y	45 (12)	43 (12)	43 (12)
Range	18 – 75	18 – 73	19 – 75
Race, n(%)			
White	294 (86%)	281 (83%)	289 (85%)
Black	30 (9%)	36 (11%)	26 (8%)
Asian	8 (2%)	4 (1%)	6 (2%)
Other	11 (3%)	19 (6%)	19 (6%)
	N=343	N=340	N=340
Number of years subject smoked			
Mean	27	26	24
Range	2 – 59	2 – 57	2 – 60
Number of cigarettes per day over past month			
Mean	23	22	22
Range	10 – 60	10 – 60	10 – 60
Previous Serious quit attempt			
None	53 (15%)	46 (14%)	45 (13%)
>1	290 (85%)	294 (86%)	295 (87%)
Longest period of abstinence in past year, d			
Mean	6.3	7.6	8.0
Range	0 – 90	0 – 90	0 – 180
Fagerstrom Test for Nicotine Dependence Score			
N	342	339	338
Mean (SD)	5.4 (2.2)	5.4 (2.2)	5.2 (2.2)

11.2.2.1.3 Dosing Information

The table below (Pfizer's Table 13, A3051036 final study report) illustrates exposure duration and compliance with medication across treatment groups. Groups were similar with respect to mean duration of exposure.

	Varenicline	Zyban	Placebo
	N = 343	N = 340	N = 340
≥1	343 (100.0)	340 (100.0)	340 (100.0)
Unknown[b]	6	7	2
>3	332 (96.8)	331 (97.4)	337 (99.1)
>7	329 (95.9)	323 (95.0)	331 (97.4)
>14	310 (90.4)	293 (86.2)	304 (89.4)
>21	296 (86.3)	282 (82.9)	287 (84.4)
>28	279 (81.3)	270 (79.4)	270 (79.4)
>35	272 (79.3)	261 (76.8)	257 (75.6)
>42	265 (77.3)	253 (74.4)	245 (72.1)
>49	259 (75.5)	248 (72.9)	233 (68.5)
>56	252 (73.5)	239 (70.3)	222 (65.3)
>63	245 (71.4)	232 (68.2)	215 (63.2)
>70	240 (70.0)	229 (67.4)	209 (61.5)
>77	235 (68.5)	222 (65.3)	204 (60.0)
>84	120 (35.0)	121 (35.6)	124 (36.5)
>91	4	5	7
Median duration	84.0	84.0	84.0
Range	7 - 102	1 - 100	3 - 133

[a] For each subject, treatment duration is calculated as the total number of days from first day of dosing through the last day of dosing, without deducting for missed doses.
[b] Unknown: subjects lost to follow-up after being dispensed study medication. Subjects are assumed to have taken at least one dose and are included in the All Subjects population.

11.2.2.1.4 Protocol Violations

Pfizer reported that

> Protocol deviations were identified programmatically by searching the database for randomized subjects who had screening or baseline values falling outside of the ranges specified by inclusion or exclusion criteria (eg, values for age, weight, medical history, smoking history, laboratory parameters, etc). The database was also searched for subjects who used prohibited medications during the study and subjects who were withdrawn from the study due to protocol deviations. In addition, lists of protocol deviations were compiled by site monitors during routine center visits or during remote review of electronic data. All deviations identified by the methods described above were reviewed for clinical significance. Those considered potentially significant are summarized in [the table below, Pfizer's Table 6]. A total of 17, 16, and 13 subjects in the varenicline, Zyban, and placebo groups had significant deviations.

	Varenicline N = 343	Zyban N = 340	Placebo N = 340
Subjects with significant protocol deviations	**17**	**16**	**13**
Subjects with significant protocol deviations (by category)[a]			
Did not meet inclusion/exclusion criteria			
Abstinence from smoking >3 months in the past year	0	0	1
Significant medical history[b]	3	1	1
Body Mass Index >38 at Screening	3	1	0
Screening or baseline systolic BP >160 mm Hg or diastolic BP >100 mm Hg	2	3	1
Screening liver function test values greater than 150% ULN	1	1	0
Positive urine drug screen at Screening	4	1	3
Used prohibited concomitant medications			
Used NRT during the treatment phase	0	3	2
Used prohibited medication other than NRT during the treatment phase[b]	5	7	6

[a]Subjects may be included in more than one category

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as several subjects who took prohibited medications during the treatment phase. These included a few subjects, distributed across treatment groups, who used nicotine replacement therapy, as well as a number of subjects who used medications unlikely to affect the efficacy outcome or interpretation of the study.

11.2.3 Efficacy Results

11.2.3.1 Abstinence Rates

11.2.3.1.1 Sponsor's Analysis

The table below shows the results calculated by Pfizer for the major efficacy outcomes analyzed

Applicant's Efficacy Results, Study A3051036

	Varenicline	Placebo	Zyban
	N=343	N=340	N=340
CQR Weeks 9-12, ITT population			
Abstinent (%)	151 (44%)	60 (18%)	102 (30%)
Odds ratio (varenicline vs.)		3.8	1.9
		(2.7, 5.5)	(1.4, 2.6)
p-value		<0.0001	<0.0001
(varenicline vs.)			
Continuous Abstinence, weeks 9-24			
Abstinent (%)	102 (30%)	45 (13%)	69 (20%)
Odds ratio (varenicline vs.)		2.8	1.7
		(1.9, 4.2)	(1.2, 2.4)
p-value		<0.0001	0.0037
(varenicline vs.)			
Continuous Abstinence, weeks 9-52	79 (23%)	35 (10%)	51 (15%)
		2.66	1.72
		(1.7, 4.1)	(1.16, 2.55)
		<0.0001	0.0062
LTQR to week 24	115 (34%)	52 (15%)	82 (24%)
Odds ratio (varenicline vs.)		2.88 (1.98, 4.20)	1.62 (1.15, 2.27)
p-value		<0.0001	0.0054
(varenicline vs.)			
LTQR to week 52	87 (25%)	43 (13%)	62 (18%)
Odds ratio (varenicline vs.)		2.4 (1.6, 3.6)	1.55 (1.07, 2.25)
p-value		<0.0001	0.0161
(varenicline vs.)			

From Tables 13 and 14 of Final Study Report

Note that although not a planned analysis, the Zyban comparison with placebo for the 4 week CQR had an odds ratio (95% CI) = 2.03 (1.41,2.94) with a nominal p value of 0.0001. The results for continuous abstinence to Week 24 showed odds ratio (95%CI) = 1.68 (1.11, 2.54); nominal p-value = 0.0130 and for continuous abstinence to Week 52, odds ratio (95%CI) = 1.54 (0.97, 2.45); nominal p-value = 0.0634.

Results of the analyses for the Evaluable and Completer populations support the robustness of the results for the All Subjects analysis. Other data presentations included seven-day "point prevalence" abstinence rates. These are not presented here because the Division's position has been that seven days of abstinence is too brief to confer any meaningful health benefit or to predict longer-term abstinence; therefore this analysis, although popular with academic researchers, is of little regulatory significance.

11.2.3.1.2 Reviewer's Analysis

Pfizer's results were audited by Dr. Joan Buenconsejo, Statistical Reviewer, who identified a small number of mis-classified subjects, and also applied the more conservative approach to missing data imputation employed in the earlier studies. The results of her analysis, shown below, confirm Pfizer's conclusions that varenicline was superior to both placebo and Zyban with respect to helping smokers achieve abstinence. In addition, Dr. Buenconsejo conducted, at the clinical team's request, several additional analyses using different definitions of treatment success, as discussed in the review of Study A3051028, above.

For the protocol-specified primary analysis, Dr. Buenconsejo's review reveals that only a few subjects required re-adjudication, and the main conclusions were unchanged, as shown in the table below:

CQR, Weeks 9-12, Study A3051036

		Study A1036	
	Varenicline	Varenicline	Varenicline
Applicant's results:			
ITT Subjects	N=343	N=340	N=340
Abstinent (%)	151 (44%)	60 (18%)	102 (30%)
Odds ratio (varenicline vs.)		3.8	1.9
		(2.7, 5.5)	(1.4, 2.6)
p-value (varenicline vs.)		<0.0001	<0.0001
Reviewer's results:			
ITT Subjects	N=343	N=340	N=340
Abstinent (%)	150 (44%)	60 (18%)	101 (30%)
Odds ratio (varenicline vs.)		3.8	1.9
		(2.7, 5.4)	(1.4, 2.6)
p-value (varenicline vs.)		<0.0001	0.0001

Additionally, Dr. Buenconsejo calculated rates of continuous abstinence from the end of a various grace periods following the TQD through the end of treatment and found that varenicline was superior to placebo no matter what grace period was applied. In addition, superiority to Zyban was also noted using any grace period of 2 weeks or more, suggesting that the finding of efficacy and the superiority to Zyban were not limited to a single analytic approach to the data. These results are illustrated below in Dr. Buenconsejo's Table 12.

	Varenicline N=349	Placebo N=344	OR Varenicline vs.	p-value	Zyban N=329	OR Varenicline vs.	p-value
			Study A3051036				
Week 3 – 12	101 (29%)	38 (11%)	3.5 (2.3, 5.3)	<0.0001	71 (21%)	1.6 (1.1, 2.3)	0.0079
Week 4 – 12	113 (33%)	42 (12%)	3.6 (2.4, 5.4)	<0.0001	79 (23%)	1.7 (1.2, 2.3)	0.0040
Week 5 – 12	121 (35%)	47 (14%)	3.5 (2.4, 5.2)	<0.0001	88 (26%)	1.6 (1.1, 2.2)	0.0063
Week 6 – 12	128 (37%)	49 (14%)	3.8 (2.5, 5.4)	<0.0001	91 (27%)	1.7 (1.2, 2.3)	0.0025
Week 7 – 12	133 (39%)	52 (15%)	3.6 (2.5, 5.3)	<0.0001	95 (28%)	1.7 (1.2, 2.3)	0.0021
Week 8 – 12	140 (41%)	53 (16%)	3.9 (2.7, 5.6)	<0.0001	99 (29%)	1.7 (1.2, 2.4)	0.0010
Week 9 – 12	150 (44%)	60 (18%)	3.8 (2.7, 5.4)	<0.0001	101 (30%)	1.9 (1.4, 2.6)	0.0001

In addition, Pfizer calculated the long-term abstinence rates among study participants. These data show that after 12 weeks of treatment, more subjects who are treated with varenicline (or Zyban) remain abstinent 40 weeks later than subjects who are treated with placebo. However, the relapse rate across groups did not support the idea that a course of treatment with varenicline necessarily renders a successful quitter less vulnerable to relapse than smokers who quit without varenicline. Pfizer also calculated a rate termed the "long term quit rate" (LTQR) which differed from continuous abstinence in that subjects could report up to six days of smoking during the non-treatment follow-up and be deemed "long-term quitters." Although, conceptually, this is unobjectionable, it is not clear that the methods used to capture the smoking histories were detailed enough to allow participants to accurately report anything other than any smoking vs. no smoking. Therefore, the LTQR may not be an accurate reflection of the smoking behavior of participants, but is shown below as an alternative definition of relapse. Notably, this alternative definition does not appear to provide evidence that varenicline treatment has a specific effect that allows former smokers to lapse without relapsing.

The rate of non-relapse at the end of the observation period (week 52) is shown below (table constructed using data from Dr. Buenconsejo's Tables 12, 13, 14, 15 and 16). The percentages shown are the proportion of subjects abstinent during weeks 9-12 who survived to week 52 according to the criteria shown.

Continuous Abstinence and Long-term Quit Rate, Study A3051036

	Varenicline N=349	Placebo N=344	Zyban N=329
Subjects abstinent at week 12	150	60	101
Subjects continuously abstinent to week 52, N (%)	74 (49%)	34 (57%)	49 (49%)
Number reporting ≤6 days smoking during follow-up, N(%)	86 (57%)	43 (71%)	61 (60%)

11.2.3.2 Subjective Measures

Pfizer also seeks to make claims about the effects of varenicline on various subjective measures of craving, withdrawal, and smoking satisfaction.

11.2.3.2.1 Minnesota Nicotine Withdrawal Scale (MNWS): Sponsor's Analysis

Pfizer's Table 19 below shows the results from the Minnesota Nicotine Withdrawal Scale.

	N	LS Mean (SE)	Difference (SE)	95% CI	p-value	Effect Size
Varenicline						
Urge to Smoke	331	1.24 (0.04)	-0.48 (0.06)	(-0.59, -0.37)	<0.0001	-0.63
Negative Affect	331	0.59 (0.03)	-0.13 (0.04)	(-0.21, -0.05)	0.0011	-0.22
Restlessness	331	0.77 (0.04)	-0.10 (0.05)	(-0.20, 0.00)	0.0539	-0.11
Increased Appetite	331	0.96 (0.04)	0.07 (0.06)	(-0.04, 0.19)	0.2198	0.09
Insomnia	331	0.74 (0.04)	0.10 (0.05)	(-0.01, 0.20)	0.0657	0.11
Placebo						
Urge to Smoke	332	1.71 (0.04)				
Negative Affect	333	0.72 (0.03)				
Restlessness	332	0.86 (0.04)				
Increased Appetite	333	0.88 (0.04)				
Insomnia	333	0.64 (0.04)				
Zyban						
Urge to Smoke	328	1.33 (0.04)	-0.38 (0.06)	(-0.49, -0.27)	<0.0001	-0.50
Negative Affect	328	0.59 (0.03)	-0.13 (0.04)	(-0.21, -0.05)	0.0014	-0.21
Restlessness	327	0.79 (0.04)	-0.07 (0.05)	(-0.17, 0.03)	0.1619	-0.08
Increased Appetite	327	0.81 (0.04)	-0.07 (0.06)	(-0.19, 0.05)	0.2299	-0.09
Insomnia	327	0.84 (0.04)	0.20 (0.05)	(0.09, 0.30)	0.0003	0.22

Pfizer's conclusions regarding these data were that

> ...results of the repeated measures analysis showed that varenicline was significantly better than placebo in reducing craving and withdrawal, as measured by 2 of the 3 subscales of primary interest: Urge to Smoke and Negative Affect... at each weekly timepoint from Week 1 through Week 7. Average scores were also numerically lower in varenicline-treated subjects than placebo-treated subjects for each weekly timepoint from Week 1 through Week 7 for the Restlessness subscale although these differences did not reach statistical significance in the repeated measures analysis. Scores for the Increased Appetite and Insomnia subscales showed no significant differences between the varenicline and placebo treatment groups.

11.2.3.2.2 MNWS: Reviewer's Analysis

The data show numerically small but statistically significant differences between varenicline and placebo on some measures. However, the selection of certain subscales from the MNWS to support a claim of "relief of withdrawal" was noted by Dr. Jane Scott of the Study Endpoints and Label Development Team to be inappropriate. Indeed, rather than relieving some symptoms of withdrawal varenicline appears (based on analysis of the adverse events dataset, as well as a slightly higher score on the MNWS) to cause insomnia and increased appetite, which are considered symptoms of nicotine withdrawal. Therefore, a claim regarding relief of "withdrawal" seems inappropriate.

11.2.3.2.3 Craving: Applicant's Analysis

In addition to the effects noted on the "urge to smoke" question on the MNWS, effects were also seen on the Brief Questionnaire of Smoking Urges (QSU-brief). Pfizer notes that "Varenicline was significantly more effective than placebo in reducing craving as measured by the Total Craving Score and the two subscales Factor 1 (characterized by a strong desire and intention to smoke with smoking perceived as pleasurable) and Factor 2 (characterized by an urgent desire to smoke and anticipation of relief from negative affect)."

Results of the MNWS urge to smoke item and the QSU-brief are shown in the table below, constructed by Dr. Buenconsejo.

	Average of Weeks 1 - 7		Comparisons vs. Placebo [a]		
	LS Mean (SE)[b]	95% CI	Difference (SE)	95% CI	p-value
	Craving				
MNWS Urge to Smoke (Item 1)					
Varenicline	1.2 (0.04)	(1.2, 1.3)	-0.5 (0.06)	(-0.6, -0.4)	<0.0001
Zyban	1.3 (0.04)	(1.3, 1.4)	-0.4 (0.06)		<0.0001
Placebo	1.7 (0.04)	(1.6, 1.8)		(-0.5, -0.3)	
QSU-Brief Total Craving Score					
Varenicline	1.8 (0.05)	(1.7, 1.9)	-0.4 (0.07)	(-0.6, -0.3)	<0.0001
Zyban	1.9 (0.05)	(1.8, 2.0)	-0.3 (0.07)		<0.0001
Placebo	2.2 (0.05)	(2.1, 2.3)		(-0.5, -0.2)	

11.2.3.2.4 Craving: Reviewer's Analysis

The effects on these measures do not appear to be in dispute; however, the use of the term "craving" to describe the phenomenon captured by these instruments is questionable. Dr. Scott noted that the measures of "craving" appear to be capturing effects best described as "urge to smoke." Therefore, although it is not clear that varenicline has an effect on "craving," *per se*, an effect on "urge to smoke" appears to have been demonstrated.

11.2.3.2.5 Smoking Satisfaction: Applicant's Analysis

The Smoking Effects Inventory (SEI) was administered only to those subjects who reported smoking since the previous visit. Pfizer concluded that:
Varenicline was significantly more effective than placebo in reducing the reinforcing effects of smoking described by 4 of the SEI subscales: Smoking Satisfaction,

Psychological Reward, Enjoyment of Respiratory Tract Sensations, and Craving Reduction. For each of these subscales, scores at each weekly timepoint were lower for varenicline than for placebo, and results of the repeated measures analysis of these subscale scores for Week 1 through Week 7 show that the treatment differences were statistically significant. This was particularly the case for Smoking Satisfaction and Psychological Reward, the two subscales of primary interest. Results for the Aversion subscale showed no statistically significant difference between the varenicline and placebo treatment groups.

11.2.3.2.6 Smoking Satisfaction: Reviewer's Analysis

Dr. Scott observed that the measures of the reinforcing effects of smoking captured all the relevant aspects of smoking reinforcement. She concluded that "reinforcing effects of smoking" is not a clearly-defined concept suitable for labeling.

11.2.3.2.6.1 Analysis by Subgroups

The table below from Dr. Buenconsejo's review shows the effect of varenicline to be consistent across demographic subgroups.

Weeks 9 – 12 CQR by Age, Gender, Race, and Baseline Smoking Characteristics – Study 36

	Varenicline % (n/N)	Zyban % (n/N)	OR (95% CI) p-value	Placebo % (n/N)	OR (95% CI) p-value
Overall	44 (150/343)	30 (101/340)	1.9 (1.4, 2.6)	18 (60/340)	3.8 (2.7, 5.4)
Gender					
Male	44 (83/189)	31 (63/206)	1.8 (1.2, 2.7)	19 (38/198)	3.5 (2.2, 5.6)
Female	44 (67/154)	28 (38/134)	2.0 (1.2, 3.4)	15 (22/142)	4.2 (2.4, 7.4)
Age					
<45 years	37 (62/166)	24 (44/182)	2.0 (1.2, 3.2)	17 (34/201)	3.1 (1.9, 5.2)
>= 45 years	50 (88/177)	36 (57/158)	1.9 (1.2, 3.0)	19 (26/139)	4.7 (2.7, 8.0)
Race					
White	47 (137/294)	30 (85/281)	2.1 (1.5, 3.0)	18 (52/289)	4.1 (2.8, 6.1)
Black	27 (8/30)	28 (10/36)	0.6 (0.2, 2.2)	19 (5/26)	1.1 (0.3, 4.5)
Others	26 (5/19)	26 (6/23)	1.0 (0.2, 4.9)	12 (3/25)	2.4 (0.4, 14.7)
Fagerstrom Score					
0 – 3	56 (40/72)	31 (21/68)	3.1 (1.5, 6.5)	21 (17/80)	5.5 (2.6, 11.8)
4 – 6	45 (70/155)	33 (54/164)	1.9 (1.2, 3.0)	20 (33/165)	3.4 (2.1, 5.8)
7 – 10	34 (39/115)	24 (26/107)	1.7 (0.9, 3.1)	10 (9/93)	5.1 (2.2, 11.5)
Average No. of Cigarettes/day, past month					
10 - <20	49 (50/102)	33 (37/111)	2.1 (1.2, 3.7)	25 (26/104)	3.3 (1.8, 6.2)
20 - <30	44 (67/152)	31 (43/140)	1.8 (1.1, 3.0)	13 (21/163)	5.5 (3.1, 9.8)
>= 30	37 (33/89)	24 (21/89)	2.2 (1.1, 4.5)	18 (13/73)	3.1 (1.4, 6.8)

11.2.3.2.6.2 Analysis by Center

See table above, in section on Enrollment by Center

11.2.3.3 Conclusions Regarding Efficacy Data in Study

This study provides evidence that varenicline is superior to placebo and to Zyban in helping smokers attain abstinence. In addition, varenicline reduces the "urge to smoke" in smokers attempting to quit.

11.2.3.4 Safety Results

The table below shows the common adverse events observed in this study, as reported by Pfizer in the final study report. Adverse events (MedDRA preferred terms) that occurred in at least 2% of subjects and at a frequency greater than placebo in either the varenicline or Zyban treatment groups are summarized below. Among varenicline-treated subjects, the most frequently reported gastrointestinal disorders were nausea, constipation, flatulence, and dyspepsia; while the most frequent psychiatric disorders were insomnia and abnormal dreams. In the nervous system, the most frequent adverse events in the varenicline treatment group were headache, dizziness, and dysgeusia.

Most Common Adverse Events Study A3051036 N (%)
Pfizer's Table 26

SOC Adverse Event (MedDRA Preferred Term)	Varenicline N = 343		Zyban N = 340		Placebo N = 340	
Gastrointestinal disorders	**162**	**(47.2)**	**94**	**(27.6)**	**91**	**(26.8)**
Nausea	101	(29.4)	25	(7.4)	33	(9.7)
Constipation	31	(9.0)	22	(6.5)	5	(1.5)
Flatulence	20	(5.8)	7	(2.1)	8	(2.4)
Dyspepsia	19	(5.5)	10	(2.9)	12	(3.5)
Dry mouth	19	(5.5)	26	(7.6)	11	(3.2)
Vomiting	18	(5.2)	7	(2.1)	6	(1.8)
Diarrhea	16	(4.7)	8	(2.4)	10	(2.9)
Psychiatric disorders	**118**	**(34.4)**	**132**	**(38.8)**	**91**	**(26.8)**
Insomnia	49	(14.3)	72	(21.2)	42	(12.4)
Abnormal dreams	45	(13.1)	20	(5.9)	12	(3.5)
Sleep disorder	16	(4.7)	23	(6.8)	9	(2.6)
Anxiety	15	(4.4)	18	(5.3)	13	(3.8)
Depression	7	(2.0)	6	(1.8)	1	(0.3)
Nervous system disorders	**100**	**(29.2)**	**85**	**(25.0)**	**97**	**(28.5)**
Headache	44	(12.8)	27	(7.9)	43	(12.6)
Dizziness	22	(6.4)	25	(7.4)	24	(7.1)
Dysgeusia	14	(4.1)	14	(4.1)	11	(3.2)
Musculoskeletal and connective tissue disorders	**34**	**(9.9)**	**45**	**(13.2)**	**39**	**(11.5)**
Back pain	13	(3.8)	14	(4.1)	9	(2.6)
Myalgia	3	(0.9)	11	(3.2)	5	(1.5)
Arthralgia	8	(2.3)	9	(2.6)	7	(2.1)
Respiratory, Thoracic, and Mediastinal Disorders	**56**	**(16.3)**	**47**	**(13.8)**	**44**	**(12.9)**
Cough	14	(4.1)	12	(3.5)	12	(3.5)
Sinus congestion	13	(3.8)	7	(2.1)	10	(2.9)
Rhinorrhea	7	(2.0)	2	(0.6)	2	(0.6)
General Disorders	**46**	**(13.4)**	**33**	**(9.7)**	**41**	**(12.1)**
Fatigue	25	(7.3)	13	(3.8)	22	(6.5)
Skin and Subcutaneous Tissue Disorders	**25**	**(7.3)**	**33**	**(9.7)**	**16**	**(4.7)**
Rash	6	(1.7)	12	(3.5)	6	(1.8)
Pruritis	3	(0.9)	7	(2.1)	2	(0.6)

11.3 Appendix 3: Protocol A3051035

A Fifty-Two-Week, Multicenter Study Evaluating the Safety and Effectiveness of Varenicline for the Maintenance of Smoking Cessation

Conducted April 13 2003 to March 3 2005

11.3.1 Protocol

11.3.1.1 Objective/Rationale

The primary objective of this study was to compare varenicline 1 mg b.i.d. to placebo for maintenance of smoking cessation during study Weeks 13 through 24, in subjects who had responded to an initial 12-week course of smoking cessation therapy with varenicline.

11.3.1.2 Overall Design

The study was a 52-week multicenter study involving 12 weeks of open-label treatment with varenicline, followed by enrollment of subjects achieved at least one week of abstinence into a 12-week, double-blind phase, with randomization to continue on varenicline or blindly switch to placebo. The open-label dosing was varenicline titrated to 1 mg b.i.d. (0.5 mg QD for 3 days, 0.5 mg b.i.d. for 4 days, and then 1 mg b.i.d. for 11 weeks). The double-blind dosing was varenicline 1 mg b.i.d. or placebo. Study drug was discontinued at Week 24 and subjects were to be followed in the nontreatment phase of the protocol for an additional 28 weeks.

11.3.1.3 Population and Procedures

11.3.1.3.1 Inclusion/Exclusion Criteria

Planned enrollment to the open-label phase was approximately 2000 subjects in order to randomize 820 to double-blind treatment (varenicline and placebo, 410 per group).

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

- Male or female cigarette smokers between the ages of 18 and 75 years, inclusive, who were motivated to stop smoking.
- For female subjects, surgical sterilization or at least 2 years postmenopausal, or using medically acceptable contraception, with negative serum β-HCG at both Screening and Baseline visits
- Smoking an average of at least 10 cigarettes per day during the past year and over the month prior to the screening visit, with no period of abstinence greater than 3 months in the past year.
- Able to be outpatients and be assessed in a clinic setting.

Subjects were to be excluded for:

- Pregnancy/nursing
- Use of another investigational drug in the preceding 30-days, or previous randomization into a varenicline study
- Serious or unstable disease within the past 6 months
- Clinically significant laboratory abnormalities
- Current or past 12 months treatment for depression.
- Current or prior history of panic disorder, psychosis, or bipolar disorder.
- Subjects with a requirement to use other medications during the study that might interfere with the evaluation of the study drug (e.g., nicotine replacement therapy, or bupropion)

- Subjects with severe chronic obstructive pulmonary disease (COPD).
- Subjects with a history of cancer (treated basal cell or squamous cellcarcinoma of the skin was allowed).
- Subjects with evidence or history of clinically significant allergic reactions (seasonal allergies allowed).
- Clinically significant cardiovascular disease in the past 6 months.
  Examples of clinically significant cardiovascular disease would include the following: myocardial infarction, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), unstable angina, a serious arrhythmia, or clinically significant ECG conduction abnormalities.
- Uncontrolled hypertension or a screening or baseline systolic blood pressure greater than 150 mm Hg or a diastolic blood pressure greater than 95 mm Hg.
- SGOT (AST) or SGPT (ALT) > 150% ULN or total bilirubin > 110% ULN.
- Body Mass Index (BMI) less than 15 or greater than 38. No subject was to be enrolled with a weight less than 100 pounds.
- History of drug (except nicotine) or alcohol abuse or dependence within the past 12 months.
- Intention to donate blood or blood components while receiving experimental drug or within 1 month of the completion of the study.
- Use of a nicotine replacement product, clonidine, or nortriptyline within the previous month.
- Use of tobacco products other than cigarettes, including pipe tobacco, cigars, snuff, and chew, or marijuana use within the past month and not agreeing to abstain from use of these products during study participation.
- Inability to to comprehend and follow the study protocol, including subjects unable and/or unwilling to participate in the nontreatment follow-up.

Disallowed concomitant medications included:

- Nicotine replacement therapy
- antidepressants, including bupropion (Wellbutrin®), citalopram (Celexa®), fluoxetine (Prozac®), mirtazepine (Remeron®), nefazodone (Serzone®), paroxetine (Paxil®), sertraline (Zoloft®), trazodone, tricyclic antidepressants, and venlafaxine (Effexor®)
- antipsychotic agents, including clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), risperidone (Risperdal®), and ziprasidone (Geodon®)
- benzodiazepines, including alprazolam, diazepam, and lorazepam
- mood stabilizers/anticonvulsants, including carbamazepine (Tegretol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), lithium, and valproate (Depakene® or Depakote®)
- naltrexone
- over-the-counter and prescribed stimulants and anorectic agents
- systemically administered steroids, including systemic anabolic steroids, glucocorticoids, and mineralocorticoids (inhaled steroid use is permitted)
- theophylline
- insulin

Allowed medications included:
Episodic Use Permitted:

- acetaminophen/**paracetamol**

- antihistamines (chronic use also permitted)
- aspirin (chronic use also permitted)
- inhaled bronchodilators (chronic use also permitted)
- inhaled steroids (chronic use also permitted)
- NSAIDs, including COX-2 inhibitors (chronic use also permitted)
- over-the-counter medications, except for kava kava and St. John's wort

Chronic Use Permitted:

- antihypertensive agents (excluding alphamethyldopa, clonidine, prazosin)
- hormone replacement therapy
- lipid-lowering agents
- oral hypoglycemic agents
- thyroid replacement
- inhaled bronchodilators
- inhaled steroids
- multivitamins
- oral contraceptives
- aspirin
- NSAIDs, including COX-2 inhibitors

11.3.1.3.2 Procedures

The protocol called for an initial screening visit, during which medical screening procedures were undertaken. A subsequent "baseline" visit was to occur 3 days – 3 weeks after the screening visit, which would be cancelled if results of laboratory tests did not confirm eligibility. At the time of screening, subjects were to select a target quit date (TQD) to coincide with the Week 1 visit, which was required to be scheduled to occur 7 days after the baseline visit, so that subjects would have a week of treatment prior to the TQD.

At the baseline visit, assessments as illustrated in the time-and-events table below were to be performed. Subjects were assigned to treatment used a single, centralized randomization sequence (block size = 4) in a ratio of 1:1 stratified by center. Investigators obtained subject identification numbers and study drug assignments via a phone-in or web-based system.

Site personnel were to dispense study drug for the first week of treatment and provide dosing instructions.

11.3.1.3.2.1 Behavioral treatment

Subjects were to be given an educational booklet on smoking cessation to review ("Clearing the Air: How to Quit Smoking...and Quit for Keeps" – National Cancer Institute Publication 95-1647) and provided up to ten minutes of counseling, in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines.

11.3.1.3.2.2 Dosing

All subjects in the 12-week open-label phase were to receive a dose of 1 mg varenicline twice daily with dose titration in the first week of treatment. Subjects were to be instructed to initiate treatment

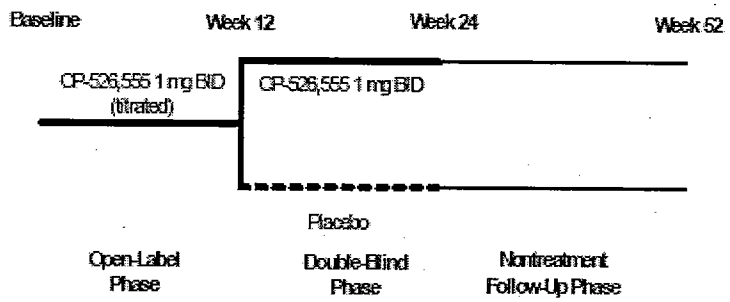
on the evening of the baseline visit. Subjects were to take 1 tablet of 0.5 mg varenicline, once daily for 3 days; then 1 tablet of 0.5 mg varenicline, twice daily for 4 days; and starting on Day 8 subjects were to take 2 tablets of 0.5 mg varenicline, twice daily for the next 11 weeks. In the double-blind phase subjects were to take either 2 tablets of blinded study medication (0.5 mg varenicline or placebo) twice daily for 12 weeks (Week 13 through Week 24). Doses were to be taken with 240 ml water, and it was be recommended that subjects eat prior to dosing. No study medication was to be administered during the nontreatment follow-up phase (Week 25 through Week 52).

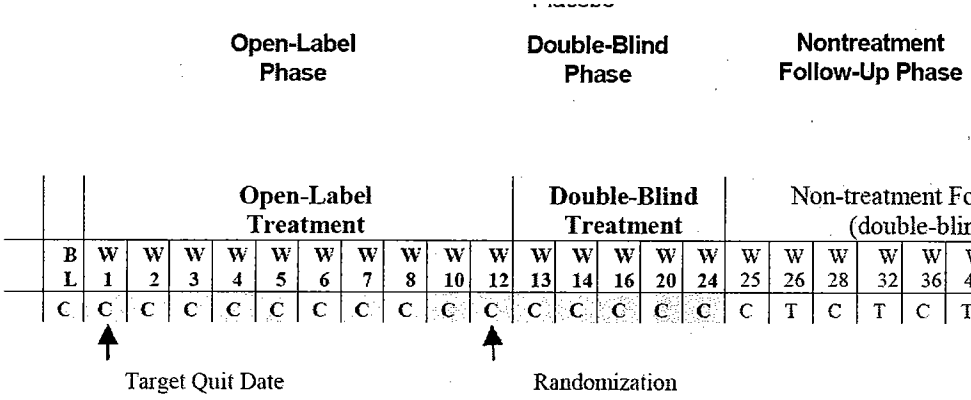
Treatment Phase	Treatment	Study Interval	Number of Tablets	Frequency
		Day 1- Day 3	1	QD (PM)
Open-label	Varenicline	Day 4- Day 7	1	b.i.d. (AM and PM)
		Week 2- Week 12	2	b.i.d. (AM and PM)
Double-blind	Varenicline	Week 13 – Week 24	2	b.i.d. (AM and PM)
	Placebo	Week 13 – Week 24	2	b.i.d. (AM and PM)

Both varenicline and its matching placebo were to be dispensed to the subjects from room temperature storage at each scheduled visit. Supplies of varenicline tartrate in a strength of 0.5 mg and matching placebo tablets were provided in high-density polyethylene (HDPE) bottles. Bottles were labeled with dosing instructions; the bottles for Week 1 had instructions for the dosing titration.

11.3.1.3.2.3 Schedule of Visits and Assessments

The overall study schematic is illustrated in the figures below.





BL = Baseline; W = Week; C = Clinic visit; T = Telephone contact

11.3.1.3.2.3.1 Open-label Phase

Subjects were to return for visits at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 12. The subjects were to attempt to quit on the target quit date prior to the Week 1 visit (7 days after the baseline visit). The quit attempt was to occur in the morning prior to the clinic visit that day, so that the subject's last cigarette prior to the quit attempt would be before midnight the night prior to the Week 1 visit. Subjects were to be called 3 days after the target quit date (TQD+3) to be reminded of study participation and to receive support for the smoking cessation attempt.

At each visit, subjects were to be asked about cigarette and other nicotine use since the last study visit and in the past 7 days (using the Nicotine Use Inventory). End-expiratory exhaled carbon monoxide was to be measured. Other subjective effects and safety measures were undertaken as per the time-and-events schedule below.

At the Week 12 visit, subjects were to be considered eligible continue in the double-blind phase if they reported that they had not smoked over the prior 7 days, had an end-expired CO $\leq$10 ppm, and were still deemed appropriate for randomization. Double-blind varenicline or placebo was to be dispensed to randomized subjects. Subjects who did not meet randomization criteria were to be discontinued from study participation.

11.3.1.3.2.3.2 Double-Blind Phase

Subjects were to return to the clinic at Weeks 13, 14, 16, 20, and 24. At each visit, subjects were to be asked about cigarette and other nicotine use since the last visit and over the past 7 days (Nicotine Use Inventory) and provide a sample for measurement of end-expired CO. All concomitant medications and any adverse events were to be recorded. Vital signs and weight were to be recorded and drug will be dispensed.

The site staff was to provide up to 10 minutes of brief counseling regarding smoking cessation, in accordance with AHRQ guidelines. At the Week 13 visit, subjects were also be administered the Minnesota Nicotine Withdrawal Scale (MNWS).

Study drug was to be discontinued at the Week 24 visit, with any unused drug returned to the site by the subject.

11.3.1.3.2.3.3 Week 25 to 52 Visits (nontreatment follow-up phase)

Clinic visits were to occur at Weeks 25, 28, 36, 44, and 52. Scheduled telephone calls were to be made to each subject at Weeks 26, 32, 40, and 48. The Nicotine Use Inventory was to be administered, asking about use of cigarettes and other nicotine-containing products in the last 7 days, since the last contact (clinic visit or telephone call), and in the last 4 weeks (Week 52 or early termination during nontreatment follow-up only). The number of days smoked since the last contact was also to be recorded, with even a puff of a cigarette counting as smoking. At each contact, up to 10 minutes of smoking cessation counseling was to be given, in accordance with AHRQ guidelines. Concomitant medications used as an aid to smoking cessation were to be recorded.

At clinic visits (Weeks 25, 28, 36, 44, and 52), weight, blood pressure, heart rate, and exhaled CO were to be measured. The MNWS was to be self-administered at Week 25. Blood was to be drawn for C-reactive protein at Week 52.

The following time-and-events tables illustrate the planned schedule of assessments:

A30511035 Study Schedule, First Twelve Weeks, Open-Label Treatment

Procedure	Screen	BL	Wk 1	TQD +3 **phone**	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 10	Wk 12	ET
Informed consent	X													
Medical history	X													
Physical examination	X												X	X
Vital signs (HR, BP), weight	X	X	X		X	X	X	X	X	X	X	X	X	X
Temperature		X												
Height	X													
Exhaled carbon monoxide (CO)		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
Adverse events		X	X		X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X		X	X	X	X	X	X	X	X	X	
Dosing record			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
Fagerström Test	X													
Electrocardiogram	X	X			X								X	X
Blood chemistry	X	X			X								X	X
CBC	X	X			X								X	X
Serum pregnancy teste	X	X			X								X	X
C-reactive protein		X											X	X
Reference serum sample		X												
Serum cotinine		X												
Urinalysis (dipstick)	X	X			X								X	X
Urine drug screenf	X													
Genotyping sample		X												
Counseling (AHRQ)		X	X		X	X	X	X	X	X	X	X	X	X
Brief telephone contact (AHRQ)				X										
Randomize responders; D/C nonresponders													X	

Double-Blind Treatment, Weeks 13-24, Study A3051035

Procedure	Wk 13	Wk 14	Wk 16	Wk 20	Wk 24	ET
Physical examination					X	X
Vital signs (HR, BP), weight	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Dispense study drug	X	X	X	X		
Dosing record	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
MNWS	X					
Electrocardiogram					X	X
Serum pregnancy testa					X	X
Blood chemistry					X	X
C-reactive protein					X	X
CBC					X	X
Urinalysis (dipstick)					X	X
Exhaled carbon monoxide (CO)	X	X	X	X	X	X
Nicotine Use Inventory	X	X	X	X	X	X
Counseling (AHRQ)	X	X	X	X	X	X

Nontreatment Follow-up (Weeks 26 through 52)

Procedure	Week 25 **clinic**	Wk 26 **phone**	Wk 28 **clinic**	Wk 32 **phone**	Wk 36 **clinic**	Wk 40 **phone**	Wk 44 **clinic**	Wk 48 **phone**	Wk 52 **clinic**	ET **clinic**
Nicotine Use Inventory	X	X	X	X	X	X	X	X	X	X
Vital signs (HR, BP), weight	X		X		X		X		X	X
Exhaled carbon monoxide (CO)	X		X		X		X		X	X
C-reactive protein									X	X
MNWS	X									
Counseling (AHRQ)	X	X	X	X	X	X	X	X	X	X

11.3.1.4 Evaluations/Endpoints
The pre-specified primary endpoint for the study was the Continuous Abstinence (CA) from Weeks 13 to 24.

Key secondary endpoints were the CA from Weeks 13 to 52 and the long-term quit rate (LTQR) to Week 52. These measures were to be obtained through reports of cigarette use confirmed by measurement of end-expired CO≤10 ppm. If any CO was > 10 ppm, the subject would be considered a smoker at that timepoint.

Long-Term Quit Rate (LTQR) to Week 52 is defined as 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 (by self-report) during the nontreatment phase of the study.

Other secondary endpoints identified in the protocol included:
7-Day Point-Prevalence of Abstinence (Proportion of subjects abstaining from smoking during the preceding 7 days; assessed at every contact, analyzed with inferential statistics at Weeks 24 and 52)

4-Week Point-Prevalence of Abstinence (Proportion of subjects abstaining from smoking during the last four weeks of the nontreatment follow-up phase (Weeks 49-52))

Time to first cigarette post-randomization, calculated from the date of first randomized therapy to the date of first cigarette smoked.

11.3.1.5 Amendments and Changes in Study Conduct
Several amendments of an editorial nature not affecting the population recruited, the treatment provided, or the key assessments, were made to the protocol.

In addition, Pfizer notes that the planned sample size was exceeded. The planned sample size for randomization to double-blind treatment was 410 subjects per treatment group. It was estimated that an enrollment of 2000 subjects in the open-label treatment phase would provide the necessary 820 eligible subjects (subjects who did not smoke during the last 7 days of open-label treatment). In reality, the smoking cessation rate at Week 12 was higher than anticipated. Due to the 12-week lag period between subject enrollment in the open-label phase and determination of eligibility for continuation in the double-blind period, the planned sample size was exceeded (1210 subjects randomized) even with reduction of open-label enrollment to 1928 subjects.

11.3.1.6 Statistical Plan
The primary analysis set was all subjects who took at least one dose of randomized study medication. Subjects who discontinue are assumed to have relapsed for the remainder of the study. In responder rates, those subjects will be represented in the denominator but not in the numerator, regardless of their last smoking status evaluation. To support the robustness of the conclusions made on the "All Subjects" population efficacy analyses for the primary endpoint will also be performed in an "Evaluable" subject subgroup (all subjects in the subgroup who were not major protocol violators and who received randomized medication for at least 14 days), and in the "Completers" subgroup.

All significance tests were to be 2-tailed using an overall level of significance of alpha=0.05. As there are two treatment groups, no adjustment for multiple comparisons would made for any analysis. A logistic regression model was to be fit for binary endpoints, to include treatment and center as independent variables. Treatment by center interaction would also be investigated in secondary analyses. The p-values reported would be based on the main effects model.

11.3.2 Results

11.3.2.1 Study Conduct/Outcome

11.3.2.1.1 Subject Characteristics

A total of 2416 subjects were screened and 1928 were assigned to open-label treatment. One subject did not initiate treatment. Of the 1927 subjects who took study medication, 1210 (62.8%) entered the double-blind phase, with 603 randomized to continue varenicline treatment and 607 switched to placebo. Subjects who did not enter the double-blind phase were discontinued from the study.

11.3.2.1.1.1 Enrollment by Center

Enrollment was distributed among centers as listed in the table below:

Center	Principal Investigators	Subimvestigators	Address	Open-Label	Double-Blind Varenicline	Double-Blind Placebo
				N=1927	N=603	N=607
1011	Dr. Gordon Ford	[redacted]	Rockyview General Hospital Room 4A - 185A 7007 - 14 Street SouthWest Calgary, Alberta T2V 1P9 CANADA	30 (2%)	7 (1%)	7 (1%)
1012	Dr. Ginette Girard	[redacted]	NOVABYSS INC. SUITE 300 1335 KING Ouest SHERBROOKE, QUEBEC J1J 2B8 CANADA	163 (8%)	53 (9%)	54 (9%)
1013	Dr. Lew Pliamm		Canadian Phase Onward Unit # 5 4646 Dufferin St. Toronto, Ontario M3H 5S4 CANADA	41 (2%)	15 (2%)	15 (2%)
1014	Dr. Andrew Pipe	[redacted]	The University of Ottawa Heart Institute 40 Ruskin Street Ottawa, Ontario K1Y 4W7 CANADA	92 (5%)	30 (5%)	30 (5%)
1015	Dr. David Ian Stewart	[redacted]	Cornwall Medical Center 446 TransCanada Highway Cornwall, Prince Edward Island C0A 1H0 CANADA	43 (2%)	17 (3%)	17 (3%)
1016	Dr. Gerald Brosky	[redacted]	CDHA Centre for Clinical Research suite 131 5790 University Ave. Victoria General Site Halifax, Nova Scotia B3H 1V7 CANADA	47 (2%)	14 (2%)	16 (3%)

11.3.2.1.1.2 Subject Disposition

A total of 1927 subjects initiated varenicline treatment. Patient disposition is illustrated in the tables below, modified from Pfizer's final study report:

Subject Disposition [Number (%) of Subjects] - Open- Label Treatment Phase

	Varenicline	
Number screened 2416		
Assigned to treatment	1928	
Treated[a]	1927	
Completed open-label phase	1210	(62.8)
Discontinued from study	717	(37.2)
Discontinuations by reason:		
Adverse events	202	(10.5)
Lack of efficacy	42	(2.2)
Protocol deviation	71	(3.7)
Pregnancy	1	(0.1)
Refusal to participate further	150	(7.8)
Lost to follow-up	132	(6.9)
Other	119	(6.1)

[a] Percentages are based on number of subjects treated.

Subject Disposition [Number (%) of Subjects] – Double-Blind Phase

		Double-blind Varenicline		Double-blind Placebo	
Randomized	1210	603		607	
Treated[a]	1206	602		604	
Completed study		494	(82.1)	463	(76.7)
Discontinued from study		108	(17.9)	141	(23.3)
Treatment Phase (Weeks 13-24)		47	(7.8)	94	(15.6)
Discontinuations by reason:					
Adverse events		8	(1.3)	8	(1.3)
Lack of efficacy		4	(0.7)	5	(0.8)
Protocol deviation		3	(0.5)	2	(0.3)
Refusal to participate further		19	(3.2)	44	(7.3)
Lost to follow-up		12	(2.0)	31	(5.1)
Other		1	(0.2)	4	(0.7)
Nontreatment Follow-up Phase		61	(10.1)	47	(7.8)
Discontinuations by reason:					
Death		2	(0.3)	0	0
Adverse Events		2	(0.4)	1	(0.2)
Lack of efficacy		0	(0.0)	2	(0.3)
Refusal to participate further		27	(4.5)	19	(3.1)
Lost to follow-up		28	(4.7)	24	(4.0)
Other		2	(0.3)	1	(0.2)

[a]Percentages based on the number of subjects treated.

"Other" reasons reported in the open-label phase included, according to the final study report, two subjects whose reasons could be considered adverse events (one with elevated

blood pressure and one with elevated ALT). The first table above has been modified to reflect these subjects as discontinuations due to AEs. The remaining discontinuations described as "other" in open-label treatment involved 41 subjects who were retrospectively determined to be ineligible for participation, 30 subjects with a variety of "personal reasons" or other reasons for discontinuation, and 63 subjects who are described as not having met double-blind entrance criteria. For some of these subjects, it was noted that the subject was smoking. These subjects (13 in number) have been added to the "lack of efficacy" category above in my modification of the table. Arguably, all 63 should be added, but as re-randomization required other criteria as well (compliance, e.g.), it is not clear whether all of the subjects who did not qualify for re-randomization were treatment failures. In any case, Dr. Buenconsejo's analysis of abstinence rates (below) shed additional light on the efficacy of varenicline in the open-label phase more definitively than the patient disposition. Most notably, this table shows that roughly 10% of subjects discontinued due to adverse events.

As shown in the second table above, the population eligible for, and agreeing to, re-randomization and participation in the double-blind phase was enriched for subjects able to tolerate varenicline. The discontinuation rate due to adverse events in the ensuing twelve-week, double-blind period was strikingly lower, at slightly over 1%.

In both phases, subjects could discontinue study medication but remain in the study. Therefore, in the context of subject disposition, "completed the study" refers to the number of subjects who participated in the study for the full period, whether or not they completed dosing during the treatment phase.

The table below, Pfizer's Table 31, illustrates the distribution of subjects temporarily or permanently discontinuing study *medication* or requiring a dose reduction because of adverse events.

Treatment Discontinuations or Dose Reductions Due to Adverse Events N (%)

	Open-label Varenicline N = 1927	Double-blind Varenicline N = 602	Double-blind Placebo N = 604
Permanent discontinuations			
All-causality	229 (12%)	10 (2%)	8 (1%)
Treatment-related	200 (10%)	6 (1%)	4 (1%)
Dose reductions or temporary discontinuations			
All-causality	80 (4%)	7 (1%)	4 (1%)
Treatment-related	57 (3%)	1 (0.2%)	3 (1%)

This table clearly illustrates that the initial open-label run-in yielded a population enriched for both responders to, and tolerators of, varenicline.

During the double-blind phase, the most frequent reasons for withdrawal were lost to follow-up and refusal to participate further. From an efficacy standpoint, treatment failure is imputed to subjects not completing the study, including those lost to follow-up and those discontinuing due to refusal to participate. There are more subjects in both of these categories in the placebo arm; this could represent a potential bias. However, relapse to smoking after treatment discontinuation is generally considered to be the rule, rather than the exception, and it seems reasonable to impute treatment failure to these subjects.

11.3.2.1.2 Demographics

The table below illustrates demographic and baseline characteristics of the treatment groups. Overall, 96% of the subjects were white, roughly half of the subjects were female, and the average age was approximately 44 years (range 18-75 years). Smoking history was similar across treatment groups, with subjects representing a population of smokers who on average had smoked for the previous 27 years (range 2-59 years) and had smoked an average of 22 cigarettes per day over the previous month. No important differences between treatment groups were apparent.

Table 7.8: Demographic and Baseline Characteristics – Study 35

	Open-label Phase	Double-blind Phase	
	Varenicline N = 1927	Double-blind Varenicline N = 602	Double-blind Placebo N = 604
Sex at birth [n (%)]			
Male	941 (48.8)	303 (50.3)	292 (48.3)
Female	986 (51.2)	299 (49.7)	312 (51.7)
Age (years)			
Mean (SD)	44.2 (10.7)	45.4 (10.4)	45.3 (10.4)
Range	18-75	18-73	20-73
Race [n (%)]			
White	1853 (96.2)	582 (96.7)	586 (97.0)
Black	35 (1.8)	9 (1.5)	10 (1.7)
Asian	14 (0.7)	3 (0.5)	4 (0.7)
Other	25 (1.3)	8 (1.3)	4 (0.7)
Number of years subject smoked			
Mean	27.2	28.2	28.1
Range	2-59	3-58	2-58
Average number of cigarettes per day (past month)			
Mean	21.6	20.7	20.7
Range	3-99	8-60	10-65
Number of lifetime serious quit attempts[a]			
None	341 (17.7)	99 (16.4)	103 (17.1)
1 or more	1586 (82.3)	503(83.6)	501(82.9)
Longest period of abstinence in past year (days)			
Mean	7.41	8.31	7.62
Range	0-200	0-90	0-90
Fagerström Score[b]			
N	1922	601	602
Mean	5.55	5.43	5.35

Source: Tables 13.2.1.1.1, 13.2.1.1.2, 13.2.1.2, 13.2.1.3

[a] Using any method

[b] Fagerström score can range from 0 to 10, with higher scores indicating greater nicotine dependence.

11.3.2.1.3 Dosing Information

The table below (Pfizer's Table 12, A3051035 final study report) illustrates exposure duration and compliance with medication across treatment groups. Groups were similar with respect to mean duration of exposure.

Table 13. Duration of Treatment by Phase in Study

Duration[a]	Number (%) of subjects		
	Open-label treatment phase	Additional treatment in Double-blind treatment phase	
	Varenicline 1 mg BID N = 1927	Double-blind Varenicline N = 602	Double-blind Placebo N = 604
Unknown[b]	1	4	5
>3 days	1904 (98.8)	597 (99.2)	599 (99.2)
>1 week (7 days)	1842 (95.6)	592 (98.3)	591 (97.8)
>2 weeks (14 days)	1749 (90.8)	579 (96.2)	572 (94.7)
>3 weeks (21 days)	1687 (87.5)	573 (95.2)	564 (93.4)
>4 weeks (28 days)	1639 (85.1)	564 (93.7)	555 (91.9)
>5 weeks (35 days)	1596 (82.8)	551 (91.5)	528 (87.4)
>6 weeks (42 days)	1546 (80.2)	549 (91.2)	517 (85.6)
>7 weeks (49 days)	1507 (78.2)	546 (90.7)	512 (84.8)
>8 weeks (56 days)	1451 (75.3)	532 (88.4)	497 (82.3)
>9 weeks (63 days)	1412 (73.3)	510 (84.7)	486 (80.5)
>10 weeks (70 days)	1379 (71.6)	496 (82.4)	480 (79.5)
>11 weeks (77 days)	1324 (68.7)	482 (80.1)	467 (77.3)
>12 weeks (84 days)	487 (25.3)	268 (44.5)	268 (44.4)
>13 weeks (91 days)	26 (1.3)	35 (5.8)	25 (4.1)
Median duration (days)	**84.0**	**84.0**	**84.0**
Range (days)	1 – 100	2 – 110	4 - 105

Source: Table 13.3.1.1

[a] For each subject, treatment duration was calculated as the total number of days from first day of dosing through the last day of dosing, without deducting for missed doses.

[b] Subjects lost to follow-up after being dispensed study drug. Subjects are assumed to have taken at least one dose and are included in the All Subjects population. Open-label: 103510271071; Double-blind varenicline: 103510011175, 103510181084, 103510241011, and 103510271124; Double-blind placebo, 103510011072, 103510241047, 103510251006, 103510251033 and 103510341031

11.3.2.1.4 Protocol Violations

Pfizer reported that

> Protocol deviations were identified programmatically by searching the database for randomized subjects who had screening or baseline values falling outside of the ranges specified by inclusion or exclusion criteria (eg, values for age, weight, medical history, smoking history, laboratory parameters, etc). The database was also searched for subjects who used prohibited medications during the study and subjects who were withdrawn from the study due to protocol deviations. In addition, lists of protocol deviations were compiled by site monitors during routine center visits or during remote review of electronic data. All deviations identified by the methods described above were reviewed for clinical significance.

Those considered potentially significant are summarized in [the table below, Pfizer's Table 5]. A total of 44 subjects entered into the open-label phase only, 16 subjects randomized to double-blind varenicline, and 24 randomized to double-blind placebo had significant protocol deviations.

Table 5. Summary of Significant Protocol Deviations (Number of Subjects)

	Subjects enrolled in open-label phase only (not randomized)	Subjects Randomized to Varenicline	Subjects Randomized to Placebo
Subjects with significant protocol deviations	**44**	**16**	**24**
Subjects with significant protocol deviations (by category)[a]			
Subject entered study more than once	1		1 (second entry)
Did not meet inclusion/exclusion criteria prior to enrollment			
Abstinence from smoking >3 months in the past year	1	0	0
Smoked <10 cigarettes/day in month prior to screening	2	3	0
Significant medical history	2	0	1
Body Mass Index >38 at Screening	1	1	1
Screening or Baseline systolic BP >160 mm Hg or diastolic BP >100 mm Hg	10	2	5
Screening liver function test values greater than 150% ULN	3	1	0
Positive urine drug screen at Screening	8	1	2
Did not meet randomization criteria			
Randomized, but smoked in Week 12 based on Nicotine Use Inventory	0	1	1
Used prohibited concomitant medications			
Used nicotine replacement therapy during the open-label phase	6	1	0
Used nicotine replacement therapy during the double-blind phase	0	0	11
Used other smoking cessation pharmacologic aids during the open-label phase	0	0	2
Used other smoking cessation pharmacologic aids during the double-blind phase	0	1	1
Used other prohibited medications during the open-label phase[b]	12	2	1
Used other prohibited medications during the double-blind phase[b]	0	5	7

Source: Appendix B0.1
ULN = upper limit of normal; BP = blood pressure
[a]Subjects may be included in more than one category
[b]Took prohibited medication (other than NRT or smoking cessation aids) for >7 days during the treatment phase

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, although three subjects randomized to double-blind varenicline did not meet the minimum smoking requirement for entry.

The most significant violations involved 12 subjects randomized to placebo who used other smoking cessation products (primarily nicotine replacement) during the double-blind phase of the study. Only one subject randomized to varenicline used a prohibited smoking cessation aid (not NRT, specific drug not reported). As these violations would tend to bias the study in favor of the placebo group, no adjustment in the analysis was made for these protocol violators. Use of other prohibited medications was evenly distributed between the treatment groups.

11.3.3 Efficacy Results

11.3.3.1 Abstinence Rates

11.3.3.1.1 Initial Abstinence: Open-label Phase

The criteria for randomization into the double-blind phase included only *one* week of abstinence at the end of the open-label phase. Pfizer chose this in order to maximize the number of subjects entering open-label treatment who would be eligible to participate in the double-blind trial; 64% of enrolled subjects met this criterion. To the extent that the study was intended to be a randomized-withdrawal design in *responders to treatment*, the Division felt that a liberal definition of treatment response, if anything, would bias the study against varenicline if subjects who were not true responders were allowed to participate. However, it was of interest to establish that "true responders" (i.e., patients who achieved four weeks of abstinence at the end of treatment) were evenly distributed between the double-blind arms. Although it was not a protocol-specified analysis, Dr. Buenconsejo calculated the proportion of subjects entering the open-label phase who met the "abstinent weeks 8-12" criterion that defined treatment success in the other 12-week studies. Data were available only from weeks 1-8, 10, and 12, so Dr. Buenconsejo used the data from weeks 8,10, and 12, and considered successful any patient with CO-confirmed abstinence at those three visits. Overall, 51% if the subjects participating in the open-label phase achieved this four-week abstinence criterion.

Of the 1210 subjects randomized to treatment in the double-blind phase, all (per protocol) met the one-week abstinence criterion, while 82% of the varenicline group and 79% of the placebo group also had been abstinent from at least week 8 (four-week abstinence).

11.3.3.1.1.1 Maintenance of Efficacy: Double-blind Phase

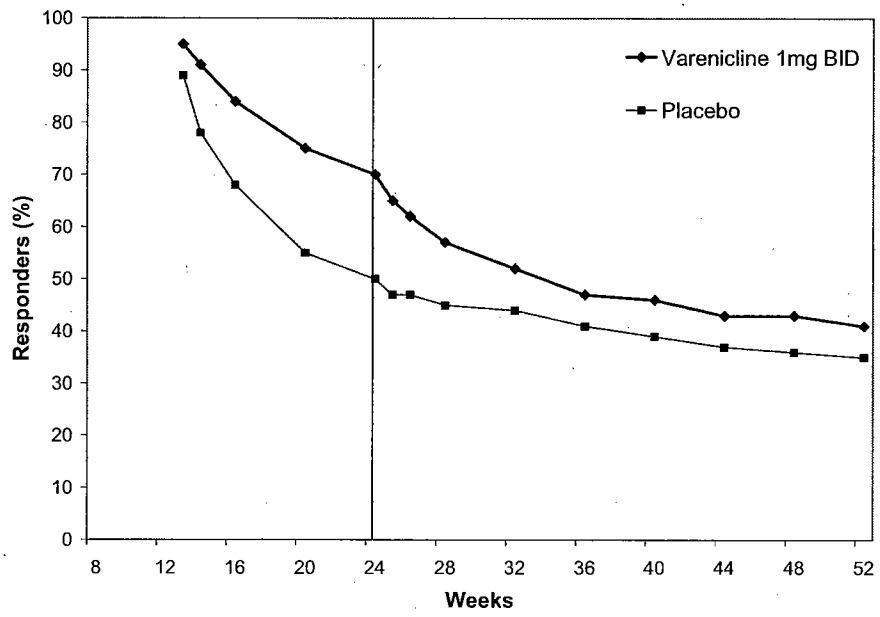
The primary efficacy analysis for this study, per protocol, was the proportion of subjects continuously abstinent from week 13 through week 24 (i.e., throughout the double-blind treatment phase). In addition, Pfizer's objective was also to show that a longer period of treatment with varenicline would improve the long-term abstinence rates, and therefore, smoking behavior post-treatment, to week 52 (28 weeks of post-treatment follow-up) was also analyzed. As in the other Phase 3 studies, a "continuous abstinence" rate was calculated as well as a "long-term quit rate" which allowed no more than 6 days of smoking during the follow-up period. Again, I have doubts about reliance on subject's ability to recall a specific number of days of smoking (vs. any smoking/no smoking, which can be recalled with reliability); therefore, I think the continuous abstinence rate is more informative than the long-term quit rate.

Because of concerns about the method of imputation of missing data, Dr. Buenconsejo applied a more conservative approach and re-calculated the abstinence rates over the week 13-24 and week 13-52 windows. Pfizer's analyses and Dr. Buenconsejo's are shown below in tables adapted from her review (tables 21, 22, and 23).

	Pfizer's analysis		Reviewer Re-analysis	
	Double-Blind Varenicline	Double-Blind Placebo	Double-Blind Varenicline	Double-Blind Placebo
Continuous Abstinence, Weeks 13-24				
ITT Subjects	N=601	N=603	N=601	N=603
Abstinent (%)	425 (71%)	301 (50%)	420 (70%)	301 (50%)
Odds ratio (95% CI) vs. placebo		2.5 (2.0, 3.2)		2.4 (1.9, 3.0)
p-value vs. placebo		<0.0001		<0.0001
Evaluable	N=574	N=574	N=574	N=574
Abstinent (%)	418 (73%)	299 (52%)	415 (72%)	299 (52%)
Odds ratio (95% CI) vs. placebo		2.5 (2.0, 3.2)		2.5 (1.9, 3.2)
p-value vs. placebo		<0.0001		<0.0001
Continuous Abstinence, Weeks 13-53				
ITT Subjects	N=601	N=603	N=601	N=603
Abstinent (%)	265 (44%)	224 (37%)	247 (41%)	214 (35%)
Odds ratio (95% CI) vs. placebo		1.3 (1.1, 1.7)		1.3 (1.0, 1.6)
p-value vs. placebo		0.0123		0.0394
Evaluable	N=574	N=574	N=574	N=574
Abstinent (%)	262 (46%)	223 (39%)	244 (43%)	214 (37%)
Odds ratio (95% CI) vs. placebo		1.3 (1.0, 1.7)		1.3 (1.0, 1.6)
p-value vs. placebo		0.0193		0.0705

The graph below from Dr. Buenconsejo's review, and of her own construction, illustrates the time course of relapse following treatment discontinuation.

Continuous Abstinence Rate from Week 13 to Week 52 – Reviewer's (A3051035)



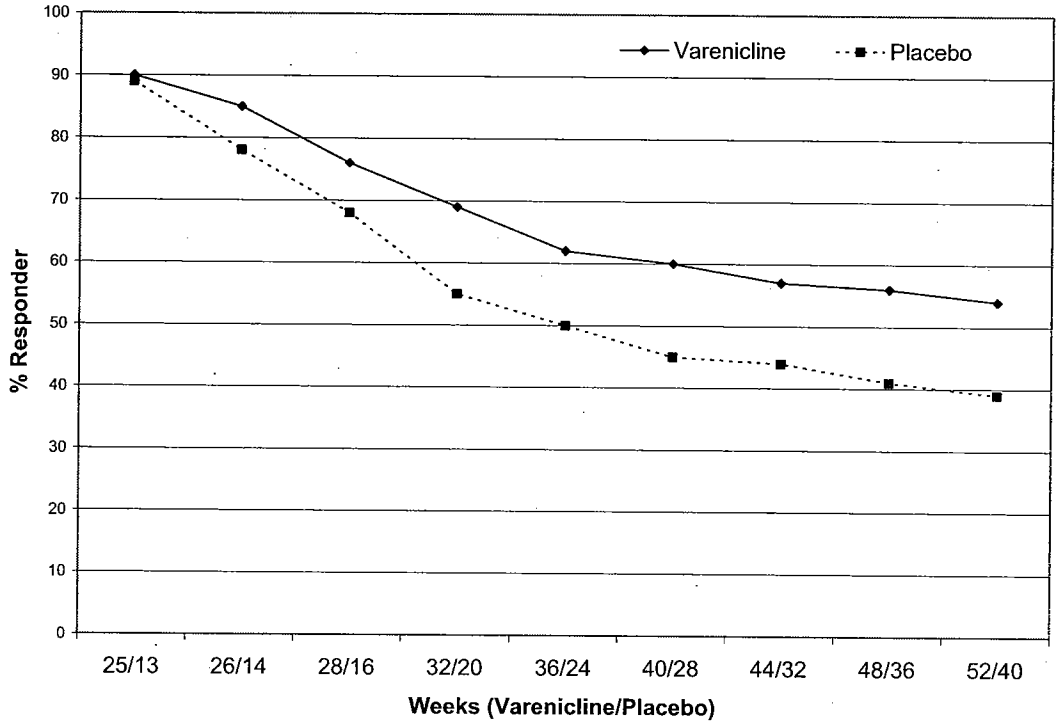
The graph illustrates that ongoing treatment with varenicline helps maintain abstinence achieved with varenicline treatment. Subjects continuing on varenicline have a shallower relapse curve than those switched to placebo. It is also notable that varenicline reduces, but does not completely prevent relapse. About 30% of subjects relapsed despite ongoing varenicline treatment.

On further review, Dr. Buenconsejo and I determined that the analytic approach taken actually compared 40 weeks of post-treatment follow-up for the placebo group (who had received 3 months of varenicline treatment) to 28 weeks of post-treatment follow-up for the varenicline group (who had received 6 months of varenicline treatment). To explore further whether 6 months of varenicline treatment is really superior to 3 months of varenicline treatment, it would be necessary to compare each group at comparable timepoints measured as *weeks since discontinuation of treatment.* If the 52 week results of superior long-term abstinence in the varenicline group can be explained entirely by the shorter period of post-treatment observation, a true effect of longer term treatment on long-term success would not be demonstrated.

Therefore, Dr. Buenconsejo graphed the proportion of subjects who were abstinent during the last week of varenicline treatment (*study week* 12 for the double-blind placebo group and *study week* 24 for the double-blind varenicline group) who maintained continuous abstinence through each post-treatment follow-up week as shown in the graph below. The x-axis aligns *Study Week 13* (post-treatment follow-up week 1 for the

double-blind placebo group) with *Study Week 25* (post-treatment follow-up week 1 for the varenicline group), and so on. This allows demonstration of the fact that, after *identical periods of post-treatment follow-up*, subjects who took varenicline for six months are more likely than subjects who took varenicline for three months to maintain abstinence for 28 weeks post-treatment. Although both groups show that the first three months after treatment discontinuation are a time when smokers are vulnerable to relapse, the relapse curve for those who had a longer period of varenicline treatment is shallower.

Continuous Abstinence Rate from Week 13/25 to Week 40/52



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Pfizer also calculated the LTQR (long-term quit rate). This analysis counted as treatment successes any subjects who reported fewer than 6 days of smoking over the observation period. Any continuously abstinent smoker would also be considered successful in the LTQR calculation, and the rates differ only by those subjects who smoked, but did so only minimally. The LTQR differs minimally from the continuous abstinence rates, suggesting that few subjects smoked in this controlled fashion.

	Continuous Abstinence		LTQR		Difference (Subjects smoking <6 cigarettes)	
	Double-Blind Varenicline N=601	Double-Blind Placebo N=603	Double-Blind Varenicline N=601	Double-Blind Placebo N=603	Double-Blind Varenicline N=601	Double-Blind Placebo N=603
Week 25	389 (65%)	286 (47%)	421 (70%)	297 (49%)	32 (5%)	11 (2%)
Week 26	370 (62%)	281 (47%)	415 (69%)	293 (49%)	45 (7%)	12 (2%)
Week 28	340 (57%)	274 (45%)	394 (66%)	289 (48%)	54 (9%)	15 (2%)
Week 32	311 (52%)	264 (44%)	374 (62%)	288 (48%)	63 (10%)	24 (4%)
Week 36	285 (47%)	246 (41%)	348 (58%)	274 (45%)	63 (10%)	28 (5%)
Week 40	276 (46%)	235 (39%)	332 (55%)	265 (44%)	56 (9%)	30 (5%)
Week 44	259 (43%)	226 (37%)	310 (52%)	259 (43%)	51 (8%)	33 (5%)
Week 48	256 (43%)	220 (36%)	301 (50%)	253 (42%)	45 (7%)	33 (5%)
Week 52	247 (41%)	214 (35%)	287 (48%)	245 (41%)	40 (7%)	31 (5%)

11.3.3.1.2 Secondary Endpoints/Subjective Measures

In addition, Pfizer calculated the long-term abstinence rates among study participants. These data show that after 12 weeks of treatment with varenicline, more subjects who continue varenicline treatment for an additional 12 weeks are abstinent at the 24-week and 52-week follow-up points than subjects who did not continue varenicline. The rate of continuous at the end of the observation periods (weeks 24 and 52) is shown below (table constructed using data from Dr. Buenconsejo's Tables 6).

Continuous Abstinence and Long-term Quit Rate, Study A3051035

	Varenicline N=602	Placebo N = 604	Odds Ratio (95% CI) p-value
Continuous abstinence Week 13-24 N (%)	425 (71%)	301 (50%)	2.47 (1.95-3.15) <.0001
Continuous abstinence Week 13-52 N(%)	265 (44%)	224 (37%)	1.35 (1.07-1.70) .0126
Relapse between Week 24 and Week 52	160/425 (38%)	77/301 (25%)	
Number reporting ≤6 days smoking during follow-up, N(%) (LTQR), Week 13-52	288 (48%)	246 (41%)	1.34 (1.07-1.69) .0119

11.3.3.2 Subjective Measures

In this study, the Minnesota Nicotine Withdrawal Scale (MNWS) was administered at the times of rerandomization and treatment discontinuation to determine whether symptoms of craving and withdrawal emerged in the context of varenicline discontinuation.

One week after open-label treatment, mean MNWS subscale scores were higher for subjects switched to placebo than those continued on double-blind varenicline treatment group, suggesting some withdrawal symptoms associated with the discontinuation of varenicline treatment. Mean differences in scores between treatments at Week 13 ranged from 0.08 on Insomnia to 0.34 on Urge to Smoke. On average, however, withdrawal symptoms tended to be "slight" or "not at all" (score of 0 indicates "not at all", 1 indicates "slight").

At Week 25, one week after discontinuation of double-blind study medication, mean scores for the withdrawal subscales, scores subjects discontinuing treatment with varenicline were slightly higher than subjects finishing the course of placebo, again suggesting that withdrawal symptoms may emerge upon varenicline discontinuation The differences included 0.02 for Restlessness and Increased Appetite, 0.09 for Negative Affect, and 0.14 for Insomnia.

Week 13 (post open-label treatment)	Remaining on varenicline			Switched to placebo		
	N	Mean	SE	N	Mean	SE
Urge to Smoke	571	0.90	(0.036)	560	1.24	(0.046)
Negative Affect	571	0.50	(0.026)	560	0.70	(0.034)
Restlessness	571	0.64	(0.036)	556	0.88	(0.044)
Increased Appetite	571	1.08	(0.047)	560	1.25	(0.050)
Insomnia	570	0.75	(0.040)	560	0.83	(0.041)

Week 25 (post double-blind treatment)	Discontinuing varenicline			Discontinuing placebo		
	N	Mean	SE	N	Mean	SE
Urge to Smoke	499	1.04	(0.044)	468	1.32	(0.054)
Negative Affect	499	0.60	(0.033)	468	0.51	(0.032)
Restlessness	499	0.67	(0.041)	467	0.65	(0.041)
Increased Appetite	499	0.98	(0.049)	467	0.96	(0.049)
Insomnia	499	0.73	(0.043)	468	0.59	(0.037)

11.3.3.2.1.1 Analysis by Subgroups

The table below from Dr. Buenconsejo's review shows the effect of varenicline to be consistent across demographic subgroups.

Weeks 13 – 24 Continuous Abstinence by Age, Gender, Race, and Baseline Smoking Characteristics – Study 35

	Varenicline % (n/N)	Placebo % (n/N)	OR (95% CI)
Overall	70 (420/601)	50 (301/603)	2.4 (1.9, 3.0)
Gender			
Male	73 (221/303)	54 (156/291)	2.5 (1.8, 3.6)
Female	67 (199/298)	46 (145/312)	2.4 (1.7, 3.3)
Age			
<45 years	67 (191/285)	51 (139/270)	2.0 (1.4, 2.8)
>= 45 years	72 (229/316)	49 (162/333)	3.0 (2.2, 4.2)
Race			
White	70 (408/581)	50 (293/585)	2.4 (1.9, 3.1)
Black	56 (5/9)	40 (4/10)	2.6 (0.3, 26.7)
Others	64 (7/11)	50 (4/8)	1.7 (0.2, 12.4)
Fagerstrom Score			
0 – 3	80 (90/113)	53 (59/111)	3.8 (1.9, 7.2)
4 – 6	69 (209/301)	49 (151/309)	2.5 (1.8, 3.5)
7 – 10	65 (121/186)	49 (89/181)	2.0 (1.3, 3.1)
Average No. of Cigarettes/day, past month			
10 - <20	73 (161/221)	52 (114/220)	2.5 (1.7, 3.8)
20 - <30	69 (201/293)	48 (141/296)	2.5 (1.7, 3.5)
>= 30	67 (58/87)	53 (46/87)	2.2 (1.1, 4.4)

11.3.3.3 Conclusions Regarding Efficacy Data in Study

This study provides support for a recommendation of three additional months of varenicline treatment in patients who successfully quit smoking using varenicline.

11.3.3.4 Safety Results: Common AEs

The table below shows the common adverse events observed in this study, as reported by Pfizer in the final study report. Adverse events (MedDRA preferred terms) that occurred in at least 1% of subjects are summarized below. During the open-label phase, the most frequently-reported terms were nausea, flatulence, constipation, dyspepsia, insomnia, abnormal dreams, irritability, sleep disorder, headache, dysgeusia, and dizziness. During double-blind treatment, all adverse events were markedly less common. As noted above, the open-label run-in selected a population able to tolerate varenicline well.

	Open-label		Double-blind Treatment Phase			
Adverse Event[a]	Varenicline		Varenicline		Placebo	
MedDRA Preferred Term	N = 1927		N = 602		N = 604	
Gastrointestinal disorders	1046	(54.3)	36	(6.0)	41	(6.8)
Nausea	645	(33.5)	7	(1.2)	4	(0.7)
Flatulence	234	(12.1)	2	(0.3)	0	
Constipation	168	(8.7)	0		3	(0.5)
Dyspepsia	133	(6.9)	9	(1.5)	6	(1.0)
Dry mouth	77	(4.0)	0		0	
Diarrhea	73	(3.8)	3	(0.5)	6	(1.0)
Vomiting	56	(2.9)	3	(0.5)	3	(0.5)
Abdominal pain	48	(2.5)	1	(0.2)	2	(0.3)
Abdominal distention	45	(2.3)	1	(0.2)	1	(0.2)
Abdominal pain upper	36	(1.9)	0		1	(0.2)
GERD	21	(1.1)	1	(0.2)	2	(0.3)
Psychiatric disorders	788	(40.9)	75	(12.5)	91	(15.1)
Insomnia	377	(19.6)	16	(2.7)	17	(2.8)
Abnormal dreams	276	(14.3)	6	(1.0)	0	
Irritability	97	(5.0)	16	(2.7)	27	(4.5)
Sleep disorder	62	(3.2)	2	(0.3)	3	(0.5)
Nightmare	54	(2.8)	1	(0.2)	0	
Nicotine dependence	40	(2.1)	14	(2.3)	29	(4.8)
Depression	40	(2.1)	13	(2.2)	17	(2.8)
Anxiety	32	(1.7)	9	(1.5)	7	(1.2)
Restlessness	27	(1.4)	6	(1.0)	6	(1.0)
Depressed mood	19	(1.0)	4	(0.7)	8	(1.3)
Nervous system disorders	540	(28.0)	30	(5.0)	34	(5.6)
Headache	304	(15.8)	17	(2.8)	12	(2.0)
Dysgeusia	83	(4.3)	0		0	
Dizziness	77	(4.0)	3	(0.5)	5	(0.8)
Somnolence	67	(3.5)	1	(0.2)	2	(0.3)
Disturbance in attention	47	(2.4)	3	(0.5)	2	(0.3)
Infections and infestations	454	(23.6)	97	(16.1)	99	(16.4)
Nasopharyngitis	145	(7.5)	29	(4.8)	32	(5.3)
Upper Respiratory Tract Infection	89	(4.6)	9	(1.5)	15	(2.5)
Influenza	70	(3.6)	15	(2.5)	9	(1.5)
Gastroenteritis	33	(1.7)	8	(1.3)	2	(0.3)
Sinusitis	31	(1.6)	10	(1.7)	6	(1.0)

11.4 Appendix 4: Protocol A3051007

A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating The Safety And Efficacy Of Four Dosing Strategies For CP-526,555 (0.5 mg b.i.d., Titrated 0.5 mg b.i.d., 1 mg b.i.d., And Titrated 1 mg b.i.d.) In Smoking Cessation

Conducted September 26 2001 – October 7 2002

11.4.1 Protocol

11.4.1.1 Objective/Rationale

The purpose of this Phase 2 study was to measure the safety and efficacy of four dosing strategies for CP-526,555 in the treatment of nicotine dependence in a population of cigarette smokers.

11.4.1.2 Overall Design

The study was a double-blind, placebo-controlled, randomized clinical trial designed to assess the efficacy and safety of varenicline in comparison to placebo in the treatment of nicotine dependence. The duration of active treatment specified in the protocol was twelve weeks. There were four different dosing strategies for varenicline: The 0.5 mg b.i.d. group (Group 1) was to be treated with 0.5 mg tablets twice per day for twelve weeks. The titrated 0.5 mg b.i.d. group (Group 2) was to be treated with 0.5 mg QD for seven days and 0.5 mg b.i.d. for eleven weeks. The 1 mg b.i.d. group (Group 3) was to be treated wtih 1 mg twice per day for twelve weeks. The titrated 1 mg b.i.d. group (Group 4) was to be treated with 0.5 mg QD for three days, 0.5 mg b.i.d. for four days, and 1 mg b.i.d. for eleven weeks. The placebo group (Group 5) was to be treated with placebo tablets for twelve weeks. Following completion of the 12 week study, subjects were to continue in a non-treatment extension protocol administratively designated Study A3051018.

11.4.1.3 Population and Procedures

11.4.1.3.1 Inclusion/Exclusion Criteria

Planned enrollment was approximately 625 subjects randomized to each of five treatment arms (125 per arm) at approximately 8 sites.

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

- Male or female cigarette smokers between the ages of 18 and 65 years, inclusive.
- For female subjects of childbearing potential, medically acceptable contraception
- Smoking an average of at least ten cigarettes per day during the past year, with no period of abstinence greater than three months in the past year.
- Able to be outpatients and be assessed in a clinic setting.
- In good health, as determined by a detailed medical history, full physical examination (including vital signs), 12-lead electrocardiogram, and clinical laboratory tests.

- Body mass index (BMI) no less than 15 and no greater than 38, weight at least 100 pounds.

Subjects were to be excluded for:

- Pregnancy/nursing
- Concomitant treatment with another investigational drug within one month of study enrollment or plans to take another investigational drug within thirty days of study completion.
- Previously randomization in a study that has included CP-526,555.
- Currently or within the past twelve months requiring treatment for depression.
- Past or present history of panic disorder, psychosis, or bipolar disorder.
- Intent to donate blood or blood components while receiving experimental drug or within 1 month of the completion of the study.
- Requirement to use other medications during the study that might interfere with the evaluation of the study drug
- Evidence or history of clinically significant allergic (except for seasonal allergies at time of dosing), endocrine, gastrointestinal, hematological, hepatic, neurologic, psychiatric, pulmonary, or renal disease or a history of cancer (excluding treated basal cell carcinoma and squamous cell carcinoma).
- Screening or baseline alkaline phosphatase, SGOT, SGPT, or bilirubin greater than 110% of the upper limit of normal.
- History of clinically significant cardiovascular disease or a clinically significant abnormal electrocardiogram at screening or baseline.
- Uncontrolled hypertension or a screening or baseline systolic blood pressure greater than 160 mm Hg or a diastolic blood pressure greater than 95 mm Hg
- History of drug (except nicotine) or alcohol abuse or dependence within the past 12 months.
- History of significant drug allergies (such as resulting in difficulty breathing) or clinically significant rash due to a medication.
- Any condition possibly affecting drug absorption.
- Use of a nicotine replacement product, ZybanÒ, or Wellbutrin® within the previous three months.
- Use of tobacco products other than cigarettes, including pipe tobacco, cigars, snuff, and chew, or marijuana use within the past month or not agreeing to abstain from use of these products during study participation.
- Current household member participating or who previously participated in this clinical study.

All use of concomitant medications required review by the Pfizer clinical monitor prior to and during enrollment in the study with the following exceptions:

Episodic Use Permitted: over-the-counter medications (excluding kava kava and St. John's Wort)
Chronic Use Permitted: hormone replacement therapy, lipid-lowering agents, multivitamins

11.4.1.3.2 Procedures

The protocol called for an initial screening visit, during which medical screening procedures were undertaken. A subsequent "baseline" visit was to occur 3 days – 3 weeks after the screening visit, which would be cancelled if results of laboratory tests did not confirm eligibility. At the time of screening, subjects were to select a target quit date (TQD) to coincide with the Week 1 visit, which was required to be scheduled to occur 8 days after the baseline visit, so that subjects would have a full 7 days of treatment prior to the TQD.

At the baseline visit, assessments as illustrated in the time-and-events table below were to be performed. The subjects were to be randomized to treatment according to a randomization list provided by Pfizer to the investigators, and provided with study medication. An educational booklet on smoking cessation ("Clearing the Air: How to Quit Smoking...and Quit for Keeps" – National Cancer Institute Publication 95-1647) was to be provided to each subject along with up to ten minutes of counseling. Subjects were also to be provided with a paper diary as well as instructions on its use. Entries were to be made into the Smoking Diary by subjects each evening, collecting information on the number of cigarettes smoked that day and times of dosing for the two days prior to the week 1, week 2, week 4 and week 12 or early termination visits. A day will be defined for subjects as beginning and ending at midnight and smoking will include even a puff of a cigarette. Subjects were to return for weekly visits to the clinic after the baseline visit over the following twelve weeks.

11.4.1.3.2.1 Dosing

Eligible subjects were to be randomized to treatment with one of four varenicline treatment regimens or placebo, including:

- Group 1 "0.5 mg, non-titrated": 0.5 mg b.i.d. group 0.5 mg tablets twice per day for twelve weeks.
- Group 2 "0.5 mg, titrated": 0.5 mg QD for seven days and 0.5 mg b.i.d. for eleven weeks.
- Group 3, "1 mg b.i.d. group, non-titrated": 1 mg twice per day for twelve weeks.
- Group 4, "1 mg b.i.d. group, titrated": 0.5 mg QD for three days, 0.5 mg b.i.d. for four days, and 1 mg b.i.d. for eleven weeks.
- Group 5, placebo: placebo treatment for twelve weeks.

Treatment was to begin on the evening of the baseline visit with two tablets. The subjects were then to take 4 tablets per day, two blinded CP-526,555 tablets in the morning and two in the evening. Subjects were to be advised that dosing should occur with 240 ml of water that it was recommended that they eat prior to dosing.

11.4.1.3.2.2 Schedule of Visits and Assessments

Subjects were to return for weekly visits to the clinic after the baseline visit over the following 12 weeks. The subjects were instructed to attempt to quit on the target quit date at the Week 1 visit (8 days after the baseline visit). The quit attempt was to occur in the morning prior to the clinic visit that day, so that the subject's last cigarette prior to the

quit attempt would be before midnight the night prior to the Week 1 visit. Subjects were to be called 3 days after the target quit date (TQD+3) to be reminded of study participation and to receive support for the smoking cessation attempt. These contacts were to be no longer than 5 minutes and counseling was to follow AHRQ guidelines.

At each visit, subjects were to be asked about cigarette and other nicotine use since the last study visit and in the past 7 days (using the Nicotine Use Inventory). End-expiratory exhaled carbon monoxide was to be measured. All concomitant medications and any adverse events were to be recorded. Other subjective effects and safety measures were undertaken as per the time-and-events schedule below.

The treatment phase was to end after 12 weeks of subject participation. During the Week 12 visit, or at early termination, subjects were to be asked about cigarette and other nicotine use since the last visit and the Smoking Diary for the previous week was to be collected and reviewed. End-expiratory exhaled carbon monoxide will be measured and up to 10 minutes of brief counseling regarding smoking cessation will be provided. Safety assessments and subjective measures were to be obtained.

Following completion of the Week 12 visit, subjects were to continue in the nontreatment extension protocol, designated Study A3051018. Subjects who had completed all 12 weeks of Study A3051007 were eligible for Study A3051018, whether or not they had quit smoking and whether or not they had completed treatment.

Nontreatment Follow-up (Weeks 13 through 52)
Subjects were to return for visits to the clinic at Week 13, Week 24, and and Week 52. At each visit, subjects were to be asked to report whether they had smoked any cigarettes or used any other nicotine-containing products since the last contact or in the last 7 days and to report the number of days on which they had smoked any cigarettes since the last contact. End-expiratory exhaled carbon monoxide was to be measured at each clinic visit (nonsmoking status would be considered confirmed with a measurement $\leq$ 10 ppm). Vital signs and weight were to be measured at each clinic visit. Concomitant medications used as an aid to smoking cessation were to be recorded. At the Week 52 (or early termination) visit, subjects were to have blood drawn for the measurement of C-reactive protein.

The MNWS (past week) was to be self-administered at the Week 13 visit, with answers based on symptoms over the prior week (Appendix I). The Smoking Cessation Quality of Life Questionnaire was to be self-administered by subjects at Week 24 and Week 52 (or early termination).

The sites were to provide up to 10 minutes of brief counseling regarding smoking cessation, in accordance with the Agency for Health Care Policy and Research (AHCPR) guidelines ("Smoking Cessation: Quick Reference Guide for Smoking Cessation Specialists") Subjects also were expected to continued to use the educational booklet on smoking cessation provided to them in Study A3051007. Additionally, the protocol specified that subjects would receive a telephone call at Weeks 16, 20, 28, 32, 36, 40, 44 and 48 during which they would be asked about cigarette use and the use of other

nicotine-containing products and any concomitant medications used as aids to smoking cessation.

11.4.1.3.2.3 Behavioral treatment

Subjects were to be given an educational booklet on smoking cessation to review ("Clearing the Air: How to Quit Smoking…and Quit for Keeps" – National Cancer Institute Publication 95-1647) and provided up to ten minutes of counseling, in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines.

The following time-and-events table illustrates the planned schedule of assessments:

Study A3051007

Procedure	Screen	BL	Wk 1	TQD +3	Wk 2[a]	Wk 3	Wk 4[b]	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	ET
Physical examination[c]	X														X	X
Vital signs (HR, BP), weight	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Temperature		X														
Height	X															
Adverse events		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dosing record			X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Fagerström Test	X															
Minnesota Nicotine Withdrawal Scale		X	X		X	X	X	X	X	X					X	X
Smoking Effects Inventory[d]		X	X		X	X	X	X	X	X						X
Smoking Cessation QOL Questionnaire		X													X	X
Electrocardiogram	X	X[e]	X				X								X	X
Serum pregnancy test	X	X					X			X					X	X
Blood chemistry	X	X	X		X		X			X					X	X
C-reactive protein		X								X					X	X
CBC	X	X	X		X		X			X					X	X
Reference serum sample		X														
Serum cotinine	X															
Plasma CP-526,555		X	X		X		X								X	X
Genotyping sample[f]		X														
Urinalysis (dipstick)	X	X	X		X		X			X					X	X
Urine Drug Screen[g]	X															
Exhaled carbon monoxide		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Counseling (AHCPR)		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Brief telephone contact (AHCPR)				X												
Treatment Recommendation Question															X	X

[a]subjects with morning appointments should hold AM dose prior to visit; [b]dose in AM prior to AM visit for PK at Tmax; [c]either screening or BL; [d]also completed daily between baseline and week 1, only required in subjects who have smoked since prior completion, to be completed at ET only up to week 7; [e]three electrocardiograms at baseline [f]optional; [g]may be completed at visits in addition to screening at discretion of investigator; BL=baseline; ET=early termination

Study A3051018 (follow-up)

Procedure	Week 13[a]	Weeks 16, 20	Week 24	Weeks 28, 32, 36, 40, 44, and 48	Week 52
Nicotine Use Questionnaire	X[b]	X[c]	X[b]	X[c]	X[b]
Weight, BP, HR	X		X		X
Exhaled CO	X		X		X
MNWS	X				
Smoking Cessation QOL Questionnaire			X		X
Counseling (AHCPR)	X		X		X

[a]all visit names refer to weeks following the baseline visit for protocol A3051007;
[b]administered during clinic visit;
[c]administered during telephone contact

11.4.1.4 Evaluations/Endpoints

The protocol-specified primary efficacy measure in the study was the Four-Week Continuous Quit Rate. This was to be measured for CP-526,555 for weeks 9 through 12 and 4 through 7 inclusive. Cessation from smoking would be assessed through weekly interviews, which would count even a puff of a cigarette as cigarette use. Self-reported smoking status was to be confirmed with exhaled carbon monoxide measurements (≤10 ppm) at the site. If any CO in the CQR window was > 10 ppm, the subject was to be considered a smoker. In the event of a self-report of abstinence and a missing carbon monoxide measurement, a subject would be considered abstinent only if the self-report was preceded and followed by a carbon monoxide confirmed self-report of abstinence. The primary analysis set specified in the protocol was all subjects who took at least one dose of randomized study medication and had an evaluation. Subjects who discontinued would be assumed to be smokers for the remainder of the study. In responder rates, those subjects would be represented in the denominator but not in the numerator, regardless of their last diary entry.

Secondary endpoints identified in the protocol included:

- continuous cessation from the target quit date
- number of cigarettes smoked during the study
- one week point-prevalence of smoking cessation
- change from baseline in weight
- changes in the Minnesota Nicotine Withdrawal Scale and the Smoking Effects Inventory.

For all these endpoints, the planned analysis was an Observed Cases (OC) approach at each time point.

11.4.1.5 Statistical Plan

In order to preserve the family-wise error rate, alpha=0.05, a step-down procedure was specified for the analysis of the primary endpoints. The hierarchy of comparisons planned was as follows: 1) Week 9 through 12 CQR, 1 mg b.i.d. (titrated and nontitrated groups combined) v. placebo, 2) Week 4 through 7 CQR, 1 mg b.i.d. (titrated and nontitrated groups combined) v. placebo, 3) Week 9 through 12 CQR, 0.5 mg b.i.d. (titrated and nontitrated groups combined) v. placebo, and 4) Week 4 through 7 CQR, 0.5 mg b.i.d. (titrated and nontitrated) v. placebo. In order to conclude statistical superiority of both dose groups v. placebo for both CQR windows, all comparisons 1 would need to attain statistical significance (alpha = 0.05). If only comparison 1 attained statistical significance then the conclusion would be that only the 1 mg b.i.d. group was significantly different from placebo for the week 9 through 12 CQR. If comparison 1 was not statistically significant (regardless of the p-value of the other comparisons), it would be concluded that none of the treatments were statistically significantly different from placebo for either endpoint. All significance tests were to be two-tailed using an overall level of significance of alpha=0.05.

11.4.2 Results

11.4.2.1 Study Conduct/Outcome

11.4.2.1.1 Subject Characteristics

Of 980 subjects screened, 647 subjects were selected for enrollment. Twenty subjects did not initiate treatment, therefore the treated population comprised 627 subjects with 124 randomized to 0.5 b.i.d. nontitrated, 129 randomized to 0.5 b.i.d. titrated, 124 randomized to 1 mg b.i.d. nontitrated, 129 randomized to 1 mg b.i.d. titrated, and 121 randomized to placebo.

11.4.2.1.1.1 Enrollment by Center

Enrollment was distributed among centers as listed in the table below:

Center Number	Principal Investigator Center Name and Address	Treatment Group	Rand	Treated N	Responders n	CQR% (n/N)
A3051007/1018						
All	**All**	V: 0.5 mg BID	259	253	114	45.1
		V: 1 mg BID	259	253	128	50.6
		Placebo	129	121	15	12.4
		Total	**647**	**627**		
1007-1001	**J. Pappas** Central Kentucky Research Associates, Incorporated, Suite 200 2801 Palumbo Drive Lexington, KY 40509	V: 0.5 mg BID	7	7	4	57.1
		V: 1 mg BID	7	6	2	33.3
		Placebo	3	3	0	0
		Total		**16**		
1007-1002	**D. Zimbroff** Pacific Clinical Research Suite 150 560 Hospitality Lane San Bernardino, CA 92408	V: 0.5 mg BID	15	15	5	33.3
		V: 1 mg BID	14	14	6	42.9
		Placebo	7	6	1	16.7
		Total		**35**		
1007-5005	**M. Nides** Los Angeles Clinical Trials Suite 308 2990 South Sepulveda Boulevard Los Angeles, CA 90064	V: 0.5 mg BID	62	61	27	44.3
		V: 1 mg BID	62	61	36	59.0
		Placebo	31	31	6	19.4
		Total		**153**		
1007-5010	**C. Oncken** University of Connecticut Health Center, Department of Medicine 263 Farmington Avenue Farmington, CT 06030-3940	V: 0.5 mg BID	44	44	24	54.6
		V: 1 mg BID	44	43	26	60.5
		Placebo	22	21	1	4.8
		Total		**108**		
1007-5011	**D. Gonzales** Oregon Health & Science University CR115 3181 South West Sam Jackson Park Road Portland, OR 97201	V: 0.5 mg BID	40	40	26	65.0
		V: 1 mg BID	40	40	22	55.0
		Placebo	20	19	2	10.5
		Total		**99**		
1007-5012	**S. Rennard** University Of Nebraska Medical Center, Pulmonary Division 985300 Nebraska Medical Center Omaha, NE 68198-5300	V: 0.5 mg BID	15	14	7	50.0
		V: 1 mg BID	15	15	10	66.7
		Placebo	7	6	0	0
		Total		**35**		

1007-5024	**R. Anthenelli** Cincinnati Veterans Affairs Medical Center Psychiatry Service (116A) 3200 Vine Street Cincinnati, OH 45220	V: 0.5 mg BID	30	30	12	40.0
		V: 1 mg BID	30	29	14	48.3
		Placebo	15	12	3	25.0
		Total		**71**		
1007-5027	**M. Friedman** Tulane University Health Sciences Center, Department of Medicine; Section of Pulmonary Diseases, Critical Care and Environmental Medicine 1430 Tulane Avenue SL 9 New Orleans, LA 70112-2699	V: 0.5 mg BID	7	7	2	28.6
		V: 1 mg BID	6	6	4	66.7
		Placebo	3	3	0	0
		Total		**16**		
1007-5028	**T. Payne** University of Mississippi Medical Center Act Center Jackson Medical Mall Suite 310 350 West Woodrow Wilson Drive Jackson, MS 39213	V: 0.5 mg BID	15	14	2	14.3
		V: 1 mg BID	17	17	1	5.9
		Placebo	9	8	0	0
		Total		**39**		
1007-5029	**J. Schmitz** University of Texas Health Science Center at Houston, Psychiatry and Behavioral Sciences 1300 Moursund Avenue Houston, TX 77030	V: 0.5 mg BID	24	21	5	23.8
		V: 1 mg BID	24	22	7	31.8
		Placebo	12	12	2	16.7
		Total		**55**		

11.4.2.1.1.2 Subject Disposition

Subject Disposition is shown in the table below, from Pfizer's final study report.

	0.5 mg b.i.d. Non-titrated N = 124	0.5 mg b.i.d. Titrated N = 129	1.0 mg b.i.d. Non-titrated N = 124	1.0 mg b.i.d. titrated N = 129	Placebo N = 121
Number Screened = 980					
Assigned to Treatment	129	130	129	130	129
Treated[a]	124	129	124	129	121
Completed Study	96 (77.4)	92 (71.3)	95 (76.6)	100 (77.5)	72 (59.5)
Discontinued Study	28 (22.6)	37 (28.7)	29 (23.4)	29 (22.5)	49 (40.5)
Discontinuations by Reason:					
Adverse events[b]	4 (3.2)	7 (5.4)	8 (6.5)	6 (4.7)	9 (7.4)
Lack of efficacy	0 (0.0)	2 (1.6)	2 (1.6)	0 (0.0)	4 (3.3)
Subject defaulted[c]	23 (18.5)	27 (20.9)	16 (12.9)	16 (12.4)	31 (25.6)
Other[d]	1 (0.8)	1 (0.8)	3 (2.4)	7 (5.4)	5 (4.1)

[a]Percentages based on number of subjects treated.
[b]Includes laboratory abnormalities
[c]Subject defaulted = subject withdrew consent or was lost to follow-up.
[d]"Other" includes the following: protocol violations, subject did not meet entry criteria, noncompliance, and personal reasons.

Subjects could discontinue study medication but remain in the study. Therefore, in the context of subject disposition, "completed the study" refers to the number of subjects who participated in the study for the full 12 weeks, whether or not they completed 12 weeks of dosing during the treatment phase.

The table below, from Pfizer's final study report, illustrates the distribution of reasons for subjects prematurely discontinuing study *medication* because of adverse events.

Discontinuations from Treatment with Study Drug [Number (%) of Subjects]

	0.5 mg b.i.d. Non-titrated N = 124	0.5 mg b.i.d. Titrated N = 129	1.0 mg b.i.d. Non-titrated N = 124	1.0 mg b.i.d. titrated N = 129	Placebo N = 121
All discontinuations	36 (29.0)	48 (37.2)	40 (32.3)	51 (39.5)	55 (45.5)
Discontinuations by Reason: Adverse events[a]	9 (7.3)	19[b] (14.7)	18[b] (14.5)	28 (21.7)	22[b] (18.2)
Lack of efficacy	0 (0.0)	2 (1.6)	2 (1.6)	0 (0.0)	4 (3.3)
Subject defaulted[c]	21 (16.9)	25 (19.4)	16 (12.9)	13 (10.1)	23 (19.0)
Other[d]	6 (4.8)	2 (1.6)	4 (3.2)	10 (7.8)	6 (5.0)

[a] Includes laboratory abnormalities considered adverse events; includes both treatment-emergent and nontreatment-emergent adverse events.
[b] In each treatment group noted, one subject discontinued due to an adverse event that was not treatment-emergent. For this reason, these numbers do not match the number of subjects who had study drug discontinued due to adverse events shown in the table below, as that table includes only discontinuations due to treatment-emergent events.
[c] Subject defaulted = subject withdrew consent or was lost to follow-up.
[d] "Other" includes the following: protocol violations, subject did not meet entry criteria, noncompliance, and personal reasons.

Treatment Discontinuations Due to Adverse Events N (%)

Treatment Discontinuations	0.5 mg b.i.d. Non-titrated N = 124	0.5 mg b.i.d. Titrated N = 129	1.0 mg b.i.d. Non-titrated N = 124	1.0 mg b.i.d. titrated N = 129	Placebo N = 121
All causalities	9 (7.3)	18 (14.0)	17 (13.7)	28 (21.7)	21 (17.4)
Last dose of study medication:					
Days 1-14	3	2	3	3	11
Day 15 or later	6	16	14	25	10

During the 12-week treatment phase, across all treatment groups, the most frequent reason for withdrawal was "subject defaulted," i.e. loss to follow-up, refusal to participate further. From an efficacy standpoint, treatment failure is imputed to subjects not completing the study, including those lost to follow-up and those discontinuing due to refusal to participate. There are more subjects in both of these categories in the placebo arm; this could represent a potential bias. However, relapse to smoking after treatment discontinuation is generally considered to be the rule, rather than the exception, and it seems reasonable to impute treatment failure to these subjects. Adverse events were the reason for premature *treatment* discontinuation in 7% of the 0.5 mg b.i.d. non-titrated group, 14% of the 0.5 mg b.i.d. titrated group, 14% of the 1 mg b.i.d. non-titrated group, 22% of the 1 mg b.i.d. titrated group, and 17% of the placebo group. The table above, however, illustrates that most discontinuations occurred after titration was complete, indicating that titration or lack thereof did not seem to affect the likelihood of premature study drug discontinuation.

11.4.2.1.2 Demographics

The table below illustrates demographic and baseline characteristics of the five treatment groups. Overall, 81% of the subjects were white, 50% of the subjects were female (47-57% across groups), and the average age was approximately 43 years (range 18-65 years). Smoking history was similar across treatment groups, with subjects representing a population of smokers who on average had smoked for the previous 25 years (range 1-51 years) and had smoked an average of 21 cigarettes per day over the previous month. More than half of the subjects in each treatment group had made at least 3 prior attempts to quit smoking. Approximately 72% of subjects had attempted to quit without any pharmacologic aid and 49% had used transdermal nicotine. The frequency of prior Zyban® use (one or more attempts) ranged from 21% to 31% across treatment groups.

	0.5 mg b.i.d. Non-titrated N = 124	0.5 mg b.i.d. Titrated N = 129	1.0 mg b.i.d. Non-titrated N = 124	1.0 mg b.i.d. titrated N = 129	Placebo N = 121
Sex [n (%)]					
Male	54 (43.5)	69 (53.5)	63 (50.8)	62 (48.1)	64 (52.9)
Female	70 (56.5)	60 (46.5)	61 (49.2)	67 (51.9)	57 (47.1)
Age (years)					
Mean (SD)	43.1 (9.9)	43.6 (10.4)	43.9 (9.9)	42.2 (10.8)	43.3 (9.5)
Range	19-63	20-64	21-65	18-65	21-64
Race [n (%)]					
White	106 (85.5)	104 (80.6)	106 (85.5)	104 (80.6)	86 (71.1)
Black 12 (9.7)		18 (14.0)	14 (11.3)	18 (14.0)	24 (19.8)
Asian	1 (0.8)	1 (0.8)	2 (1.6)	2 (1.6)	3 (2.5)
Hispanic	2 (1.6)	5 (3.9)	1 (0.8)	3 (2.3)	4 (3.3)
Other	3 (2.4)	1 (0.8)	1 (0.8)	2 (1.6)	4 (3.3)
Number of years subject smoked					
Mean	26.1	25.2	25.9	24.1	25.6
Range	5-50	1-52	5-53	3-51	3-48
Average number of cigarettes per day					
Mean	20.8	21.2	21.1	20.9	20.3
Range	8-50	10-60	10-80	7-45	7-50
Number of lifetime serious quit attempts					
None	12 (9.7)	14 (10.9)	8 (6.5)	5 (3.9)	8 (6.6)
1	17 (13.7)	20 (15.5)	19 (15.3)	21 (16.3)	19 (15.7)
2	23 (18.5)	19 (14.7)	24 (19.4)	23 (17.8)	22 (18.2)
3 or more	72 (58.1)	76 (58.9)	73 (58.9)	80 (62.0)	72 (59.5)
Longest period of abstinence in past year (days)					
Mean	8.97	11.3	5.44	6.36	7.95
Range	0-90	0-90	0-90	0-90	0-90
Fagerström Test for Nictoine Dependence Scorea					
N	122	129	124	129	120
Mean	5.47	5.43	5.58	5.35	5.77

11.4.2.1.3 Dosing Information

The table below from Pfizer's final study report illustrates exposure duration and compliance with medication across treatment groups. Groups were similar with respect to mean duration of exposure.

	0.5 mg b.i.d. Non-titrated N = 124	0.5 mg b.i.d. Titrated N = 129	1.0 mg b.i.d. Non-titrated N = 124	1.0 mg b.i.d. titrated N = 129	Placebo N = 121
Duration (Days)					
≤1	0	1	0	1	1
2-7	6	2	5	2	3
8-14	5	5	6	5	12
15-28	7	16	8	15	19
29-60	13	16	15	22	16
61-90	93	87	88	83	69
≥91	0	2	2	1	1
Median duration (days)	84.0	83.0	83.0	82.0	80.0
Range (days)	3-90	1-91	2-96	1-99	1-91

11.4.2.1.4 Protocol Violations

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as a few subjects, distributed across treatment groups, who used nicotine replacement therapy. Several subjects also took less than 14 days of study medication within the first 21 days of the study. These subjects were excluded from the "evaluable" population as defined by Pfizer.

11.4.3 Efficacy Results

11.4.3.1 Abstinence Rates

11.4.3.1.1 Sponsor's Analysis

The table below (from Dr. Buenconsejo's Tables 27 and 28) shows the results calculated by Pfizer for the major efficacy outcomes analyzed

Four-Week Abstinence, Study A3051007

	Varenicline				
	0.5 mg b.i.d. Nontitrated	0.5 mg b.i.d. Titrated	1.0 mg b.i.d. Nontitrated	1.0 mg b.i.d. Titrated	Placebo
Abstinence Weeks 4-7					
ITT Subjects	N=124	N=129	N=124	N=129	N=121
Abstinent (%)	48 (39%)	46 (36%)	50 (40%)	52 (40%)	14 (12%)
Odds ratio (95% CI) vs. placebo	5.0 (2.6, 9.9)	4.6 (2.3, 8.8)	5.5 (2.8, 10.8)	5.6 (2.8, 10.9)	
p-value vs. placebo	<0.0001	<0.0001	<0.0001	<0.0001	
Evaluable	N=113	N=118	N=114	N=121	N=104
Abstinent (%)	47 (42%)	44 (37%)	50 (44%)	52 (43%)	14 (13%)
Odds ratio (95% CI) vs. placebo	4.6 (2.3, 9.1)	3.9 (2.0, 7.8)	5.2 (2.6, 10.3)	5.0 (2.5, 9.9)	
p-value vs. placebo	<0.0001	0.0001	<0.0001	<0.0001	
Abstinence Weeks 9-12					
ITT Subjects	N=124	N=129	N=124	N=129	N=121
Abstinent (%)	61 (49%)	53 (41%)	57 (46%)	71 (55%)	15 (12%)
Odds ratio (95% CI) vs. placebo	7.2 (3.7, 13.8)	5.2 (2.7, 9.9)	6.4 (3.3, 12.4)	9.6 (5.0, 18.4)	
p-value vs. placebo	<0.0001	<0.0001	<0.0001	<0.0001	
Evaluable	N=113	N=118	N=114	N=121	N=104
Abstinent (%)	60 (53%)	52 (44%)	57 (50%)	71 (59%)	15 (14%)
Odds ratio (95% CI) vs. placebo	6.9 (3.5, 13.5)	4.9 (2.5, 9.5)	6.1 (3.1, 12.0)	9.1 (4.6, 17.8)	
p-value vs. placebo	<0.0001	<0.0001	<0.0001	<0.0001	

Results of the analyses for the Completer population support the robustness of the results for the All Subjects and Evaluable Subjects analysis. Other data presentations included seven-day "point prevalence" abstinence rates and presentations of mean number of cigarettes smoked per day. These are not presented here because the Division's position has been that seven days of abstinence is too brief to confer any meaningful health benefit or to predict longer-term abstinence; therefore this analysis, although popular with academic researchers, is of little regulatory significance. In addition, smoking reductions short of abstinence are not regarded as a validated surrogate for health benefit, and therefore this data is also not discussed here.

11.4.3.1.2 Reviewer's Analysis

Pfizer's results were audited by Dr. Joan Buenconsejo, Statistical Reviewer, who confirmed Pfizer's conclusions that all four dosing regimens of varenicline were superior to both placebo with respect to helping smokers achieve abstinence. In addition, Dr. Buenconsejo conducted, at the clinical team's request, several additional analyses using different definitions of treatment success, as discussed in the review of Study A3051036, above. Her analysis is shown in the table below. In this analysis, the titrated and non-titrated arms were combined for each dose level. Similar findings were evident when the groups were examined separately.

Study A3051007 Four-Week Abstinence

	Weeks 4 – 7			Weeks 9 – 12		
	Varenicline			Varenicline		
	0.5 mg b.i.d.	1.0 mg b.i.d.	Placebo	0.5 mg b.i.d.	1.0 mg b.i.d.	Placebo
ITT Subjects	N=253	N=253	N=121	N=253	N=253	N=121
Abstinent (%)	94 (37%)	102 (40%)	14 (12%)	114 (45%)	128 (51%)	15 (12%)
Odds ratio (95% CI) vs. placebo	4.7 (2.5, 8.8)	5.5 (3.0, 10.3)		6.1 (3.3, 11.1)	7.8 (4.3, 14.3)	
p-value vs. placebo	<0.0001	<0.0001		<0.0001	<0.0001	
Evaluable	N=231	N=235	N=104	N=231	N=235	N=104
Abstinent (%)	91 (39%)	102 (43%)	14 (13%)	112 (49%)	128 (54%)	15 (14%)
Odds ratio (95% CI) vs. placebo	4.2 (2.3, 8.0)	5.1 (2.7, 9.6)		5.8 (3.1, 10.7)	7.5 (4.1, 13.9)	
p-value vs. placebo	<0.0001	<0.0001		<0.0001	<0.0001	
Completer	N=169	N=162	N=66	N=169	N=162	N=66
Abstinent (%)	84 (50%)	82 (51%)	12 (18%)	105 (62%)	108 (67%)	14 (21%)
Odds ratio (95% CI) vs. placebo	4.6 (2.3, 9.4)	4.8 (2.3, 9.7)		6.8 (3.4, 13.5)	7.9 (3.9, 15.9)	
p-value vs. placebo	<0.0001	<0.0001		<0.0001	<0.0001	

Additionally, Dr. Buenconsejo calculated rates of continuous abstinence from the end of a various grace periods following the TQD through the end of treatment and found that varenicline was superior to placebo no matter what grace period was applied. These results are illustrated below in Dr. Buenconsejo's Table 29.

	Varenicline 0.5 mg b.i.d. N=253	Varenicline 1.0 mg b.i.d. N=253	Placebo N=121
Week 3 – 12	81 (32%)	83 (33%)	11 (9%)
Week 4 – 12	84 (33%)	96 (38%)	12 (10%)
Week 5 – 12	90 (36%)	108 (43%)	13 (11%)
Week 6 – 12	97 (38%)	115 (45%)	13 (11%)
Week 7 – 12	100 (40%)	117 (46%)	14 (12%)
Week 8 – 12	107 (42%)	123 (49%)	15 (12%)
Week 9 – 12 *	114 (45%)	128 (51%)	15 (12%)

Pfizer enrolled study completers into a non-treatment follow-up protocol designated Study A3051018 to determine the long-term abstinence rates among study participants. These data show that after 12 weeks of treatment, more subjects who are treated with varenicline remain abstinent 40 weeks later than subjects who are treated with placebo. However, the relapse rate across groups did not support the idea that a course of treatment with varenicline necessarily renders a successful quitter less vulnerable to relapse than smokers who quit without varenicline.

The rate of continuous abstinence from Week 9 through various timepoints is shown below in Dr. Buenconsejo's Table 30.

Continuous Abstinence from Week 9

	Varenicline 0.5 mg b.i.d. N=253	Varenicline 1.0 mg b.i.d. N=253	Placebo N=121
Double-Blind Treatment Phase			
Week 12	114 (45%)	128 (51%)	15 (12%)
Non-Treatment Follow-up Phase			
Week 13	94 (37%)	112 (44%)	9 (7%)
Week 16	86 (34%)	102 (40%)	9 (7%)
Week 20	74 (29%)	88 (35%)	9 (7%)
Week 24	61 (24%)	75 (30%)	7 (6%)
Week 28	60 (24%)	73 (29%)	7 (6%)
Week 32	58 (23%)	71 (28%)	7 (6%)
Week 36	58 (23%)	68 (27%)	7 (6%)
Week 40	55 (22%)	67 (26%)	6 (5%)
Week 44	53 (21%)	65 (26%)	5 (4%)
Week 48	53 (21%)	64 (25%)	5 (4%)
Week 52	48 (19%)	58 (23%)	5 (4%)

11.4.3.2 Subjective Measures

11.4.3.2.1 Minnesota Nicotine Withdrawal Scale (MNWS)

According to Pfizer,

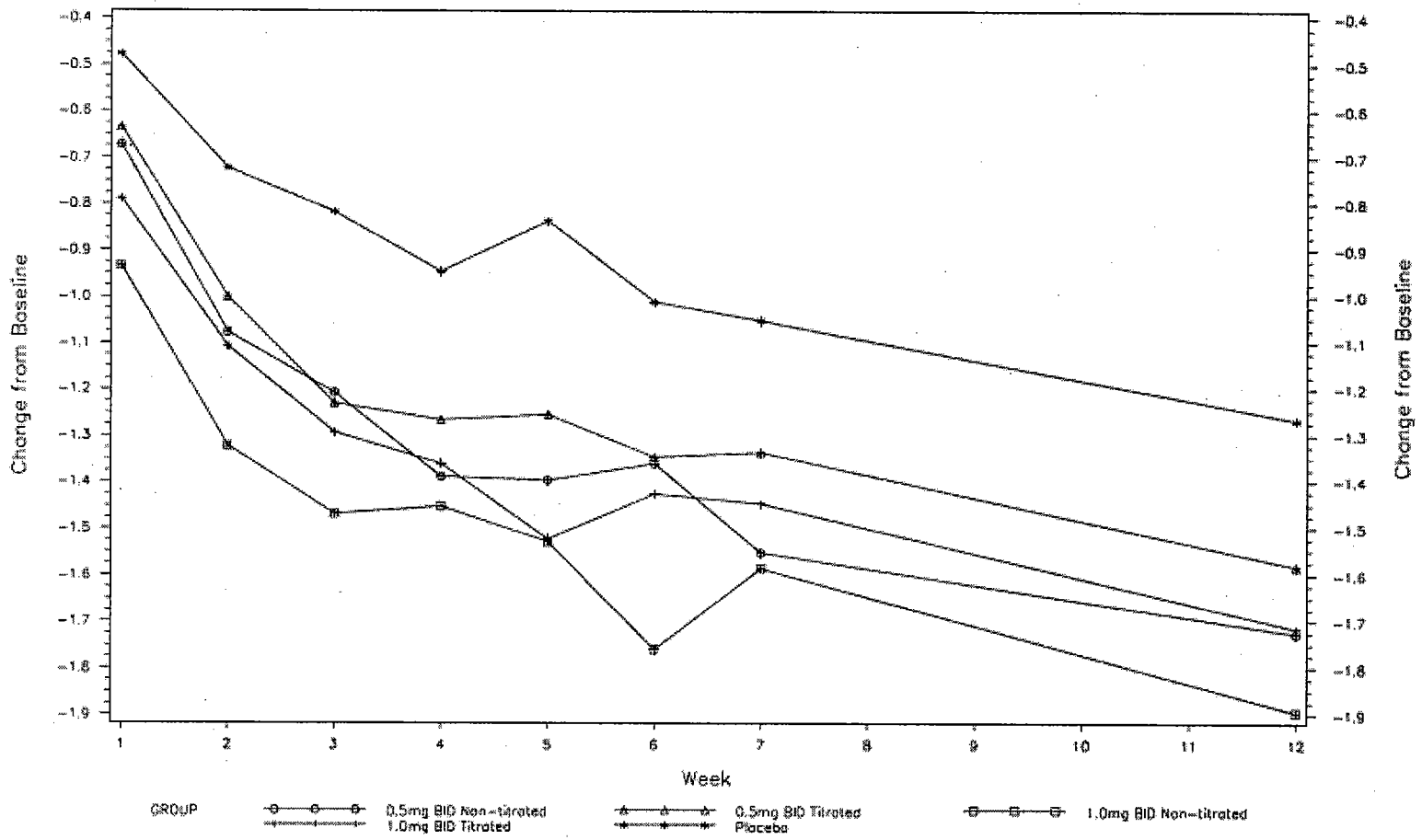
> The composite score for withdrawal effects (sum of Items 2-9) showed that, in general, symptoms of withdrawal in all treatment groups (including placebo) were mild (mean increase from baseline ≤3.0); and this was true for the All Subjects population as well as for the subset of Cessators. No clear treatment effects on composite score change from baseline were seen.

Inspection of data reveals numerically small and inconsistent differences between varenicline and placebo on some measures, with differences in both directions (i.e., placebo better on some measures/timepoints). Therefore, a claim regarding relief of withdrawal is not supported by this data.

11.4.3.2.2 Craving

Pfizer identified an effect of varenicline on the "urge to smoke" question on the MNWS. The figure below shows the mean change from baseline on this measure over the weeks of the study. These results are consistent with other findings involving this subscore of the MNWS and suggest an effect on "urge to smoke." As noted above, this is regarded as a more accurate description of the concept affected, as opposed to the Applicant's proposed term, "craving."

Appears This Way
On Original


Change from Baseline
Week
GROUP
0.5mg BID Non-titrated
1.0mg BID Titrated
0.5mg BID Titrated
Placebo
1.0mg BID Non-titrated

11.4.3.2.3 Smoking Satisfaction

The Smoking Effects Inventory (SEI) was administered only to those subjects who reported smoking since the previous visit. Pfizer concluded that:

> At the...Week 1 visit, [varenicline] was statistically superior to placebo on the Psychological Reward subscale for the 1.0 mg b.i.d. nontitrated treatment group; no other significant treatment differences were found. After Week 1, [varenicline] was more effective than placebo in reducing smoking satisfaction, psychological reward, and enjoyment of respiratory tract sensations. Significant differences from placebo were seen on these subscales for all [varenicline] treatment groups, with the most consistent effects at Weeks 2, 3, 4, and 7 for the Satisfaction and Psychological Reward subscales and at Weeks 3, 4, and 7 for the Enjoyment subscale.

However, Dr. Scott observed that the measures of the reinforcing effects of smoking captured all the relevant aspects of smoking reinforcement. She concluded that "reinforcing effects of smoking" is not a clearly-defined concept suitable for labeling.

11.4.3.2.3.1 Analysis by Subgroups

The table below from Dr. Buenconsejo's review shows the effect of varenicline to be consistent across demographic subgroups.

Weeks 9 – 12 CQR by Age, Gender, Race, and Baseline Smoking Characteristics

	Varenicline 0.5 mg b.i.d. % (n/N)	OR (95% CI) p-value	Varenicline 1.0 mg b.i.d. % (n/N)	OR (95% CI) p-value	Placebo % (n/N)
Overall	45 (114/253)	6.1 (3.3, 11.1)	51 (128/253)	7.8 (4.3, 14.3)	12 (15/121)
Gender					
Male	44 (54/123)	4.1 (1.9, 8.8)	50 (62/125)	5.3 (2.5, 11.4)	17 (11/64)
Female	46 (60/130)	12.3 (4.1, 36.7)	52 (66/128)	17.2 (5.7, 51.6)	7 (4/57)
Age					
<45 years	44 (55/126)	6.2 (2.7, 14.5)	45 (61/135)	6.3 (2.7, 14.4)	12 (8/65)
>= 45 years	46 (59/127)	6.2 (2.6, 14.9)	57 (67/118)	10.4 (4.2, 25.4)	13 (7/56)
Race					
White	45 (95/210)	8.2 (3.8, 17.4)	51 (107/210)	10.7 (5.0, 22.8)	10 (9/86)
Black	43 (13/30)	3.4 (0.9, 13.3)	44 (14/32)	3.7 (1.0, 14.6)	17 (4/24)
Others	46 (6/13)	2.6 (0.3, 22.3)	64 (7/11)	4.4 (0.5, 38.3)	18 (2/11)
Fagerstrom Score					
0 – 3	60 (24/40)	15.9 (3.0, 83.7)	52 (25/48)	10.6 (2.1, 54.2)	10 (2/21)
4 – 6	43 (57/133)	4.0 (1.7, 9.4)	60 (70/116)	8.1 (3.4, 19.3)	17 (8/48)
7 – 10	41 (32/78)	7.0 (2.4, 20.1)	37 (33/89)	7.0 (2.4, 20.3)	10 (5/51)
Average No. of Cigarettes/day, past month					
10 - <20	56 (43/77)	9.6 (2.9, 31.3)	51 (44/86)	8.6 (2.6, 27.9)	11 (4/35)
20 - <30	45 (56/125)	5.1 (2.3, 11.0)	54 (65/120)	6.9 (3.2, 14.9)	14 (10/69)
>= 30	29 (15/51)	9.3 (1.1, 79.9)	40 (19/47)	17.3 (2.0, 151.4)	6 (1/17)

11.4.3.2.3.2 Analysis by Center
See table above, in section on Enrollment by Center

11.4.3.3 Conclusions Regarding Efficacy Data in Study
This study provides evidence that varenicline at either 0.5 mg b.i.d. or 1 mg b.i.d. is superior to placebo in helping smokers achieve abstinence. The efficacy of 1 mg b.i.d. is only slightly higher than that of 0.5 mg b.i.d., suggesting that it is not necessary to recommend a 1 mg b.i.d. dose (as proposed by Pfizer) as the only dosing option. Dose titration does not appear to have an effect on efficacy. As noted below, a number of dose-related adverse events should be considered in determining the recommended dose.

11.4.3.4 Safety Results: Common AEs
Although dose titration at the initiation of treatment did not reduce the likelihood of premature treatment discontinuation due to adverse events, Pfizer observed that the rate of nausea was reduced when initial dose titration was employed. Based on this observation, a titrated scheme was used in subsequent studies including the Phase 3 program. However, examination of the common AE tables from this study suggests that few specific AEs were affected by the presence or absence of titration for the 1 mg b.i.d. dose (increased appetite and diarrhea are other examples of AEs seen more frequently in the non-titrated groups than the same-dose titrated groups). A clearer effect of titration is seen with the 0.5 mg b.i.d arms. However, dose-dependency of several adverse events is apparent when comparing the two titrated regimens to one another or the two non-titrated regimens, as shown in the table below from Pfizer's final study report. This table employs COSTART, not MedDRA, coding, and shows treatment-emergent adverse events occurring in ≥5% of any varenicline treatment group and at a higher frequency in any varenicline treatment group than with placebo. It is arranged by decreasing frequency among all subjects taking 1.0 mg b.i.d. varenicline. Comparisons of particular interest, showing a higher incidence of certain events in the 1 mg b.i.d., titrated arm compared to the 0.5 mg b.i.d., titrated arm are bolded and italicized below (my emphasis):

Most Frequent Treatment Emergent Adverse Events [Number (%) of Subjects]

COSTART Preferred Term	CP-526,555				Placebo
	0.5 mg b.i.d. nontitrated N = 124	0.5 mg b.i.d. titrated N = 129	1.0 mg b.i.d. nontitrated N = 124	1.0 mg b.i.d. titrated N = 129	N = 121
Nausea	28 (22.6)	***21 (16.3)***	52 (41.9)	***45 (34.9)***	18 (14.9)
Insomnia	42 (33.9)	***27 (20.9)***	27 (21.8)	***48 (37.2)***	14 (11.6)
Headache	34 (27.4)	25 (19.4)	30 (24.2)	29 (22.5)	21 (17.4)
Abnormal dreams	21 (16.9)	***15 (11.6)***	21 (16.9)	***25 (19.4)***	6 (5.0)
Taste perversion	20 (16.1)	***10 (7.8)***	17 (13.7)	***15 (11.6)***	5 (4.1)
Dyspepsia	11 (8.9)	***8 (6.2)***	12 (9.7)	***19 (14.7)***	9 (7.4)
Flatulence	19 (15.3)	11 (8.5)	14 (11.3)	13 (10.1)	7 (5.8)
Constipation	8 (6.5)	***6 (4.7)***	13 (10.5)	***14 (10.9)***	3 (2.5)
Somnolence	7 (5.6)	***7 (5.4)***	13 (10.5)	***12 (9.3)***	2 (1.7)
Thinking abnormal	8 (6.5)	8 (6.2)	11 (8.9)	11 (8.5)	5 (4.1)
Vomiting	4 (3.2)	***1 (0.8)***	8 (6.5)	***12 (9.3)***	3 (2.5)
Increased appetite	10 (8.1)	***5 (3.9)***	11 (8.9)	***8 (6.2)***	2 (1.7)
Asthenia	6 (4.8)	***5 (3.9)***	7 (5.6)	***10 (7.8)***	7 (5.8)
Diarrhea	7 (5.6)	***2 (1.6)***	11 (8.9)	***6 (4.7)***	7 (5.8)
Accidental injury	10 (8.1)	11 (8.5)	7 (5.6)	8 (6.2)	5 (4.1)
Back pain	6 (4.8)	8 (6.2)	10 (8.1)	4 (3.1)	8 (6.6)
Rash	5 (4.0)	***2 (1.6)***	3 (2.4)	***8 (6.2)***	3 (2.5)
Pharyngitis	10 (8.1)	7 (5.4)	7 (5.6)	4 (3.1)	4 (3.3)
Pain	8 (6.5)	5 (3.9)	6 (4.8)	4 (3.1)	5 (4.1)
Myalgia	7 (5.6)	5 (3.9)	2 (1.6)	5 (3.9)	3 (2.5)
Menstrual disorder	4 (5.7)	0	0	1 (1.5)	2 (3.5)

11.5 Appendix 5: Protocol A3051016

A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating The Safety And Efficacy Of a Flexible Dosing Strategy For CP-526,555 (0.5 to 2.0 mg total daily dose) in Smoking Cessation

Conducted December 26 2001 – September 18 2002

11.5.1 Protocol

11.5.1.1 Objective/Rationale

The purpose of this Phase 2 study provide information regarding the efficacy and safety of the nicotine partial agonist CP-526,555 [varenicline] for the treatment of nicotine dependence.

11.5.1.2 Overall Design

The study design was a 12-week, parallel-group, double-blind, randomized, multicenter study comparing a flexible dosing strategy for varenicline with placebo in smoking cessation. The dose of varenicline was to be titrated over 1 week to 0.5 mg b.i.d.. After the first week, subjects were able to adjust their total daily dose within the range of 0.5 mg to 2.0 mg. Following completion of the 12 week study, subjects were to continue in a non-treatment extension protocol administratively designated Study A3051019.

11.5.1.3 Population and Procedures

11.5.1.3.1 Inclusion/Exclusion Criteria

Planned enrollment was approximately 300 subjects randomized 1:1 to varenicline or placebo at approximately six sites.

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

- Male or female cigarette smokers between the ages of 18 and 65 years, inclusive.
- For female subjects of childbearing potential, medically acceptable contraception
- Smoking an average of at least ten cigarettes per day during the past year, with no period of abstinence greater than three months in the past year.
- Able to be outpatients and be assessed in a clinic setting.
- In good health, as determined by a detailed medical history, full physical examination (including vital signs), 12-lead electrocardiogram, and clinical laboratory tests.
- Body mass index (BMI) no less than 15 and no greater than 38, weight at least 100 pounds.

Subjects were to be excluded for:

- Pregnancy/nursing
- Concomitant treatment with another investigational drug within one month of study enrollment or plans to take another investigational drug within thirty days of study completion.

- Previously randomization in a study that has included CP-526,555.
- Currently or within the past twelve months requiring treatment for depression.
- Past or present history of panic disorder, psychosis, or bipolar disorder.
- Intent to donate blood or blood components while receiving experimental drug or within 1 month of the completion of the study.
- Requirement to use other medications during the study that might interfere with the evaluation of the study drug
- Evidence or history of clinically significant allergic (except for seasonal allergies at time of dosing), endocrine, gastrointestinal, hematological, hepatic, neurologic, psychiatric, pulmonary, or renal disease or a history of cancer (excluding treated basal cell carcinoma and squamous cell carcinoma).
- Screening or baseline alkaline phosphatase, SGOT, SGPT, or bilirubin greater than 110% of the upper limit of normal.
- History of clinically significant cardiovascular disease or a clinically significant abnormal electrocardiogram at screening or baseline.
- Screening or baseline systolic blood pressure greater than 160 mm Hg or a diastolic blood pressure greater than 95 mm Hg
- History of drug (except nicotine) or alcohol abuse or dependence within the past 12 months.
- History of significant drug allergies (such as resulting in difficulty breathing) or clinically significant rash due to a medication.
- Any condition possibly affecting drug absorption.
- Use of a nicotine replacement product or bupropion within the previous three months.
- Regular use of tobacco products other than cigarettes, including pipe tobacco, cigars, snuff, and chew, or marijuana use within the past month or not agreeing to abstain from use of these products during study participation.
- Current household member participating or who previously participated in this clinical study.

All use of concomitant medications required review by the Pfizer clinical monitor prior to and during enrollment in the study with the following exceptions:

Episodic Use Permitted: over-the-counter medications (excluding kava kava and St. John's Wort)
Chronic Use Permitted: hormone replacement therapy, lipid-lowering agents, multivitamins

11.5.1.3.2 Procedures

The protocol called for an initial screening visit, during which medical screening procedures were undertaken. A subsequent "baseline" visit was to occur 3 days – 3 weeks after the screening visit, which would be cancelled if results of laboratory tests did not confirm eligibility. At the time of screening, subjects were to select a target quit date (TQD) to coincide with the Week 1 visit, although subjects were permitted to quit before the Week 1 visit if they so chose.

At the baseline visit, assessments as illustrated in the time-and-events table below were to be performed. The subjects were to be randomized to treatment according to a randomization list provided by Pfizer to the investigators, and provided with study medication. An educational booklet on smoking cessation ("Clearing the Air: How to Quit Smoking...and Quit for Keeps" – National Cancer Institute Publication 95-1647) was to be provided to each subject along with up to ten minutes of counseling. Subjects were also to be provided with a paper diary as well as instructions on its use. Entries were to be made into the Smoking Diary by subjects each evening, collecting information on the number of cigarettes smoked that day and times of dosing for the two days prior to the week 1, week 2, week 4 and week 12 or early termination visits. A day will be defined for subjects as beginning and ending at midnight and smoking will include even a puff of a cigarette. Subjects were to return for weekly visits to the clinic after the baseline visit over the following twelve weeks.

11.5.1.3.2.1 Dosing
Eligible subjects were to be randomized to treatment varenicline or placebo.

The active treatment group was to take varenicline, 0.5 mg QD for 3 days, followed by 0.5 mg b.i.d. for 4 days. After day 7, if subjects developed adverse effects or if they wanted to try a lower dosage, they could decrease their dose to a minimum of 0.5 mg QD (taken either morning or evening). If subjects were not responding sufficiently or if they wanted to try a higher dosage, they could increase their dose to a maximum of 1.0 mg b.i.d.. Total daily dose could range from 0.5 to 2.0 mg. Subjects were permitted to adjust their dosage as often as they wished. Total treatment time was to be 12 weeks.

The placebo group received the same dosing instructions as the active treatment group.

Varenicline 0.5 mg and matching placebo were to be dispensed to subjects at each visit.

Subjects were to receive the following written instructions:

> Take each pill from the proper box on the blister card. The boxes are marked by day and by "A.M." or "P.M." Leave any unused pills on the blister card. Bring the blister card to your next appointment.
>
> It is recommended that all study pills be taken after eating and with a glass (8 oz.) of water.
>
> For the first 3 days, take 1 pill in the evening. For the next 4 days, take 1 pill in the morning and 1 in the evening.
>
> *After the first 7 days*:
> If you feel you are getting unpleasant effects from the medication or if you want to try a lower dose, you may reduce the dosage so long as you take at least 1 pill a day (morning or evening).

If you feel the pills are not working well enough or if you want to try a higher dose, you may increase your dosage up to a maximum of 2 pills in the morning and 2 pills in the evening (total 4 pills a day).

11.5.1.3.2.2 Schedule of Visits and Assessments

Subjects were to return for weekly visits to the clinic after the baseline visit over the following 12 weeks. The subjects were instructed to attempt to quit on the target quit date at the Week 1 visit (8 days after the baseline visit). The quit attempt was to occur in the morning prior to the clinic visit that day, so that the subject's last cigarette prior to the quit attempt would be before midnight the night prior to the Week 1 visit. Subjects were to be called 3 days after the target quit date (TQD+3) to be reminded of study participation and to receive support for the smoking cessation attempt. These contacts were to be no longer than 5 minutes and counseling was to follow AHCPR guidelines.

At each visit, subjects were to be asked about cigarette and other nicotine use since the last study visit and the Smoking Diary was to be collected and reviewed. The site staff was to instruct the subject to record smoking from the day of the visit on the new diary provided. End-expiratory exhaled carbon monoxide was to be measured. All concomitant medications and any adverse events were to be recorded. Other subjective effects and safety measures were undertaken as per the time-and-events schedule below.

The treatment phase was to end after 12 weeks of subject participation. During the Week 12 visit, or at early termination, subjects were to be asked about cigarette and other nicotine use since the last visit and the Smoking Diary for the previous week was to be collected and reviewed. End-expiratory exhaled carbon monoxide will be measured and up to 10 minutes of brief counseling regarding smoking cessation will be provided. Safety assessments and subjective measures were to be obtained. Subjects were also to be asked if they would recommend the treatment to a friend.

Following completion of the Week 12 visit, subjects were to continue in the nontreatment extension protocol, designated Study A3051019.

Nontreatment Follow-up (Weeks 13 through 52)

Subjects were to return for visits to the clinic at Week 13, Week 24, and and Week 52. At each visit, subjects were to be asked to report whether they had smoked any cigarettes or used any other nicotine-containing products since the last contact or in the last 7 days and to report the number of days on which they had smoked any cigarettes since the last contact. End-expiratory exhaled carbon monoxide was to be measured at each clinic visit (nonsmoking status would be considered confirmed with a measurement $\leq$ 10 ppm). Vital signs and weight were to be measured at each clinic visit. Concomitant medications used as an aid to smoking cessation were to be recorded. At the Week 52 (or early termination) visit, subjects were to have blood drawn for the measurement of C-reactive protein.

The MNWS (past week) was to be self-administered at the Week 13 visit, with answers based on symptoms over the prior week (Appendix I). The Smoking Cessation Quality of

Life Questionnaire was to be self-administered by subjects at Week 24 and Week 52 (or early termination).

The sites were to provide up to 10 minutes of brief counseling regarding smoking cessation, in accordance with the Agency for Health Care Policy and Research (AHCPR) guidelines ("Smoking Cessation: Quick Reference Guide for Smoking Cessation Specialists") Subjects also were expected to continued to use the educational booklet on smoking cessation provided to them in Study A3051007. Additionally, the protocol specified that subjects would receive a telephone call at Weeks 16, 20, 28, 32, 36, 40, 44 and 48 during which they would be asked about cigarette use and the use of other nicotine-containing products and any concomitant medications used as aids to smoking cessation.

11.5.1.3.2.3 Behavioral treatment

Subjects were to be given an educational booklet on smoking cessation to review ("Clearing the Air: How to Quit Smoking...and Quit for Keeps" – National Cancer Institute Publication 95-1647) and provided up to ten minutes of counseling, in accordance with AHCPR guidelines.

The following time-and-events table illustrates the planned schedule of assessments:

Appears This Way
On Original

Procedure	Screen	BL	Wk 1	TQD + 3	Wk 2	Wk 3	Wk 4[a]	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	ET
Physical Examination[b]	X														X	X
Vital Signs (HR, BP), weight	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Temperature		X														
Height	X															
Adverse Events		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dosing Record			X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Fagerström Test	X															
Minnesota Nic. Withdrawal Scale		X	X		X	X	X	X	X	X					X	X
Smoking Effects Inventory[c]		X	X		X	X	X	X	X	X						X
Smoking Cessation QOL Quest.		X													X	X
Electrocardiogram	X	X[d]	X				X[e]								X	X
Serum Pregnancy Test	X	X					X			X					X	X
Blood Chemistry	X	X	X		X		X			X					X	X
CBC	X	X	X		X		X			X					X	X
Reference serum sample		X														
C-reactive protein		X								X					X	X
Serum cotinine	X															
Plasma CP-526,555		X	X[f]		X[fg]		X[f]								X[f]	X
Genotyping Sample[h]		X														
Urinalysis (dipstick)	X	X	X		X		X			X					X	X
Urine drug screen[i]	X															
Exhaled Carbon Monoxide		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Counseling (AHCPR)		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Brief telephone contact (AHCPR)				X												
Treatment Recommend. Question															X	X

[a]week 4 visit should be in the morning [b]may also be completed at baseline visit

[c]also completed daily between baseline and week 1; completed after week 1 visit if subject has smoked since previous visit; to be completed at Early Termination visits only if they are on or before week 7 and subject has smoked since previous visit
[d]at baseline, 3 ECG tracings should be done with a 1 to 5 minute interval between successive tracings
[e]week 4 ECG should be completed before blood drawing
[f]subjects should record in their diary time of doses for 2 days prior to these visits
[g]for subjects with week 2 visit in morning, hold dose of study medication until after sample is drawn
[h]optional
[i]may be completed at visits in addition to screening at discretion of investigator
BL=baseline; ET=early termination

Study A3051018

Procedure	Week 13[a]	Weeks 16, 20	Week 24	Weeks 28, 32, 36, 40, 44, and 48	Week 52
Nicotine Use Questionnaire	X[b]	X[c]	X[b]	X[c]	X[b]
Weight, BP, HR	X		X		X
Exhaled CO	X		X		X
MNWS	X				
Smoking Cessation QOL Questionnaire			X		X
Counseling (AHCPR)	X		X		X

[a]all visit names refer to weeks following the baseline visit for protocol A3051016;
[b]administered during clinic visit;
[c]administered during telephone contact

11.5.1.4 Evaluations/Endpoints

The primary efficacy measure was the CO-confirmed 4-week continuous quit rate (CQR) for Weeks 9 through 12 and Weeks 4 through 7 of treatment. The 4-week CQRs were defined as the proportion of subjects abstaining from smoking during the specified 4-week periods. For this parameter, subjects were considered to be responders (ie, abstinent) since the prior clinic visit if they:

- Responded "no" to the question, "Has the subject smoked any cigarettes (even a puff) *since the last study visit*?"; ***and***
- Responded "no" to the question, "Has the subject used any other nicotinecontaining products...*since the last study visit*?"; ***and***
- Had an exhaled carbon monoxide measurement of ≤10 ppm.

If any carbon monoxide level in the continuous quit rate window is >10 ppm, the subject would be considered a smoker. In the event of a self-report of abstinence and a missing carbon monoxide measurement, a subject would be considered abstinent only if the self-report was preceded and followed by a carbon monoxide confirmed self-report of abstinence.

The primary analysis set specified was all subjects who took at least one dose of randomized study medication and had an evaluation. Subjects who discontinue are assumed to be smokers for the remainder of the study. In responder rates, those subjects will be represented in the denominator but not in the numerator, regardless of their last diary entry.

Secondary endpoints identified in the protocol included:

- continuous cessation from the target quit date
- number of cigarettes smoked during the study
- one week point-prevalence of smoking cessation
- change from baseline in weight
- changes in the Minnesota Nicotine Withdrawal Scale and the Smoking Effects Inventory.

For all these endpoints, the planned analysis was an Observed Cases (OC) approach at each time point.

11.5.1.5 Statistical Plan

In order to preserve the family-wise error rate, alpha=0.05, a step-down procedure was pre-specified for the analysis of the primary endpoints. The hierarchy of comparisons was as follows: 1) week 9 to 12 continuous quit rate, CP-526,555 versus placebo, and 2) week 4 to 7 continuous quit rate, CP-526,555 versus placebo. In order to conclude statistical superiority of CP-526,555 versus placebo for both continuous quit rate windows, both comparisons 1 and 2 would need to attain statistical significance (alpha=0.05). If only comparison 1 attained statistical significance, then the conclusion would be that CP-526,555 is significantly different from placebo only for the week 9 to 12 continuous quit rate. If comparison 1 was not statistically significant (regardless of the p-value of

comparison 2), then the conclusion would be that CP-526,555 is not statistically significant from placebo for either endpoint

11.5.2 Results

11.5.2.1 Study Conduct/Outcome
11.5.2.2 Investigators/Locations
Enrollment by center was not reported. The following investigators/centers were listed in the study protocol.

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11.5.2.2.1 Subject Characteristics

Of 434 subjects screened, 320 subjects were selected for enrollment. Eight subjects did not initiate treatment, therefore the treated population comprised 312 subjects with 157 in the varenicline arm and 155 in the placebo arm.

11.5.2.2.1.1 Subject Disposition

Subject Disposition is shown in the table below, from Pfizer's final study report.

	Varenicline	Placebo
Number Screened = 434		
Assigned to Treatment	160	160
Treated[a]	157	155
Completed Study	122 (77.7)	110 (71.0)
Discontinued Study	35 (22.3)	45 (29.0)
Discontinuations by Reason:		
Adverse events[b]	7 (4.5)	2 (1.3)
Lack of efficacy	0 (0.0)	7 (4.5)
Subject defaulted[c]	24 (15.3)	34 (21.9)
Other[d]	4 (2.5)	2 (1.3)

[a] Percentages based on number of subjects treated
[b] Includes laboratory abnormalities
[c] Subject defaulted = subject withdrew consent or was lost to follow-up.
[d] "Other" includes protocol violations and non-compliance.

Subjects could discontinue study medication but remain in the study. Therefore, in the context of subject disposition, "completed the study" refers to the number of subjects who participated in the study for the full 12 weeks, whether or not they completed 12 weeks of dosing during the treatment phase.

The table below, from Pfizer's final study report, illustrates the distribution of reasons for subjects prematurely discontinuing study *medication* because of adverse events.

Discontinuations from Treatment with Study Drug [Number (%) of Subjects]

	Varenicline	Placebo
	N = 157	N = 155
All discontinuations	48 (30.6)	53 (34.2)
Adverse events[a]	11 (7.0)	7 (4.5)
Lack of efficacy	0 (0.0)	7 (4.5)
Subject defaulted[b]	23 (14.6)	33 (21.3)
Other[c]	14 (8.9)	6 (3.9)

[a] Includes laboratory abnormalities considered adverse events.
[b]Subject defaulted = subject withdrew consent or was lost to follow-up.
[c] "Other" includes the following: protocol violations and non-compliance.

During the 12-week treatment phase, across both treatment groups, the most frequent reason for withdrawal was "subject defaulted," i.e. loss to follow-up, refusal to participate further. From an efficacy standpoint, treatment failure is imputed to subjects not completing the study, including those lost to follow-up and those discontinuing due to refusal to participate. There are more subjects this category in the placebo arm; this could represent a potential bias. However, relapse to smoking after treatment discontinuation is generally considered to be the rule, rather than the exception, and it seems reasonable to impute treatment failure to these subjects. Adverse events were the reason for premature *treatment* discontinuation in 7% of the varenicline group and 5% of the placebo group. Additionally, 19 (12%) of the varenicline group and 4 (3%) of the placebo group required temporary treatment discontinuation or dose reduction due to adverse events.

11.5.2.2.2 Demographics

The table below illustrates demographic and baseline characteristics of the five treatment groups. Overall, 91% of the subjects were white, 48% of the subjects were female (47-57% across groups), and the average age was approximately 42 years (range 18-65 years). Smoking history was similar across treatment groups, with subjects representing a population of smokers who on average had smoked for the previous 25 years (range 1-51 years) and had smoked an average of 20 cigarettes per day over the previous month. More than half of the subjects in each treatment group had made at least 3 prior attempts to quit smoking. Approximately 61% of subjects had attempted to quit without any pharmacologic aid and 54% had used transdermal nicotine. About 25% (23% of varenicline group and 28% of placebo group) had tried Zyban.

Subject Demographics, Study A3051016

Sex [n (%)]	Varenicline	Placebo
Male	79 (50.3)	83 (53.5)
Female	78 (49.7)	72 (46.5)
Age (years)		
Mean (SD)	41.5 (11.3)	42.1 (11.7)
Range	19-65	18-65
Race [n (%)]		
White	146 (93.0)	137 (88.4)
Black	8 (5.1)	14 (9.0)
Asian	3 (1.9)	0
Hispanic	0	3 (1.9)
Other	0	1 (0.6)
Fagerström Scorea		
N	157	153
Mean	5.40	5.35
Number of years subject smoked		
Mean	24.9	25.7
Range	4-50	2-46
Average number of cigarettes per day		
Mean	19.9	20.6
Range	5-45	10-40
Number of lifetime serious quit attempts (any method) [n (%)]		
None	17 (10.8)	19 (12.3)
1	21 (13.4)	21 (13.5)
2	23 (14.7)	23 (14.8)
3 or more	96 (61.1)	92 (59.4)
Longest period of abstinence in past year		
Mean	8.38	8.59
Range	0-90	0-90

11.5.2.2.3

11.5.2.2.4 Dosing Information

The median duration of study drug treatment was 83 days for both CP-526,555 and placebo treatment. In the following table (from Pfizer's final study report), which summarizes the modal daily doses over the 12 weeks of treatment, placebo dosing is expressed in mg equivalents based on the number of tablets taken. The mean modal dose for all 12 weeks of treatment was 1.35 mg/day for active treatment and 1.63 mg/day for placebo treatment.

Modal Daily Dose (mg or mg Equivalents) by Week

	Varenicline			Placebo		
	N	Mean	Range	N	Mean	Range
Week 1	157	0.89	0.50-1.00	155	0.89	0.50-1.00
Week 2	153	1.65	0.50-2.00	149	1.73	0.00-2.00
Week 3	148	1.55	0.50-2.00	137	1.76	0.00-2.00
Week 4	145	1.46	0.00-2.00	131	1.73	0.00-2.00
Week 5	136	1.50	0.00-2.00	124	1.72	0.50-2.00
Week 6	132	1.40	0.00-2.00	119	1.73	0.50-2.00
Week 7	130	1.37	0.00-2.00	118	1.77	0.50-2.00
Week 8	128	1.32	0.00-2.00	114	1.70	0.50-2.00
Week 9	125	1.30	0.00-2.00	110	1.66	0.00-2.00
Week 10	121	1.23	0.00-2.00	108	1.63	0.00-2.00
Week 11	118	1.18	0.00-2.00	107	1.59	0.00-2.00
Week 12	112	1.18	0.50-2.00	103	1.60	0.00-2.00
All Weeks	157	1.35	0.00-2.00	155	1.63	0.00-2.00
Duration of dosing						
Median (days)			83.0			83.0
Range (days)			5-92			1-90

In the CP-526,555 treatment group, the mean modal dose generally decreased from Week 2 to Week 12, with the mean modal dose slightly greater than 1.0 mg/day for the last 7 weeks. For the placebo treatment group, the mean modal dose remained above 1.5 mg/day from Week 2 onward. The number of subjects with a given modal dose (0.5, 1.0, 1.5, or 2.0 mg) by week is summarized in the table below. This table shows that 62% of subjects titrated to the maximum allowable dose during week two (titration above 1 mg/day was not permitted until after day 7, per directions provided), but few subjects chose to remain at that dose. A substantial number of subjects appear to have achieved either satisfactory results or maximum tolerability at lower doses. Adverse events accounted for premature study drug discontinuation in 7% of subjects on active treatment; therefore the gradual decline in the number of subjects using the 2 mg/day dose (from a maximum of 62% in week 2 to minimum of 29% in week 12) cannot be entirely attributed to dropout for tolerability reasons. Indeed, 12% of the varenicline group (vs. 3% of the placebo group) required dose reduction or temporary discontinuation due to adverse events; this suggests some tapering due to tolerability issues partially explains the declining use of the 2 mg/day dose. In the placebo group, a larger proportion of subjects titrated to the maximum allowable dose and the use of this dose was relatively steady over the study. As with most titration-to-effect studies, the

most treatment-resistant patients and those who do not experience efficacy at lower doses (due to placebo treatment) cluster at the higher doses.

Number of Subjects with Modal Daily Dose by Week

Week	(Days)	CP-526,555 0.5 mg	CP-526,555 1.0 mg	CP-526,555 1.5 mg	CP-526,555 2.0 mg	Placebo* 0.5 mg	Placebo* 1.0 mg	Placebo* 1.5 mg	Placebo* 2.0 mg
1	(1 - 7)	33 (21.02)	124 (78.98)	0 (0.00)	0 (0.00)	34 (21.94)	121 (78.06)	0 (0.00)	0 (0.00)
2	(8 - 14)	7 (4.55)	36 (23.38)	14 (9.09)	96 (62.34)	5 (3.38)	22 (14.86)	8 (5.41)	111 (75.00)
3	(15 - 21)	11 (7.43)	45 (30.41)	9 (6.08)	83 (56.08)	3 (2.19)	24 (17.52)	6 (4.38)	103 (75.18)
4	(22 - 28)	12 (8.45)	47 (33.10)	10 (7.04)	72 (50.70)	4 (3.10)	22 (17.05)	7 (5.43)	96 (74.42)
5	(29 - 35)	13 (9.63)	41 (30.37)	7 (5.19)	73 (54.07)	5 (4.03)	24 (19.35)	6 (4.84)	89 (71.77)
6	(36 - 42)	25 (19.08)	36 (27.48)	8 (6.11)	62 (47.33)	8 (6.72)	17 (14.29)	6 (5.04)	88 (73.95)
7	(43 - 49)	25 (19.53)	35 (27.34)	12 (9.38)	56 (43.75)	7 (5.93)	14 (11.86)	6 (5.08)	91 (77.12)
8	(50 - 56)	25 (20.00)	37 (29.60)	12 (9.60)	51 (40.80)	7 (6.14)	22 (19.30)	4 (3.51)	81 (71.05)
9	(57 - 63)	29 (23.58)	36 (29.27)	7 (5.69)	51 (41.46)	7 (6.48)	20 (18.52)	5 (4.63)	76 (70.37)
10	(64 - 70)	31 (25.62)	40 (33.06)	9 (7.44)	40 (33.06)	8 (7.62)	20 (19.05)	4 (3.81)	73 (69.52)
11	(71 - 77)	36 (30.77)	37 (31.62)	8 (6.84)	36 (30.77)	9 (8.65)	22 (21.15)	4 (3.85)	69 (66.35)
12	(78 - 84)	33 (29.46)	39 (34.82)	7 (6.25)	33 (29.46)	8 (7.92)	24 (23.76)	3 (2.97)	66 (65.35)
All Weeks		32 (20.51)	49 (31.41)	6 (3.85)	69 (44.23)	13 (8.44)	34 (22.08)	3 (1.95)	104 (67.53)

*mg equivalence to CP-526,555 as calculated by the number of pills taken multiplied by 0.5
Source Data: Section 13, Table 2.11 Date of Reporting Dataset Creation: 29SEP2003 Date of Table Generation: 06OCT2003 (11:24)

11.5.2.2.5 Protocol Violations

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as a few subjects, distributed across treatment groups, who used nicotine replacement therapy. Several subjects also took less than 14 days of study medication within the first 21 days of the study. These subjects were excluded from the "evaluable" population as defined by Pfizer.

11.5.3 Efficacy Results

11.5.3.1 Abstinence Rates

11.5.3.1.1 Sponsor's Analysis

The table below (from Dr. Buenconsejo's Table 31) shows the results calculated by Pfizer for the major efficacy outcomes analyzed

Four-Week Continuous Quit Rate (Study 16)

	Weeks 4 – 7		Weeks 9 – 12	
	Varenicline	Placebo	Varenicline	Placebo
ITT Subjects	N=157	N=155	N=157	N=155
Abstinent (%)	60 (38%)	18 (12%)	63 (40%)	18 (15%)
p-value vs. placebo		<0.0001		<0.0001
Evaluable	N=145	N=138	N=145	N=138
Abstinent (%)	59 (41%)	18 (13%)	62 (43%)	18 (13%)
p-value vs. placebo		<0.0001		<0.0001

Results of the analyses for the Completer population support the robustness of the results for the All Subjects and Evaluable Subjects analysis. Other data presentations included seven-day "point prevalence" abstinence rates and presentations of mean number of cigarettes smoked per day. These are not presented here because the Division's position has been that seven days of abstinence is too brief to confer any meaningful health benefit or to predict longer-term abstinence; therefore this analysis, although popular with academic researchers, is of little regulatory significance. In addition, smoking reductions short of abstinence are not regarded as a validated surrogate for health benefit, and therefore this data is also not discussed here.

11.5.3.1.2 Reviewer's Analysis

Pfizer's results were audited by Dr. Joan Buenconsejo, Statistical Reviewer, who confirmed Pfizer's conclusions that the flexible-dosing regimen of varenicline was superior to placebo with respect to helping smokers achieve abstinence.

Additionally, Dr. Buenconsejo calculated rates of continuous abstinence from the end of a various grace periods following the TQD through the end of treatment and found that varenicline was superior to placebo no matter what grace period was applied. These results are illustrated below in Dr. Buenconsejo's Table 32.

Continuous Abstinence Rate from Weeks 3 through Timepoints – Number (%) of Subjects

	Varenicline N=157	Placebo N=155
Week 3 – 12	45 (29%)	14 (9%)
Week 4 – 12	48 (31%)	16 (10%)
Week 5 – 12	51 (32%)	16 (10%)
Week 6 – 12	56 (36%)	16 (10%)
Week 7 – 12	59 (38%)	17 (11%)
Week 8 – 12	61 (39%)	17 (11%)
Week 9 – 12 *	63 (40%)	18 (12%)

Pfizer enrolled study completers into a non-treatment follow-up protocol designated Study A3051019 to determine the long-term abstinence rates among study participants. These data show that after 12 weeks of treatment, more subjects who are treated with varenicline remain abstinent 40 weeks later than subjects who are treated with placebo. However, the relapse rate across groups did not support the idea that a course of treatment with varenicline necessarily renders a successful quitter less vulnerable to relapse than smokers who quit without varenicline.

The rate of continuous abstinence from Week 9 through various timepoints is shown below in Dr. Buenconsejo's Table 33.

Continuous Abstinence Rate from Week 9 Through Each Timepoints

	Varenicline N=157	Placebo N=155
Double-Blind Treatment Phase		
Week 12	63 (40%)	18 (12%)
Non-Treatment Follow-up Phase		
Week 13	56 (36%)	17 (11%)
Week 16	52 (33%)	16 (10%)
Week 20	50 (32%)	16 (10%)
Week 24	44 (28%)	14 (9%)
Week 28	44 (28%)	13 (8%)
Week 32	41 (26%)	12 (8%)
Week 36	40 (26%)	12 (8%)
Week 40	39 (25%)	12 (8%)
Week 44	39 (25%)	12 (8%)
Week 48	38 (24%)	12 (8%)
Week 52	35 (22%)	12 (8%)

11.5.3.2 Subjective Measures

11.5.3.2.1 Minnesota Nicotine Withdrawal Scale (MNWS)

According to Pfizer,

> Among Cessators, CP-526,555 was significantly superior to placebo in treating symptoms of withdrawal from smoking at every weekly timepoint from Week 2 through Week 5. By Week 7, withdrawal symptoms scores among placebo-treated subjects had decreased to low levels (increase from baseline <4). At most timepoints, reduction in the craving score (Item 1) from baseline was numerically greater among Cessators treated with CP-526,555 than among those treated with placebo, although the differences were statistically significant only at Week 3.

Inspection of data reveals that, in the population of "cessators" (i.e., abstinent subjects), the MNWS scores are lower in varenicline-treated than in placebo-treated subjects. This population is appropriate to examine because withdrawal is unlikely in ongoing smokers.

11.5.3.2.2 Craving

Pfizer reported that on Item 1 (urge to smoke) on the MNWS varenicline reduced scores significantly more than placebo at every weekly timepoint assessed (Weeks 1 through 7, and Week 12) ($p \leq 0.0075$).

11.5.3.2.3 Smoking Satisfaction

The Smoking Effects Inventory (SEI) was administered only to those subjects who reported smoking since the previous visit. Pfizer concluded that:

> At the ...Week 1 visit, there were no significant treatment differences for any of the SEI subscales. Starting at Week 2, Satisfaction subscale scores showed CP-526,555 was more effective than placebo in reducing the satisfying effects of smoking ($p<0.05$ at Weeks 2, 3, 4, and 5). In addition, based on scores for the Craving subscale, CP-526,555 reduced craving to a greater extent than did placebo. This finding was consistent for all weeks from Week 2 through Week 7, although treatment differences were not statistically significant.

These inconsistent effects on different subscales do not support a conclusion of an effect on smoking satisfaction. Moreover, Dr. Scott observed that the measures of the reinforcing effects of smoking captured all the relevant aspects of smoking reinforcement. She concluded that "reinforcing effects of smoking" is not a clearly-defined concept suitable for labeling.

11.5.3.2.3.1 Analysis by Subgroups

The table below from Dr. Buenconsejo's review shows the effect of varenicline to be consistent across demographic subgroups.

Weeks 9 – 12 CQR by Age, Gender, Race, and Baseline Smoking Characteristics – Study 16

	Varenicline % (n/N)	Placebo % (n/N)	OR (95% CI)
Overall	40 (63/157)	15 (18/155)	5.7 (3.1, 10.4)
Gender			
Male	43 (34/79)	14 (12/83)	5.5 (2.4, 12.5)
Female	37 (29/78)	8 (6/72)	6.7 (2.5, 17.9)
Age			
<45 years	40 (36/90)	15 (12/81)	4.0 (1.9, 8.6)
>= 45 years	40 (27/67)	8 (6/74)	9.9 (3.4, 28.4)
Race			
White	42 (61/146)	11 (15/137)	6.7 (3.5, 12.9)
Black	13 (1/8)	7 (1/14)	1.3
Others	33 (1/3)	50 (2/4)	-
Fagerstrom Score			
0 – 3	43 (12/28)	19 (6/31)	4.8 (1.2, 18.6)
4 – 6	42 (33/78)	14 (11/76)	4.9 (2.2, 11.2)
7 – 10	35 (18/51)	2 (1/46)	28.3 (3.2, 254.2)
Average No. of Cigarettes/day, past month			
10 - <20	35 (19/55)	14 (7/50)	3.7 (1.3, 10.1)
20 - <30	38 (30/78)	9 (7/79)	7.1 (2.8, 18.4)
>= 30	58 (14/24)	15 (4/26)	-

11.5.3.2.3.2 Analysis by Center

Not reported.

11.5.3.3 Conclusions Regarding Efficacy Data in Study

This study provides evidence that varenicline in a flexible dosing regimen titrated to tolerability and effect between 0.5 mg/day and 2 mg/day is superior to placebo in helping smokers achieve abstinence. Successful quitters chose a range of doses, indicating that doses lower than 2 mg/day are sufficient for many patients.

11.5.3.4 Safety Results: Common AEs

The table below (from Pfizer's study report), which uses COSTART rather than MedDRA terminology, lists the treatment-emergent adverse events occurring in at least 3% of either treatment group, arranged by decreasing frequency in the varenicline arm.

Most Frequent Adverse Events [Number (%) of Subjects]

COSTART Preferred Term	CP-526,555 N = 157	Placebo N = 155
Insomnia	34 (21.7)	17 (11.0)
Headache	25 (15.9)	20 (12.9)
Respiratory Tract Infection	25 (15.9)	15 (9.7)
Nausea	21 (13.4)	8 (5.2)
Asthenia	11 (7.0)	7 (4.5)
Dyspepsia	10 (6.4)	3 (1.9)
Accidental Injury	9 (5.7)	3 (1.9)
Irritability	8 (5.1)	6 (3.9)
Flu Syndrome	8 (5.1)	7 (4.5)
Thinking Abnormal	8 (5.1)	6 (3.9)
Pharyngitis	8 (5.1)	2 (1.3)
Abdominal Pain	7 (4.5)	6 (3.9)
Constipation	7 (4.5)	3 (1.9)
Abnormal Dreams	7 (4.5)	7 (4.5)
Rash	7 (4.5)	3 (1.9)
Back Pain	6 (3.8)	6 (3.9)
Chest Pain	6 (3.8)	3 (1.9)
Pain	5 (3.2)	5 (3.2)
Weight Gain	5 (3.2)	5 (3.2)
Anxiety	5 (3.2)	6 (3.9)
Depression	5 (3.2)	4 (2.6)
Taste Perversion	5 (3.2)	5 (3.2)
Urinary Tract Infection	5 (3.2)	2 (1.3)
Dizziness	4 (2.5)	8 (5.2)
Sinusitis	2 (1.3)	6 (3.9)
Diarrhea	2 (1.3)	5 (3.2)

11.6 Appendix 6: Protocol A30510002

A Seven-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating The Safety And Efficacy Of Three Doses of CP-526,555 (0.3 mg QD, 1 mg QD and 1 mg b.i.d.) in Comparison with Zyban in Smoking Cessation

Conducted February 21 2000 – January 3 2002

11.6.1 Protocol

Note that this study was the initial Phase 2 exploratory efficacy study. It was not reviewed in-depth but the design and results are presented below for completeness' sake because it contributes to the overall assessment of efficacy.

11.6.1.1 Objective/Rationale

The purpose of this Phase 2 study was to measure the safety and efficacy of three dose regimens of varenicline for smoking cessation in a population of healthy smokers.

11.6.1.2 Overall Design

The study design was a 12-week, parallel-group, double-blind, randomized, multicenter, placebo- and active-controlled study. The study comprised a 7-week treatment phase, followed by a nontreatment phase that was to continue through 52 weeks from the baseline visit. Subjects were randomized to treatment with one of three varenicline dose regimens (0.3 mg QD, 1.0 mg QD, or 1.0 mg b.i.d.); to Zyban(sustained-release bupropion, 150 mg b.i.d.); or to placebo. The varenicline dosages and regimens were selected on the basis of tolerability data from Phase 1 clinical studies which suggested that the maximum tolerated daily dosage is 2.0 mg/day, but that the incidence of nausea and vomiting is lower when that dosage is administered as two divided doses rather than as a single 2.0 mg dose. The regimen of Zyban selected (150 mg b.i.d., titrated according to the US Zyban label) is the recommended regimen and maximum dose for the marketed product. Duration of active treatment in this study was 7 weeks for Zyban, as this was the duration of treatment in two of the three pivotal clinical trials that provided substantial evidence of the efficacy of Zyban and led to its approval for marketing as a smoking cessation treatment. Dosing of CP-526,555 was limited to 6 weeks, this being the duration of dosing covered by preclinical toxicological data at this stage of clinical development. During the seventh week of dosing, subjects in the CP-526,555 dosage groups received blinded placebo.

11.6.1.3 Population and Procedures

11.6.1.3.1 Inclusion/Exclusion Criteria

Planned enrollment was approximately 625, with 125 subjects randomized to each of the five treatment arms at approximately six sites.

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

- Male or female cigarette smokers between the ages of 18 and 65 years, inclusive.
- For female subjects of childbearing potential, medically acceptable contraception
- Smoking an average of at least ten cigarettes per day during the past year, with no period of abstinence greater than three months in the past year.

- Able to be outpatients and be assessed in a clinic setting.
- In good health, as determined by a detailed medical history, full physical examination (including vital signs), 12-lead electrocardiogram, and clinical laboratory tests.
- Body mass index (BMI) no less than 15 and no greater than 35, weight at least 100 pounds.

Subjects were to be excluded for:

- Pregnancy/nursing
- Concomitant treatment with another investigational drug within one month of study enrollment or plans to take another investigational drug within thirty days of study completion.
- Previously randomization in a study that has included CP-526,555.
- Episode of major depression requiring treatment within the past year.
- Past or present history of panic disorder, psychosis, or bipolar disorder.
- Current or prior diagnosis of anorexia or bulimia
- Treatment with bupropion in past year
- History of seizures
- Intent to donate blood or blood components while receiving experimental drug or within 1 month of the completion of the study.
- Requirement to use other medications during the study that might interfere with the evaluation of the study drug
- Evidence or history of clinically significant allergic (except for seasonal allergies at time of dosing), endocrine, gastrointestinal, hematological, hepatic, neurologic, psychiatric, pulmonary, or renal disease or a history of cancer (excluding treated basal cell carcinoma and squamous cell carcinoma).
- Screening or baseline alkaline phosphatase, SGOT, SGPT, or bilirubin greater than the upper limit of normal.
- Any history of cardiovascular disease including myocardial infarction, significant arrhythmia, poorly-controlled hypertension, or PR interval $\geq$0.20 seconds.
- History of drug (except nicotine) or alcohol abuse or dependence within the past 12 months.
- History of significant drug allergies (such as resulting in difficulty breathing) or clinically significant rash due to a medication.
- Any condition possibly affecting drug absorption.
- Use of a nicotine replacement product within the previous three months.
- Regular (>3 x/week) use of tobacco products other than cigarettes, including pipe tobacco, cigars, snuff, and chew, or marijuana use within the past month or not agreeing to abstain from use of these products during study participation.
- Current household member participating or who previously participated in this clinical study.
- Prior allergic reaction to bupropion.
- Current use of bupropion
- Use of MAO-inhibitor in past 14 days

All use of concomitant medications required review by the Pfizer clinical monitor prior to and during enrollment in the study with the following exceptions:

Episodic Use Permitted: over-the-counter medications (excluding kava kava and St. John's Wort)
Chronic Use Permitted: hormone replacement therapy, lipid-lowering agents, multivitamins

11.6.1.3.2 Procedures

The protocol called for an initial screening visit, during which medical screening procedures were undertaken. A subsequent "baseline" visit was to occur 3 days – 3 weeks after the screening visit, which would be cancelled if results of laboratory tests did not confirm eligibility. At the time of screening, subjects were to select a target quit date (TQD) to coincide with the day after the Week 1 visit, which was to be at least 8 days after the baseline visit to allow for 7 days of treatment prior to the quit attempt.

At the baseline visit, assessments as illustrated in the time-and-events table below were to be performed. The subjects were to be randomized to treatment according to a randomization list provided by Pfizer to the investigators, and provided with study medication. An educational booklet on smoking cessation ("Clearing the Air: How to Quit Smoking...and Quit for Keeps" – National Cancer Institute Publication 95-1647) was to be provided to each subject along with up to ten minutes of counseling. Subjects were also to be provided with a paper diary as well as instructions on its use. Entries were to be made into the Smoking Diary by subjects each evening, collecting information on the number of cigarettes smoked that day and times of dosing for the two days prior to the week 1, week 2, week 4 and week 12 or early termination visits. A day will be defined for subjects as beginning and ending at midnight and smoking will include even a puff of a cigarette.

Subjects were to take study medication for 1 week before attempting to quit smoking. This stipulation was in keeping with product labeling for Zyban, which recommended that subjects set a "target quit date" in the second week of dosing, since approximately 1 week of treatment is required to achieve steady-state blood levels of bupropion.

The subjects were also to be instructed that they were permitted to make efforts to quit during the time period between the start of treatment and the target quit date. The protocol called for the subjects to be informed "You will be taking one of three different types of treatment during this study. The possibilities include either one of three dose levels of the study medication CP-526,555, or placebo, or Zyban. Previous information about one of the treatments suggests that it may work better if you continue to smoke for the first week of treatment, allowing the drug concentration to accumulate. Your target quit date is the date you choose to stop smoking. However, you are permitted to quit as soon as you wish after starting treatment."

The study then required weekly clinic visits over the next 7 weeks, followed by a period of non-treatment follow-up.

11.6.1.3.2.1 Dosing
Subjects were randomized to treatment with:

Varenicline (0.3 mg QD, 1.0 mg QD, or 1.0 mg b.i.d.)
Zyban (150 mg b.i.d.)
or
Placebo b.i.d.
Duration of treatment was 6 weeks for varenicline (plus one week of matching placebo) and 7 weeks for Zyban and placebo.

Study medication was to be dispensed to subjects weekly in two separate blister-pack cards, one containing varenicline and/or its matching placebos, and one containing Zyban or its matching placebos. The Zyban tablets were purchased commercially and blinded by removal of tablet markings (deinking) with an ethanol soaked cloth. Results from dissolution testing showed that the deinking process does not affect the performance of the blinded Zyban tablets. The medication cards for varenicline were kept in refrigerated storage (2-8° C/36-46° F) at the study sites, while the Zyban cards were stored at room temperature (20-25° C/68-77° F). The site marked the varenicline cards with "AM" over the first two columns of tablets and "PM" over the third column. Subject instructions were to store the medications at room temperature, to take the doses morning and evening (at least 8 hours apart) with 240 mL of water, and it was recommended that subjects eat prior to dosing. Treatment was to begin on the day after the baseline visit. Subjects were to take a total of 4 tablets per day for the first three days of the dosing period as follows: in the morning, the first two blinded CP-526,555 tablets and the first blinded Zyban tablet on the dosing cards; and in the evening, the third blinded CP-526,555 tablet. Thereafter, dosing increased to five tablets per day, three in the morning (the first two blinded CP-526,555 tablets and the first blinded Zyban tablet) and two in the evening (the third blinded CP-526,555 tablet and the second blinded Zyban tablet), for the remainder of the study.

11.6.1.3.2.2 Schedule of Visits and Assessments
Subjects were to attend weekly clinic visits at which efficacy assessments included smoking diary collection and oral self-reporting (yes, no) of smoking since the last visit and smoking during the past 7 days, accompanied by quantification of exhaled carbon monoxide (CO). Other measures of efficacy included 4 self-administered rating scales [Minnesota Nicotine Withdrawal Scale (MNWS); Smoking Effects Inventory (SEI); Brief Questionnaire of Smoking Urges (QSU-Brief); and Smoking Cessation Quality of Life (SCQoL)]. Body weight was also assessed. Safety assessments included adverse events, clinical laboratory values, vital signs, and ECGs.

After completing the 7-week treatment phase, subjects were to be followed in the nontreatment phase. During this phase, they were to attend clinic visits at Week 12, Week 24, and Week 52, and also were followed by phone contact every 4 weeks. At each

contact, subjects were questioned about their use of cigarettes or other tobacco products over the past week and since the last study contact. They were also asked whether they had taken any medications for smoking cessation (NRT, Zyban, or antidepressants) since the last contact. At the clinic visits, vital signs and exhaled CO were also assessed, and the Smoking-Related Quality of Life questionnaire was administered.

Nontreatment Follow-up (Weeks 13 through 52)
Subjects were to return for visits to the clinic at Week 13, Week 24, and and Week 52. At each visit, subjects were to be asked to report whether they had smoked any cigarettes or used any other nicotine-containing products since the last contact or in the last 7 days and to report the number of days on which they had smoked any cigarettes since the last contact. End-expiratory exhaled carbon monoxide was to be measured at each clinic visit (nonsmoking status would be considered confirmed with a measurement $\leq$ 10 ppm). Vital signs and weight were to be measured at each clinic visit. Concomitant medications used as an aid to smoking cessation were to be recorded. At the Week 52 (or early termination) visit, subjects were to have blood drawn for the measurement of C-reactive protein.

The MNWS (past week) was to be self-administered at the Week 13 visit, with answers based on symptoms over the prior week (Appendix I). The Smoking Cessation Quality of Life Questionnaire was to be self-administered by subjects at Week 24 and Week 52 (or early termination).

The sites were to provide up to 10 minutes of brief counseling regarding smoking cessation, in accordance with the Agency for Health Care Policy and Research (AHCPR) guidelines ("Smoking Cessation: Quick Reference Guide for Smoking Cessation Specialists") Subjects also were expected to continued to use the educational booklet on smoking cessation provided to them in Study A3051007. Additionally, the protocol specified that subjects would receive a telephone call at Weeks 16, 20, 28, 32, 36, 40, 44 and 48 during which they would be asked about cigarette use and the use of other nicotine-containing products and any concomitant medications used as aids to smoking cessation.

11.6.1.3.2.3 Behavioral treatment
Subjects were to be given an educational booklet on smoking cessation to review ("Clearing the Air: How to Quit Smoking...and Quit for Keeps" – National Cancer Institute Publication 95-1647) and provided up to ten minutes of counseling, in accordance with AHCPR guidelines, at each visit.

11.6.1.4 Evaluations/Endpoints
The protocol-specified primary endpoint for the study was to evaluate the potential superiority of varenicline versus placebo on the Four-Week Continuous Quit Rate (CQR). This was defined as 28 days of continuous cessation and would be classified as a response during any timeframe within the seven weeks of treatment assignment to the varenicline, Zyban, and placebo groups. For example, a subject who fully abstained from smoking beginning on day 5 and maintained that abstinence through day 32, with a resumption of smoking on day 33, would be considered a cessator, having achieved 28

full days of smoking cessation. This measure was to be obtained through weekly reports from the subjects of their daily cigarette use confirmed by a review of their Smoking Diary entries and a measurement of an exhaled carbon monoxide concentration that is ≤10 ppm.

Secondary measures identified in the protocol included:

- a fixed Four-Week CQR measured from weeks four through seven (inclusive), as in previous Zyban studies.
- a fixed Four-Week CQR from week three through six (inclusive)
- distribution of time to the onset of the Four-Week CQR
- the number of cigarettes smoked during the study
- the duration of continuous cessation among responders
- change from baseline in weight
- changes in the Minnesota Nicotine Withdrawal Scale and the Smoking Effects Inventory.

For all these endpoints, analyses were to include the last visit (LOCF) analyses, Observed Cases (OC) analyses and LOCF analyses at each time point. Dunnett's test was to be used to compare each dose versus placebo. All significance tests were to be two-tailed using an overall level of significance of alpha=0.05.

11.6.2 Results

11.6.2.1 Study Conduct/Outcome

11.6.2.1.1 Investigators/Locations

Enrollment by center is illustrated in the table below:

Centre Number	Principal Investigators	Subinvestigators	Varenicline			Zyban	Placebo
			0.3 mg QD N=128	1 mg QD N=128	1 mg BID N=127	N=128	N=127
5005	Mitchell Nides, PhD Los Angeles Clinical Trials 2990 S. Sepulveda Blvd. Ste 308 Los Angeles, CA 90064		32	33	32	32	32
5007	Alexander Glassman, MD New York State Psychiatric Institute Clinical Psychopharmacology 1051 Riverside Drive Box 116 New York, NY 10032		15	15	16	16	15
5010	Cheryl Oncken, MD University of Connecticut Health Center Clinical Research and Evaluation Unit – MC2103 263 Farmington Avenue Farmington, CT 06030		21	21	20	22	22
5011	David Gonzales, PhD Oregon Health Sciences University 3181 SW Sam Jackson Park Road CR115 Portland, OR 97201		26	26	26	26	26

Centre Number	Principal Investigators	Subinvestigators	Varenicline			Zyban	Placebo
			0.3 mg QD N=128	1 mg QD N=128	1 mg BID N=127	N=128	N=127
5012	Stephen Rennard, MD University of Nebraska Medical Center Internal Medicine – Pulmonary Research 982465 Nebraska Medical Center Omaha, NE 66198-2465		14	15	14	14	14
5013	Elbert Glover, PhD WVU Clinical Research Center Health Sciences Center 1 Medical Center Drive P.O. Box 9300 Morgantown, WV 26506		13	12	12	12	12
5015	Sharon Allen, MD Tobacco Use Research Center 2701 University Avenue SE, Ste 201 Minneapolis, MN 55414		7	6	7	6	6

11.6.2.1.2 Subject Characteristics

Of 1023 subjects screened, 638 subjects were selected for enrollment. Twelve subjects did not initiate treatment, therefore the treated population comprised 626 subjects with 128 in the 0.3 mg arm, 128 in the 1 mg arm, 127 in the 1 mg b.i.d. arm, 128 in the Zyban arm, and 127 in the placebo arm.

11.6.2.1.2.1 Subject Disposition

Subject Disposition is shown in the table below, from Pfizer's final study report.

Number screened = 1023	0.3 mg QD	1.0 mg QD	1.0 mg b.i.d.	Zyban 150 b.i.d.	placebo
Assigned to treatment	128	128	127	128	127
Treateda	126	126	125	126	123
Completed study	65 (51.6)	77 (61.1)	77 (61.6)	68 (54.0)	66 (53.7)
Discontinued study	61 (48.4)	49 (38.9)	48 (38.4)	58 (46.0)	57 (46.3)
Discontinuations by reason:	7 (5.6)	6 (4.8)	6 (4.8)	9 (7.1)	5 (4.1)
Adverse eventsb					
Lack of efficacy	1 (0.8)	4 (3.2)	2 (1.6)	4 (3.2)	7 (5.7)
Subject defaultedc	41 (32.5)	31 (24.6)	31 (24.8)	38 (30.2)	33 (26.8)
Otherd	12 (9.5)	8 (6.3)	9 (7.2)	7 (5.6)	12 (9.8)

a Percentages based on number of subjects treated
bIncludes laboratory abnormalities
cSubject defaulted = subject withdrew consent or was lost to follow-up.
d"Other" includes protocol violations and non-compliance.

Subjects could discontinue study medication but remain in the study. Therefore, in the context of subject disposition, "completed the study" refers to the number of subjects who participated in the study for the full 12 weeks, whether or not they completed 12 weeks of dosing during the treatment phase. The table below, from Pfizer's final study report, illustrates the distribution of reasons for subjects prematurely discontinuing study *medication* because of adverse events.

	0.3 mg QD	1.0 mg QD	1.0 mg b.i.d.	Zyban 150 b.i.d.	Placebo
	N = 126	N = 126	N = 125	N = 126	N = 123
All discontinuations	40 (31.7)	37 (29.4)	39 (31.2)	36 (28.6)	41 (33.3)
Discontinuations by Reason					
Adverse events[a]	18 (14.3)	17 (13.5)	15 (12.0)	21[b] (16.7)	12 (9.8)
Lack of efficacy	1 (0.8)	2 (1.6)	2 (1.6)	2 (1.6)	3 (2.4)
Subject defaulted[c]	12 (9.5)	9 (7.1)	14 (11.2)	8 (6.3)	16 (13.0)
Otherd	9 (7.1)	9 (7.1)	8 (6.4)	5 (4.0)	10 (8.1)

a Includes laboratory abnormalities considered adverse events; includes both treatment-emergent and nontreatment-emergent adverse events.
b One subject discontinued due to a laboratory value abnormality that was not treatment-emergent. For this reason, this number (21) does not match the number of subjects discontinued study drug due to adverse events shown in Table 6.1.1 (20), as that table includes only discontinuations due to treatmentemergent
events.
c Subject defaulted = subject withdrew consent or was lost to follow-up.
d "Other" includes the following: protocol violations, subject did not meet entry criteria, noncompliance, and personal reasons.

During the 7-week treatment phase, across all treatment groups, the most frequent reason for withdrawal was "subject defaulted," i.e. loss to follow-up, refusal to participate further. From an efficacy standpoint, treatment failure is imputed to subjects not

completing the study, including those lost to follow-up and those discontinuing due to refusal to participate. Relapse to smoking after treatment discontinuation is generally considered to be the rule, rather than the exception, and it seems reasonable to impute treatment failure to these subjects. Adverse events were the reason for premature *treatment* discontinuation in 12-14% of the varenicline groups, 17% of the Zyban group, and 10% of the placebo group.

11.6.2.1.3 Demographics

The table below illustrates demographic and baseline characteristics of the five treatment groups. Approximately 87% of subjects were white, and the mean age was approximately 42 years (range 18-65 years). Subjects represented a population of smokers who on average had smoked about 20 cigarettes per day for an average of approximately 24 years. More than half of the subjects in each treatment group had made at least 3 prior attempts to quit smoking, and the frequency of prior Zyban use (one or more attempts) ranged from 13% to 21% across treatment groups.

	0.3 mg QD	1.0 mg QD	1.0 mg b.i.d.	Zyban 150 b.i.d.	Placebo
	N = 126	N = 126	N = 125	N = 126	N = 123
Sex [n (%)]					
Male	63 (50.0)	55 (43.7)	63 (50.4)	57 (45.2)	64 (52.0)
Female	63 (50.0)	71 (56.3)	62 (49.6)	69 (54.8)	59 (48.0)
Age (years)					
Mean (SD)	41.9 (10.6)	42.9 (10.5)	41.9 (9.8)	40.5 (10.8)	41.6 (10.4)
Range	18-63	20-65	20-65	18-63	19-64
Race [n (%)]					
White	111 (88.1)	111 (88.1)	107 (85.6)	105 (83.3)	108 (87.8)
Black	6 (4.8)	7 (5.6)	10 (8.0)	9 (7.1)	10 (8.1)
Asian	1 (0.8)	4 (3.2)	2 (1.6)	6 (4.8)	2 (1.6)
Hispanic	7 (5.6)	1 (0.8)	6 (4.8)	3 (2.4)	2 (1.6)
Other	1 (0.8)	3 (2.4)	0 (0.0)	3 (2.4)	1 (0.8)
Fagerström Scorea					
N	125	123	122	126	120
Mean	5.7	5.5	5.6	5.2	5.5
Number of years subject smoked					
Mean	24.6	25.4	23.4	23.4	23.9
Range	4-50	2-50	2-52	2-45	3-49
Average number of cigarettes per day					
Mean	20.3	20.1	18.9	19.5	21.5
Range	5-40	7-50	5-44	5-50	4-60
Number of lifetime serious quit attempts					
None	8 (6.3)	9 (7.1)	6 (4.8)	12 (9.5)	13 (10.6)
1	21 (16.7)	20 (15.9)	23 (18.4)	17 (13.5)	20 (16.3)
2	26 (20.6)	21 (16.7)	17 (13.6)	22 (17.5)	21 (17.1)
3 or more	71 (56.3)	76 (60.3)	79 (63.2)	75 (59.5)	69 (56.1)
Longest period of abstinence in past year (days)					
Mean	6.28	6.55	5.73	6.46	7.63
Range	0-90	0-60	0-90	0-90	0-90

11.6.2.1.4 Dosing Information

The median duration of study drug use was 41-42 in the varenicline groups and 47-48 in the placebo and Zyban groups due to the protocol-specified difference in treatment time.

11.6.2.1.5 Protocol Violations

Protocol violations two subjects (one in the varenicline 1 mg b.i.d. group and one in the Zyban group) who did not meet the minimum smoking level for enrollment. Several subjects, distributed across treatment groups, took less than 14 days of study medication within the first 21 days of the study. These subjects were excluded from the "evaluable" population as defined by Pfizer. Two subjects in the varenicline 1 mg b.i.d. group and one in the plaebo group used nicotine replacement during the study.

11.6.3 Efficacy Results

Only the Applicant's analysis is shown below. Dr. Buenconsejo did not audit and review this initial Phase 2 study. It is presented here because it provides supportive evidence for the 1 mg/day dose tested in Study A3051007, although the regimen differs.

11.6.3.1 Abstinence Rates

The protocol-specified analysis was a "floating" four-week quit rate. However, this particular analysis is not of interest as the Division does not consider subjects who relapse on-treatment to be treatment successes. Therefore, I will present Pfizer's secondary analyses, which used a fixed four-week window at the end of treatment. Two windows were analyzed because treatment ended for the varenicline-treated subjects one week earlier than the placebo-treated and Zyban-treated subjects. Varenicline-treated subjects were blindly switched to placebo for the final week of the study. Pfizer's report states:

> Results of analyses for the CO-confirmed 4-week fixed window CQR were similar to those for the primary parameter, with quit rates increasing with increasing dose (see table below). All 3 doses of CP-526,555 were statistically superior to placebo in both the Week 3-6 and Week 4-7 analyses (Dunnett's adjustment was not used in analyse of secondary efficacy criteria). Treatment differences from placebo were also significant for Zyban. At both timepoints, the 4-week fixed window CQRs for the 1 g b.i.d. P-526,555 treatment group were approximately 3 times that of placebo, whereas the Zyban response rates were approximately twice that of placebo.

Appears This Way
On Original

Subjects with CO-confirmed Abstinence Through Weeks 3-6 or Weeks 4-7

	Varenicline			Zyban	Placebo
	0.3 mg/day	1 mg/day	1 mg b.i.d.		
	N = 126	N = 126	N = 125	N = 126	N = 123
Weeks 3-6	28 (22%)	37 (29%)	45 (36%)	32 (25%)	15 (12%)
p-value vs placebo	.03335	.0007	<.0001	.0060	
Weeks 4-7	32 (25%)	39 (31%)	51 (41%)	36 (29%)	17 (14%)
	.0186	0.0009	<0.0001	0.0033	

Results of the analyses for the Evaluable Subjects and Completer populations were similar.

Post-treatment follow-up continued to week 52. As shown below, the number of subjects continuously abstinent from week 4 to weeks 12, 24, and 52 are shown below.

	Varenicline			Zyban	Placebo
	0.3 mg/day	1 mg/day	1 mg b.i.d.		
Abstinence From Week 4 to:	N = 126	N = 126	N = 125	N = 126	N = 123
Week 12	21 (17%)	20 (16%)	36 (29%)**	27 (21%)*	13 (11%)
Week 24	12 (10%)	13 (10%)	27 (22%)**	14 (11%)	10 (8%)
Week 52	10 (8%)	7 (6%)	21 (17%)**	8 (6%)	6 (5%)

*p<0.05 vs. placebo
**p<0.001 vs placebo

11.6.3.2 Subjective Measures

11.6.3.2.1 Minnesota Nicotine Withdrawal Scale (MNWS)

According to Pfizer, there were no clear treatment effects on composite score change from baseline.

11.6.3.2.2 Craving

Pfizer reported that on Item 1 (urge to smoke) on the MNWS, varenicline 1 mg b.i.d. reduced scores significantly more than placebo at every weekly timepoint assessed (Weeks 1 through 6). The 1 mg QD dose also reduced craving at most time points. Results on the QSU-Brief at Week 6 were consistent with the MNWS results.

11.6.3.2.3 Smoking Satisfaction

The Smoking Effects Inventory (SEI) was administered only to those subjects who reported smoking since the previous visit. Pfizer concluded that:

At the Week 1 primary timepoint, significant differences from placebo were observed

for the CP-526,555 1.0 mg b.i.d. treatment group on 3 subscales. CP-526,555 1.0 mg QD and 0.3 mg QD and Zyban showed no statistically significant differences from placebo for any of the 5 subscales at Week 1. On the daily assessments, completed during the first week of dosing, an effect on the Satisfaction subscale but not on other subscales was observed.

These inconsistent effects on different subscales do not support a conclusion of an effect on smoking satisfaction. Moreover, Dr. Scott observed that the measures of the reinforcing effects of smoking captured all the relevant aspects of smoking reinforcement. She concluded that "reinforcing effects of smoking" is not a clearly-defined concept suitable for labeling.

11.6.3.2.3.1 Analysis by Center
Not reported.

11.6.3.3 Conclusions Regarding Efficacy Data in Study
This study provides supportive evidence that varenicline at doses ranging from 0.3 mg/day to 2 mg day are superior to placebo in helping smokers achieve abstinence.

11.6.3.4 Safety Results: Common AEs
The table below (from Pfizer's study report), which uses COSTART rather than MedDRA terminology, lists the treatment-emergent adverse events occurring in at least 5% of either treatment group, arranged by decreasing frequency in the varenicline arm.

	Varenicline			Zyban	Placebo
	0.3 mg/day	1 mg/day	1 mg b.i.d.		
	N = 126	N = 126	N = 125	N = 126	N = 123
Nausea	22 (17.5)	47 (37.3)	65 (52.0)	27 (21.4)	23 (18.7)
Insomnia	25 (19.8)	34 (27.0)	44 (35.2)	57 (45.2)	27 (22.0)
Headache	34 (27.0)	34 (27.0)	30 (24.0)	38 (30.2)	33 (26.8)
Abnormal dreams	10 (7.9)	14 (11.1)	19 (15.2)	15 (11.9)	10 (8.1)
Taste perversion	11 (8.7)	18 (14.3)	19 (15.2)	14 (11.1)	9 (7.3)
Irritability	15 (11.9)	17 (13.5)	15 (12.0)	14 (11.1)	12 (9.8)
RTI	32 (25.4)	18 (14.3)	15 (12.0)	20 (15.9)	31 (25.2)
Asthenia	13 (10.3)	10 (7.9)	13 (10.4)	9 (7.1)	10 (8.1)
Dyspepsia	10 (7.9)	8 (6.3)	11 (8.8)	14 (11.1)	9 (7.3)
Somnolence	8 (6.3)	9 (7.1)	11 (8.8)	6 (4.8)	8 (6.5)
Flatulence	7 (5.6)	7 (5.6)	10 (8.0)	0 (0.0)	1 (0.8)
Increased appetite	18 (14.3)	13 (10.3)	10 (8.0)	9 (7.1)	7 (5.7)
Thinking abnormal	7 (5.6)	10 (7.9)	8 (6.4)	7 (5.6)	8 (6.5)
Abdominal pain	11 (8.7)	2 (1.6)	7 (5.6)	7 (5.6)	3 (2.4)
Constipation	8 (6.3)	8 (6.3)	7 (5.6)	17 (13.5)	5 (4.1)
Dry mouth	4 (3.2)	11 (8.7)	7 (5.6)	15 (11.9)	7 (5.7)
Pharyngititis	6 (4.8)	5 (4.0)	7 (5.6)	4 (3.2)	2 (1.6)
Flu syndrome	11 (8.7)	4 (3.2)	6 (4.8)	8 (6.3)	4 (3.3)
Agitation	10 (7.9)	5 (4.0)	5 (4.0)	6 (4.8)	2 (1.6)
Arthralgia	5 (4.0)	7 (5.6)	4 (3.2)	9 (7.1)	2 (1.6)
Depression	5 (4.0)	7 (5.6)	3 (2.4)	8 (6.3)	3 (2.4)
Diarrhea	3 (2.4)	7 (5.6)	3 (2.4)	2 (1.6)	4 (3.3)

11.7 Appendix 7: Subjective Endpoints

11.8 Minnesota Nicotine Withdrawal Scale- Self Report (MNWS-Self)

The MNWS was originally developed to assess the magnitude of signs and symptoms of nicotine withdrawal as defined in the DSM-III. It was designed for clinical research through a review of the literature including two earlier studies that established the relevance of these symptoms from a patient perspective. The instrument includes eight items that capture the impact of withdrawal symptoms (depressed mood, irritability, anxiety, concentration, restlessness, increased appetite, difficulty going to sleep, and difficulty staying asleep). A ninth item assesses craving by asking about "urge to smoke."

The MNWS includes questions on the urge to smoke (one item), irritability (one item), anxiety (one item), concentration (one item), restlessness (one item), appetite (one item), depressed mood (one item) and insomnia (two items) using a 5-point Likert scale where scores range from 0 (not at all) to 4 (extreme). This questionnaire was developed to be self-administered and refers to the 24-hour period that immediately precedes the administration of the scale.

Minnesota Nicotine Withdrawal Scale					
For each of the following, rate yourself on how you have been feeling over the past twenty-four hours. Mark the number that applies to you:					
	Not at all	Slight	Moderate	Quite a bit	Extreme
Urge to smoke Item 1	0	1	2	3	4
Depressed mood Item 2	0	1	2	3	4
Irritability, frustration, or anger Item 3	0	1	2	3	4
Anxiety Item 4	0	1	2	3	4
Difficulty concentrating Item 5	0	1	2	3	4
Restlessness Item 6	0	1	2	3	4
Increased appetite Item 7	0	1	2	3	4
Difficulty going to sleep Item 8	0	1	2	3	4
Difficulty staying asleep Item 9	0	1	2	3	4

11.9 Brief Questionnaire of Smoking Urges (QSU-Brief)

The Brief Questionnaire on Smoking Urges (QSU-Brief) was developed to assess smoking urge in adult smokers aged 18 or older. Pfizer indicates that this instrument was selected because it is a multi-item questionnaire that assesses the patient's immediate experience of craving (a term Pfizer uses somewhat interchangeably with "urge to smoke"). The QSU-Brief was based on standard development processes for multi-item assessments. It was derived from a longer questionnaire that was developed with patient input (the Questionnaire on Smoking Urges). The QSU was developed to provide a reliable measure of craving by measuring four theoretically important aspects of smoking urges: desire to smoke, anticipation of positive outcomes from smoking, anticipation of relief from nicotine withdrawal or from withdrawal associated negative affect, and intention to smoke. The QSU-Brief consists of 10 self-administered items covering several aspects of craving. Subjects' respond on a 7-point Likert scale (strongly disagree to strongly agree). This questionnaire asks patients to refer to their current urges at the time of questionnaire completion. This timeframe is more immediate than that of the MNWS and was chosen because cravings can vary significantly within short intervals.

Brief Questionnaire of Smoking Urges

Indicate the extent to which you agree or disagree with each of the following statements by mark number between **STRONGLY DISAGREE** (1) and **STRONGLY AGREE** (7). The closer you select a nu to one end or the other indicates the strength of your agreement or disagreement. Please complete item. We are interested in how you are thinking or feeling right now as you are filling out the questionna

1. I have a desire for a cigarette right now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

2. Nothing would be better than smoking a cigarette right now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

3. If it were possible, I probably would smoke now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

4. I could control things better right now if I could smoke.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

5. All I want right now is a cigarette.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

6. I have an urge for a cigarette.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

7. A cigarette would taste good now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

8. I would do almost anything for a cigarette now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

9. Smoking would make me less depressed.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

10. I am going to smoke as soon as possible.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

11.10 Modified Cigarette Evaluation Questionnaire (mCEQ, aka Smoking Effects Inventory)

This questionnaire is derived from the 11-item Cigarette Evaluation Questionnaire, which was developed from the recommendations presented in the 1988 Surgeon General's Report on nicotine addiction. The purpose of the Cigarette Evaluation Questionnaire is to evaluate the reinforcing effects of smoking. The original CEQ contained 11 items; a twelfth item was added in the varenicline development program to assess enjoyment from smoking. The 12-item instrument used within the varenicline development program has been referred to in documentation for the Phase 2/3 program as the Smoking Effects Inventory (SEI). However, the name of the 11-item scale in the literature has evolved over time to be the Cigarette Evaluation Questionnaire (CEQ). Therefore, in order to correspond with the usage of the parent CEQ already existing in the literature, Pfizer has begun referring to the 12-item instrument as the Modified Cigarette Evaluation Questionnaire (mCEQ) in documentation.

The Smoking Effects Inventory (SEI), also known as the modified Cigarette Effects Questionnaire (mCEQ) uses a 7-point rating scale with scores ranging from 1 (not at all) to 7 (extremely). It was administered to only those subjects who had smoked since the prior assessment, and it required subjects to refer to the last time they smoked

Smoking Effects Inventory

(also known as the Modified Cigarette Evaluation Questionnaire)

If you have smoked since your last visit (or last completed this form), please mark the number that best represents how smoking made you feel.

1. Was smoking satisfying?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

2. Did cigarettes taste good?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

3. Did you enjoy the sensations in your throat and chest?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

4. Did smoking calm you down?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

5. Did smoking make you feel more awake?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

6. Did smoking make you feel less irritable?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

7. Did smoking help you concentrate?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

8. Did smoking reduce your hunger for food?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

9. Did smoking make you dizzy?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

10. Did smoking make you nauseous?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

11. Did smoking immediately relieve your craving for a cigarette?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

12. Did you enjoy smoking?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

11.11 Appendix 8: MNWS post-discontinuation

Study A3051028

Table 20. MNWS – Weeks 12 and 13

	Varenicline			Placebo			Zyban		
	N	Mean*	(SE)	N	Mean	(SE)	N	Mean	(SE)
Week 12									
Urge to Smoke	256	0.70	(0.06)	218	1.25	(0.07)	224	1.05	(0.07)
Negative Affect	256	0.38	(0.04)	218	0.55	(0.04)	223	0.48	(0.04)
Restlessness	255	0.42	(0.04)	218	0.56	(0.05)	223	0.57	(0.06)
Increased Appetite	256	0.98	(0.07)	217	0.82	(0.07)	224	0.88	(0.07)
Insomnia	256	0.51	(0.05)	218	0.48	(0.05)	224	0.66	(0.06)
Week 13									
Urge to Smoke	244	0.76	(0.06)	206	1.34	(0.07)	216	1.07	(0.07)
Negative Affect	244	0.48	(0.04)	206	0.49	(0.04)	216	0.48	(0.05)
Restlessness	242	0.52	(0.05)	206	0.50	(0.05)	215	0.50	(0.05)
Increased Appetite	243	0.89	(0.06)	206	0.66	(0.06)	216	0.88	(0.07)
Insomnia	244	0.47	(0.04)	206	0.48	(0.05)	215	0.50	(0.05)

Source: Table 13.4.7.2
SE = standard error
*Higher scores indicate greater intensity of symptoms.

Study StudyA3051036

Table 21. MNWS – Weeks 12 and 13

	Varenicline			Placebo			Zyban		
	N	Mean*	(SE)	N	Mean	(SE)	N	Mean	(SE)
Week 12									
Urge to Smoke	258	0.78	(0.06)	221	1.36	(0.07)	238	0.99	(0.06)
Negative Affect	258	0.42	(0.04)	221	0.52	(0.04)	238	0.41	(0.04)
Restlessness	258	0.54	(0.05)	221	0.62	(0.05)	236	0.50	(0.05)
Increased Appetite	257	0.84	(0.06)	221	0.81	(0.06)	238	0.82	(0.07)
Insomnia	258	0.53	(0.04)	221	0.55	0.06	238	0.55	(0.05)
Week 13									
Urge to Smoke	249	0.99	(0.06)	209	1.30	(0.07)	231	1.08	(0.06)
Negative Affect	249	0.44	(0.04)	209	0.49	(0.04)	230	0.43	(0.04)
Restlessness	249	0.49	(0.05)	209	0.62	(0.06)	230	0.45	(0.05)
Incressed Appetite	249	0.86	(0.06)	209	0.74	(0.06)	231	0.87	(0.07)
Insomnia	249	0.48	(0.04)	209	0.54	(0.06)	231	0.41	(0.04)

Source: Table 13.4.7.2

Study A305007/018

Minnesota Nicotine Withdrawal Scale – Comparison of Week 12 (A3051007) and Week 13 (A3051018) [Mean[a] (SE)[b]]

	CP-526,555								Placebo	
	0.5 mg BID non-titrated		0.5 mg BID titrated		1.0 mg BID non-titrated		1.0 mg BID titrated			
	Week 12	Week 13	Week 12	Week 13	Week 12	Week 13	Week 12	Week 13	Week 12	Week 13
Q1	1.0 (0.11)	1.1 (0.11)	1.1 (0.13)	1.1 (0.13)	0.9 (0.11)	1.3 (0.12)	0.8 (0.11)	1.0 (0.09)	1.6 (0.15)	1.8 (0.18)
Q2	0.4 (0.10)	0.4 (0.07)	0.5 (0.12)	0.5 (0.09)	0.3 (0.09)	0.4 (0.09)	0.3 (0.08)	0.4 (0.08)	0.5 (0.13)	0.6 (0.15)
Q3	0.6 (0.10)	0.8 (0.11)	0.7 (0.11)	0.7 (0.11)	0.5 (0.11)	0.8 (0.11)	0.4 (0.10)	0.6 (0.08)	0.8 (0.15)	0.8 (0.12)
Q4	0.6 (0.10)	0.7 (0.10)	0.7 (0.10)	0.6 (0.10)	0.4 (0.10)	0.6 (0.10)	0.3 (0.09)	0.5 (0.08)	0.9 (0.14)	0.7 (0.10)
Q5	0.4 (0.09)	0.5 (0.08)	0.5 (0.09)	0.4 (0.07)	0.3 (0.10)	0.5 (0.10)	0.3 (0.08)	0.3 (0.07)	0.6 (0.10)	0.5 (0.13)
Q6	0.5 (0.11)	0.6 (0.09)	0.6 (0.11)	0.6 (0.09)	0.5 (0.10)	0.7 (0.11)	0.5 (0.11)	0.6 (0.09)	0.6 (0.11)	0.5 (0.11)
Q7	1.1 (0.14)	0.9 (0.13)	1.0 (0.11)	0.7 (0.10)	0.7 (0.12)	0.8 (0.11)	1.1 (0.10)	0.9 (0.11)	0.8 (0.15)	0.7 (0.14)
Q8	0.4 (0.11)	0.5 (0.09)	0.6 (0.12)	0.4 (0.11)	0.3 (0.10)	0.4 (0.09)	0.4 (0.11)	0.5 (0.10)	0.4 (0.14)	0.3 (0.12)
Q9	0.6 (0.13)	0.6 (0.09)	0.8 (0.13)	0.6 (0.11)	0.5 (0.11)	0.5 (0.09)	0.6 (0.11)	0.6 (0.10)	0.5 (0.11)	0.4 (0.13)

Source: Table 5.5 (A3051018) and Table 5.7.1.2 (A3051007)
[a] Mean of individual scores for question specified.
[b] Standard Error
Number of subjects who answered questions ranged from 97 to 120 (See Table 5.5 (A3051018) and Table 5.7.1.2 (A3051007).
Q1- Urge to smoke. Q2- Depressed mood. Q3- Irritability, frustration, or anger. Q4- Anxiety. Q5- Difficulty concentrating. Q6- Restlessness. Q7- Increased appetite. Q8- Difficulty going to sleep. Q9- Difficulty staying asleep. Individual scores range from 0 to 4, where 0 = Not at all, 1= Slight, 2=Moderate, 3=Quite a bit, and 4=Extreme. Higher scores indicate greater intensity of craving or withdrawal symptom.

Study A305016/019

Minnesota Nicotine Withdrawal Scale – Comparison of Week 12 (A3051016) and Week 13 (A3051019) [mean[a] (SE)[b]]

	CP-526,555			Placebo	
	Week 12	Week 13		Week 12	Week 13
Q1	1.1 (0.11)	1.4 (0.10)	Q1	1.7 (0.09)	1.9 (0.10)
Q2	0.4 (0.07)	0.5 (0.07)	Q2	0.4 (0.08)	0.5 (0.07)
Q3	0.7 (0.10)	0.8 (0.08)	Q3	0.8 (0.10)	0.8 (0.09)
Q4	0.6 (0.09)	0.7 (0.08)	Q4	0.7 (0.10)	0.8 (0.10)
Q5	0.4 (0.07)	0.5 (0.07)	Q5	0.5 (0.08)	0.6 (0.08)
Q6	0.6 (0.08)	0.6 (0.08)	Q6	0.8 (0.10)	0.7 (0.09)
Q7	0.9 (0.11)	1.0 (0.09)	Q7	0.9 (0.11)	0.9 (0.10)
Q8	0.5 (0.09)	0.4 (0.08)	Q8	0.6 (0.08)	0.6 (0.09)
Q9	0.5 (0.09)	0.6 (0.09)	Q9	0.6 (0.08)	0.6 (0.10)

Source: Table 5.5 and Table 5.7.1.2 (A3051016)
[a] Mean of individual scores for specified question.
[b] Standard Error
N, number of subjects who answered questions, ranged from 97 to 120.
Q1- Urge to smoke. Q2- Depressed mood. Q3- Irritability, frustration, or anger. Q4- Anxiety. Q5- Difficulty concentrating. Q6- Restlessness. Q7- Increased appetite. Q8- Difficulty going to sleep. Q9- Difficulty staying asleep. Individual scores range from 0 to 4, where 0 = Not at all, 1= Slight, 2=Moderate, 3=Quite a bit, and 4=Extreme. Higher scores indicate greater intensity of craving or withdrawal symptom.

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Week 13 (post open-label treatment)	Remaining on varenicline			Switched to placebo		
	N	Mean	SE	N	Mean	SE
Urge to Smoke	571	0.90	(0.036)	560	1.24	(0.046)
Negative Affect	571	0.50	(0.026)	560	0.70	(0.034)
Restlessness	571	0.64	(0.036)	556	0.88	(0.044)
Increased Appetite	571	1.08	(0.047)	560	1.25	(0.050)
Insomnia	570	0.75	(0.040)	560	0.83	(0.041)

Week 25 (post double-blind treatment)	Discontinuing varenicline			Discontinuing placebo		
	N	Mean	SE	N	Mean	SE
Urge to Smoke	499	1.04	(0.044)	468	1.32	(0.054)
Negative Affect	499	0.60	(0.033)	468	0.51	(0.032)
Restlessness	499	0.67	(0.041)	467	0.65	(0.041)
Increased Appetite	499	0.98	(0.049)	467	0.96	(0.049)
Insomnia	499	0.73	(0.043)	468	0.59	(0.037)

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/s/

Celia Winchell
5/9/2006 03:19:31 PM
MEDICAL OFFICER

3/10/06

STUDY ENDPOINT REVIEW

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REVIEW DIVISION	Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
MEDICAL REVIEWER	Howard Josefsberg
REVIEW DIVISION PM	Dominic Chiapperino
SEALD REVIEWER(S)	Jane Scott
REVIEW COMPLETION DATE	March 10, 2006
ESTABLISHED NAME	Varenicline tartrate
TRADE NAME	CHAMPIX
THERAPEUTIC CLASS	partial agonist of the $\alpha 4\beta 2$ nicotinic receptor subtype (smoking cessation aid)
APPLICANT	Pfizer
PRIORITY DESIGNATION	Priority
ENDPOINT(S) CONCEPT(S)	Craving, withdrawal symptoms, reinforcing effects of smoking
INSTRUMENT(S)	Minnesota Nicotine Withdrawal Scale (MNWS), the Brief Questionnaire on Smoking Urges (QSU-Brief), Modified Cigarette Evaluation Questionnaire (mCEQ)
FORMULATION	Varenicline tartrate 0.5 mg and 1 mg film coated tablet
DOSING REGIMEN	1 mg BID for 12 weeks
INDICATION	Smoking cessation
INTENDED POPULATION(S)	Adults who seek medical help to quit smoking cigarettes

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1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) regarding the adequacy of study endpoints used in the development trials for varenicline tartrate (CHAMPIX) for the smoking cessation. The SEALD review of the expert report on the development and validation of the patient reported outcome (PRO) instruments submitted by Pfizer in the original submission to NDA 21-928 [1] and other documents addresses the appropriateness of statements for the varenicline product label that are based on endpoints measured using PRO measures, specifically the Minnesota Nicotine Withdrawal Scale (MNWS), the Brief Questionnaire on Smoking Urges (QSU-Brief), and the Modified Cigarette Evaluation Questionnaire (mCEQ). The concepts Pfizer targeted for labeling claims are "craving" (measured with one item from the MNWS and the Total Score for the 10-items from the QSU-Brief), Withdrawal symptoms (measured as scores on four domains of the MNWS), and "reinforcing effects of smoking" (measured by five domain scores from the mCEQ).

Key Findings:

- The concept "urge to smoke" is more appropriate for labeling than the term "craving."
- The MNWS single item measure of "urge to smoke" may be sufficient to support claims regarding changes in urge to smoke. This can be confirmed by comparison with results based on the QSU-Brief total and empirically derived domain scores for positive and negative aspects of craving.
- The content validity of both the "symptoms of withdrawal" and the "reinforcing effects of smoking" measures have not been adequately documented. Therefore it is not clear that these measures are sufficient to support statements in labeling.

2 RECOMMENDATIONS FOR REGULATORY ACTION

The following recommendations are based on SEALD review of a report submitted in the original application for NDA 21-928 that describes the rationale for selecting the endpoint measures used in the clinical development trials for varenicline tartrate and provides empirical data to support the psychometric adequacy of scores proposed as measures of the concepts targeted for labeling.

2.1 Adequacy of patient reported outcome (PRO) instruments to support labeling statements regarding "craving," "symptoms of withdrawal," and "reinforcing effects of smoking"

SEALD review evaluated information submitted to demonstrate the validity and reliability of these instruments to determine whether specific labeling concepts were adequately measured.

2.1.1 Craving as measured by the QSU-Brief and one item of the MNWS

1. "Urge to smoke" describes the concept measured more accurately than "craving." The term "craving" is a value-laden term that is not part of the psychiatric definitions of nicotine withdrawal syndrome in either the DSM-IV or the ICD-10. Inclusion of it in these studies is based on recommendations by a Work Group that has not been confirmed by the larger scientific community.
2. There is no information demonstrating that patients in the target population have confirmed the content validity of the QSU-brief to measure what is important to patients regarding the urge to smoke or craving. It is not clear that smokers in the USA who are attempting to quit smoking would describe their desire for a cigarette as "craving" or that the items used measure an intensity of sensation sufficient to be described as craving.
3. The empirically derived domain scores for the QSU-brief need to show consistent results to confirm results based on total scores.

2.1.2 Symptoms of Withdrawal as measured by four domains of the MNSW

1. There was no information submitted to demonstrate that the symptoms of withdrawal from the MNWS provide a comprehensive measure of the symptoms of withdrawal that patients with nicotine dependence experience when they quit smoking.
    a. The MNWS [See Appendices 4.3, 4.4] does not assess all of the symptoms of nicotine withdrawal included in DSM-IV diagnostic criteria [See Appendix 4.1].
    b. The ICD-10 does not directly parallel DSM-IV and provides a longer list of symptoms associated with nicotine withdrawal for use in diagnosing a tobacco withdrawal state [See Appendix 4.2].
    c. The symptoms use to support statements about symptoms of withdrawal in this submission reflect recommendations of the Society for Research on Nicotine and Tobacco (SRNT) Work Group on the Assessment of Craving and Withdrawal in Clinical Trials.
2. Only the two multiple item domains were targeted as measures of withdrawal. To support claims related to withdrawal, it would be important to show that results for all domains of the MNWS withdrawal measure improve with treatment.

2.1.3 Reinforcing Effects of Smoking as measured by the mCEQ

1. It is not clear that all the reinforcing effects of smoking are reflected in these 12 items. As with the other measures, there is no evidence that patients in the target population confirmed that each domain of the mCEQ captures the most important aspects of the intended concept.
2. The use of recall to the last cigarette smoked during the prior week introduces recall bias that undermines the validity of data for assessments completed more than a few hours previously, particularly if the patient has smoked a number of times in the recall period.

2.2 Additional Recommendations for the Review Division

SEALD recommends that the review division evaluate the following during the NDA review:

1) Were specified cutoff points used to evaluate whether improvements were meaningful? If so, is the proposed interpretation of scores used to measure each concept reasonable and consistent with emerging standards for review of PRO measured endpoints? (see PRO draft guidance)
2) If translations were used, does the submission describe the processes used to produce and validate translations of each PRO assessment used in the trials?

3 ENDPOINT REVIEW NOTES

Varenicline tartrate is a selective partial agonist of the α4β2 nicotinic receptor subtype that combines both agonist and antagonist properties at the α4β2 nicotinic receptor subtype. Pfizer maintains that varenicline provides a more effective and better-tolerated smoking cessation therapy than those currently available because its mechanism of action reduces reinforcing effects of smoking as well as the symptoms of withdrawal and craving.

3.1 Endpoint Concepts: Craving, Withdrawal Symptoms, and Reinforcing Effects of Smoking

The rationale for including measures of craving, withdrawal symptoms and reinforcing effects of smoking in the varenicline development trials is that these are the most important concepts for evaluating efficacy in products for smoking cessation. The Diagnostic and Statistical Manual – Fourth Edition (DSM-IV) requires that a patient who has smoked tobacco for several weeks and recently quit smoking must experience at least four of eight symptoms of nicotine withdrawal to support a diagnosis of nicotine dependence. The Society for Research on Nicotine and Tobacco (SRNT) Work Group on the Assessment of Craving and Withdrawal in Clinical Trials added the concept of "craving" to that of withdrawal symptoms. SRNT recommends that craving and specific symptoms of withdrawal from the DSM-IV be used to evaluate therapies developed for smoking cessation. A third concept, "reinforcing effects of smoking," was identified from the literature that suggests that smoking tobacco ameliorates most of the symptoms of withdrawal. As these effects of smoking are immediate sources of pleasure and relief of withdrawal symptoms, their ability to reinforce smoking behavior is argued to be a primary cause of continued smoking. Pfizer proposes that varenicline can reduce the withdrawal symptoms and urge to smoke patients experience when they quit smoking, and can limit the beneficial effects of smoking on withdrawal symptoms. Table 1 (below) that was from the report submitted to document the appropriateness of the PRO measures as endpoint assessments to support labeling claims summarizes the concepts and their related symptoms.

Table 1. Comparison of DSM-IV withdrawal symptoms, SRNT recommendations for assessment of craving and withdrawal in clinical trials, and symptoms affected by smoking

DSM-IV symptoms of withdrawal	SRNT recommendations for evaluation of craving and withdrawal in clinical trials	Symptoms which reinforce smoking behavior

Irritability	Irritability	Decreased irritability
Anxiety	---	Relief from anxiety
Restlessness	Restlessness	Relaxation
Depressed mood	Depressed mood	---
Difficulty concentrating	Difficulty concentrating	Improved cognitive functioning; increased alertness
Increased appetite and/or weight gain	Increased appetite and/or weight gain	Reduced hunger
Sleep disturbance	Sleep disturbance	---
Decreased heart rate	---	---
---	Craving	Reduced craving

Pfizer has incorporated three questionnaires to evaluate the effects of smoking cessation on nicotine craving, nicotine withdrawal symptoms, and the reinforcing effects of smoking:

- Minnesota Nicotine Withdrawal Scale (MNWS)
- Brief Questionnaire on Smoking Urges (QSU-Brief)
- Modified Cigarette Evaluation Questionnaire (mCEQ)

Endpoint concepts and associated instruments (from a report included in the original NDA application entitled 'Validation of Instruments assessing craving, withdrawal and reinforcing effects of smoking") are summarized in Table 2.

Table 2: Concepts, Instruments, Domains, and Items proposed as measures of Craving, Withdrawal Symptoms, and Reinforcing Effects of Smoking

Concept	Instrument	Domain	Items
Craving	MNWS	Urge to smoke	Urge to smoke
	QSU-Brief	Craving	I have a desire for a cigarette right now. Nothing would be better than smoking a cigarette right now. If it were possible, I probably would smoke now. I could control things better right now if I could smoke. All I want right now is a cigarette. I have an urge for a cigarette. A cigarette would taste good now. I would do almost anything for a cigarette now. Smoking would make me less depressed. I am going to smoke as soon as possible.
Withdrawal	MNWS	Negative Affect	Depressed mood Irritability, frustration or anger

			Anxiety Difficulty concentrating
		Insomnia	Difficulty going to sleep Difficulty staying asleep
		Restlessness	Restlessness
		Increased Appetite	Increased Appetite
Reinforcing Effects of Smoking	mCEQ	Smoking Satisfaction	Was smoking satisfying? Did cigarettes taste good? Did you enjoy smoking?
		Psychological Reward	Did smoking calm you down? Did smoking make you feel more awake? Did smoking make you feel less irritable? Did smoking help you concentrate? Did smoking reduce your hunger for food?
		Enjoyment of Respiratory Tract Sensations	Did you enjoy the sensations in your throat and chest?
		Aversion	Did smoking make you dizzy? Did smoking make you nauseous?
		Craving Relief Upon Smoking	Did smoking immediately relieve your craving for a cigarette?

3.2 Adequacy for Labeling of the Concepts measured using PRO Instruments

Craving. It is not clear that the SRNT Work Group recommendations are appropriate to define endpoints that will support product claims. We question the appropriateness of the concept of "craving" in the context of smoking cessation. Craving is a term used in addiction treatment and research to refer to irresistible urges to use an addictive substance that can be accompanied by physical. It is not clear that this is the appropriate concept for product claims. "Urge to smoke" more accurately reflects the items in the QSU-Brief and directly reflects the single item from the MNWS.

Withdrawal symptoms. Symptoms of withdrawal appear to be a clinically meaningful concept based on the ICD-10 and DSM-IV, but it is not clear what symptoms must be measured to accurately describe the impact of treatment on withdrawal symptoms.

Reinforcing Effects of Smoking. This is an exploratory concept that is not well defined in the supplemental report. It is not clear that all the factors that could be considered reinforcing effects of smoking are captured in these questions or the endpoint scores.

3.3 Adequacy of the Development and Validation of the PRO Endpoint Measures

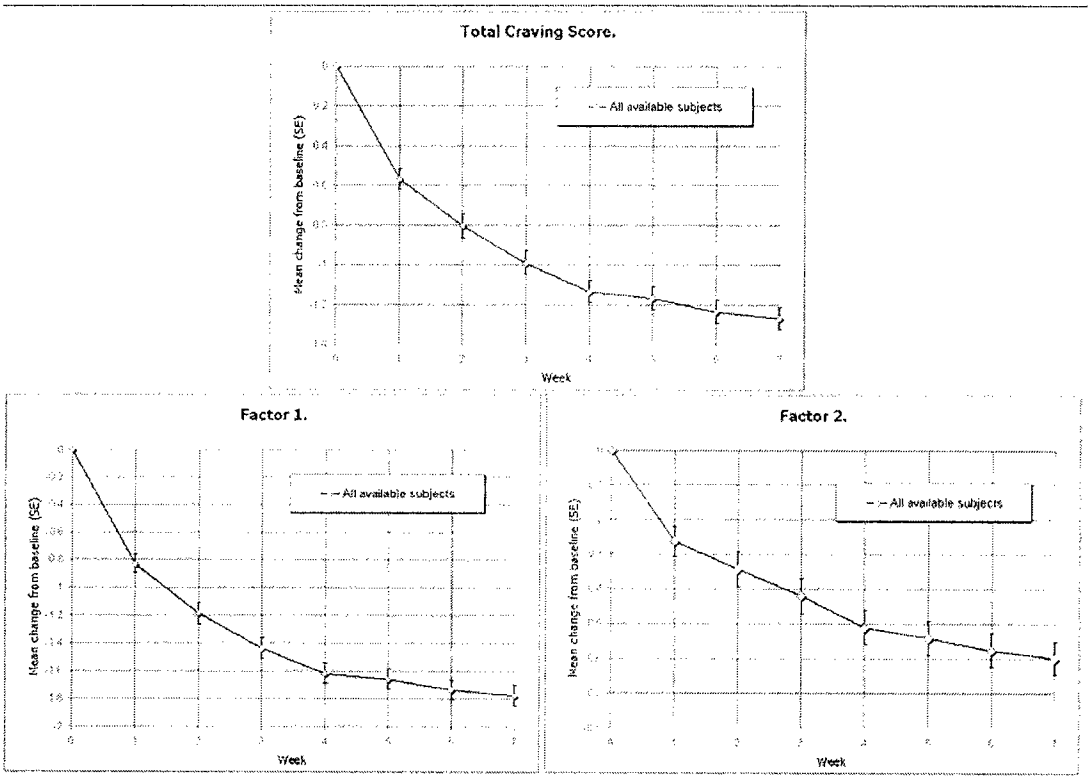
1) These instruments originally were developed for use in various settings, not specifically clinical trials. Some have been modified for use in this product development program. There is no evidence that patients in the target population confirmed that each endpoint measure provides a comprehensive measure of the important aspects of the concept(s) (e.g., craving, withdrawal symptoms, impact of smoking/smoking cessation on health-related quality of life) it was intended to measure in the trials.

2) Measurement properties of these instruments, including validity, reliability, and responsiveness to change was evaluated in the report entitled Validation of Instruments Assessing Craving, Withdrawal and the Reinforcing Effects of Smoking. The following summarizes the findings of the SEALD review of this report.

   a) Withdrawal Symptoms (MNWS). Withdrawal symptoms were conceptualized in the MNWS as consisting of four domains – negative affect, insomnia, restlessness, and increased appetite.
      i) Psychometric properties of the withdrawal symptoms domain scores supported the scoring of the negative affect and insomnia domains (the two multiple item domains) based on consistent evidence of adequate scaling properties, reliable (test-retest and internal consistency) scores, and construct validity (factorial validity) based on confirmatory factor analysis in multiple study populations.
      ii) Only the two multiple item domains were targeted as measures of withdrawal. To support claims related to withdrawal, it would be important to show that results for all domains of the MNWS withdrawal measure improve with treatment.
      iii) Targeting only two domains of a multidomain concept as study endpoints is appropriate but not sufficient to confirm that the larger concept (symptoms of withdrawal) have been adequately measured to support claims of reduction in withdrawal symptoms.

   b) Craving (QSU-Brief). Confirmatory factor analysis of the items intended to measure craving demonstrated that these items measure two distinct concepts -- one related to more positive reasons for smoking (desire and pleasure related with smoking) and the other related to negative consequences of not smoking (avoidance of withdrawal). The conceptual framework for the craving measure provided in this report did not anticipate two dimensions to the concept of craving, hence a total QSU score was used in the analysis of the clinical trials and reported in the draft label that does not reflect the distinctiveness of these domains. Adding two domains together may be acceptable as long as treatment comparisons find both domains produce consistent results. The psychometric model appears to be identifying differences from the expected structure of the items because the desire to smoke "craving" items resolve more quickly than the avoidance of negative symptoms of craving items resolve.

This is evident in the following graphs of the scores over time:



Factor 1 represents a desire or intention to smoke along with perceiving smoking as rewarding and pleasurable;
Factor 2 represents an anticipation of relief from negative affect and an urgent desire to smoke.

Results of Factor analysis of the two domains of craving from the QSU-Brief in Phase 3 generally supported the conclusions from the preliminary study that identified two domains. However, the item 10 ("I'm going to smoke as soon as I can") failed to conform to the predicted structure for Week 1 post treatment. It is not clear how this finding should be interpreted because the pattern was inconsistent across study time points, but the consistent finding in both phase III trials of an anomalous finding suggests this may reflect lack of willpower or other symptoms that are more commonly present early in smoking cessation but resolve over time.

Together these findings do not confirm a simple total score for evaluating craving is sufficient. The review of the content of these items also suggests that the term "craving" overstates the severity of the items assessed in the QSU-brief instrument.

Craving Endpoint Recommendation:

- Revise description to reflect "urge to smoke" rather than "craving"

- Confirm that both domains of craving identified in the confirmatory factor analyses showed consistent treatment benefit across studies.

c) Reinforcing Effects of Smoking (mCEQ) – the five domains of the mCEQ assess four aspects of enjoyment of smoking (satisfaction with smoking, impact of smoking on emotions and appetite, enjoyable sensations of smoking, relief of craving) and aversive response to smoking (dizziness or nausea when smoking). The mCEQ uses a 7-point scale (1=not at all to 7=extremely) and requires that a patient recall their sensations when they last smoked a cigarette.
   i) It is not clear that all the reinforcing effects of smoking are reflected in these 12 items. As with the other measures, there is no evidence that patients in the target population confirmed that each domain of the mCEQ captures the most important aspects of the intended concept.
   ii) The use of recall to the last cigarette smoked during the prior week introduces recall bias that undermines the validity of data for assessments completed more than a few hours previously, particularly if the patient has smoked a number of times in the recall period.

4 APPENDICES

4.1 DSM-IV diagnosis of nicotine dependence

For a DSM-IV diagnosis of nicotine dependence, a smoker must meet three or more of the following six major criteria:

1. Tolerance (e.g., the absence of nausea or dizziness despite substantial levels of smoking)
2. Withdrawal

   A. Daily use for at least several weeks

   B. After abrupt cessation, reports of four or more of the following signs:

   (1) dysphoric or depressed mood
   (2) insomnia
   (3) irritability, difficulty managing anger
   (4) anxiety
   (5) difficulty in concentration
   (6) restlessness
   (7) decreased heart rate
   (8) increased appetite or weight gain

3. Repeated unsuccessful attempts to quit or reduce nicotine use
4. Reduction or elimination of social or occupational activities because smoking tobacco is not allowed in those settings
5. Continued use despite medical or psychological harm
6. Use that is often greater than intended or more frequent than intended

4.2 International Classification of Diseases – Version 10 (ICD-10)

World Health Organization's
International Classification of Diseases – 10th Edition
Research Criteria for "Tobacco Withdrawal State"
(ICD-10 Diagnostic Criteria for Research, p 61)

A. There must be clear evidence of recent cessation or reduction of substance use after repeated, and usually prolonged and/or high-dose, use of that substance.

B. Symptoms and signs are compatible with the known features of a withdrawal state from the particular substance or substances (see below).

C. Symptoms and signs are not accounted for by a medical disorder unrelated to substance use, and not better accounted for by another mental or behavioural disorder.

D. Any two of the following signs must be present:

1) craving for tobacco (or other nicotine-containing products)
2) malaise or weakness
3) anxiety
4) dysphoric mood
5) irritability or restlessness
6) insomnia
7) increased appetite
8) increased cough
9) mouth ulceration
10) difficulty in concentrating

4.3 Minnesota Nicotine Withdrawal Scale- Self Report (MNWS-Self)

Minnesota Nicotine Withdrawal Scale					
For each of the following, rate yourself on how you have been feeling over the past twenty-four hours. Mark the number that applies to you:					
	Not at all	Slight	Moderate	Quite a bit	Extreme
Urge to smoke Item 1	0	1	2	3	4
Depressed mood Item 2	0	1	2	3	4
Irritability, frustration, or anger Item 3	0	1	2	3	4
Anxiety Item 4	0	1	2	3	4
Difficulty concentrating Item 5	0	1	2	3	4
Restlessness Item 6	0	1	2	3	4
Increased appetite Item 7	0	1	2	3	4
Difficulty going to sleep Item 8	0	1	2	3	4
Difficulty staying asleep Item 9	0	1	2	3	4

Appears This Way
On Original

4.4 Minnesota Nicotine Withdrawal Scale – Observer Rated (MNWS-Observer)

Behavioral Rating Scale

OBSERVER RATING

06/03

Rate the subject on the following symptoms according to whether you observed the symptom in the subject during the period. It does not matter whether the subject complained of the symptom. We want to know whether you noticed the symptom.

0 = not at all, 1 = slight, 2 = mild, 3 = moderate, 4 = sad

a. Angry/irritable/frustrated	0	1	2	3	4
b. Anxious/tense	0	1	2	3	4
c. Restless/Impatient	0	1	2	3	4
d. Depressed	0	1	2	3	4

1. How confident are you that this rating is accurate?

   0 = not at all

   1 = somewhat confident

   2 = moderately confident

   3 = very confident

4.5 Brief Questionnaire of Smoking Urges (QUE-Brief)

Brief Questionnaire of Smoking Urges

Indicate the extent to which you agree or disagree with each of the following statements by mark number between **STRONGLY DISAGREE** (1) and **STRONGLY AGREE** (7). The closer you select a nu to one end or the other indicates the strength of your agreement or disagreement. Please complete item. We are interested in how you are thinking or feeling right now as you are filling out the questionnai

1. I have a desire for a cigarette right now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

2. Nothing would be better than smoking a cigarette right now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

3. If it were possible, I probably would smoke now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

4. I could control things better right now if I could smoke.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

5. All I want right now is a cigarette.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

6. I have an urge for a cigarette.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

7. A cigarette would taste good now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

8. I would do almost anything for a cigarette now.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

9. Smoking would make me less depressed.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

10. I am going to smoke as soon as possible.

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

4.6 Modified Cigarette Evaluation Questionnaire (mCEQ, aka Smoking Effects Inventory)

Smoking Effects Inventory

(also known as the Modified Cigarette Evaluation Questionnaire)

If you have smoked since your last visit (or last completed this form), please mark the number that best represents how smoking made you feel.

1. Was smoking satisfying?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

2. Did cigarettes taste good?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

3. Did you enjoy the sensations in your throat and chest?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

4. Did smoking calm you down?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

5. Did smoking make you feel more awake?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

6. Did smoking make you feel less irritable?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

7. Did smoking help you concentrate?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

8. Did smoking reduce your hunger for food?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

9. Did smoking make you dizzy?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

10. Did smoking make you nauseous?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

11. Did smoking immediately relieve your craving for a cigarette?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

12. Did you enjoy smoking?

1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

5 REFERENCES

[1] "Validation of Instruments Assessing Craving, Withdrawal and the Reinforcing Effects of Smoking" September 14, 2005 Drafted by Mapi Values, Revised and updated by The MEDTAP Institute at UBC, Data supplied and analyzed by Pfizer. Legacy Report included in NDA 21-928.

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Concur	3/10/06 lb

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/s/

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CLINICAL SAFETY REVIEW

Application Type	21-928
Submission Number	000
Submission Code	Type 1P
Letter Date	09NOV05
Stamp Date	11NOV05
EDR Date	23NOV05
PDUFA Goal Date	10MAY06
Reviewer Name	Howard Josefberg, M.D.
Review Completion Date	03APR06
Established Name	Varenicline tartrate
(Proposed) Trade Name	Champix™ → Chantix™
Therapeutic Class	2030700
Applicant	Pfizer, Inc.
Priority Designation	Priority
Formulation	Oral tablet
Dosing Regimen	1-mg BID
Indication	Aid to smoking cessation
Intended Population	Adult smokers

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ABBREVIATIONS

ACP23	'All Completed Phase-2/3 Studies' database
AHRQ	Agency for Healthcare Research and Quality
ANC	Absolute neutrophil count
BDI - II	Beck Depression Inventory - II
CGI	Clinical Global Impression Scale (includes multiple subscales)
CI	Confidence interval
CMC	Chemistry, Manufacturing and Controls
CMH	Cochran Mantel-Haenszel chi-square
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
DAARP	Division of Analgesia, Anesthesia and Rheumatology Products
DACCADP	Division of Anesthetic, Critical Care and Addiction Drug Products
DM	Diabetes mellitus
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
EMEA	European Agency for the Evaluation of Medicinal Products
EOP2	End-of-Phase-2 (Meeting)
ET	End-of-treatment visit or early-termination visit
FDPC	Fixed-dose, placebo-controlled studies (all Phase 2/3)
FTND	Fagerström Test for Nicotine Dependence
GCP	Good Clinical Practices
HgA1c	Glycosylated hemoglobin
LFT	Liver function tests (includes AST, ALT, SGOT, SGPT, GGT, T. Bilirubin)
LS-mean	Least-squares mean
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-models repeated measures
NT	Non-titrated dosing (during the first treatment week)
OCPB	The Office of Clinical Pharmacology and Biopharmaceutics
PBO	Placebo
PCSA	Potentially clinically significant (laboratory) abnormality
PID	Patient identification number (unique)
pNDA	Pre-NDA (Meeting)
PT	Preferred Term (MedDRA)
QSU-Brief	Questionnaire on Smoking Urges-Brief Form
SAP	Statistical analysis plan
SEALD	Study Endpoints and Labeling Development
SMQ	Standardized MedDRA Query
SOC	System Organ Class (MedDRA)
T	Titrated dosing (during the first treatment week)
TEAE	Treatment-emergent adverse event
TQD	Target Quit Date
ULN	Upper limit of normal
VRN	Varenicline
WHO-DRL	World Health Organization Drug Reference List

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend an approval action for NDA 21-928, pending the final report from the Division of Scientific Investigations. The applicant has provided substantial evidence of product safety and efficacy for the proposed indication. All three Phase-3 trials yielded supportive efficacy results, achieving their primary outcome measures, and most key secondary measures. Existing safety concerns, principally with respect to possible cardiovascular effects, can be addressed in the Warnings or Precautions section of the product label.

1.2 Recommendation on Postmarketing Actions

I have no recommendations for post-approval commitments at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Pfizer began with a thorough Phase-2 dose-finding and tolerability program (Studies A3051002, A3051007, and A3051016). Study A3051002 compared three doses of varenicline (0.3 mg QD, 1-mg QD, and 1 mg BID), to placebo, and also incorporated a Zyban® arm. This study provided evidence that varenicline 1 mg BID was superior to placebo and to 1-mg QD, also suggesting varenicline superiority to Zyban®. Study 3051007 evaluated two doses, 0.5-mg BID and 1-mg BID, both with or without gradual up-titration during the first therapy week. Both doses were superior to placebo. Study 3051016 evaluated a patient-directed flexible dosing regimen, also providing positive efficacy findings.

Phase-3 Studies 3051028 and 3051036 were identical 12-week trials, in which the 1-mg BID dose was compared with Zyban® 150-mg BID (for 7-weeks, as labeled) and placebo. Both trials demonstrated varenicline superiority to Zyban®, and to placebo. 'Maintenance of efficacy' Study 3051035 showed that for clinical responders, 12 additional treatment weeks (with 1-mg BID) increases abstinence rates during treatment Weeks 12 to 24, and also during off-drug follow-up to Week-52.

Study 3051037, a placebo-controlled safety trial provides evidence of varenicline 1-mg BID safety over a 52-week treatment period.

1.3.2 Efficacy

Applicant-identified pivotal Phase-3 Studies 3051028 and 3051036 provide substantial evidence of efficacy of varenicline 1-mg BID as an aid to smoking cessation, and substantial evidence of the 1-mg BID dose's superiority to Zyban® (when used for smoking cessation according to the labeled dosing regimen). These studies also provide evidence that varenicline decreases quitters' "urge to smoke" as measured by two validated instruments (Pfizer proposes to use the word "craving").

Study 3051035 provides evidence that the efficacy of varenicline (1-mg BID) is maintained over a 12-week follow-up period, for smokers able to abstain during the last week of an initial 12-week open-label treatment period with 1-mg BID. That is, smokers who successfully quit smoking during varenicline treatment are more likely to maintain abstinence if varenicline treatment is continued for three additional months.

Phase-2 and exposure-response data show the incremental benefit of the 1-mg BID dose over that for

0.5-mg BID to be minimal, though clearly associated with decreased tolerability. This issue is discussed in Section 1.3.4 below.

1.3.3 Safety

The serious adverse event data suggest that varenicline may, possibly increase the risk of cardiac events, both ischemic and arrhythmic, particularly over longer treatment periods. This finding, however, is far from definitive. (Although six deaths occurred during development, three or four in varenicline-treated patients, no specific safety concerns emerge.)

Adverse event related discontinuations (at the 1-mg BID dose) were relatively uncommon, but increased with increasing treatment duration, from about 12% with a 12-week course to over 25% in the 52-week study. It should be noted, however, that some patients discontinuing during later treatment months had already achieved abstinence, and may have had decreased willingness to tolerate drug side effects. Adverse event related discontinuations were least frequent (7%) in Study A3051016, where patients self-titrated their dose, in most cases only to 1.5-mg/day or 1.0-mg/day.

The overall adverse event data show that varenicline at the proposed dose is commonly associated with nausea (± vomiting), insomnia, abnormal dreams and other sleep disturbances, and headache. Nausea, by far the most common adverse event, was clearly dose-related. Although occurring in 30% to 40% of patients, depending on dose and treatment duration, only about 3% of patients discontinued because of it. Insomnia, abnormal dreams and other sleep disturbances were also dose-related in varenicline-treated patients. Most of the commonly reported AEs appear more likely to occur relatively early in treatment, though not exclusively so. Study A3051037, however, shows that some patients may report specific adverse events for the first time months after initiating treatment.

Treatment with varenicline for up to 24-weeks does not appear to increase the incidence of clinically relevant laboratory, vital sign or ECG abnormalities. Several concerns raised by the Phase-1 laboratory findings appear not to have Phase-2/3 correlates.

1.3.4 Dosing Regimen and Administration

The varenicline development program included evaluation of three varenicline (daily) doses, evaluated under six different dosing regimens; 0.3-mg QD, 0.5-mg BID non-titrated, 0.5-mg BID titrated, 1-mg QD, 1-mg BID non-titrated, and 1-mg BID titrated. The superiority of the 1 mg BID dose over the labeled regimen for Zyban® was clearly demonstrated. The 1-mg BID dose appears to be only marginally more effective than 0.5-mg BID, in comparison to placebo, but clearly less well tolerated. Pfizer also demonstrated varenicline superiority to placebo under a flexible dosing regimen (0.5-mg to 2-mg/day), in which most patients chose to take 1-mg or 1.5-mg per day. A dosing and administration section calling for a flexible-dosing scheme beginning at 0.5 mg/day, as in the flexible dosing study, seems most appropriate.

The proposed label [redacted] The adverse event and MNWS data show, however, that abrupt cessation is associated in some patients with nicotine withdrawal like symptoms (i.e., irritability), thus a brief taper would be advisable.

Proposed dosing and related issues are discussed in Section 6.1.4.1 (Dose-Response Evaluation) and Section 5.3 (Exposure-Response Evaluation).

1.3.5 Drug-Drug Interactions

Coadministration with other approved smoking cessation products was shown to increase the incidence of nausea and other commonly occurring AEs. Systolic blood pressure was also noted to increase (10-20 mmHg) after Zyban®/varenicline and nicotine/varenicline co-administration, for some subjects (2/41, 1/17, respectively). There were no pharmacokinetic interactions in these two studies.

Pharmacokinetic or pharmacodynamic changes were not noted with the coadministration of multiple doses of varenicline with multiple doses of either digoxin or warfarin (narrow therapeutic index drugs).

1.3.6 Special Populations

Dose adjustment is required in subjects with severe impairment of renal function. Dose adjustment is not required with respect to age (except as related to renal function), gender, race, body weight and hepatic dysfunction, as variability in pharmacokinetics is not explained by these covariates in the population pharmacokinetic analyses.

Variability in pharmacokinetics of varenicline is only explained by changes in renal function in terms of glomerular filtration rate (GFR). Varenicline clearance is predicted to decrease from 10.4 L/hr for a typical subject with normal renal function (estimated GFR = 100 mL/min) to 4.4 L/hr (estimated GFR = 20 mL/min) for a typical subject with severe renal impairment, thus resulting in an overall increase in daily steady-state exposure of 2.4-fold from the minimum to maximum of this renal function range.

Varenicline undergoes negligible hepatic metabolism. The effect of hepatic insufficiency on total body clearance of varenicline has not been studied but is expected to be minimal. No dose adjustments requirements are anticipated, however, for patients with mild to moderate hepatic impairment.

Gender analysis indicates that there are no significant varenicline exposure differences due to gender, and that no dose adjustment is required.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Varenicline tartrate is a first-in-class, new molecular entity (NME) under development by Pfizer as an aid to smoking cessation. Formerly called CP-526,555, varenicline is a partial nicotinic agonist, selective for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype. NDA 21-928 is for an immediate release (IR) film-coated tablet formulation (developed under IND 58,994). [

]

Pfizer's rationale for the use of varenicline in smoking cessation is based on published literature indicating that the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype mediates the dependence producing effects of nicotine. Pfizer states that;

> This research supports the hypothesis that an a4ß2-selective nicotinic receptor partial agonist may provide relief from craving and withdrawal symptoms. Additionally, a partial agonist would be expected to block the behaviorally reinforcing effects of exogenous nicotine. Thus, varenicline, which combines both agonist and antagonist properties at the a4ß2-subtype nicotinic acetylcholine receptor, may provide a more effective and better-tolerated therapy for smoking cessation than those currently available.

In the application Pfizer reports results from preclinical studies showing that varenicline activated dopamine turnover and release in the nucleus accumbens to a level approximately 50% of that induced by nicotine. Oral varenicline attenuated these effects, when they were initially elicited by nicotine. Varenicline generalized to a nicotine cue in drug discrimination studies, and reduced the amount of nicotine that rats self-administered.

2.2 Currently Available Treatment for Indication

Products available as aids to smoking cessation include:

- Nicorette Gum (Glaxo SmithKline) and generic nicotine gum(s)
- Commit Lozenge, a buccal delivery system in the form of a lozenge (Glaxo SmithKline) and a generic lozenge
- Transdermal nicotine systems, including Nicoderm patch (Glaxo SmithKline), Habitrol patch (Novartis), Nicotrol patch (Pharmacia/Pfizer), and private brand/generics
- Nicotrol nasal spray (Pharmacia/Pfizer)
- Nicotrol inhaler (a buccal delivery system) (Pharmacia/Pfizer)
- Zyban® (bupropion sustained-release), a non-nicotine oral tablet (Glaxo SmithKline)

Several other products are under development, including additional nicotine replacement products and a variety of new molecular entities.

2.3 Availability of Proposed Active Ingredient in the United States

The applicant, Pfizer, holds patents on several steps in the varenicline manufacturing process. No other domestic varenicline sources are known.

2.4 Important Issues with Pharmacologically Related Products

As of April 1, 2006 no $\alpha_4\beta_2$ nicotinic agonist medications have been approved for use, in the United State or elsewhere. [

2.5 Presubmission Regulatory Activity

Varenicline was developed under Investigational New Drug Applications (INDs)-IND 58,994 for the immediate release formulation, [ ] in the Division of Anesthetic, Critical Care, and Addiction Drug Products (now the Division of Analgesia, Anesthesia and Rheumatology Products). This New Drug Application (NDA) is for the immediate release formulation only.

Table 2-1 below lists dates for key Pfizer-FDA pre-submission regulatory interactions, along with very brief summaries of content, where applicable. Module-1 of the application includes a Pfizer document summarizing all varenicline-related pre-submission regulatory activity ('Interactions with FDA'). My review of this document finds it to be accurate with respect to timing and content.

Table 2-1: Pre-Submission Regulatory Activity, NDA 21-928

Date	Event	Detail
	Clinical	
09/14/99	IND 58,994 opened	Proposed indication: [ ] (DAACADP)
10/12/99	Teleconference	To discuss initial IND (Revision submitted 10/13/99)
09/05/01	Meeting	To discuss Phase-2B plan (including A3051028/1036 and OL extensions)
09/26/01	FDA minutes	EOP2 meeting minutes received by Pfizer (Pfizer response 11/16/01)
11/04/02	[ ]	]
12/09/02	EOP2 meeting	Discussion of pivotal studies (endpoints, active comparator), safety DB,
12/17/02	EOP2 Pfizer minutes	cardiovascular safety, , pediatric plan, abuse liability assessment
02/09/03	EOP2 FDA minutes	labeling and patient-reported outcome measures (PROs)
10/20/04	Pfizer submission	CHAMPIX™ trademark submitted for review
06/09/05	Pre-NDA meeting	Adequacy of clinical studies, analysis and presentation of data, eCTD
06/20/05	Pfizer submission	Examples of AE tabulations, MedDRA terms
08/04/05	Pfizer email	Regarding presentation of safety data
08/16/05	Advice letter	FDA response regarding EOP2 meeting, and 06/20 and 08/04 submissions
10/28/05	Meeting	Pfizer demonstration of planned eCTD submission
11/09/05	NDA submission	
	Abuse Liability	
12/22/03	Pfizer submission	Briefing package submitted
3/22/04	FDA info request	Concerning 12/22/03 submission
04/13/04	Pfizer submission	Response to FDA request for additional information
11/30/04	Advice letter	With assessment of 04/13/04 submission
12/09/04	Protocol submission	A3051039 submitted
12/22/04	Pfizer submission	Pfizer response to 11/30/04 advice letter
04/22/05	Pfizer submission	Proposed revision to SAP, request for meeting with DAACADP and CSS
05/11/05	Pfizer submission	Revised statistical analysis plan with questions
08/03/05	Pfizer submission	Amended Protocol A3051039 submitted
08/18/05	Meeting	Meeting held
09/16/05	FDA minutes	FDA minutes received by Pfizer
10/24/05	Pfizer submission	Pfizer response to FDA's meeting minutes
	Pharm/Tox	
04/29/02	Pfizer submission	Dose level rationale for two-year carcinogenicity studies
06/13/02	Advice letter	Advice letter regarding dosing for two-year carcinogenicity studies
04/14/04	Teleconference	To discuss mortality in carcinogenicity studies
	CMC	
10/09/03	EOP2 CMC Meeting	Starting material, [ ]
03/19/04	T/C re: EOP2 CMC	solubility and dissolution rate criteria (no concerns), [ ] / data,
10/14/04	Type C Meeting	To discuss two comparability protocols ([ ]
04/19/05	Meeting	To discuss Pfizer proposal for participation in ONDC pilot program
06/15/05	Meeting	ONDC initiated follow-up meeting
07/22/05	Pfizer submission	Formal application for pilot program
08/11/05	Meeting	To discuss comprehensive QOS content

Source: Clinical reviewer from text/tables in Module-1 document 'Interactions-with-FDA' and from IND submissions

A summary of key interactions and agreements, as they relate to the clinical development program appears below.

09/2001 (Phase-2b Meeting)
A meeting was held 09/05/01 to discuss proposed Studies A3051018 and A3051019, the non-treatment follow-up extensions to Studies A3051007 and A3051019, respectively, as well as the planned Phase-3 program. The Divison advised that smokers with common co-morbid medical conditions be enrolled in planned Phase-3 Studies A3051028 and A3051036, and that ECG and LFT monitoring be ongoing during the Phase-3 studies, and not just at beginning and end of treatment.

Pfizer inquired about the establishment of superiority claims against competitor drugs. The Division reiterated that determination of the efficacy of the drug product is based solely on its superiority over placebo, and if Pfizer is pursuing a superiority claim against Zyban®, careful attention should be paid not to include in the trial previous Zyban® failures or drop-outs. The Zyban® arm of these trials should also follow the labeled Zyban® regimen.

12/2002 (End-of-Phase-2 Meeting)
Efficacy Endpoints/Comparative Claims
Pfizer asked about the feasibility of including label claims derived from measures of patient-reported outcomes. The Division advised that that Pfizer would need to provide justification for the choice of instruments. Any instrument to be considered must have demonstrated validity and reliability, as well as clinical relevance

06/2005 (Pre-NDA Meeting)
In general, the Division agreed that the presentation of data to support the review of an NDA was acceptable. In response to Pfizer's question regarding whether appropriate and adequate safety evaluations have been conducted to support the review of an NDA, the Division acknowledged that a dedicated QT-interval study would not be expected in the initial submission. The Division requested that all of the cardiac data be provided in a single location in the application. If a safety signal is detected during review, the Division would request a study be conducted before approval.

The Division requested that the 120-day safety update data be fully integrated, but, following discussion, agreed to defer a decision on the need for integration until after lock of the safety update database. The acceptability of a non-integrated update would be dependent on the data.

Dr. Winchell noted that the ongoing A3051044 comparative study versus nicotine replacement therapy is open label and reminded Pfizer that, for comparative claims, two blinded studies would be required.

The Division requested data on cytochrome P450 induction and rationale for selection of doses for renal impaired patients. Pfizer agreed to provide the information in the NDA.

Abuse Liability Assessment
In the FDA minutes of the 12/02 EOP2 meeting, the Divison indicated that additional data would be needed to support the claim that varenicline has a low abuse potential. Pfizer provided a briefing package with the proposed assessment program (13 April 2004, Serial # 0112). In a letter dated 11/30/2004, the Division generally concurred with Pfizer's proposed approach for assessment of abuse potential. The choices of population, endpoints and comparator for the abuse potential study A3051039

were considered acceptable. FDA requested clarification on certain issues and suggested revisions to the clinical protocol. FDA also provided suggestions for additional information to be included in the abuse liability assessment section of the NDA. Pfizer incorporated the suggested revisions, and on 12/22/2004 submitted revised Protocol A3051039, along with an overview of the revised analysis plan, and a request for a meeting (to include the Controlled Substances Staff) to discuss the study.

Pfizer submitted additional questions regarding the proposed analysis plan revision on 05/11/2005. Protocol A3051039 was amended as proposed, and submitted on 08/03/2005. Pfizer met with CSS and DAARP on 08/15/2005 to discuss the protocol. The CSS emphasized their interest in seeing individual subjects' response data, noting that that the state of the art for assessing abuse potential was not optimal. CSS pointed out that overall study design was, the choice of comparator, amphetamine, would only allow for conclusions regarding varenicline in relation to a Schedule-2 drug.

2.6 Other Relevant Background Information

2.6.1 Applicant Request for Priority Review

At the time of NDA submission, the applicant requested a priority review for this product. This request was granted.

MaPP 6020.3 provides for priority review of new drugs that "...if approved, would be a *significant improvement compared to marketed products*...in the treatment, diagnosis or prevention of a disease." Preliminary review of the clinical data suggested that varenicline, a first-in-class, new molecular entity, would offer a significant efficacy improvement compared to marketed smoking cessation products (extended release bupropion, and nicotine replacement products).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The Chemistry review team found the CMC portion of the application to be acceptable. No approvability issues were identified regarding the manufacturing process or manufacturing sites. Adequate CMC information for synthesis, purification, and controls of the drug substance were submitted, and appropriate stability data to support expiration dating were provided.

As of 04/03/06 three CMC issues remain outstanding, but it is expected that these will be adequately addressed in a soon-to-arrive CMC regulatory agreement. These issues are;

- The specification sheet for the drug substance is to include a footnote to indicate that all genotoxic structural alert impurities are collectively being limited to NMT [ ] based on process capability of the synthetic process
- The [ ] specification for varenicline tartrate will include : [ ]
- The dosage form monograph for the drug product will state that [ ] testing are carried out to assure tablet homogeneity

[

]

As of 04/03/06 three CMC issues remain outstanding, however;

The DESCRIPTION section from Pfizer's proposed label appears below.

DESCRIPTION

[

]

The chemical structure is:

[DIAGRAM]

CHAMPIX 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. [ ] the following 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.

3.2 Animal Pharmacology/Toxicology

No approvability issues were identified, though several findings were identified as appropriate for inclusion in labeling. Preclinical studies included toxicology studies in rats, dogs, mice and monkeys with duration of single dose to 12 months, 2-year carcinogenicity studies in mice and rats, genotoxic studies, reproductive toxicity studies in rats and rabbits, and special toxicology studies. The major target organs were brain/central nervous system (CNS), gastrointestinal tract (GI), and lymphoid system. Effects were also observed in embryonic development, the cardiovascular and hepatic systems, and in oncogenicity.

General Toxicity and Safety Pharmacology
CNS and gastrointestinal clinical signs (emesis, loose stool, and salivation) were noted sporadically in all dose groups in all species studied, therefore, similar treatment related clinical signs were predicted in humans. Decrease in body weight and food consumption >10% were observed in the dose > NOAEL doses. Dr. De considered the proposed safety margins (comparison of NOAEL dose with the maximal proposed human dose) to be acceptable, however.

In two pivotal repeat dose (9-month) toxicity studies in Cynomolgus monkeys, increase in monocyte and lymphocyte counts were noted at ≥0.2 mg/kg/day. These increases were within the historical control range. An increase in lymphocyte infiltration in various organs (trachea, thyroid etc), along with the chronic inflammation observed histopathlogically in some tissue (heart) at the same dose range. These changes were thought to suggest a possible varenicline effects on the lymphoid system, although they could also be stress-related. Increased fibrinogen level was observed in doses above ≥ 0.2 mg/kg/day, also suggesting underlying increased inflammatory processes. Dr. De considered the biological significance of these findings to be uncertain, however. Changes in WBC counts were also noted with all doses at Week -13 which normalized by Week-26.

Varenicline had no pro-convulsant effects and did not appear to affect cardiopulmonary or cardiovascular function. No cardiac safety signal was detected.

Mutagenicity and Carcinogenicity
In the 2-year carcinogenicity studies, drug-related neoplastic alterations were limited to hibernoma in male rats, a rare tumor finding in rodents; 1/65 male rats showed benign hibernoma at the mid-range dose (10 mg/kg dose); 2/65 male rats showed malignant hibernoma at the high dose (15 mg/kg dose). This finding was not statistically significant. Because of hibernoma's rarity, Dr. De considered these findings treatment related, and necessary for labeling. No apparent drug-related neoplastic findings were observed in female rats at doses up to 15 mg/kg (HED=145 mg) or in mice in both sexes at doses up to 20 mg/kg (HED= 97.5 mg).

Reproductive Toxicology
In the reproductive toxicity studies a decrease in the pregnancy rate was observed in F_0 and F_1. Decrease in behavioral pattern in the F_2 (like rearing, auditory startle) indicating a decrease in motor coordination and exploratory behavior is noted.

Local Toxicology
In the tissue distribution study (where 1.30 μCi of ^{14}C was tagged with the compound to analyze the tissue distribution) in rat single administration of 3.4 mg/kg (HED = 33 mg considering 60 kg man)

showed drug distribution in the different ocular tissues for a long period of time at least 7 days. A decreasing trend of the exposure of test article in all different tissues was noted after a peak exposure at 18 hrs. No major toxicity related to the skin and eye was observed in non clinical species, however, the melanin deposition is a pharmacological characteristic of nicotine. The compound being a partial agonist of nicotine might show related toxicity in the melanin containing tissues and the effect might vary demographically.

Receptor Binding and Self-Administration

Varenicline functions as a partial agonist in both *in vitro* and *in vivo* models of nicotinic receptor function. In binding assays, varenicline has high affinity only for the a4ß2 subtype neuronal nicotinic receptor, which is thought to mediate the behaviorally reinforcing effects of nicotine. In both *in vitro* and *in vivo* models of mesolimbic dopamine system function, varenicline functions as a partial agonist. Varenicline activates this pathway to levels only about 50% of those induced by nicotine, and when administered with nicotine, reduces mesolimbic dopamine system activation to levels observed with varenicline alone.

Pfizer contends that varenicline does not produce detectable withdrawal effects in animal models, and that it appears to be "...less reinforcing than nicotine, because rats will work harder for nicotine than for varenicline." Varenicline generalizes to a nicotine cue in drug discrimination studies. In self-administration studies varenicline reduced nicotine self-administration in rodents.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

New Drug Application 21-928 was dated 11/09/2005, logged into the FDA Electronic Document Room 11/17/2005 and made available for review the following week. The application adhered to Electronic Common Technical Document (eCTD) formatting conventions. The original NDA submission appeared to include all FDA-required items.

All data utilized for this review derive from the original application and its [ ] IND (58,994 and [ ], along with amendments submitted in response to information requests.

This review is based on information included in the original NDA submission as well as:
- Materials and correspondence submitted to IND: [ ] 58,994 (see Table 2-1)
- Proposed product label
- Consultation responses from SEALD, ODS, DDMAC and CSS reviewers
- Preliminary DSI reports from field investigators
- Statistics, OPCB, Pharmacology/Toxicology and CMC reviews of this application
- Safety update (submitted at 90-days)
- Applicant responses to information and data requests as listed in Table 4-1

Table 4-1: NDA 21-928 Amendments (Responses Unless Otherwise Indicated, with Request Date)

Seq. #	Dated*	Content
001	01/13/06	Meeting request (Type C)
002	02/07/06	CMC stability data update
003	02/03/06	CSS re: amphetamine qualifying procedure, eCTD navigability (01/27)
004	02/09/06	Three-month safety update, Final CSR for A3051050
005	02/14/06	CSS – VAS scale interpretation, NTF criteria, (01/27)
006	03/03/06	OCPB – Bootstrapping, predictive checks, datasets (1008, 1016) (2/28)
007	03/07/06	Request to allow pre-approval importation of drug product (OC)
008	03/08/06	Corrected book marking of Sections 2.7.3 (SCE) and 2.7.4 (SCS) (3/06)
009	03/10/06	CSS – regarding A3051039 and overall safety database (3/10)
010	03/14/06	Alternative trade names proposed, CHANTIX or [ ] (03/06)
012	03/14/06	Common adverse event tables, HLGT ≥5%, PT ≥1% (3/07)
013	03/15/06	Revised presentation of A3051012 ECG data (3/10)
014	?	? (No document in EDR)**
015	03/23/06	SAE tabulations (03/20)
016	03/24/06	Breakdown of common AEs by dose (3/21)
017	03/29/06	CSS – A3051039 source data (SAS Transport file) 3/23
018	03/29/06	Summary and analyses, patients with elevated CPK (3/20)
019	03/31/06	AEs during 1 to 7 days following treatment discontinuation (3/27)
020	03/31/06	CSS - Updated VAS-Nausea Scales (Revision to #017) (3/30)
021(?)	04/??/06	Analyses of weight change in quitters and non-quitters (3/27)

*Pfizer letter date, not EDR availability date ** As of 04/05/2006 Source: Clinical reviewer

4.2 Tables of Clinical Studies

Twenty-four Phase-1 studies were conducted, enrolling a total of 795 subjects, 540 of whom received varenicline. Table 7-57 lists and Table 11-5 and Table 11-6 detail the Phase-1 studies. Four Phase-2 trials and four Phase-3 trials were conducted, summarized in Table 4-2 below.

Table 4-2: Phase-2 and Phase-3 Trials

Study/Objective	Design	RX Duration	Treatment Groups	N
PHASE-3				
A3051028 Efficacy Zyban® comparison	R, PG, DB, PC active comparator	12 weeks RX then F/U to Wk-52	Varen 1 mg BID Zyban® 150 mg BID Placebo Total:	349 329 344 1022
A3051036 Efficacy Zyban® comparison	R, PG, DB, PC active comparator	12 weeks RX then F/U to Wk-52	Varen 1 mg BID Zyban® 150 mg BID Placebo Total:	343 340 340 1023
A3051035 Maintenance dosing	OL Varen 1 mg BID Then responders DB - Varen 1 mg BID OR - Placebo	12 weeks OL, then 12 weeks DB, then F/U to Wk-52	OL Varen 1 mg BID Followed by - DB Varen 1 mg BID - OR, DB Placebo Total:	1927 602 604 1927
A3051037 OL Safety 'Long-term'	R, PG, DB, PC	52 weeks RX	Varen 1 mg BID Placebo Total:	251 126 377
PHASE-2				
A3051002 Dose-Ranging	R, PG, DB, PC active comparator	(Varenicline 6-weeks then Placebo 1-week) OR (Zyban® 7-weeks)	Varen 0.3 mg QD Varen 1 mg QD Varen 1 mg BID Zyban® 150 mg BID Placebo Total:	126 126 125 126 123 626
A3051007 Dose Titration (Off-drug follow-up in A3051018)	R, PG, DB, PC	12 weeks RX, then F/U to Wk-52	Varen 0.5 mg BID NT* Varen 0.5 mg BID T* Varen 1 mg BID NT Varen 1 mg BID T Placebo Total:	124 129 124 129 121 627
A3051016 Flexible Dosing (Off-drug F/U in A3051019)	R, PG, DB, PC	12 weeks RX, then F/U to Wk-52	Varen flexible doing 0.5 -2.0 mg/day Placebo Total:	 157 155 312
A3051043 Japan pilot study	OL	7-weeks	Varen 0.5-mg BID Total:	30 30

*Non-titrated = NT, Titrated = T Source: Modified from Table 1, Section 2.7.

4.3 Review Strategy

The safety review utilized several Pfizer-defined cohorts:

- The pooled **Phase-1 Studies** cohort consists of 23 studies, which treated a total of 750 subjects. Table 7-57 below provides an overview of the Phase-1 program. Appendix Table 11-5 and Table 11-6 summarize pertinent details about the Phase-1 studies.
- The '**Phase-2/3, Fixed-dose, Placebo-controlled**' cohort includes data from four randomized, double-blind, placebo-controlled studies (A3051002, A3051007, A3051028, and A3051036), in which 2365 patients received varenicline. Treatment duration was 12-weeks in three of these studies. In the fourth, A3051002, treatment was for six (varenicline) to seven (Zyban®) weeks. Varenicline doses investigated in these studies were 0.3 mg QD, 1 mg QD, 0.5 mg BID and 1 mg BID. For most analyses, however, the applicant pooled all doses below the proposed 1-mg BID dose. The applicant has designated this cohort as the '**Primary Safety Cohort**' for the purposes of comparisons across treatment groups, and for analyses of special population subgroups.
- The '**All Completed Phase-2/3 Studies**' cohort includes data from all eight completed Phase-2/3 trials, in which a total of 3940 patients received varenicline.

The safety review focused mainly on data from Phase-2/3. For the purposes of assessing drug-control group comparisons most safety analyses focused on the Phase-2/3, Fixed-dose, Placebo-controlled data. These data are compared with those from the 'All Completed Phase-2/3 Studies' data where the additional exposure duration was expected to be informative.

For evaluation of longer-term exposure safety data from 52-week Study A3051037 were also reviewed on their own, and in comparison to the pooled data.

Phase-1 safety data were reviewed for the pooled cohort (for laboratory outliers and changes, and lab-related AEs), as well as on a study-by-study basis for specific findings (i.e., ECG and PK findings in 3051012 and 3051014).

For all serious adverse events (SAEs) individual data line listings and narratives were reviewed, along with laboratory, ECG and vital sign data where pertinent. Events that were clearly not related to study drug treatment were excluded from my own summary tables and narrative discussions. Examples of such events include pre-scheduled elective surgery, motor vehicle accidents as passenger and surgical intervention for chronic intervertebral disc degeneration. Cardiac SAEs received particular scrutiny, because of their frequency, and their potential ramifications.

Dr. Winchell's efficacy review utilized clinical data from Phase-3 trials 1028, 1036 and 1035, and from Phase-2 trials 1002, 1007 and 1016. Particular attention was given to the Phase 3 studies involving the dose proposed by Pfizer for marketing, 1 mg BID (A3051028 and A3051036, the Zyban® comparison studies; and A3051035, the "maintenance" study), and to those Phase 2 studies which provided information concerning the efficacy of lower doses given over 12 weeks (studies A3051007 and A3051016). Pfizer identified Studies 1028, 1036 and 1035 as pivotal efficacy trials.

4.4 Data Quality and Integrity

(Also see Sections 7.2.8 'Assessment of Quality and Completeness of Data', and 7.1.2 'Other Serious Adverse Events')

Data quality and completeness were good. Adverse event elicitation was appropriate and coding appeared satisfactory. There appeared to be no evidence of fraud. Responses to information requests were prepared promptly and appropriately.

Clinical management, reporting and follow-up of adverse events and SAEs appear to have been appropriate, throughout varenicline development. SAE presentations and analyses in the application are acceptable.

Pfizer's SAE summary tables and data listings were derived from a centralized SAE monitoring database that is separate from the varenicline 'project database.' The centralized SAE database collects (and generates) expedited reports, and remains open to data updates; it does not get locked. Due to differences in the way data are entered and maintained in the two databases (e.g.. a reporting lag of 30 days for the separate safety database versus 7 days for the varenicline project database, several (small) discrepancies were found between the adverse event data line listings. In five or six cases, one of the all adverse event SOC totals appearing in individual study report appendix tables was lower (by one or two) than the corresponding total appearing within the text of the ISS. Each difference could be readily reconciled by finding the 'missing' SAE.

In a handful of cases (about one dozen) reasons cited for treatment discontinuation appear to have been coded incorrectly. On the other hand, in at least two cases, discontinuation appears to have been inappropriately attributed to a treatment emergent adverse event.

The AE datasets included all five MedDRA term levels, as well as investigator verbatim terms, treatment start and stop dates and dosing information. I was able to replicate Pfizer's adverse event summary tables using the datasets provided.

4.4.1 Report from DSI Clinical Inspections

Although the official DSI report is not yet available, preliminary reports indicate that no serious study conduct or data management issues were identified at the individual clinical sites.

Four clinical sites were chosen for routine DSI inspection. Two of these sites were selected because of what appeared to be nearly identical efficacy data for two patients, one at each site (Dr. Throne, Radiant Research, Atlanta and Dr. Rigotti, MGH, Boston). Dr. Pappas' site (Central Kentucky Research Associates, Inc.) was selected because it enrolled patients into all three Phase-3 efficacy studies; it was also one of only five US sites (of 27 in total) for Study A3051035, the 'maintenance of efficacy' study. Dr. Hays' site (Mayo Clinic, Rochester, MN) was chosen because of unusually positive efficacy findings in Study A3051036

One [redacted] inspection was also issued [redacted]
because of concerns arising from a patient complaint [redacted]

Table 4-3 below summarizes enrollment by study for the five sites chosen for inspection.

Table 4-3: Varenicline Clinical Site Inspections

Primary Investigator/Clinical Site	Studies	N	Total*
Routine			
M. Throne, Radiant Research Incorporated, Atlanta, GA	3051028	70	70
N. Rigotti, Massachusetts General Hospital, Tobacco Research & Treatment Center, Boston, MA	3051036	55	55
J. Pappas, Central Kentucky Research Associates, Inc. Lexington, KY	3051028 3051035 3051007	34 81 16	131
J. Hays, Mayo Clinic, Rochester, MN	3051036	62	62
[ ]			
[ ]	[ ] [ ]	- -	[ ]

*Total treated with at least one dose Source: Clinical reviewer

4.5 Compliance with Good Clinical Practices

All Phase-2/3 varenicline clinical study reports included statements attesting to ethical study conduct identical (or very similar to) the following, excerpted from Section 1.2 of the A3051028 report;

> This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with IRB, informed consent regulations, and International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants. The clinical protocol was also conducted in accordance with FDA Regulations (Title 21 Code of Federal Regulations [21 CFR], Parts 50, 56, and 312).

All Phase-2/3 studies utilized similar measures to ensure adherence to Good Clinical Practice (GCP) guidelines, including, but not limited to;

- Studies were designed to comply with the ICH Good Clinical Practice guidelines
- Site visits were conducted periodically by Pfizer monitors to ensure adherence to these guidelines
- All investigators were notified (and required to acknowledge) that CRFs are legal documents intended for submission to regulatory agencies, and that any corrections to CRFs, or to any other source documents must be made so as not to obscure the original entry
- Pfizer had access to all records necessary to ensure the integrity of the data, and periodically reviewed the progress of the study with each investigator.

Management of clinical trial data at Pfizer was performed using the following procedures:

- Data entry, verification, and validation were carried out using ClinTrial Version 4.1
- Electronic Case Report Forms were employed in the Phase-3 (and some Phase-2) studies, reducing the need for manual data entry. Where necessary, a double-entry method was used to ensure accurate data transfer from source material to the study database.
- All discrepancies were investigated until resolution.

The MedDRA dictionary (Version 7.1) was used to report adverse events in Phase 3 studies and recent Phase 1 studies. Phase-2 (and some Phase-1) studies were reported using a modified COSTART dictionary. To facilitate integrated adverse event presentations, Pfizer recoded the COSTART investigator terms to MedDRA terms. No change was made to individual clinical study reports, but all

studies reported using the COSTART dictionary have equivalent MedDRA 'adverse event' and 'adverse events resulting in discontinuation' tables appended to the study reports in Module-5. Module-5 also included a thesaurus listing all investigator-reported verbatim terms, by MedDRA System Organ Class, High Level Group Term and Preferred Term.

Concomitant medication use was documented using the World Health Organization Drug Reference List (WHO-DRL, Version 97.4).

4.6 Financial Disclosures

Nineteen of the varenicline clinical studies were covered under 21CFR54.2 (Disclosure: Financial Interests and Arrangements of Clinical Investigators). Pfizer states that the covered studies were not funded via variable compensation and none of the investigators in the studies hold any form of propriety interest in varenicline. Information regarding. Pfizer also reports that it has examined its financial data regarding significant payments of other sorts made to all study investigators, and equity information as provided by the investigators, as defined in 21 CFR 54.2 (Module 1, Section 1.3.6.4).

A total of 805 investigators are listed for the multi-centered studies. Of these, 792 are certified as having no Financial Arrangements as defined in 21 CFFR 54.2. Eleven investigators had financial information to disclose, representing the remaining 13 listed investigators. (Two had enrolled to multiple protocols, and thus filed multiple FDA Forms 3455.) Specifically, two investigators held equity (> $50,000) and eleven received payments of other sorts (detailed below).

Dr. Buenconsejo re-analyzed the Phase-3 efficacy data (Studies 1028, 1036, and 1035), both the primary and key secondary endpoints, excluding data from sites with financially conflicted investigators. The statistical significance levels for all efficacy findings remained unchanged.

Study Investigators with Financial Conflicts of Interest

- [redacted] site [redacted] received a total of $101,750 [redacted] and [redacted] (in payments each less than $2500).
- [redacted] site [redacted] received $193,600 [redacted] payments ≤ $4000).
- [redacted] site [redacted] received $201,100 [redacted] payments ≤ $4000).
- [redacted] site [redacted] received $34,925 [redacted] payments ≤ $2000).
- [redacted] site [redacted] received $54,963, a single $53,963 payment on [redacted] and two $500 payments [redacted] and [redacted]. (Two forms)
- [redacted] site [redacted] received a total of $28,500 between [redacted] and [redacted] (in payments each less than $1000)
- [redacted] site [redacted] held $300,000 in Pfizer shares [redacted]
- [redacted] site # [redacted] received $149,888 [redacted]
- [redacted] site [redacted] received $39,977, $38,605 [redacted] and $1373 [redacted]
- [redacted] site [redacted] received $25,020 [redacted] payments ≤ $1400).
- [redacted] disclosed that [redacted] held Pfizer equity valued at $484,000 [redacted] but no longer did [redacted] reported no Pfizer holdings.
- [redacted] site [redacted] received a total of $47,750 [redacted] and [redacted] (in payments each less than $2500)

5 CLINICAL PHARMACOLOGY

[Portions of this section were excerpted from the OPCB review, prepared by Drs. Nallani and Zheng, and from the proposed product label.]

No approvability issues were identified. The NDA 21-928 clinical pharmacology data and findings considered to be acceptable by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

The OCPB reviewers have recommended a dosing regimen that differs from the one proposed and replicated by the applicant, however, based upon their analyses of the exposure-response data.

Pfizer proposes;
- 0.5-mg QD for Days 1 to 3, then
- 0.5-mg BID fro Days 4 through 7, then
- 1.0-mg BID from Day-8 through the end of treatment (including maintenance)

Drs. Nallani and Zheng have recommended
- 0.5-mg QD for Days 1 to 3, then
- 0.5-mg BID fro Days 4 through the end of treatment
- BUT, for patients who do not respond to 0.5-mg BID, and can tolerate a higher dose
  - 1.0-mg BID from Day-8 through the end of treatment

5.1 Pharmacokinetics

Absorption
Varenicline is highly soluble and highly permeable *in vitro* and *in vivo*. Absorption of varenicline is virtually complete (>90%) after oral administration and systemic availability is high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Maximum plasma concentrations of varenicline occur typically about 3-hours after oral dosing (1–6 hours). Following administration of multiple oral doses of varenicline, steady-state conditions are reached within 4 days. Varenicline exhibits linear kinetics when given as single or repeated doses over the 0.3-mg to 3.0-mg range.

Distribution
Plasma protein binding of varenicline is low (10%-20%) and independent of both age and renal function. Salivary secretion of varenicline in parallel to appearance of drug in plasma was noted in pharmacokinetics studies. Preclinical findings also suggest distribution of varenicline into $\alpha 4\beta 2$-nicotine receptor rich parts of brain. Varenicline appears to distribute to tissues with higher levels of melanin. The melanin-rich components of the eye (choroid, ciliary body, and iris) and skin follicles contained the highest concentrations of varenicline-associated radioactivity at all sampling times up to 168 hours. The lens and vitreous body of the eye, which are devoid of melanin, were the only tissues that were without varenicline-associated radioactivity.

Metabolism/Elimination
Varenicline is primarily eliminated in the urine as unchanged drug with an elimination half-life of approximately20 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2. The renal clearance-

mediated elimination process is independent of dose regimen, and was not altered with repeat dosing. Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine. To the small extent (<10%) that is metabolized, hepatic enzymes are not involved.

5.1.1 Pharmacokinetics in Special Patient Populations

No clinically meaningful differences were found in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, 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 patients 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), varenicline was efficiently removed by hemodialysis.

Pfizer's proposed label states "... no dosing adjustment is necessary for patients with mild to moderate renal impairment, [redacted]

Geriatric

A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1-mg varenicline given QD or BID to 16 healthy elderly male and female smokers (aged 65–75 yrs) for 7 consecutive days was similar to that of younger subjects.

Pediatric

One study evaluated varenicline pharmacokinetics in 22 pediatric patients, aged 12 to 17 years (inclusive). Each received a single 0.5-mg dose and a single 1-mg dose of varenicline. The pharmacokinetics of varenicline was approximately dose proportional between the 0.5 mg and 1 mg doses. Systemic exposure, as assessed by $AUC_{(0-\infty)}$, and renal clearance of varenicline were comparable, though not identical, to those in the adult population.

Hepatic Impairment

Varenicline pharmacokinetics are expected to be unaffected in patients with hepatic insufficiency, due to the absence of significant hepatic metabolism, Pfizer considers the potential for clinically meaningful drug interactions between varenicline and metabolic inhibitors/inducers to be low. The preliminary draft of the OPCB review does not dispute this contention.

5.1.2 Brief Overview of Clinical Pharmacology Program

Varenicline demonstrated linear pharmacokinetics when administered as single (0.1 mg to 3 mg) or repeated doses (1 to 3 mg/day) in Study 305-001. Study 3051004 demonstrated that following oral administration (1 mg of radiolabeled varenicline), material was almost all excreted in urine, indicating virtually complete absorbed with high systemic availability. Permeability across the human gastrointestinal epithelium was shown to be high, not concentration-dependent, and not mediated by

transport efflux in Study DM2003–526555-053. Based on these properties (high solubility, high intestinal permeability and nearly full recovery of varenicline in the urine as unchanged drug), Pfizer contended that it would not be necessary to perform an absolute bioavailability study with an intravenous formulation to further assess systemic varenicline availability following oral administration. This position was accepted by OPCB.

Study A3051008 was conducted to investigate multiple-dose varenicline pharmacokinetics in subjects with varying degrees of renal impairment (Study A3051008). Nonclinical and clinical evidence also suggested a minor role for active tubular secretion in the renal elimination of varenicline. *In vitro* renal transport studies demonstrated that varenicline, a small cationic molecule, has a low to moderate affinity as a substrate for, and is transported by, the human organic cation transporter, hOCT2 (DM2003-526555-052). Additionally, specific drug-drug interaction studies investigated the potential for varenicline to interact with cimetidine, a known inhibitor of hOCT2 (Study A3051010), and with metformin, another renally secreted cationic drug and hOCT2 substrate (Study A3051038).

In vitro studies suggested that varenicline undergoes minimal hepatic metabolism in humans; it is not metabolized by hepatic microsomal cytochrome (CYP) P450 enzymes (DM1998-526555-008) and does not inhibit (DM2001-526555-045) or induce (RR764-04912) activities of any of the major CYP-P450 isoenzymes. For these reasons, Pfizer considered it unnecessary to perform drug-drug interaction studies with specific inhibitors or inducers of cytochrome P450 isoenzymes. This position was also accepted by OPCB. (Clinical studies in subjects with hepatic impairment were not performed)

In anticipation of their possible (off-label) concomitant use in a patient setting, drug interaction studies were conducted with Zyban® (150 mg BID; Study A3051034) and with an NRT patch (Study A3051033). Because of the known effects of nicotine on blood pressure and heart rate, the objectives of the NRT study were specifically focused on cardiovascular safety.

Because initial clinical studies indicated that nausea was the dose-limiting adverse event, studies were conducted to determine the impact of dosing regimen (titrated vs. nontitrated; Study A3051014) and time of dosing (morning vs. bedtime; Study A3051015) on tolerability.

Population pharmacokinetic data were collected in two Phase-2 (3051002 and 3051007) and three Phase-3 (3051028, 3051036, and 3051037) studies.

5.2 Pharmacodynamics

Effect on QT/QTc

In lieu of a prospectively designed thorough QT prolongation study, a report was submitted summarizing preclinical, clinical and PK/PD assessments to support cardiovascular safety of varenicline.

Electrocardiogram data were collected from eight Phase-2/3 efficacy safety studies and 24 Phase-1 studies. A categorical summary of post-baseline ECG data was presented separately for Phase-1, Phase 2/3 clinical studies with regard to dose.

Continued Smoking
No specific pharmacodynamic evaluation in smokers was undertaken.

5.3 Exposure-Response Relationships

The concentration-response analyses were conducted with data from Phase-2 Studies 3051002 and 3051007, and Phase-3 Studies 3051028, 3051036 and 3051037.

Safety
Nausea, for most patients the dose-limiting effect, was clearly shown to be exposure-related in Dr. Zheng's analyses. Furthermore, females were about forty percent more likely to experience nausea than males, at a given exposure level (over the 0.5-mg/day to 2-mg/day dose range). Dr. Zheng's analysis (Table 5-1) shows observed and predicted nausea rates for the combined 1007/1028/1036/1037 data.

Table 5-1: Observed and Predicted Nausea Incidence, by Dose and Gender

Dose	Sex	Observed Rate % (N with Nausea/Total N)	Model Predicted
Placebo	Female	13% (57/423)	14%
	Male	7% (35/509)	7%
0.5 mg BID	Female	18% (23/130)	25%
	Male	10% (13/123)	12%
1.0 mg BID	Female	42% (242/582)	40%
	Male	22% (133/618)	20%

Source: Dr. J. J. Zheng, OPCB-2

The most commonly occurring psychiatric AEs, insomnia, abnormal dreams and sleep disturbance were also exposure related. Gender differences were not seen for these AEs, though.

Efficacy
Dr. Zheng's model predicts the probability of quitting smoking to increase from about 45% to about 50% with a dose increase from 0.5-mg BID to 1-mg BID. No gender differences are expected, however, for this relationship.

6 INTEGRATED REVIEW OF EFFICACY

This section summarizes findings from the separate Review of Clinical Efficacy

6.1 Indication

Pfizer proposes the following Indication statement:

CHAMPIX™ is indicated for smoking cessation

Two twelve-week efficacy trials were conducted with the intent to support the proposed *smoking cessation* indication, including a comparative efficacy claim (with Zyban®), A3051028 and A3051036.

6.1.1 Methods

Clinical data from Phase-3 trials 1028, 1036 and 1035, and from Phase-2 trials 1002, 1007 and 1016 were reviewed for efficacy findings, for the proposed indication (smoking cessation [redacted]). Particular attention was given to the Phase 3 studies involving the dose proposed by Pfizer for marketing, 1 mg BID (A3051028 and A3051036, the Zyban® comparison studies; and A3051035, the "maintenance" study), and to those Phase 2 studies which provided information concerning the efficacy of lower doses given over 12 weeks (studies A3051007 and A3051016).

Table 6-1 and Table 6-2 below summarize key features of the Phase-3 and Phase-2 trials, respectively.

Table 6-1: Phase 3 Trials Reviewed for Efficacy Findings

Study/Objective	Design	RX Duration	Treatment Groups	N
A3051028 Efficacy Zyban® comparison	R, PG, DB, PC active comparator	12 weeks RX then F/U to Wk-52	Varen 1 mg BID Zyban® 150 mg BID Placebo Total:	349 329 344 1022
A3051036 Efficacy Zyban® comparison	R, PG, DB, PC active comparator	12 weeks RX then F/U to Wk-52	Varen 1 mg BID Zyban® 150 mg BID Placebo Total:	343 340 340 1023
A3051035 Maintenance dosing	OL Varen 1 mg BID Then responders DB - Varen 1 mg BID OR - Placebo	12 weeks OL, then 12 weeks DB, then F/U to Wk-52	OL Varen 1 mg BID Followed by - DB Varen 1 mg BID - OR, DB Placebo Total:	1927 602 604 1927

Source: Modified from Table 1, Section 2.7.4

Table 6-2: Phase 2 Trials Reviewed for Efficacy Findings

Study/Objective	Design	Treatment Duration	Treatment Groups	N
A3051002 Dose-Ranging	R, PG, DB, PC active comparator	(Varenicline 6-weeks then Placebo 1-week) OR (Zyban® 7-weeks)	Varen 0.3 mg QD	126
			Varen 1 mg QD	126
			Varen 1 mg BID	125
			Zyban® 150 mg BID	126
			Placebo	123
			Total:	626
A3051007 Dose Titration (Off-drug follow-up in A3051018)	R, PG, DB, PC	12 weeks RX, then F/U to Wk-52	Varen 0.5 mg BID NT*	124
			Varen 0.5 mg BID T*	129
			Varen 1 mg BID NT	124
			Varen 1 mg BID T	129
			Placebo	121
			Total:	627
A3051016 Flexible Dosing (Off-drug F/U in A3051019)	R, PG, DB, PC	12 weeks RX, then F/U to Wk-52	Varen flexible doing 0.5 -2.0 mg/day	157
			Placebo	155
			Total:	312

*Non-titrated = NT, Titrated = T Source: Modified from Table 1, Section 2.7.4

6.1.2 General Discussion of Endpoints

6.1.2.1 Efficacy Endpoints in Short-Term Studies (1002, 1007, 1016, 1028, 1036)

In the four 12-week studies (007, 016, 028, 036) the pre-specified primary endpoint was the 4-week Continuous Quit Rate (CQR) during the last four weeks of treatment (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 $\leq$ 10 ppm. An additional analysis of interest to the division was the proportion of subjects initiating abstinence by week-3 (2 weeks from the target quit date) and maintaining abstinence throughout treatment. This two week "grace" period is in keeping with the analytic approach to other nicotine agonist drugs.

In seven-week Study A3051002 the protocol-specified primary efficacy was 4-week CQR assessed during any 4-week (by self-report and exhaled CO).

Patient-reported smoking status
Patients recorded their smoking status daily using paper diaries, to be brought to each clinic visit for data transfer. At each visit patients were also queried regarding smoking during the preceding week.

Carbon Monoxide
Exhaled carbon monoxide (CO) was measured at each weekly clinic visit. Patients were required to have exhaled CO $\leq$10 ppm to be considered as abstinent.

Key secondary endpoints specified in the protocols (except 1002) included:
- Continuous Abstinence Rate from Week 9 through Week 52

- Long-term Quit Rate through Week 52 (the proportion of subjects who successfully quit during the treatment phase of the study, based on the 4-week CQR from Week 9 through Week 12, and who had no more than 6-days of smoking during the nontreatment phase)

Other secondary endpoints included:
- Continuous Abstinence Rate 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
- Change from baseline in body weight

Minnesota Nicotine Withdrawal Scale, the Brief Questionnaire of Smoking Urges, and the Smoking Effects Inventory
Craving, withdrawal, and reinforcing effects of smoking were assessed through subject self-report using a battery of three valid and reliable Patient Reported Outcome (PRO) measures: Minnesota Nicotine Withdrawal Scale (MNWS), Brief Questionnaire of Smoking Urges (QSU-Brief), Smoking Effects Inventory/ Modified Cigarette Evaluation Questionnaire (SEI/mCEQ).

6.1.2.2 Efficacy Endpoints in 'Maintenance of Efficacy' Study 1035

The maintenance of efficacy study, A3051035, examined whether an additional 12 weeks of dosing with varenicline 1 mg BID would increase long-term smoking abstinence rates. Enrolled subjects were entered into a 12-week open-label phase during which all subjects were treated with varenicline 1 mg BID (titrated from 0.5 QD to 1 mg BID over a week) and attended clinic visits at Weeks 1 through 8, 10 and 12 with a TQD set at the Week 1 visit. Smoking status was assessed at each visit through self-report and exhaled CO. At the Week 12 visit, subjects who were abstinent for the previous 7 days were eligible for re-randomization to either continue on treatment or switch (blindly) to placebo for an additional 12 weeks of treatment. After re-randomization, study visits occurred at Weeks 13, 14, 16, 20 and 24. Smoking status and exhaled CO was obtained at each visit. The study included non-treatment follow-up of smoking status up to Week 52. Subjects attended clinic visits at Weeks 25, 28, 36, 44, and 52 and were contacted via telephone at Weeks 26, 32, 40, and 48.

The A3050135 efficacy criteria are shown below (Pfizer's Table-S3 from 3051035 study report):

Table 6-3: A3051035 Efficacy Criteria

Primary Endpoint:	
Continuous Abstinence (CA) Rate Weeks 13 to 24	Proportion of subjects abstinent from day of first dose of double-blind medication through Week 24 visit
Key Secondary Endpoints:	
Continuous Abstinence (CA) Rate Weeks 13 to 52	Proportion of subjects abstinent from day of first dose of double-blind medication through Week 52 visit
Long Term Quit Rate at Week 52	Proportion of subjects who maintained abstinence through double-blind treatment (Weeks 13-24), and had ≤6 days of smoking during non-treatment follow-up phase
Additional Secondary Endpoints:	
7-Day Point-Prevalence of Abstinence	Proportion of subjects abstaining from smoking during the preceding 7 days; assessed at every contact, analyzed with inferential statistics at Weeks 24 and 52
4-Week Point-Prevalence of Abstinence	Proportion of subjects abstaining from smoking during the last four weeks of the nontreatment follow-up phase (Weeks 49-52)
Time to first cigarette post-randomization	Calculated from the date of first randomized therapy to the date of first cigarette smoked

6.1.2.3 Patient Reported Outcome Measures

Cigarette Craving

Pfizer intended to assess patients' 'cigarette craving' using the Questionnaire on Smoking Urges-Brief Version (QSU-Brief), and also a single item from the Minnesota Nicotine Withdrawal Scale (MNWS)

Symptoms of Withdrawal

Pfizer intended to use four domains from the MNWS to measure patients' 'symptoms of withdrawal.'

Reinforcing Effects of Smoking

The Modified Cigarette Evaluation Questionnaire (mCEQ, also known as Smoking Effects Inventory) was intended to assess the reinforcing effects of smoking for patients.

6.1.3 Study Design

6.1.3.1 Design of Short-Term Trials

A3051028 and A3051036, the principal Phase-3 efficacy studies, used the same study design, patient population, entry criteria, treatments and efficacy endpoints. Both were double-blind, placebo-controlled, parallel-group studies, incorporating a Zyban® comparator arm. Fairly healthy current cigarette smokers (>10 cigarettes/day) who were motivated to quit were recruited, and screened for eligibility. Eligible subjects were randomized (1:1:1) to receive one of three treatments; varenicline 1-mg BID, Zyban® 150-mg BID or placebo.

Concomitant pharmacotherapy for smoking cessation was prohibited. Psychosocial treatment was not extensively described in the protocols. Each study flow-chart indicated that 'smoking status and counseling' would be assessed/conducted at every clinic visit. The protocols specified that "...counseling of up to ten minutes could be provided," following AHRQ guidelines. Subjects were

each lent an educational booklet to assist in their cessation attempt ("Clearing the Air: How to Quit Smoking...and Quit for Keeps" – National Cancer Institute Publication 95- 1647).

Baseline visit
The subjects were given the educational booklet on smoking cessation.

First treatment week
The target quit date (TQD) was seven days after treatment initiation, the day of the Week-1 visit. The quit attempt was to be in the morning, so that the last cigarette prior to the quit attempt would have been the preceding evening. Subjects were called three days after the target quit date (TQD+3) to be reminded of study participation, and to receive support for the smoking cessation attempt. Telephone contact was no longer than five minutes, and any counseling followed AHRQ guidelines. Subjects were also asked to complete the Minnesota Nicotine Withdrawal Scale and the Brief Questionnaire of Smoking Urges in the morning, on day of the TQD+3 call.

Week 1 to 12 visits (weekly)
At each visit subjects were queried about smoking during the preceding seven days, and end-expiratory carbon monoxide was measured. (Efficacy assessment is described in more detail in Section 6.1.2.1 above.). The Smoking Effects Inventory was self-administered from Week 1 through Week 7. The Minnesota Nicotine Withdrawal Scale and the Brief Questionnaire of Smoking Urges were self-administered from Week 1 through Week 7 and Week 12 or early termination. Sites could provide up to ten minutes of smoking cessation counseling, per AHRQ guidelines.

Table 6-4: Study Schematic for Twelve-Week Phase-3 Efficacy Trials (A3051028, A3051036)

<table>
<tr><th>Screening</th><th colspan="3">Double-Blind Treatment</th><th>Off-Treatment Follow-Up</th></tr>
<tr><td></td><td>Pre-TQD</td><td colspan="2"></td><td></td></tr>
<tr><td>D(-14) to D(0)
W(-2) to W(0)</td><td>D1 to D7
Week-1</td><td>Week-2 to</td><td>Week-12
W9 to W12</td><td></td></tr>
<tr><td></td><td colspan="2"></td><td>Efficacy Assessment</td><td></td></tr>
<tr><td>No study medication</td><td colspan="3">Varenicline 1-mg BID
OR
Zyban® 150-mg BID
OR
Placebo</td><td>No study medication</td></tr>
</table>

6.1.3.2 Design of Maintenance of Efficacy Study A3051035

A3051035 was a multiple-country, parallel-group study that utilized a randomized withdrawal design. A3051035 examined whether 12 additional weeks of varenicline 1-mg BID would increase smoking abstinence rates in patients able to abstain during the final week of the initial 12-week open-label treatment period, in which all patients received active drug.

Enrolled subjects began a 12-week open-label phase during which all were treated with varenicline 1-mg BID (titrated from 0.5 QD to 1 mg BID over a week), and attended clinic visits at Weeks 1 through

8, 10 and 12. The TQD was set for the Week-1 visit, and smoking status was assessed at each visit through self-report and exhaled CO. At the Week-12 visit, subjects who were abstinent for the previous 7 days were eligible for randomization to the double-blind treatment phase, in which they would receive either varenicline 1-mg BID or placebo for 12-weeks.

After randomization study visits occurred at Weeks 13, 14, 16, 20 and 24. Smoking status was assessed at each visit (self-report and exhaled CO).. The study included non-treatment follow-up of smoking status up to Week 52. Subjects attended clinic visits at Weeks 25, 28, 36, 44, and 52 and were contacted via telephone at Weeks 26, 32, 40, and 48. Table 6-5 outlines the overall study design.

Table 6-5: A3051035 Study Schematic

Screening	Run-In	Primary Efficacy Assessment	Secondary Efficacy Assessment	Safety Follow-Up
No RX	Open-Label Treatment	Double-Blind Treatment	Post-Treatment	
	Randomization→ Week-12** →→	Varenicline 1-mg BID	No Treatment	
No Treatment	Open-Label Varenicline 1-mg BID*	Placebo	No Treatment	
Day(-14) to 0	Weeks 1 to 12	Weeks 13 to 24	Weeks 25 to 52	

*Titration during Week-1 **Randomization required Week-12 abstinence only

6.1.4 Efficacy Findings

6.1.4.1 Dose-Response Evaluation

Pfizer conducted a thorough Phase 2 program to choose the dose to be studied in the Phase 3 program, and the administration regimen. The varenicline development program included evaluation of three daily doses administered using six different dosing regimens; 0.3-mg QD, 0.5-mg BID non-titrated, 0.5-mg BID titrated, 1-mg QD, 1-mg BID non-titrated, and 1-mg BID titrated.

The initial proof-of-concept efficacy study, Study A3051002, compared three doses of varenicline (0.3 mg QD, 1 mg QD, and 1 mg BID, to placebo, and incorporated a Zyban® arm but did not seek to support a comparative claim. This shorter-term (6-7 weeks) study gave Pfizer initial evidence that varenicline at 1 mg BID had efficacy superior to Zyban®. In this study 1 mg BID also appeared clearly

more effective than 1 mg QD. Studies designed and conducted prior to the conclusion of A3051002 explored 0.5 mg BID and 1 mg BID, as well as a flexible-dosing regimen in which subjects could self-titrate to effect or tolerability. These two studies (A3051007 and A3051016) could be interpreted to support recommending a dose of 0.5 mg BID; however, before these were completely analyzed, Pfizer had initiated the Phase-3 program using the 1 mg BID dose in the comparative studies. Evidence, including dose/response analyses conducted by Drs. Nallani and Zheng, demonstrates that 0.5 mg BID is an effective dose, with modest incremental efficacy at the 1 mg BID dose.

6.1.4.2 Primary Efficacy Results, Twelve Week Trials

The primary efficacy measure in both twelve-week trials was continuous four-week abstinence during Study/Treatment Weeks 9 through 12. Patients were assessed for abstinence at each weekly visit during this period. Patients were considered abstinent for that week only if both abstinence criteria were met:

- Self-reported (complete) abstinence at each weekly visit
- Exhaled carbon monoxide < 10 ppm at each weekly visit

Table 6-6 below, from Dr. Buenconsejo's review, summarizes the results of the five studies involving varenicline treatment for 12 weeks or more, showing the proportion of subjects meeting responder criteria (abstinent weeks 9-12). For A3051035, determination of the abstinence rate during weeks 8-12 of the open-label varenicline run-in was not a protocol-specified analysis, but these figures were calculated by Dr. Buenconsejo from the Pfizer's datasets to provide additional confirmation of the findings from the other studies.

Table 6-6: Primary Efficacy Criterion – Four-Week Continuous Quit Rate (Weeks 9 to 12)

	Varenicline 0.5 mg BID	**Varenicline 1.0 mg BID**	**Varenicline Flexible**	**Zyban®**	**Placebo**
Study A3051028 (%) OR (95% CI) vs. varenicline		44%		30% 1.9 (1.4, 2.6)	17% 3.9 (2.7, 5.5)
Study A3051036 (%) OR (95% CI) vs. varenicline		44%		30% 1.9 (1.4, 2.6)	18% 3.8 (2.7, 5.4)
Study A3051035 (%)		51%*			
Study A3051007 (%) OR (95%) vs. placebo	45% 6.1 (3.3, 11.1)	51% 7.8 (4.3, 14.3)			12%
Study A3051016 (%) OR (95%) vs. placebo			40% 5.7 (3.1, 10.4)		15%

* Post-hoc calculation based on Weeks 8 – 12 data during the open-label phase of Study A1035.

As is obvious from the table above, 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. On this basis, this application was accorded priority review status. Notably, Zyban® was also demonstrated to be superior to placebo in all studies incorporating a Zyban® arm

6.1.4.3 Primary Efficacy Results, Maintenance of Efficacy Study 1035

Of 1927 subjects entering the 12-week open-label treatment phase, 1236 achieved abstinence during the final week, 1210 (63%) of whom met all other criteria for randomization to double-blind treatment. Table 6-7 shows that the varenicline group demonstrated significantly higher Continuous Abstinence rates (during Weeks 13 to 24) than the placebo group.

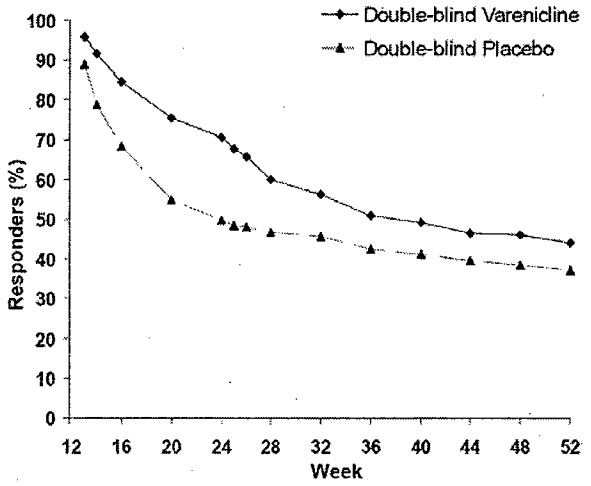
Table 6-7: Study A3051035 Continuous Abstinence, Weeks 13 through 24, per Applicant

	Double-Blind Varenicline	**Double-Blind Placebo**
ITT Subjects	N=601	N=603
Abstinent (%)	425 (71%)	301 (50%)
Odds ratio (95% CI) vs. placebo		2.5 (2.0, 3.2)
p-value vs. placebo		<0.0001
Evaluable	N=574	N=574
Abstinent (%)	418 (73%)	299 (52%)
Odds ratio (95% CI) vs. placebo		2.5 (2.0, 3.2)
p-value vs. placebo		<0.0001
Completer	N=494	N=474
Abstinent (%)	385 (78%)	284 (60%)
Odds ratio (95% CI) vs. placebo		2.4 (1.8, 3.2)
p-value vs. placebo		<0.0001

Source: Dr. Buenconsejo's Table-17

Data for the key secondary endpoint 'Continuous Abstinence, Weeks 13 to 52) show the treatment difference to diminish with time, but statistical significance is maintained (44.0% varenicline vs. 37.1% placebo, p=0.0126).

The graph below, modified from Pfizer's Figure 13.4.3.1 (A3051035 study report) shows Continuous Abstinence rates over the Week 13 to 24 (primary) and Week 13 to 52 (secondary) intervals..



6.1.4.3.1 DAARP Analysis of A3051035 Primary Efficacy Data

Because of concerns with the method used for imputation of missing efficacy data, Dr. Buenconsejo reanalyzed the Study 1035 data applying the imputation rule used for Phase-2 Studies 07 and 016. Applying these more stringent criteria (for meeting the Weeks 13 to 24 abstinence definition), Dr. Buenconsejo found five patients that no longer met abstinence criteria, all varenicline-treated. Overall efficacy conclusions were unaffected.

6.1.5 Efficacy Conclusions

Applicant-identified pivotal Phase-3 Studies 3051028 and 3051036 provide substantial evidence of efficacy of varenicline 1-mg BID as an aid to smoking cessation, and substantial evidence of the 1-mg BID dose's superiority to Zyban® (when used for smoking cessation according to the labeled dosing regimen). These studies also provide evidence that varenicline decreases quitters' "urge to smoke" as measured by two validated instruments (Pfizer proposes to use the word "craving").

Study 3051035 provides evidence that the efficacy of varenicline (1-mg BID) is maintained over a 12-week follow-up period, for smokers able to abstain during the last week of an initial 12-week open-label treatment period with 1-mg BID. That is, smokers who successfully quit smoking during varenicline treatment are more likely to maintain abstinence if varenicline treatment is continued for three additional months.

Phase-2 and exposure-response data show the incremental benefit of the 1-mg BID dose over that for 0.5-mg BID to be minimal, though clearly associated with decreased tolerability.

7 INTEGRATED REVIEW OF SAFETY

Based upon preclinical and preliminary clinical data, the most prominent safety concerns during review of NDA 21-928 involved assessment of potential hematologic, gastrointestinal and hepatic effects in humans. Given that varenicline is a first-in-class, CNS-active new molecular entity, potential neuropsychiatric effects were also of concern. Renal effects were another area of interest, greater than 90% of varenicline elimination is via the renal route. Because varenicline acts at a nicotinic receptor subtype, adverse events suggestive of withdrawal and abuse-related phenomena were of particular interest. Finally, because of its high distribution to melanin containing organs, special attention was also given to evaluation of skin and ocular effects.

Section 7.2 below describes the extent of drug exposure during clinical testing, the overall safety database, and the database subsets defined in order to conduct safety analyses. As discussed in that section, the overall number of patients treated, and the treatment durations were adequate. Four-hundred and fifty-six patients (N=456) received varenicline for more than 24-weeks, and112 received it for one year.

7.1 Methods and Findings

For deaths all pertinent data line listings were reviewed (AEs, laboratory data, concomitant medications, etc.) along with the case report forms (CRFs) and patient narratives.

For all serious adverse events (SAEs) narratives, CRFs and non-serious AEs were reviewed, along with individual data line listings for laboratory, ECG and vital sign data where pertinent. Events that were clearly not related to study drug treatment were excluded from my own summary tables and narrative discussions. Examples of such events include pre-scheduled elective surgery, motor vehicle accidents as passenger and intervertebral disc degeneration.

Pfizer defined several cohorts for the purposes of analyzing the varenicline safety data:

- The pooled **Phase-1 Studies** cohort consists of 23 studies, which treated a total of 750 subjects. Table 7-57 in Section 7.2.1.1 below provides an overview of the Phase-1 program. Appendix Table 11-5 provides additional details about the Phase-1 studies.
- The '**Phase-2/3, Fixed-dose, Placebo-controlled**' cohort includes data from four randomized, double-blind, placebo-controlled studies (A3051002, A3051007, A3051028, and A3051036), in which 2365 patients received varenicline. Treatment duration was 12-weeks in three of these studies. In the fourth, A3051002, treatment was for six (varenicline) to seven (Zyban®) weeks. Varenicline doses investigated in these studies were 0.3 mg QD, 1 mg QD, 0.5 mg BID and 1 mg BID. For most analyses, however, the applicant pooled all doses below the proposed 1-mg BID dose. The applicant has designated this cohort the '**Primary Safety Cohort**' for the purposes of comparisons across treatment groups, and for analyses of special population subgroups.
- The '**All Completed Phase-2/3 Studies**' cohort includes data from all eight completed Phase-2/3 trials, in which a total of 3940 patients received varenicline.

7.1.1 Deaths

Five deaths had been reported in varenicline study participants (N=6739) as of 07/15/05. Three deaths occurred in varenicline recipients, all Phase 2/3 patients (3940 patients received varenicline in completed Phase 2/3 studies). One death occurred in the Zyban® group (N=795) and one in placebo (N=1209). One additional death was reported in the safety update (through 12/16/05), a patient who

completed ongoing Study A3051046. Study A3051046 is not yet unblinded, but participants had a 75% chance of having received varenicline (treatment arms were 0.25-mg BID, 0.5-mg BID, 1-mg BID and placebo).

Table 7-1 summarizes mortality rates (crude, and by patient-years exposure) by treatment condition. The numbers of Zyban® and placebo exposed patients were relatively low, and exposure duration was limited (for all treatments), but varenicline does not appear to increase mortality. The blinded-therapy patient was assumed to have received varenicline. The safety update did not provide updated cumulative exposure totals (patient-exposure-years), thus mortality per 100 PEY is estimated using cumulative exposure as of 07/15/05. The varenicline to placebo exposure ratio in the ongoing studies is approximately 3:1.

The patient-exposure-years totals include data available as of 07/15/05. Both varenicline and, to a lesser extent, placebo cumulative exposure have increased since that time.

Table 7-1: Varenicline Development Program Mortality by Treatment Group

Treatment Group	Patients	Deaths	Crude Mortality	Patient-Years	Mortality per 100 PEY
Varenicline, All Doses					
Completed Trials (Phases 1/2/3)	4690	3	0.000639	948.6	0.316
Completed + Ongoing*	4825	4*	0.000829	(948.6+)*	<<0.422*
Zyban®	795	1	0.001257	130.0	2.500
Placebo	1242	1	0.000827	(254.1+)*	<1.181

*Assuming blinded-therapy patient received varenicline, and patient-exposure-years unchanged from 07/15/05
Source: Clinical reviewer

Table 7-2 below summarizes pertinent treatment and demographic information for the six varenicline clinical trial participants that died; three varenicline patients, one Zyban® patient, one placebo patient and one blinded therapy patient. Five deaths were post-treatment in completed (Phase-3) studies, while one death was on-treatment in ongoing Study A3051046. All deaths occurred post-treatment. All but one patient had completed the designated treatment period.

Table 7-2: Deaths during Varenicline Development (to 12/15/2005)

Patient ID	Age/Race/Sex	Treatment Day	Exposure	Cause (per Investigator)
Varenicline 1-mg BID				
103510121069	61/W/M	Day 196 (post-therapy Day 27)	169 days	Suicide (+ h/o MDD with suicidality)
103510241019	71/W/M	Day 188 (post-therapy Day 19)	169 days	Massive pericardial exudate Cardiac arrest, Lung cancer Lymph metastasis, Pneumonia
103510241063	29/W/M	Day 218[a] (post-therapy Day 197)	15 days	Rectal sarcoma Discontinued when diagnosed
Zyban® 150-mg QD				
103610091020	46/W/M	Day 222 (post-therapy Day 137)	85 days	Accidental death 'Fatal motorcycle accident'
Placebo				
102810181032	64/W/M	Day 352 (post-therapy Day 239)	84 days	Death unexplained (fall, collapse of lung, elbow fracture)
Blinded Therapy	**Varenicline**	**(0.5–2-mg/d) or Placebo**		
104610161030	31/A/M	Day 191 (post-therapy Day 99)	82 days	Accidental death 'Road traffic accident'

[a] Patient was diagnosed with sarcoma on treatment Day-15 Source: Modified from Table 24 (Section 2.7.4)

Patient 103510121069 represents the most potentially concerning case, a 61 year-old male who committed suicide by hanging 27-days after completing the 24-week varenicline treatment period (1-mg BID). The narrative summary states that the patient had been hospitalized for major depressive disorder with suicidal ideation in [ ] The patient had failed to divulge this history at screening, also reporting that he had never been treated with antidepressant medication. (It was unknown if there were any prior suicide attempts.) The narrative reports that the major depression lasted 1-year, then became chronic and was ongoing at the time of death. No other details regarding the [ ] MDD episode were provided. An autopsy was not performed.

Illnesses present at the time of suicide and other relevant medical history, according to the post-mortem narrative, included "burnout" (depression related to work 8 years ago), hypertension, and sciatica, major depression with suicidal ideation, gastroenteritis and rash. The patient had also reported experiencing an allergic reaction to bupropion in the past (hives). Concomitant therapy taken within 2 weeks of suicide included enalapril maleate, arachis oil/ mineral oil emulsion (Derma Mousse®), and multivitamins.

Patient 103510241019, a 71 year-old male with a > 50 pack-year smoking history, COPD and hypertension was hospitalized 19 days after completing 24-weeks of varenicline treatment with 'suspected cardiac decompensation.' He died that day. He was found to have a right sided lung mass

with numerous mediastinal lymph node metastases, along with 'massive pericardial exudate' and right sided pneumonia.

Patient 103510241063, a 29 year-old man was diagnosed with a highly aggressive rectal sarcoma, 15-days after beginning varenicline (1-mg BID). He discontinued varenicline at that time. The patient had been experiencing worsening back pain for months preceding enrollment, but had not sought medical care. He was found to have a massive rectal tumor on post-treatment Day-3, and underwent surgical resection shortly thereafter, followed with adjuvant chemotherapy and radiotherapy. He died approximately 200-days after discontinuing varenicline.

Patient 104610161030 was a 31 year-old Japanese man who died in "road traffic accident" 99-days after successful completion of Study A3051046. (Study A3051046 is an ongoing double-blind efficacy study in Japan, in which 618 patients received varenicline 0.25-mg BID, 0.5-mg BID, 1-mg or placebo.) No additional information was provided.

7.1.2 Other Serious Adverse Events

Serious Adverse Events were defined as those adverse events which:

- Resulted in death
- Were life threatening at the time of the event (not events which might have caused death had they been more severe)
- Required inpatient hospitalization, or prolonged existing hospitalization
- Resulted in persistent or significant disability or incapacity
- Were congenital anomalies or birth defects
- Were "medically important" events

Pfizer reported SAEs on a case-by-case basis, utilizing the concept of '**SAE cases**.' An 'SAE case' was defined as a single (adverse) event, or a series of events not separated in time, occurring in a single patient. A patient could have multiple serious (and non-serious) adverse events within a single SAE case, and they could also have multiple 'SAE cases,' even for the same Preferred Term, during the course of a study.

By agreement, narratives were provided for all patients experiencing SAEs. As of 7/15/2005 a total of 174 SAEs had been reported, in 134 patients, in 32 completed Phase 1, 2, and 3 varenicline studies (including IR and CR studies). Also as of 7/15/2005, 18 (of 1342) patients in ongoing Phase-2/3 studies had reported SAEs (8 in 540 subjects in A3051044, 2 in 184 subjects in A3051045, and 8 in 618 subjects in A3051046.

Limitations of the Data (also discussed in Section 7.2 below)
Elicitation, clinical management, reporting and follow-up of SAEs appear to have been appropriate, throughout varenicline development. SAE presentations and analyses in the application are acceptable.

SAE Review Methodology
Narrative summaries and Case Report Forms (CRFs) were provided for all SAEs. For each SAE both narrative summary and CRF were reviewed, along with data line listings where appropriate (i.e., laboratory and ECG data). For each patient that experienced an SAE, all non-serious AEs were individually reviewed as well.

The AE datasets (across all five MedDRA levels and verbatim terms) were also searched for certain sentinel terms; aplastic anemia, anemia aplastic, thrombocytopenia, platelets decreased, platelets low, neutropenia, white count (+/- blood cells) decreased, white count (+/- blood cells) low, red (blood) cells, seizure(s), renal failure, liver failure, hepatic failure, Stevens-Johnson, toxic epidermal necrosis, skin necrosis, necrosis skin). I uncovered no listings suggestive of bone marrow suppression, autoimmunologic reaction, dermal or otherwise, or hepatic or renal failure.

The individual study AE datasets and the two integrated AE datasets were also examined, looking for unflagged (as 'serious') adverse events.

In addition to review of the two integrated adverse event datasets, one for Phase-1 and one for Phase-2/3, I also reviewed those provided with each individual clinical study report. Besides searching for unflagged (as 'serious') AEs. All apparent SAEs were flagged accordingly, and accounted for in Pfizer's safety analyses.

Pfizer's SAE summary tables and data listings were derived from a centralized SAE monitoring database that is separate from the varenicline 'project database.' The centralized SAE database collects (and generates) expedited reports, and remains open to data updates; it does not get locked. Due to differences in the way data are entered and maintained in the two databases (e.g.. a reporting lag of 30 days for the separate safety database versus 7 days for the varenicline project database, several (small) discrepancies were found between the adverse event data line listings. In five or six cases, one of the all adverse event SOC totals appearing in individual study report appendix tables was lower (by one or two) than the corresponding total appearing within the text of the ISS. Each difference could be readily reconciled by finding the 'missing' SAE.

7.1.2.1 Phase 1 SAEs

Phase-1 SAEs

In the Phase-1 studies there were 6-SAE cases (5 varenicline, and 1 placebo) reported in 6-subjects. All cases had their onset during or soon after treatment (7-days or less). There have been no SAEs reported in the 29 subjects enrolled in the ongoing varenicline controlled release (CR) studies (12 subjects in A3051050, 17 subjects in A3051051). Table 7-3 summarizes Phase-1 SAEs by treatment group. Table 7-4 below lists the six events.

Table 7-3: SAE Incidence in Phase-1 Trials, Number of 'SAE Cases*' AND Overall Number of SAEs

	<2-mg/d (N=282)	**2-mg/d (N=309)**	**>2-mg/d (N=154)**	**VRN+ OTH (N=146)**	**OTH (N=183)**	**PBO (N=122)**	**VRN CR (N=122)**
	N	N	N	N	N	N	N
SAE Cases/# SAEs	3 3	0	1 5	0	0	1 3	1 1
On Treatment → Discontinuation	0	0	1	0	0	1	1
SAE < 30-days Post-Treatment	3	0	0	0	0	0	0

*'SAE cases' = Discrete episodes in which a subject/patient experienced one or more SAEs (defined in Section 7.1.2)
Source: Modified from Tables 28 (Section 2.7.4)

The first two cases are discussed in more detail in Section 7.1.2.2 below (Cardiac SAEs).

- 100850203101, a 57-year-old Native American male with normal renal function was diagnosed with multiple vessel CAD and underwent CABG in the course of study participation.
- 100850192502, a 64 year-old female with ESRD, cardiomyopathy and mitral insufficiency, developed progressive cardiovascular symptomatology during study participation

The third case is also listed in Section 7.1.2.2 below

- 103910011110, a 20-year-old Asian male in abuse liability Study 3051039 received a single 3-mg varenicline dose, shortly (15-minutes) after which he experienced tachycardia, nausea, tachypnea, feeling warm (coded as pyrexia) and numbness of his upper and lower extremities and face (coded as hypoaesthesia). This event resulted in the reporting of five individual SAEs. His heart rate increased to 125 bpm, and then to 144 bpm (baseline not stated), but blood pressure and temperature remained normal, and his ECG remained unchanged (sinus tachycardia only). Emergency department evaluation was, his symptoms resolved without specific treatment and he was sent home. One day later his temperature was recorded at 38.9, for which he took acetaminophen. Treatment was discontinued. He recovered without sequelae. The basis for meeting seriousness criteria is not clear.

The remaining two cases were;

- 305-1008, a 47 BM diagnosed with lung cancer 6-days after completing 12-days treatment with varenicline 0.5-mg QD.
- 305-1013-22010 –48 WF reported multiple AEs during (brief) treatment with varenicline 4-mg/day (CR) including recurrent headache, dizziness, fingertip numbness, arm tingling, foot tingling, 'heart racing,' and chest burning. This event was categorized as 'non cardiac chest pain,' a determination that seems reasonable.

Table 7-4: Phase-1 SAEs

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Verbatim Term	Preferred Term Related PMH	Event Onset Day[b]	Last dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
Cardiac Disorders								
10085019-2502 64/W/F	0.5 mg	Congestive heart failure	Cardiac failure congestive PMH ±	22	12	None	Post therapy (10)	Recovered
10085020-3101 57/O/M	0.5 mg	Coronary artery disease	Coronary artery disease PMH Yes +++ESRD	19	12	None	Post therapy (7)	Recovered
Neoplasms								
100850192501 47/B/M	0.5 mg	Lung cancer	Lung neoplasm malignant PMH ±	18	12	None	Post therapy (6)	Not recovered
General								
101310222010 48/W/F	4 mg[e]	Chest pain, non-cardiac	Non-cardiac chest pain PMH ±	12	12	Perm D/C	Yes	Recovered
Cardiac Disorders /Gastrointestinal Disorders/General disorders/Nervous system disorders/Respiratory, thoracic and mediastinal disorders								
103910011110	3 mg	Tachycardia	Tachycardia – PMH No	1	1	Perm D/C	Yes	Recovered
20/A/M		Nausea	Nausea – PMH No					
		Fever	Pyrexia– PMH No					
		Tachypnea	Tachypnea– PMH No					
		Numbness of lower extremities	Hypoaesthesia– PMH No					
		Numbness of upper extremities	Hypoaesthesia– PMH No					
		Numbness facial	Hypoaesthesia– PMH No					
PLACEBO								
00150030139 41/W/F	PBO	Perianal abscess Post-op wound infection Anal cancer	Perianal abscess PMH No Postoperat infection PMH No Anal cancer PMH No	11	15	Perm D/C	Yes	Not Recovered

Source: Clinical reviewer

7.1.2.2 Phase 2/3 SAEs

In the 'All Completed Phase-2/3 Studies' database overall SAE incidence was relatively low, and similar between treatment groups, once adjusted for patient-exposure time. There were 128 'SAE cases' (91 varenicline, 17 Zyban®, 20 placebo) in 118 patients (82 varenicline, 17 Zyban®, 19 placebo). Of these, 93 SAE cases (66 varenicline, 11 Zyban®, and 16 placebo) occurred while the patient was on study drug treatment, or within seven days of discontinuation. The remaining 25 SAE cases occurred during the post-treatment follow-up study periods; 28 to 40 additional weeks after discontinuation of treatment. Some of the SAEs reported in the application, though, occurred well over one year after treatment discontinuation.

In the ongoing Phase-2/3 studies 17 SAE cases had been reported, as of 07/05. Three of these SAE cases appear to be possibly treatment related; two in varenicline (1 in A3051044 and 1 in A3051046) and one in the blinded therapy group (A3051046). Discussion of these three cases is included below, as part of the overall SAE discussion.

Table 7-5 below shows, for each treatment group in the overall database, the number of patients that experienced SAEs, the number of SAE cases, and the number of on-treatment SAE cases, correcting for total exposure (patient-exposure-years). Both SAE and 'SAE case' incidence appear to be nominally increased in the varenicline group, compared with placebo. SAEs and SAE cases were more frequent in Zyban®-treated patients, though, with the Zyban > varenicline differences exceeding the varenicline > placebo differences.

Table 7-5: SAE Incidence per Patient-Exposure-Year*, Phase-2/3 Trials
Number of Patients Experiencing ≥ One SAE, AND Overall Number of SAEs

	All Varenicline All doses		Completed Zyban 150-mg BID		Phase-2/3 Placebo	
Patients →	**(N=3940)**		**(N=795)**		**(N=1209)**	
Pt-Years Exposure	**948.60**		**129.97**		**254.05**	
	N	**N/PEY**	**N**	**N/PEY**	**N**	**N/PEY**
Pts. with any SAE	82		17		19	
Patients with SAEs / Patient-Exposure-Years		0.086		0.131		0.075
Number of SAE Cases	91		17		20	
SAE Cases / Patient-Exposure-Years		0.096		0.131		0.079
On-Drug^ SAE Cases	66		11		16	
On-Drug SAE Cases / Patient-Exposure-Years		0.070		0.085		0.063

*Patient-exposure-year estimated, SAEs occurring after database lock and in ongoing trials are included
^ On-Drug period covers events up to 7-days after treatment discontinuation Source: Clinical reviewer

Table 7-6: SAEs in Completed Phase-2/3 Varenicline Studies

Number of Patients Treated **Number of 'SAE Cases' (Patients/SAEs)** **Patient-Exposure-Years**	**Varenicline (N=3940)** **91 (82/118)** **948.60**	**Zyban (N=795)** **17 (17/20)** **129.97**	**Placebo (N=1209)** **20 (19/24)** **254.05**
SAE cases on treatment	66	11	16
SAE cases ≤30 days post therapy	15	4	2
SAE cases >30 days post therapy	10	2	2
SAE cases leading to discontinuation	29	8	8
Cardiac SAE cases	25	0	4
Cardiac SAE cases <30 days post therapy*	18	0	4
Cardiac SAE cases <30 days post therapy/100 PEY	1.90	NA	1.57
Possibly treatment related SAE cases**	47	15	18
Possibly treatment related SAE cases**/100 PEY	4.95	11.54	7.09

*Except Patients 103910011110 and 103510241019; see discussion of cardiac SAEs below
** My assessment of possible treatment-relatedness; Zyban and placebo totals = all SAE cases up to 30-days post-RX
Source: Clinical reviewer with data from Tables 3b, A14.1, A14.2 and 28 (Section 2.7.4)

Table 7-7 below shows that cardiac SAEs occurred most commonly overall and more commonly in varenicline than placebo treated patients. Neoplasms and nervous system disorders also appear to have been more frequent in the varenicline group. Otherwise no individual SOC category appeared to be clearly related to varenicline treatment.

Table 7-7: 'SAE Cases'^ in Phase 2/3, All Completed Phase-2/3 Studies

Patient-Years Exposure →	Varenicline N=3940 948.6	VRN→PBO* N=604 ??	Zyban® N=795 130.0	Placebo N=1209 245.1
'SAE Cases' (Patients/SAEs) →	**91 (82/118)**	**6 (5/6)**	**17 (17/20)**	**20 (19/24)**
↓ Individual SAEs, by SOC ↓				
Cardiac	25**	0	0	4
Neoplasms	12	0	1	2
Infections/Infestations	11	1	3	4
Nervous System	11	1	6	1
Gastrointestinal	9	1	1	1
General/Admin. Site	6**	0	1	3
Psychiatric	6	0	0	2
Vascular	6	0	0	1
Eye	5	0	0	0
Injury/Poisoning	6	0	3	5
Investigations	5	0	0	0
Musculoskeletal	4	0	1	0
Metabolism/Nutrition	3	0	0	0
Renal/Urinary	3	0	0	0
Hepatobiliary	2	1	1	0
Pregnancy/Puerperium	2	0	2	0
Reproductive/Breast	2	2	0	1
Respiratory/Thoracic	2	0	0	2
Ear and Labyrinth	1	0	0	0
Immune System	0	0	0	1
Skin/Subcutaneous Tissue	0	0	1	0

^ 'SAE cases' defined above
** I identified one case not categorized correctly (General →Cardiac)
* Patients that received placebo during DB phase of maintenance study 3051035
* These SAEs occurred ≥ 30 days after randomization to placebo (discontinuation of varenicline)
Source: Modified from Tables A13.1, A13.2 and 29 (Section 2.7.4)

7.1.2.2.1 Cardiac SAEs (Including Phase-1)

The overall incidence of cardiac SAEs (predominately ischemic in patients with known disease) appears to be increased in varenicline-treated patients, even after correcting for patient-exposure-time. It should be noted that of the 187 study patients treated for more than 48-weeks, 130 received varenicline. Of approximately 2000-patients on-treatment for more than 12, but less than 24-weeks, about 75% received varenicline.

Of the 25-SAEs, or 22 SAE cases, I consider most to be possibly treatment-related (gray shaded PIDs), in part because of their relatively high frequency and temporal proximity to treatment. Many of these patients had known cardiac disease (mostly CAD), in some cases with histories of multiple interventions, while others were clearly at high risk based upon their risk factor profiles. Such patients should have been represented in the placebo and Zyban® groups in similar proportions, however. Although the apparent increase in varenicline cardiac SAEs may be due, in part to the longer exposure duration for each individual in the varenicline group, it is also possible that varenicline played a role in precipitating events in patients with pre-existing or occult cardiac disease.

For calculation of event rate per varenicline exposure-time I counted each cardiac SAE case reported within 30-days of varenicline discontinuation, as possibly drug-related, with one exception;

- 103910011110, a 20-year-old Asian male in abuse liability Study 3051039 received a single 3-mg varenicline dose. Fifteen minutes later after he experienced nausea, tachypnea, feeling warm (coded as pyrexia) and numbness of his extremities and face, and then tachycardia. His heart rate increased to 125 bpm, and then to 144 bpm (baseline not stated), but blood pressure and temperature remained normal. His ECG remained unchanged (sinus tachycardia only). Emergency department evaluation was unremarkable. His symptoms resolved without specific treatment and he was discharged. His temperature the next day reached 38.9° for which he took acetaminophen. He recovered without sequelae. The basis for meeting seriousness criteria is not clear.

My total of 18 cardiac SAE cases was arrived at by subtracting seven SAEs from Pfizer's total of 24, and adding one case inappropriately categorized as 'non cardiac chest pain' under SOC 'General';

- The 20 year-old healthy volunteer described in the paragraph above. (-1)
- Patient 103510241019 was a 71 year-old man that died of lung cancer 19-days after completion of treatment in 24-week Study 1035 (Cardiac arrest, pericardial effusion). These two cardiac events were almost certainly not primary cardiac events. (-2)
- Patient 103710061019, a 71 year-old WM with an extensive past cardiac history including CABG, and conduction system disease. On Day-259 (1-mg BID) he was admitted to the hospital with symptoms of inferior ischemia. He was readmitted on Day-315 for elective angioplasty, largely as a result of his Day-259 event. I consider these three cardiac SAEs, counted as two cardiac SAE cases by Pfizer to represent one actual event, thus I counted this patient's cardiac SAEs once. (-2)
- 1 (SVT) reported in PID 103510311006, a 56 year-old man with history of WPW. This event occurred 30-days after treatment discontinuation (143-days treatment) (-1)
- 1 newly diagnosed unstable angina (PID 10025005100) in a 41 year-old WM 50-days after completion of Study 1002 (1-mg/d for 42-days). He discontinued early because of newly diagnosed Type-2 DM, but aside for a brief URI had no other on-treatment AEs. This event was most likely not drug-related, given its occurrence seven weeks after treatment discontinuation (-1)
- Patient 103710061009, a 48 year-old WM with a known history of CAD, including CABG, MI and stable exertional angina, IDDM (with neuropathy) and COPD, experienced retrosternal chest pain and pressure with radiation to his neck while sedentary, on treatment, Day-208 (1-mg BID). He was hospitalized, treated with aspirin, SL nitroglycerin and enoxaparin, and cathed. The cath showed patent grafts, and no obviously new occlusions, but this event should certainly not be considered 'non cardiac' and categorized under SOC 'General Disorders and Administrative Site Conditions.' (+1)

My review of 'chest pain' SAEs categorized under SOC 'General Disorders and Administrative Site Conditions' for all dose conditions identified one incorrectly categorized case, listed immediately above.

Table 7-8 below summarizes all cardiac SAE cases by presumed primary disturbance, in an attempt to provide the reader with additional context. Given that rhythm disturbances can be precipitated by ischemia, and vice versa, it should be kept in mind that any such categorization is somewhat arbitrary, especially given the limited information available for most cases. It appears, though, that for varenicline the ratio of ischemic to electrophysiologic cases is roughly 3:1, regardless of causality.

Table 7-8: 'Cardiac SAE Case' Type (Reviewer Assessment, All Reported Cases)

	Varenicline Possibly Related	Varenicline All	Placebo
Patient-Exposure-Years	948.6	948.6	245.1
Total (per 100 PEY)	18 (1.90) *	22 (2.32) *	4 (1.63)
Ischemic (per 100 PEY)	14 (1.48) *	17 (1.79) *	3 (1.22)
Arrhythmic (per 100 PEY)	5 (0.53) *	6 (0.63) *	1 (0.41)
Ischemic + Arrhythmic (per 100 PEY)*	1 (0.11)	1 (0.11)	--
Malignancy (per 100 PEY)	--	1 (0.11)	--

One SAE-case (103710061019) counted twice, once in 'ischemic' and once in 'arrhythmic'
Source: Clinical reviewer

Table 7-9 below lists all 25 cardiac SAEs (22 cardiac 'SAE cases') that occurred in varenicline-treated patients during varenicline clinical development (through 07/15/05). My summaries of the individual cases follow the table. Table 7-10 lists the four cardiac SAEs that occurred in placebo-treated patients.

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Table 7-9: Cardiac SAEs during Varenicline Development (Through 07/15/05): Varenicline Treatment

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Verbatim Term	Preferred Term Related PMH	Event Onset Day[b]	Last dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
Cardiac Disorders								
103610051011 50/W/M	2 mg	Acute coronary syndrome	Acute coronary syndrome PMH Yes	70	70	Perm D/C	Yes	Recovered
102810231018 75/W/M	2 mg	Atrial fibrillation	Atrial fibrillation PMH Yes	84[c]	84	None	Post therapy (0)	Recovered
103510301014 73/W/M	2mg	Atrial fibrillation	Atrial fibrillation PMH No	29	28	Perm D/C	Yes	Recovered
103710011021 59/W/M	2mg	Coronary artery disease	Coronary artery disease PMH ++Risks	191	191	Perm D/C	Yes	Recovered
103710061025 60/W/M	2mg	Coronary artery disease	Coronary artery disease PMH Yes	362	365	None	No	Recovered
103510341063 65/O/M	2 mg	Myocardial infarct	Myocardial infarction PMH Yes	158	NA	MultiChallenge/ Rechallenge	No	Recovered
103510291026 45/O/M	2mg	Myocardial infarction	Myocardial infarction PMH No	102	84	None	Post therapy (18)	Unknown
10075011594 44/W/F	2 mg	Paroxysmal supraventricular tachycardia	Supraventricular tachycardia PMH Yes	51	51	Perm D/C	Yes	Recovered
103510311006 56/W/M	2 mg	Supraventricular tachycardia	Supraventricular tachycardia PMH Yes	173	143	None	Post therapy (29)	Recovered
103710061033 44/W/F	2 mg	Tachycardia	Tachycardia PMH No	171	N/A	MultiChallenge/ Rechallenge	No	Recovered
1016503148 52/W/M	2 mg	Ventricular fibrillation	Ventricular fibrillation PMH No	101	87	None	Post therapy (14)	Recovered
10075028336 48/W/M	1 mg	Intermediate coronary syndrome (unstable angina)	Angina unstable PMH No	59	60	Perm D/C	Yes	Recovered
10025005100 40/W/M	1 mg	Unstable angina	Angina unstable PMH No	92	42	None	Post therapy (50)	Recovered
10165031173 54/W/M	1 mg	Myocardial infarction	Myocardial infarction	57	50	None	Post therapy (7)	Recovered

(Continued)

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Verbatim Term	Preferred Term Related PMH	Event Onset Day[b]	Last dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
Cardiac Disorders								
10085019-2502 64/W/F	0.5 mg	Congestive heart failure	Cardiac failure congestive PMH ±	22	12	None	Post therapy (10)	Recovered
10085020-3101 57/O/M	0.5 mg	Coronary artery disease	Coronary artery disease PMH Yes +++ESRD	19	12	None	Post therapy (7)	Recovered
Incorrectly Coded	**to**	**General Disorders/Administ.**						
103710061009 48/W/M	2 mg	Chest pain	Chest pain	208	N/A	None	No	Recovered
Cardiac disorders/Vascular disorders								
103710061019	2 mg	Ventricular bigeminy	**Extrasystoles** – PMH Yes	241	N/A	None	No	Recovered
75/W/M		Worsening sinus bradycardia	**Sinus bradycardia** PMH Yes					
		Coronary angioplasty	**Coronary artery disease** Yes	315	NA	None	No	Recovered
		Hypotension	Hypotension					
103710061052	2 mg	Myocardial infarction	**Myocardial infarct**. PMH No	7	7	Perm D/C	Yes	Recovered
55/W/F		Deep vein thrombosis	Deep vein thrombos PMH No					
Cardiac Disorders /Gastrointestinal Disorders/General disorders/Nervous system disorders/Respiratory, thoracic and mediastinal disorders								
103910011110	3 mg	Tachycardia	**Tachycardia** – PMH No	1	1	Perm D/C	Yes	Recovered
20/A/M		Nausea	Nausea – PMH No					
		Fever	Pyrexia– PMH No					
		Tachypnea	Tachypnea– PMH No					
		Numbness of lower extremities	Hypoaesthesia– PMH No					
		Numbness of upper extremities	Hypoaesthesia– PMH No					
		Numbness facial	Hypoaesthesia– PMH No					
Cardiac Disorders/Neoplasms benign, malignant and unspecified (including cysts and polyps) Infections and infestations								
103510241019	2 mg	Cardiac arrest	**Cardiac arrest**	188	169	None	Post therapy	Death
71/W/M		Massive pericardial exudate	**Pericardial effusion**				(19)	
		Lung cancer	Lung neoplasm malignant					
		Lymph node metastasis	Metastases to lymph nodes					
		Right side pneumonia	Pneumonia					
Cardiac Disorders/Renal and urinary disorders/Reproductive system and breast disorders								
103510171142	2 mg	Myocardial infarction	**Myocardial infarction**PMH+	101	N/A	Multi challenge/	No	Recovered
59/W/F		Bladder prolapse	Bladder/uterine prolapse			Rechallenge		

Table 7-10: Cardiac SAEs during Varenicline Development (Through 07/15/05): Placebo Treatment

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
PLACEBO								
Cardiac disorders								
102810031045 55/B/M	PBO	Acute myocardial infarction	Acute myocardial infarction	28	27	Perm D/C	Yes	Recovered
102810181032 64W/M	PBO	Atrial fibrillation	Atrial fibrillation	85	85	None	No, EOT Visit	Not Recovered
103710101005 56/W/M	PBO	Worsening coronary artery disease	Coronary artery disease	114	N/A	MultiChallenge/ Rechallenge	No	Recovered
103610081084 74/W/M	PBO	Ischemic heart disease	Myocardial ishaemia	23	N/A	None	No	Recovered

Cardiac/Gastrointestinal/General/Nervous System/Respiratory
103910011110, a 20-year-old Asian male in abuse liability Study 3051039 received a single 3-mg varenicline dose, shortly (15-minutes) after which he experienced tachycardia, nausea, tachypnea, feeling warm (coded as pyrexia) and numbness of his upper and lower extremities and face (coded as hypoaesthesia). This event resulted in five simultaneous SAE reports, one of which as cardiac 'tachycardia.' His heart rate increased to 125 bpm, and then to 144 bpm (baseline not stated), but blood pressure and temperature remained normal, and his ECG remained unchanged (sinus tachycardia only). Emergency department evaluation was unremarkable. His symptoms resolved without specific treatment and he was discharged. One day later his temperature was recorded at 38.9, for which he took acetaminophen. Treatment was discontinued. He recovered without sequelae. The basis for meeting seriousness criteria is not clear. (Not counted in my cardiac SAE analysis)

Cardiac/Renal/Reproductive
103510171142, 59 WF smoker with history of hypertension, hypercholesterolemia, hypothyroidism, thyrotoxicosis, insomnia, migraine headaches, and dyspepsia, using losartan potassium/ hydrochlorothiazide (Hyzaar®), HCTZ, and levothyroxine, completed both phases of Study 1035 (169-days,1-mg BID), but continued smoking. On [ ] (Day-101) complained of pain and frequency on urination. She was diagnosed with prolapsed uterus and bladder and underwent surgical genitoplasty [ ] Varenicline was temporarily discontinued during hospitalization [ ] [ ] Her end-of-treatment ECG [ ] revealed P wave changes, confirmed on repeat ECG [ ] The investigator suspected perioperative MI, but, reportedly, no ECGs were obtained prior to or after surgery. She was asymptomatic, however (with respect to cardiac symptoms).

Cardiac/Vascular
103710061019, a 71 year-old WM with an extensive past cardiac history including CABG, angioplasty and conduction system disease completed treatment (363-days, 1-mg BID) in 52-week Study 1037. On Day-259 he was admitted to the hospital with symptoms of inferior ischemia (worsening bradycardia, progression of bigeminy, hypotension, vomiting). Nuclear cardiac imaging confirmed that the patient was having recurrent ischemia, and he was discharged three days later. The narrative does not comment on medication changes, except to state that varenicline was continued. He was re-admitted Day-315 for elective angioplasty, largely as a result of his Day-259 event. A stent was placed in his circumflex artery and he was discharged the following day. No additional cardiac AEs were reported. (Counted as one cardiac SAE case for my analysis).

103710061052, a 55 WF with an 80 pack-year smoking history, but no known cardiovascular disease, experienced chest pain on Day-7, during her first (titration 0.5-mg/day→1-mg/day→2-mg/day) week of varenicline. She was diagnosed with right-sided myocardial infarction, and underwent cardiac catheterization and stenting of her RCA. The following day (Post-therapy Day-1) she experienced shortness of breath for which a spiral CT scan of the chest was performed, showing multiple pulmonary emboli, saddle pulmonary embolus, and thrombus in the inferior vena cava and deep veins of both legs. An IVC filter was placed and she was anticoagulated. She was discharged on post-therapy Day-9.

Cardiac (Only SOC)

103610051011, a 50 WM with PMH of CAD, LBBB and stable exertional angina, HTN and dyspepsia, were treated for 70-days with 1-mg BID. He began omeprazole on Day-61 for dyspepsia, was evaluated by his PCP on Day-70 for dyspepsia → ER, CPK-MB 8.7 and 7.3, troponin-T 0.17 and 0.23, underwent angioplasty (no details re: anatomy), and was discharged the following day.

102810231018, 75 WM with 100+ pack-year smoking history, and history of CAD with system disease (screening ECG first degree AV-block, RBBB, LAHB) COPD, hypothyroidism treated with Synthroid®. He completed treatment in Study 1028 (1-mg BID), but at his end-of-treatment visit on Day-84, was found to be in atrial fibrillation with ventricular response rate of 95 (asymptomatic).

103510301014, a 73 WM with PMH significant for COPD but no known cardiac history, experienced new onset atrial fibrillation (rapid rate) on Day-27 (1-mg BID). He was admitted to the hospital and varenicline was permanently discontinued. He had missed several doses of varenicline prior to the onset of atrial fibrillation; he did not take varenicline from [ ] (Study Day 19) to [ ] (Study Day 21) because of vomiting or from [ ] (Study Day 23) to [ ] (Study Day 27) because of stomach discomfort. He spontaneously converted back to sinus rhythm and he was discharged on [ ] A cardiology consultation noted elevation of brain natriuretic peptide consistent with elevated left sided pressures, consistent with underlying diastolic dysfunction. The event was considered resolved on [ ] Concomitant therapy taken within 2 weeks before the onset of atrial fibrillation included rofecoxib, teriparatide, adalimumab, and tamsulosin hydrochloride. Because the patient had not actually taken varenicline during the four days preceding the event, this event may not have been related to varenicline treatment.

103710011021, a 58-year-old WM with past medical history of DM and hyperlipidemia received varenicline 1-mg BID (titrated) for a total of 191 days. On [ ] (Day-79) he presented with right-sided chest pain, which had been occurring off and on since [ ] (Study Day 28). A stress test was performed on [ ] (Study Day 183). On [ ] (Day-191) he underwent cardiac catheterization, resulting in hospitalization with a diagnosis of coronary artery disease. On [ ] (Study Day 192), the subject underwent a three-vessel CABG. He was discharged from the hospital on [ ] (Day-197). Varenicline was permanently discontinued on [ ] (Day-191) in response to the CAD diagnosis. The event was considered resolved on [ ] Meds taken before event included metformin hydrochloride, rosiglitazone, glipizide, simvastatin, sildenafil citrate, and enalapril maleate.

103710061025, was a 60-year-old WM smoker with history of hypertension (on three-drug regimen), chest pain, migraine headache, lumbar spinal stenosis, and erectile dysfunction. He received varenicline 1-mg BID (titrated) for 365-days ([ ] As of [ ], the subject reported smoking. He complained of chest pain on [ ] On [ ] (Day-362) he underwent cardiac catheterization revealing single-vessel disease. He was admitted electively for stent placement on [ ] Concomitant therapy taken preceding the event included sublingual nitroglycerin, hydrochlorothiazide, acetylsalicylic acid, lisinopril, and atenolol.

103510341063, 65 y/o HM, multiple CAD risk factors, using rofecoxib, HCTZ, lisinopril, rosuvastatin, admitted to hospital treatment Day-158 (1-mg BID) with AIWMI (peak MB=140), multiple vessel CAD with 95+% RCA, had PTCA/stent, discharged next day. This event may have been drug-related.

103510291026, 45 y/o M with 40 pack-year smoking history and hypertension, completed 12-weeks open-label treatment (1-mg BID) but was not re-randomized (still smoking). On post-therapy Day-18 he experienced chest pressure (no further description provided), and was hospitalized with a diagnosis of high lateral MI, had PTCA. He had had several mildly elevated blood pressure readings on treatment (diastolic ≈90-95 mmHG), but study ECGs were normal. He did, however, report an episode of "heart pounding" on [ ] . (treatment Day-18) which was coded as 'arrhythmia' and not coded as resolved until [ ] Because of the ongoing on-treatment symptoms, I consider this SAE to be treatment –related, despite its occurrence 18-days after treatment discontinuation.

10075011594, a 44 WF with no known cardiac history (50 pack-year smoking history, positive family history) received 1-mg BID for 51-days. On Day-51 she experienced sudden onset palpitations, diaphoresis, lightheadedness and heartburn. She was evaluated at her local emergency department 40-minutes later symptom onset and found to be in PSVT at 175-bpm, which resolved with IV adenosine. The investigator attributed this event to her (unchanged) caffeine intake of cups of coffee per day.

103510311006, a 56 WM with history of Wolfe Parkinson White Syndrome (including multiple previous episodes of SVT), HTN, and hyperlipidemia. He received OL 1-mg BID for 12-weeks, then DB 1-mg BID, from [ ] (57 days DB, 143 days total). He experienced a brief episode of SVT 30-days after drug discontinuation. Total exposure to varenicline was 143 days. ((Not counted in my cardiac SAE analysis)

103710061033, a 44-year-old WF with no cardiac risk factors except smoking (25 pack-year), received 1-mg BID beginning 01/05/2004.,. As of 03 Jan 2005 she was still smoking. On [ ] (Study Day 171) she experienced tachycardia, which led to inpatient hospitalization. She had sudden onset of palpitations, with heart rate ≈150 bpm while at work. The symptoms lasted approximately 2 hours. On [ ], a cardiac catheterization and stress echocardiogram revealed no structural abnormality. The cardiac catheterization revealed normal sinus rhythm and ventricular dysfunction, and presumably normal coronary artery flow.

101650310148, 52 WM with 60 pack-year smoking history but no other known medical history experienced ventricular fibrillation 14 days after completing flexible dosing study 1016 (87-days flexible dosing with a maximum daily dose of 2-mg, but a mean dose < 1.5-mg/day).. He was found unconscious in his car and defibrillated by police. ECG showed anterior ST-segment elevation and T-wave inversion (consistent with anteroseptal ischemia). Cardiac catheterization revealed a 99% proximal LAD lesion (100% distal occlusion), and an ejection fraction of 45%. The cath findings (hardened plaque) were considered to be indicative of chronic atherosclerotic disease.

100750280336, 48 WM with 140 pack-year smoking history, no other known medical history (family history positive for early CAD), receiving varenicline 0.5-mg BID (through Day-60), experienced exertional chest pain (Day-59), had cath revealing RCA occlusion, which was stented. He was discharged two days later.

10025005100, a 41 year-old WM experienced an SAE coded as 'unstable angina' 50-days after completion of Study 1002 (1-mg/day for 42-days). He discontinued early because of newly diagnosed Type-2 DM, but aside for a brief URI had no other on-treatment AEs. This event was most likely not drug-related, given its occurrence seven weeks after treatment discontinuation

101650310173, 54 WM with 80 pack-year smoking history but no known cardiac history discontinued treatment due to an episode of chest pain (Day-50, 1-mg BID). Seven days later he presented to an ED with acute MI. He underwent angioplasty (RCA and LAD stenting).

Subject 100850203101 in renal PK/PD Study 1008, a 57-year-old Native American man with normal renal function and no known cardiac disease (in retrospect recently experiencing exertional chest pressure). Screening ECG (Day-(-8)) showed findings consistent with ischemia but (in the absence of symptoms) the investigator interpreted the results as not clinically significant, Baseline ECG (Day-(-1)) showed similar abnormalities. He completed study participation (0.5-mg QD X 12 days). On Post-Therapy Day-7 he experienced 4-5 hours of left sided chest pressure (no associated symptoms). He presented to clinic on Post- Therapy Day 10 with recurrent chest pain. ECG showed persistent (or worsened) abnormalities, and echocardiogram showed multiple RWMA with mildly decreased LVEF and left atrial enlargement. He refused admission but returned on Post- therapy Day-13 with recurrent exertional chest pressure. He was admitted, underwent catheterization (Post-RX Day-14) revealing numerous occlusions, and had a four-vessel CABG that day.

Subject 100850192502 in renal PK/PD Study 1008, a 64 year-old female with ESRD, cardiomyopathy and mitral insufficiency, received 0.5-mg/day for 12-days, completing treatment. On Day-4 she complained of cough, shortness of breath and paroxysmal nocturnal dyspnea. Examination on Day-8 revealed expiratory wheezes for which she was started on amoxicillin (Day-9). On 29 Post-Therapy Day-10 she was admitted by her physician for evaluation of what was first thought to be pneumonia, but later identified as congestive heart failure. On Post-Therapy Day-11 echocardiogram revealed LVEF of 30- 35%, LVH and moderate to severe mitral regurgitation (worsened since [ ]). On Post-Therapy Day-13 catheterization revealed severe mitral insufficiency and 'moderate coronary vascular disease.' She underwent 2-vessel CABG and mitral valve repair on Post-Therapy Day 47.

7.1.2.2.2 Nervous System and Psychiatric SAEs

Overall, there were 15 SAE cases involving a total of 17 SAEs related to the Nervous System or Psychiatric Disorders for varenicline-treated subjects in all completed varenicline clinical trials. The event terms included: cerebral infarction, cerebral thrombosis, cerebrovascular accident, cervical cord compression (event occurred during double-blind placebo phase of Study A3051035), grand mal convulsion, headache, hypoaesthesia, loss of consciousness, multiple sclerosis, transient ischaemic attack, acute psychosis, affect lability, completed suicide, depression, and suicidal ideation. All events were reported in only one patient with the exceptions of grand mal convulsion, multiple sclerosis, and acute psychosis, each of which was reported in two subjects. I consider seven of these 17 events to be possibly, though not clearly, treatment related (one seizure case, both multiple sclerosis cases, stroke, TIA/transient blindness, hypoaesthesia and headache).

All individual SAEs (grouped by 'SAE case') are listed in Appendix Table 11-1 through

Table 11-4, corresponding to the four treatment groups, varenicline, varenicline → placebo (in A3051035), bupropion and placebo, respectively.

Table 7-11 below lists non-cardiac SAEs in varenicline-treated patients I consider to be possibly drug related, or for which no other plausible explanation could be found and all malignant neoplasm SAEs, regardless of my assessment of relatedness. Summaries of each case appear after Table 7-11.

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Table 7-11: Possibly Treatment-Related SAEs and SAE Cases by System Organ Class and Treatment Group: Varenicline Treatment

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Verbatim Term	Preferred Term Related PMH	Event Onset Day[b]	Last dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
Ear and Labyrinth/General								
103610141100	2 mg	Vertigo worsening	Vertigo PMH Yes	64	63	Perm D/C	Yes	Recovered
		Chest pain	Chest pain PMH Yes					
43/B/F		Elevated blood pressure	BP increased ±? PMH Yes					
Eye disorders								
103510151038	2 mg	Diminished vision	Visual acuity reduced	42	N/A	None	No	Recovered
55/W/M			PMH Yes					
103510231034	2 mg	Transient vision loss both eyes	Blindness transient	124	141	Perm D/C	Yes	Recovered
55/W/F			PMH Yes					
Eye disorders/Nervous system disorders								
10025005-27	2 mg	Transient loss of vision	Blindness transient	20	35	Perm D/C	Yes	Recovered
52/W/M		Transient ischemic attack	Transient ischaemic attack	20	35	Perm D/C	Yes	Recovered
Gastrointestinal disorders								
102810071069	2 mg	Abdominal pain	Abdominal pain	63	62	Perm D/C	Yes	Recovered
42/W/M			PMH No					
103510231019	2 mg	Abdominal pain	Abdominal pain	48	70	Perm D/C	Yes	Recovering
50/W/F			PMH No					
Investigations								
103510271179	2 mg	Elevated ALT	ALT increased – PMH No	83	N/A	Multiple	No	Recovered
31/W/M		Elevated AST	AST increased – PMH No			Challenge/		
		Elevated CPK	CPK increased– PMH No			Rechallenge/		
		Elevated lactate dehydrogenase	LDH increased– PMH No			Interrupt		
Neoplasms benign, malignant and unspecified (including cysts and polyps)								
103510121147	2 mg	Glandular adenocarcinoma	Adenocarcinoma	57	86	Perm D/C	Yes	Not Recovered
42/W/M			PMH No					
103610021078	2 mg	Carcinoma brain	Brain neo. Malignant PMH ±	15	28	Perm D/C	Yes	Not Recovered
58/W/F		Lung cancer	Lung neo. Malignant PMH ±					
10075010476	2 mg	Carcinoid colon cancer	Colon cancer	94	85	None	Post therapy (9)	Recovering
65/W/M			PMH No					

(Continued)

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Verbatim Term	Preferred Term Related PMH	Event Onset Day[b]	Last dose Day[b]	Action Taken	DC Treatment[*] (Day)	Outcome
Neoplasms benign, malignant and unspecified (including cysts and polyps)								
103510171011 59/W/F	2 mg	Colon cancer	Colon cancer PMH No	165	N/A	None	No	Recovered
103510271079 56/W/M	2 mg	Nasopharyngeal carcinoma	Nasopharyngeal cancer PMH No	30	N/A	None	No	Not Recovered
10075011259 49/W/M	1 mg	Right ear cholesteatoma	Cholesteatoma PMH Yes	27	57	Perm D/C	Yes	Recovered
100850192501 47/B/M	0.5 mg	Lung cancer	Lung neoplasm malignant PMH No	18	12	None	Post therapy (6)	Not recovered
10025010-380 39/W/F	0.3 mg	Crohn's disease Adenocarcinoma	Crohn's disease PMH Yes Adenocarcinoma PMH No	163	44	None	Post therapy (119)	Recovering
See PID 103510241019 in Cardiac Disorders/Neoplasms/ Infections and infestations			Lung neoplasm malignant PMH No					
Nervous system disorders								
103510241217 42/W/F	2 mg	Cerebral infarct Deep cerebral vein thrombosis	Cerebral infarction PMH ?? Cerebral thrombosis PMH ??	161	N/A[f]	Perm D/C	Yes	Recovering
103710061022 41/O/M	2 mg	Stroke	Cerebrovascular accident PMH ±	118	117	N/A	No	Recovered with sequelae
103510271307 48/W/M	2 mg	Grand mal convulsion	Grand mal convulsion PMH No	41	41	Perm D/C	Yes	Recovered
103510231013 51/W/M	2 mg	Headache	Headache PMH Yes	36	44	Perm D/C	Yes	Recovered
10025005-56 40/B/F	2 mg	Multiple sclerosis	Multiple sclerosis PMH No	101	42	None	Post therapy (59)	Not Recovered
10075011540 52/W/F	2 mg	Relapsing remitting multiple sclerosis	Multiple sclerosis PMH Yes	59	60	Perm D/C	Yes	Not Recovered
See PID 10025005-27 in Eye disorders/Nervous System			Transient ischaemic attack					
Pregnancy, puerperium and perinatal conditions								
103510341066 43/W/F	2 mg	Miscarriage	Abortion spontaneous PMH - ??	97	85	None	Post therapy (12)	Recovered
10165035136 30/W/F	1.5 mg	Spontaneous abortion	Abortion spontaneous PMH - ??	94	84	None	Post therapy (10)	Recovered

(Continued)

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Verbatim Term	Preferred Term Related PMH	Event Onset Day[b]	Last dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
Psychiatric disorders								
103510241209 46/W/F	2 mg	Acute psychosis	Acute psychosis PMH - No	7	8	Perm D/C	Yes	Recovered
103610141087 42/W/F	2 mg	Acute psychosis Emotional lability	Acute psychosis – PMH No Affect lability – PMH No	57	69	Perm D/C	Yes	Recovered
103510121069 61/W/M	2 mg	Suicide	Completed suicide PMH - Yes (MDD)	196	169	None	Post therapy (27)	Death
103510121089 45/W/F	2 mg	Suicidal ideation	Suicidal ideation Yes	74	73	None	Post therapy (1)	Recovered

Source: Section 2.7.4 Table A14.1 and adverse event datasets

[a] Race: W =White, B=Black, A=Asian, O=Other; Gender: M-male, F=Female; d/c=discontinued.

[b] Days are relative to start of treatment; for Study A3051035 start of treatment=start of open-label treatment.

* Treatment discontinuation due to this SAE

[c] Atrial fibrillation was first noted on Day 84, SAE triggered by hospitalization on Day 91.

[d] Varenicline/Placebo represents those subjects that were randomized to placebo after open-label varenicline treatment period in Study A3051035.

Ear and Labyrinth Disorders
103610141100, a 43-year-old black female with PMH significant for vertigo, hypertension, gastroesophageal reflux disease, tension headache, and back pain, received varenicline 1-mg BID from [ ] a total of 63 days. Medication was discontinued because of vertigo. Her only chronic use medication was lansoprazole. On [ ] (Pre-Study) her blood pressure was 120/84 mmHg sitting and 124/86 mmHg standing. On [ ] (Day-57) her blood pressure was 130/82 mmHg sitting and 132/84 mmHg standing. She chose to discontinue study treatment.

On Post-Therapy Day-1 she developed 'worsening vertigo' and was admitted to the hospital. The narrative states that concurrent with her admission for vertigo she '...developed an elevated blood pressure and chest pain' but preadmission and admission vital signs are not provided. She was treated with meclizine and Percocet®, and discharged the next day. According to the narrative, she was not treated for hypertension in the hospital, nor discharged on an antihypertensive. She followed in (study) clinic over the next several weeks, with blood pressures in the 140/85 range, but then was lost to follow-up. Her long-term outcome is not known.

Eye
103510231034, 55 WF with PMH of 'night blindness' was treated with varenicline 1-mg BID in both phases of study. On Day-113 he complained of 'blurred vision' that he had been having over the preceding two to three weeks. Serial optometric/ophthalmologic exams verified decreasing visual acuity, and the patient discontinued treatment on Day-141.

100250050027, 52 WM, TIA with ocular manifestations, see 'Nervous System Disorders'

103510151038, a 55-year-old WM with PMH significant for bilateral cataract surgery (R-1996, L-1997), peripheral vascular disease, hypertension, hyperlipidemia, alcohol abuse, lacunar infarct, transient ischemic attacks, bilateral cataract repairs, and > 150 pack-year smoking history, completed both study phases (OL and DB), receiving varenicline 1-mg BID for 169 days. Chronic use medications were simvastatin, ramipril, clopidogrel sulfate, and acetylsalicylic acid.

On [ ] (Study Day 42), he experienced diminished vision bilaterally, described as continuously blurry with both near and far objects. There was no history of eye trauma, recent or in the past. No ophthalmologic exam had been performed at baseline. The patient had stated that he did not need glasses and his vision was 20/20.

Ophthalmologic evaluation on [ ] was essentially normal, though the patient was refracted and corrective lenses were prescribed with which vision improved to 20/20. The etiology of the sudden visual change was described as 'uncertain.' No other problems were found, and a neurology consult was not performed at that time. Varenicline treatment continued unchanged. On [ ] (Study Day 103), the subject reported his vision was normal again, even without the use of eyeglasses.

The patient had been scheduled for neurological evaluation, and on [ ] (Study Day 136) a CT head scan revealed no new infarcts (lacunar infarct 2000). On [ ] the consulting neurologist stated that the patient had '...a possible long standing problem and a possible inherited condition, including spinal muscular atrophy.' Electromyography was performed on [ ] revealing evidence of neurogenic dysfunction in the left upper and lower extremities, seen only on needle exam, predominantly affecting distal muscles. The report added '...in the proximal muscles, there may be

very mild myopathic changes which must be closely associated with the clinical condition.' The report concluded that the onset and disappearance of the visual problem was most keeping with an episode of ischemia in the posterior circulation.

Investigations/Hepatic
Patient 103510271179 experienced an 'SAE case' in which four laboratory-related SAEs were reported; elevated AST, ALT, lactate dehydrogenase, and creatinine phosphokinase (Day-84, 1-mg BID). The patient's brief inpatient workup may only have resulted from his CPK value (12594), however. The patient's AST increased to about 7 X his baseline, his ALT to less than 2 X his elevated baseline and his LDH to 3 X baseline. The laboratory findings were attributed to a recent muscle injury. BUN and creatinine values remained normal, and urinalysis values are not available. Varenicline treatment was interrupted for about one-week. By Day-365 ALT had decreased to near its baseline elevated value (65), and AST to 42. Hepatitis virus titers are not provided.

Gastrointestinal
102810071069, 42 WM no relevant PMH, tolerating varenicline relatively well, experiencing some mild to moderate nausea during his first several treatment weeks. He woke from sleep on Day-63 with diffuse abdominal pain. ER workup ruled out suggested possible acute appendicitis, for which he was admitted, but his symptoms soon resolved spontaneously and he was discharged. He discontinued varenicline, and experienced a similar episode five weeks later, for which there is still no definitive diagnosis.

103510231019, 50 year-old WF without relevant past medical history, receiving varenicline 1-mg BID open-label. On treatment Day-48 she developed abdominal pain with meteorism and constipation. The abdominal pain was characterized both as 'colic-like' and diffuse. She self-treated with OTC antacids, simethicone and bisacodyl, with no relief of symptoms. Her physician suspected a right-sided abdominal abscess and referred her to the hospital, where she had a negative workup.

Her symptoms continued intermittently. Varenicline was discontinued on Day-70 due to the abdominal pain. Her 'diffuse pain with meteorism and constipation' persisted. Further workup 3-weeks later, including abdominal ultrasound was negative. She was hospitalized subsequently, however, for treatment of her abdominal pain, though dates are not provided. A colonoscopy on Post-Therapy Day 43) revealed no abnormalities. A gastroenterology consultation reported the pain to be due to 'meteorism and constipation' but the final diagnosis was unknown. As of Post-Therapy Day 91 her symptoms were ongoing, though decreasing in intensity.

Neoplasms
103510181002, 58 year old WF, received VRN to Day-142, withdrew early, on Post-RX Day-367 diagnosed with 'abdominal neoplasm.'

103510181020, 47 year old WF with past medical history including ovarian cysts, obesity, Bechterew's disease, post-menopausal symptoms, back pain, using norethisterone acetate, received 29 days VRN in DB phase, pt. self DCd for lack of efficacy, U/S revealed 'ovarian tumor' post-RX Day-33, non-malignant.

103610021078, a 58 year old WF with PMH significant for hysterectomy (1986) and right anterior chest pain (and > 120 pack-year smoking history), discontinued treatment (1-mg BID) on Day-28

because of newly diagnosed lung cancer. Screening chest radiography had shown an 'abnormal swelling/enlargement' in her right lung. Follow-up MRI (Day-15) revealed bilateral lung masses, and subsequent workup indicated that she had 'advanced stage' disease with extensive metastases, including to the brain.

103510121147, 42 year old WM with 50 pack-year smoking history but no other relevant medical history was diagnosed with metastatic glandular adenocarcinoma on treatment Day-57 (1-mg BID), but continued varenicline until Day-86 (the end of his participation in the open-label phase of the study). The narrative states that right clavicular adenopathy had been noted earlier, but does not provide additional information (nor does the CRF). At the time of the last report to Pfizer the glandular adenocarcinoma 'was still present and resolution was not expected.'

On 16 Feb 2004 (Study Day 57), the subject was diagnosed with metastatic glandular adenocarcinoma (primary site unknown), which the investigator considered an important medical event. In response to the glandular adenocarcinoma varenicline therapy was permanently discontinued. At the time of the last report the glandular adenocarcinoma was still present and resolution was not expected.

10075010476, a 65-year-old white male with a history of colonic polyps and a 100 pack-year smoking history received varenicline 1-mg BID for 85-days, completing the study. On [ ] (Post Treatment Day 8) he experienced abdominal cramping that felt like constipation, but had two normal bowel movements the same day. On [ ] (Post Treatment Day 9) CT scan indicated possible appendicitis. He went to surgery for presumed acute appendicitis, at which time he was found to have a colonic malignancy (carcinoid). "A section of the large intestine, a small section of the small intestine and a small section of the liver" were resected, along with his normal appendix. He was discharged from the hospital on [ ] and considered to be was recovering from the event.

103510171011, a 59 year old WF with a PMH of 'liver rupture', tuberculosis, and malaria, received varenicline (1-mg BID) for a total of 140-days (83 OL, 57 DB), discontinuing several weeks before the end of the DB phase because she had successfully quit smoking (09 FEB 2004). On [ ] (Post-treatment Day-25, Study Day 165) she was diagnosed with colon cancer. She underwent resection, and the colon cancer was considered resolved on [ ]

103510271079, a 56 year-old WM received open-label varenicline 1-mg BID [ ], for a total of 84 days, and then DB placebo [ ] for a total of 56 days. On [ ] (Study Day —, he reported swelling in the neck. On [ ] (Study Day 185), a lymph node biopsy revealed type-3 nasopharyngeal carcinoma. On [ ] (Study Day 192), he underwent lymph node resection and tonsillectomy. The date of hospital discharge was not provided. He refused further study participation.

10075011259, a 49 year-old WM with a history of perforated right tympanic membrane, right hearing loss and 'episodic drainage,' and otitis, with ≈100 pack-year smoking history, received varenicline 0.5-mg BID for 57-days (of 84-planned, [ ]). On [ ] (Study Day 27) he was referred to an otorhinolaryngologist due to a history of 'bilateral ear symptoms.' He was found to have a cholesteatoma of the right ear. Varenicline was discontinued on [ ] (Study Day 57) in preparation for surgery. He was hospitalized on [ ] and underwent right tympanoplasty with atticotomy and mastoidectomy. The cholesteatoma had not penetrated the neural endothelium; however, the head of the malleus was involved.

10025010-380, 29 WF with PMH of Crohn's disease, was diagnosed with Crohn's exacerbation and adenocarcinoma (colon?) 118-days after completing 44-days of treatment with varenicline 0.3-mg QD. No narrative summary is available.

Nervous System

103510241217, a 42 year old WF with PMH significant for 30 pack-year smoking history and oral contraceptive use (about 2-3 months). She received OL varenicline 1-mg BID for 12-weeks, then DB for the next 59-days. On [ ] (Study Day 160) she fell while bicycle riding, hitting her unprotected head. The next day she was found at home on the floor by a neighbor, and was admitted to the hospital. Blunt head trauma was noted (parietal-temporal 4 X 5 cm elevation). CT scan revealed a 4 cm X 3 cm space occupying lesion at the right anterior horn, fresh bleeding at the right caput nucleus caudatus, a hyperdensity region, and possible thrombosis. MRI revealed multiple bilateral infarcts in the thalamus with petechial bleeding in the right basal ganglia, and complete thrombosis of the internal veins, vena galeri and transverse sinus on the left side, and partial thrombosis with narrow recanalization of the sinus rectus. Platelet count was within normal limits. She was diagnosed with a deep cerebral vein thrombosis (sinus thrombosis), with secondary infarction of the thalamus and the basal ganglia. Coagulation workup was negative.

Her condition deteriorated ([ ] Post-Therapy Day 20), necessitating intubation. She was noted to have new left hemiparesis and decreased level of consciousness, and was intubated. MRI on ([ ] (Post-Therapy Day-26) showed stable findings. She developed and was treated for ventilator associated pneumonia. At the time of last report ([ ] (Post-Therapy Day 102), however, she was recovering at home, living alone managing well.

103710061022, 41-year-old male smoker, relevant medical history included hypercholesterolemia, atypical chest pain, and hyperlipidemia. He received varenicline 1-mg BID (titrated), [ ] for a total of 117 days. On [ ] (Post-Therapy Day 1) he presented to an emergency department "for complex migraine headaches." He was admitted to the hospital with a presumptive diagnosis of CVA, and discharged on [ ] with sequelae of residual left arm weakness, daily headaches and left eye peripheral vision loss. Information about the final diagnosis and hospital treatment were not available "... due to lack of subject cooperation." The patient was lost to follow-up.

103510271307, 48 WM with a 40 pack-year smoking history, and possibly hypertension, complained of insomnia beginning treatment Day-4 (OL 1-mg BID) which improved with dose reduction to 0.5-mg BID. When the 1-mg BID dose was resumed so did the insomnia. He experienced a grand mal seizure on Day-41. MRI Day-104 normal. There is no other apparent cause for this patient's new onset seizure, aside from varenicline administration.

103510231013, 51 WM with history of benign coital cephalalgia 21-yrs prior, received varenicline 1-mg BID for 44-days. He reported nausea on Day-15 nausea. His dose was reduced (to 1-mg/day) for two weeks. When he resumed 2-mg/day (Day-36) he began to experience "severe, explosive and unsufferable" headache during coital intercourse. Headache/nausea recurred with coitus several times, and the patient discontinued varenicline on Day-62.

10025005-56, 40 year-old BF, with past medical history of intermittent 'muscle weakness on the left side' over the preceding two years, sciatica and hypothyroidism, received varenicline 1-mg BID

[ ]), and then placebo [ ]. The serious adverse event of 'Multiple Sclerosis' was diagnosed on [ ]

The patient experienced left eye pain on [ ]. She saw an ophthalmologist on [ ], reporting loss of color vision. A follow-up visit on [ ] with the same ophthalmologist noted that her vision had worsened, and she was diagnosed with idiopathic optic neuritis. At about this time she informed the study investigator for the first time that she had experienced minor left-sided weakness over the last two years, which she had attributed to being overweight.

On [ ] an MRI demonstrated "Foci of increased signal intensity in the white matter bilaterally. One of these foci shows some focal enhancement in the left parietal lobe. There is no surrounding mass effect or edema. Consideration is given to a demyelinating process." On [ ] she was evaluated by a neurologist and was diagnosed with optic neuritis of the left eye. She underwent additional imaging studies and lumbar puncture over the next two months, and on [ ] was diagnosed with 'probable multiple sclerosis.' Other adverse events during the study included nausea, anxiety, decreased appetite, headache, and influenza.

10075011540, a 52 year old WF with past medical history of migraine headaches, paresthesias and shingles received varenicline 1-mg BID [ ] (Study Day 1) [ ] a total of 60 days. In [ ] she had experienced paresthesias on the right upper abdomen and right leg (numbness and tingling) that had initially been attributed to herpes zoster. In [ ] the symptoms recurred and the subject was treated with acyclovir. She entered the trial reporting recent paresthesias of the abdomen and right thigh. Brain MRI was performed on Day-10 with results 'inconclusive for multiple sclerosis (MS)'. Lumbar puncture was performed Day-49, and the results were characterized as 'most likely non-progressive MS. Varenicline was discontinued on Day-60.

100250050027, 52 WM taking 1-mg BID experienced transient ischemic attacks manifested by transient loss of vision in the left eye (with halo effect) on treatment Day-20. He was diagnosed with an ocular TIA. Carotid Doppler showed mild left proximal carotid stenosis.

103510151038, 55 WM with PMH of 'lacunar infarct and other TIAs,' alcohol abuse, and bilateral cataract repairs, completed both study phases (169-Days exposure). On Day-42 he complained of 'diminished vision' but his ocular exam was essentially normal. He continued on varenicline (1-mg BID) and his vision normalized spontaneously within 2-months. Neurological evaluation two weeks prior to resolution suggested "...a possible long-standing problem and a possible inherited condition, including spinal muscular atrophy." On [ ] electromyography revealed evidence of neurogenic dysfunction in the left upper and lower extremities, seen only on needle exam, predominantly affecting distal muscles.

Pregnancy, Puerperium and Perinatal Conditions

Patient 103510341066, a 43 year-old WF experienced a spontaneous abortion 12 days after completing the open-label phase of Study 1035 (1-mg BID). She had not been randomized to the double-blind phase because she was still smoking. Estimated gestational age of the fetus and serum B-HCG are not provided. She recovered without sequelae.

Patient 1016035136, a 30 year-old WF experienced a spontaneous abortion 10 days after completing flexible-dose Study 1016 (1.5-mg/day). Estimated gestational age of the fetus and serum B-HCG are not provided. She recovered without sequelae.

Psychiatric Disorders
103510241209, a 46 year-old W/F with no known psychiatric history or substance abuse disorder, experienced acute psychosis one day after discontinuing varenicline (1-mg BID), which she had taken for only seven days. She was not using any other medications. She had reported insomnia, though this is not given as the reason for discontinuation (which is unclear). On post-treatment Day-1 she arrived at work "acting strangely," agitated, talking incoherently, confronting her colleagues, and turning over furniture. She was subsequently hospitalized and admitted to the psychiatric ward for acute psychosis. Later reports indicated that the subject had been experiencing auditory hallucinations, suicidal thoughts and symptoms of psychosis prior to first dosing with varenicline.

103610141087, a 42 year old WF with no significant past medical or psychiatric history and no family history of psychiatric illness experienced 'bizarre behavior' worsening over 2-weeks beginning around Day-57 (1-mg BID), for which she was hospitalized (Day-70), with hallucinations, delusions, marked anxiety, delusions. Her family reported that she had typically drank one to two beers daily, but shortly after beginning the study, and quitting smoking, she increased her intake to 15 to 15 beers per day. She had also been complaining of insomnia. Concomitant medications included Benadryl and ibuprofen. She was discharged about two weeks later, her psychotic symptoms resolved. She had not experienced a reoccurrence, as of [ ] (about ten months after discharge).

103510121069, a 61 year old white male, committed suicide 27-days after completing 24-weeks of treatment with varenicline 1-mg BID. See discussion in Section 7.1.1 above.

103510121089, a 45 year old WF with history of MDD [ ], insomnia and multiple somatic symptoms, discontinued varenicline on Day-73 "...because she wanted to resume cigarettes." (The discontinuation reason cited was refusal to participate further.) The data listings show that the following day Preferred Terms 'Major depression' and 'Suicidal ideation' were reported. She had also reported AE terms fatigue, irritability and insomnia while on treatment. She was started on citalopram, and her suicidality was considered resolved the following month.

Vascular
103710061046, 69 BM, h/o PVD, CAD, stable exertional angina, Day-78 left saphenous vein occlusion, ischemic right foot Day-110

(New) SAEs Reported in the Safety Update

Fifteen new SAE cases were reported (2 varenicline, 4 NRT, and 9 blinded therapy), summarized in Table 7-12. The System Organ Classes most commonly represented were Injury/Poisoning (5) and Infections/Infestations (4). No new safety concerns emerge, but the cases of depression (varenicline) and unstable angina (possibly varenicline) are noteworthy, as is the number of accidents.

Table 7-12: SAEs Reported in (90-Day) Safety Update

PID/Treatment Age/Race/Gender	Daily Dose	MedDRA Preferred Term	Related PMH	Onset Day	Last Dose	Action Taken DC RX-Day
VARENICLINE						
104410061014 45/W/M	2 mg	Alcohol poisoning	Yes	98	84	Post-RX
104410241006 35/W/F	2 mg	Depression	Yes	21	49	Perm D/C Day-21
BLINDED =	**NRT**	**OR VARENICLINE**				
104510031021 47/A/M	BL	Angina unstable	Yes	50	52	Perm D/C Day-50
104610161030 31/A/M	BL	Accidental death Motorcycle	??	181	82	**Death**
104510031030 47/A/M	BL	Knee injury/ Road traffic accident	NA	20	NA	No action taken
104510081003 52/A/M	BL	Peritonitis/ Appendicitis	No	79	81	Perm D/C Day-81
104510081026 35/A/M	BL	Pyelonephritis acute	Yes	80	81	Perm D/C
104610021012 51/A/F	BL	Herpes zoster	??	321	85	Post-RX
10461031005 31/A/M	BL	Gastroenteritis	Yes	222	85	Perm D/C
104610161002 52/A/M	BL	Foot fracture	NA	220	85	Post-RX
104610161030 31/A/M	BL	Accidental death	NA	181	82	Post-RX
104610181008 57/A/M	BL	Gastric cancer, Stage-1	No	NA	85	Post-RX
NRT						
104410081027 50/W/F	NRT 14-mg/d	Cyst	No	NA	46	Post-RX
104410151002 33/W/F	NRT 7-mg/d	Traumatic injury	NA	46	74	Post-RX
104410271031 56/W/M	NRT 21-mg/d	Myocardial infarction	±	34	NA	Challenge/ Re-challenge
104410281019 74 W/M	NRT 7-mg/d	Prostate cancer	??	125	70	Post-RX

Source: Clinical reviewer

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of study dropouts

Phase-1 Studies

Table 7-13 below shows TEAE-related discontinuation rates, by treatment group, in the Phase-1 studies. Overall, AE-related discontinuations were relatively infrequent, and treatment group sizes were small. Subjects in the drug-interaction studies ('varenicline + other' treatment, NRT or bupropion) appear to have a considerably higher AE-related dropout rate (10%) than those in the other groups. The higher rate of adverse event treatment discontinuations in the varenicline + other group is due in part to the number of discontinuations (10/22) among subjects in the 'varenicline + NRT' arm of A3051033.

Otherwise, the incidence of discontinuation from treatment due to adverse events increased with increasing varenicline dose, with the highest incidence in the 'varenicline >2-mg/day' group; 4%, similar to the rate in the 'other drug only' group.

Table 7-13: Phase-1 Discontinuations Attributed to Adverse Events (per Applicant)

Permanent Discontinuation Due to Adverse Event	Varenicline <2-mg/day N=241	Varenicline 2-mg/day N=309	Varenicline >2-mg/day N=112	Varenicline + Other N=146	Other Only N=141	Placebo N=255
Number of Subjects (%)	1 (0.4)	6 (1.9)	4 (3.6)	14 (9.6)	5 (3.5)	1 (0.4)

Source: Clinical reviewer

Phase-2/3 Studies

In the 'Phase 2/3 Fixed-dose, Placebo-controlled Studies' (FDPC), the incidence of treatment discontinuation due to adverse event was 12.1%, 11.7%, 14.3% and 9.7% in the varenicline < 1-mg BID, varenicline 1-mg BID, Zyban® 150-mg BID and placebo groups, respectively (by Pfizer's report). In the 'All Completed Phase 2/3 Studies' (ACP23) database 12.9% of varenicline-treated patients (all doses), 14.3% of placebo-treated patients and 9.0% of placebo-treated patients discontinued due to adverse events (also by Pfizer's report). My review of the disposition and adverse event data leads me to believe that Pfizer correctly attributed causality (for premature discontinuations) in nearly all cases.

Table 7-14 summarizes TEAE-related discontinuations rates, and time to discontinuation for the 'Fixed-dose, Placebo-controlled Studies' database, including a categorical breakdown (by treatment group) of time to discontinuation. Discontinuation rates were similar across treatment arms, though slightly more frequent in the Zyban® arm, and less frequent in the placebo arm. Interestingly, patients in the two varenicline treatment arms appear to discontinue later, especially those in the 1-mg BID arm, while Zyban® (and to a lesser extent placebo) patients discontinued early in treatment.

Table 7-14: Discontinuations due to Treatment-Emergent AEs, Phase-2/3, per Applicant, FDPC Studies

Patient-Exposure-Years →	Varenicline <1mg BID N=505 74.7	Varenicline 1mg BID N=1070 187.4	Zyban® 150-mg BID N=795 130.0	Placebo N=928 149.7
Number of TEAE-Related Discont. (%)	61 (12.1%)	125 (11.7%)	114 (14.3%)	90 (9.7%)
Time to Discontinuation (Days) (%)				
1-14	17 (30)	30 (24)	55 (48)	35 (39)
15-28	17 (30)	33 (26)	31 (27)	31 (34)
29-42	14 (23)	25 (20)	11 (9)	13 (14)
>42	13 (21)	37 (30)	17 (15)	11 (12)
Median Time to Discontinuation (Range)	26 (1-83)	28 (1-82)	15 (1-91)	18 (1-81)
TEAE-Related Discontinuations Patient-Exposure-Years	0.82	0.67	0.88	0.60

Source: Modified from Tables A16.1a and 34 (Section 2.7.4)

7.1.3.2 Adverse events associated with dropouts

Phase-1 Studies

The only adverse events that resulted in discontinuation from treatment for more than one Phase-1 subject receiving varenicline alone were nausea and vomiting. Discontinuation due to nausea occurred in 2 subjects in the varenicline 2-mg group and 3 subjects in the 'varenicline + other treatment' (NRT) group. Discontinuation due to vomiting occurred in 3 subjects in the varenicline 2 mg group, 4 subjects in the varenicline > 2 mg group, and 2 subjects in the 'varenicline + other' treatment group. All three discontinuations for urticaria occurred in subjects that received 'other drug; 2 subjects in the 'varenicline + other' treatment group and 3 subjects in the 'other treatment' group.

Phase-2/3 Studies

Only three individual adverse event Preferred Terms resulted in treatment discontinuation in ≥1.0% of patients in either of the varenicline treatment groups (in the FDPC trials): nausea, headache and insomnia. Only nausea showed a dose-related incidence, resulting in 3.1% treatment discontinuations in the varenicline 1-mg BID group. Among the 33 subjects in the varenicline 1-mg BID group who discontinued treatment due to nausea, only 5 had nausea with an intensity rated as severe, though.

Table 7-15 below shows the Phase-2/3 adverse events associated with discontinuation in one percent or more of patients (in any varenicline dose group), for both 'Fixed-dose, Placebo-controlled Studies' and for the varenicline-treated patients in 'All Completed Phase-2/3 Studies.'

It should be noted that adverse event related discontinuations were more common in longer-term study 3051037.

Table 7-15: AEs Resulting in Treatment Discontinuation (≥ 1% in Any Varenicline Group), per Applicant Fixed-Dose, Placebo-Controlled Phase-2/3 Studies, and All Completed Phase-2/3 Studies (Varenicline Only)

	Fixed	Dose	Placebo	Controlled	All
Patient-Years Exposure →	Varenicline <1mg BID N=505 74.7	Varenicline 1mg BID N=1070 187.4	Zyban® N=795 130.0	Placebo N=928 149.7	Varenicline Phase 2/3 N=3940 948.6
ALL	**61 (12.1)**	**125 (11.7)**	**114 (14.3)**	**90 (9.7)**	**510 (12.9)**
GASTROINTESTINAL	**12 (2.4)**	**45 (4.2)**	**27 (3.4)**	**17 (1.8)**	**134 (4.9)**
Nausea	5 (1.0)	33 (3.1)	8 (1.0)	5 (0.5)	121 (3.1)
NERVOUS SYSTEM	**12 (2.4)**	**(25 (2.3)**	**29 (3.6)**	**21 (2.3)**	**91 (2.3)**
Headache	6 (1.2)	6 (0.6)	9 (1.1)	8 (0.9)	39 (1.0)
Dizziness	0 (0)	7 (0.7)	4 (0.5)	3 (0.3)	14 (0.4)
PSYCHIATRIC	**20 (4.0)**	**35 (3.3)**	**38 (4.8)**	**35 (3.8)**	**148 (3.8)**
Insomnia	3 (0.6)	13 (1.2)	17 (2.1)	10 (1.1)	43 (1.1)
Anxiety	4 (0.8)	4 (0.4)	6 (0.8)	8 (0.9)	13 (0.3)
Irritability	4 (0.8)	5 (0.5)	4 (0.5)	5 (0.5)	14 (0.4)

Source: Modified from applicant Tables A8.1a, A15.1a, 33 and 34

7.1.3.3 Other significant adverse events

Neuropsychiatric

See Section 7.1.4 (Other Search Strategies).

Skin/Immune System

Non-serious skin-related adverse events, mostly various rashes, were more common in varenicline patients as in placebo patients (8% vs. 5%), but less common than in Zyban® patients (10%). No specific rash type appeared to predominate, though. The only preferred terms that occurred at ≥1% in any treatment group in the Phase 2/3 Fixed-dose, Placebo-controlled Studies were rash, pruritus, and urticaria. Urticaria was reported at ≥1% in the Zyban® treatment group, but not in either of the varenicline treatment groups. Nearly all cases resolved within hours to days, mostly with OTC antihistamine or with no treatment at all.

Most patients experiencing these adverse events completed treatment. In the All Completed Phase 2/3 Studies, 27 varenicline-treated patients discontinued treatment for skin-related adverse event PTs. The MedDRA Preferred Terms were: 'rash' (11 patients or 0.3%); urticaria (6 patients or 0.2%), pruritus (5 patients or 0.1%), and peripheral oedema, pharyngeal oedema, face oedema, pustular rash, generalized rash (1 patient each). Meanwhile 28 Zyban®-treated patients (3.5%) discontinued for skin AEs. Of note, about two-thirds of varenicline patients discontinuing because of skin-related AEs were in the longer-term studies.

During the entire varenicline development program, the single SAE case for skin and subcutaneous tissues disorder occurred in a Zyban®-treated subject (angioneurotic oedema, Patient 103610061014). I also queried the safety database looking for patients with AE Preferred Terms; edema, face edema, peripheral edema, and generalized edema, reviewing the CRFs and narrative summaries for the handful of patients identified.

The 'Immune System Disorders' SOC was also examined for AE Preferred Terms suggestive of drug sensitivity. In the Phase 2/3 Fixed-dose, Placebo-controlled Studies, immune system PTs were reported in 1.0% at <1-mg BID, in 1.1% at 1-mg BID and at 1.1% in placebo. Many of these AE terms were seasonal allergies, food allergies, or other non-drug allergies. 'Drug hypersensitivity' was reported for only two patients (one treated with varenicline 1 mg BID, and one treated with Zyban®).

Eye

I queried the integrated safety database for AEs related to the eyes including Preferred Terms vision abnormal, diplopia, amblyopia, retinal edema, retinal disorder, eye disorder, and visual field defect. The CRFs and narrative summaries for all patients identified were carefully reviewed.

Overall, ocular adverse events were not more common in varenicline-treated patients. A total of five varenicline-treated patients in the Phase 2/3 Fixed-dose, Placebo-controlled Studies permanently discontinued treatment due to an 'Eye Disorder' adverse event, however; 4 in the <1 mg BID group and 1 in the 1 mg BID group. The patients discontinued due to severe conjunctivitis; moderate transient blindness; mild abnormal sensation in eye along with mild vision blurred; mild vision blurred; and moderate vision blurred. Three placebo patients permanently discontinued treatment due to ocular adverse events including moderate cataract; moderate vision blurred along with moderate blindness transient (treatment related); and mild photophobia. No Zyban®-treated patients discontinued due to ocular adverse events.

A total of 5 of the 3940 varenicline-treated patients in All Completed Phase 2/3 Studies reported SAEs related to eye disorders; no Phase 1 subjects had eye-related SAEs. Of these 5 cases, 2 may have been treatment related: transient loss of vision and transient vision loss both eyes. Both events resulted in permanent treatment discontinuation.. There appears to be no similarities between the 2 cases of transient blindness. One occurred in a 55 year-old white female subsequent to a viral influenza infection and the other occurred in a 52 year-old white male, and was subsequently diagnosed as an ocular transient ischemic attack.

Renal

The adverse event profile from the Phase-2/3 studies does not suggest any safety concerns related to renal function. The frequency of renal and urinary disorders in the Phase 2/3 Fixed-dose, Placebo-controlled Studies was 12/505 (2.4%) in the varenicline <1 mg BID group, 20/1070 (1.9%) in the varenicline 1 mg BID group, 19/795 (2.4%) in the Zyban® group, and 9/928 (1.0%) in the placebo group.

No varenicline-treated patients (in the Phase 2/3 Fixed-dose, Placebo-controlled Studies) discontinued for a urinary or renal disorder. One varenicline patient in the All Completed Phase-2/3 Studies database discontinued treatment due to a renal/urinary SAE,' ureteral calculus' which he had a prior history of. Two additional patients had SAEs classified as renal disorders (bladder prolapse and nephrolithiasis) but these did not result in permanent discontinuation of treatment.

Clinical laboratory assessments of renal function included BUN, creatinine, and qualitative urinalysis tests. No varenicline-treated patients in the Phase 2/3 Fixed-Dose, Placebo-Controlled Studies had a clinically significant elevation of BUN or creatinine. Among the 3940 varenicline-treated patients in the Phase 2/3 studies, 3 had clinically significant elevations of BUN, and none had clinically

significant elevations of creatinine. Renal and urinary laboratory findings are discussed in Section 7.1.7 below.

7.1.4 Other Search Strategies

Also see Section 7.1.3.3 above.

7.1.4.1 Psychiatric and Nervous System Adverse Events

As a nicotinic agonist, varenicline is not expected to be associated with increased rates of depression and suicidality. MedDRA coding divides depression-related adverse event Preferred Terms across multiple HLGTs and SOC categories, though, making recognition of depressive symptomatology more difficult. A search (of the adverse events) was performed in order to identify all AEs suggestive of depression and depressive symptoms.

Depression/Depressive Symptoms Search Strategy

A search for MedDRA Preferred Terms (PT) indicative of depressive symptoms or behavior was performed, using those PTs specified in the Standardized MedDRA Query for 'Depression.'

Table 7-16: Depression Preferred Term Search (SMQ Narrow Terms)

Adjustment disorder with depressed mood	Depressive symptom
Adjustment disorder with mixed anxiety and depressed mood	Dysphoria
Anhedonia	Dysthymic disorder
Antidepressant therapy	Electroconvulsive therapy
Decreased interest	Feeling guilty
Depressed mood	Feeling of despair
Depression	Feelings of worthlessness
Depression postmenopausal	Major depression
Depression postoperative	Postpartum depression

Table 7-17 below shows that the SMQ search (for depression-related MedDRA Preferred Terms) yielded identical incidence rates to the use of the HLGT 'Depressed mood disorders and disturbances' alone (comprised of two HLTs, 'Depressive disorders' and 'Mood alterations with depressive symptoms'), in all but the 1-mg BID group, for which the SMQ identified one additional patient. This indicates (that for NDA 21-928) the MedDRA HLGT should suffice for the purposes of identifying patients with depressive symptomatology.

Table 7-17: Incidence of Depression/Anxiety by Treatment Group, Fixed-Dose, Placebo-Controlled*

Population/Studies	< 1-mg BID N=505	1-mg BID N=1070	Zyban® N=795	Placebo N=928
FDPC				
Depressive symptoms SMQ**	24 (4.8)	30 (2.8)	23 (2.9)	17 (1.8)
HLGT Depressed mood disorders and disturbances	24 (4.8)	29 (2.7)	23 (2.9)	17 (1.8)
Anxiety/Nervousness/Agitation	37 (7.3)	51 (4.8)	60 (7.5)	56 (6.0)

* Studies 02/07/28/36 ** Depression SMQ described above Source: Clinical reviewer from AE datasets

7.1.4.1.1 Search for Adverse Events Suggestive of Suicidality

As a nicotinic agonist, varenicline is not expected to be associated with increased rates of depression and suicidality. Nevertheless, a search (of the adverse events) was performed in order to identify all AEs suggestive of potential suicidality. The search included the MedDRA Preferred Terms listed in Table 7-18, along with the text string "SUI*" (verbatim terms, and all MedDRA levels). No cases beyond those identified by Pfizer were identified.

Table 7-18: Suicidality Preferred Term Search

Completed suicide
Depression suicidal
Intentional overdose
Intentional self-injury
Multiple drug overdose intentional
Poisoning deliberate
Self injurious behaviour
Self-injurious ideation
Self mutilation
Suicidal ideation
Suicide attempt

Source: Clinical reviewer

One suicide and eight additional suicide-related adverse events (occurring in seven patients) were identified. These patients are listed in Table 7-19 below. The suicide patient had completed 24-weeks of varenicline treatment 27-days prior. He is discussed in Section 7.1.1 above. Of the remaining patients, only two (#10351012108 and #101650350037) had received varenicline. These patients are discussed in Section 7.1.2.2 above (SAEs).

Table 7-19: HLT = HLGT 'Suicidal and self-injurious behaviour' All Completed Phase-2/3 Studies

Patient ID	Preferred Term	Verbatim Term	Treatment*	AE Onset Day/ Drug Stop Day
HLGT (=HLT) 'Suicidal and Self-Injurious Behaviour'				
100750240523	Suicide attempt	Suicidal attempt, drug overdose intentional	Placebo	35/17
103510121069	Completed suicide	Suicide	1-mg BID	196/169
103510121089	Suicidal ideation	Suicidal ideation with plan	1-mg BID	74/73
103610061014	Suicidal ideation	Suicidal thoughts	Zyban®	30/19
103610141106	Suicidal ideation	Suicidal ideation	Placebo	65/83
103610141106	Suicidal ideation	Suicidal ideation	Placebo	???
HLGT 'Injury, Poisoning and Procedural Complications'				
100250110138	Intentional overdose	Overdose (intentional)	Zyban®	52/42
101650350037	Intentional overdose	Intentional overdose (X2) with study medication	3-mg/day* 2-mg/day*	72/84

*Study 3051016 allowed for patient-directed dose-titration Source: Clinical reviewer

7.1.5 Common Adverse Events

Phase-1 Common AEs

The 24 Phase-1 studies enrolled 795 subjects, 750 of whom received varenicline. The majority of subjects received varenicline. The overall incidence of adverse events at the 2-mg/day dose was 54.4%. This was slightly higher than the overall AE incidence rates for subjects who received <2-mg per day (48.5%), or >2-mg/day group (49.1%). Most exposure at the > 2-mg/day dose was in single-dose studies, however. 'Nervous System' (dizziness, headache) and 'Gastrointestinal' AEs (nausea) were most common, for subjects in all active-drug treatment groups (Nervous System AEs were also common in placebo-treated subjects). Vomiting occurred commonly in the >2-mg/day group (24/112, or >21%).

Phase-2.3 Common AEs

Table 7-20 shows Phase-2/3 adverse event incidence rates for each treatment group (for the two main safety analysis populations), by total patient exposure. Adverse events were reported by the majority of Phase-2/3 patients, in all treatment arms. In both databases, adverse event rates (per patient-exposure-year) were nearly identical across treatment groups, except for the <1-mg/day 'Fixed-dose, Placebo-controlled' patients. This is likely due to the fact that much of the <1-mg BID cohort consisted of patients that did not have dose titration during the first treatment week (all A3051002 patients, and the non-titrated 0.5-mg BID A3051007 patients). Titration clearly seemed to help reduce nausea incidence, by far the most commonly occurring AE (and also vomiting incidence). Adverse events from the GI, Psychiatric and CNS MedDRA System Organ Classes were reported most frequently in all groups.

Table 7-20: Treatment-Emergent Adverse Event Incidence, Phase-2/3 Trials

	Fixed-Dose		**Placebo-**		**Controlled**		**Phase-2/3**		**All Completed**		**Phase-2/3**	
	Varenicline		**Varenicline**		**Zyban®**		**Placebo**		**Varenicline**		**Placebo**	
	<1-mg BID		**1-mg BID**		**150-mg BID**				**All doses**			
Patients →	**(N=505)**		**(N=1070)**		**(N=795))**		**(N=928)**		**(N=3940)**		**(N=1209)**	
Pt-Years Exposure	**74.70**		**187.36**		**129.97**		**149.67**		**948.60**		**254.05**	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Pts. with any TEAE	438	(86.7)	885	(82.7)	633	(79.6)	719	(77.5)	3274	(83.1)	925	(76.5)
TEAEs Pt-Years		5.86		4.72		4.87		4.80		3.45		3.64

Source: Clinical reviewer

7.1.5.1 Eliciting adverse events data in the development program

The same adverse event elicitation and reporting procedures were used in all Phase-2/3 studies (and also in most Phase-1 studies). Adverse events (including those thought to represent nicotine withdrawal) were recorded on electronic Case Report Forms, whether spontaneously reported by patients, or elicited or observed by investigators. Serious adverse events (SAEs) were also reported, in an expedited fashion, to a Pfizer centralized database, and to the appropriate regulatory agencies.

Exacerbations of pre-existing illnesses were also recorded as adverse events. An "exacerbation of a pre-existing illness" was defined as a manifestation (sign or symptom) of the illness that indicated a significant increase in the severity of the illness, as compared to the severity noted at the start of the

trial. This included worsening or increase in severity of signs or symptoms, increase in frequency of signs or symptoms of an intermittent illness, or the appearance of a new manifestation/complication.

Insufficient clinical response, benefit, efficacy, therapeutic effect, or pharmacologic action, was not to be recorded as an adverse event.

Clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, x-ray, ECG) were also to be recorded as adverse events. The criteria for determining whether an abnormal objective test finding should be reported as an adverse event were as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy; and/or
- Test result leads to any of the outcomes included in the definition of a serious adverse event; and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the other listed conditions, however, would not qualify for reporting as an adverse event.

Symptoms and clinical signs whose onset occurred, severity worsened or intensity increased *during the treatment period* (or within seven days of study drug cessation) were to be categorized as treatment-emergent adverse events (TEAEs). This included exacerbations and increases in frequency of medical conditions which were present at baseline.

Adverse events which occurred during crossover studies were counted in the treatment period of AE onset. AEs which occurred during one treatment period, resolved, and then reoccurred during a subsequent treatment period were reported in both periods. AEs which started in one treatment period and carried into a subsequent period without an interval of resolution were only counted in the period of onset.

Immediate Post-Treatment Adverse Events (≤ 7-Days Post Treatment)
There is evidence for (re)emergence of nicotine withdrawal symptoms in the immediate post-treatment period, from the MNWS data, as well as from the adverse event data. The severity of these symptoms and their clinical implications are not yet clear, however.

Post-treatment, 'treatment emergent' adverse events
Pfizer defined "Post-treatment adverse events" as "those which occurred more than 7-days after the last dose of study drug. In all double-blind studies, the last dose of study drug is defined as the last dose in the double-blind period." All AEs for which the date of the first dose of study medication was missing were considered treatment-emergent. AEs with missing end dates were considered ongoing.

Phase-1 trials
During Phase-1 single dose trials and multiple-dose, one day trials, subjects were assessed for adverse events at Screening, and then throughout the course of the dosing session, until three to four hours after the final dose. During multiple-day Phase 1 trials monitoring and adverse event elicitation was similar to that in the Phase-2/3 studies.

Phase-2/3 trials

During the Phase-2/3 twelve-week trials (1007, 1016, 1028, 1036, and OL phase of 1035) patients were evaluated at the investigational site weekly during the double-blind treatment period (Weeks 1 through 12). Spontaneously reported and investigator observed adverse events were recorded for participants at the initial screening and at all subsequent study visits. Seven-week dose-ranging trial 1002 called for weekly clinic visits also. During post-treatment follow-up (to Week-52 in all but trial 1002) patients were seen in clinic monthly, sometimes with interspersed telephone contact. Patients were also seen in clinic weekly during the double-blind phase (second twelve weeks) of 1035. During trial 1037 (52-week open-label safety trial) patients were seen in clinic weekly up to Week-8, then every four-weeks until Week-52 (or ET). A Week-53 follow-up visit was also included.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Closely related investigator verbatim terms were grouped using a dictionary of MedDRA Preferred Terms. The application included two complete MedDRA thesauruses (one for Phase-1, the other for Phase-2/3), listing every verbatim term subsumed under each MedDRA Preferred Term employed, along with the respective MedDRA hierarchical terms. Verbatim term coding was appropriate. I found no verbatim terms, or multiple-term events, that were coded to MedDRA incorrectly or misleadingly.

Pfizer did not use any grouping strategy for tabulation and presentation of related Preferred Terms. This did not appear to have 'hidden' any potentially concerning adverse events, however.

7.1.5.3 Incidence of common adverse events

The main common adverse event analyses focused on the fixed-dose, placebo-controlled Phase-2/3 studies database.

Phase-1 Studies

Nausea and vomiting were seen in all varenicline treatment groups, with increasing rates at increasing doses. Vomiting was reported for 21.4% of subjects who received daily doses of varenicline >2 mg. The other frequently reported gastrointestinal adverse events (constipation, flatulence, and dyspepsia) did not show consistent increase with increasing varenicline dose, but were higher in the 'varenicline + other drug' treatment group than for subjects who received other drugs without varenicline.

The majority of Phase-1 subjects received varenicline. For subjects who received a daily varenicline dose of 2-mg, the overall incidence of adverse events was 54.4%. This was slightly higher than the overall AE incidence rate for subjects who received <2-mg per day (48.5%). The overall AE incidence rate in the >2-mg/day group was only 49.1%, but most exposure (at the > 2-mg/day dose) was in single-dose studies. Table 7-21 below summarizes the most commonly occurring AEs, across all Phase-1 studies. 'Nervous System' and 'Gastrointestinal' AEs were most common, for subjects in all active-drug treatment groups (Nervous System AEs were also common in placebo-treated subjects). Erythema and pruritus were reported at ≥5% only for subjects treated with drugs other than varenicline.

Table 7-21: Most Frequent Phase-1* Adverse Events (≥ 5% in Any Treatment Group)

MedDRA SOC Preferred Term Number (%)	Varen <2mg/day N=241	Varen 2mg/day N=309	Varen >2mg/day N=112	Varen + Other** N=116	Other Drug Only** N=141	Placebo N=255
Any AE	117 (48.5)	168 (54.4)	55 (49.1)	96 (65.8)	80 (56.7)	112 (43.9)
AE → Discontinuation	1 (0.4)	6 (1.9)	4 (3.6)	14 (9.6)	5 (3.5)	1 (0.4)
Nervous System	**73 (30.3)**	**91 (29.4)**	**37 (33.0)**	**56 (38.4)**	**52 (36.9)**	**74 (29.0)**
Dizziness	30 (12.4)	11 (3.6)	7 (6.3)	14 (9.6)	7 (5.0)	12 (4.7)
Headache	44 (18.3)	77 (24.9)	29 (25.9)	42 (28.8)	38 (27.0)	57 (22.4)
Somnolence	10 (4.1)	8 (2.6)	6 (5.4)	10 (6.8)	8 (5.7)	14 (5.5)
Gastrointestinal	**50 (20.7)**	**89 (28.8)**	**38 (33.9)**	**61 (41.8)**	**46 (32.6)**	**31 (12.2)**
Constipation	2 (0.8)	3 (1.0)	0 (0)	14 (9.6)	7 (5.0)	4 (1.6)
Dyspepsia	1 (0.4)	12 (3.9)	1 (0.9)	17 (11.6)	7 (5.0)	4 (1.6)
Flatulence	0 (0)	2 (0.6)	0 (0)	11 (7.5)	9 (6.4)	1 (0.4)
Nausea	35 (14.5)	67 (21.7)	34 (30.4)	36 (24.7)	17 (12.1)	13 (5.1)
Vomiting	5 (2.1)	27 (8.7)	24 (21.4)	14 (9.6)	5 (3.5)	6 (2.4)
General/Admin. Site Conditions	**26 (10.8)**	**19 (6.1)**	**7 (6.3)**	**35 (24.0)**	**28 (19.9)**	**14 (5.5)**
Fatigue	12 (5.0)	6 (1.9)	5 (4.5)	19 (13.0)	11 (7.8)	10 (3.9)
Skin/Connective Tissue	**5 (2.1)**	**10 (3.2)**	**1 (0.9)**	**24 (16.4)**	**26 (18.4)**	**2 (0.8)**
Erythema	0 (0)	0 (0)	1 (0.9)	4 (2.7)	9 (6.4)	0 (0)
Pruritis	0 (0)	0 (0)	0 (0)	7 (4.8)	7 (5.0)	1 (0.4)
Psychiatric Disorders	**8 (3.3)**	**3 (1.0)**	**2 (1.8)**	**27 (18.5)**	**21 (14.9)**	**5 (2.0)**
Insomnia	2 (0.8)	0 (0)	2 (1.8)	10 (6.8)	13 (9.2)	1 (0.4)
Irritability	0 (0)	0 (0)	0 (0)	8 (5.5)	1 (0.7)	0 (0)

* Protocols included in: 'Phase-1 Studies' cohort ** 'Other' = Zyban® or NRT, used in drug-drug interaction studies
Source: Section 2.7.4 Tables A81c, A101c and Table 25

Adverse Events in Drug-Drug Interaction Studies
There were relatively high adverse event rates in the drug interaction studies, Study A3051033 with NRT, and Study A3051034 with Zyban®. This explains, in part, why adverse event rates for the 'Varenicline + Other Drug' and 'Other Drug (Only)' groups in Table 7-21 are higher than for other treatment conditions.

Phase 2/3 Studies
TEAEs were reported by most Phase-2/3 patients. As in the Phase-1 studies, nausea is clearly varenicline dose related. In the 'Fixed-dose, Placebo-controlled' trials nausea was reported by 34% of varenicline 1-mg BID patients, by 23% of varenicline < 1-mg BID patients, and by only 11% of placebo patients. Nausea was reported by 32% of varenicline-treated patients in the 'All Completed Phase-2/3 Studies' population as well (>80% of whom received the 1-mg BID dose)

Overall, adverse events related to the, Gastrointestinal, Psychiatric and Nervous System MedDRA SOC categories were reported with the greatest frequency in the varenicline 1-mg BID group; 52%, 39% and 36%, respectively, as opposed to 31%, 29% and 30% in the placebo group. The GI Preferred Terms most commonly reported in the 1-mg BID group were nausea (as noted above), constipation, flatulence, dry mouth, dyspepsia and vomiting.

MedDRA High Level Group Terms (HLGT) reported by 5% or more of patients in any treatment group are listed in Table 7-22 below. For each of these HLGTs, all Preferred Terms reported by 1% or more of patients (in any group) are also shown.

Table 7-22: Most Frequent AE HLGTs (≥ 5% Any Group), with Subordinate PTs (≥ 1% Any Group) Phase 2/3 Fixed-Dose, Placebo-Controlled Studies, AND Varenicline Patients in All Phase-2/3 Studies

System Organ Class High Level Group Term Preferred Term	Fixed Dose VRN 0.5 mg BID N=253	Fixed Dose VRN 1mg BID N=1070	Placebo Zyban® 150mg BID N=795	Controlled Placebo N=928	All Compl. VRN All N=3940	Phase-2/3 Placebo N=1209
GASTROINTESTINAL	106 (41.9)	554 (51.8)	270 (34.0)	284 (30.6)	2081 (52.8)	363 (30.0)
GI Signs and Symptoms	41 (32.5)	484 (45.2)	168 (21.1)	191 (20.6)	1794 (45.5)	241 (19.9)
(Nausea and/or Vomiting)	52 (20.6)	373 (34.9)	103 (13.0)	111 (12.0)	--	--
Nausea	49 (19.4)	361 (33.7)	92 (11.6)	103 (21.1)	1260 (32.0)	121 (10.0)
Abdominal pain*	14 (5.5)	78 (7.3)	34 (4.3)	49 (5.3)		
Flatulence	29 (11.5)	71 (6.6)	21 (2.6)	25 (2.7)	382 (9.7)	39 (3.2)
Dyspepsia	16 (6.3)	58 (5.4)	27 (3.4)	32 (3.4)	275 (7.0)	38 (3.1)
Vomiting	5 (2.0)	57 (5.3)	24 (3.0)	15 (1.6)	151 (3.8)	19 (1.6)
GI Motility/Defecation Conditions	25 (9.9)	137 (12.8)	88 (11.1)	60 (6.5)	520 (13.2)	91 (7.5)
Constipation	14 (5.5)	84 (7.9)	62 (7.8)	26 (2.8)	325 (8.2)	38 (3.1)
Diarrhoea	9 (3.6)	45 (4.2)	19 (2.4)	34 (3.7)	161 (4.1)	51 (4.2)
Gastroesophageal reflux disease	2 (1.0)	10 (0.9)	6 (0.8)	1 (0.1)	44 (1.1)	4 (0.3)
Salivary Gland Conditions	22 (8.6)	61 (5.7)	71 (8.9)	42 (4.5)	194 (4.9)	53 (4.4)
Dry Mouth	11 (4.3)	58 (2.4)	70 (8.8)	40 (4.3)	176 (4.5)	50 (4.1)
PSYCHIATRIC DISORDERS	113 (44.7)	412 (38.5)	335 (42.1)	270 (29.1)	1632 (41.4)	340 (28.1)
Sleep Disorders/Disturbances	87 (34.3)	338 (31.6)	268 (33.7)	177 (19.1)	1298 (32.9)	221 (18.3)
Insomnia**	63 (24.9)	208 (19.4)	202 (25.4)	130 (14.0)	754 (19.1)	118 (12.7)
Abnormal dreams ±Nightmare	36 (14.2)	151 (14.1)	56 (7.0)	48 (5.2)	--	--
Sleep disorder	6 (2.4)	57 (5.3)	46 (5.8)	24 (2.6)	145 (3.7)	28 (2.3)
Depressed Mood Disorder/Disturb^	11 (4.3)	29 (2.7)	23 (2.9)	17 (1.8)	167 (4.2)	25 (2.1)
Personality Disorders/Disturbances	13 (5.1)	71 (6.6)	46 (5.8)	63 (6.8)	288 (7.3)	76 (6.3)
Irritability	13 (5.1)	69 (6.4)	46 (5.8)	62 (6.7)	265 6.7)	75 (6.2)
Anxiety Disorders/Symptoms	15 (5.9)	55 (5.1)	65 (8.2)	59 (6.4)	191 (4.8)	71 (5.9)
Anxiety	13 (5.1)	39 (3.6)	44 (5.5)	47 (5.1)	120 (3.0)	54 (4.5)
Agitation	2 (0.1)	8 (0.7)	11 (1.4)	6 (0.6)	38 (1.0)	9 (0.7)

(Continued)

System Organ Class High Level Group Term Preferred Term	Fixed Dose VRN 0.5 mg BID N=253	 VRN 1mg BID N=1070	Placebo Zyban® 150mg BID N=795	Controlled Placebo N=928	All Compl. VRN All N=3940	Phase-2/3 Placebo N=1209
INFECTIONS/INFESTATIONS	175 (34.7)	277 (25.9)	201 (25.3)	275 (29.6)	1155 (29.3)	367 (30.4)
Pathogen Class Unspecified	136 (26.9)	230 (21.5)	163 (21.5)	233 (25.1)	943 (23.9)	315 (26.1)
URI and/or Nasopharyngitis	99 (2.0)	165 (1.5)	111 (1.4)	187 (2.0)	--	--
Sinusitis	10 (2.0)	18 (1.7)	12 (1.5)	19 (2.0)	88 (2.2)	33 (2.7)
Tooth Infection	6 (1.2)	5 (0.5)	7 (0.9)	0 (0)	32 (0.8)	2 (0.2)
Urinary tract infection	5 (1.0)	3 (0.3)	5 (0.6)	4 (0.4)	34 (0.9)	10 (0.8)
Viral Infectious Disorders	36 (7.1)	54 (5.0)	35 (4.4)	48 (5.2)	247 (6.3)	63 (5.2)
Influenza	20 (4.0)	31 (2.9)	18 (2.3)	29 (3.1)	158 (4.0	37 (3.1)
Gastroenteritis viral	11 (2.2)	8 (0.7)	4 (0.5)	8 (0.9)	40 (1.0)	12 (1.0)
NERVOUS SYSTEM	106 (41.9)	388 (36.3)	244 (30.7)	279 (30.1)	1325 (33.6)	359 (29.7)
Headaches (HLGT)	59 (23.3)	194 (18.1)	117 (14.7)	145 (15.6)	732 (18.6)	194 (16.0)
Neurological Disorders NEC	59 (23.3)	196 (18.3)	120 (15.1)	127 (13.1)	652 (16.5)	160 (13.2)
Dysgeusia	30 (11.6)	78 (7.3)	49 (6.2)	40 (4.3)	252 (6.4)	48 (4.0)
Dizziness	16 (6.3)	72 (6.7)	55 (6.9)	68 (7.3)	216 (5.5)	82 (6.8)
Somnolence	9 (3.6)	43 (4.0)	10 (1.3)	24 (2.6)	145 (3.7)	26 (2.2)
Lethargy	3 (1.2)	15 (1.4)	6 (0.8)	2 (0.2)	35 (0.9)	5 (0.4)
Paresthesia	2 (0.8)	10 (0.9)	8 (1.0)	7 (0.8)	26 (0.7)	11 (0.9)
Mental Impairment Disorders	16 (6.3)	62 (5.8)	43 (5.4)	52 (5.6)	178 (4.5)	63 (5.2)
Disturbance in attention	15 (5.9)	54 (5.0)	38 (4.8)	47 (5.1)	151 (3.8)	56 (4.6)
GENERAL DISORDERS	30 (11.9)	132 (12.3)	82 (10.3)	111 (12.0)	582 (14.8)	143 (11.8)
General Disorders NEC	29 (11.5)	122 (11.4)	74 (9.3)	103 (11.1)	547 (13.9)	133 (11.0)
Asthenia ± Fatigue ± Malaise	10 (4.0)	77 (7.2)	34 (4.3)	57 (6.1)	--	--
Pain	3 (1.2)	14 (1.3)	5 (0.6)	9 (1.0)	22 (0.6)	14 (1.2)
Chest pain ± Chest discomfort	5 (1.0)	17 (1.6)	16 (2.0)	15 (1.6)	--	--
Thirst	3 (1.2)	8 (0.7)	3 (0.4)	6 (0.6)	40 (1.0)	7 (0.6)
Influenza like illness	2 (0.8)	3 (0.3)	1 (0.1)	4 (0.4)	40 (1.0)	5 (0.4)
RESPIR/THORACIC/MEDIAST	44 (17.4)	137 (12.8)	101 (12.7)	109 (11.7)	498 (12.6)	138 (11.4)
Respiratory Disorders NEC	31 (12.3)	98 (9.2)	68 (8.6)	71 (7.7)	370 (9.4)	87 (7.2)
Cough	14 (2.8)	26 (2.4)	18 (2.3)	23 (2.5)	83 (2.1)	31 (2.6)
Pharyngolaryngeal pain^^	6 (2.4)	32 (3.0)	20 (2.5)	27 (2.9)	--	--
Dyspnoea	3 (1.2)	12 (1.1)	2 (0.3)	4 (0.4)	50 (1.3)	7 (0.6)
MUSCULOSKEL./CONNECTIVE	52 (20.6)	137 (12.8)	95 (11.9)	112 (12.1)	545 (13.9)	153 (12.7)
Musculoskel/Connect. Tissue NEC	36 (7.1)	73 (6.8)	44 (5.5)	63 (6.8)	269 (6.8)	88 (7.3)
Back pain	22 (4.4)	42 (3.9)	30 (3.8)	33 (3.6)	147 (3.7)	45 (3.7)
Joint Disorders	17 ((6.7)	42 (3.9)	28 (3.5)	28 (3.0)	138 (3.5)	39 (3.2)
Arthralgia	13 (5.1)	38 (3.6)	23 (2.9)	24 (2.6)	116 (2.9)	33 (2.7)

(Continued)

System Organ Class High Level Group Term Preferred Term	Fixed Dose VRN 0.5 mg BID N=253	 VRN 1mg BID N=1070	Placebo Zyban® 150mg BID N=795	Controlled Placebo N=928	All Compl. VRN All N=3940	Phase-2/3 Placebo N=1209
SKIN/SUBCUTANEOUS TISSUE	31 (12.3)	89 (9.3)	85 (10.7)	50 (5.4)	377 (9.6)	69 (5.7)
Epidermal and Dermal Conditions	22 (8.7)	65 (6.1)	52 (6.5)	35 (3.8)	257 (6.5)	49 (4.1)
Rash	5 (2.0)	26 (2.4)	19 (2.4)	17 (1.8)	86 (2.2)	23 (1.9)
Pruritis	3 (1.2)	15 (1.4)	13 (1.6)	5 (0.5)	53 (1.3)	8 (0.7)
METABOLISM & NUTRITION	21 (8.3)	79 (7.4)	56 (7.0)	41 (4.4)	318 (8.1)	53 (4.4)
Appetite/General Nutrit. Disorders	18 (7.1)	71 (6.6)	50 (6.3)	35 (3.8)	274 (7.0)	44 (3.6)
Increased appetite	15 (5.9)	47 (4.4)	27 (3.4)	21 (2.3)	220 (5.6)	27 (3.2)
Decreased appetite ± Anorexia	3 (1.2)	23 (2.1)	23 (2.9)	13 (1.4)	--	--

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia, Initial insomnia, Middle insomnia, Early morning awakening
^ Numerous closely-related Preferred Terms, HLGT listed 'Depressed mood disorders/disturbances' includes HLTs 'Depressive disorders' and HLT 'Mood alterations with depressive symptoms'
^^ Includes PTs Pharyngolaryngeal pain and Throat irritation
Source: Clinical reviewer from applicant Tables A10.1a, A10.1b, (2.7.4) and AE datasets

The increased incidence of HLGT 'Joint disorders' (under SOC Musculoskeletal and Connective Tissue Disorders) seen in the varenicline <1-mg BID group, in the Fixed-dose, Placebo-controlled Studies cohort is likely due, at least in part, to greater enrollment of patients with related disorders at baseline in Phase-2 Studies A3051002 and A3051007.

Table 7-23 below shows the most frequently reported adverse event terms in 52-week safety study A3051037 (5% or greater in either treatment group). Not surprisingly, given the longer exposure duration, for the most commonly occurring AEs, the differences in incidence rates between varenicline and placebo were even greater than observed in the shorter-term studies. For nausea the rates were 40% and 8% (in varenicline and placebo, respectively), for vomiting 7% and < 2%, for abnormal dreams (without 'nightmares') 23% and 7%, and for insomnia > 20% and ≈ 10% (miscellaneous insomnia Preferred Terms, such as 'middle insomnia' were not grouped in for this analysis).

Table 7-23: Long-Term Study A3051037, Most Frequent Preferred Terms (≥ 5% Any Group)

MedDRA System Organ Class Preferred Term	Varenicline N=251 (%)	Placebo N=126 (%)
Any Adverse Event	242 (96.4)	104 (82.5)
Discontinuation due to Adverse Event	71 (28.3)	12 (9.5)
Gastrointestinal Disorders	179 (71.3)	48 (38.1)
Nausea	101 (40.2)	10 (7.9)
Dyspepsia	33 (13.1)	3 (2.4)
Constipation	31 (12.4)	9 (7.1)
Flatulence	31 (12.4)	12 (9.5)
Diarrhea	20 (8.0)	12 (9.5)
Vomiting	17 (6.8)	2 (1.6)
Dry mouth	11 (4.4)	8 (6.3)
Infections & Infestations	123 (49.0)	58 (46.0)
Nasopharyngitis	38 (15.1)	20 (15.9)
Upper respiratory tract infection	34 (13.5)	12 (9.5)
Sinusitis	17 (6.8)	8 (6.3)
Influenza	15 (6.0)	3 (2.4)
Bronchitis	3 (1.2)	7 (5.6)
Psychiatric Disorders	109 (43.4)	39 (31.0)
Abnormal dreams	57 (22.7)	9 (7.1)
Insomnia	48 (19.1)	12 (9.5)
Irritability	13 (5.2)	7 (5.6)
Nervous System	108 (43.0)	45 (35.7)
Headache	43 (17.1)	26 (20.6)
Dysgeusia	27 (10.8)	3 (2.4)
Dizziness	19 (7.6)	6 (4.8)
Musculoskeletal/Connective Tissue Disorders	65 (25.9)	25 (19.8)
Arthralgia	18 (7.2)	7 (5.6)
Back Pain	16 (6.4)	6 (4.8)
Investigations	50 (19.9)	12 (9.5)
Weight increased	17 (6.8)	5 (4.0)
General Disorders/Administration Site Conditions	42 (16.7)	20 (15.9)
Fatigue	6 (2.4)	8 (6.3)
Metabolism & Nutrition Disorders	28 (11.2)	8 (6.3)
Increased appetite	13 (5.2)	4 (3.2)
Vascular Disorders	26 (10.4)	11 (8.7)
Hypertension	15 (6.0)	5 (4.0)

Source: A3051037 Clinical Study Report Tables 13.6.2.1, 13.6.2.3.1

'Hypertension' is a commonly occurring PT in A3051037, but there were no vital sign-related SAEs or vital sign-related discontinuations. There were no treatment group differences in measures of central tendency. In the varenicline group there were 9/249 (3.6%) patients with diastolic and 2/249 (0.8%) with systolic shifts (from normal to elevated), while in the placebo group there were 4/15 (3.2%) patients with systolic shifts and 0/125 with systolic shifts.

Table 7-24 shows that most varenicline-related common adverse events occur less frequently with the patient-directed flexible dosing regimen than with the fixed 1-mg BID regimen.

Table 7-24: Flexible Dose Study 3051016 Common Adverse Events

COSTART Preferred Term	Varenicline N=157 (%)	Placebo N=155 (%)
Any Adverse Event	242 (96.4)	104 (82.5)
Discontinuation due to Adverse Event	11 (7.0)	7 (4.5)
Insomnia	34 (21.7)	17 (11.0)
Headache	25 (15.9)	20 (12.9)
Respiratory Tract Infection	25 (15.9)	15 (9.7)
Nausea	21 (13.4)	8 (5.2)
Asthenia	11 (7.0)	7 (4.5)
Dyspepsia	10 (6.4)	3 (1.9)
Accidental Injury	9 (5.7)	3 (1.9)
Irritability	8 (5.1)	6 (3.9)
Flu Syndrome	8 (5.1)	7 (4.5)
Thinking Abnormal	8 (5.1)	6 (3.9)
Pharyngitis	8 (5.1)	2 (1.3)
Abdominal Pain	7 (4.5)	6 (3.9)
Constipation	7 (4.5)	3 (1.9)
Abnormal Dreams	7 (4.5)	7 (4.5)
Rash	7 (4.5)	3 (1.9)
Back Pain	6 (3.8)	6 (3.9)
Chest Pain	6 (3.8)	3 (1.9)
Pain	5 (3.2)	5 (3.2)
Weight Gain	5 (3.2)	5 (3.2)
Anxiety	5 (3.2)	6 (3.9)
Depression	5 (3.2)	4 (2.6)
Taste Perversion	5 (3.2)	5 (3.2)
Urinary Tract Infection	5 (3.2)	2 (1.3)
Dizziness	4 (2.5)	8 (5.2)
Sinusitis	2 (1.3)	6 (3.9)
Diarrhea	2 (1.3)	5 (3.2)

Source: Tables 6.1.1 and 6.1.2, A3051016 study report

SOC Nervous System Disorders and SOC Psychiatric Disorders

Table 7-25, listing Nervous System and Psychiatric PTs reported in≥ 1% of any treatment group (by HLGT) is included because varenicline is a centrally acting new molecular entity,. Findings are consistent with the overall common adverse event summary tables.

Table 7-25: Nervous System and Psychiatric AEs Reported in ≥ 1% in Any Varenicline Group

	Fixed Dose		Placebo	Controlled	All
	Varenicline <1mg BID N=505	Varenicline 1mg BID N=1070	Zyban® 150-mg BID N=795	Placebo N=928	Varenicline Phase 2/3 N=3940
Patient-Years Exposure →	**74.7**	**187.4**	**130.0**	**149.7**	**948.6**
NERVOUS SYSTEM	**219 (43.4)**	**388 (36.3)**	**244 (30.7)**	**279 (30.1)**	**1325 (33.6)**
Headaches	**127 (25.1)**	**194 (18.1)**	**117 (14.7)**	**145 (15.6)**	**732 (18.6)**
Headache	123 (24.4)	183 (17.1)	111 (14.0)	136 (14.7)	698 (17.7)
Mental Impairment Disorders	**34 (6.7)**	**62 (5.8)**	**43 (5.4)**	**52 (5.6)**	**178 (4.5)**
Disturbance in attention	30 (5.9)	54 (5.0)	38 (4.8)	47 (5.1)	151 (3.8)
Movement Disorders	**7 (1.4)**	**10 (0.9)**	**18 (2.3)**	**5 (0.5)**	**36 (0.9)**
Tremor	5 (1.0)	8 (0.7)	14 (1.8)	3 (0.3)	30 (0.8)
Neurological Disorders NEC	**116 (23.0)**	**196 (18.3)**	**120 (15.1)**	**127 (13.7)**	**652 (16.5)**
Dizziness	36 (7.1)	72 (6.7)	55 (6.9)	68 (7.3)	216 (5.5)
Dysgeusia	59 (11.7)	78 (7.3)	49 (6.2)	40 (4.3)	252 (6.4)
Lethargy	5 (1.0)	15 (1.4)	6 (0.8)	2 (0.2)	35 (0.9)
Somnolence	22 (4.4)	43 (4.0)	10 (1.3)	24 (2.6)	145 (3.7)
PSYCHIATRIC	**224 (44.4)**	**412 (38.5)**	**335 (42.1)**	**270 (29.1)**	**1632 (41.4)**
Anxiety Disorders and Symptoms	**41 (8.1)**	**55 (5.1)**	**65 (8.2)**	**59 (6.4)**	**191 (4.8)**
Agitation	6 (1.2)	8 (0.7)	11 (1.4)	6 (0.6)	38 (1.0)
Anxiety	29 (5.7)	39 (3.6)	44 (5.5)	47 (5.1)	120 (3.0)
Changes in Physical Activity	**14 (2.8)**	**15 (1.4)**	**16 (2.0)**	**9 (1.0)**	**69 (1.8)**
Restlessness	12 (2.4)	15 (1.4)	14 (1.8)	9 (1.0)	66 (1.7)
Depressed Mood Disorder/Disturb	**24 (4.8)**	**29 (2.7)**	**23 (2.9)**	**17 (1.8)**	**167 (4.2)**
Depressed mood	11 (2.2)	10 (0.9)	11 (1.4)	5 (0.5)	49 (1.2)
Depression	12 (2.4)	19 (1.8)	13 (1.6)	12 (1.3)	108 (2.7)
Mood Disorders and Disturbances	**18 (3.6)**	**30 (2.8)**	**15 (1.9)**	**24 (2.6)**	**103 (2.6)**
Flat affect	9 (1.8)	9 (0.8)	6 (0.8)	13 (1.4)	18 (0.5)
Personality Disord/Behaviour Disturb	**45 (8.9)**	**69 (6.4)**	**46 (5.8)**	**62 (6.7)**	**265 (6.7)**
Irritability	45 (8.9)	69 (6.4)	46 (5.8)	62 (6.7)	265 (6.7)
Psychiatric/Behavioral Symptoms	**3 (0.6)**	**0 (0)**	**1 (0.1)**	**1 (0.1)**	**75 (1.9)**
Nicotine dependence	3 (0.6)	0 (0)	1 (0.1)	0 (0)	74 (1.9)
Sleep Disorders and Disturbances	**159 (31.5)**	**338 (31.6)**	**268 (33.7)**	**177 (19.1)**	**1298 (32.9)**
Abnormal dreams	54 (10.7)	146 (13.6)	53 (6.7)	46 (5.0)	545 (13.8)
Early morning awakening	5 (1.0)	5 (0.5)	7 (0.9)	2 (0.2)	25 (0.6)
Initial insomnia	12 (2.4)	16 (1.5)	9 (1.1)	8 (0.9)	37 (0.9)
Middle insomnia	93 (18.4)	178 (16.6)	180 (22.6)	118 (12.7)	754 (19.1)
Nightmare	9 (1.8)	14 (1.3)	7 (0.9)	5 (0.5)	31 (0.8)
Sleep disorder	6 (1.2)	7 (0.7)	4 (0.5)	2 (0.2)	68 (1.7)

Source: Modified from Tables A10.1a, A10.1b and 38 (Section 2.7.4)

7.1.5.4 Common adverse event tables

As noted above (Section 7.1.5.3) the most commonly reported TEAEs during the Phase-2/3 studies were predominately gastrointestinal and psychiatric/neurologic. The most common gastrointestinal TEAEs were nausea, constipation, flatulence, dry mouth, dyspepsia and vomiting. The most commonly reported psychiatric TEAE Preferred Terms were insomnia (and related terms), abnormal dreams and sleep disorder. The most commonly reported nervous system TEAEs were headache, dysgeusia and somnolence. Table 7-26 lists the most commonly occurring adverse events. The fifth (treatment group) column shows AE incidence rates in the 'all completed Phase-2/3 studies' database. Some AEs, such as nausea, constipation and fatigue, were more likely to be reported in the overall varenicline-treated population than in the fixed-dose, placebo-controlled varenicline 1-mg BID group. This is most likely attributable to the inclusion of patients exposed for longer periods of treatment, such as in 52-week safety study A3051037.

Table 7-26: Common TEAEs (≥ 1% in any Varenicline, AND at least 0.5% ≥ Placebo in FDPC Studies)

System Organ Class High Level Group Term Preferred Term	Fixed Dose VRN 0.5 mg BID N=253	Fixed Dose VRN 1mg BID N=1070	Placebo Zyban® 150mg BID N=795	Controlled Placebo N=928	All Compl. VRN All N=3940	Phase-2/3 Placebo N=1209
GASTROINTESTINAL	106 (41.9)	554 (51.8)	270 (34.0)	284 (30.6)	2081 (52.8)	363 (30.0)
GI Signs and Symptoms	41 (32.5)	484 (45.2)	168 (21.1)	191 (20.6)	1794 (45.5)	241 (19.9)
(Nausea and/or Vomiting)	52 (20.6)	373 (34.9)	103 (13.0)	111 (12.0)	--	--
Nausea	49 (19.4)	361 (33.7)	92 (11.6)	103 (21.1)	1260 (32.0)	121 (10.0)
Abdominal Pain*	14 (5.5)	78 (7.3)	34 (4.3)	49 (5.3)	--	--
Flatulence	29 (11.5)	71 (6.6)	21 (2.6)	25 (2.7)	382 (9.7)	39 (3.2)
Dyspepsia	16 (6.3)	58 (5.4)	27 (3.4)	32 (3.4)	275 (7.0)	38 (3.1)
Vomiting	5 (2.0)	57 (5.3)	24 (3.0)	15 (1.6)	151 (3.8)	19 (1.6)
GI Motility/Defecation Conditions	25 (9.9)	137 (12.8)	88 (11.1)	60 (6.5)	520 (13.2)	91 (7.5)
Constipation	14 (5.5)	84 (7.9)	62 (7.8)	26 (2.8)	325 (8.2)	38 (3.1)
Salivary Gland Conditions	22 (8.6)	61 (5.7)	71 (8.9)	42 (4.5)	194 (4.9)	53 (4.4)
PSYCHIATRIC DISORDERS	113 (44.7)	412 (38.5)	335 (42.1)	270 (29.1)	1632 (41.4)	340 (28.1)
Sleep Disorders/Disturbances	87 (34.3)	338 (31.6)	268 (33.7)	177 (19.1)	1298 (32.9)	221 (18.3)
Insomnia**	63 (24.9)	208 (19.4)	202 (25.4)	130 (14.0)	--	--
Abnormal dreams ± Nightmare	36 (14.2)	151 (14.1)	56 (7.0)	48 (5.2)	--	--
Sleep disorder	6 (2.4)	57 (5.3)	46 (5.8)	24 (2.6)	145 (3.7)	28 (2.3)
NERVOUS SYSTEM	106 (41.9)	388 (36.3)	244 (30.7)	279 (30.1)	1325 (33.6)	359 (29.7)
Headaches (HLGT)	59 (23.3)	194 (18.1)	117 (14.7)	145 (15.6)	732 (18.6)	194 (16.0)
Neurological Disorders NEC	59 (23.3)	196 (18.3)	120 (15.1)	127 (13.1)	652 (16.5)	160 (13.2)
Dysgeusia	30 (11.9)	78 (7.3)	49 (6.2)	40 (4.3)	252 (6.4)	48 (4.0)
Somnolence	9 (3.6)	3 (4.0)	10 (1.3)	24 (2.6)	145 (3.7)	26 (2.2)
Lethargy	3 (1.2)	15 (1.4)	6 (0.8)	2 (0.2)	35 (0.9)	5 (0.4)
GENERAL DISORDERS	30 (11.9)	132 (12.3)	82 (10.3)	111 (12.0)	582 (14.8)	143 (11.8)
General Disorders NEC	29 (11.5)	122 (11.4)	74 (9.3)	103 (11.1)	547 (13.9)	133 (11.0)
Fatigue/Malaise/Asthenia	10 (4.0)	77 (7.2)	34 (4.3)	57 (6.1)	--	--

(Continued)

System Organ Class High Level Group Term Preferred Term	Fixed VRN 0.5 mg BID N=253	Dose VRN 1mg BID N=1070	Placebo Zyban® 150mg BID N=795	Controlled Placebo N=928	All Compl. VRN All N=3940	Phase-2/3 Placebo N=1209
RESPIR/THORACIC/MEDIASTIN	44 (17.4)	137 (12.8)	101 (12.7)	109 (11.7)	498 (12.6)	138 (11.4)
Respiratory Disorders NEC	31 (12.3)	98 (9.2)	68 (8.6)	71 (7.7)	370 (9.4)	87 (7.2)
Pharyngolaryngeal pain^	6 (2.4)	25 (2.3)	7 (0.9)	4 (0.4)	92 (2.3)	26 (2.2)
Dyspnoea	3 (1.2)	12 (1.1)	2 (0.3)	4 (0.4)	50 (1.3)	7 (0.6)
MUSCULOSKEL./CONNECTIVE	52 (20.6)	137 (12.8)	95 (11.9)	112 (12.1)	545 (13.9)	153 (12.7)
Joint Disorders	17 (6.7)	42 (3.9)	28 (3.5)	28 (3.0)	138 (3.5)	39 (3.2)
Arthralgia	13 (5.1)	38 (3.6)	23 (2.9)	24 (2.6)	116 (2.9)	33 (2.7)
SKIN/SUBCUTANEOUS TISSUE	31 (12.3)	89 (9.3)	85 (10.7)	50 (5.4)	377 (9.6)	69 (5.7)
Epidermal and Dermal Conditions	22 (8.7)	65 (6.1)	52 (6.5)	35 (3.8)	257 (6.5)	49 (4.1)
Rash	5 (2.0)	26 (2.4)	19 (2.4)	17 (1.8)	86 (2.2)	23 (1.9)
Pruritis	3 (1.2)	15 (1.4)	13 (1.6)	5 (0.5)	53 (1.3)	8 (0.7)
METABOLISM & NUTRITION	21 (8.3)	79 (7.4)	56 (7.0)	41 (4.4)	318 (8.1)	53 (4.4)
Appetite/General Nutrit. Disorders	18 (7.1)	71 (6.6)	50 (6.3)	35 (3.8)	274 (7.0)	44 (3.6)
Increased appetite	15 (5.9)	47 (4.4)	27 (3.4)	21 (2.3)	220 (5.6)	27 (3.2)
Decreased appetite ± Anorexia	3 (1.2)	23 (2.1)	23 (2.9)	13 (1.4)	--	--

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening
^ PTs Pharyngolaryngeal pain and Throat irritation Source: Clinical reviewer from Tables A10.1a, A10.1b, AE datasets

Table 7-27: Common TEAEs, Short-Term Trials vs. A3051037 (52-Weeks)

System Organ Class High Level Group Term Preferred Term	Fixed VRN 0.5 mg BID N=253	Dose VRN 1mg BID N=1070	Placebo Zyban® 150mg BID N=795	Controlled Placebo N=928	3051037 VRN 1-mg BID N=251	3051037 Placebo N=126
GASTROINTESTINAL	106 (41.9)	554 (51.8)	270 (34.0)	284 (30.6)	179 (71.3)	48 (38.1)
GI Signs and Symptoms	41 (32.5)	484 (45.2)	168 (21.1)	191 (20.6)	157 (62.5)-	31 (24.6)-
(Nausea and/or Vomiting)	52 (20.6)	373 (34.9)	103 (13.0)	111 (12.0)	107 (42.6)-	12 (9.5)-
Nausea	49 (19.4)	361 (33.7)	92 (11.6)	103 (21.1)	101 (40.2)	10 (7.9)
Abdominal Pain*	14 (5.5)	78 (7.3)	34 (4.3)	49 (5.3)	36 (14.3)-	3 (2.4)-
Flatulence	29 (11.5)	71 (6.6)	21 (2.6)	25 (2.7)	31 (12.4)	12 (9.5)
Dyspepsia	16 (6.3)	58 (5.4)	27 (3.4)	32 (3.4)	33 (13.1)	3 (2.4)
Vomiting	5 (2.0)	57 (5.3)	24 (3.0)	15 (1.6)	17 (6.8)	2 (1.6)
GI Motility/Defecation Conditions	25 (9.9)	137 (12.8)	88 (11.1)	60 (6.5)	50 (19.9)-	-22 (17.5)
Constipation	14 (5.5)	84 (7.9)	62 (7.8)	26 (2.8)	31 (12.4)	9 (7.1)
Salivary Gland Conditions	22 (8.6)	61 (5.7)	71 (8.9)	42 (4.5)	11 (4.4)	8 (6.3)
PSYCHIATRIC DISORDERS	113 (44.7)	412 (38.5)	335 (42.1)	270 (29.1)	109 (43.4)	39 (31.0)
Sleep Disorders/Disturbances	87 (34.3)	341 (31.9)	268 (33.7)	178 (19.3)	95 (37.8)	24 (19.0)
Insomnia**	63 (24.9)	208 (19.4)	202 (25.4)	130 (14.0)	52 (20.7)	13 (10.3)
Abnormal dreams ± Nightmare	36 (14.2)	151 (14.1)	56 (7.0)	48 (5.2)	58 (23.1)	11 (8.7)
Sleep disorder	6 (2.4)	57 (5.3)	46 (5.8)	24 (2.6)	7 (2.8)	3 (2.4)
DEPRESSION HLGT					16 (6.3)	4 (3.2)

(Continued)

System Organ Class High Level Group Term Preferred Term	Fixed Dose VRN 0.5 mg BID N=253	 VRN 1mg BID N=1070	Placebo Zyban® 150mg BID N=795	Controlled Placebo N=928	3051037 VRN 1-mg BID N=251	3051037 Placebo N=126
NERVOUS SYSTEM	106 (41.9)	388 (36.3)	244 (30.7)	279 (30.1)	108 (43.0)	45 (35.7)
Headaches (HLGT)	59 (23.3)	194 (18.1)	117 (14.7)	145 (15.6)	43 (17.1)	29 (20.6)
Neurological Disorders NEC	59 (23.3)	196 (18.3)	120 (15.1)	127 (13.1)	65 (25.9)	21 (16.7)
Dysgeusia	30 (11.9)	78 (7.3)	49 (6.2)	40 (4.3)	27 (10.8)	3 (2.4)
Dizziness	16 (6.3)	72 (6.7)	55 (6.9)	68 (7.3)	(7.6)	(4.8)
Somnolence	9 (3.6)	3 (4.0)	10 (1.3)	24 (2.6)	10 (4.0)	2 (1.6)
Lethargy	3 (1.2)	15 (1.4)	6 (0.8)	2 (0.2)	2 (0.8)	3 (2.4)
GENERAL DISORDERS	30 (11.9)	132 (12.3)	82 (10.3)	111 (12.0)	44 (17.5)	20 (15.9)
General Disorders NEC	29 (11.5)	122 (11.4)	74 (9.3)	103 (11.1)	43 (17.1)	18 (14.3)
Fatigue/Malaise/Asthenia	10 (4.0)	77 (7.2)	34 (4.3)	57 (6.1)	13 (5.2)	10 (7.9)
RESPIR/THORACIC/MEDIAST	44 (17.4)	137 (12.8)	101 (12.7)	109 (11.7)	47 (18.7)	19 (15.1)
Respiratory Disorders NEC	31 (12.3)	98 (9.2)	68 (8.6)	71 (7.7)	30 (12.0)	11 (8.7)
Pharyngolaryngeal pain^	6 (2.4)	25 (2.3)	7 (0.9)	4 (0.4)	6 (2.4)	3 (2.4)
Dyspnoea**	3 (1.2)	12 (1.1)	2 (0.3)	4 (0.4)	11 (4.4)	3 (2.4)
MUSCULOSKEL./CONNECTIVE	52 (20.6)	137 (12.8)	95 (11.9)	112 (12.1)	65 (25.9)	25 (19.8)
Joint Disorders	17 ((6.7)	42 (3.9)	28 (3.5)	28 (3.0)	21 (8.4)	9 (7.1)
Arthralgia	13 (5.1)	38 (3.6)	23 (2.9)	24 (2.6)	18 (7.2)	7 (5.6)
SKIN/SUBCUTANEOUS TISSUE	31 (12.3)	89 (9.3)	85 (10.7)	50 (5.4)	40 (15.9)	14 (11.1)
Epidermal and Dermal Conditions	22 (8.7)	65 (6.1)	52 (6.5)	35 (3.8)	22 (8.8)	10 (7.9)
Rash	5 (2.0)	26 (2.4)	19 (2.4)	17 (1.8)	9 (3.6)	4 (3.2)
Pruritis	3 (1.2)	15 (1.4)	13 (1.6)	5 (0.5)	4 (1.6)	2 (1.6)
METABOLISM & NUTRITION	21 (8.3)	79 (7.4)	56 (7.0)	41 (4.4)	28 (11.2)	8 (6.3)
Appetite/General Nutrit. Disorders	18 (7.1)	71 (6.6)	50 (6.3)	35 (3.8)	-	-
Increased appetite	15 (5.9)	47 (4.4)	27 (3.4)	21 (2.3)	13 (5.2)	4 (3.2)
Decreased appetite ± Anorexia	3 (1.2)	23 (2.1)	23 (2.9)	13 (1.4)	5 (2.0)	1 (0.8)

Source: Clinical reviewer *Dypnoea

7.1.5.5 Identifying common and drug-related adverse events

Certain adverse events are indisputably varenicline-related, due to consistent differences from placebo, both across and within studies. The most obvious examples are nausea and vomiting, for which there are clear dose-related increases in incidence, as well as convincing (pharmacokinetic) exposure-response data. The increased incidence of nausea was seen in all studies in which multiple doses were evaluated, as well as in the pooled data. Other gastrointestinal AEs are very likely varenicline-related include flatulence, dyspepsia, constipation, and possibly abdominal pain.

Psychiatric adverse events that seem very clearly to be varenicline-related include insomnia, abnormal dreams (with or without nightmares) and 'sleep disorders.' Overall, events categorized under HLGT 'Depressed Mood Disorders and Disturbances' may also be more common in the varenicline group, though still relatively infrequent (3% to 4%, compared with 2% in placebo).

Headaches (SOC 'Nervous System') are consistently more common in varenicline patients. Adverse event totals for the entire HLGT 'Neurological Disorders NEC' are also consistently higher in varenicline groups, though differences for its individual Preferred Terms (dysgeusia, somnolence, lethargy, dizziness), between varenicline and placebo, are sometimes minimal.

Likewise, SOC 'Skin and Subcutaneous Tissue' AEs are more common the varenicline group, but the differences for its individual Preferred Terms (i.e., rash, pruritus) are less apparent.

7.1.5.6 Additional analyses and explorations

Dose-dependency for common adverse events is addressed in Section 7.4.2.1. The time-dependency of, and adaptation to, the most common adverse events are addressed in Section 7.4.2.2.

Drug-demographic interactions are explored in Section 7.4.2.3, drug-disease interactions in Section 7.4.2.4 and drug-drug interactions in Section 7.4.2.5.

7.1.6 Less Common Adverse Events

Adverse events in the Psychiatric, GI and Nervous System SOC categories occurred commonly. Only a handful of specific Preferred Terms accounted for most AEs reported in these categories (as well a several others).

I found no adverse event cases of aplastic anemia, Stevens - Johnson syndrome (or toxic epidermal necrosis), acute renal or hepatic failure, or other sentinel events

Also, see Section 7.1.3.3 (Other significant adverse events).

7.1.7 Laboratory Findings

Treatment with varenicline for up to 24-weeks does not appear to increase the risk of clinically significant laboratory abnormalities. Several concerns raised by the Phase-1 findings proved not to have Phase-2/3 correlates.

The incidence of clinical laboratory abnormalities was similar for all Phase-2/3 treatment groups. Laboratory abnormalities were infrequent, with the exception of elevated triglycerides and cholesterol, but these were distributed roughly equally across treatment groups. There were a small number of treatment-emergent increases in AST, ALT, total bilirubin, or alkaline phosphatase that met the criteria for potential clinical significance, but hepatic adverse events, other than 'Investigations' themselves, were not increased. There were no large differences between treatment groups in baseline values or median changes from baseline.

7.1.7.1 Overview of laboratory testing

Phase-1

Laboratory assessments in Phase-1 studies varied according to study design. The standard Phase-1 laboratory assessment battery, performed at Baseline and End-of-Treatment (at a minimum), included hematology, chemistry, metabolic, renal and liver function testing, and urinalysis, similar to testing in the Phase-2/3 program (outlined in Table 7-30 below). Pregnancy testing (serum β-HCG +/- FSH) was

also standard for females (of childbearing potential). Urine toxicology and viral hepatitis serology were performed at Screening or Baseline in most Phase-1 studies.

In the single-dose, and multi-dose, single-day studies safety labs were obtained at Screening, Baseline and (3 to 4 hours) post-treatment. In the multiple-day Phase-1 studies testing was performed at those timepoints, at a minimum. In within-subject, multiple session crossover studies, Baseline testing was repeated at the beginning of each dosing phase.

The 7 to 21-day varenicline (only) studies included at least one additional assessment during treatment (but prior to end of treatment). The laboratory assessment schedules during the six drug-drug interaction studies are outlined in Table 7-28.

Table 7-28: Laboratory Testing Schedule during Phase-1 Drug-Interaction Studies

Study/ Objectives	Design/ Number	Dosage/Regimen/ Duration	Comparator	Lab Assessment Schedule*
A3051010 Cimetidine Renal interaction	OL, XO N=12	Varenicline 2-mg SD + Cimetidine 300-mg QID X 5 days	Cimetidine 300 mg QID	2-periods Hours 0, 48 each
A3051031 Digoxin PK Interaction	R, ISBSO, PC 2-way XO N=18	Digoxin 0.2 mg QD + Varenicline 1-mg BID X 14 days	Digoxin 0.2 mg mg QD + placebo	2-periods Days 0, 15 each and follow-up
A3051032 Warfarin PK/PD interaction	R, ISBSO, PC 2-way XO N=24	Warfarin 25-mg SD + Varenicline 1-mg BID X 14 days	Warfarin 25-mg SD + placebo	2-periods Days 0, 14 each
A3051033 NRT PK/PD Interaction	R, DB, PC, 2-way XO N=24	NRT Patch 21-mg/24-hr + Varenicline 1-mg BID X 14 days	NRT Patch 21-mg/24-hr + placebo	2-periods Days 0, 10, 15 each
A3051034 Zyban® PK/PD Interaction	R, ISBSO, PC, 2-way XO N=46	Zyban® 150 mg BID + Varenicline 1-mg BID X 14 days	Zyban® 150 mg BID + placebo	2-periods Days 0, 8, 15 each
A3051038 Metformin PK/PD; Renal interaction	R, OL, PC, 3-way XO N=30	Metformin 500 mg BID + Varenicline 1-mg BID X 7 days	Metformin 500 mg BID	2-periods Days 0, 3, 7 each

*Exclusive of PK sampling, in addition to Screening and End-of-Treatment Source: Clinical reviewer

Phase-2/3

In the Phase 2/3 trials blood samples were collected for assessment of chemistry and hematology at Screening, at Baseline, at Early Termination and at the following protocol-specified time points:

Appears This Way
On Original

Table 7-29: Phase 2/3 Laboratory Testing Schedule

Phase	Studies	Assessment Week	Cohort/Database*
Phase-3:	A3051028	Weeks 2, 12	Fixed-dose, Placebo-controlled Studies*
	A3051036	Weeks 2, 12	Fixed-dose, Placebo-controlled Studies*
	A3051035	Weeks 2, 12, 24	All Completed Phase-2/3 Studies
	A3051037	Weeks 2, 12, 24, 36, 52	All Completed Phase-2/3 Studies
Phase-2:	A3051007	Weeks 1, 2, 4, 7, 12	Fixed-dose, Placebo-controlled Studies*
	A3051016	Weeks 1, 2, 4, 7, 12	All Completed Phase-2/3 Studies
	A3051002	Weeks 1, 2, 4, 6, 7	Fixed-dose, Placebo-controlled Studies*
	A3051043	Weeks 1, 2, 4, 7	All Completed Phase-2/3 Studies

'Fixed-dose, Placebo-controlled Studies' are included in the 'All Completed Phase-2/3 Studies' database
Source: Clinical reviewer

Chemistry testing included sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, inorganic phosphorus, SGOT (AST), SGPT (ALT), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, cholesterol, triglycerides, albumin, and total protein. Hematology testing included complete blood count with differential and platelet count. Table 7-30 summarizes the 'routine' safety laboratory values collected during the Phase-2 and Phase-3 studies.

Table 7-30: Standard Safety Laboratory Testing During Phase-1/2/3 Studies

Hematology	Serum Chemistry	
Hematocrit	Electrolytes:	Liver function:
Hemoglobin	Sodium	ALT
RBC	Potassium	AST
Platelet count	Chloride	GGT
WBC	Bicarbonate	Bilirubin—total
Basophils: % and absolute value	CO2	Bilirubin—direct
Eosinophils: % and absolute value	Calcium	Alkaline phosphatase
Lymphocytes: % and absolute value	Magnesium	
Monocytes: % and absolute value	Phosphate	
Neutrophils: % and absolute value		

Metabolic Function		Renal Function	Urinalysis - Dip
Cholesterol-total	Albumin	BUN	pH, Specific gravity
Triglycerides	Total protein	Creatinine	Protein, Ketones
Glucose			HGB, Bilirubin
LDH			RBCs, WBCs

Source: Clinical reviewer

Serum pregnancy testing was performed concurrent with chemistry and hematology testing, as was dipstick urinalysis. In the event of potentially clinically significant urinalysis abnormalities, urine samples were sent to the central laboratory for quantitative analysis. Urine toxicology was obtained only at the Screening visit.

Blood was also drawn to test for C-reactive protein at Baseline, Week 12, and Week 52 (or Early Termination), and an additional 5-mL sample was collected at Baseline for possible use as a baseline reference in the event that additional laboratory tests were indicated.

Subjects who had at least one laboratory assessment at baseline and at least one post-baseline laboratory evaluation were evaluable for laboratory abnormalities. Baseline was defined as the last value prior to treatment.

Reference ranges from the central laboratory, in those studies which used the services of a central laboratory, were used to create the shift tables. In those studies that did not use a central laboratory, the local laboratory reference ranges were used. Gender specific reference ranges were used where applicable.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The review of laboratory findings focused mainly on data from Phase-2/3. Most summary tables below present only the fixed-dose, placebo-controlled data. Some tables also include data from the all completed Phase-2/3 studies database. These data were included where they were not obviously consistent with the FDPC data, and where the additional exposure duration (from the all completed studies data) was thought to be informative.

Phase-1 data were also reviewed, principally for extreme changes and outliers, and for laboratory value related SAEs.

Phase-1 Studies

Laboratory data from 750 varenicline-treated subjects (in 24 Phase-1 studies) were pooled for analysis. Of these subjects, 241 received varenicline < 2-mg/day, 309 received 2-mg/day, 112 received > 2-mg/day and 146 received varenicline plus another drug. Two-hundred and fifty nine Phase-1 subjects received placebo, and 114 received another active drug, but not varenicline. (Subjects may have received more than one treatment, however.) This pooled cohort included data from subjects who received immediate release formulations in two studies of controlled-release formulations (A3051012 and A3051013).

Safety data from the abuse potential study (A3051039, N=45) were not pooled with the other Phase-1 data because the study's database was locked later than those for the other studies.

Subjects who received the controlled release formulation (N= 150) in Studies A3051012, A3051013, A3051023 and A3051024 were included in the analysis of lab-value related SAEs only.

Phase 2/3 Studies

Data from 5944 patients in all treatment groups were analyzed. Three-thousand nine-hundred and forty (N=3940) of these patients received varenicline.

7.1.7.3 Standard analyses and explorations of laboratory data

Phase-1

Phase-1 laboratory abnormalities were isolated and minor, with similar incidences between varenicline and placebo groups (where used). All identified laboratory abnormalities appear to be minor. There were no within-study, across dose group differences in mean laboratory values. No Phase-1 laboratory-related SAEs were identified in the varenicline-treated groups.

Phase 2/3
Median changes from Baseline to final values (up to 7-days after the last dose of study drug) are summarized by treatment group for the 'Phase 2/3 Fixed-dose, Placebo-controlled Studies' and the 'All Completed Phase 2/3 Studies' cohorts. Summary tables for the 'Phase 2/3 Fixed-dose, Placebo-controlled Studies,' the 'All Completed Phase 2/3 Studies,' and 'Phase 1 Studies' cohorts report the number and percentage of subjects in each treatment group who had laboratory test abnormalities that were clinically significant according to predetermined criteria that are indicated on the summary tables.

Categorical baseline-to-endpoint and baseline-to-worst-value shift tables were also presented, showing the number and percent of patients with normal above normal, and below normal lab values at baseline, at endpoint, and at any time during treatment.

Patients with potentially clinically significant abnormalities (PCSAs) and outlying values, and those that discontinued due to laboratory abnormalities were identified, and their cases reviewed in detail (Section 7.1.7.3.1 below). I also searched through the laboratory data line listings for patients with PCSAs that had not been reported, but found no additional cases.

7.1.7.3.1 Analyses focused on measures of central tendency
Phase 1
Assessment and interpretation of (between) treatment group differences for individual laboratory tests in the Phase-1 program is difficult, because of issues inherent to pooling of data from studies utilizing different designs, treatment durations and patient populations. Half of the Phase-1 studies were single-dose trials, about one third enrolled 12 subjects or less, and one quarter were drug-drug interaction studies. For these reasons, I reviewed the Phase-1 laboratory measures of central tendency study by study.

My review focused on the larger studies and those with longer treatment durations (i.e., A3051014 - titration and tolerability, N=120, 21-days), those likely to yield the most relevant safety findings (i.e., A3051033 – NRT PK/PD interaction study, N=24, 14-days; A3051034 – Zyban® PK/PD interaction study, N=46, 14-days), and those in which subjects were dosed supra-therapeutically (A305-001 – ADME study, SD up to 10-mg (N=102), MD up to 3-mg QD X 14-days (N=44); A3051039 – abuse potential, SD at 1-mg and 3-mg, N=45). My review of these data revealed no discernable treatment group differences for any of the laboratory parameters assessed (within the individual studies).

Phase 2/3 Fixed-Dose Placebo-Controlled Studies and All Completed Phase 2/3 Studies

There were no apparent differences between treatment groups in baseline values or median changes from baseline. No baseline-to-end-of-treatment treatment group mean (laboratory value) changes were found for any of the repeatedly measured parameters (electrolytes, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, calcium, total cholesterol, triglycerides, neutrophils, hemoglobin, red blood cells, and platelets), in either the 'All Completed Phase-2/3 Studies' cohort or the 'Fixed-dose, Placebo-controlled Phase-2/3 Studies' cohort. Table 7-31 summarizes data from the FDPC studies. Findings from 'All Completed Phase-2/3 Studies' are similar.

Table 7-31: Laboratory Value Baseline-to-Endpoint Changes, Fixed-Dose, Placebo-Controlled Studies

		Varenicline < 1-mg/BID N=496[a]		Varenicline 1-mg/BID N=1000[a]		Zyban® 150-mg BID N=721[a]		Placebo N=851[a]	
Analyte	**Units**	**Baseline[b]**	**Change[b]**	**Baseline[b]**	**Change[b]**	**Baseline[b]**	**Change[b]**	**Baseline[b]**	**Change[b]**
HGB	G/DL	15.7	-0.3	15.9	-0.3	15.8	-0.3	15.9	-0.2
HCT	%	47.2	-1.1	47.8	-1	47.7	-0.9	47.7	-0.5
RBC Count	10^6/MM^3	5.07	-0.09	5.07	-0.08	5.08	-0.09	5.08	-0.06
Platelets	10^3/MM^3	274	1	265	-3	259	-5	260	-3
WBC Count	10^3/MM^3	7.9	-0.4	7.8	-0.6	7.5	-0.6	7.8	-0.4
Lymphocytes (%)	%	30.3	1	28.7	1	29.2	-0.7	28.3	1
Neutrophils (ANC)	10^3/MM^3	4.8	-0.36	4.82	-0.43	4.5	-0.35	4.73	-0.34
Neutrophils (%)	%	61.5	-1.6	62	-1.8	60.7	0.1	62	-1.3
Basophils (%)	%	0.7	0	0.6	0	0.6	0	0.6	0
Eosinophils (%)	%	2	0.1	1.8	0.1	2	0.1	1.8	0.1
Monocytes (%)	%	4.7	0.4	5	0.4	5.1	0.4	5	0.2
Total Bilirubin	MG/DL	0.4	0	0.4	0	0.4	0	0.4	0
AST (SGOT)	IU/L	20	1	20	1	20	1	20	1
ALT (SGPT)	IU/L	22	1	24	1	25	2	24	1
LDH	IU/L	392	0	393	0	395	5	393	-2
Creatinine kinase	IU/L	NA	NA	NA	NA	NA	NA	NA	NA
Alkaline Phosphat.[†]	IU/L	83	-1	82	-1	80	1	81	-1
Total Protein	G/DL	7.1	0	7.1	0	7.1	-0.1	7.1	-0.1
Albumin	G/DL	4.2	-0.1	4.3	0	4.3	0	4.3	0
BUN	MG/DL	29	1.3	29	1.3	29	0	29	0
Creatinine	MG/DL	1	0	1	0	1	0	1	0
Cholesterol	MG/DL	191	-1	188	-1	188	-1	189	-2
Triglycerides	MG/DL	104	2	130	2	137	2	126	-2
Sodium	MEQ/L	140	0	139	0	139	0	139	0
Potassium	MEQ/L	4.2	0	4.2	0	4.2	0	4.2	0
Chloride	MEQ/L	104	0	103	0	103	0	103	0
Calcium	MG/DL	9.7	0	9.4	0	9.4	0	9.4	0
Phosphate	MG/DL	3.2	0.1	3.2	0.1	3.2	0	3.2	0
Bicarbonate	MEQ/L	25.8	0.6	24	1	24	1	24	0.6
Glucose	MG/DL	86	0	89	0	91	1	89	0

[a]There were a few missing values in each group [b]Medians [†]Too few observations Source: Table A19.4a

Creatinine phosphokinase was not included in the Phase-3 standardized laboratory testing battery. Less than fifty patients per treatment group had even a single CPK value available, thus calculation of changes in mean and median values is not warranted.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Phase-1 Studies

Table 7-32 summarizes the incidence of categorical shifts (to abnormal) in laboratory values, in the Phase-1 studies. Overall, the incidence of (shifts to) post-treatment laboratory abnormalities seems to be clearly increased in the varenicline >2-mg/day group. Laboratory value related discontinuations were not, however, higher for the >2-mg/day subjects.

Table 7-32: Incidence of Clinically Significant Laboratory Abnormalities in Phase-1 Studies (Number with Abnormality/Number Evaluable (%))

	Varenicline <2-mg	Varenicline 2-mg	Varenicline > 2-mg	Varen. + Other	Other Only	Placebo
Number Treated →	**N=241**	**N=309**	**N=112**	**N=146**	**N=141**	**N=255**
Evaluable →	**N=240 (99.6%)**	**N=258 (83.5%)**	**N=112 (100%)**	**N=146 (100%)**	**N=129 (91.5%)**	**N=203 (79.6%)**
Regardless of Baseline						
	100/241 (41.5)	94/258 (36.4)	82/112 (73.2)	39/146 (26.7)	35/129 (27.1)	100/2 (49.3)
Considering Baseline						
Normal Baseline	66/241 (27.4)	75/258 (29.1)	72/112 (64.3)	34/146 (23.3)	30/129 (23.3)	80/203 (39.4)
Abnormal Baseline	38/181 (21.0)	18/186 (9.7)	16/92 (17.4)	7/88 (8.0)	7/74 (9.5)	24/156 (15.4)

Source: Tables A19.1c, A19.2c, A19.3c, and 53 (2.7.4)

Much of the increase (in incidence of abnormal values) in the >2-mg/day group derives from urinalysis and hematology findings, as shown in Table 7-33 and Table 7-34 below. Specifically, urine specific gravity was increased for about 40% of the >2-mg/day subjects, hemoglobin decreased for about 8%, and eosinophils and monocytes increased for about 10%.

Phase-1 Urinalysis Categorical Shifts

My review of the Phase-1 categorical shift tables for shows that most of the increase in shifts to abnormal values, in the >2-mg/day group can be attributed to urinalysis findings. Many of these cases involved increased urine specific gravity (only). There were, however, considerably higher percentages of subjects with WBCs ≥6/HPF at varenicline doses ≥2-mg/day than at doses <2-mg/day (and placebo). Subjects at the 2-mg/day dose were also more likely to have RBCs ≥6/HPF (25%) compared with placebo and >2-mg/day subjects (6% and 3%, respectively).

Table 7-33 summarizes the Phase-1 urinalysis (qualitative and microscopic) categorical shift data. Given the lack of subjects with concomitant or subsequent increases in BUN and/or creatinine, the clinical significance of these findings is questionable. It should be kept in mind, however, that urinalysis abnormalities might be expected to precede findings of actual renal impairment or damage. The Phase-2/3 data should help to put the Phase-1 urinalysis findings in perspective.

Table 7-33: Clinically Significant Laboratory Abnormalities in Phase-1 Studies, Urinalysis, BUN, Creatinine (Number with Abnormality/Number Evaluable (%))

Lab Parameter Abnormality	Varenicline <2-mg/day N=241	Varenicline 2-mg/day N=258	Varenicline <2-mg/day N=112	Varenicline + Other N=146	Other Only N=129	Placebo N=203
Urinalysis						
Dipstick						
Spec. gravity; >1.030	21/156 (13)	18/227 (8)	35/89 (39)	1/131 (1)	4/119 (3)	31/165 (19)
pH ≤4.5	1/210 (0)	0/257	0/112	0/145	0/129	0/203
pH ≥9.0	1/210 (0)	1/257 (0)	1/112 (1)	0/145	1/129 (1)	0/203
Glucose ≥1	0/196	1/245 (0)	0/112	0/145	0/129	0/192
Ketones ≥1	2/209 (1)	2/242 (1)	0/112	1/140 (1)	1/127 (1)	1/192 (1)
Protein ≥1	0/196	2/245 (1)	1/112 (1)	0/145	0/129	0/192
Blood/Hgb ≥1	11/203 (5)	14/245 (6)	4/111 (4)	13/138 (9)	8/124 (6)	8/196 (4)
Bilirubin ≥1	0/67	0/109	0/80	0/3	0/1	1/99 (1)
Microscopy						
RBCs ≥6/HPF	0/67	9/36 (25)	1/30 (3)	3/25 (14)	5/24 (21)	3/53 (6)
WBCs ≥6/HPF	4/76 (5)	17/52 (33)	11/44 (25)	7/26 (27)	6/25 (24)	8/58 (14)
Granular casts ≥1	0/16	NA	NA	NA	NA	NA
Hyaline Casts ≥3	0/16	NA	NA	NA	NA	NA
Renal Function						
BUN (mg/dl)	1/217 (0)	0/256	0/101	0/143	0/124	0/196
Creatinine(mg/dl)	0/220	0/256	0/111	0/143	0/125	0/201
Uric acid (mg/dl)	1/234 (0)	0/240	0/112	0/141	0/125	0/190

[a]For patients Source: Tables A19.1a, A19.2a, and A19.3a Section (2.7.4)

Phase-1 Hematology Categorical Shifts

There were also higher percentages of subjects whose hemoglobin and hematocrit decreased, and whose monocyte count increased, in the >2-mg/day group than in all other treatment conditions. Eosinophilia occurred more commonly as well in the >2-mg/day and in the 'varenicline + other drug' groups (≈10% vs. 3-5%). As with the urinalysis data, these findings (summarized in Table 7-35), while concerning, are of unclear clinical relevance.

Table 7-34: Clinically Significant Laboratory Abnormalities in Phase-1 Studies (Number with Abnormality/Number Evaluable (%))

Lab Parameter Abnormality	Varenicline <2-mg/day N=241	Varenicline 2-mg/day N=258	Varenicline >2-mg/day N=112	Varenicline + Other N=146	Other Only N=129	Placebo N=203
Hematology						
Hemoglobin (g/dl)						
<0.8 baseline	1/211 (0)	0/243	7/100 (7)	2/131 (2)	1/115 (1)	5/188 (3)
Hematocrit (%)						
<0.8 baseline	0/211	1/239 (0)	9/96 (9)	1/132 (1)	1/119 (1)	6/181 (3)
Lymphocytes (%)						
<0.8xLLN	2/159 (1)	1/103 (1)	0/93 (0)	0/145 (0)	0/127 (0)	0/124 (0)
>1.2xLLN	1/159 (1)	2/103 (2)	1/93 (1)	0/145 (0)	0/127 (0)	1/124 (1)
Neutrophils,$10^3/mm^3$						
ANC <0.8 x LLN*	1/176 (1)	2/214 (1)	3/101 (3)	0/133 (0)	0/119 (0)	0/143 (0)
ANC >1.2 x ULN	0/176 (0)	6/214 (3)	2/94 (2)	0/133 (0)	1/119 (1)	0/143 (0)
Basophils, $10^3/mm^3$						
>1.2 x ULN	0/131 (0)	1/221 (0)	0/92 (0)	0/146 (0)	0/129 (0)	0/127 (0)
Eosinophils						
Absolute >1.2 x ULN	3/124 (2)	5/210 (2)	10/88 (11)	12/140 (9)	8/124 (6)	6/116 (5)
(%) >1.2 x ULN	5/159 (3)	3/106 (3)	7/87 (8)	4/40 (10)	3/33 (9)	3/139 (2)
Monocytes						
Absolute >1.2 x ULN	1/128 (1)	3/214 (1)	7/87 (8)	0/145	0/127	7/121 (6)
(%) >1.2 x ULN	2/152 (1)	3/103 (3)	12/85 (14)	1/42 (2)	0/35	12/139 (9)

[a]For patients Source: Tables A19.1a, A19.2a, and A19.3a Section (2.7.4)

Phase-1 Chemistry/LFT Categorical Shifts

Serum chemistry (electrolytes, glucose, and liver function tests) categorical shifts were rare during the Phase-1 program, with few abnormal values in any of the treatment conditions.

Phase-2/3 Studies

Table 7-35 presents the overall rates of clinically significant laboratory abnormalities by treatment group in the Phase 2/3 Fixed-dose, Placebo-controlled Studies. Table 7-32 presents the same information for the 'All Completed Phase 2/3 Studies' cohort. In both populations the incidence of potentially clinically significant laboratory abnormalities was similar across treatment groups.

Table 7-35: Incidence of PCSA Labs, Phase 2/3 Fixed-Dose, Placebo-Controlled Studies

	Fixed Dose		Placebo Controlled	
Number (%) Evaluable	**Varenicline <1mg BID N=505 496 (98.2)**	**Varenicline 1mg BID N=1070 1009 (94.3)**	**Zyban® N=795 722 (90.8)**	**Placebo N=928 853 (91.9)**
Any Laboratory Abnormality	280/496 (56.5)	493/1009 (48.9)	350/722 (48.5)	407/853 (47.7)
Considering Baseline				
Normal Baseline	176/496 (35.5)	270/1008 (26.7)	194/722 (26.9)	223/851 (26.2)
Abnormal Baseline	56/419 (13.4)	108/790 (13.7)	79/591 (13.4)	93/679 (13.7)

Source: Modified from Tables A3a, A19.1a/b/c, Table 48 (Section 2.7.4)

Table 7-36: Incidence of PCSA Labs, All Completed Phase 2/3 Studies

	Varenicline	Zyban®	Placebo
Number (%) Evaluable	**N=3940 3759 (95.4)**	**N=795 722 (90.8)**	**N=1209 1125 (93.1)**
Any Laboratory Abnormality	1925/3759 (51.2)	350/722 (48.5)	597/1125 (53.1)
Considering Baseline			
Normal Baseline	1106/3758 (29.4)	194/722 (26.9)	342/1123 (30.5)
Abnormal Baseline	446/3042 (14.7)	79/591 (13.4)	125/922 (13.6)

Source: Modified from Tables A3b, A19.1b Table 59 (Section 2.7.4)

Table 7-37 summarizes categorical changes in LFTs (from baseline to worst value) in both the FDPC and the 'All Completed Phase-2/3 Studies' cohorts. In the fixed-dose placebo-controlled studies, minor SGPT elevations appear to be slightly more common in the varenicline group(s), but incidence rates are still very low (<1%). Like wise, the magnitude of change was also small. There were no values reaching 5 X ULN, and all cases resolved spontaneously. Findings were similar for the 'All Completed Phase-2/3 Studies' group.

Creatinine phosphokinase values were not routinely assessed. Both baseline and follow-up CPK values are available, though, for about sixty patients (in the all-completed studies database), obtained by investigators or hospitals because of LFT or urinalysis abnormalities (not per protocol). Overall, ten of these patients (six varenicline, four placebo) experienced shifts from normal to >2.0 X ULN, in some cases reaching values exceeding ten times the upper limit of normal. No cases of rhabdomyolysis were reported, nor were any adverse events coded as 'Myopathy' or related terms. Additional information regarding these cases has been requested (3/22/07) in order to better assess varenicline's potential for causing CPK elevations, and possible rhabdomyolysis.

Table 7-37: Phase-2/3 Clinically Significant LFT Abnormality Incidence – Number with Abnormality/Number Evaluable (%)

Baseline Status Lab Parameter	Criteria	Fixed-Dose, Placebo-Controlled Studies				All Phase-2/3 Studies	
		<1-mg BID N=496	1-mg BID N=1008	Zyban® N=722	Placebo N=851	Any Dose N=3758	Placebo N=1123
Any Baseline							
Total Bilirubin	>1.5 x ULN	1/496 (0.2)	1/1007 (0.1)	0/721 (0)	0/851 (0)	4/3730	1/1116
AST (SGOT)	>3.0 x ULN	2/496 (0.4)	3/1006 (0.3)	1/721 (0.1)	7/851 (0.8)	11/3701	6/1099
ALT (SGPT)	>3.0 x ULN	2/496 (0.4)	7/1006 (0.7)	1/721 (0.1)	1/851 (0.1)	9/3594	1/1074
Alkaline Phosph	>3.0 x ULN	0/496 (0)	0/1006 (0)	0/721 (0)	0/851 (0)	0/3675	0/1100
LDH	>3.0 x ULN	1/495 (0)	0/989 (0)	1/704 (0)	1/825 (0)	1/3669	1/1085
CPK	>2.0 x ULN	0/0	1/16	0/17	3/19	6/38	4/25
Normal Baseline							
Total Bilirubin	>1.5 x ULN	0/493 (0)	1/1000 (0.1)	0/715 (0)	0/846 (0)	--	--
AST (SGOT)	>3.0 x ULN	2/493 (0.4)	2/994 (0.2)	1/701 (0.1)	5/831 (0.6)	--	--
ALT (SGPT)	>3.0 x ULN	2/483 (0.4)	3/994 (0.3)	1/676 (0.1)	1/812 (0.1)	--	--
Alkaline Phosph	>3.0 x ULN	0/486 (0)	0/976 (0)	0/713 (0)	0/836 (0)	--	--
Abnormal BL[a]							
Total Bilirubin	>1.5 x BL &						
	>1.5 x ULN	1/3 (33.3)	0/7 (0)	0/6 (0)	5/0 (0)	--	--
AST (SGOT)	>1.5 x BL &						
	>3.0 x ULN	0/3 (0)	1/12 (8.3)	0/20 (0)	2/20 (10.0)	--	--
ALT (SGPT)	>1.5 x BL &						
	>3.0 x ULN	0/13 (0)	3/57 (5.3)	0/45 (0)	0/41 (0)	--	--
Alkaline Phosph	>1.5 x BL &						
	>3.0 x ULN	0/10 (0)	0/30 (0)	0/8 (0)	0/15 (0)	--	--

[a]For patients with abnormal baseline, both criteria were required Source: Tables 50, A19.1a and A19.2a (2.7.4)

Table 7-38 summarizes the incidence in shifts from normal to PCSA for urinalysis parameters, and for BUN and creatinine.. Less than 50% of patients had both baseline and on-treatment urinalysis. The incidence of shifts (from normal to abnormal) in urinalysis parameters appears similar across treatment groups, for both databases, except for a higher rate of microscopic hematuria in the <1-mg BID group. This finding may be attributable to the small sample size. Only 39 of 496 subjects in the <1-mg BID group had two or more urine microscopy values, though. Urine microscopy was only done for subjects with abnormal dipstick urinalysis. The fact that so few tests were performed, is in itself, reassuring, especially in light of the dipstick urinalysis, and BUN/creatinine findings.

Table 7-38: Incidence of Shifts to Clinically Significant Renal Function and Urinalysis Values Phase 2/3 Studies (Number with Abnormality/Number Evaluable (%))

Baseline Status Normal Lab Parameter	**Fixed-Dose Controlled** **Varenicline <1-mg BID N=496**	**Varenicline 1-mg BID N=1008**	**Placebo Zyban® N=722**	**Placebo N=851**	**All Studies Varenicline All doses N=3490**
Urinalysis					
Spec. gravity; >1.030	11/285 (3.9)	9/300 (3.0)	9/250 (3.6)	7/269 (2.6)	26/1019 (2.6)
Glucose (qualitative), ≥1	5/285 (1.8)	8/300 (2.7)	5/250 (2.0)	7/269 (2.6)	30/1049 (2.9)
Protein (qualitative), ≥1	1/273 (0)	1/287 (0)	2/250 (0)	3/262 (1)	17/1024 (1.7)
Ketones(qualitative), ≥1	3/285 (1.1)	4/300 (1.3)	5/250 (2.0)	6/269 (2.2)	25/1020 (2.5)
Blood/Hgb (qualit.), ≥1	56/284 (19.7)	69/300 (23.0)	59/250 (23.6)	58/269 (21.6)	329/1048 (31.4)
Bilirubin (qualitative), ≥1	7/249 (2.8)	9/269 (3.3)	5/250 (2.0)	4/251 (1.6)	20/926 (2.2)
RBCs ≥6/HPF	12/39 (30.8)	21/180 (11.7)	14/130 (10.8)	21/149 (14.1)	84/653 (12.9)
WBCs ≥6/HPF	5/39 (12.8)	13/180 (7.2)	10/130 (7.7)	9/149 (6.0)	78/653 (11.9)
Renal Function (mg/dl)					
BUN >1.3 X ULN	0/494	0/998	0/721	1/847 (0)	3/3749 (0)
Creatinine >1.3 X ULN	0/496	0/1004	0/721	0/851 (0)	0/3749 (0)

[a]For patients Source: Tables 49, A19.1a, A19.2a, and A19.3a (2.7.4)

In the 'All Completed Phase-2/3 Studies' database dipstick hematuria appears to have been more common in the varenicline group (31%) than in the placebo group (21%). Microscopic hematuria, however, occurred with nearly similar frequency in the two groups (≈13%).

Table 7-39 below summarizes categorical shifts in hematology, chemistry and metabolic values for the fixed-dose, placebo-controlled database. No abnormalities appear to have occurred more commonly in varenicline-treated patients, except possibly for increased triglycerides. Anemia, monocytosis and eosinophilia do not appear to have occurred more commonly in varenicline-treated patients than in those treated with Zyban® or with placebo. Findings for the all completed Phase-2/3 studies database are similar, with elevated monocyte and eosinophil counts (%) found in about 3% of patients in both the varenicline and placebo groups.

Table 7-39: Clinically Significant Lab Abnormality Incidence - Phase 2/3 Fixed-Dose, Placebo-Controlled (Number with Abnormality/Number Evaluable (%))

Test Group Lab Parameter	Varenicline <1-mg BID	Varenicline 1-mg BID	Zyban® 150-mg BID	Placebo
Hematology				
Hemoglobin (g/dl)				
<0.8 baseline	0/496 (0)	0/1007 (0)	1/719 (0)	1/851 (0)
Hematocit (%)				
<0.8 baseline	1/496 (0)	0/1007 (0)	2/719 (0)	2/851 (0)
Lymphocytes (%)				
<0.8xLLN	13/496 (2.6)	23/1007 (2.3)	21/719 (2.9)	15/851 (1.8)
Neutrophils (ANC), $10^3/mm^3$				
<0.8 x LLN*	3/496 (0.6)	10/1007 (1.0)	2/719 (0.3)	6/851 (0.7)
>1.2 x ULN	56/496 (11.3)	65/1007 (6.5)	35/719 (4.9)	70/851 (8.2)
Basophils, (%)				
>1.2 x ULN	7/496 (1.4)	6/1007 (0.6)	8/719 (1.1)	6/851 (0.7)
Eosinophils, (%)				
>1.2 x ULN	15/496 (3.0)	31/1007 (3.1)	23/719 (3.2)	25/851 (2.9)
Monocytes, (%)				
>1.2 x ULN	12/496 (2.4)	26/1007 (2.6)	17/719 (2.4)	26/851 (3.1)
Chemistry				
Sodium, mEq/L				
<0.95 x LLN	0/496 (0)	0/1006 (0)	1/721 (0)	0/851 (0)
>1.05 x ULN	2/496 (0)	0/1006 (0)	0/721 (0)	1/851 (0)
Potassium, mEq/L				
<0.9 x LLN	0/496 (0)	3/1006 (0.3)	0/721 (0)	1/851
>1.1 x ULN	7/496 (1.4)	3/1006 (0.3)	3/721 (0.4)	4/851 (0.5)
Phosphate, mg/dL				
<0.8 x LLN	9/496 (1.8)	6/1006 (0.6)	5/721 (0.7)	5/851 (0.6)
>1.2 x ULN	7/496 (1.4)	4/1006 (0.4)	0/721 (0)	2/851 (0.2)
Bicarbonate, mEq/L				
<0.9 x LLN	8/496 (1.6)	41/1006 (4.1)	28/721 (3.9)	38/851 (4.5)
>1.1 X ULN	1/496 (0)	1/1006 (1)	0/721 (0)	0/851 (0)
Glucose, mg/dL				
>1.5 x ULN	6/496 (1.2)	7/1006 (0.7)	3/721 (0.4)	8/851 (0.9)
Creatinine kinase, U/L				
>2.0 x ULN	0/0	1/16	0/17	3/19
Lipids (mg/dL)				
Cholesterol (>1.3 x ULN)	7/496 (1.4)	2/1006 (0.2)	2/721 (0.3)	0/851 (0)
Triglycerides(>1.3 x ULN)	156/496 (31.4)	268/1003(26.8)	187/716 (26.1)	202/851 (23.7)

[a]For patients Source: Tables 49, A19.1a, A19.2a, and A19.3a (2.7.4)

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Phase-1 Studies

In the Phase 1 studies, there were 5 subjects who discontinued due to laboratory abnormalities. One subject in the 'varenicline <2-mg/day' group discontinued due to an elevated CPK (< 5 X ULN). Two subjects discontinued due to elevated ALT and AST (one in the 'varenicline 2-mg/day' group and one in the 'varenicline + other drug' group). Two additional patients discontinued because of elevated AST alone (one in the varenicline 2-mg/day group and one in the 'varenicline + other drug' group). No 'varenicline > 2-mg/day' or placebo subjects discontinued because of laboratory findings.

Phase-2/3 Fixed-dose, Placebo-Controlled

Few specific lab abnormalities resulted in discontinuation for more than one patient, as shown in Table 7-40. Most discontinuations resulted from LFT abnormalities. Not all patients that discontinued because of lab findings had abnormal values meeting PCSA criteria (and not all patients with potentially clinically significant laboratory abnormalities discontinued from treatment).

Table 7-40: Laboratory Test Related Dropouts – Phase 2/3 Fixed-Dose, Placebo-Controlled

Preferred Term	Varenicline <1-mg BID N=505	Varenicline 1-mg BID N=1070	Zyban® 150-mg BID N=795	Placebo N=928
Blood creatinine kinase increased	0 (0)	0 (0)	0 (0)	1 (0.1)
Blood LDH increased	0 (0)	0 (0)	0 (0)	1 (0.1)
Hemoglobin decreased	1 (0.2)	0 (0)	0 (0)	0 (0)
Platelet count decreased	0 (0)	0 (0)	0 (0)	1 (0.1)
ALT increased	4 (0.8)	4 (0.4)	2 (0.3)	1 (0.1)
AST increased	1 (0.2)	1 (0.1)	0 (0)	3 (0.3)
± Blood bilirubin increased*	0 (0)	1 (0.1)	0 (0)	0 (0)
Hepatic enzyme increased	1 (0.2)	0 (0)	0 (0)	0 (0)
Liver function test abnormal	1 (0.2)	4 (0.4)	0 (0)	1 (0.1)
Blood glucose increased	1 (0.2)	0 (0)	0 (0)	0 (0)
Blood urine present	0 (0)	0 (0)	1 (0.1)	0 (0)
Glucose urine present	1 (0.2)	0 (0)	0 (0)	0 (0)

*Baseline value reported to patient at Week-2 visit Source: Applicant Tables 54 and A15.1a (Section 2.7.4)

My review of the AE and disposition data did not identify any additional patients that appeared to have been laboratory related discontinuation because of laboratory abnormalities.

Transaminase and bilirubin elevations (> 1.5 X ULN) at baseline precluded Phase-3 participation, thus few patients (in any treatment group) had abnormal baseline AST, ALT, or total bilirubin. The Phase 2/3 protocols included instructions to investigators to report as AEs any laboratory abnormalities that resulted in permanent or temporary treatment discontinuation, or in dose reduction. Investigators were also instructed to discontinue treatment immediately for any subject with marked liver function abnormalities (AST or ALT ≥3X ULN, T. bilirubin ≥2 X ULN or alkaline phosphatase ≥1.5X ULN

Renal/Urinary Value Abnormalities

Clinical laboratory assessments of renal function included BUN, creatinine, and qualitative urinalysis tests. No varenicline-treated patients in the Phase 2/3 Fixed-Dose, Placebo-Controlled Studies had a clinically significant elevation of BUN or creatinine. Among the 3940 varenicline-treated patients in

the Phase 2/3 studies, 3 had clinically significant elevations of BUN, and none had clinically significant elevations of creatinine. Renal and urinary adverse events are discussed in Section 7.1.3.3 above.

7.1.7.3.4 Liver Function Test Abnormalities

There were no cases meeting 'Hy's Law' criteria. Seven Phase-2/3 varenicline patients (and no placebo patients) had PCSA total bilirubin elevations, all of which were < 2.3 X ULN, and not accompanied by marked transaminase elevations. One additional patient (#103510321029), varenicline 1-mg BID) chose to discontinue because of an elevated baseline total bilirubin of 1.7, reported to him at the Week-2 visit (increased from 1.1 at screening nine days prior). His Week-2 total bilirubin value had returned to 1.1. His transaminases remained normal throughout the entire period.

Phase-2/3 Fixed-Dose, Placebo-Controlled Studies

There were 21 varenicline-treated patients and 7 placebo-treated patients who had clinically significant LFT values and/or treatment discontinuations due to LFT elevations. Eighteen of the varenicline-treated patients reported LFT-associated adverse events. Overall, these adverse events and/or laboratory findings led to discontinuation of treatment for 15 patients (both varenicline and placebo).

Five varenicline patients had clinically significant increases (≥3X ULN) of AST, and 9 had clinically significant increases (3X ULN) of ALT. Transaminase values were decreasing by the final measurement for all but one of the 21 varenicline-treated patients with LFT-related adverse events and/or PCSA LFT values; Patient 100750100131 had an adverse event of 'LFTs abnormal' that resulted in discontinuation, but none of his LFT abnormalities reached PCSA criteria.

Seven placebo-treated patients had LFT-related adverse events associated or PCSA LFT values. Four of these patients permanently discontinued, while two temporarily interrupted treatment. No placebo-treated subjects had PCSA bilirubin elevations, 7 had clinically significant increases (3X ULN) of AST, and 1 had a clinically significant increase (3X ULN) of ALT.

All Completed Phase-2/3 Studies

The All Completed Phase 2/3 studies included 43 varenicline-treated patients and 9 placebo patients who had PCSA LFT values and/or LFT-related treatment discontinuations. Thirty (30) of the varenicline patients reported adverse events associated with LFTs. These adverse events led to permanent discontinuation for 23 patients, and temporary treatment interruption for 3 patients. Values were decreasing by the final measurement for 37 of the 43 varenicline patients, many of whom continued treatment. Twelve varenicline patients had PCSA AST increases, fifteen had PCSA ALT increases and, as noted above, seven had PCSA bilirubin increases.

Patient 103510271179 experienced an 'SAE case' in which four laboratory-related SAEs were reported; elevated AST, ALT, lactate dehydrogenase, and creatinine phosphokinase (Day-84, 1-mg BID). The patient's brief inpatient workup may only have resulted from his CPK value (12594), however. The patient's AST increased to about 7 X his baseline, his ALT to less than 2 X his elevated baseline and his LDH to 3 X baseline. The laboratory findings were attributed to a recent muscle injury. BUN and creatinine values remained normal, and urinalysis values are not available. Varenicline treatment was interrupted for about one-week. By Day-365 ALT had decreased to near its baseline elevated value (65), and AST to 42. Hepatitis virus titers are not provided. Of the 6 remaining

patients, 3 had laboratory abnormalities reported as adverse events, including #103510321029 (described above), who discontinued at Week-2 because of an elevated baseline value.

Table 7-41 below lists all Phase-2/3 varenicline patients with PCSA LFT values and/or LFT-related discontinuations. Table 7-42 does the same for placebo-treated patients.

Table 7-41: LFT-Related Discontinuations AND PCSA Values, All Completed Phase-2/3 Studies

Patient ID	MedDRA PT	Analyte	Baseline Value	First Day Elevated	Last RX Day	Highest Day	Highest Value	Last Day	Last Value
0.3mg QD									
100250110500	AST increased*+	AST	19	29	32	29	96H	58	28
	ALT increased*+	ALT§	20	29		29	197H	58	42
		Alk phos	113	8		8	122H	58	111
100250120601	Hepatic enzymes	AST	15	29	34	29	60H	51	16
	increased*+	ALT	11	29		29	102H	51	14
0.5 mg BID									
100750120143	ALT increased*+	ALT	35	14	31	29	91H	49	36
100750120361	ALT increased*+	ALT	17	30	46	43	129H	84	21
	Alk Phos increased	Alk Phos	104	50		50	150H	84	99
100750050569	(None)	Bilirubin§	1.4H	1	63	29	2.2H	85	2.0H
1 mg QD									
100250050073	LFTs abnormal*	AST§	31	14	16	14	326H	52	23
		ALT§	23	14		18	141H	52	20
		LDH§	149	14		14	761H	52	143
		CPK§	-	-		18	7050H	25	345H
100250120130	ALT increased*+	ALT	38	7	33	49	111H	88	34
100250150430	(None)	AST§	26	14	42	14	134H	63	34
		LDH	162	14		14	514H	63	201
		CPK§	-	21		21	1090H	63	780H
1 mg BID									
100250050104	LFTs abnormal	AST§	15	46	46	46	353H	52	152H
		ALT§	30	46		46	232H	52	154H
		LDH	124	46		46	393H	52	242
		CPK§	-	-		46	16220H	-	-
100250110633	ALT increased*+	ALT	24	16	24	22	68H	50	29
100750050553	Bilirubin increase.*	Bilirubin§	1.1	15	71	50	2.1H	88	1.7H
100750100131	LFTs abnormal*	ALT	58H	1	18	15	59H	85	73H
100750110535	AST increased*+	AST	37H	35	44	42	62H	92	53H
	ALT increased*+	ALT	47H	1		42	107H	92	87H
100750290247	ALT increased*+	ALT	42	9	22	20	94H	35	49H
101650310310	ALT increased*+	ALT	27	14	32	14	114 H	84	26
		AST	22	14		14	59 H	84	20
101650320087	AST increased*	AST§	18	29	32	29	133 H	57	20
	Blood LDH ↑*	LDH	196	29		29	300 H	57	170
	Blood CPK ↑*	CPK	-	-		29	4740 H	57	88
102810051065	ALT increased *+	ALT§	66H	-6	42	91	177H	133	83H
	CPK increased	CPK§	n/a	91		91	8065H	133	743H
102810131003	(None)	ALT§	93H	0	87	87	98H	92	48H
		AST	89H	0		0	89H	92	49H
		LDH	332H	0		87	335H	87	335H
103510011008	(None)	ALT§	23	86	107	86	157H	170	55H

(Continued)

Patient ID	MedDRA PT	Analyte	Baseline Value	First Day Elevated	Last RX Day	Highest Day	Highest Value	Last Day	Last Value
1 mg BID									
103510121151	Hepatic enzyme ↑	ALT§	79H	1	8	8	183H	122	288H
103510141120	Hepatic enzyme ↑*	ALT[c]	47H	-18	119	113	148H	197	127H
103510151041	(None)	Bilirubin§	0.9	15	76	15	2.3H	85	1.2
103510171094	(None)	ALT§	54H	-10	87	87	154H	376	50H
103510171115	(None)	Bilirubin§	1.3H	1	84	85	1.9H	169	1.9
103510191032	(None)	AST§	21	15	79	15	136H	171	18
103510211015	ALT increased*+	ALT§	11	15	17	15	409H	42	204H
	AST increased+	AST§	19	15		15	434H	42	154H
	Alk Phos ↑*	Alk Phos	86	15		17	275H	42	181H
103510241011	(None)	AST§	19	15	86	86	139H	90	84H
103510251034	(None)	Bilirubin§	1.1	15	85	85	2.3H	85	1.6H
103510271179	ALT increased^	ALT	65H	-10	84	92	119H	365	88H
	AST increased^	AST§	28	84		84	177H	365	42H
	LDH increased^	LDH	148	84		84	479H	176	200
	CPK increased^	CPK	--	84		84	12594H	365	232
103510271291	(None)	Bilirubin§	0.7	14	89	14	2.2H	89	0.6
103510301015	Hepatic enzyme ↑	AST§	13	85	85	85	235H	169	20
103510321029	Bilirubin increased	Bilirubin	1.1	1	12	1	1.7H	20	1.1
103510321036	ALT increased*+d	ALT§	22	15	53	56	159H	103	88H
103610021012	LFTs abnormal*+	ALT§	50H	0	59	54	259H	85	23
		AST	35	15		54	102H	85	22
		Alk Phos§	126H	0		54	187H	85	123
		LDH	227H	0		15	237H	85	183
103610021034	LFTs abnormal*+	ALT§	60H	-8	25	22	158H	85	52H
		AST	30	22		22	64H	85	35
		Alk Phos§	117	22		22	129H	85	99
		LDH	214	15		15	316H	85	198
103610021071	LFTs abnormal*+	ALT§	21	15	20	15	268H	99	43
		AST§	48H			15	282H	99	41
103610031006	CPK increased+	CPK §	n/a	22	20	22	9024H	70	303H
		ALT	12	27		27	76H	41	17
		AST§	17	22		22	130H	41	18
		LDH	129	22		22	533H	41	139
103610101099	ALT increased+	ALT§	33	85	85	85	137H	91	65H
	AST increased+	AST	32	85		85	88H	91	32
103710031039	AST increased*	AST§	30	90	191	177	143H	364	18
103710111062	ALT increased*+	ALT§	33	15	93	36	144H	155	45
103710031025	(None)	Bilirubin§	2.3H	-9	120	120	2.6H	127	1.8H
103710071018	(None)	Bilirubin§	1.3H	-13	152	155	1.9H	155	1.9H
103710011023	CPK increased	CPK	21986H	1	362	1	21986H	15	367H
	Hepatic enzyme ↑	ALT	143H	1		1	143H	373	24
		AST	406H	1		1	406H	373	38
		LDH	975H	1		1	975H	373	208

§ At least one value during treatment or within 7-days of last dose met criteria for clinically important elevation (>3x ULN)
+ Possibly treatment-related (reviewer assessment) Source: Tables A18.3, A19.2 and A19.3
* Resulted in permanent treatment discontinuation * Resulted in temporary treatment discontinuation

Table 7-42: LFT-Related Discontinuations AND PCSA Values, All Completed Phase-2/3 Studies

Patient ID	MedDRA PT	Analyte	Baseline Value	First Day Elevated	Last RX Day	Highest Day	Highest Value	Last Day	Last Value
Placebo									
100250100379	AST increased *+	AST§	20	35	42	42	148 H	56	83 H
	ALT increased	ALT	18	28		56	175 H	56	175 H
100750050027	ALT increased^	ALT§	28	17	33	17	177 H	85	31
	AST increased^	AST§	20	17		17	212 H	85	22
	Blood CPK	CPK	--	--		--	10885 H	57	1531 (h)
		LDH§	153	17		17	914H	85	168
100750110373	LFTs abnormal*+	AST§	21	11	13	11	291 H	25	20
		ALT	9	11	--	11	64 H	25	11
		LDH	123	11		11	340 H	25	110
100750120355	AST increased *+	AST§	26	8	8	8	157 H	37	25
	ALT increased *+	ALT	22	8	--	8	67 H	37	21
	LDH increased*+	LDH	152	8		8	546H	14	189
	CPK increased *+	CPK	--	8		8	9450H	37	230
100750240200	Hepatic enzyme↑*+	AST§	17	50	84	50	143 H	85	26
		ALT	16	50		50	55 H	85	15
		LDH	161	50		50	356 H	85	177
101650310145	AST increased *	AST	27	30	33	30	74H	86	19
	ALT increased *	ALT§	64H	1		30	196H	86	23
101650310190	(None)	AST§	13	9	89	9	157 H	89	13
		ALT	12	9		9	66 H	89	16
		CPK	--	9		9	14720H	--	--
		LDH	135	9		9	606H	89	145
101650340268	ALT increased *+	ALT	17	29	72	71	135H	85	40
102810211039	AST increased *	AST§	59H	-10	25	74	160H	88	132H
103610051057	CPK increased ^+	CPK§	--	15	91	15	2390 H	61	386 H
	LFTs abnormal ^+	ALT	26	15		15	79 H	91	35
		AST§	44 H	0		15	136 H	91	52 H
		LDH	174	15		15	243 H	91	181
103710121041	(None)	Bilirubin§	0.8	1	355	91	1.4H	369	1.1

§ At least one value during treatment or within 7-days of last dose met criteria for clinically important elevation (>3x ULN)
+ Possibly treatment-related (reviewer assessment) Source: Tables A18.3, A19.2 and A19.3
* Resulted in permanent treatment discontinuation * Resulted in temporary treatment discontinuation

LFT shifts and LFT-related discontinuations occurred more commonly in the 1-mg BID group than in placebo. I reviewed each case for possible treatment relatedness. Table 7-43 below summarizes my findings. Overall, LFT abnormalities and discontinuations appear to be more common in the 1-mg BID group. Treatment-related cases appear to be roughly twice as common in the 1-mg BID group as in the placebo group, but the absolute number of cases is limited.

Table 7-43: LFT Shifts by Treatment-Relatedness (Reviewer Assessment)
Phase-2/3 Fixed-Dose, Placebo-Controlled Studies

Evaluable →	Varenicline <1-mg BID N=496	Varenicline 1-mg BID N=1006	Placebo N=851
Patients with LFT Abnormality			
Total	8 (1.6%)	35 (3.5%)	11 (1.3%)
Related	5 (1.0%)	13 (1.3%)	6 (0.7%)

Source: Clinical reviewer

7.1.7.3.5 Markedly Elevated CPK Values

Because the incidence of markedly elevated CPKs appeared to be increased in varenicline-treated patients, the varenicline laboratory test databases (All Completed Phase 2/3 Studies, Phase 1 Studies) were searched for all subjects with CPK values > 5x ULN. In all, there were 40 patients with post randomization CPK values that reached 5 times the upper limit of normal (one was a subject in Phase-1 Study 1026);. 19 varenicline, 17 placebo and 4 Zyban®. Twelve of the varenicline patients received 1-mg BID and five had received 1-mg/day. Two, in the flexible dosing study had been taking 1.0-1.5 mg per day.

Pfizer was asked to provides summary information for these patients, including all adverse event listings and relevant laboratory data (i.e., BUN, creatinine, urinalysis, LFTs). Summary narratives were prepared for each patient, including the requested data, where available.

My review of the individual case narratives and laboratory data shows no apparent relationship between varenicline use (and duration) and CPK increase. Several of the patients had compelling alternative explanations, such as recent musculoskeletal injuries and viral illnesses accompanied by fever, while others had concomitantly drawn laboratory values indicating hemolysis of the samples. Follow-up values are not available for all patients, but those that are normalized, or decreased dramatically. Follow-up BUN and creatinine values were available for these patients, however. In no cases were increases seen, either during or after CPK peak.

Discontinuations After Randomization/Exposure Due to Abnormal Screening Lab Values

No patients were discontinued subsequent to treatment exposure, because of abnormal baseline or screening laboratory values.

7.1.7.4 Additional analyses and explorations

Clinical Laboratory Findings from Individual Longer-Term Phase 2/3 Studies

Safety Study (A3051037)

The planned duration of varenicline treatment (1-mg BID) was 52 weeks. In this study, there were 112 subjects who received varenicline for 52-weeks, and 95 subjects who had > 52 weeks of treatment. The protocol called for laboratory tests at Screening, Baseline, and Weeks 2, 12, 24, and 52.

The overall rate of laboratory test abnormalities (regardless of baseline abnormalities) was 62% (147/239) for varenicline-treated subjects and 60% (72/120) for placebo-treated subjects. There were no apparent increases in the rates of abnormalities or median changes from baseline for individual laboratory tests. Overall, longer-term treatment with varenicline does not appear to increase the risk of clinically significant laboratory abnormalities.

Maintenance Study (A3051035)

Subjects in Study A3051035 received 12 weeks of open-label varenicline 1-mg BID, then, if abstinent, were randomized to 12 additional weeks of treatment, with either varenicline 1 mg BID or with placebo. Laboratory tests were obtained at Screening, Baseline, Week 2, Week 12 and Week 24. Changes from baseline were determined for 2 different Baseline values: the open-label baseline (the last observation before the initial 12-week treatment period) and the double-blind Baseline (the last observation before initiation of the second 12-week treatment phase).

Overall, the frequency of clinically significant laboratory test abnormalities was low, and there were no apparent differences in the rates of abnormalities or in the median changes from baseline (for individual lab tests) between varenicline and placebo-treated subjects in the double-blind phase. No subjects discontinued from either phase of the study due to laboratory abnormalities. These results suggest that there is no increased risk of clinically significant laboratory abnormalities associated with extending the duration of varenicline treatment from 12 to 24 weeks.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Phase-1 Studies

Vital signs measured in Phase-1 studies varied according to the study design. All studies assessed vital signs at Baseline and End-of-Treatment (at a minimum). Most studies also incorporated multiple on-treatment assessments.

In the single-dose, and multi-dose, single-day studies vital signs were measured at Screening, Baseline and (3 to 4 hours) post-treatment. In the multiple-day Phase-1 studies vital signs were measured at those timepoints, at a minimum. Most multiple-day studies also measured vital signs at several additional on-treatment timepoints. In within-subject, multiple session crossover studies, Baseline and end-of treatment measurements were repeated at the beginning and end-of-treatment, for each treatment period.

Phase-2/3 Studies

During the Phase-2/3 studies blood pressure and pulse were measured at all clinic visits in both treatment and nontreatment phases. Blood pressure and pulse were measured in the dominant (writing) arm after the subject had been seated for 5 minutes and were then measured again after the subject had been standing for 2-minutes. Blood pressures were recorded to the nearest mm Hg. Body weight was also measured at all clinic visits. Body temperature and height were measured at Screening and Baseline only.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Phase-1 Studies

All Phase-1 studies collected vital sign data before during and after treatment.

Phase-2/3 Studies

Baseline measurements were those measurements obtained prior to dosing. In those cases where multiple measurements were obtained during the baseline period, those obtained during the final pre-treatment visit were considered to be baseline. Where multiple measures were obtained on the final pre-treatment visit day, and all values were within normal range, the mean of the values was used.

The 'study day' of a measurement was calculated as the number of days since the patient had begun taking study medication, even if medication had already been discontinued.

Vital sign endpoint values were the last values obtained, up to 7-days after treatment discontinuation.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Phase-1

My review of the measures of central tendency in the Phase-1 vital sign data revealed no apparent treatment related effects.

Phase-2/3

As noted above, blood pressure and pulse rate were measured at all clinic visits. Table 7-44 summarizes the median baseline values for blood pressure and pulse rate measurements and the median changes from baseline to last measurement on study medication, or within 7-days of last dose.

Table 7-44: Vital Signs, Median (Treatment Group) Change, Baseline-to-Last-Value[a], Phase-2/3

	Fixed-Dose, Placebo-Controlled Phase-2/3 Studies								**All Phase-2/3**	
	Varenicline <1-mg BID N=495		**Varenicline 1-mg BID N=1043[b]**		**Zyban® 150-mg BID N=764[b]**		**Placebo N=904**		**Varenicline All Doses N=3940**	
Sitting	BLV	LV	BLV	LV	BLV	LV	BLV	LV	BLV	LV
Systolic BP (mm Hg)	116	-2.0	120	0.0	118	0.0	120	0.0	120	0.0
Diastolic BP (mm Hg)	74	0.0	76	0.0	76	0.0	76	-1.0	80	0.0
Pulse Rate (bpm)	76	-2.0	76	-2.0	74	0.0	74	0.0	80	-2.0
Standing										
Systolic BP (mm Hg)	115	-2.0	119	0.0	118	0.0	118	0.0	120	0.0
Diastolic BP (mm Hg)	77	0.0	78	0.0	78	0.0	78	0.0	78	0.0
Pulse Rate (bpm)	80	-2.0	80	-1.0	78	0.0	78	-1.0	76	-2.0

[a]Last value on-treatment to 7-days post [b]One 'standing' value missing Source: Tables A20.1a and 55, 2.7.4

There were no changes in mean or median values of sitting or standing blood pressure or heart rate in varenicline-treated patients, in either the FDPC or the 'All Completed Phase-2/3 Studies' cohorts.

Likewise, in 52-week safety study A3051037 there were no between group differences in baseline to end of treatment vital sign changes, as can be seen in Table 7-45 below.

Table 7-45: Vital Signs, A3051037
Median (Treatment Group) Change
Baseline-to-Last-Value

	Varenicline 1-mg BID N=249		Placebo N=125	
Sitting	BLV	LV	BLV	LV
Systolic BP (mm Hg)	120	2.0	120	-2.0
Diastolic BP (mm Hg)	78	0.0	80	-2.0
Pulse Rate (bpm)	76	-2.0	80	0.0
Standing				
Systolic BP (mm Hg)	120	2.0	122	-2.0
Diastolic BP (mm Hg)	78	0.0	80	-2.0
Pulse Rate (bpm)	80	-2.0	76	-0.0

[a]Last value on-treatment to 7-days post
Source: A3051037 Table 13.8.1

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Phase-1 Studies
Although the rates of post-baseline categorical changes in blood pressure were higher for varenicline than in the Phase-2/3 studies, study populations were smaller, and the absolute number of events was still low and did not show any apparent dose-relatedness. The incidence of clinically significant changes in pulse rate was also low and similar for all treatment groups.

Phase-2/3 Studies
Table 7-46 below summarizes categorical vital sign changes for the Phase-2/3 Fixed-dose, Placebo-controlled patients. Although the incidence of clinically significant categorical changes in blood pressure or pulse rate was low and similar for all treatment groups, there does appear to be a slightly greater incidence of decreased blood pressure (systolic > diastolic, sitting > standing) in the varenicline 1-mg BID group.

Table 7-46: Categorical Vital Sign Changes, Baseline → On-Treatment[a], Phase-2/3 Studies

Vital Sign Measurement	Fixed-Dose, Placebo-Controlled Phase-2/3			
	Varenicline <1-mg BID	Varenicline 1-mg BID	Zyban®	Placebo
Sitting	N=495	N=1043	N=764	N=904
Systolic (mm Hg)				
Increase (BP >180 & change ≥20)	0 (0)	0 (0)	0 (0)	0 (0)
Decrease (BP <90 & change ≤-20)	4 (0.8)	12 (1.2)	2 (0.3)	5 (0.6)
Diastolic (mm Hg)				
Increase (BP >105 & change ≥15)	2 (0.4)	4 (0.4)	3 (0.4)	2 (0.2)
Decrease (BP <50 & change ≤-15)	1 (0.2)	5 (0.5)	1 (0.1)	2 (0.2)
Pulse Rate (bpm)				
Increase (PR >120 & change ≥15)	0 (0)	1 (0.1)	0 (0)	1 (0.1)
Decrease (PR <50 & change ≤-15)	3 (0.6)	6 (0.6)	4 (0.5)	4 (0.4)
Standing	N=495	N=1042	N=763	N=904
Systolic (mm Hg)				
Increase (BP >180 & change ≥20)	0 (0)	2 (0.2)	0 (0)	1 (0.1)
Decrease (BP <90 & change ≤-20)	6 (1.2)	16 (1.5)	8 (1.0)	5 (0.6)
Diastolic (mm HG)				
Increase (BP >105 &change ≥15)	3 (0.6)	8 (0.8)	4 (0.5)	8 (0.9)
Decrease (BP <50 &change ≤-15)	1 (0.2)	3 (0.3)	1 (0.1)	2 (0.2)
Pulse Rate (bpm)				
Increase (PR >120 & change ≥15)	3 (0.6)	9 (0.9)	1 (0.1)	5 (0.6)
Decrease (PR <50 & change ≤-15)	1 (0.2)	3 (0.3)	3 (0.4)	0 (0)

[a]On-treatment' = up to 7-days post RX discontinuation Source: Tables A20.2a and 56 (2.7.4)

Categorical changes in post-baseline vital signs data for subjects in 'All Completed Phase 2/3 Studies' were similar to those described above for the Phase 2/3 Fixed-dose, Placebo-controlled Studies. Median changes from baseline in blood pressure and pulse rate either remained unchanged or decreased slightly from baseline for all treatment groups. There were very few clinically significant categorical changes in blood pressure or pulse rate.

Table 7-47 shows vital sign categorical changes (from normal to abnormal value, at any time on treatment) from Study A3051037, a 52-week placebo-controlled safety study. The incidence of elevated diastolic blood pressure measurements is higher in this study than in the 'Phase-2/3 Fixed-dose, Placebo-controlled' database, but similarly so for both varenicline and placebo treated patients. Given the longer on-treatment assessment period, each patient's chance of having at least one elevated measure was likely higher.

Table 7-47: Categorical Vital Sign Changes, Baseline → On-Treatment[a], A3051037

Vital Sign Measurement	Varenicline 1-mg BID	Placebo
Sitting	N=249	N=125
Systolic (mm Hg)		
Increase (BP >180 & change ≥20)	0 (0)	0 (0)
Decrease (BP <90 & change ≤-20)	4 (1.6)	2 (1.6)
Diastolic (mm Hg)		
Increase (BP >105 & change ≥15)	2 (0.8)	1 (0.8)
Decrease (BP <50 & change ≤-15)	2 (0.8)	3 (1.4)
Pulse Rate (bpm)		
Increase (PR >120 & change ≥15)	0 (0)	0 (0)
Decrease (PR <50 & change ≤-15)	3 (1.2)	2 (1.6)
Standing	N=495	N=1042
Systolic (mm Hg)		
Increase (BP >180 & change ≥20)	2 (0.8)	0 (0)
Decrease (BP <90 & change ≤-20)	1 (0.4)	3 (1.4)
Diastolic (mm HG)		
Increase (BP >105 &change ≥15)	9 (3.6)	4 (3.2)
Decrease (BP <50 &change ≤-15)	1 (0.4)	1 (0.8)
Pulse Rate (bpm)		
Increase (PR >120 & change ≥15)	1 (0.4)	1 (0.8)
Decrease (PR <50 & change ≤-15)	2 (0.8)	0 (0)

[a]On-treatment' = up to 7-days post RX discontinuation
Source: A3051037 Table 13.8.3

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Overall, nine patients discontinued because of blood pressure increases; six varenicline, one Zyban® and two placebo. All documented increases were rather modest, however, on the order of 10 to 30 mmHg systolic. In some cases the abnormal value was not even (recorded as) verified by repeat measurement. None of these blood pressure increases necessitated hospitalization.

In 52-week safety study A3051037, although adverse event term 'hypertension' was reported in 6% of varenicline (1-mg BID) patients, and in 4% of placebo patients, there were no vital sign related SAEs or discontinuations.

Review of the adverse event and patient disposition data listings did not reveal any additional vital sign related dropouts beyond those reported by the applicant.

7.1.9 Electrocardiograms (ECGs)

The Agency agreed to accept this application for review without a thorough QT study (TQT), because the development program was nearing completion prior to finalization of the TQT guidance document.

7.1.9.1 Overview of ECG testing in the varenicline development program

Phase-1 Studies

ECGs were obtained at Screening, pre-dose, and at protocol-specified intervals after drug administration in 19 of 24 Phase-1 studies. The procedures used for assessment of Baseline ECG values varied somewhat by study, though. In 7 of these studies, QT intervals from electronic ECG tracings were measured by a blinded centralized reader. Two of these studies, A3051012 and A3051014, employed standardized methods for the assessment of QTc. Both studies performed baseline and post-baseline measurements in triplicate, measured QTc at the approximate Tmax, standardized the timing of ECGs with regard to meals, enrolled males and females, included a within subject placebo control condition and included pharmacokinetic sampling to provide matched ECG/PK data.

Phase-2/3 Studies

Electrocardiograms were performed in the Phase-2/3 trials according to the following schedule;

Table 7-48: Phase 2/3 ECG Schedule

Phase	Studies	Assessment Week	Cohort/Database*
Phase-3:	A3051028	Weeks 2, 12	Fixed-dose, Placebo-controlled Studies*
	A3051036	Weeks 2, 12	Fixed-dose, Placebo-controlled Studies*
	A3051035	Weeks 2, 12, 24	All Completed Phase-2/3 Studies
	A3051037	Weeks 2, 24, 52	All Completed Phase-2/3 Studies
Phase-2:	A3051007	Weeks 1, 4, 12	Fixed-dose, Placebo-controlled Studies*
	A3051016	Weeks 1, 4, 12	All Completed Phase-2/3 Studies
	A3051002	Weeks 1, 2, 4, 6	Fixed-dose, Placebo-controlled Studies*
	A3051043	Weeks 1, 4, 7	All Completed Phase-2/3 Studies

'Fixed-dose, Placebo-controlled Studies' are included in the 'All Completed Phase-2/3 Studies' database
Source: Clinical reviewer

Baseline values were defined as the last observation before initiation of study medication. All ECG tracings from Phase 2/3 studies were sent to a central ECG reader. Two Phase 2 studies, A3051002 and A3051007, had baseline values calculated as the mean of triplicate readings conducted with a 1 to 5 minute interval between tracings.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Phase-1 Studies

Among the 19 Phase-1 studies that collected (on treatment) ECG data, Studies A3051012 and A3051014 employed the most rigorous methods for the assessment of QT/QTc, following single dose and multiple dose administration of varenicline, respectively. These two studies were among the 7 Phase-1 studies in which QT intervals from electronic ECG tracings were measured by a blinded centralized reader. In both studies baseline and post-baseline measurements were performed in triplicate, at the approximate Tmax with standardized ECG times in relation to meals. Both studies enrolled both males and females, included a within subject placebo control group and included pharmacokinetic sampling to provide for ECG/PK time matched pairs. Study A3051014 is noteworthy for the number of subjects (n=120, 40 per treatment arm), and also for including a 1.5 mg BID dose. (As described below, in these two studies, the placebo-adjusted mean changes from baseline in QTcF

were generally 0 (zero) msec or less, with isolated increases of <4 msec. For all measurements the nominal 90% CI excluded 10 msec, the threshold of concern proposed in the ICH E14 guidance.

Baseline measurements were those measurements obtained prior to dosing. In those cases where multiple measurements were obtained during the baseline period, those obtained during the final pre-treatment visit were considered to be baseline. Where multiple measures were obtained on the final pre-treatment visit day, and all values were within normal range, the mean of the values was used.

Phase-2/3 Studies
The ECG safety review focused on data from the eight Phase 2/3 studies (as well as from the Phase-1 exposure-response studies described above).

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Phase-1 Studies
Phase-1 ECG data were not pooled for analyses of measures of central tendency. Two Phase-1 protocols, however, A3051014 and A3051012, called for rigorous collection of multiple ECGs following single and multiple-dose varenicline administration. In both studies placebo adjusted mean changes from baseline QTc were approximately 0 msec, with isolated values of less than 2 msec in A3051014 and less than 4 msec in A3051012.

Phase-2/3 Studies
Review of the ECG data for all Phase 2/3 studies revealed no apparent clinically relevant group mean changes in any of the standard ECG measurements/intervals. Table 7-49 summarizes mean baseline and mean changes from baseline for electrocardiogram data from patients in the Phase 2/3 Fixed-dose, Placebo-controlled Studies.

Table 7-49: ECG Data: Mean Baseline ± SD and Mean Change from Baseline ± SD, FDPC Cohort

Parameter	Varenicline < 1-mg BID N=493		Varenicline 1-mg BID N=1009		Zyban® N=722		Placebo N=849	
HR (bpm)	70.0±10.3	-3.0±9.2	71.5±10.9	-2.5±9.6	70.0±10.4	-0.8±6.2	71.4±10.7	-3.0±9.8
QT (msec)	368±25.3	7.4±20.5	371±26.5	5.3±21.6	373 ±25.3	1.1±20.9	370±25.8	6.8±21.7
QTcB	395±21.9	-0.8±19.1	403±21.7	-1.6±19.5	400 ±22.6	-1.0±20.0	401±22.0	-1.4±18.7
QTcF	386±19.0	2.1±15.5	392±18.9	0.8±16.0	391 ±19.1	-0.3±16.0	390±19.2	1.5±15.3
PR (msec)	154±18.5	-1.2±13.1	155±20.8	0.4±13.3	155 ±19.2	-0.2±12.1	155±20.4	-0.2±12.3
QRS (msec)	88.6±7.6	0.7±7.1	85.3±8.5	0.8±7.4	85.2±0.9	0.4±7.6	84.9±8.5	0.4±7.8

Source: Tables A12.1a and 58 (Section 2.7.4)

Mean changes from baseline for these ECG parameters were small and comparable between treatment groups. Specifically, the mean change from baseline in QTcF in the varenicline 1-mg BID group was 0.8 msec, compared with 1.5 msec in the placebo group. Findings in the 'All Completed Phase-2/3 Studies' population were similar.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Phase-1 Studies

A categorical summary of post-baseline ECG data for subjects in Phase-1 studies is presented in Table 7-50. QTcF increases of 30-60 msec, and also of ≥60 msec are more common in the >2-mg/day group It should be noted, however, that this treatment group included patients in A3051012 and A3051014, in which patients received up to 4-mg/day varenicline.

Table 7-50: ECG Data Categorical Changes, Phase-1 Studies

Single or Daily Dose → ECG Parameter	Varenicline <2-mg N=196	Varenicline 2-mg N=285	Varenicline > 2-mg N=112	VRN+Oth N=146	Other N=129	Placebo N=231
QT interval (msec)						
≥500	2 (1.0)	0 (0)	0 (0)	1 (0.7)a	0 (0)	0 (0)
QTcB						
≥500	2 (1.0)	0 (0)	0 (0))	1 (0.7)	0 (0)	0 (0)
30 to <60 msec increase	38 (19.4)	44 (15.4)	35 (31.3)	8 (5.5)	12 (9.3)	73 (31.6)
≥60 msec increase	4 (2.0)	4 (1.4)	8 (7.1)	1 (0.7)a	0 (0)	2 (0.9)
QTcF						
≥500	1 (0.5)	0 (0)	0 (0)	1 (0.7)[a]	0 (0)	0 (0)
30 to <60 msec increase	17 (8.7)	31 (10.9)	19 (17.0)	6 (4.1)	7 (5.4)	31 (13.4)
≥60 msec increaseb	1 (0.5)	1 (0.4)	0 (0)	1 (0.7)[a]	0 (0)	0 (0)
PR interval (msec)						
≥300	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥25% increase	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥50% increase	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)
QRS interval (msec)						
≥200	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥25% increase	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥50% increase	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)

Source: Tables A21.2c and 62 (2.7.4)

There were few categorical outliers in the Phase-1 studies, except for 30 to < 60 msec QTc increases (from baseline). Many of these are from Study A3051014 (described further below), in which ECGs were collected more frequently than in other Phase-1 studies and which a relatively high rate of QTc abnormalities was observed in all treatment groups. Most of the subjects in the > 2 mg dose group of the pooled Phase-1 studies were from Study A3051014, accounting for the higher rate of QTc abnormalities in this group compared with the other treatment groups.

In the Phase-1 program, one subject had a QTcF value during varenicline treatment of ≥500 msec; this subject and one other subject had a QTcB value ≥500 msec. Both of these subjects were individuals with end stage renal disease who received 0.5 mg QD in Study A3051008. Subject 50192502 had a Screening QTcF value on Day (–11) = 508 msec, a Baseline value = 464 msec, and a Day-1 value of 515 msec (3 hours post-dose). The corresponding QTcB was 558 msec (Baseline = 507 msec; Screening = 537 msec). Throughout the remainder of the study period this subject had no QTcB/QTcF values ≥ 500 msec. Subject 50192501 had a QTcB of 519 msec 3 hours after his Day-12 dose (Baseline value = 469 msec) with corresponding QTcF = 499 msec.

In addition, Subject 103310011046, who was in a study of varenicline plus NRT dosing, had a transient increase in QTc (QTcB = 513 msec, QTcF = 513 msec, HR 60 BPM; Baseline values = 383 msec and 378 msec respectively for QTcB and QTcF) 10 hours after application of the NRT patch on Day-1 of the study period. Although attributed to the 'Varenicline + Other' dose group, this subject had not yet started varenicline at the time of these elevated values (varenicline began on Day-3). Throughout the remainder of the study period this subject had no QTc values of potential concern.

Phase-2/3 Studies

Table 7-51 summarizes the numbers of subjects in both the 'Phase 2/3 FDPC' and 'All Completed Studies' databases who had post-baseline values or increases from baseline exceeding categorical thresholds for ECG parameters.

Table 7-51: ECG Data Categorical Changes, in Phase-2/3, (Number (%) of Evaluable[a] Patients)

	Fixed-Dose, Placebo-Controlled Studies				All Completed Phase-2/3	
ECG Parameter	**Varenicline <1-mg BID (N=505)**	**Varenicline 1-mg BID (N=1070)**	**Zyban® (N=795)**	**Placebo (N=928)**	**Varenicline All Doses (N=3940)**	**Placebo All Studies (N=1209)**
Evaluable →	**n=493[a]**	**n=1009[a]**	**n=722[a]**	**n=849[a]**	**n=3713[a]**	**n=1119[a]**
Heart rate (bpm)						
>120 and ≥25% increase[b]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
>120 and ≥25% increase[b]	9 (1.8)	7 (0.7)	2 (0.3)	10 (1.2)	34 (0.9)	13 (1.2)
QT interval (msec)						
≥500	0 (0)	1 (0.1)	0 (0)	1 (0.1)	1 (0)	1 (0.1)
QTcB						
450 to <480 (msec)	9 (1.8)	16 (1.6)	13 (1.8)	22 (2.6)	80 (2.2)	30 (2.7)
480 to <500 (msec)	0 (0)	3 (0.3)	0 (0)	2 (0.2)	5 (0.2)	3 (0.3)
≥500 (msec)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)	0 (0.0)
30 to <60 msec increase	65 (13.2)	84 (8.3)	77 (10.7)	66 (7.8)	358 (9.6)	91 (8.1)
≥60 msec increase	1 (0.2)	2 (0.2)	1 (0.1)	0 (0)	15 (0.4)	1 (0.1)
QTcF						
450 to <480	1 (0.2)	7 (0.7)	2 (0.3)	10 (1.2)	18 (0.5)	12 (1.1)
480 to <500	0 (0)	0 (0)	0 (0)	1 (0.1)	2 (0.1)	1 (0.1)
≥500	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
30 to <60 msec increase	42 (8.5)	53 (5.3)	39 (5.4)	39 (4.6)	267 (7.1)	60 (5.4)
≥60 msec increase	0 (0)	0 (0)	0 (0)	1 (0.1)	5 (0.1)	2 (0.2)
PR interval (msec)						
≥200	11 (2.2)	36 (3.6)	20 (2.8)	26 (3.1)	134 (3.6)	34 (3.0)
≥240	0 (0)	4 (0.4)	0 (0)	1 (0.1)	12 (0.3)	2 (0.2)
≥25% increase[b]	3 (0.6)	12 (1.2)	9 (1.2)	9 (1.1)	48 (1.3)	16 (1.4)
QRS interval (msec)						
≥25% increase[b]	16 (3.2)	15 (1.5)	13 (1.8)	11 (1.3)	95 (2.6)	13 (1.2)

[a] n= Number of patients with post- baseline ECG, obtained on study treatment or within 7-days of last dose
[b] Change from baseline (where baseline is the last ECG taken on or before the first dose of study medication)
Source: Tables A21.2a and 59 (2.7.4)

Fixed-Dose, Placebo-Controlled Phase-2/3 Studies

Two subjects had QT intervals of ≥500 msec (1 in the varenicline 1-mg BID group, and 1 in the placebo group), but neither had QTcF or QTcB ≥500 msec. No varenicline-treated subject had an increase of QTcF ≥60 msec, but three varenicline-treated subjects had a QTcB increase of ≥60 msec. A number of subjects had smaller increases of QTc (between 30 and <60 msec), but these were seen at similar frequencies in the varenicline 1-mg BID, Zyban® and placebo groups. The incidence of increases between 30 and 60 msec in the varenicline <1 mg BID group (only Phase-2 studies) was higher than for the varenicline 1-mg BID group. No subjects had increases in heart rate (>120 bpm and ≥25% increase from baseline), but a number of subjects in all treatment groups, including placebo, had decreases in heart rate (<50 bpm and ≥25% decrease from baseline).

All Completed Phase-2/3 Studies

The categorical summary of post-baseline ECG data presented in Table 7-51 above shows that in the larger group of varenicline subjects (some of whom received 1-mg BID for up to one year) there were no patients who had a QTcF ≥500 msec. There were, however, five patients (as opposed to zero in the FDPC group) that had increases in QTcF of 60 msec or greater (0.1%). All had low baseline QTcF values. Two additional varenicline-treated patients each had a QTcF ≥480 msec. These two patients also had QTcB ≥500 msec, but both had ECG abnormalities in their Screening and Baseline ECGs. (One placebo subject had a QTcF ≥480 msec and 2 placebo subjects had QTcF increases from baseline ≥60 msec.)

Pertinent details about these seven varenicline-treated patients are summarized in Table 7-52 below.

Overall, review of the Phase-2/3 ECG data showed four cases in which patients with normal ECGs at baseline appeared to develop abnormalities on treatment. In all four cases repeat ECGs were normal.

QTc increases of 30 to <60 msec are likely within the normal physiologic range (of variability) for some subjects. The cases are roughly equally distributed across treatment groups, except, again, for the higher predominance in the <1-mg BID group. In the context of the other cardiovascular safety findings, these ECG categorical shifts do not raise safety concerns.

Table 7-52: Varenicline Patients with Post-Baseline QTcF ≥480 msec or Increase ≥ 60 msec All Completed Phase-2/3 Studies (All Listed Patients Treated with 1-mg BID)

Patient ID	QTc abnormalities	Baseline QTc (msec)	On-Treatment QTc (msec)	Relevant AEs Med. History, Concomitant Meds ECG Findings
103510011168	QTcF values 480 to <500	446	485 (Day 85)	AEs: None Med Hx: Hypertension Con Meds: Diltiazem, desloratidine
	QTcB value (single) ≥500	459	501 (Day 85)	ECG: right bundle branch block; left posterior hemiblock on all study ECGs, including screening and baseline.
103510221001	QTcF values 480 to <500	429	486 (Day 17)	AEs: Hypertension Med Hx: None Con Meds: None
	QTcB value (single) ≥500		505 (Day 17)	ECG: left bundle branch block on all study ECGs, including screening and baseline
103510141134	QTcF increase ≥60 msec	387	451 (Day 168)	AEs: None Med Hx: None Con Meds: None
103510271002	QTcF increase ≥60 msec	342	410 (Day 85)	AEs: ALT elevated Med Hx: None ECG: sinus bradycardia at Baseline, Day 15 & Day 169, but not at Day 85
103510341027	QTcF increase > 60 msec	356	425 (Day 85)	AEs: None Med Hx: Shortness of breath Con Meds: None
103510341068	QTcF increase > 60 msec	361	423 (Day 43)	AEs: Eye pain/blurry vision, CP, SOB, HA Med Hx: CABG, MI, CAD, HTN, hypercholesterolemia, chest pain Con Meds: lisinopril, simvastatin, ASA, metformin, diltiazem for hypertension ECG: complete RBBB on all ECGs, including Screening and Baseline
103710061047	QTcF increase ≥60 msec	402	464 (Day 174)	AEs: Hypertension, intermittent lightheadedness (both continued post-treatment, considered related) Med Hx: Hyperlipidemia, sinus bradycard. Con Meds: hydrochlorothiazide, lisinopril

Source: Table 61 (2.7.4)

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Phase-1 Studies

Only one Phase-1 subject was discontinued due to ECG findings. Subject 10011008 (in A3051034) was discontinued from the because of second-degree atrioventricular block (Wenckebach) that started 3.1 hours after the first combined dose (Zyban® 150-mg + varenicline 1-mg). No other AEs were reported for this subject. The pre-dose ECG showed sinus bradycardia, first degree AV block, and sinus arrhythmia. No AV block was evident on ECGs performed the day after and 9 days after the subject's withdrawal from the study. She underwent 24-hour Holter monitoring ten days after withdrawal, showing ectopic atrial rhythm and blocked atrial beats without associated symptoms.

All Completed Phase-2/3 Studies

Table 7-53 below lists all Phase-2/3 discontinuations attributed to HLGT 'cardiac investigations' and to HLGT 'arrhythmias (under SOC 'Cardiac disorders'). In most varenicline cases the ECG finding of concern had occurred (in that patient) before. None of the ECG findings resulted in hospitalization or electrophysiology workup, although cardiac medications were changed for some patients.

Table 7-53: Discontinuations ECG Findings/Arrhythmia and Hypertension, All Phase-2/3 Studies

	Varenicline N=3940		Zyban® N=795		Placebo N=1209	
SOC INVESTIGATIONS	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
HLGT Cardiac/vascular excluding enzymes	10	(0.3)	2	(0.3)	3	(0.2)
Blood pressure increased	6	(0.2)	1	(0.1)	2	(0.2)
ECG PR prolongation	1	(0.1)	0	0	0	0
ECG T wave amplitude decreased	1	(0.1)	0	0	0	0
ECG abnormal	1	(0.1)	0	0	1	(0.1)
Heart rate increased	1	(0.1)	1	(0.1)	0	0
SOC CARDIAC DISORDERS	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
HLGT Arrhythmias	10	(0.3)	0	0	0	0
Atrial fibrillation	1	(0.1)	0	0	0	0
Cardiac flutter	1	(0.1)	0	0	0	0
Extrasystoles	2	(0.1)	0	0	0	0
Sinus bradycardia	1	(0.1)	0	0	0	0
Supraventricular tachycardia	1	(0.1)	0	0	0	0
Tachycardia	2	(0.1)	0	0	0	0
Ventricular extrasystoles	2	(0.1)	0	0	0	0

Source: Clinical reviewer from Tables A15.1b (Section 2.7.4) and AE datasets

7.1.10 Immunogenicity

This section is not applicable to this review.

7.1.11 Human Carcinogenicity

Table 7-54 lists all malignant neoplasms identified during varenicline development. Neoplasm incidence rates were calculated for varenicline, Zyban® and placebo exposed patients. As discussed in Section 7.1.2.2 above, these findings may be misleading, even after correction for patient-exposure-time, but this finding may be misleading. Most patients treated for durations over 24-weeks received varenicline. Also, of approximately 2000-patients on-treatment for more than 12, but less than 24-weeks, about 75% received varenicline.

Groupwise exposure time corrections are helpful, but one (long-time smoking) patient treated and followed for one-year has a higher cumulative probability of malignancy diagnosis than four patients treated and followed for 12-weeks each. (It should be noted, however, that all Phase-3 protocols called for off-treatment follow-up to one-year after treatment initiation.) Most malignancies were diagnosed well after treatment completion, while several were diagnosed within days of beginning treatment, possibly as a result of increased scrutiny and diagnostic testing inherent to late-stage clinical trial participation. Malignant and other neoplastic serious adverse events are discussed in Section 7.1.2.2 above.

Table 7-54: Malignant Neoplasms Diagnosed During Varenicline Development

PID/Treatment Age/Race/Gender	Daily Dose	MedDRA Preferred Term	Related PMH	Onset Day	Last Dose	Action Taken DC RX-Day
VARENICLINE						
103510121147 42/W/M	2 mg	(Glandular) adenocarcinoma	No	57	57	Perm D/C Day-57
103610021078 58/W/F	2 mg	Lung neoplasm malignant Brain neoplasm malignant	No	15	15	Perm D/C Day-15
10075010476 65/W/M	2 mg	(Carcinoid) colon cancer	No	94	85	Post-RX Day-9
103510171011 59/W/F	2 mg	Colon cancer	No	165	NA	No action taken
103510271079 56/W/M	2 mg	Nasopharyngeal carcinoma	No	30	NA	No action taken
10075011259 49W/M	1 mg	Cholesteoma	No	27	57	Yes
100850192501 47/B/M	0.5 mg	Lung cancer	??	18	12	Post-RX Day-6
10025010380 39/W/F	0.3 mg	Crohn's disease Adenocarcinoma	Yes No	163	44	Post-RX Day-119
103510241063 29/W/M		Rectal sarcoma Back pain worsening	No Yes	9	15	Perm-D/C Day-9
103510241019 71/W/M	2 mg	Lung neoplasm malignant	??	188	169	Death Post-RX, D19
BUPROPION						
103610141094 43/W/F	300 mg	Breast cancer female	No	48	35	Post-RX Day-13
PLACEBO						
102810031042 50/W/M	PBO	Lung neoplasm malignant	No	24	30	Perm D/C Day-24
ONGOING STUDIES						
NRT						
104410281019 74 W/M		Prostate cancer	??	125	70	Post-RX
BLINDED						
104610181008 57/A/M		Gastric cancer, Stage-1	No	NA	85	Post-RX

Source: Clinical reviewer

7.1.12 Special Safety Studies

7.1.12.1 Abuse liability Study A3051039

(Also see Section 7.1.13 below.)

In a human laboratory abuse liability study conducted with non-smoking subjects experienced with stimulants, a single oral dose of 1-mg varenicline produced increases in subjective responses for "good drug effects" and "high" that were statistically significantly greater than placebo, but less than those (responses produced on the same scales) by a single oral dose of amphetamine at either 15-mg or 30-mg. Only varenicline (1-mg) produced statistically significantly greater increases in subject-rated "nausea" compared to placebo; neither amphetamine dose did.

In individuals who have both smoked cigarettes and used stimulants, 1-mg varenicline did not produce statistically significant increases in the positive or negative subjective measures. In contrast, amphetamine (15 and 30 mg) produced statistically significant increases in positive and negative subjective responses in this subject population.

A 3-mg dose of varenicline uniformly produced unpleasant subjective responses in subjects with a history of stimulant abuse, regardless of cigarette smoking history.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No clinical studies were conducted specifically to evaluate withdrawal and/or rebound following discontinuation of treatment with varenicline. As noted in Section 6.1.4.3 above, although frank withdrawal phenomena were not observed, even with abrupt discontinuation of 1-mg BID, nicotine withdrawal appeared to re-occur in some patients.

Several adverse events were more common during the initial seven-day post-treatment period, in varenicline-treated (1-mg BID) than in placebo-treated patients. That is, abrupt discontinuation of varenicline 1-mg BID appears to be associated with increased incidence of several adverse events, compared to abrupt cessation of placebo.

Specifically, overall SOC Neurologic and SOC Psychiatric AEs were reported more frequently after varenicline cessation. The greatest differences between treatment groups were for AE Preferred Terms and AE High Level Group Terms likely representative of nicotine withdrawal, such as PTs 'irritability' (3.6% vs. 0.2%) and 'nicotine dependence' (3.1% vs. 0%), and HLGT 'Sleep disorders and disturbances' (2.85 and 0.2%). 'Neurologic Disorder' AEs such as 'headache' and 'dizziness' were also reported more commonly after varenicline discontinuation (≈1% vs. 0% in placebo). (Incidence rates from Study A3051035 in which patients were randomized to receive either varenicline or placebo after initial open-label treatment with varenicline.)

Appendix Table 11-9 and Table 11-10 summarize these data for Study A3051035 and for the 'All Completed Phase-2/3 Studies' database, respectively.

7.1.14 Human Reproduction and Pregnancy Data

The number of on-treatment pregnancies was surprisingly high, given the contraception requirements. These cases all resulted in treatment discontinuation (for patients still on-treatment), thus AE narrative summaries were available. A total of 28 (all unintended) pregnancies were reported during varenicline development, all in Phase-2/3. Twenty six of these were reported in completed trials, and two in ongoing trials. In the completed trials 17 pregnancies were in varenicline patients, six in Zyban® patients and three in placebo patients. Of the two pregnancies in ongoing studies, one was reported in a patient receiving NRT, while the other was reported in a blinded therapy patient. Both elected to terminate their pregnancies. Most pregnancies were documented well after treatment completion. In some cases conception was also known to have occurred after treatment completion.

Unfortunately, many of the narratives omitted relevant information, such as estimated gestational age at time of diagnosis. It appears clear, however, that varenicline has not been demonstrated to be safe for use in pregnancy. (The preclinical data also show decreased fertility in several species.) Table 7-55 and Table 7-56 below list all pregnancies identified during clinical development, along with the available details, in varenicline-exposed, and in Zyban® or placebo-exposed patients, respectively.

Table 7-55: Pregnancies in Varenicline-Exposed Patients

Patient ID	Age/ Race	Treatment	Pregnancy Outcome	Patient Exposure Days/ Estimated Fetal Exposure
100750280456	34/W	0.5 mg BID	Carried to term; healthy baby	88/<39
1013100222022	35/W	(CR) 3 mg QD	Carried to term; healthy baby	14/14
101650350136	30/W	Flexible; 1.5-mg/day	Miscarriage	84/<12
102810031002	20/W	1 mg BID	Elective termination	83/unknown
102810071098	25/W	1 mg BID	Carried to term; healthy baby	85/0 (Post-RX conception)
103510121085	28/W	OL 1 mg BID → PBO (DB)	Elective termination	85/0 (conception during or post DB placebo treatment)
103510151003	35/W	OL 1 mg BID → PBO (DB)	Unknown	86/0 (conception post DB placebo treatment)
103510161005	35/W	1 mg BID	Carried to term; healthy baby	46/19
103510271083	30/W	1 mg BID	Carried to term; healthy baby	14e/<22
103510311065	33/W	OL 1 mg BID → PBO (DB)	Elective termination	88/0 (conception during DB placebo treatment)
103510341066	43/W	1 mg BID	Miscarriage (Mircette® use)	85/10
103610011018	24c/W	1 mg BID	Carried to term; healthy baby	86/0 (Post-RX conception)
103610071040	19/W	1 mg BID	Carried to term; healthy baby	83/0 (Post-RX conception)
103610131041	27/W	1 mg BID	Elective termination	85/<85
103610141035	24/W	1 mg BID	Lost to follow-up	56/29
103710011024	23/W	1 mg BID	Elective termination	366/~42
103710071016	31/W	1 mg BID	Elective termination	297/14

Source: Modified from Table A18.2, Section 2.7.4

Table 7-56: Pregnancies in Zyban®, Placebo, NRT and Blinded Therapy Exposed Patients

Patient ID	Age/ Race	Treatment	Pregnancy Outcome	Patient Exposure Days/ Estimated Fetal Exposure
Zyban®				
100250110444	45/W	150 mg BID	Unwilling to provide informat.	53/unknown
103610041031	32/W	150 mg BID	Ectopic, surgical removal	12/<12
103610081020	38/W	150 mg BID	Elective termination	19/0 (Post-RX conception)
103610081048	22/W	150 mg BID	Elective termination	6/6
103610121085	26/W	150 mg BID	Carried to term; healthy baby	84/20
103610131040	27/W	150 mg BID	Miscarriage	80/0 (Post-RX conception)
Placebo				
102810031063	32/B	Placebo	Elective termination	NA
102810131005	21/W	Placebo	Carried to term; healthy baby	NA
103610121077	24/W	Placebo	Carried to term; healthy baby	NA
Ongoing Trials				
104610021063	30/A	Blinded RX	Elective termination	74/50
104410211028	27/W	NRT	Elective termination	NA/16

Source: Modified from Table A18.2, Section 2.7.4

7.1.15 Assessment of Effect on Growth

Potential growth effects were not evaluated. The applicant was advised by the Division to seek a pediatric written waiver request and to submit a request for deferral of studies in adolescents, subsequent to approval.

7.1.16 Overdose Experience

Two cases of intentional varenicline overdose were reported during Phase-2/3 testing. No adverse events or laboratory or vital sign derangements were reported, except for vomiting in one of the two patients.

My search of the adverse event data listings (verbatim terms and all MedDRA levels, for both development programs) for 'OVERDOSE,' 'POISONING,' 'INTENTIONAL,' 'EXPOSURE,' 'OVERUSE,' and 'MISUSE' yielded no additional events. (Two ethanol poisoning cases were also reported).

Aside from these two cases, intentional dose escalation appears not to have occurred during the Phase-2/3 studies. The opposite was observed in Study A3051016 (patient-directed flexible dosing). About 40 % of patients that initially titrated themselves up to the full 1-mg BID dose, later decreased their dose but completed the study treatment period. In most cases patients attributed the dose decrease to nausea. Also in A3051016, over 25% of patients completed study treatment without ever titrating themselves up to the 1-mg BID dose.

7.1.17 Postmarketing Experience

Varenicline has not received marketing approval anywhere in the world as of March 31, 2006. Applications were submitted to the European Medicines Agency and to FDA in November, 2005.

7.2 Adequacy of Patient Exposure and Safety Assessments

Overall varenicline exposure was sufficient to allow for adequate safety review, given appropriate monitoring, data management and reporting on the part of the applicant.

A total of 4690 subjects and patients (of 6739 enrolled) received varenicline in 32 completed studies (24 Phase-1 and 8 Phase-2/3) conducted between late 1999 and July 2005. Three Phase-2/3 studies were ongoing at the time of database lock (7/15/05). These data were not included by the applicant in the Summary of Clinical Safety, nor were data from abuse liability study A3051039, which enrolled 45 subjects (SAE reports were included, however).

7.2.1 Description of Primary Clinical Data Sources Used to Evaluate Safety

Pfizer defined several cohorts for the purposes of analyzing the varenicline safety data:

- The pooled **Phase-1 Studies** cohort consists of 23 studies, which treated a total of 750 subjects. Table 7-57 below provides an overview of the Phase-1 program. Appendix Table 11-5 and Table 11-6 summarize pertinent details about the Phase-1 studies.
- The '**Phase-2/3, Fixed-dose, Placebo-controlled**' cohort includes data from four randomized, double-blind, placebo-controlled studies (A3051002, A3051007, A3051028, and A3051036), in which 2365 patients received varenicline. Treatment duration was 12-weeks in three of these studies. In the fourth, A3051002, treatment was for six (varenicline) to seven (Zyban®) weeks. Varenicline doses investigated in these studies were 0.3 mg QD, 1 mg QD, 0.5 mg BID and 1 mg BID. For most analyses, however, the applicant pooled all doses below the proposed 1-mg BID

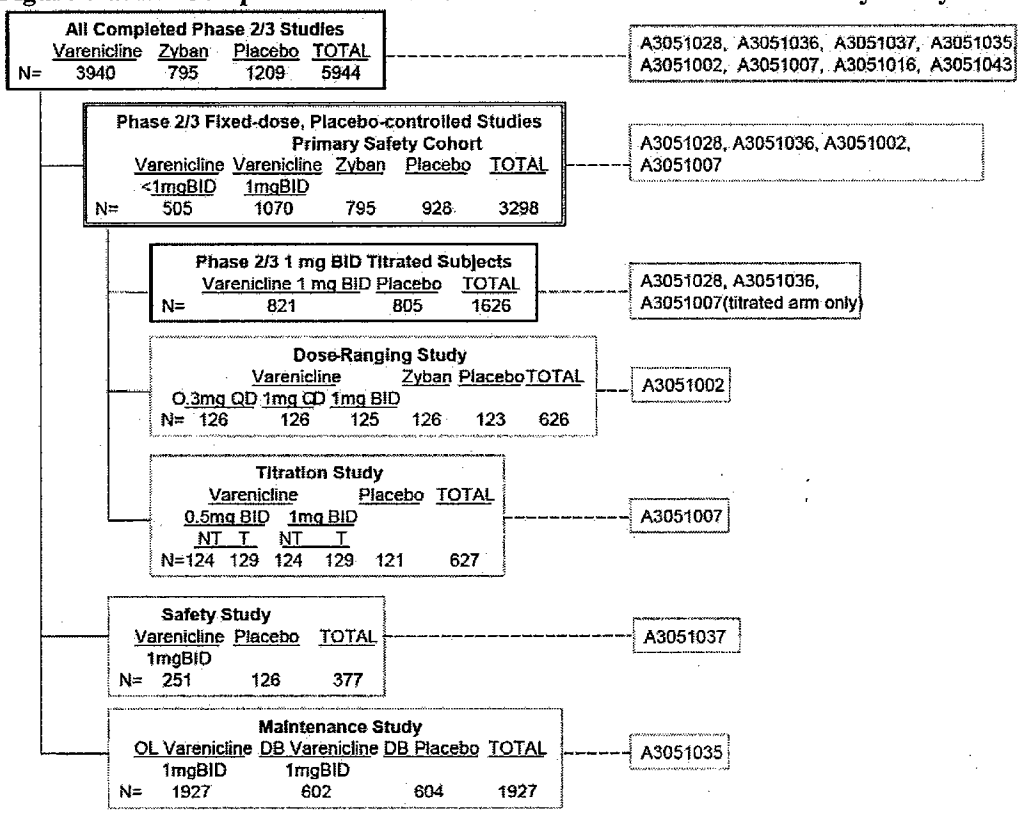
dose. The applicant has designated this cohort as the **'Primary Safety Cohort'** for the purposes of comparisons across treatment groups, and for analyses of special population subgroups.

– The **'All Completed Phase-2/3 Studies'** cohort includes data from all eight completed Phase-2/3 trials, in which a total of 3940 patients received varenicline.

"The treatment group of greatest interest" in Pfizer's safety analyses was "...the 1 mg BID group since this represents the recommended varenicline dose." Other dose groups, all from Phase 2 studies (0.3 mg QD, 0.5 mg QD, 1 mg QD, 0.5 mg BID) were grouped together (as subjects who received <1 mg BID) because "... the number of subjects in some individual dose groups is small."

Figure 7-1 delineates the Pfizer-defined Phase 2/3 cohorts used for the safety analyses.

Figure 7-1: All Completed Phase 2/3 Studies - Cohorts Defined for Safety Analyses



7.2.1.1 Study type and design/patient enumeration

The varenicline clinical program included 8 Phase-2/3 efficacy and safety studies and 24 Phase-1 studies. Table 7-57 on page on page 125 lists the Phase-1 studies, including number of patients treated, by study and by dose (category). Table 11-5 and Table 11-6 in Appendix Section 11 provide details about the objectives, design and populations in the Phase-1 studies.

Table 7-58 and Table 7-59 list the Phase-2 and Phase-3 studies, respectively, summarizing treatment by dose for each study. The eight Phase 2/3 studies included:

- A3051002, a fixed dose, dose-ranging study (0.3 mg QD, 1 mg QD, 1 mg BID varenicline) with a 6- week varenicline treatment period
- A3051007, fixed-dose, dose titration study (0.5 mg or 1 mg BID) with a 12-week treatment period
- A3051016, a flexible dosing study (0.5 to 2 mg per day) with a 12-week treatment period
- A3051028 and A3051036, identical placebo-controlled, Zyban®-comparison studies of 1 mg BID varenicline with a 12-week treatment periods
- A3051035, a maintenance study (1 mg BID) with a 12-week open label phase before randomization and double-blind treatment of subjects, who had stopped smoking, to varenicline or placebo for 12 additional weeks
- A3051037, a placebo-controlled safety study (1 mg BID) with a 52-week dosing duration
- A3051043, a pilot study (7 weeks OL dosing with 0.5 mg BID) in 30 subjects conducted in Japan

Table 7-57: Overview of Phase-1 Safety Database

	Study Design	Varen <2mg	Varen 2mg	Varen >2mg	Varen + Other[a]	Other[a]	Placebo	Any RX Total
Single Dose Studies								
305-001 (First in human, single-dose)	PG	44		24			34	102
A3051001 (Relative BA; food effect; AM vs. PM dose)	XO		11					11
A3051004 (Metabolism and excretion)	SD	6						6
A3051005 (Relief of craving)	XO		39				39	40
A3051006 (BE, food effect)	XO	15						15
A3051010 (Cimetidine drug-drug interaction)	SEQ		12		12	12		12
A3051012 (PK and relative BA [b])	XO		17				16	17
A3051026 (BE, fed)	XO	14						14
A3051027 (Single-dose PK in Japanese)	XO	14	11				7	14
A3051029 (PK in adolescents)	PG	22					5	27
A3051030 (BE, fasted)	XO	12						12
A3051042 (Food effect)	XO	12						12
Multiple Dose Studies								
305-001 (First in human, multiple-dose)	PG	8	14	8			14	44
A3051008 (PK in renally impaired)	PG	30						30
A3051009 (PK in elderly)	PG	8	8				8	24
A3051013 (PK and relative BA [b])	PG		20				20	40
A3051014 (Titration and tolerability)	PG	40	80	80			80	120
A3051015 (QAM/QHS dosing and tolerability)	XO		44					44
A3051031 (Digoxin drug-drug interaction)	XO				18	18		18
A3051032 (Warfarin drug-drug interaction)	XO		24		24	24	24	24
A3051033 (NRT drug-drug interaction)	XO				22	17		24
A3051034 (Zyban® drug-drug interaction)	XO				41	41		46
A3051038 (Metformin drug-drug interaction)	XO		29		29	29		30
A3051041 (Multiple-dose PK in Japanese)	PG	16					8	24
Total Pooled Phase 1		241	309	112	146	141	255	750
A3051039 (Abuse potential)	XO	41		42		42	42	45

[a] Other=Drugs used in interaction studies [b] Only IR and placebo treatment arms Source: Applicant Table 2.7.4 A2.2

Table 7-58: Phase 2 Trials Reviewed for Safety Findings

Study	Design	Treatment Duration	Treatment Groups	N
A3051002 Dose-Ranging	R, PG, DB, PC active comparator	(Varenicline 6-weeks then Placebo 1-week) OR (Zyban® 7-weeks)	Varen 0.3 mg QD Varen 1 mg QD Varen 1 mg BID Zyban® 150 mg BID Placebo Total:	126 126 125 126 123 626
A3051007 Dose Titration (Off-drug follow-up in A3051018)	R, PG, DB, PC	12 weeks RX, then F/U to Wk-52	Varen 0.5 mg BID NT* Varen 0.5 mg BID T* Varen 1 mg BID NT Varen 1 mg BID T Placebo Total:	124 129 124 129 121 627
A3051016 Flexible Dosing (Off-drug F/U in A3051019)	R, PG, DB, PC	12 weeks RX, then F/U to Wk-52	Varen flexible doing 0.5 -2.0 mg/day Placebo Total:	 157 155 312
A3051043 Japan pilot study	OL	7-weeks	Varen 0.5-mg BID Total:	30 30

*Non-titrated = NT, Titrated = T Source: Modified from Table-1, Section 2.7.4

Table 7-59: Phase 3 Trials Reviewed for Safety Findings

Study	Design	RX Duration	Treatment Groups	N
A3051028 Efficacy Zyban® comparison	R, PG, DB, PC active comparator	12 weeks RX then F/U to Wk-52	Varen 1 mg BID Zyban® 150 mg BID Placebo Total:	349 329 344 1022
A3051036 Efficacy Zyban® comparison	R, PG, DB, PC active comparator	12 weeks RX then F/U to Wk-52	Varen 1 mg BID Zyban® 150 mg BID Placebo Total:	343 340 340 1023
A3051035 Maintenance dosing	OL Varen 1 mg BID Then responders DB - Varen 1 mg BID OR - Placebo	12 weeks OL, then 12 weeks DB, then F/U to Wk-52	OL Varen 1 mg BID Followed by - DB Varen 1 mg BID - OR, DB Placebo Total:	1927 602 604 1927
A3051037 OL Safety 'Long-term'	R, PG, DB, PC	52 weeks RX	Varen 1 mg BID Placebo Total:	251 126 377

Source: Modified from Table-1, Section 2.7.4

7.2.1.2 Demographics

Phase-1 Studies

Although most of the Phase-1 studies enrolled smokers (under 55 years of age), the demographic characteristics of the overall Phase-1 population differ from those of the US smoking population. Differences between treatment groups are less apparent, though still present. To some extent these differences are unavoidable, given the nature of the applicant's clinical pharmacology program. Overall, 76% of patients were between 18 and 44 years old, nearly 70% were male, and 20% were Black. In the 'varenicline >2-mg/day' group, however, 54% of the 112 subjects were Black.

Table 7-60: Demographic Characteristics – Phase-1 Studies

Number (%)	All Subjects N=750	Varen <2mg/day* N=241	Varen 2mg/day* N=309	Varen >2mg/day* N=112	Varen + Other N=116	Other Drug Only N=141	Placebo N=255
Gender							
Male	510 (68.0)	179 (74.3)	186 (60.2)	72 (64.3)	100 (68.5)	98 (69.5)	168 (65.9)
Female	240 (32.0)	62 (25.7)	123 (39.8)	40 (35.7)	46 (31.5)	43 (30.5)	87 (34.1)
Age (years)							
<18	27 (3.6)	22 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2.0)
18-44	573 (76.4)	168 (69.7)	245 (79.3)	92 (82.1)	109 (74.7)	104 (73.8)	203 (79.6)
45-64	126 (16.8)	43 (17.8)	56 (18.1)	20 (17.9)	37 (25.3)	37 (26.2)	39 (15.3)
≥65	24 (3.2)	8 (3.3)	8 (2.6)	0 (0)	0 (0)	0 (0)	8 (3.1)
Mean±SD	34.0±12.6	33.5±13.6	34.1±12.1	36.3±8.4	35.3±10.5	35.8±10.6	34.5±12.0
Range	12-75	12-75	18-75	20-55	18-55	18-55	13-74
Race							
White	509 (67.9)	145 (60.2)	202 (65.4)	50 (44.6)	105 (71.9)	97 (68.8)	148 (58.0)
Black	151 (20.1)	33 (23.7)	76 (24.6)	60 (53.6)	30 (20.5)	31 (22.0)	79 (31.0)
Asian	43 (5.7)	57 (13.3)	14 (4.5)	0 (0)	1 (0.7)	1 (0.7)	15 (5.9)
Other	47 (6.3)	7 (2.9)	17 (5.5)	2 (1.8)	10 (6.8)	12 (8.5)	13 (5.1)
Weight (kg)							
Males							
Mean±SD	75.8±10.9	74.0±11.2	76.8±11.2	77.8±9.9	77.9±10.6	78.2±10.8	75.7±11.0
Females							
Mean±SD	70.0±10.5	68.1±10.5	70.8±10.1	75.3±9.7	69.2±9.9	70.1±9.1	72.7±11.1

Source: Section 2.7.4 Table A5c Protocols included: 305-001, A3051001, A3051004, A3051005, A3051006, A3051008, A3051009, A3051010, A3051012-IR, A3051013-IR, A3051014, A3051015, A3051026, A3051027, A3051029, A3051030, A3051031, A3051032, A3051033, A3051034, A3051038, A3051041, A3051042 *Total daily doses

Note: A single subject is counted only once in any given treatment group, but may be counted in multiple treatment groups.

Phase-2/3 Studies

The characteristics of the overall Phase-2/3 patient population were fairly consistent with known epidemiological data describing the smoking (patient) population in the USA, except perhaps for race and age. In the overall Phase-2/3 database nearly 90% of varenicline-treated patients were white, though only 83% of placebo-treated patients were. Likewise, less than 3% of patients studied were 65 years of age or older.

Table 7-61: Demographic Characteristics, Phase-2/3 Patients

	Fixed-Dose, Placebo-Controlled Phase-2/3 Studies [a]				All Phase-2/3 Studies [b]	
Number (%)[c]	**Varenicline < 1 mg BID N= 505**	**Varenicline 1 mg BID N= 1070**	**Zyban® N= 795**	**Placebo N=928**	**Varenicline All doses N= 3940**	**Placebo N=1209**
Gender						
Males	241 (47.7%)	552 (51.6%)	455 (57.2%)	512 (55.2%)	1959 (49.7%)	656 (54.3%)
Females	264 (52.3%)	518 (48.4%)	340 (42.8%)	416 (44.8%)	1981 (50.3%)	553 (45.7%)
Age (years):						
<18	0	0	0	0	0	0
18-44	273 (54.1%)	575 (53.7%)	462 (58.1%)	542 (58.4%)	2035 (51.6%)	678 (56.1%)
45-64	231 (45.7%)	474 (44.3%)	308 (38.7%)	366 (39.4%)	1797 (45.6%)	499 (41.3%)
≥65	1 (0.2%)	21 (2.0%)	25 (3.1%)	20 (2.2%)	108 (2.7%)	32 (2.6%)
Mean±SD	42.9±10.4	43.2±10.9	42.2±11.6	42.5±11.3	43.8±11.0	42.9±11.5
Range	18-65	18-75	18-75	18-75	18-75	18-75
Race[b]						
White	432 (85.5%)	889 (83.1%)	650 (81.8%)	745 (80.3%)	3538 (89.8%)	998 (82.5%)
Black	43 (8.5%)	107 (10.0%)	73 (9.2%)	109 (11.7%)	211 (5.4%)	129 (10.7%)
Other	30 (6.0%)	74 (6.9%)	72 (9.1%)	74 (8.0%)	191 (4.8%)	82 (6.8%)
Weight (kg)						
Males (N)	238	551	454	512	1953	656
Mean±SD	83.5±13.9	86.8±15.3	85.5±14.3	85.4±14.6	85.4±14.7	85.4±14.9
Females (N)	264	517	339	414	1978	550
Mean±SD	70.0±14.2	71.2±15.0	70.9±14.2	71.1±14.3	69.9±13.3	70.8±13.8

[a] Protocols: A3051002, A3051007, A3051028, A3051036
[b] Protocols: 'Fixed-dose, placebo-controlled' +,A3051016, A3051035, A3051037, A3051043
[c] Exposed subjects only
Source: Applicant Tables 7 and 8, Section 2.7.4

Phase-2/3 Patient Baseline Medical Conditions

See Section 7.2.3.1 (Appropriateness of Patient Populations Exposed)

7.2.1.3 Extent of exposure

Overall extent of exposure was adequate, meeting ICH criteria. Table 7-64 below summarizes overall Phase 2/3 exposure (patient-days) by study, and by analysis cohort.

7.2.1.3.1 Extent-of-Exposure in Phase-1 Studies

Phase-1

Seven-hundred and fifty (N=750) subjects (of 795 enrolled) received varenicline immediate release in 24 completed Phase-1. The pooled **Phase-1 Studies** cohort consists of 23 studies, which enrolled a total of 750 subjects. The database for Study A3051039 (abuse potential assessment, N=45) was not locked in time to be included with the pooled Phase-1 data.

Safety data from these 750 varenicline-treated subjects (of 795 enrolled in 23 Phase-1 studies) were pooled for analysis. Of these subjects, 241 received varenicline < 2-mg/day, 309 received 2-mg/day, 112 received > 2-mg/day and 255 received placebo. Also, 146 received varenicline plus another drug, while 141 received another active drug only (in the drug-drug interaction studies). Subjects may have received more than one treatment, however. This pooled cohort also includes data from subjects who received immediate release formulations in two 'controlled-release formulation' studies (A3051012 and A3051013). Phase-1 exposure (by dose category and duration) is summarized in Table 7-62 below.

Subjects who received the controlled release formulation (N= 150) in Studies A3051012, A3051013, A3051023 and A3051024 were included in the analysis of SAEs only.

Table 7-62: Treatment Duration, Phase-1 Studies (Immediate Release Formulation)

Treatment Duration	Varen < 2-mg/d N=241	Varen 2-mg/d N=309	Varen > 2-mg/d N=112	Varen + Other N=146	Other Active N=141	Placebo Only N=255
≤ 1 day	74	81	24	1	12	102
2-7 days	114	117	80	70	55	74
8-14 days	46	105	8	75	74	72
15-28 days	7	6	0	0	0	7
Median Duration	3.0	7.0	7.0	9.5	14.0	7.0
Range	1 - 15	1 - 15	1 - 9	1 - 14	1 - 14	1 - 15

Source: Modified from Table A4c in Section 2.7.4

The Phase 1 studies were planned to be of short duration. Many were designed as crossover studies with a single dose per study period. Most varenicline-treated subjects received study drug for less than 14 days, and many received only 1-day of treatment.

7.2.1.3.2 Extent of Exposure in Phase-2/3

The eight completed Phase 2/3 studies enrolled 5944 patients, 3940 of whom received varenicline. Over 70% of these patients completed their planned treatment course (12-weeks in most protocols). One-hundred and twelve (N=112) patients received varenicline for 52-weeks or more. Most (>80%) Phase 2/3 patients received the 1-mg BID dose. Table 7-63 summarizes exposure by dose for the two main analysis cohorts, and for each of the individual Phase-2/3 studies.

Table 7-63: Overview of Varenicline Phase-2/3 Safety Database

Cohort/Database Study Number	0.3mg QD	1mg QD	0.5mg BID	1mg BID	Flex Dose	All Varen	Zyban*	PBO	Total
Fixed-dose, Placebo-Controlled									
A3051002 (Dose ranging)	126	126		125			126	123	626
A3051007 (Titration)			253	253				121	627
A3051028 (Zyban®-Comparator)				349			329	344	1022
A3051036 (Zyban®-Comparator)				343			340	340	1023
FDPC Subtotal	126	126	253						
FDPC Subtotal	←	**505**	→	**1070**		1575	**795**	**928**	**3298**
Other Completed Phase 2/3 Studies									
A3051035 (Maintenance)				1927					1927
A3051037 (Safety)				251				126	377
A3051016 (Flexible dose)					157			155	312
A3051043 (OL in Japan)			30						30
Other Phase 2/3 Subtotal			30	2178	157	2365			
All Phase-2/3 Studies Database	126	126	283	3248	157				
All Phase-2/3 Studies Database		→		→		**3940**	**795**	**1209**	**5944**

Source: Modified from applicant Table 2.7.4 A2.1 *Zyban® dosed at 150-mg BID, after titration

The total estimated exposure of the 3940 subjects who received varenicline in 'All Completed Phase 2/3 Studies' was 346466 patient-days, or 948.6 patient-years. More than half of this exposure was in double-blind studies; the open-label varenicline exposure was 132339 patient-days from Study A3051035 plus 1108 patient-days from Study A3051043; or 133447 patient-days (38.5% of the total). These data are summarized in Table 7-64.

Table 7-64: Patient-Days Exposure, by Study, and Median Duration of Exposure by Cohort

All Completed Phase 2/3 Studies	<1mg BID	1mg BID	Zyban®	Placebo
Fixed-dose, Placebo-Controlled Studies				
Study A3051028	--	23679	20342	21090
Study A3051036	--	23060	22077	21633
Study A3051007	17098	16642	--	7030
Study A3051002	10186	5053	5053	4912
Patient-days[a]	27284	68434	47472	54665
Median Duration days (range)	49 (1-91)	83 (1-102)	83 (1-107)	80 (1-133)
Number of Subjects	505	1070	795	928
Other Phase 2/3 Studies				
Study A3051037	--	60140	--	27967
Study A3051035				
Open-label		132339	--	--
Double-blind		46181	--	
Study A3051043	1108	--	--	--
Study A3051016	10980			10159
All Completed Phase 2/3 Studies				
Patient-days[a]	346466		47472	92791
Median Duration days (range)	84 (1-413)		83 (1-107)	83 (1-379)
Number of Subjects	3940		795	1209

Source: Modified from applicant Table 6, Section 2.7.4

Exposure duration in the 'Phase 2/3 Fixed-dose, Placebo-controlled Studies,' and in the 'All Completed Phase 2/3 Studies' cohorts, is shown in Table 7-65 and Table 7-66, respectively, below. Many of Pfizer's safety analyses focused on the Phase-2/3, Fixed-dose, Placebo-controlled database (Studies A3051002, A3051007, A3051028 and A3051036). The breakdown of exposure duration beyond 12-weeks, however, is summarized only in Pfizer's "All Completed Phase-2/3 Studies" table, in which all varenicline doses are grouped together. For these reasons, both tables are included in this review. All varenicline exposures ≥ 12-weeks were at the 1-mg BID dose, though. In both, duration of treatment was calculated from the first and last days that a subject received study medication, regardless of missed doses or temporary discontinuation of treatment.

Phase-2/3 Fixed-Dose, Placebo-Controlled Studies

Table 7-65 shows that overall (in the Phase 2/3 Fixed-dose, Placebo-controlled Studies), the median duration of exposure in the varenicline 1-mg BID, Zyban® and placebo groups was similar, and close to the proposed 12-week treatment period. The number of patients treated with varenicline 1-mg BID was about 15% greater than the number treated with placebo, and about 35% greater than the number treated with Zyban®.

Table 7-65: Dose-by-Duration, Phase 2/3 Fixed-Dose, Placebo-Controlled Studies (07/05)

Treatment Duration	Varenicline < 1-mg BID N=505	Varenicline 1-mg BID N=1070	Zyban® 150-mg BID N=795	Placebo N=928
Unknown[b]	0	12	16	9
>2 weeks (≥15 days)	459	973	676	820
>6 weeks (≥43 days)	376	819	570	633
>11 weeks (≥78 days)	167	636	424	471
>12 weeks (≥85 days)	87	314	222	283
Median Duration (Range)	49.0 (1-91)	83.0 (1-102)	83.0 (1-107)	80.0 (1-133)

Source: Section 2.7.4 Table A4a Protocols included: A3051002, A3051007, A3051028, and A3051036
[a] Treatment duration calculated from first & last days of treatment, regardless of missed doses or temporary discont.
[b] Unknown represents subjects lost to follow-up after baseline and whose treatment stop dates were unknown.

Subjects counted as receiving > 11 weeks of treatment are mostly those who completed the protocol-specified 12-week treatment periods. Three of the four fixed-dose, placebo-controlled studies had a planned treatment duration of 12 weeks (84 days). The fourth (A3051002) treated patients with varenicline for 6-weeks (0.3-mg QD, 1-mg QD, or 1-mg BID), or with Zyban® or placebo for 7-weeks. Because varenicline doses < 1-mg BID are derived only from Phase-2 Studies A3051002 and A3051007, the duration of treatment in the < 1-mg BID group is lower than for the other treatment groups.

All Completed Phase 2/3 Studies

The majority of additional exposure in the 'All Completed Phase 2/3 Studies' cohort comes from Safety Study A3051037 in which subjects received double-blind varenicline (1-mg BID) or placebo for up to 52 weeks, and from Study A3051035 in which subjects received 12 weeks open-label varenicline (1-mg BID) followed by 12 additional weeks of double-blind varenicline (1-mg BID) or placebo. Duration of exposure in this cohort is summarized in Table 7-66.

Table 7-66: Dose-by-Duration, All Completed Phase 2/3 Studies as of 07/05 Database Lock

Treatment Duration[a]	Varenicline N=3940	Zyban® N=795	Placebo N=1209
Unknown[b]	18	16	10
>2 weeks (≥15 days)	3592	676	1079
>6 weeks (≥43 days)	3110	570	855
>11 weeks (≥78 days)	2425	424	663
>12 weeks (≥85 days)	1531	222	426
>20 weeks (≥141 days)	697	0	76
>24 weeks (≥169 days)	456	0	72
>48 weeks (≥337 days)	130	0	57
≥52 weeks (≥365 days)	112	0	43*
Median Duration (Range)	84.0 (1 - 413)	83.0 (1 - 107)	83.0 (1 - 379)

Source: Section 2.7.4 Table A4b Footnotes a, b as in Table 7-65 * Placebo=43 for >52-weeks
Protocols: A3051002, A3051007, A3051016, A3051028, A3051035, A3051036, A3051037, A3051043

Safety data from Phase-2 Studies A3051016 (12 weeks of patient-chosen flexible dosing of 0.5 to 2 mg per day) and A3051043 (7 weeks treatment with open-label varenicline at 0.5 mg BID) are also

included in the 'All Completed Phase 2/3 Studies' pooled data. Because this cohort included some studies with treatment periods longer than 12 weeks (A3051037 and A3051035), some with treatment periods shorter than 12 weeks (A3051002 and A3051043), and four studies with 12-week treatment periods, the median duration of treatment for the varenicline group remained 12 weeks (84 days).

For Study A3051035, only safety data collected on varenicline treatment (dosing period plus 7-day lag) are included in the pooled dataset. Subjects who received varenicline in both the open-label and double-blind phases have their duration of exposure calculated continuously from the first open-label dose to the last double- blind dose. Safety data collected during double-blind placebo treatment are included only if within 7 days of the end of varenicline treatment (in which case AE and laboratory findings would be attributed to varenicline).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Preliminary data from three ongoing studies were also reviewed for safety findings. For the most part, however, only SAE reports were available from these studies.

7.2.2.2 Postmarketing experience

This section is not applicable for this NDA review as the drug has not yet been approved or marketed anywhere in the world.

7.2.2.3 Literature

No additional studies from the literature were used in the evaluation of the clinical safety data contained in this NDA submission, beyond those provided by the applicant. Pfizer included several dozen articles, mostly from the non-clinical literature related to animal models of nicotine addiction, and to anticipated reproductive toxicology and CNS binding findings. Articles from the clinical literature addressing psychological and psychopharmacological aspects of nicotine addiction, as well as the use of patient reported outcome measures of nicotine and cigarette craving were also included. No description of the methods used to search the literature was included.

7.2.3 Adequacy of Overall Clinical Experience

The placebo-controlled trials performed were adequate to assess the efficacy of varenicline for the smoking cessation indication (the primary objective). Overall, the applicant exposed an adequate number of patients to varenicline in the Phase-2/3 trials (N = 3940, >80% at proposed dose), for adequate duration, to assess product safety (with use up to ≈ 24 to 52 weeks). As is typically the case, however, exposure may be insufficient to identify very rare but potentially serious events.

Over 80% of these were treated with the 1-mg BID dose. Nearly 1600 patients received varenicline in the four 'Fixed-dose, Placebo-controlled' trials, but the four additional studies (including the 52-week safety study) also included placebo treatment arms. The doses and durations of exposure were also adequate to assess safety for the applicant's proposed prescribing instructions.

The demographic and medical characteristics of the overall patient population enrolled in the Phase-2/3 studies were not inconsistent with known epidemiological data describing the overall smoking (patient) population in the USA. The gender ratio of the Phase-2/3 varenicline-treated patients was roughly 1:1. The 'Fixed-dose, Placebo-controlled' population was 86% Caucasian, 9% Black and 6% 'Other' (percentages rounded off); in the 'All Phase-2/3 Studies' population these numbers were 90%,

5% and 5%, respectively. Latino and Asian patients, then, appear to have been somewhat underrepresented, though less so in the FDPC trials.

Patients with most expected comorbid conditions were included as well, though not those with many commonly occurring psychiatric diagnoses, and those with severe respiratory disease. Patients with diabetes requiring any from of pharmacologic treatment were excluded from A3051028 and A3051036, the two main Phase-3 efficacy trials. or psychiatric disease, or with diabetes requiring pharmacologic treatment (See Section 7.2.3.1 below).

Laboratory, vital sign and ECG monitoring were also adequate. During the clinical development of varenicline, safety monitoring consisted of spontaneous reporting of AEs, measurements of vital signs at each visit, regular laboratory evaluations, and ECGs (recorded at the expected time of peak plasma levels) taken at baseline, periodically while on treatment, and at the end of treatment.. Varenicline plasma levels were measured in several patient sub-populations also to characterize population-specific exposure-response relationships. The applicant evaluated patients for post discontinuation adverse events and residual effects as well.

7.2.3.1 Appropriateness of Patient Populations Exposed

Phase 1 Studies

Most of the Phase-1 studies enrolled smokers between the ages of 18 and 55 with no clinically significant disease. The inclusion criteria were similar to Phase 2/3 studies, but the exclusion criteria regarding concomitant medications and past or present medical conditions were generally more stringent. Overall, appropriate patient populations were studied in Phase-1.

Phase-2/3 Studies

The varenicline Phase-2/3 protocols used study entry criteria that were generally appropriate with respect to patients' baseline medical status and smoking history. Patients with severe chronic obstructive respiratory disease (COPD) were excluded, but those with mild to moderate disease were not.

The population studies may, however, been too carefully screened with respect to baseline psychiatric illness. Patients treated for depression within 12 months of study enrollment were excluded, as were those with histories of panic disorder, psychosis or bipolar disorder.

Patients "... for whom treatment with Zyban® was not appropriate" were also excluded from studies that included a Zyban® treatment arm (Studies A3051028, A3051036 and A3051002 – all included in the 'Phase-2/3 Fixed-dose, Placebo-controlled' database). By Pfizer's definition this included patients with diabetes mellitus requiring any pharmacologic treatment, as well as those "...with hepatic or renal impairment." Thus diabetic patients were not adequately represented in the pivotal efficacy trials. They were, however, included in the 52-week open-label safety trial, and in the 24-week maintenance of efficacy study.

Table 7-67 below summarizes the Phase-2/3 patients' baseline medical conditions, but only lists Preferred Terms reported by 5% or more of patients in any treatment arm; the only SOC categories listed are those in which at least one Preferred Term met the ≥ 5% criterion. This type of presentation makes it difficult to ascertain whether patients with the expected comorbid conditions were adequately represented. My review of the data listings, shows that certain groups of patients may have been

underrepresented Notably underrepresented are patients with psychiatric disease. The patient population studied, then, may not represent the true target population should varenicline be approved for the smoking cessation indication. The medical history and baseline characteristics of the enrolled patient population were, however, similar across treatment groups and studies.

Section 7.2.1.2 above discusses patient Demographics.

Table 7-67: Baseline Medical Conditions (SOC ≥ 5% in Any Group)
'Fixed-Dose, PC, Phase-2/3 Studies', and 'All Completed Phase-2/3 Studies' (Varenicline Group Only)

	Fixed-Dose, Placebo-Controlled Studies				All Studies
MedDRA System Organ Class Preferred Term	Varenicline < 1-mg BID N=505 (%)	Varenicline 1-mg BID N=1070 (%)	Zyban® N=795 (%)	Placebo N=928 (%)	Varenicline All Doses N=3940 (%)
Any medical condition at baseline	411 (81.4)	861 (80.5)	631 (79.4)	756 (81.5)	2910 (73.9)
Gastrointestinal disorders	97 (19.2)	193 (18.0)	168 (21.1)	195 (21.0)	654 (16.6)
Dyspepsia	47 (9.3)	98 (9.2)	83 (10.4)	93 (10.0)	280 (7.1)
Immune system disorders	118 (23.4)	265 (24.8)	180 (22.6)	221 (23.8)	863 (21.9)
Drug hypersensitivity	0 (0)	60 (5.6)	53 (6.7)	59 (6.4)	247 (6.3)
Seasonal allergies	81 (16.0)	148 (13.8)	98 (12.3)	140 (15.1)	456 (11.6)
Metabolic/nutritional disorders	37 (7.3)	107 (10.0)	81 (10.2)	103 (11.1)	441 (11.2)
Hyperlipidemia	27 (5.3)	39 (3.6)	26 (3.3)	32 (3.4)	134 (3.4)
Hypercholesterolemia	3 (0.6)	47 (4.4)	41 (5.2)	44 (4.7)	219 (5.6)
Musculoskeletal/connective tissue	154 (30.5)	314 (29.3)	205 (25.8)	251 (27.0)	996 (25.3)
Arthralgia	31 (6.1)	68 (6.4)	45 (5.7)	38 (4.1)	161 (4.1)
Back pain	38 (7.5)	99 (9.3)	74 (9.3)	76 (8.2)	291 (7.4)
Nervous system disorders	144 (28.5)	360 (33.6)	249 (31.3)	330 (35.6)	937 (23.8)
Headache	116 (23.0)	239 (22.3)	167 (21.0)	228 (24.6)	581 (14.7)
Vascular disorders	17 (3.4)	84 (7.9)	51 (6.4)	83 (8.9)	338 (8.6)
Hypertension	14 (2.8)	73 (6.8)	42 (5.3)	66 (7.1)	281 (7.1)

Source: Modified from applicant Tables 10, 11, A6a and A6b, Section 2.7.4

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Pharmacology/Toxicology review team considers the pre-clinical testing program adequate to explore general and reproductive toxicity.

Controlled Substances Staff reviewers consider the *in vitro* assays performed to be adequate (number and types of studies).

7.2.5 Adequacy of Routine Clinical Testing

Overall, routine clinical testing of was adequate and appropriate. Vital sign, ECG and laboratory data were collected using appropriate methods, frequency and timing. The laboratory testing panel varied little between the different Phase-2/3 studies. (Table 7-29 and Table 7-30 in Section 7.1.7.1 above provide an overview of the laboratory testing schedules, and the laboratory parameters assessed during the Phase-2/3 studies, respectively.)

Table 7-68 below details the clinical safety testing schedule during Phase-3 trials A3051028/ A3051036 and the open-label phase (first 12-weeks) of A3051035). Testing during off-treatment follow-up is outlined in Table 7-69; from Week-13 for Studies 1028/1036 and from Week-24 for Study 1035.

Table 7-70 below details the clinical testing schedule during the double-blind treatment period of A3051035 (second 12-weeks).

Clinical safety testing during the first 24-weeks of 52-week open-label study A3051037 was essentially the same as that outlined in Table 7-68 and Table 7-70. Safety testing during the final 28-weeks of A3051037 repeated the A3051035 Week-24 testing (shown in Table 7-70) at four-week intervals, except for C-reactive protein, which was obtained only at the end-of-study (or early termination) visit.

Efforts to elicit adverse event and concomitant medication usage reports were also acceptable. In studies where clinic visits were scheduled more than two weeks apart, telephone contact was interspersed between visits.

The adequacy of specific testing to assess for possible ophthalmologic adverse events is discussed under subheading 7.2.7 below.

Table 7-68: On-Treatment Schedule forA3051028/1036 and for 1035 Open-Label Treatment Period (Weeks 1 to 12)

Assessment	Screen	BL	Wk 1	TQD+3	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	ET
Medical history, Informed consent	X															
Physical examination	X														X	X
Vital signs (HR, BP), weight	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Temperature		X														
Height	X															
Adverse events		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dosing record			X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Fagerström Test for Nicotine Depend.	X															
Nicotine Use Inventory		X	X		X	X	X	X	X	X	X	X	X	X	X	X
MNWS, QSU-Brief		X	X	X[c]	X	X	X	X	X	X					X	X
Smoking Effects Inventory		X	X		X	X	X	X	X	X						X
Smoking Cessat. QoL Questionnaire		X													X	X
Chemistry, CBC, ECG, Pregnancy	X	X			X										X	X
C-reactive protein		X													X	X
Reference serum sample		X														
Serum cotinine	X															
Plasma pharmacokinetic sample					X										X	X
Genotyping sample		X														
Urinalysis (dipstick)	X	X			X										X	X
Urine Drug Screen[f]	X															
Exhaled carbon monoxide		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Counseling (AHRQ guidelines)		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X		X	X	X	X	X	X	X	X	X	X		
Telephone contact (AHRQ guidelines)				X												

Source: Modified from A3051028 clinical study report, Appendix 'Final Protocol' page 7

Table 7-69:A3051028/A3051036/A3051035 (Weeks 24 to 52 or ET) Non-Treatment Follow-Up Schedule

Assessment	Week 13 (clinic)	Week 16, 20 (telephone)	Week 24 (clinic)	Week 28, 32 (telephone)	Week 36 (clinic)	Week 40 (telephone)	Week 44 (clinic)	Week 48 (telephone)	Week 52 (clinic)	ET (clinic)
Nicotine Use Inventory	X	X	X	X	X	X	X	X	X	X
Weight, BP, HR	X		X		X		X		X	X
Exhaled CO	X		X		X		X		X	X
Concomitant meds (for smoking cessation)	X	X	X	X	X	X	X	X	X	X
C-reactive protein									X	X
MNWS (past week)	X									
Smoking Cessation Quality of Life Questionnaire			X						X	X
Counseling (AHRQ guidelines)	X		X		X		X		X	X

Source: Modified from Table appearing in A3051036 study report, Appendix A1, page-8 ET = early termination

Table 7-70: A3051035 Study Schedule, Double-Blind Phase (Weeks 13 to 24)

Assessment/Procedure	Wk 13	Wk 14	Wk 16	Wk 20	Wk 24	ET
Physical examination					X	X
Vital signs (HR, BP), weight	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Dispense study drug	X	X	X	X		
Dosing record	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
MNWS	X					
Electrocardiogram					X	X
Serum pregnancy test					X	X
Blood chemistry					X	X
C-reactive protein					X	X
CBC					X	X
Urinalysis (dipstick)					X	X
Exhaled carbon monoxide (CO)	X	X	X	X	X	X
Nicotine Use Inventory	X	X	X	X	X	X
Counseling (AHRQ)	X	X	X	X	X	X

Source: Modified from applicant unnumbered table on page 1076 of A3051035 study report

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Pfizer evaluated varenicline both as a substrate for interactions (interference with its clearance) and as an inducer or inhibitor of the clearance of other drugs.

The studies performed, as summarized in Section 5, were adequate to assess:

- The enzymatic pathways responsible for varenicline clearance, and the effects of inhibition of those pathways
- The effect of the drug on CYP450 enzymes (inhibition, induction)
- The potential safety consequences of drug-drug interactions

Further details regarding these assessments can be found in Section-5 of this review, and, of course, in the OPCB Clinical Pharmacology Review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events

Specific adverse events of most interest, and potentially concern, were related to the psychiatric, neurologic and gastrointestinal organ systems, as well as potential skin, eye and renal toxicity.

As described in Section 7.1.7.5, study protocols included algorithms for evaluation and management of neuropsychiatric and cardiovascular events.

7.2.8 Assessment of Quality and Completeness of Data
(See also Section 7.1.2)

Data quality and completeness were good. Adverse event elicitation was appropriate and coding appeared satisfactory. There appeared to be no evidence of fraud. Responses to information requests were prepared promptly and appropriately.

SAEs were reported on a case-by-case basis, utilizing the concept of 'SAE cases.' An 'SAE case' was defined as a single (adverse) event, or a series of events not separated in time, occurring in a single patient. A patient could have multiple serious (and non-serious) adverse events within a single SAE case, and they could also have multiple 'SAE cases,' even for the same Preferred Term, during the course of a study.

In a handful of cases (about one dozen) reasons cited for treatment discontinuation appear to have been coded incorrectly. On the other hand, in at least two cases, discontinuation appears to have been inappropriately attributed to a treatment emergent adverse event.

7.2.9 Additional Submissions, Including Safety Update
The safety update was submitted 90-days after the application (data through 12/16/05). One new death was reported, a patient who completed ongoing Study A3051046. Study A3051046 is not yet unblinded, but participants had a 75% chance of having received varenicline (treatment arms were 0.25-mg BID, 0.5-mg BID, 1-mg BID and placebo).

Fifteen new SAE cases were reported (2 varenicline, 4 NRT, and 9 blinded therapy), summarized in Table 7-12. The System Organ Classes most commonly represented were Injury/Poisoning (5) and Infections/Infestations (4). No new safety concerns emerge, but the cases of depression (varenicline) and unstable angina (possibly varenicline) are noteworthy, as is the number of accidents.

7.3 Summary of Selected Drug-Related AEs, Data Limitations, and Conclusions

The overall adverse event data show that varenicline at the proposed dose is commonly associated with nausea (± vomiting), insomnia, abnormal dreams and other sleep disturbances, and headache. Nausea, by far the most common adverse event, was clearly dose-related, and more common in females than in males. Although occurring in 30% to 40% of patients, depending on dose and treatment duration, only about 3% of patients discontinued because of it. Insomnia, abnormal dreams and other sleep disturbances were also dose-related in varenicline-treated patients. Most of the commonly reported AEs appear more likely to occur relatively early in treatment, though not exclusively so. Study A3051037, however, shows that patients may report specific adverse events for the first time months after initiating treatment. Black patients appear slightly less likely to report nausea and insomnia than white patients.

Patients with histories of psychiatric illness were excluded from participation in the Phase-3 studies.

7.4 General Methodology

The safety review focused mainly on data from Phase-2/3. Most summary tables present only the fixed-dose, placebo-controlled data. Some tables also include data from Study A3051037 or from the all completed Phase-2/3 studies database. These data were included where they were not obviously consistent with the FDPC data, or where the additional exposure duration was thought to be informative.

Phase-1 data were also reviewed, principally for extreme changes and outliers, and for laboratory value related adverse events.

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The pooled **Phase-1 Studies** database consists of 23 studies, in which 750 subjects received varenicline (Table 7-57 above provides an overview of the Phase-1 program, and Appendix Table 11-5 and Table 11-6 provide additional study details.) The pooled Phase-1 data were reviewed for adverse event, laboratory, vital sign and ECG findings. Phase-1 laboratory and vital sign data were also reviewed on a study-by-study basis, predominately for laboratory and ECG findings, and for adverse events in the drug-drug interaction studies and at supratherapeutic dosing.

The two Phase-2/3 safety populations defined by Pfizer, the 'Phase-2/3 Fixed-dose, Placebo-controlled Studies' database and the 'All Completed Phase-2/3 Studies' database were used for many of my own safety analyses (i.e., overall serious and common adverse event profiles, common AE dose and time dependency, drug demographic and, where possible, drug-disease interactions). For other analyses these two databases, predominately the "Phase-2/3 Fixed-dose, Placebo-controlled' data, were compared to data from individual studies.

Because of the 52-week placebo-controlled treatment period, the A3051037 data were reviewed on their own, and also in comparison to data from the shorter-term studies. Likewise with the A3051035 data, given that study's 24-week treatment duration (for many of its patients). Data from flexible dosing Study A3051016 were also reviewed separately, principally for adverse events and discontinuation findings.

7.4.1.2 Combining data

All analyses of pooled safety data summarized findings by total numbers of patients exposed in each treatment group. Analyses of deaths, serious adverse events and in some cases common adverse events, also considered cumulative exposure for each treatment condition, in terms of patient-exposure-years.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

In the pooled data only gastrointestinal adverse events appear to be clearly dose-related, primarily nausea (See Table 7-22 and Table 7-26 above). The A3051002 data, however, shown below in Table 7-71, suggest that insomnia and other sleep disorders are also dose-related.

Table 7-71: A3051002 (Dose-Ranging Study) Adverse Events, N(%)

COSTART PT	0.3 mg QD (N=126)	1-mg QD (N=126)	1-mg BID (N=125)	Zyban® (N=126)	Placebo (N=123)
Nausea	22 (17.5)	47 (37.3)	65 (52.0)	27 (21.4)	23 (18.7)
Insomnia	25 (19.8)	34 (27.0)	44 (35.2)	57 (45.2)	27 (22.0)
Headache	34 (27.0)	34 (27.0)	30 (24.0)	38 (30.2)	33 (26.8)
Abnormal dreams	10 (7.9)	14 (11.1)	19 (15.2)	15 (11.9)	10 (8.1)
Taste perversion	11 (8.7)	18 (14.3)	19 (15.2)	14 (11.1)	9 (7.3)
Irritability	15 (11.9)	17 (13.5)	15 (12.0)	14 (11.1)	12 (9.8)
RTI	32 (25.4)	18 (14.3)	15 (12.0)	20 (15.9)	31 (25.2)
Asthenia	13 (10.3)	10 (7.9)	13 (10.4)	9 (7.1)	10 (8.1)
Dyspepsia	10 (7.9)	8 (6.3)	11 (8.8)	14 (11.1)	9 (7.3)
Somnolence	8 (6.3)	9 (7.1)	11 (8.8)	6 (4.8)	8 (6.5)
Flatulence	7 (5.6)	7 (5.6)	10 (8.0)	0 (0.0)	1 (0.8)
Increased appetite	18 (14.3)	13 (10.3)	10 (8.0)	9 (7.1)	7 (5.7)
Thinking abnormal	7 (5.6)	10 (7.9)	8 (6.4)	7 (5.6)	8 (6.5)
Abdominal pain	11 (8.7)	2 (1.6)	7 (5.6)	7 (5.6)	3 (2.4)
Constipation	8 (6.3)	8 (6.3)	7 (5.6)	17 (13.5)	5 (4.1)
Dry mouth	4 (3.2)	11 (8.7)	7 (5.6)	15 (11.9)	7 (5.7)
Pharyngitis	6 (4.8)	5 (4.0)	7 (5.6)	4 (3.2)	2 (1.6)
Flu syndrome	11 (8.7)	4 (3.2)	6 (4.8)	8 (6.3)	4 (3.3)
Agitation	10 (7.9)	5 (4.0)	5 (4.0)	6 (4.8)	2 (1.6)
Arthralgia	5 (4.0)	7 (5.6)	4 (3.2)	9 (7.1)	2 (1.6)
Depression	5 (4.0)	7 (5.6)	3 (2.4)	8 (6.3)	3 (2.4)
Diarrhea	3 (2.4)	7 (5.6)	3 (2.4)	2 (1.6)	4 (3.3)

Source: Study A3051002 study report table 6.1.3 (Module-5)

7.4.2.2 Explorations for time dependency for adverse findings

All commonly reported AEs were most often, though not exclusively reported within the first several weeks of study drug treatment. One point worth noting, though, is that about two-thirds of varenicline patients discontinuing because of skin-related AEs were in the longer-term studies.

The onset of nausea was most frequent during the first two weeks of treatment. The prevalence of nausea decreased with time on treatment. It was 21.5% for the varenicline 1 mg BID group and 6.6% in the placebo group during Week 1 of treatment; by Week 12 it had decreased to 8.0% for the varenicline 1 mg BID group and 1.2 % for the placebo group.

The duration and time to onset of nausea AEs are summarized in Table 7-72 below. In this analysis, each period of consecutive days of nausea is considered a discrete event (regardless of changes in

severity during that period). The collection and analysis of adverse event data in these studies could not distinguish between nausea experienced continuously or intermittently within a time interval or across contiguous intervals. All events of nausea for an individual patient are included in the analysis.

Table 7-72: Time to and Duration of Nausea Adverse Events, Fixed-Dose, Placebo-Controlled Studies

	<1-mg BID (N=505)	**1-mg BID (N=1070)**	**Zyban® (N=795)**	**Placebo (N=928)**
Patients with at least one nausea event N (% of treated subjects)	118 (23.4)	361 (33.7)	92 (11.6)	103 (11.1)
Patients with more than one nausea event N (% of treated subjects)	11 (9.3)	53 (14.7)	7 (7.6)	4 (3.9)
Patients with treatment D/C due to nausea N (% of treated subjects)	5 (1.0)	33 (3.1)	8 (1.0)	5 (0.5)
Patients with onset of first nausea AE within 7 days N (% of subjects who had nausea)	94 (79.7)	231 (64.0)	52 (56.5)	62 (60.2)
Patients with onset of first nausea AE within 14 days N (% of subjects who had nausea)	103 (87.3)	287 (79.5)	70 (76.1)	82 (79.6)
Median days to onset of first event	3 (1-88)	4 (1-82)	6 (1-82)	6 (1-77)
Quartiles 25%, 75%	1, 6	2, 12	2, 12.5	3, 12
Median days duration of first event (range)	7 (1-68)	11 (1-104)	5 (1-90)	5 (1-85)
Quartiles 25%, 75%	2, 15	3, 38	2, 16	2, 15
Median days duration all events (range)	7 (1-68)	10 (1-104)	5 (1-90)	5 (1-85)
Quartiles 25%, 75%	2, 15	3, 35	2, 17	2, 15
Median days to RX D/C from first dose (range)	7 (5-26)	20 (2-70)	6 (1-11)	22 (1-24)
Quartiles 25%, 75%	6, 8	8, 35	5, 10	3, 23
Median days to RX D/C from start of first AE (range)	6 (3-22)	12 (2-58)	3 (1-6)	12 (1-21)
Quartiles 25%, 75%	5, 7	5, 29	1.5, 4.5	3, 18

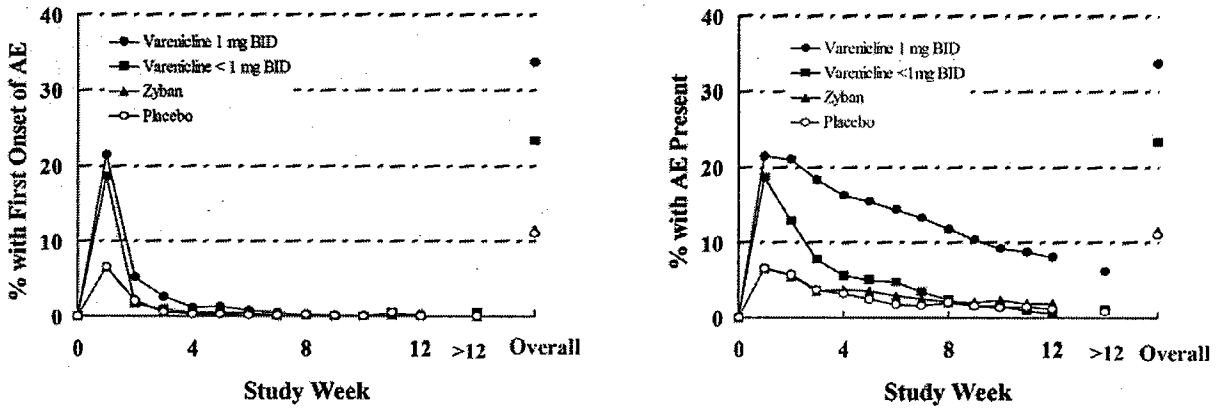
Source: Table 44, Section 2.7.4

The majority of patients who experienced nausea had onset soon after starting dosing. Among those who experienced nausea on 1-mg BID varenicline, nausea onset was within the first week for 64% and within the first two weeks for 80%. The greater proportion of subjects with onset in the first week in the varenicline < 1 mg BID group compared with the varenicline 1 mg BID group may be due to the fact that most subjects in the < 1 mg BID group did not have dose titration in the first week (all patients in Study A3051002 and the non-titrated 0.5 mg BID arm in Study A3051007).

Nausea usually had a limited duration. For patients in the 1-mg BID group, the median duration of a nausea event was 10-days and 75% of nausea events lasted 38 days or less. For those few patients in this group who discontinued treatment due to nausea, the median time to discontinuation was 12 days from the onset of the nausea, or 20 days from the start of varenicline dosing.

These data are consistent with the analyses of onset and prevalence of adverse events over time shown in Figure 7-2 below. In this analysis, the incidence of nausea is examined over consecutive weekly time frames, over the entire 12- week treatment period.

Figure 7-2: Onset and Presence of Nausea by Study Week, Fixed-Dose, Placebo-Controlled Studies



Source: Figure 4 in Section 2.7.4

Figure 7-3 and Figure 7-4 below (Pfizer's Figure-3, Section 2.7.4) show that the most frequently reported sleep AEs (abnormal dreams and insomnia) usually had their onset early in treatment. These AEs continued to be present throughout treatment, with the incidence of insomnia decreasing over time. Insomnia incidence appears to increase again at Week-8 in the <1-mg BID group, but this timepoint coincides with treatment completion in Study A3051002, which contributed the majority of the <1-mg BID patients.

Figure 7-3: Onset and Presence of Abnormal Dreams, Phase-2/3 Fixed-Dose, Placebo-Controlled

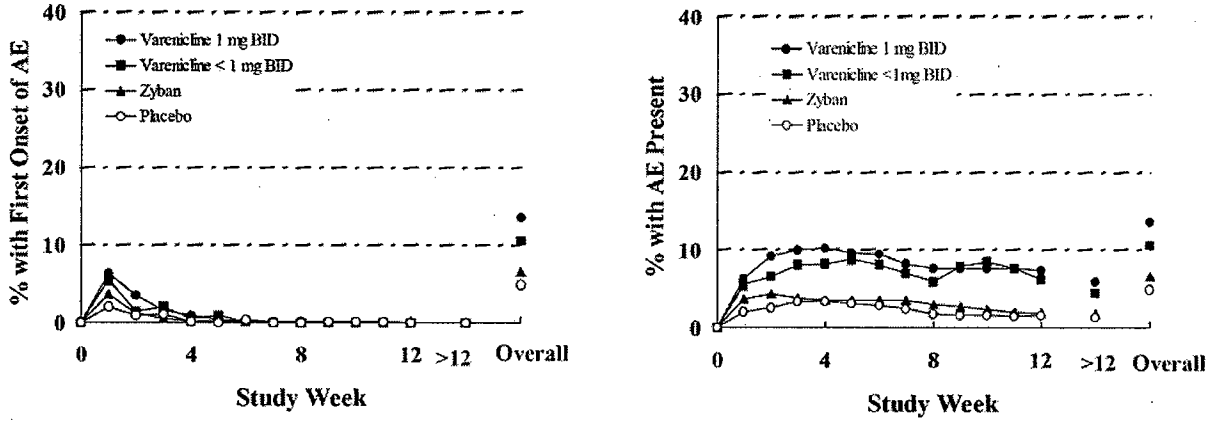
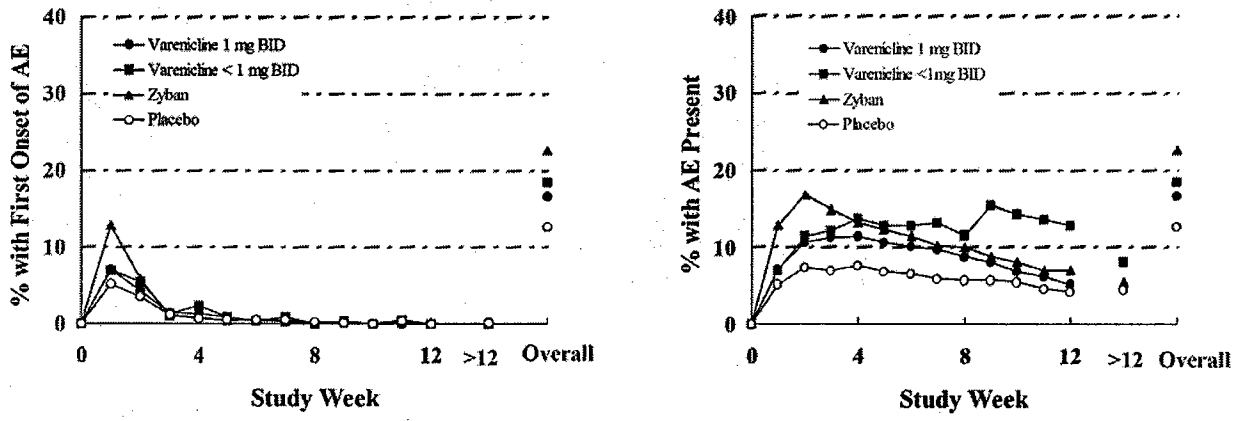


Figure 7-4: Onset and Presence of Insomnia, Phase-2/3 Fixed-Dose, Placebo-Controlled Studies



7.4.2.3 Explorations for drug-demographic interactions

Gender

Nausea and headache were reported more commonly in females than in males (with varenicline treatment). Females did not appear more likely to experience lab, vital sign or ECG abnormalities.

Race

Overall, black patients were less likely to report treatment-emergent adverse events than white patients (45% vs. 60%). Much of this difference can be accounted for by slightly decreased incidence rates for the most commonly occurring AEs (nausea, insomnia and sleep disturbances). Black patients did not appear more likely to experience lab, vital sign or ECG abnormalities, or to discontinue because of adverse events.

Asian and Latino representation was not adequate to make similar comparisons.

Age

Common adverse event incidence rates and patterns were similar between patients less than 65 years of age, and those older. Less than 3% of Phase-2/3 patients were ≥ 65, though, and all were relatively healthy, limiting our ability to extrapolate to the overall elderly smoking population.

7.4.2.4 Explorations for drug-disease interactions

Study populations were carefully screened, and patients with (known) clinically significant psychiatric disease were excluded. Those with all but minor psychiatric conditions were ineligible for entry.

Patients with baseline respiratory compromise (mild to moderate COPD), although eligible for study entry, were not well represented. Patients with baseline respiratory disease appeared to experience similar AE rates, and types of AEs, as the placebo population, however.

Patients with baseline cardiovascular disease are discussed in Section 7.1.2.2 above. These patients did not appear more likely to experience AEs (of any type), or lab, vital sign or ECG abnormalities, than those without baseline cardiovascular disease (in the varenicline-treated groups).

Patients with mild to moderate renal compromise experienced only exposure related AEs, most often only nausea.

7.4.2.5 Explorations for drug-drug interactions

Commonly occurring adverse events were reported more frequently with varenicline-NRT and with varenicline- Zyban® coadministration, in the drug-drug interaction studies. Pharmacokinetic interactions were not expected, and none were found.

7.4.3 Causality Determination

For common adverse events, all treatment-emergent events were assumed to be drug-related. For deaths and serious adverse events I reviewed each case in order to determine whether the event occurred during or shortly after drug exposure, and whether any other compelling alternative explanation was provided.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The varenicline development program included evaluation of three varenicline (daily) doses, evaluated under six different dosing regimens; 0.3-mg QD, 0.5-mg BID non-titrated, 0.5-mg BID titrated, 1-mg QD, 1-mg BID non-titrated, and 1-mg BID titrated. The superiority of the 1 mg BID dose over the labeled regimen for Zyban® was clearly demonstrated. The 1-mg BID dose appears to be only marginally more effective than 0.5-mg BID, in comparison to placebo, but clearly less well tolerated. Pfizer also demonstrated varenicline superiority to placebo under a flexible dosing regimen (0.5-mg to 2-mg/day), in which most patients chose to take 1-mg or 1.5-mg per day. A dosing and administration section calling for a flexible-dosing scheme beginning at 0.5 mg/day, as in the flexible dosing study, seems most appropriate.

The proposed label [redacted] The adverse event and MNWS data show, however, that abrupt cessation is associated in some patients with nicotine withdrawal like symptoms (i.e., irritability), thus a brief taper would likely be advisable.

Proposed dosing and related issues are discussed in Section 6.1.4.1 (Dose-Response Evaluation) and Section 5.3 (Exposure-Response Evaluation).

8.2 Drug-Drug Interactions

Coadministration with other approved smoking cessation products was shown to increase the incidence of nausea and other commonly occurring AEs. Systolic blood pressure was also noted to increase (10-20 mmHg) after Zyban/varenicline and nicotine/varenicline co-administration, for some subjects (2/41, 1/17, respectively). There were no pharmacokinetic interactions in these two studies.

Pharmacokinetic or pharmacodynamic changes were not noted with the coadministration of multiple doses of varenicline with multiple doses of either digoxin or warfarin (narrow therapeutic index drugs).

8.3 Special 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 undergoes minimal metabolism, with 92% excreted unchanged in urine. The influence of end stage renal disease (ESRD) on the pharmacokinetics of varenicline has not been systematically evaluated in a dedicated study, though several ESRD patients were studied during development.

Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min). In patients 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), varenicline was efficiently removed by hemodialysis.

Pfizer's proposed label states "... no dosing adjustment is necessary for patients with mild to moderate renal impairment, [redacted]

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

Pediatric
One study evaluated varenicline pharmacokinetics in 22 pediatric patients, aged 12 to 17 years (inclusive). Each received a single 0.5-mg dose and a single 1-mg dose of varenicline. The pharmacokinetics of varenicline was approximately dose proportional between the 0.5 mg and 1 mg doses. Systemic exposure, as assessed by $AUC_{(0-\infty)}$, and renal clearance of varenicline were comparable, though not identical, to those in the adult population.

Varenicline safety and effectiveness were not evaluated in pediatric patients. The development plan for varenicline in pediatric patients was discussed at the End-of-Phase 2 meeting. At the Pre-NDA meeting it was agreed that a waiver of the requirement for data in children less than 12 would be acceptable, and that a deferral for patients between 12 and 16 would be acceptable.

The Agency requested that a proposed pediatric study request not be provided until after NDA approval. The Agency would prefer to assess the safety and efficacy data in adults before commencing studies in pediatric population. Pfizer proposes labeling the product as "...not recommended for use in patients under 18 years of age."

Hepatic Impairment
Varenicline pharmacokinetics are expected to be unaffected in patients with hepatic insufficiency, due to the absence of significant hepatic metabolism, Pfizer considers the potential for clinically meaningful drug interactions between varenicline and metabolic inhibitors/inducers to be low. The preliminary draft of the OPCB review does not dispute this contention.

No dose adjustments are recommended in patients with mild or moderate hepatic impairment. (The effect of severe hepatic impairment on varenicline pharmacokinetics has not been assessed.)

8.4 Pediatrics

New Drug Application 21-928 complies with applicable requirements under the Pediatric Research Equity Act (PREA). Varenicline safety and effectiveness were not evaluated in pediatric patients. The development plan for varenicline in pediatric patients was discussed at the End-of-Phase 2 meeting. At the Pre-NDA meeting it was agreed that a waiver of the requirement for data in children less than 12 would be acceptable, and that a deferral for patients between 12 and 16 would be acceptable.

The Agency requested that a proposed pediatric study request not be provided until after NDA approval. The Agency would prefer to assess the safety and efficacy data in adults before commencing studies in pediatric population. Pfizer proposes labeling the product as "...not recommended for use in patients under 18 years of age."

One study evaluated varenicline pharmacokinetics in 22 pediatric patients, aged 12 to 17 years (inclusive). Each received a single 0.5-mg dose and a single 1-mg dose of varenicline. The pharmacokinetics of varenicline was approximately dose proportional between the 0.5 mg and 1 mg doses. Systemic exposure, as assessed by $AUC_{(0-\infty)}$, and renal clearance of varenicline were comparable to those in the adult population.

8.5 Advisory Committee Meeting

An advisory committee meeting was not considered to be necessary during this review cycle.

8.6 Literature Review

No additional review of the literature was undertaken for this review.

8.7 Postmarketing Risk Management Plan

NDA 21-928 includes a proposed postmarketing risk management plan, but there appears to be no need for such a plan at this time. The overall Phase-2/3 data indicate that patient (self) dose escalation does not occur. Flexible dosing Study A3051016 shows that most (successfully abstinent) patients never titrate themselves up to the 1-mg BID dose, while others decrease their dose, either in the setting of commonly occurring adverse events, or once abstinence is attained. About one-third of the A3051016 study completers (abstinent and otherwise) never titrated themselves up to the full 2-mg/day dose. Only one A3051016 patient (#101650350037) is reported to have escalated their dose beyond the labeled range, to 3.0 mg/day. This patient did so, however, in the context of a suicide attempt (or gesture).

Study A3051039, although flawed, also suggests that varenicline is unlikely to be sought or used as a drug of abuse.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.1.1 Efficacy

Applicant-identified pivotal Phase-3 Studies 3051028 and 3051036 provide substantial evidence of efficacy of varenicline 1-mg BID as an aid to smoking cessation, and substantial evidence of the 1-mg BID dose's superiority to Zyban® (when used for smoking cessation according to the labeled dosing regimen). These studies also provide evidence that varenicline decreases quitters' "urge to smoke" as measured by two validated instruments (Pfizer proposes to use the word "craving").

Study 3051035 provides evidence that the efficacy of varenicline (1-mg BID) is maintained over a 12-week follow-up period, for smokers able to abstain during the last week of an initial 12-week open-label treatment period with 1-mg BID. That is, smokers who successfully quit smoking during varenicline treatment are more likely to maintain abstinence if varenicline treatment is continued for three additional months.

Phase-2 and exposure-response data show the incremental benefit of the 1-mg BID dose over that for 0.5-mg BID to be minimal, though clearly associated with decreased tolerability. This issue is discussed in Section 1.3.4 above.

9.1.2 Safety

The serious adverse event data suggest that varenicline may, possibly increase the risk of cardiac events, both ischemic and arrhythmic, particularly over longer treatment periods. This finding, however, is far from definitive. (Although six deaths occurred during development, three or four in varenicline-treated patients, no specific safety concerns emerge.)

Adverse event related discontinuations (at the 1-mg BID dose) were relatively uncommon, but increased with increasing treatment duration, from about 12% with a 12-week course to over 25% in the 52-week study. It should be noted, however, that some patients discontinuing during later treatment months had already achieved abstinence, and may have had decreased willingness to tolerate drug side effects.

The overall adverse event data show that varenicline at the proposed dose is commonly associated with nausea (± vomiting), insomnia, abnormal dreams and other sleep disturbances, and headache. Nausea, by far the most common adverse event, was clearly dose-related. Although occurring in 30% to 40% of patients, depending on dose and treatment duration, only about 3% of patients discontinued because of it. Insomnia, abnormal dreams and other sleep disturbances were also dose-related in varenicline-treated patients. Most of the commonly reported AEs appear more likely to occur relatively early in treatment, though not exclusively so. Study A3051037, however, shows that some patients may report specific adverse events for the first time months after initiating treatment.

Treatment with varenicline for up to 24-weeks does not appear to increase the incidence of clinically relevant laboratory, vital sign or ECG abnormalities. Several concerns raised by the Phase-1 laboratory findings appear not to have Phase-2/3 correlates.

9.1.3 Dosing Regimen and Administration

The varenicline development program included evaluation of three varenicline (daily) doses, evaluated under six different dosing regimens; 0.3-mg QD, 0.5-mg BID non-titrated, 0.5-mg BID titrated, 1-mg QD,

1-mg BID non-titrated, and 1-mg BID titrated. The superiority of the 1 mg BID dose over the labeled regimen for Zyban® was clearly demonstrated. The 1-mg BID dose appears to be only marginally more effective than 0.5-mg BID, in comparison to placebo, but clearly less well tolerated. Pfizer also demonstrated varenicline superiority to placebo under a flexible dosing regimen (0.5-mg to 2-mg/day), in which most patients chose to take 1-mg or 1.5-mg per day. A dosing and administration section calling for a flexible-dosing scheme beginning at 0.5 mg/day, as in the flexible dosing study, seems most appropriate.

The proposed label [redacted]. The adverse event and MNWS data show, however, that abrupt cessation is associated in some patients with nicotine withdrawal like symptoms (i.e., irritability), thus a brief taper would likely be advisable.

Proposed dosing and related issues are discussed in Section 6.1.4.1 (Dose-Response Evaluation) and Section 5.3 (Exposure-Response Evaluation).

9.2 Recommendation on Regulatory Action

I recommend approval for NDA 21-928, pending final DSI report and labeling adequate to address minimum-effective-dose issues. The 'Warnings' and 'Precautions' sections of the proposed label are inadequate and will need revision.

9.3 Recommendation on Postmarketing Actions

I have no recommendations for post-marketing actions at this time.

9.4 Comments to Applicant

See action letter.

Appears This Way
On Original

10 APPENDIX ONE: LINE BY LINE LABELING REVIEW

See separate document.

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11 APPENDIX TWO: TABLES AND REFERENCES

Table 11-1: List of SAEs by System Organ Class and Treatment Group: Varenicline Treatment

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
Cardiac Disorders								
103610051011 50/W/M	2 mg	Acute coronary syndrome	Acute coronary syndrome	70	70	Perm D/C	Yes	Recovered
102810231018 75/W/M	2 mg	Atrial fibrillation	Atrial fibrillation	84[c]	84	None	Post therapy (0)	Recovered
103510301014 73/W/M	2mg	Atrial fibrillation	Atrial fibrillation	29	28	Perm D/C	Yes	Recovered
103710011021 59/W/M	2mg	Coronary artery disease	Coronary artery disease	191	191	Perm D/C	Yes	Recovered
103710061019 75/W/M	2 mg	Coronary artery disease	Coronary artery disease	315	N/A	None	No	Recovered
103710061025 60/W/M	2mg	Coronary artery disease	Coronary artery disease	362	365	None	No	Recovered
103510341063 65/O/M	2 mg	Myocardial infarct	Myocardial infarction	158	NA	MultiChallenge/ Rechallenge	No	Recovered
103510291026 45/O/M	2mg	Myocardial infarction	Myocardial infarction	102	84	None	Post therapy (18)	Unknown
10075011594 44/W/F	2 mg	Paroxysmal supraventricular tachycardia	Supraventricular tachycardia	51	51	Perm D/C	Yes	Recovered
103510311006 56/W/M	2 mg	Supraventricular tachycardia	Supraventricular tachycardia	172	143	None	Post therapy (29)	Recovered
103710061033 44/W/F	2 mg	Tachycardia	Tachycardia	171	N/A	MultiChallenge/ Rechallenge	No	Recovered
1016503148 52/W/M	2 mg	Ventricular fibrillation	Ventricular fibrillation	101	87	None	Post therapy (14)	Recovered
10075028336 48/W/M	1 mg	Intermediate coronary syndrome (unstable angina)	Angina unstable	59	60	Perm D/C	Yes	Recovered
10025005100 40/W/M	1 mg	Unstable angina	Angina unstable	92	42	None	Post therapy (50)	Recovered
10165031173 54/W/M	1 mg	Myocardial infarction	Myocardial infarction	57	50	None	Post therapy (7)	Recovered

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
Cardiac Disorders								
10085019-2502 64/W/F	0.5 mg	Congestive heart failure	Cardiac failure congestive	22	12	None	Post therapy (10)	Recovered
10085020-3101 57/O/M	0.5 mg	Coronary artery disease	Coronary artery disease	19	12	None	Post therapy (7)	Recovered
Cardiac Disorders/Neoplasms benign, malignant and unspecified (including cysts and polyps) Infections and infestations								
103510241019	2 mg	Cardiac arrest	Cardiac arrest	188	169	None	Post therapy	Death
71/W/M		Massive pericardial exudate	Pericardial effusion				(19)	
		Lung cancer	Lung neoplasm malignant					
		Lymph node metastasis	Metastases to lymph nodes					
		Right side pneumonia	Pneumonia					
Cardiac Disorders/Renal and urinary disorders/Reproductive system and breast disorders								
103510171142	2 mg	Myocardial infarction	Myocardial infarction	101	N/A	Multi challenge/	No	Recovered
59/W/F		Bladder prolapse	Bladder prolapse			Rechallenge		
		Uterine prolapse	Uterine prolapse					
Cardiac disorders/Vascular disorders								
103710061019	2 mg	Bigeminy	Extrasystoles	241	N/A	None	No	Recovered
74/W/M		Sinus bradycardia	Sinus bradycardia					
		Hypotension	Hypotension					
103710061052	2 mg	Myocardial infarction	Myocardial infarction	7	7	Perm D/C	Yes	Recovered
55/W/F		Deep vein thrombosis	Deep vein thrombosis					
Cardiac Disorders /Gastrointestinal Disorders/General disorders/Nervous system disorders/Respiratory, thoracic and mediastinal disorders								
103910011110	3 mg	Tachycardia	Tachycardia	1	1	Perm D/C	Yes	Recovered
20/A/M		Nausea	Nausea					
		Fever	Pyrexia					
		Tachypnea	Tachypnea					
		Numbness of lower extremities	Hypoaesthesia					
		Numbness of upper extremities	Hypoaesthesia					
		Numbness facial	Hypoaesthesia					

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
Ear and labyrinth disorders/General disorders and Administration site conditions/Investigations								
103610141100	2 mg	Vertigo worsening	Vertigo	64	63	Perm D/C	Yes	Recovered
43/B/F		Elevated blood pressure	Blood pressure increased					
		Chest pain	Chest pain					
Eye disorders								
10025011-580 36/W/M	2 mg	Bilateral posterior subcapsular cataracts	Cataract subcapsular	318	33	None	Post therapy (285)	Not Recovered
103710021034 51/W/F	2 mg	Subcapsular cataract	Cataract subcapsular	125	169	Perm D/C	Yes	Recovered
103510151038 55/W/M	2 mg	Diminished vision	Visual acuity reduced	42	N/A	None	No	Recovered
103510231034 55/W/F	2 mg	Transient vision loss both eyes	Blindness transient	124	141	Perm D/C	Yes	Recovered
Eye disorders/Nervous system disorders								
10025005-27	2 mg	Transient loss of vision	Blindness transient	20	35	Perm D/C	Yes	Recovered
52/W/M		Transient ischemic attacks	Transient ischaemic attack	20	35	Perm D/C	Yes	Recovered
Gastrointestinal disorders								
102810071069 42/W/M	2 mg	Abdominal pain	Abdominal pain	63	62	Perm D/C	Yes	Recovered
103510231019 50/W/F	2 mg	Abdominal pain	Abdominal pain	48	70	Perm D/C	Yes	Recovering
103710061045 50/W/M	2mg	Suspected gastrointestinal bleed	Gastrointestinal hemorrhage	24	N/A	MultiChallenge/ Rechallenge	No	Recovered
103710061062 54/W/M	2mg	Ileus	Ileus	37	N/A	MultiChallenge/ Rechallenge	No	Recovered
103510271054 47/W/M	2 mg	Acute pancreatitis	Pancreatitis acute	50	N/A	MultiChallenge/ Rechallenge	No	Recovered
1007500543 50/W/M	1 mg	Duodenal ulcer	Duodenal ulcer	5	9	Perm D/C	Yes	Recovering
See PID 103910011110 in Cardiac Disorders/ Gastrointest/ General disorders /Nervous system /Respiratory, thoracic			Nausea					
See PID 103510341062 in Injury, poisoning, and procedural complications/Gastrointestinal /Neoplasms			Tooth loss					
10025010-380	0.3 mg	Crohn's disease	Crohn's disease	163	44	None	Post therapy	Recovering

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
39/W/F		Adenocarcinoma	Adenocarcinoma				(119)	
General disorders and administration site conditions								
101310222010 48/W/F	4 mg[c]	Chest pain, non-cardiac	Non-cardiac chest pain	12	12	Perm D/C	Yes	Recovered
103610101184 44/B/F	2 mg	Chest pain	Chest pain	78	78	Perm D/C	Yes	Recovered
103710061009** 48/W/M	2 mg	Chest pain	**Chest pain****	208	N/A	None	No	Recovered
102810051050 41/W/M	2 mg	Non cardiac chest pain	Non- cardiac chest pain	61	50	None	Post therapy (11)	Recovered
See PID 103610141100 in Ear and labyrinth/General			Chest pain					
See PID 103710121025 in Infections and infestations/ General disorders and administration site conditions			Chest pain					
See PID 10391001110 Cardiac Disorders/Gastrointestinal/ General disorders/Nervous system/Respiratory, thoracic			Pyrexia					
Hepatobiliary disorders								
10075012353 58/W/F	2 mg	Cholelithiasis	Cholelithiasis	115	64	None	Post therapy (51)	Recovered
10025005-504 56/W/F	1 mg	Impacted gallstones	Cholelithiasis	110	15	None	Post therapy (95)	Recovered
Infections and infestations								
102810081042 37/O/F	2 mg	Acute appendicitis	Appendicitis	109	86	None	Post therapy (23)	Recovered
103710121025 59/W/F	2 mg	Acute exacerbation of chronic bronchitis	Bronchitis acute	78	N/A	None	No	Recovered
103710121025 59/W/F	2 mg	Acute exacerbation of chronic bronchitis	Bronchitis acute	306	N/A	None	No	Recovered
103710121025 60/W/F	2 mg	Acute exacerbation of chronic bronchitis	Bronchitis acute	340	N/A	None	No	Recovered
103710121025 60/W/F	2 mg	Acute exacerbation of chronic bronchitis	Bronchitis acute	358	N/A	None	No	Recovered
1007500598 45/B/F	2 mg	Aseptic meningitis	Meningitis aseptic	66	66	Perm D/C	Yes	Recovered

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
102810241038 50/W/F	2 mg	Pneumonia	Pneumonia	12	N/A	MultiChallenge/ Rechallenge	No	Recovered
See PID 103610131023 in Metabolism and nutrition disorders/infections and infestations			Periorbital cellulitis					
Infections and infestations/General disorders and administration site conditions								
103710121025	2mg	Pneumonia	Pneumonia	168	N/A	None	No	Recovered
59/W/F		Acute bronchitis exacerbation	Bronchitis acute					
		Chest pain	Chest pain					
Injury, poisoning, and procedural complications								
103510221131	2 mg	Alcohol poisoning	Alcohol poisoning	163	N/A	None	No	Recovered
63/W/M		Costal fracture	Rib fracture					
103510141050	2 mg	Injury to anterior tibial artery	Arterial injury	148	N/A	None	No	Recovered
57/W/M			Intentional misuse					
103510221090 37/W/M	2 mg	Accidental injury	Injury	28	NA	None	No	Recovered
103710121025 59/W/F	2 mg	Rib fracture	Rib fracture	29	NA	None	No	Recovered
Injury, poisoning, and procedural complications/Gastrointestinal disorders								
103510341062	2 mg	Left shoulder dislocation	Joint dislocation	60	N/A	None	No	Recovered
53/W/M		Loss of front teeth	Tooth loss					with sequelae
Investigations								
103510271179	2 mg	Elevated ALT	ALT increased	83	N/A	Multiple	No	Recovered
31/W/M		Elevated AST	AST increased			Challenge/		
		Elevated CPK	CPK increased			Rechallenge		
		Elevated lactate dehydrogenase	LDH increased					
See PID 103610141100 in Ear and labyrinth disorders/General disorders /Investigations			Blood pressure increased					
Metabolism and nutrition disorders								
103710061009 48/W/M	2mg	Hypoglycemia	Hypoglycemia	237	N/A	None	No	Recovered
10075012361 47/W/F	1 mg	Diabetes mellitus	Diabetes mellitus	85	46	None	Post therapy (39)	Not Recovered
Metabolism and nutrition disorders/infections and infestations								

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
103610131023	2 mg	Dehydration	Dehydration	23	N/A	None	No	Recovered
44/A/F		Periorbital cellulitis	Periorbital cellulitis					
Musculoskeletal and connective tissue disorders								
103710071022 40/W/F	2 mg	Chest wall pain	Chest wall pain	47	N/A	MultiChallenge/ Rechallenge/ Interrupt	No	Recovered
103710011025 42/W/M	2 mg	Herniated disc C5-C6 on left	Intervertebral disc protrusion	48	N/A	MultiChallenge/ Rechallenge/ Interrupt	No	Recovered
103710121059 61/W/F	2 mg	Spinal stenosis	Spinal column stenosis	N/A	N/A	MultiChallenge/ Rechallenge/ Interrupt	No	Recovered
See PID 103510241063 in Neoplasms/Musculoskeletal			Back pain					
Neoplasms benign, malignant and unspecified (including cysts and polyps)								
103510121147 42/W/M	2 mg	Glandular adenocarcinoma	Adenocarcinoma	57	86	Perm D/C	Yes	Not Recovered
103610021078	2 mg	Carcinoma brain	Brain neoplasm malignant	15	28	Perm D/C	Yes	Not Recovered
58/W/F		Lung cancer	Lung neoplasm malignant					
10075010476 65/W/M	2 mg	Carcinoid colon cancer	Colon cancer	94	85	None	Post therapy (9)	Recovering
103510171011 59/W/F	2 mg	Colon cancer	Colon cancer	165	N/A	None	No	Recovered
103510271079 56/W/M	2 mg	Nasopharyngeal carcinoma	Nasopharyngeal cancer	30	N/A	None	No	Not Recovered
10075011259 49/W/M	1 mg	Right ear cholesteatoma	Cholesteatoma	27	57	Perm D/C	Yes	Recovered
100850192501 47/B/M	0.5 mg	Lung cancer	Lung neoplasm malignant	18	12	None	Post therapy (6)	Not recovered
See PID 10025010-380 in Gastrointestinal / Neoplasms			Adenocarcinoma					
See PID 103510241019 in Cardiac Disorders/Neoplasms/ Infections and infestations			Lung neoplasm malignant Metastases to lymph nodes					
Neoplasms benign, malignant and unspecified (including cysts and polyps)/ Musculoskeletal and connective tissue disorders								
103510241063	2 mg	Rectal sarcoma	Sarcoma	9	15	Perm D/C	Yes	Death
29/W/M		Worsening back pain	Back pain					

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
Nervous system disorders								
103510241217	2 mg	Cerebral infarct	Cerebral infarction	161	N/A[f]	Perm D/C	Yes	Recovering
42/W/F		Deep cerebral vein thrombosis	Cerebral thrombosis					
103710061022 41/O/M	2 mg	Stroke	Cerebrovascular accident	118	117	N/A	No	Recovered with sequelae
103510271307 48/W/M	2 mg	Grand mal convulsion	Grand mal convulsion	41	41	Perm D/C	Yes	Recovered
103510231013 51/W/M	2 mg	Headache	Headache	36	44	Perm D/C	Yes	Recovered
10025005-56 40/B/F	2 mg	Multiple sclerosis	Multiple sclerosis	101	42	None	Post therapy (59)	Not Recovered
10075011540 52/W/F	2 mg	Relapsing remitting multiple sclerosis	Multiple sclerosis	59	60	Perm D/C	Yes	Not Recovered
10075012149 40/W/M	1 mg	Generalized tonic-clonic seizure	Grand mal convulsion	43	42	Perm D/C	Yes	Recovered
10075012148 47/W/M	1 mg	Blacked out	Loss of consciousness	22	23	Perm D/C	Yes	Recovered
See PID 103910011110 in Cardiac Disorders/ Gastrointestinal/General /Nervous system /Respiratory			Hypoaesthesia x 3					
See PID 10025005-27 in Eye disorders/Nervous System			Transient ischaemic attack					
Pregnancy, puerperium and perinatal conditions								
103510341066 43/W/F	2 mg	Miscarriage	Abortion spontaneous	97	85	None	Post therapy (12)	Recovered
10165035136 30/W/F	1.5 mg	Spontaneous abortion	Abortion spontaneous	94	84	None	Post therapy (10)	Recovered
Psychiatric disorders								
103510241209 46/W/F	2 mg	Acute psychosis	Acute psychosis	7	8	Perm D/C	Yes	Recovered
103610141087	2 mg	Acute psychosis	Acute psychosis	57	69	Perm D/C	Yes	Recovered
42/W/F		Emotional lability	Affect lability					
103510121069 61/W/M	2 mg	Suicide	Completed suicide	196	169	None	Post therapy (27)	Death
10025007-622 25/W/M	2 mg	Depression	Depression	176	44	None	Post therapy (132)	Recovered

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE								
103510121089 45/W/F	2 mg	Suicidal ideation	Suicidal ideation	74	73	None	Post therapy (1)	Recovered
Renal and urinary disorders								
103510331057 37/W/F	2 mg	Ureteral stone	Calculus ureteric	27	21	Perm D/C	Yes	Recovered
103510341052 37/W/M	2 mg	Worsening kidney stones	Nephrolithiasis	35	N/A	None	No	Recovered
See PID 103510171142 in Cardiac/Renal and /Reproductive			Uterine prolapse					
Reproductive system and breast disorders								
103510011028 47/W/F	2 mg	Indeterminate pathology on right breast female	Breast disorder female	9	N/A	None	No	Not recovered
See PID 103510171142 in Cardiac/Renal and /Reproductive			Uterine prolapse					
Respiratory, thoracic and mediastinal disorders								
103510341002 33/W/M	2 mg	Epistaxis	Epistaxis	35	39	Perm D/C	Yes	Recovered
See PID 103910011110 in Cardiac/ Gastrointestinal/General/Nervous System /Respiratory			Tachypnea					
Vascular disorders								
103710061046 68/B/M	2 mg	Ischemia peripheral	Peripheral ischemia	-1	N/A	None	No	Recovered
103710061046	2 mg	Peripheral ischemia	Peripheral ischemia	78	N/A	None	No	Recovered
68/B/M		Saphenous vein occlusion, right	Peripheral occlusive disease					
103710061046 69/B/M	2 mg	Ischemia peripheral	Peripheral ischemia	203	N/A	None	No	Recovered
See PID 103710061052 in Cardiac disorders/Vascular			Deep vein thrombosis					
See PID 103710061019 in Cardiac disorders/Vascular			Hypotension					

Source: Section 2.7.4 Table A14.1 and adverse event datasets [a] Race: W =White, B=Black, A=Asian, O=Other; Gender: M-male, F=Female; d/c=discontinued.
[b] Days are relative to start of treatment; for Study A3051035 start of treatment=start of open-label treatment.
* Treatment discontinuation due to this SAE
[c] Atrial fibrillation was first noted on Day 84, SAE triggered by hospitalization on Day 91.
[d] Varenicline/Placebo represents those subjects that were randomized to placebo after open-label varenicline treatment period in Study A3051035.
[e] Subject received a controlled-release formulation of varenicline [f] Last known dose was at Day 143

Table 11-2: List of SAEs by System Organ Class and Treatment Group: Varenicline Open-Label to Placebo Double-Blind (Study A3051035)

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
VARENICLINE → PLACEBO[d]								
Gastrointestinal disorders								
103510321038 56/W/F	2 mg/ PBO	Abdominal pain	Abdominal pain	169	85	None	Post therapy (84)	Recovered
Hepatobiliary disorders								
103510011063 62/W/F	2 mg/ PBO	Acute cholecyststis	Cholecystitis acute	98	77	None	Post therapy (21)	Recovered
Infections and infestations								
103510141005 57/W/M	2 mg/ PBO	Appendicitis	Appendicitis	174	84	None	Post therapy (7)	Recovered
Nervous system disorders								
103510161036 53/W/F	2 mg/ PBO	Cervical spinal cord compression	Cervical cord compression	100	84	None	Post therapy (16)	Recovered
Reproductive system and breast disorders								
103510121101 43/W/F	2 mg/ PBO	Increased dysmenorrhea Hypermenorrhea	Dysmenorrhea Menorrhagia	54	85	None	No	Recovered

Source: Section 2.7.4 Table A14.1 and adverse event datasets

[a] Race: W =White, B=Black, A=Asian, O=Other; Gender: M-male, F=Female; d/c=discontinued.

[b] Days are relative to start of treatment; for Study A3051035 start of treatment=start of open-label treatment.

* Treatment discontinuation due to this SAE

[c] Atrial fibrillation was first noted on Day 84, SAE triggered by hospitalization on Day 91.

[d] Varenicline/Placebo represents those subjects that were randomized to placebo after open-label varenicline treatment period in Study A3051035.

[e] Subject received a controlled-release formulation of varenicline

[f] Last known dose was at Day 143

Table 11-3: List of SAEs by System Organ Class and Treatment Group: Bupropion Treatment

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
BUPROPION								
Gastrointestinal disorders								
10025015-534 45/W/F	300 mg	Persistent intermittent bloody diarrhea	Diarrhea hemorrhagic	13	13	Perm D/C	Yes	Not Recovered
General disorders and administration site conditions								
103610091020 46/W/M	300 mg	Accidental death	Accidental death	222	85	None	Post therapy (137)	Death
Hepatobiliary disorders								
See PID 102810131030 in Infections/Hepatobiliary			Cholecystitis					
Infections and infestations								
102810071074 37/W/M	300 mg	Appendicitis	Appendicitis	94	85	None	Post therapy (9)	Recovered
102810101083 41/O/M	300 mg	Urinary tract infection	Urinary tract infection	95	84	None	Post therapy (11)	Recovered
Infections and Hepatobiliary disorders								
102810131030 69/W/F	300 mg	Septic shock Cholecystitis	Septic shock Cholecystitis	8	8	Perm D/C	Yes	Recovered
Injury, poisoning and procedural complications								
103610081039 23/W/F	300 mg	Gun shot would to left shoulder	Gun shot wound Intentional misuse	11	N/A	Multi Challenge Rechallenge	No	Recovered
103610081092 45/W/M	300 mg	Postoperative bleeding	Post procedural hemorrhage	46	N/A	Multi Challenge Rechallenge/	No	Recovered
Musculoskeletal and connective tissue disorders								
103610111039 42/ B/M	300 mg	Right leg pain below knee	Pain in extremity	60	N/A	None	No	Recovered
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
103610141094	300 mg	Breast cancer female	Breast cancer female	48	35	Perm D/C	Yes	Unknown

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
BUPROPION								
43/W/F								
Nervous system disorders								
10025005-55 18/O/M	300 mg	Possible seizure	Convulsion	30	28	None	Post therapy (2)	Recovered
		Syncope	Syncope					
10025010-384 31/W/F	300 mg	Generalized seizure	Convulsion	35	35	Perm D/C	Yes	Recovered
102810231069 47/W/M	300 mg	Grand mal seizure	Grand mal convulsion	20	20	Perm D/C	Yes	Recovered
102810211035 60/W/F	300 mg	Headache	Headache	69	72	Perm D/C	Yes	Recovered
Nervous system disorders/Injury, poisoning and procedural complications								
10025011-138	300 mg	Possible seizure	Convulsion	66	49	None	Post therapy	Recovered
52/W/F		Intentional overdose	Intentional misuse				(17)	
Pregnancy, puerperium and perinatal conditions								
103610131040 27/W/F	300 mg	Miscarriage	Abortion spontaneous	164	80	None	Post therapy (84)	Recovered
103610041031 32/W/F	300 mg	Ectopic pregnancy	Ectopic pregnancy	12	12	Perm D/C	Yes	Recovered
Skin and subcutaneous tissue disorders								
103610061014 40/A/M	300 mg	Angioedema	Angioineurotic oedema	18	19	Perm D/C	Yes	Recovered

Source: Section 2.7.4 Table A14.1 and adverse event datasets, Footnotes as for preceding table

Table 11-4: List of SAEs by System Organ Class and Treatment Group: Placebo Treatment

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
PLACEBO								
Cardiac disorders								
102810031045 55/B/M	PBO	Acute myocardial infarction	Acute myocardial infarction	28	27	Perm D/C	Yes	Recovered
102810181032 64W/M	PBO	Atrial fibrillation	Atrial fibrillation	85	85	None	No, EOT Visit	Not Recovered
103710101005 56/W/M	PBO	Worsening coronary artery disease	Coronary artery disease	114	N/A	MultiChallenge/ Rechallenge	No	Recovered
103610081084 74/W/M	PBO	Ischemic heart disease	Myocardial ishaemia	23	N/A	None	No	Recovered
Gastrointestinal disorders								
103610101072 38/W/M	PBO	Ruptured appendix	Appendicitis perforated	46	N/A	MultiChallenge/ Rechallenge	No	Recovered
General disorders and administration site conditions								
102810081124 53/B/M	PBO	Chest pain	Chest pain	78	N/A	MultiChallenge/ Rechallenge	No	Recovered
102810181080 62/W/M	PBO	Chest pain (under arms)	Chest pain	37	37	Perm D/C	Yes	Recovered

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
PLACEBO								
General disorders and administration site conditions/Injury, poisoning and procedural complications								
102810181032	PBO	Death unexplained	Death	324	85	None	Post therapy	Death
64/W/M		Fall	Fall				(239)	
		Collapse of lung	Collapse of lung					
		Elbow fracture	Upper limb fracture					
Immune system disorders								
103610121022 24/W/F	PBO	Allergic reaction	Hypersensitivity	7	7	Perm D/C	Yes	Recovered
Infections and infestations								
102810131005 21/W/F	PBO	Urinary tract infection	Urinary tract infection	10	N/A	MultiChallenge/ Rechallenge	No	Recovered
103610101273 49/B/F	PBO	Pneumonia	Pneumonia	69	67	Perm D/C	Yes	Recovered
See PID 00150030139 in Neoplasms benign, malignant and unspecified (incl cysts and polyps/Infections and infestation			Perianal abscess/ Postoperative infection					
Injury, poisoning and procedural complications								
10025011-446 37/W/M	PBO	Bilateral elbow torn ligaments	Ligament injury	N/A	42	None	Post therapy (N/A)	Recovered
103710061006 75/W/M	PBO	Spinal compression fracture	Spinal compression fracture	50	N/A	MultiChallenge/ Rechallenge	No	Recovered
See PID 102810181032 in General disorders and administration site conditions/Injury, poisoning			Collapse of lung/ Fall/Elbow fracture					
Neoplasms benign, malignant and unspecified (including cysts and polyps)								
102810031042 50/W/M	PBO	Lung cancer	Lung neoplasm malignant	24	30	Perm D/C	Yes	Recovered
Neoplasms benign, malignant and unspecified (including cysts and polyps/Infections and infestations								
00150030139	PBO	Anal cancer	Anal cancer	11	15	Perm D/C	Yes	Not Recovered
41/W/F		Perianal abscess	Perianal abscess					
		Post-op wound infection	Postoperative infection					
Nervous system disorders								
10075028460	PBO	Syncope	Syncope	2	2	Perm D/C	Yes	Recovered

PID/Treatment Age/Race/Gender[a]	Daily Dose	Investigator Event Term	MedDRA Event Term	Event Onset Day[b]	Last Dose Day[b]	Action Taken	DC Treatment* (Day)	Outcome
PLACEBO								
58/W/M								
Psychiatric disorders								
102810061065 32/W/M	PBO	Paranoid schizophrenia chronic state with acute exacerbation	Schizophrenia, paranoid type	15	31	Perm D/C	Yes	Not Recovered
10075024523 34/W/M	PBO	Suicide attempt (intentional drug overdose)	Suicide attempt	35	17	None	Post therapy (18)	Recovered
Reproductive system and breast disorders								
103610081011 34/W/F	PBO	Ruptured ovarian cyst	Ovarian cyst ruptured	70	N/A	None	No	Recovered
Respiratory, thoracic and mediastinal disorders								
102810131027 30/W/M	PBO	Mediastinal mass	Mediastinal mass	40	27	None	No	Recovered
Respiratory, thoracic and mediastinal disorders/Vascular disorders								
103710061017	PBO	Pulmonary embolism	Pulmonary embolism	15	14	Perm D/C	Yes	Recovered
61/W/M		Deep vein thrombosis left leg	Deep vein thrombosis					
Vascular disorders								
See PID 103710061017 in Respiratory, thoracic/Vascular			Deep vein thrombosis					

Source: Section 2.7.4 Table A14.1 and adverse event datasets, Footnotes as for preceding table

Table 11-5: Varenicline Phase-1 Studies (From Applicant Table-2, Section 2.7.4)

Study No, Objectives	Design	Dosage/ Regimen/ Duration	Comparator	No. of Subjects
STUDIES INCLUDED IN THE POOLED PHASE-1 STUDIES COHORT				
Bioavailability/Bioequivalence Studies				
A3051001 Food effect; Relative BA (succinate salt)	OL, 4-way XO	2 mg SD	None	11
A3051006 Food effect; Relative bioavailability (tartrate, succinate salt)	OL, 3-way XO	1 mg SD	None	15 smokers and non- smokers
A3051026 BE of Phase 3 / Phase 2 IR tablet (tartrate salt); dose proportionality of Phase 3 tablet	OL, 3-way XO	0.5, 1 mg SD	None	12
A3051030 BE of commercial IR tablet w/ Phase 3/Phase 2 IR (tartrate salt)	OL, 3-way XO	1 mg SD Commercial, Phase 2 and Phase 3 formulations	None	12
A3051042 Food effect of commercial IR tablet (tartrate salt)	OL, 2-way XO	1 mg SD	None	12
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
A3051004 ADME	OL	1 mg SD	None	6 3 smokers/3 nonsmokers
Special Populations				
A3051008 Renal, PK	OL, PG	0.5 mg QD 12 days	None	30 various renal impairment; Smokers and nonsmokers
A3051009 Elderly, PK	R, DB, PC, PG	1 mg QD, 1 mg BID 7 days	Placebo	24 smokers (≥ 65 yrs)
A3051027 SD Japanese	R, DB, PC, XO	0.25, 0.5, 1.0, 2.0 mg SD	Placebo	14
A3051029 SD PK Adolescents	R, ISBSO, PC, PG	0.5 mg single dose 1 mg single dose Placebo	Placebo	27 smokers (12-17 yrs)
A3051041 MD Japanese	R, DB, PC, PG	0.5, 1.0 mg BID 14 days	Placebo	24

Table 11-6: Varenicline Phase-1 Studies (Continued) (From Applicant Table-2, Section 2.7.4)

Study No, Objectives	Design	Dosage/ Regimen/ Duration	Comparator	No. of Subjects
STUDIES INCLUDED IN THE POOLED PHASE-1 STUDIES COHORT				
Drug Interaction Potential				
A3051010 Cimetidine renal interaction	OL, XO	2 mg varenicline SD + Cimetidine 300 mg QID x 5 days	Cimetidine 300 mg QID	12
A3051031 Digoxin PK Interaction	R, ISBSO, PC, 2-way XO	Digoxin 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
A3051038 Metformin PK/PD; renal interaction	R, OL, PC, 3-way XO	Metformin 500 mg BID + Varenicline 1 mg BID; x 7 days	Metformin 500 mg BID	30
Pharmacodynamic Studies				
A3051005 Relief of craving	R, DB, PC, XO	SD	Placebo	40
A3051014 Titration, improved tolerability	R, DB, PG, PC	VRN titr. Wk-1 to 1 to 1.5 BID, then 1mg BID, then Varenicline 1 mg BID X 2 wks then placebo X 1 week, OR Placebo for 2 weeks, then Varenicline 1.5 mg BID for 1 week (positive control)	Placebo	120
A3051015 AM/QHS tolerability	R, DB, 2-way XO	2 mg QAM 7 days; 2 mg QHS 7 days	None	44
Controlled-Release Formulation Studies				
A3051012-IRb	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-IRb	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)
NOT INCLUDED IN THE POOLED PHASE-1 STUDIES COHORT **Abuse Liability Assessment (Not Included in Pooled Phase-1 Data)**				
A3051039 Human abuse potential	R, DB, PC, XO	1, 3 mg SD	Amphetamine 15, 30mg, SD Placebo	45 smokers and nonsmokers

Table 11-7: Fixed-Dose, Placebo-Controlled Cohort, Number (%) of Patients with TEAE by SOC

MedDRA System Organ Class	< 1-mg BID N=505	>1-mg BID N=1070	Zyban® N=795	Placebo N=928
ANY BASELINE	438 (86.7)	885 (82.7)	633 (79.6)	719 (77.5)
GASTROINTESTINAL DISORDERS	223 (44.2)	554 (51.8)	270 (34.0)	284 (30.6)
PSYCHIATRIC DISORDERS	224 (44.4)	412 (38.5)	335 (42.1)	270 (29.1)
NERVOUS SYSTEM DISORDERS	219 (43.4)	388 (36.3)	244 (30.7)	279 (30.1)
INFECTIONS AND INFESTATIONS	175 (34.7)	277 (25.9)	201 (25.3)	275 (29.6)
MUSCULOSKELETAL/CONNECTIVE TISSUE	87 (17.2)	137 (12.8)	95 (11.9)	112 (12.1)
RESPIRATORY/THORACIC/MEDIASTINAL	77 (15.2)	137 (12.8)	101 (12.7)	109 (11.7)
GENERAL DISORDERS/ADMIN. SITE CONDS.	76 (15.0)	132 (12.3)	82 (10.3)	111 (12.0)
SKIN/SUBCUTANEOUS TISSUE DISORDERS	43 (8.5)	89 (8.3)	85 (10.7)	50 (5.4)
METABOLISM AND NUTRITION DISORDERS	55 (10.9)	79 (7.4)	56 (7.0)	41 (4.4)
INVESTIGATIONS	37 (7.3)	61 (5.7)	42 (5.3)	50 (5.4)
INJURY/POISONING /PROCEDURAL COMPLICAT	38 (7.5)	50 (4.7)	48 (6.0)	47 (5.1)
REPRODUCTIVE SYSTEM AND BREAST	14 (2.8)	30 (2.8)	13 (1.6)	28 (3.0)
EYE DISORDERS	24 (4.8)	25 (2.3)	13 (1.6)	18 (1.9)
CARDIAC DISORDERS	7 (1.4)	22 (2.1)	12 (1.5)	10 (1.1)
RENAL AND URINARY DISORDERS	12 (2.4)	20 (1.9)	19 (2.4)	9 (1.0)
VASCULAR DISORDERS	13 (2.6)	19 (1.8)	16 (2.0)	16 (1.7)
EAR AND LABYRINTH DISORDERS	11 (2.2)	12 (1.1)	27 (3.4)	7 (0.8)
IMMUNE SYSTEM DISORDERS	5 (1.0)	12 (1.1)	9 (1.1)	10 (1.1)
SURGICAL AND MEDICAL PROCEDURES	2 (0.4)	7 (0.7)	5 (0.6)	1 (0.1)
NEOPLASMS, BENIGN/MALIGNANT/UNSPEC.	1 (0.2)	5 (0.5)	3 (0.4)	1 (0.1)
BLOOD AND LYMPHATIC SYSTEM	0	2 (0.2)	5 (0.6)	0
ENDOCRINE DISORDERS	0	1 (0.1)	0	2 (0.2)
HEPATOBILIARY DISORDERS	0	0	1 (0.1)	0
SOCIAL CIRCUMSTANCES	1 (0.2)	0	0	(1 (0.1)
CONGENITAL/FAMILIAL/GENETIC DISORDERS	0	0	1 (0.1)	0
PREGNANCY	0	0	0	1 (0.1)

**Percent of females (only) Source: AE datasets

Table 11-8: Most Frequent AEs (≥ 5% Any Group) Phase 2/3 Fixed-Dose, Placebo-Controlled Studies, AND Varenicline-Treated Patients in All Completed Phase-2/3 Studies

	Fixed Dose		Placebo Controlled		ALL
Patient-Years Exposure →	VRN <1mg BID N=505 74.7	VRN 1mg BID N=1070 187.4	Zyban® N=795 130.0	Placebo N=928 149.7	VRN All N=3940 948.6
GASTROINTESTINAL	223 (44.2)	554 (51.8)	270 (34.0)	284 (30.6)	2081 (52.8)
Nausea	118 (23.4)	361 (33.7)	92 (11.6)	103 (11.1)	1260 (32.0)
Constipation	30 (5.9)	84 (7.9)	62 (7.8)	26 (2.8)	325 (8.2)
Flatulence	41 (8.1)	71 (6.6)	21 (2.6)	25 (2.7)	382 (9.7)
Dry mouth	26 (5.1)	58 (5.4)	70 (8.8)	40 (4.3)	176 (4.5)
Dyspepsia	30 (5.9)	58 (5.4)	27 (3.4)	32 (3.4)	275 (7.0)
NERVOUS SYSTEM	219 (43.4)	388 (36.3)	244 (30.7)	279 (30.1)	1325 (33.6)
HLGT HEADACHES	127 (25.1)	194 (18.1)	117 (14.7)	145 (15.6)	732 (18.6)
Headache	123 (24.4)	183 (17.1)	111 (14.0)	136 (14.7)	698 (17.7)
Dysgeusia	59 (11.7)	78 (7.3)	49 (6.2)	40 (4.3)	252 (6.4)
Dizziness	36 (7.1)	72 (6.7)	55 (6.9)	68 (7.3)	216 (5.5)
Disturbance in attention	30 (5.9)	54 (5.0)	38 (4.8)	47 (5.1)	151 (3.8)
PSYCHIATRIC	224 (44.4)	412 (38.5)	335 (42.1)	270 (29.1)	1632 (41.4)
Insomnia	93 (18.4)	178 (16.6)	180 (22.6)	118 (12.7)	754 (19.1)
Abnormal dreams	54 (10.7)	146 (13.6)	53 (6.7)	46 (5.0)	545 (13.8)
Irritability	45 (8.9)	69 (6.4)	46 (5.8)	62 (6.7)	256 (6.7)
Sleep disorder	14 (2.8)	57 (5.3)	46 (5.8)	24 (2.6)	145 (3.7)
Anxiety	29 (5.7)	39 (3.6)	44 (5.5)	47 (5.1)	120 (3.0)
GENERAL DISORDERS	76 (15.0)	132 (12.3)	82 (10.3)	111 (12.0)	582 (14.8)
Fatigue	30 (5.9)	62 (5.8)	29 (3.6)	48 (5.2)	280 (7.1)
INFECTIONS/INFESTATIONS	175 (34.7)	277 (25.9)	201 (25.3)	275 (29.6)	1155 (29.3)
Upper respiratory tract infection	32 (6.3)	92 (8.6)	67 (8.4)	114 (12.3)	277 (7.0)
Nasopharyngitis	68 (13.5)	73 (6.8)	45 (5.7)	73 (7.9)	362 (9.2)
METABOLISM & NUTRITION	55 (10.9)	79 (7.4)	56 (7.0)	41 (4.4)	318 (8.1)
Increased appetite	45 (8.9)	47 (4.4)	27 (3.4)	21 (2.3)	220 (5.6)
MUSCULOSKEL/CONNECTIVE	87 (17.2)	137 (12.8)	95 (11.9)	112 (12.1)	545 (13.9)
HLGT JOINT DISORDERS	31 (6.1)	42 (3.9)	28 (3.5)	28 (3.0)	138 (3.5)
Arthralgia	25 (5.0)	38 (3.6)	23 (2.9)	24 (2.6)	116 (2.9)

Source: Modified from applicant Tables 15, 21, A8.1a and A10.1a, Section 2.7.4

Table 11-9: Post-Treatment (Days 1 to 7) Adverse Events, Study A3051035

	End of Period-1		End of Period-2	
↓ SOC ↓ High Level Group Term ↓ Preferred Term	OL →DB 1-mg BID→ DB 1-mg BID	OL→DB 1-mg BID→ DB Placebo	DB→End-RX Post-RX DB 1-mg BID	DB→End-RX Post-RX DB Placebo
Evaluable→	**N=602**	**N=604**	**N=602**	**N=604**
With AEs (%)→	**80 (13.3)**	**122 (20.2)**	**54 (9.0)**	**33 (5.5)**
PSYCHIATRIC	**23 (3.9)**	**58 (9.6)**	**26 (4.3)**	**2 (0.3)**
Sleep Disorders and Disturbances	9 (1.5)	17 (2.8)	7 (1.2)	1 (0.2)
Insomnia/Initial insomnia	7 (1.2)	14 (2.3)	6 (1.2)	1 (0.2)
Personality Disord/Behaviour Disturb	5 (0.8)	22 (3.6)	10 (1.7)	1 (0.2)
Irritability	5 (0.8)	20 (3.3)	10 (1.7)	1 (0.2)
Anxiety Disorders and Symptoms	3 (0.5)	6 (1.0)	4 (0.7)	0
Changes in Physical Activity	3 (0.5)	6 (1.0)	3 (0.5)	0
Depressed Mood Disorder/Disturb	3 (0.5)	13 (2.2)	6 (1.0)	0
Depression	2 (0.3)	11 (1.8)	5 (0.8)	0
Psychiatric/Behavioral Symptoms	2 (0.3)	19 (3.1)	5 (0.8)	0
Nicotine dependence	2 (0.3)	19 (3.1)	5 (0.8)	0
Mood Disorders and Disturbances	1 (0.2)	3 (0.5)	1 (0.2)	0
NERVOUS SYSTEM	**7 (1.2)**	**16 (2.6)**	**3 0.5)**	**2 (0.3)**
Headaches	5 (0.8)	7 (1.2)	1 (0.2)	1 (0.2)
Mental Impairment Disorders	2 (0.3)	3 (0.5)	1 (0.2)	0
Neurological Disorders NEC	0	6 (1.0)	1 (0.2)	1 (0.2)
Dizziness	0	5 (0.8)	0	0
INFECTIONS/INFESTATIONS	**17 (2.8)**	**15 (2.5)**	**10 (1.7)**	**8 (1.3)**
Upper respiratory tract infection	2 (0.3)	6 (1.0)	2 (0.3)	1 (0.2)
METABOLISM/NUTRITION DIS.	**6 (1.0)**	**13 (2.2)**	**5 (0.8)**	**0**
Increased appetite	5 (0.8)	13 (2.2)	5 (0.8)	0
RESPIR/THORACIC/MEDIASTIN.	**6 (1.0)**	**9 (1.5)**	**2 (0.3)**	**0**
Respiratory Disorders NEC	4 (0.7)	8 (1.3)	1 (0.2)	0

Source: Modified from Tables a9-1a and a9-1b (Amendment #019, Study A3051037)

Table 11-10: Post-Treatment (Days 1 to 7) Adverse Events, All Completed Phase-2/3 Studies

↓ SOC ↓ High Level Group Term ↓ Preferred Term	All Varenicline All Doses	Completed Zyban® 150-mg BID	Phase-2/3 Placebo
Evaluable→ **With AEs (%)→**	**N=3940** **374 (9.5)**	**N=795** **66 (8.3)**	**N=1209** **59 (4.9)**
NERVOUS SYSTEM	**58 (1.5)**	**18 (2.3)**	**7 (0.6)**
Headaches	28 (0.7)	9 (1.1)	6 (0.5)
Mental Impairment Disorders	6 (0.2)	2 (0.3)	0
Neurological Disorders NEC	**24 (0.6)**	**8 (1.0)**	**2 (0.2)**
Dizziness	13 (0.3)	4 (0.5)	1 (0.1)
PSYCHIATRIC	**127 (3.2)**	**9 (1.1)**	**9 (0.7)**
Sleep Disorders and Disturbances	39 (1.0)	6 (0.8)	2 (0.8)
Personality Disord/Behaviour Disturb	**39 (1.0)**	**2 (0.3)**	**3 (0.2)**
Irritability/Aggression	39 (1.0)	2 (0.3)	2 (0.2)
Anxiety Disorders and Symptoms	**16 (0.4)**	**1 (0.1)**	**4 (0.3)**
Changes in Physical Activity	**8 (0.2)**	**0**	**0**
Restlessness	8 (0.2)	0	0
Depressed Mood Disorder/Disturb	**30 (0.8)**	**1 (0.1)**	**0**
Depression (includes one MDD)	26 (0.7)	1 (0.1)	0
Depressed mood	4 (0.1)	0	0
Psychiatric/Behavioral Symptoms	**27 (0.7)**	**0**	**0**
Nicotine dependence	27 (0.7)	0	0
Mood Disorders and Disturbances	**10 (0.3)**	**0**	1 (0.1)
Deliria (Incl. Confusion)	1	0	0
Confusional state	1	0	0
Schizophrenia/Psychotic Disorders	1	0	0
Psychotic disorder	1	0	0
INFECTIONS AND INFESTATIONS	**66 (1.7)**	**12 (1.5)**	**14 (1.2)**
METABOLISM/NUTRITION DISORD.	**19 (0.5)**	**1 (0.1)**	**0**
Increased appetite	19 (0.5)	1 (0.1)	0
RESPIR/THORACIC/MEDIASTIN.	23 (0.6)	6 (0.8)	5 (0.4)
Respiratory Disorders NEC	16 (0.4)	4 (0.5)	1 (0.1)
CARDIAC DISORDERS	**9 (0.2)**	**0**	**1 (0.1)**
Cardiac Arrhythmias	7 (0.2)	0	0
Palpitations	2 (0.1)	0	0

Source: Modified from Tables a9-3b and a9-3c (Amendment #019)

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/s/

Howard Josefberg
5/8/2006 07:57:07 PM
MEDICAL OFFICER

Celia Winchell
5/9/2006 11:02:10 AM
MEDICAL OFFICER
I concur in general with Dr. Josefberg's conclusions. See my review.