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APPLICATION NUMBER

NDA 21-928

Statistical Review(s)



U.S. Department of Health and Human Services
Food and Drug Administration

Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

(AN ADDENDUM)

NDA: 21928

Drug Name: CHAMPIX™ (Varenicline Tartrate) Tablets

Applicant: Pfizer Inc.

Indication: Smoking cessation

Biometrics Division: Biometrics Division 6

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This addendum is to correct the p-values of two tests for positive trend in tumor incidence in the original statistical review and evaluation report put into DFS on March 17, 2006.

In table 4 on page 6 of the original report, the p-values of the dose-response trend tests for benign hibernomas should be 0.3642 (was reported as 0.4351), and for malignant hibernomas should be 0.0349 (was report as 0.0034).

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIostatISTICS

Statistical Review and Evaluation CLINICAL STUDIES

NDA: 21-928/N000
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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Varenicline at the recommended dosing of 1.0 mg BID for 12 weeks appears to be superior to placebo for smoking cessation at the end of the treatment period, and at one year from the start of the treatment. There is evidence that varenicline is superior to Zyban.

In subjects who stopped smoking at the end of 12 weeks, an additional 12 weeks of treatment appears to be more beneficial than placebo in maintaining abstinence to the end of treatment and to one year from the start of treatment.

Furthermore, based on Studies 07 and 16, varenicline 0.5 mg BID appears to work as well as varenicline 1.0 mg BID, so that subjects who cannot tolerate varenicline 1.0 mg BID should take varenicline 0.5 mg BID.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The applicant, Pfizer Inc., is seeking FDA approval to market CHANTIX™ (varenicline tartrate immediate release tablet) 1.0 mg BID as an aid to smoking cessation. This submission included eight Phase 2/3 clinical trials with 5944 subjects (3940 varenicline, 795 Zyban, 1209 placebo). According to the applicant, six of the eight studies provided efficacy data in support of the smoking cessation indication (five of which were smoking cessation studies and one “maintenance” study). The focus of the statistical review will be on the two Phase 3 studies, Study 28 and Study 36, which were identical 12-week Zyban comparator trials; two Phase 2 studies, a 12-week fixed dose titration study (Study 07/18) and a 12-week flexible dose study (Study 16/19); and a “maintenance” study (Study 35). All these studies included double-blind post-treatment follow-up of smoking status to Week 52. The first three studies (Study 28, Study 36 and Study 07/18) were referred to as the “principal smoking cessation studies” by the applicant, because they claimed that these studies support the recommended varenicline dosing regimen of 1 mg BID for 12 weeks. They also claimed that studies 28 and 36 support a comparative claim against the only other currently-marketed non-nicotine smoking cessation product, Zyban. Study 35 examined the benefit of 12 additional weeks of treatment in successful abstainers and is referred to as the “Maintenance of Abstinence Study.” Although study 16/19 was considered supportive by the applicant, I am including this on my review for the reason that this study, along with Study 07/18 could provide us with information on the efficacy of 0.5 mg BID dose of varenicline as an alternative dosing regimen for subjects who cannot tolerate the 1.0 mg BID. It was documented in Study 07/18 that there were higher incidence of nausea-related dropouts among the varenicline 1.0 mg BID group compared to varenicline 0.5 mg BID group. I did not include Study 02 in my review because the study was short (seven weeks) compared to the others.

1.3 STATISTICAL ISSUES AND FINDINGS

There are no major statistical issues in this NDA submission that could not be handled by recoding and re-analyzing the data. Examples of these issues are the missing data imputation used by the applicant regarding the carbon monoxide measurements and on responders (abstinence) in the Phase 3 studies (28, 36 and 35), as well as the lack of prespecified procedure in handling multiple endpoints.

As mentioned in the review, the claims of “craving reduction,” “symptoms of withdrawal,” and/or “reduction of reinforcing effects of smoking” should not be granted because according to Jane Scott (SEALD reviewer), the content validity of both the “symptoms of withdrawal” and the “reduction of reinforcing effects of smoking” are not well documented, and the concept of “urge to smoke” is more appropriate for labeling compared to “craving reduction.”

Lastly, because the results in both study 28 and 36 were so similar, the medical reviewers and I felt the need to investigate whether the data submitted for the two studies were accurate. Based on the preliminary results from the Division of Scientific Inspection (DSI) investigation, it appears that the data from the two studies were accurate. Subjects who were randomly chosen and contacted by the DSI investigators confirmed their existence and the data reported on their study records were correct.

2 INTRODUCTION

2.1 OVERVIEW

Varenicline is a new chemical entity being developed for smoking cessation based on its properties as a partial agonist at $\alpha 4\beta 2$ -subtype neuronal nicotinic acetylcholine receptors. Currently, nicotine replacement therapy delivered as gum, patch, inhaler, or nasal spray and Zyban (sustained release bupropion), a drug originally approved as an atypical antidepressant (Wellbutrin), are the only pharmacotherapies approved for smoking cessation in the U.S.

The applicant, Pfizer Inc., is seeking FDA approval to market CHANTIX (varenicline tartrate immediate release tablet) as an aid to smoking cessation. This submission included eight Phase 2/3 clinical trials (Table 1) with 5944 subjects (3940 varenicline, 795 Zyban, 1209 placebo). According to the applicant, six of the eight studies provided efficacy data in support of the smoking cessation indication (five of which were smoking cessation studies). Of these, three Phase 2 studies constituted a dose-finding program that included a 7-week dose ranging study (A3051002 or Study 02), a 12-week fixed dose titration study (A3051007/1018, or Study 07/18) and a 12-week flexible dose study (A3051016/1019 or Study 16/19). In addition, two Phase 3 studies, namely A3051028 (Study 28) and A3051036 (Study 36), were identical 12-week Zyban comparator trials. The sixth efficacy study was the "maintenance" study A3051035; (Study 35) this study examined the benefit of an additional 12 weeks of treatment in subjects who had stopped smoking after an initial 12 weeks of open-label varenicline. All these studies included double-blind post-treatment follow-up of smoking status to Week 52. An additional Phase 3 study A3051037 (Study 37), collected safety data for varenicline exposures up to 52 weeks. Data from one small Phase 2 open-label pilot study conducted in Japan (A3051043 or Study 43) are also included in the combined Phase 2/3 studies safety database.

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Table 1: 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	N=126 N=126 N=125 N=126 N=123	6 weeks + 1 week placebo 7 weeks 7 weeks
			0.5 mg QD		
			1 mg QD		
			1 mg BID		
			Zyban ^b		
			Placebo		
					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	Randomized, Parallel Group, Double-blind, Placebo-controlled	Varenicline	N=124 N=129 N=124 N=129	12 week treatment period
			1 mg BID NT		
			1 mg BID T ^e		
			0.5 mg BID NT		
	A3051018 21 Dec 2001/ 21 July 2003		0.5 mg BID T ^e		Nontreatment follow-up to 1 yr from start of treatment
			Placebo		
Flexible-dose A3051016/1019 ^d United States [5]	A3051016 26 Dec 2001/ 18 Sept 2002	Randomized, Parallel Group, Double-blind, Placebo-controlled	Varenicline	N=157 N=155	12 week treatment period
			Flexible dosing (0.5 mg QD to 1mg BID)		
			Placebo		
	A3051019 19 Mar 2002/ 24 June 2003				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	N=349 N=329 N=344	12 week treatment period
			1mg BID		
			Zyban ^b		
			150 mg BID		Nontreatment follow-up to 1 yr from start of treatment
			Placebo		
Zyban Comparator A3051036 United States [14]	26 Jun 2003/ 21 Mar 2005	Randomized, Parallel Group, Double-blind, Placebo-controlled, Active Comparator	Varenicline	N=343 N=340 N=340	12 week treatment period
			1mg BID		
			Zyban ^b		
			150 mg BID		Nontreatment follow-up to 1 yr from start of treatment
			Placebo		
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	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
			Varenicline		
			1mg BID		
			DB		
			Varenicline		
			1 mg BID		
			Placebo		

Table 1 (Continued)

Protocol Type & Number Country [no of sites]	Study start/stop dates	Design	Treatment Group, Regimen, Number of Subjects ^a	Duration of Treatment/Study	
Safety: 52-Week Safety Study					
A3051037 United States [8] Australia [1]	13 Oct 2003/ 02 Mar 2005	Randomized, Parallel Group, Double-blind, Placebo-controlled	Varenicline 1 mg BID Placebo	N=251 N=126	52 weeks
Phase 2 Japanese Pilot Study					
A3051043 Japan [8]	26 May 2004/ 20 Aug 2004	Open-label	Varenicline 0.5 mg BID	N=30	7 weeks

BID = Twice per day; QD = Once daily; OL = Open label; DB = Double blind

^aNumber of subjects who received at least one dose of study drug

^bZyban was given at 150 mg QD for 3 days, then 150 mg BID to end of treatment

^c0.5 mg BID T: Varenicline was given at 0.5 mg QD for 7 days, then 0.5 mg BID to end of treatment; 1 mg BID T:

Varenicline at 0.5 mg QD for 3 days, 0.5 mg BID for 4 days, then 1 mg BID to end of treatment.

^dNontreatment follow-up was conducted under a separate protocol and reported as a separate clinical study report. Because the combined protocols constitute a single study, they are referred to as 3051007/1018 and A3051016/1019 in this Overview.

Source: Clinical Overview Module 2 (page 15-16)

According to the applicant,

All Phase 2/3 studies enrolled subjects who were smoking at least 10 cigarettes per day and who were motivated to stop smoking. Subjects set their own Target Quit Day one week from the start of treatment. During the treatment period, smoking assessments were made at weekly clinic visits. Smoking status was assessed using standardized questions regarding cigarette smoking and use of nicotine or tobacco-containing products; collected data were binary (yes/no). The strictest definition of abstinence was applied, so that even a puff of a cigarette, any tobacco use, or any use of a nicotine-containing product during a prespecified assessment period was considered a failure. Self-reported smoking status was confirmed at each clinic visit with exhaled carbon monoxide (CO) measurements (<=10 ppm).

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). All subjects received a National Cancer Institute educational booklet on smoking cessation at the baseline visit and up to 10 minutes of individualized counseling in accordance with the AHRQ guidelines at each visit during both the treatment and nontreatment periods.

The primary goal of varenicline treatment was to maximize the number of subjects who achieved stable abstinence at the end of the treatment period. Consequently the primary efficacy endpoint was complete abstinence during the last 4 weeks of the treatment period. Study A3051035 was an exception in that the primary efficacy endpoint was the maintenance of complete abstinence during the additional dosing period from Weeks 13 to 24.

All studies included double-blind post-treatment follow-up to one year from the start of treatment (Week 52). Clinic visits were further apart and interspersed with telephone contacts during the nontreatment phase. Smoking assessments were based on subject responses to standardized questions regarding use of cigarettes or tobacco-containing products, confirmed with CO measurement at clinic visits. In most studies, the nontreatment phase was included in the primary protocol. For administrative reasons, Studies A3051007 and A3051016 continued the double-blind follow-up as separate protocols, A3051018 and A3051019, respectively; the combined protocols are reported throughout the efficacy discussion as A3051007/1018 and A3051016/1019.

The Phase 2 program focused on identifying the dose and duration of treatment that would yield the highest stable abstinence rates at the end of treatment. The dosing strategies examined included: fixed doses of 0.3 mg QD, 1 mg QD and 1 mg BID for 6 weeks (A3051002); 0.5 mg BID and 1 mg BID for 12 weeks, with or without dose titration in Week 1 (A3051007/1018); and subject-directed flexible dosing 0.5 mg to 2 mg daily for 12 weeks

(A3051016/1019). The end-of-treatment and Week 52 smoking cessation rates and tolerability data from these studies, as well as the results of population pharmacokinetic/pharmacodynamic modeling analyses, identified 1 mg BID for 12 weeks (with titration over the first week) as the single varenicline dose regimen to be taken forward into Phase 3 studies.

The principal Phase 3 confirmatory efficacy studies, A3051028 and A3051036, included Zyban as an active comparator. Zyban (150 mg BID) was selected as the active comparator in Phase 3 because it is the most commonly prescribed oral pharmacotherapy for smoking cessation. Based on preliminary observations in Study A3051002, the comparison of varenicline and Zyban for efficacy in smoking cessation was specified a priori as a primary inference. Zyban was administered for 12 weeks to be consistent with the varenicline dosing interval. Because the Zyban treatment duration was within United States Product Insert (USPI) specifications (i.e., 7 to 12 weeks of treatment) but longer than that recommended by the Summary of Product Characteristics (SmPC) (7 to 9 weeks treatment), the Phase 3 efficacy studies were conducted in the United States.

Study A3051035 was conducted because published literature (Hughes 2003b; Ferguson 2005) as well as observations from the varenicline Phase 2 studies suggest that most relapses to smoking occur in the first several weeks/months following the end of treatment. This study examined whether an additional 12 weeks of dosing with varenicline 1 mg BID would increase long-term smoking abstinence rates. The study had three consecutive phases: a 12-week open-label treatment period in which all subjects received 12 weeks of varenicline 1 mg BID; a 12-week double-blind treatment phase in which subjects who achieved a minimum of 7 days abstinence at the end of the open-label period were randomized either to continue varenicline 1 mg BID or shift to placebo; and finally, double-blind nontreatment follow up to Week 52.

2.2 DATA SOURCES

This statistical review is based on data submitted in studies 28, 36, 35, 07, 18, 16 and 19.

The electronic submission of this NDA can be found at:

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3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The varenicline clinical development program comprised eight Phase 2/3 studies. Of these eight studies, six (five smoking cessation studies and one maintenance study) were classified by the applicant as the efficacy studies that would support the use of varenicline (1 mg BID) for smoking cessation in adult smokers motivated to quit.

The focus of the statistical review will be on the two Phase 3 studies, Study 28 and Study 36, which were identical 12-week Zyban comparator trials; two Phase 2 studies, a 12-week fixed dose titration study (Study 07/18) and a 12-week flexible dose study (Study 16/19); and a “maintenance” study (Study 35). All these studies included double-blind post-treatment follow-up of smoking status to Week 52. The first three studies (Study 28, Study 36 and Study 07/18) were referred to as the “principal smoking cessation studies” by the applicant, because they claimed that these studies support the recommended varenicline dosing regimen of 1 mg BID for 12 weeks. They also claimed that studies 28 and 36 support a comparative claim against the only other currently-marketed non-nicotine smoking cessation product, Zyban. Study 35 examined the benefit of 12 additional weeks of treatment in successful abstainers and is referred to as the “Maintenance of Abstinence Study.” Although study 16/19 was considered supportive by the applicant, I am including this on my review for the reason that this study, along with Study 07/18 could provide us with information on the efficacy of

0.5 mg BID dose of varenicline as an alternative dosing regimen for subjects who cannot tolerate the 1.0 mg BID. It was documented in Study 07/18 that there were higher incidence of nausea-related dropouts among the varenicline 1.0 mg BID group compared to varenicline 0.5 mg BID group. I did not include Study 02 in my review because the study was short (seven weeks) compared to the others.

3.1.1 STUDY DESIGN AND ANALYSIS PLAN

In each of the principal smoking cessation studies, varenicline was administered for 12 weeks at 1 mg BID with subsequent nontreatment follow-up to one year from the start of treatment (i.e., 12 weeks + 40 weeks). The applicant claims that

The dose and duration of varenicline treatment were selected based on the results of Phase 2 Studies A3051002, A3051007/1018, and A3051016/1019. Based on a comparison of titrated and nontitrated regimens in Study A3051007/1018, Phase 3 studies titrated varenicline from 0.5 mg QD to 1 mg BID during the first week of treatment to improve tolerability. The one-year follow-up period from the start of treatment is a precedented design element, widely used in the smoking cessation field (Jorenby 1999; Maguire 2001; West 2001) and recommended by smoking cessation experts (Hughes 2003a, West 2005). To standardize the level of counselling within and across studies, all subjects received a National Cancer Institute educational booklet on smoking cessation at the baseline visit and up to 10 minutes of individualized counselling at each visit in accordance with the AHRQ guidelines. The level of behavioral support provided in the varenicline program is considered representative of that afforded patients in clinical practice.

The applicant further claims that because of the positive results obtained from a post hoc comparison of varenicline and Zyban in the Phase 2 study A3051002, they designed two identical Phase 3 trials (A3051028 and A3051036) to demonstrate the superior efficacy of varenicline compared with Zyban. However, in order to support a comparative claim against Zyban, it is important that the population to which the trial is being conducted 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. Dr. Winchell found that the protocols indicate that these conditions were met. Dr. Winchell's conclusion was "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". Furthermore, according to Dr. Winchell, the method used to blind the Zyban does not affect the performance of Zyban.

Nicotine use questions were used to assess smoking status in all the efficacy trials; collected data were binary (yes/no). The nicotine use questionnaire was formalized as the Nicotine Use Inventory in Phase 3 studies. For both the treatment and nontreatment intervals, the applicant defined smoking cessation in terms of absolute abstinence (i.e., "not a puff"). Self-reports of smoking abstinence were also confirmed biochemically at clinic visits by exhaled carbon monoxide (CO) measurements of ≤ 10 ppm. According to the applicant, this value is based on the Society for Research on Nicotine and Tobacco (SRNT) Subcommittee on Biochemical Verification. Subjects visited the clinic weekly during the treatment phase of all smoking cessation studies and less frequently (minimum interval: 8 weeks) during the nontreatment period.

Four major endpoints were derived from the nicotine use questions: 4-week Continuous Quit Rate (CQR), Continuous Abstinence (CA) rate, Long-term Quit Rate (LTQR), and 7-day point prevalence.

The primary endpoint in all the efficacy studies is the 4-week CQR, defined as the proportion of subjects who maintained absolute abstinence between weeks 9 – 12 (4-week end of treatment) confirmed biochemically at clinic visits by exhaled CO measurements ≤ 10 ppm.

Continuous abstinence (CA) is designated as the secondary endpoint, 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.

In addition to CA, the varenicline program designated LTQR as a second measure of long-term abstinence, which the applicant claims would recognize the reality of occasional lapses in abstinence. This endpoint, which allows a limited number of lapses (up to 6 days of smoking during the nontreatment period through Week 52), reflects the recommendation of West (2005) for a less stringent outcomes measure than continuous “not a puff” abstinence.

The 7-day point prevalence endpoint was included in these trials because it is widely used in the literature to report smoking cessation rates and thereby allows for a direct comparison between varenicline and other smoking cessation pharmacotherapies.

Although it is common in epidemiology to distinguish point prevalence from period prevalence, in this context the term *point prevalence* is redundant. The abstinence being calculated is always at a point in time, so that a term such as *weekly abstinence* would suffice. Nonetheless, I will use either *abstinence by visit* or *weekly abstinence* in place of *weekly point prevalence abstinence*, as well as *abstinence at week 52* in place of *point prevalence abstinence at end of study* (i.e. Week 52).

Three additional subject-reported endpoints were explored in all efficacy studies. These are craving, withdrawal, and the reinforcing effects of smoking.

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.

For exploratory purposes, it is acceptable to examine these subject-reported endpoints. However, as stated in the end-of-phase 2 meeting on December 9, 2002, there is a need to verify the validity and reliability of the instruments used. According to the findings of Dr. Jane Scott (Study Endpoints and Label Development or SEALD reviewer),

The concept “urge to smoke” is more appropriate for labeling than the term “craving. Furthermore, 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.

Therefore, the claims of “craving reduction”, “symptoms of withdrawal” and/or “reduction of reinforcing effects of smoking” should not be granted. However, if there are consistent and compelling findings to suggest a reduction in the “urge to smoke”, this claim is appropriate for labeling.

The applicant describes the methods of analysis as follows:

The primary efficacy analyses set is the All Subjects population, defined as all randomized subjects who took at least one dose (including partial doses) of randomized study medication. In addition to this primary “Full Analysis Set” (ITT), efficacy analyses for primary and key secondary endpoints were secondarily conducted for

Evaluable Subjects, and Completer Subjects “Per Protocol” populations. Data were summarized at each collection visit using descriptive statistics based on data from the All Subjects population.

All measures of abstinence used in the study were analyzed as binary data. Subjects were classified as responders or non-responders for each parameter and time point. In the analyses of these parameters, subjects who withdrew from the study and were lost to follow-up for subsequent visits were assumed to be smokers (non-responders) for the remainder of the study, regardless of their smoking status at the last recorded visit.

Logistic regression models were used to evaluate treatment effects for these binary endpoints. The models included terms for treatment group and center. The logistic regression was chosen for the inferential analyses both to provide direct model-based estimates of the odds ratio and to allow subsequent exploratory evaluation of other covariates (eg, gender, age, and smoking status as well as interactions of these covariates with treatment) in secondary models. Treatment by center interaction was investigated, though the primary model from which inferential statistics were derived excludes interactions such as treatment by center. The procedure for handling small centers (<2 subjects in any treatment group) was not required for any of the Phase 2/3 studies. Hypothesis testing was carried out using the likelihood ratio chi-squared statistic, with all tests being two-sided at $\alpha=0.05$.

Binary data pooled across studies were analyzed using the same methodology described above for individual studies, with the only difference being that the logistic model included study, instead of center, in the primary model.

The secondary efficacy endpoints include patient reported craving, withdrawal, and reinforcing effects of smoking. The Urge to Smoke item under MNWS for craving and the Negative Affect and Restlessness subscales for withdrawal were prespecified as the subscales of primary interest. For each endpoint, the hypothesis was that varenicline would result in reduced values relative to placebo. The Total Craving Score from QSU-Brief, where the hypothesis was that, relative to placebo, varenicline would result in a reduced total score, was prespecified as the endpoint of primary interest. Lastly, Smoking Satisfaction and Psychological Reward, where the hypothesis was that, relative to placebo, varenicline would result in a reduction in these reinforcing effects of smoking, were prespecified as the subscales of primary interest.

In Phase 3, data from all subscales were subjected to statistical testing as a composite over Weeks 1 to 7. This differs from Phase 2 methodology where the data were subjected to statistical testing by visit (i.e., Week 1, 2, etc). Inferential analyses used data collected at each planned weekly study visit occurring after the planned time of smoking cessation and through the first 7 weeks of the treatment phase. The analysis was a repeated-measures analysis over time applying PROC MIXED in SAS (with an unstructured covariance) with the post-treatment measure as the dependent variable, treatment group as the explanatory variable of interest, baseline measure, center and visit as covariates, and interaction of treatment by visit. Model estimates on the average effect were obtained by contrasting the average of weeks 1 to 7 between drug and placebo in an ESTIMATE statement. If the model using unstructured covariance did not converge, compound symmetry was used for the covariance structure of subjects over time. Although certain subscales were selected, a priori, to test the effect of varenicline on craving, withdrawal, and the reinforcing effects of smoking in Phase 3, data for all scales comprising the three questionnaires were analyzed and the full results are presented within the clinical study reports.

The analyses pooling data across studies used the same methodology described above for the individual studies, a repeated-measures analysis over time, with the only difference being that study (instead of center) was a covariate in the primary model.

The principal smoking cessation studies, A3051028, A3051036, and A3051007/1018 all had prespecified multiple comparisons of primary interest. In order to preserve the family-wise type I error rate (at $\alpha=0.05$) for multiple contrasts within each endpoint, a step-down procedure was employed for the analysis of the primary and key secondary endpoints. The order of comparisons was specified in the protocols and analysis plans. Based on the predefined order of comparisons, statistical significance is declared, for each pair-wise comparison in the predefined order until $p > 0.05$, at which time all subsequent comparisons are considered non-significant regardless of p-value.

The primary inference for Studies A3051028 and A3051036 was prespecified as the comparison of varenicline 1 mg BID with both placebo and with Zyban for smoking cessation. The hierarchy of comparisons within each endpoint was (1) varenicline vs placebo, and (2) varenicline vs Zyban.

In order to conclude statistical superiority of varenicline versus both placebo and Zyban for a given endpoint, both comparisons 1 and 2 required p-values < 0.05 .

Study A3051007/1018 used two doses of varenicline (1 mg BID and 0.5 mg BID) and specified two time points for the primary efficacy parameter (4-Week CQR for Weeks 9-12 and for Weeks 4 – 7 for titrated and nontitrated groups combined). The order of comparisons of active treatment versus placebo was (1) Weeks 9 – 12; 1 mg BID, (2) Weeks 4 – 7; 1 mg BID, (3) Weeks 9 – 12; 0.5mg BID, and (4) Weeks 4 – 7; 0.5mg BID.

No adjustments for multiple comparisons were made for the other secondary measures of abstinence.

No adjustments for multiple comparisons were made for the secondary measures of craving, withdrawal, and the reinforcing effects of smoking; however, the multiplicity was substantially reduced by a priori selection of subscales and times to be analyzed and of which were considered of primary interest.

Although the applicant prespecified a step-down procedure in order to preserve the family-wise type I error rate for multiple contrasts, this procedure is only employed within each endpoint. There is no prespecification on how type I error rate could be preserved in testing of multiple secondary endpoints.

Another issue I noticed relates to the secondary outcome variables involving the patient-reported outcomes (e.g. craving, withdrawal, and the reinforcing effects of smoking). Even though there is *a priori* selection of subscales and times to be analyzed for these secondary measures, multiplicity is still an issue and a procedure to control the Type I error should have been prespecified.

In terms of missing data, 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:

Nicotine Use Data

For Phase 3 studies, 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).

In Phase 2 studies, various imputation methods were applied to missing data. In Studies A3051007 and A3051016, subjects missing the required Nicotine Use Questions response(s) for a single visit within the 4-week period of interest were still considered responders for that visit if they were responders at the next visit and had negative CO data (i.e., ≤ 10 ppm) at both the visit before and the visit after the missed visit. Subjects missing data for more than one visit in the 4-week period were considered non-responders for that period. No attempt was made to impute missing data from subject diaries or other weekly interview questions. The primary efficacy measure for Study A3051002 was the 4-week floating window 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. In the case of missing diary data, smoking status was imputed based on the weekly report of smoking "since the last study visit".

For Point Prevalence of abstinence (7-days), missing weekly interview questions of whether the subject has 'smoked in the last 7 days' were not imputed in Phase 2 or Phase 3 studies. For the LTQR, if the number of days smoked was missing for a subject visit, the CA responder status of the subject at that visit determined the imputation. If the subject was a responder, the number of days was imputed as 0; if the subject was a non-responder, the number of days was imputed as 7. Thus a CA non-responder with a missing number of days smoked was also a LTQR non-responder.

CO Data

For Phase 3 studies, missing CO was imputed as negative (i.e., not disqualifying the subject as a responder).

Missing CO values in Phase 2 studies were imputed based on CO measurements at the previous visit and at the subsequent visit (both had to be ≤ 10 ppm); if there were more than one missing CO measurement in the series, the subject was considered a non-responder for that week.

Measures of Craving, Withdrawal, and the Reinforcing Effects of Smoking

If, at a time point a subject's response on greater than 50% of the individual questions of a subscale were missing, the subscale score for that subject was designated as missing for that time point. Otherwise, the score was calculated as the average of the non-missing item scores.

After consulting with Dr. Winchell, we find that the methods of imputation for the Phase 3 studies are unacceptable. After redoing the analysis of the two Phase 3 studies, I believe that subjects who had missing data for more than one visit in the four-week period can still be considered responders for that period if they were responders at the next non-missing visit. Furthermore, missing CO was imputed as negative. Dr. Winchell and I think the methods of imputation should be as in the Phase 2 studies (07 and 16) where subjects who had missing data for more than one visit in the four-week period were considered non-responders for that period, and missing CO values were imputed based on CO measurements at the previous visit and at the subsequent visit.

3.1.2 RESULTS OF SMOKING CESSATION STUDIES (TAKEN FROM APPLICANT'S STUDY REPORT)

Brief descriptions of the five individual studies relevant to the efficacy evaluation of varenicline are provided below. A summary of the efficacy analysis results in these studies are also provided.

3.1.2.1 Subject Disposition across studies

A short description of patient disposition of the individual studies is described below. The primary population for all efficacy and safety analyses in all five studies was the All Subjects population (treated). Efficacy analyses for primary and secondary endpoints were also conducted using data for the Evaluable population (i.e. < 14 days study medication in the first 21 days), and Completer subjects population (i.e. took $< 80\%$ of 12-week treatment), which according to the Applicant, "to support the robustness of the conclusions made using data for the All Subjects population."

3.1.2.1.1 Zyban Comparator Studies

Studies 28 and 36 were identical 12-week Zyban comparator trials in which the applicant was able to demonstrate the efficacy of varenicline 1.0 mg BID compared to placebo and compared to Zyban on abstinence from tobacco use in cigarette smokers.

As background, 1483 subjects were screened in Study 28 of whom 458 subjects were not randomized. Three subjects assigned to varenicline did not take any study drug, giving 1022 subjects (varenicline 349, Zyban 329, and placebo 344) treated with study drug (Appendix 7, Table 7.1). More than half the subjects in each treatment group completed the study: 61%, 56%, and 54% in the varenicline, Zyban and placebo groups, respectively. Note that subjects could discontinue study medication but remain in the study. Therefore, in the context of subject disposition, the applicant stated that "completed the study refers to the number of subjects who participated in the study for the full 52 weeks as recorded in the Disposition page of the End of Study eCRF, whether or not they completed 12 weeks of dosing during the treatment phase". Most discontinuations occurred during the treatment phase, in which 26%, 32%, and 38% of subjects in the varenicline, Zyban, and placebo groups, respectively, discontinued the study. During the treatment phase, the

most common reasons for premature withdrawal were lost to follow-up, refusal to participate further, and adverse events. There were 46 subjects (varenicline 11, Zyban 13, and placebo 22) identified to have significant protocol violations. The number of subjects in the varenicline group given in the study report was 12. However, when cross-checked with the patient listing found in the study report's Appendix B0.1, one subject (10031025) was miscoded as varenicline, but should be in the Zyban group. The most common violation was the "use of prohibited medication other than NRT" for > 7 days during the treatment phase.

Similarly, in Study 36, 1413 subjects were screened of whom 386 subjects were not randomized. Four subjects did not take any study drug, giving 1023 subjects (varenicline 343, Zyban 340, and placebo 340) that were treated with study drug. The only difference from Study 28 is the proportion of subjects who completed the study. In this study, almost two-thirds of the subjects in each treatment group completed the study: 70%, 65%, and 60% in the varenicline, Zyban and placebo groups, respectively. Like Study 28, subjects could discontinue study medication, but remain in the study. Most discontinuations occurred during the treatment phase, in which 24%, 29%, and 35% of subjects in the varenicline, Zyban, and placebo groups, respectively, discontinued the study. During the treatment phase, the most common reasons for premature withdrawal were also lost to follow-up, refusal to participate further, and adverse events. There were also 46 subjects (varenicline 17, Zyban 16, and placebo 13) identified to have significant protocol violations. The most common violation is the "use of prohibited medication other than NRT" for > 7 days during the treatment phase.

3.1.2.1.2 Maintenance of Abstinence Study

Study 35 is a 52-week multicenter study evaluating the safety and efficacy of varenicline for the maintenance of smoking cessation.

As background, 2416 subjects were screened and 1928 were assigned to open-label treatment (Appendix 7, Table 7.2). After being assigned to treatment, one subject refused to participate further and did not take any study medication. Of the 1927 subjects who took the study medication, 1210 (63%) entered the double-blind phase. The most frequent reason for withdrawal from the open-label treatment phase was adverse events (10%), followed by subject's refusal to participate further (8%), other¹ (7%), and lost to follow-up (7%).

Of the 1927 subjects who took the study medication in the open-label phase, 1236 (64%) subjects achieved abstinence for at least the last seven days of the open-label treatment phase and 1210 subjects met all other eligibility criteria and were randomized to double-blind study medication (varenicline 603, placebo 607) according to the applicant. Re-analysis of the data showed that 1239 (64%) subjects achieved abstinence for at least the last seven days of the open-label treatment phase. Two of the 1210 subjects randomized to double-blind study medication did not achieve abstinence for at least the last seven days (or at Week 12) of the open-label treatment phase (varenicline 1, placebo 1). Because one subject randomized to varenicline and three subjects randomized to placebo did not take any double-blind study medication, therefore, in the double-blind phase, a total of 601 subjects were treated with varenicline and 603 subjects were treated with placebo.

At least 75% of the randomized subjects in each treatment group completed the study (through week 52): 82% and 77% in the varenicline and placebo groups, respectively. Note that subjects could discontinue study medication, but remain in the study. Approximately half of the discontinuations occurred during the treatment phase. At least 8% and 15% of subjects in the varenicline and placebo groups, respectively,

¹ Other: Did not meet open-label inclusion/exclusion criteria 31%; Did not meet double-blind entrance criteria 47%; Other reason like personal, noncompliance, started prohibited medication 22%

discontinued the study during the treatment phase, and around 10% and 8% of subjects in the varenicline and placebo group, respectively, discontinued the study during the non-treatment phase. During both the treatment and non-treatment phase, the most common reasons for premature withdrawal were refusal to participate and lost to follow-up.

There were 87 subjects (open-label varenicline 44, double-blind varenicline 15, and double-blind placebo 28) identified to have significant protocol violations. The number of subjects in the double-blind placebo group given in the study report was 24, however, when cross-checked with the patient listing found in the study report's Appendix B0.1, there were 29 subjects found to be protocol violators. Because two subjects (varenicline 1, placebo 1) did not achieve abstinence for at least the last seven days of the open-label treatment phase, these two subjects were not counted in the double-blind treatment phase. Thus, protocol violators were 15 in the varenicline group (instead of 16) and 28 in the placebo group (instead of 29). The most common violation is the "use of prohibited concomitant medication".

3.1.2.1.3 Phase 2 Studies

Study 07 is a 12-week double-blind, placebo-controlled, randomized, multicenter study evaluating the safety and efficacy of four dosing strategies for varenicline (0.5 mg BID, titrated 0.5 mg BID, 1 mg BID, and titrated 1 mg BID) in smoking cessation. In order to measure the long-term efficacy of varenicline following 12 weeks of treatment in Study 07, the applicant conducted a forty-week, double-blind, multicenter, nontreatment extension (Study 18). Therefore, Week 13 is 13 weeks after Baseline in Study 07, and one week after entry into the follow-up Study 18.

As background, 980 subjects were screened and 647 were assigned to treatment (Appendix 7, Table 7.3). After being assigned to treatment, 20 subjects did not take any study medication. Thus a total of 627 subjects took study medication and were evaluated for safety and efficacy (varenicline 0.5 mg 253, varenicline 1.0 mg 253, placebo 121). In the active treatment groups, 188 (74%) subjects in the varenicline 0.5 mg group completed the study, and 195 (77%) subjects completed the study in the varenicline 1.0 mg group; whereas 60% of placebo-treated groups completed the study. The most frequent reason for withdrawal was subject defaulted (i.e. subject withdrew consent or lost to follow-up). Note that subjects could discontinue study medication, but remain in the study. Therefore, in the context of subject disposition, the sponsor stated that "completed the study refers to the subjects having completed the study" (i.e. continued in study through the Week 12 visit), rather than having completed 12 weeks of dosing with study medication. The rates of early discontinuation of study medication are 33% for varenicline 0.5 mg, 36% for varenicline 1.0 mg, and 45% for placebo. Like study discontinuation, subject defaulted was the most frequent reason for early discontinuation of study in both varenicline 0.5 mg BID dosage group and the placebo group, while adverse events were the most frequent reason for early discontinuation in the 1.0 mg BID dosage group.

There were 90 subjects (varenicline 0.5 mg 35, varenicline 1.0 mg 34, and placebo 21) identified to have significant protocol violations. The most common violation was subject receiving less than 14 days of study medication in the first 21 days of study.

Three hundred ninety eight subjects (63%) entered the 40-week nontreatment phase (varenicline 0.5 mg BID 165, varenicline 1.0 mg BID 179, and placebo 54). Of the 398 subjects, 309 subjects completed the study (varenicline 0.5 mg BID 123, varenicline 1.0 mg BID 146, and placebo 40). Subjects who discontinued from this extension study defaulted either by withdrawing consent, or were lost to follow-up.

Study 16 is another Phase 2 study that could provide us with information about the efficacy of 0.5 mg BID. This is a 12-week, double-blind, placebo-controlled, randomized, multicenter study evaluating the safety and efficacy of a flexible-dosing strategy for Varenicline (0.5 mg to 2.0 mg total daily dose, administered BID) in smoking cessation. In order to measure the long-term efficacy of varenicline following 12 weeks of treatment in Study 16, the applicant conducted a forty-week, double-blind, multicenter, nontreatment extension (Study 19). Therefore, Week 13 is 13 weeks after Baseline in Study 16, and one week after entry into the follow-up Study 19. In this study, the dosing regimen is as follows:

Study Medication

Test Product/Strength	FID #	Lot #
CP-526,555 (0.5 mg tablet)	G02306AA	ED-G-286-701
Placebo (0 mg tablet)	G02328AA	ED-G-106-301

Dosing: CP-526,555: 0.5 mg QD for 3 days, followed by 0.5 mg BID for 4 days; after Day 7, dosing schedule was flexible (minimum of 0.5 mg QD, maximum of 1.0 mg BID)
 Placebo: one tablet QD for 3 days, followed by one tablet BID for 4 days; after Day 7, dosing schedule was flexible (minimum of one tablet QD, maximum of 2 tablets BID)

Duration: 12 weeks for CP-526,555 and placebo

As background, 434 subjects were screened and 320 were assigned to treatment (Appendix 7, Table 7.4). After being assigned to treatment, eight subjects did not take any study medication (varenicline 3, placebo 5). Thus a total of 312 subjects took study medication and were evaluated for safety and efficacy (varenicline 157, placebo 155). In the active treatment groups, 122 (78%) subjects in the varenicline group completed the study, while 71% of placebo-treated groups completed the study. Like Study 07, the most frequent reason for withdrawal was subject defaulted (i.e. subject withdrew consent or lost to follow-up). Note that subjects could discontinue study medication, but remain in the study. Therefore, in the context of subject disposition, the sponsor stated that “completed the study refers to the subjects having completed the study” (i.e. continued in study through the Week 12 visit), rather than having completed 12 weeks of dosing with study medication. The rates of early discontinuation of study medication are 31% for varenicline, and 34% for placebo. Like study discontinuation, subject defaulted was the most frequent reason for early discontinuation of study in both varenicline group and the placebo group.

There were 37 subjects (varenicline 13, and placebo 24) identified to have significant protocol violations. The most common violation was subject receiving less than 14 days of study medication in the first 21 days of study.

Two hundred twenty subjects (71%) entered the 40-week nontreatment phase (varenicline 120, and placebo 100). Of the 220 subjects, 189 subjects completed the study (varenicline 100, and placebo 89). Majority of subjects who discontinued from this extension study defaulted either by withdrawing consent, or were lost to follow-up.

3.1.2.2 Demographic and Baseline Characteristics

In all five studies, the demographic and baseline characteristics were comparable across treatment groups.

3.1.2.2.1 Zyban Comparator Studies

In both studies 28 and 36, the demographic characteristics and baseline characteristics were similar across treatment groups (Appendix 7, Table 7.5). In Study 28, 54% of the population were male, 79% were white, and average age was 42 (range 18 – 75 years), while in study 36, 58% were male, 84% were white, and the average age was 43 (18 – 75 years). Smoking history was also similar across treatment groups in both studies 28 and 36, with subjects representing a population of smokers who on average had smoked for the previous 24 years (range 1 – 61 years) and 26 (range 2 – 60 years), respectively, and had smoked an average of 21 cigarettes and 22 cigarettes per day over the previous month, respectively. Subjects' scores on the Fagerstrom test for nicotine dependence and histories of attempts to stop smoking were comparable across treatment groups in both studies. The longest period of abstinence during the year before the study was an average of 5 – 6 days for all treatment groups (range 0 – 97 days) in Study 28. Slightly longer periods of abstinence were recorded in Study 36 with an average of 6 – 8 days for all treatment groups (range 0 – 180 days).

In Study 28, approximately 73% of subjects in each treatment group reported using one or more medications prior to the study. Meanwhile, approximately 80% of subjects in each treatment group took at least one concomitant medication. The most commonly reported medications used prior to the study or concomitant usage included analgesics, anti-inflammatory and antirheumatic products, other gynecologicals, and topical products for joint and muscular pain. Usage of each of these therapeutic classes was similar across treatment groups. The median duration of treatment was 84 days in each of the 3 treatment groups. The sponsor calculated the treatment duration from the first day of treatment through the last day of treatment, without deducting for missed doses (Appendix 7, Table 7.6)

In Study 36, approximately 80% of subjects in each treatment group reported using 1 or more medications prior to the study. From 80 to 85% of subjects in each treatment group took at least one concomitant medication. Like Study 28, the most commonly reported medications used prior to the study, as well as to some extent concomitant usage were analgesics, anti-inflammatory and antirheumatic products, other gynecologicals, and topical products for joint and muscular pain. Usage of each of these therapeutic classes was also similar across treatment groups. Like Study 28, the median duration of treatment was 84 days in each of the 3 treatment groups. The sponsor calculated the treatment duration from the first day of treatment through the last day of treatment, without deducting for missed doses (Appendix 7, Table 7.7).

3.1.2.2.2 Maintenance of Abstinence

Like studies 28 and 36, the demographic characteristics and baseline characteristics were similar across treatment groups during the double-blind phase, as well as to those in the open-label phase (Appendix 7, Table 7.8). In the open-label phase, 49% of the population was male, 96% were white, and the average age was 44 (range 18 – 75 years). Likewise in the double-blind phase, around 49% were male, 97% were white, and the average age was 45 (18 – 73). Smoking history was also similar across treatment groups in the double-blind phase, as well as to those in the open label phase with subjects representing a population of smokers who on average had smoked for the previous 28 years (range 2 – 59 years), and had smoked an average of 21 – 22 cigarettes per day over the previous month, respectively. Subject's scores on the Fagerstrom test for nicotine dependence and histories of attempts to stop smoking were comparable across treatment groups in both open-label and double-blind treatment phase. The longest period of abstinence during the year before the study was an average of 7 days in the open-label phase (range 0 – 200 days), and average of 8 days in the double-blind phase (range 0 – 90 days).

Approximately 47% of subjects treated in the open-label reported using one or more medications prior to the study. Prior medication use in subjects enrolled in double-blind varenicline and double-blind placebo groups were comparable to each other and to those in the open-label phase. Meanwhile, approximately 70% of subjects took at least one concomitant medication during the open-label phase. Like studies 28, and 36, analgesics, and anti-inflammatory and anti-rheumatic products were also the most frequently reported medications used. Use of concomitant medications in subjects enrolled in double-blind varenicline and double-blind placebo groups were comparable to each other and to those in the open-label phase. The median duration of treatment was 84 days in both open-label and double-blind phase.

3.1.2.2.3 Phase 2 Studies

According to the applicant, the demographic and baseline characteristics of Study 07 (Appendix 7, Table 7.9) are the following:

Approximately 81% of subjects were white, and the mean age was approximately 43 years (range 18-65). Smoking history was similar across treatment groups, with subjects representing a population of smokers who on average had smoked about 21 cigarettes per day for an average of approximately 25 years. 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. The longest period of abstinence during the past year was on average about 8 days. Subjects' degree of nicotine dependence, as measured by baseline Fagerström Test for Nicotine Dependence score, was similar across treatment groups, with mean values ranging from 5.35 to 5.77.

Moreover, according to the applicant, treatment groups were comparable with regard to baseline values for the self-administered rating scales such as the Minnesota Nicotine Withdrawal Scale for craving and withdrawal symptoms, as well as the Smoking Effects Inventory. Medical histories, including past and present conditions and medications and nondrug treatments prior to the start of the study, were also comparable across treatment groups, according to the applicant. Like the Phase 3 studies, the median duration of study drug treatment was similar across all treatment groups, ranging from 80 to 84 days.

According to the applicant, the demographic and baseline characteristics of Study 16 (Appendix 7, Table 7.10) are the following:

Most subjects were white (91%), male (52%), and the mean age was approximately 42 years. Smoking history was similar across treatment groups; subjects had smoked about 20 cigarettes per day for approximately 25 years. More than half of the subjects in each treatment group had made at least 3 prior attempts to quit smoking, and the frequency distribution of specific methods used in these attempts was similar for both treatment groups. The longest period of abstinence during the past year was on average about 8 days. Medical histories, including past and present conditions and medications and non-drug treatments prior to the start of the study, were comparable for both treatment groups.

Moreover, according to the applicant, treatment groups were comparable with regard to baseline values for the self-administered rating scales such as the Minnesota Nicotine Withdrawal Scale for craving and withdrawal symptoms, as well as the Smoking Effects Inventory. Like Study 07, the median duration of study drug treatment was 83 days for both treatment groups. 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. 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 (Appendix 7, Table 7.11).

3.1.2.3 Efficacy Analyses

The following is the summary of the applicant's efficacy analyses results across studies.

3.1.2.3.1 Primary Endpoint: Four-week Continuous Quit Rate

According to the applicant, the efficacy results of the three principal smoking cessation studies were robust and highly reproducible.

Varenicline versus Placebo

As shown in Table 2, the 4-week CQRs for subjects receiving varenicline (1 mg BID) were significantly higher ($p < 0.0001$) than those of the corresponding placebo-treated subjects in all 3 studies. For Weeks 9 – 12, the odds for smoking cessation on varenicline were 3.91, 3.85, and 7.84 times those of cessation on placebo (Table 2, Figure 1, Panel A).

Including Phase 2 Studies A3051002 and A3051016/1019, a total of 5 double-blind, placebo-controlled studies demonstrated the superiority of varenicline versus placebo for smoking cessation at the end-of-treatment.

Varenicline versus Zyban

In the Zyban Comparator Studies A3051028 and A3051036, the end-of-treatment (Weeks 9 – 12) abstinence rates of Zyban were significantly higher ($p < 0.001$) than for placebo (Table 2), consistent with previous reports of Zyban's effectiveness as a smoking cessation treatment (Hurt 1997; Jorenby 1999).

The varenicline comparison with Zyban was prespecified in the Study A3051028 and A3051036 protocols as a primary statistical inference. As shown in

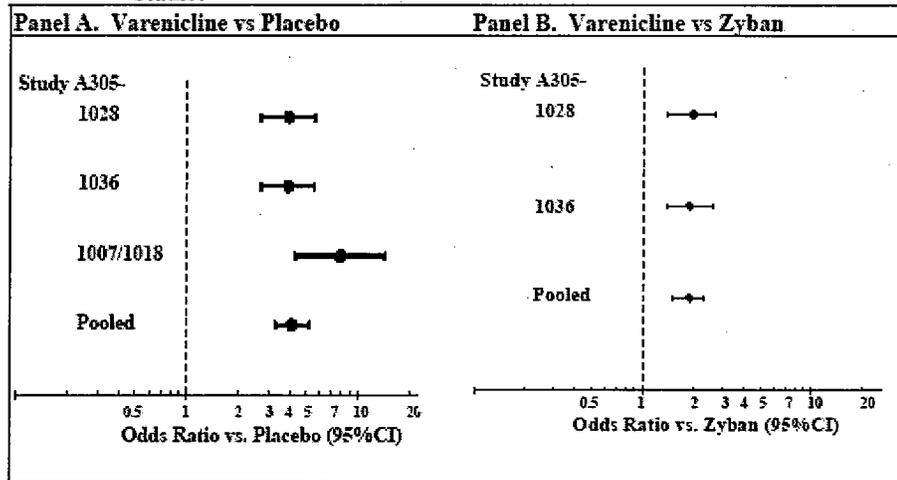
Table 2, the two trials were consistent in demonstrating the superiority ($p < 0.0001$) of varenicline versus Zyban for smoking cessation as measured by the Weeks 9-12 CQR. The odds of smoking cessation on varenicline were 1.96 (Study A3051028) and 1.89 (Study A3051036) times those on Zyban

Table 2: 4-Week CQR (Weeks 9-12) and Treatment Effect (as Odds Ratio) for Varenicline (1 mg BID) versus Placebo and Zyban: Studies A3051028, A3051036, A3051007/1018

Treatment	n/N (%)	Odds Ratio (95% CI) vs placebo	P value vs placebo	Odds Ratio (95% CI) vs Zyban	P value vs Zyban
Study A3051028					
Varenicline	155/349 (44.4)	3.91 (2.74, 5.59)	<0.0001	1.96 (1.42, 2.72)	<0.0001
Zyban	97/329 (29.5)	2.00 (1.38, 2.89)	0.0002		
Placebo	61/344 (17.7)				
Study A3051036					
Varenicline	151/343 (44.0)	3.85 (2.69, 5.50)	<0.0001	1.89 (1.37, 2.61)	<0.0001
Zyban	102/340 (30.0)	2.03 (1.41, 2.94)	0.0001		
Placebo	60/340 (17.7)				
Study A3051007/1018					
Varenicline	128/253 (50.6)	7.84 (4.29, 14.3)	<0.0001	--	--
Placebo	15/121 (12.4)				

Sources: Clinical Study Reports A3051028 Table 13.4.2.1 and A3051036 Table 13.4.2.1; Section 2.7.3 Table A16.5

Figure 1: Treatment Effect (as Odds Ratio) for 4-Week CQR (Weeks 9-12): Varenicline (1 mg BID) versus Placebo and Zyban, Individual and Pooled Studies



Source: Clinical Study Reports A3051028 Table 13.4.2.1; A3051036 Table 13.4.2.1; Section 2.7.3 Tables A7.1, A7.2, A16.5
 Note: Pooled vs Placebo = Studies A3051028, A3051036 and 1 mg BID arm of Study A3051007/1018;
 Pooled vs Zyban = Studies A3051028 and A3051036

3.1.2.3.2 Secondary Endpoints: Continuous Abstinence and Long-term Quit Rate

There were two secondary endpoints in the three principal smoking cessation studies: continuous abstinence rate from week 9 to 52, and the long term quit rate at Week 52. The applicant's summary is provided below.

Varenicline versus Placebo

As is typical for smoking cessation clinical trials, continuous abstinence to one year was considered a surrogate for long-term abstinence. The varenicline group CA rates were significantly higher ($p < 0.0001$) than those of the placebo group for both Weeks 9 – 24 and Weeks 9 – 52 in all three principal smoking cessation studies (Table 3). The odds that subjects in the varenicline group would remain abstinent were 3.73, 2.83, and 7.18 times those of the placebo group for Weeks 9 – 24 and 3.13, 2.66, and 7.19 times those of the placebo group for Weeks 9 – 52 in Studies A3051028, A3051036, and A3051007/1018, respectively (Table 3, Figure 2, Panel A). For comparison, both NRT and Zyban approximately double the odds of abstinence at 6 or 12 months compared with placebo (Silagy 2005; Hughes 2005a).

The LTQR at Week 52 for varenicline-treated subjects was similar to the Weeks 9 – 52 CA rate and significantly higher ($p < 0.0001$) than the LTQR in placebo-treated subjects (Table 4).

Varenicline versus Zyban

Continuous abstinence rates in Phase 3 Studies A3051028 and A3051036 were similar in the two studies; the varenicline group demonstrated consistently higher continuous abstinence rates than the Zyban group for both Weeks 9 – 24 ($p < 0.01$) and Weeks 9 – 52 ($p = 0.0640$ Study A3051028; $p = 0.0062$ Study A3051036) (Table 3). As would be expected from the similarity in results of the two Zyban comparator trials, pooling the data results in robust evidence of superiority (Figure 2, Panel B). The odds of remaining abstinent on varenicline for Weeks 9 – 24 were 1.65 and 1.69 those of remaining abstinent on Zyban in Studies A3051028 and A3051036, respectively. The corresponding odds of remaining abstinent on varenicline for Weeks 9 – 52 were 1.45 (Study A3051028) and 1.72 (Study A3051036) times those on Zyban (Table 3; Figure 2, Panel B).

The LTQR at Week 52 for varenicline-treated subjects was similar to the Weeks 9 – 52 CA rate and superior ($p < 0.05$) to the Zyban-treated subjects LTQR in both studies (Table 4). As noted in Section 2.5.1.5 of the clinical overview study report, Zyban was administered for 12 weeks to match the varenicline treatment interval. This

duration of treatment is consistent with the USPI (i.e., 7 to 12 weeks) but longer than the 7 to 9 weeks recommended in the SmPC. No increase in the number of drop-outs (i.e., failures in the statistical analysis) was observed during the last weeks of treatments; no safety implications worthy of note were evident with longer treatment as the number of discontinuations for adverse events was minimal after Week 6. Thus, the longer treatment duration did not appear to disadvantage Zyban as a comparator for either efficacy or safety.

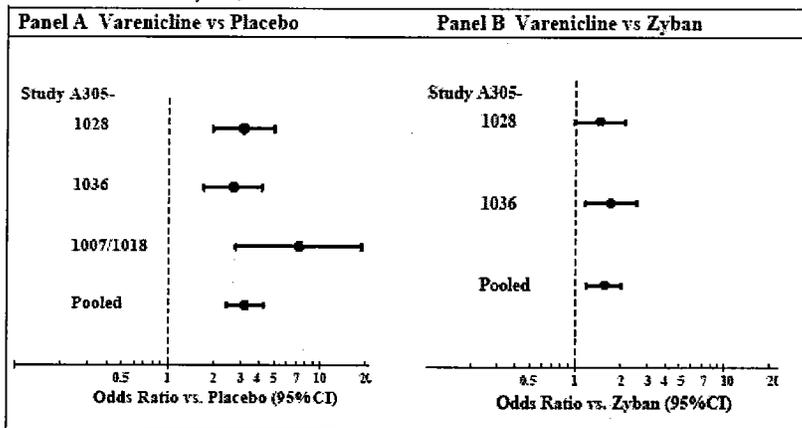
The overall weight of evidence indicates that varenicline is superior to Zyban for smoking cessation at both the end of treatment and through Week 52.

Table 3: Continuous Abstinence (Weeks 9 – 24 and Weeks 9 - 52) and Treatment Effect (as Odds Ratio) for Varenicline (1 mg BID) versus Placebo and Zyban: Studies A3051028, A3051036, A3051007/1018

Study/ Treatment	n/N (%)	Odds Ratio (95% CI) vs placebo	P value vs placebo	Odds Ratio (95% CI) vs Zyban	P value vs Zyban
Study A3051028					
Continuous Abstinence Weeks 9-24					
Varenicline	104/349 (29.8)	3.73 (2.45, 5.67)	<0.0001	1.65 (1.15, 2.36)	0.0060
Zyban	68/329 (20.7)	2.26 (1.45, 3.52)	0.0002		
Placebo	36/344 (10.5)				
Continuous Abstinence Weeks 9-52					
Varenicline	77/349 (22.1)	3.13 (1.97, 4.97)	<0.0001	1.45 (0.98, 2.14)	0.0640
Zyban	54/329 (16.4)	2.16 (1.33, 3.51)	0.0014		
Placebo	29/344 (8.4)				
Study A3051036					
Continuous Abstinence Weeks 9-24					
Varenicline	102/343 (29.7)	2.83 (1.91, 4.20)	<0.0001	1.69 (1.18, 2.40)	0.0037
Zyban	69/340 (20.3)	1.68 (1.11, 2.54)	0.0130		
Placebo	45/340 (13.2)				
Continuous Abstinence Weeks 9-52					
Varenicline	79/343 (23.0)	2.66 (1.72, 4.11)	<0.0001	1.72 (1.16, 2.55)	0.0062
Zyban	51/340 (15.0)	1.54 (0.97, 2.45)	0.0634		
Placebo	35/340 (10.3)				
Study A3051007/1018					
Continuous Abstinence Weeks 9-24					
Varenicline	75/253 (29.6)	7.18 (3.18, 16.2)	<0.0001	--	--
Placebo	7/121 (5.8)				
Continuous Abstinence Weeks 9-52					
Varenicline	58/253 (22.9)	7.19 (2.79, 18.5)	<0.0001	--	--
Placebo	5/121 (4.1)				

Source: Clinical Study Reports A3051028 and A3051036 Table 13.4.3.1; Section 2.7.3 Table A16.7

Figure 2: Treatment Effect (as Odds Ratio) for Continuous Abstinence (Weeks 9 – 52): Varenicline (1 mg BID) versus Placebo and Zyban, Individual and Pooled Studies



Source: Clinical Study Reports A3051028 Table 13.4.3.1; A3051036 Table 13.4.3.1; Section 2.7.3 Tables A8.1, A8.2, A16.7

Note: Pooled vs Placebo = Studies A3051028, A3051036 and 1 mg BID arm of Study A3051007/1018; Pooled vs Zyban = Studies A3051028 and A3051036

Table 4: Long-Term Quit Rate at Week 52 and Odds Ratio for Varenicline (1 mg BID) versus Placebo and Zyban: Studies A3051028, A3051036, A3051007/1018

Study/ Treatment	n/N (%)	Odds Ratio (95% CI) vs placebo	P value vs placebo	Odds Ratio (95% CI) vs Zyban	P value vs Zyban
A3051028					
Varenicline	89/349 (25.5)	3.30 (2.13, 5.11)	<0.0001	1.58 (1.09, 2.31)	0.0161
Zyban	59/329 (17.9)	2.08 (1.31, 3.30)	0.0015	--	--
Placebo	33/344 (9.6)	--	--	--	--
A3051036					
Varenicline	87/343 (25.4)	2.40 (1.60, 3.60)	<0.0001	1.55 (1.07, 2.25)	0.0205
Zyban	62/340 (18.2)	1.55 (1.01, 2.37)	0.0434	--	--
Placebo	43/340 (12.6)	--	--	--	--
A3051007/1018					
Varenicline	68/253 (26.9)	8.96 (3.49, 23.0)	<0.0001	--	--
Placebo	5/121 (4.1)	--	--	--	--

Sources: Clinical Study Reports A3051028 Tables 13.4.4.1; A3051036 Tables 13.4.4.1; Section 2.7.3 Table A16.8

LTQR= defined "responders" as those subjects who successfully stopped smoking (ie, had 4 of weeks of continuous abstinence at the end of the treatment phase) and had no more than 6 days of smoking during the nontreatment phase.

3.1.2.3.3 Craving, Withdrawal, and Reinforcing Effects of Smoking

The effects of varenicline on craving, withdrawal, and the reinforcing effects of smoking are reported by individual study (A3501028, A3501036, and A3051007/1018). They were also reported by pooling the two Phase 3 studies. The results are summarized below.

Varenicline significantly reduced craving compared with placebo, as measured by both MNWS Urge to Smoke and QSU-Brief Total Craving Score (Table 5). Significant reductions were also found in both of the QSU-Brief subscales, one reflecting craving in which smoking is perceived as pleasurable, and the other reflecting anticipation of relief from negative affect of not smoking.

Withdrawal characterized by symptoms of negative affect (depressed mood, irritability, frustration, or anger, anxiety, and difficulty concentrating) was significantly reduced in varenicline-treated subjects compared with placebo. Effects on other symptoms of withdrawal, such as restlessness, increased appetite, and insomnia, were less pronounced.

Varenicline was superior to placebo in significantly reducing reinforcing effects of smoking (as measured by the SEI/mCEQ) in subjects who smoked over treatment. In particular, the most pronounced reductions were in Smoking Satisfaction (satisfaction, taste, and enjoyment of smoking) and Psychological Reward (feeling calmer, more awake, less irritable, improved concentration, and decreased hunger associated with smoking).

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Table 5: Repeated Measures Analysis of Prespecified PRO Scales Assessing Craving, Withdrawal, and Reinforcing Effects of Smoking: Pooled Zyban Comparator Studies A3051028 and A3051036.

	Average of Weeks 1-7		Difference (SE)	Comparison vs Placebo		Effect Size
	LS Mean (SE)	95% CI		95% CI	p-value	
Craving						
MNWS Urge to Smoke (Item 1)						
Varenicline (N=672)	1.18 (0.03)	1.12, 1.24	-0.51 (0.04)	-0.59, -0.42	<0.0001	-0.65
Zyban (N=646)	1.38 (0.03)	1.32, 1.44	-0.31 (0.04)	-0.39, -0.23	<0.0001	-0.40
Placebo (N=669)	1.69 (0.03)	1.63, 1.74	--	--	--	--
QSU-Brief Total Craving Score						
Varenicline (N=671)	1.73 (0.03)	1.67, 1.80	-0.44 (0.05)	-0.53, -0.35	<0.0001	-0.33
Zyban (N=646)	1.90 (0.03)	1.83, 1.96	-0.28 (0.05)	-0.37, -0.19	<0.0001	-0.21
Placebo (N=670)	2.18 (0.03)	2.11, 2.24	--	--	--	--
Withdrawal						
MNWS Negative Affect (Items 2-5)^a						
Varenicline (N=672)	0.60 (0.02)	0.56, 0.64	-0.16 (0.03)	-0.22, -0.11	<0.0001	-0.27
Zyban (N=646)	0.62 (0.02)	0.57, 0.66	-0.15 (0.03)	-0.21, -0.09	<0.0001	-0.24
Placebo (N=670)	0.76 (0.02)	0.72, 0.80	--	--	--	--
MNWS Restlessness (Item 6)^b						
Varenicline (N=671)	0.75 (0.03)	0.70, 0.80	-0.12 (0.04)	-0.19, -0.05	0.0009	-0.14
Zyban (N=644)	0.79 (0.03)	0.74, 0.84	-0.08 (0.04)	-0.16, -0.01	0.0246	-0.10
Placebo (N=669)	0.87 (0.03)	0.82, 0.92	--	--	--	--
Reinforcing Effects of Smoking						
SEL/mCEQ Smoking Satisfaction (Questions 1, 2 & 12)^c						
Varenicline (N=598)	2.57 (0.05)	2.47, 2.67	-0.51 (0.07)	-0.64, -0.38	<0.0001	-0.41
Zyban (N=594)	2.85 (0.05)	2.75, 2.94	-0.24 (0.07)	-0.37, -0.11	0.0004	-0.19
Placebo (N=639)	3.08 (0.05)	3.00, 3.17	--	--	--	--
SEL/mCEQ Psychological Reward (Questions 4-8)^d						
Varenicline (N=598)	2.14 (0.04)	2.06, 2.22	-0.40 (0.06)	-0.51, -0.29	<0.0001	-0.29
Zyban (N=594)	2.28 (0.04)	2.20, 2.36	-0.26 (0.06)	-0.37, -0.15	<0.0001	-0.19
Placebo (N=639)	2.54 (0.04)	2.47, 2.62	--	--	--	--

Source: Section 2.7.3 Tables A10.2, A11, A11.2

Note: Effect Size = LS mean treatment differences / pooled standard deviation at baseline (pooled by center and study)

Scoring: MNWS: Scores ranged from 0 (Not at all) to 4 (Extreme) with higher scores indicating greater intensity.

QSU-Brief Scores range from 1 (strongly disagree) to 7 (strongly agree) with higher scores indicating greater craving.

SEL/mCEQ: Scores ranged from 1 (not at all) to 7 (extremely) with higher scores indicating greater intensity

^aNegative Affect scale = average of MNWS items # 2 (depressed mood), #3 (irritability, frustration, or anger); #4 (anxiety) and #5 (difficulty concentrating). ^bRestlessness scale = MNWS item # 6 (restlessness)

^cSmoking Satisfaction scale = average of SEL/mCEQ questions #1 (Was smoking satisfying?), #2 (Did cigarettes taste good?), and # 12 (Did you enjoy smoking?); ^dPsychological Reward scale = average of SEL/mCEQ questions #4 (Does smoking calm you down?), #5 (Did smoking make you feel more awake?), # 6 (Did smoking make you feel less irritable?), #7 (Did smoking help you concentrate?) and #8 (Did smoking reduce your hunger for food?)

3.1.2.3.4 Maintenance of Abstinence

According to the applicant, Study A3051035 was conducted because published literature (Hughes 2003b; Ferguson 2005) as well as observations from the varenicline Phase 2 studies suggest that most relapses to smoking occur in the first several weeks/months following the end of treatment. This study examined whether an additional 12 weeks of dosing with varenicline 1 mg BID would increase long-term smoking abstinence rates. The study was conducted in three phases: a 12-week open-label phase in which all subjects received varenicline 1 mg BID; a 12-week double-blind treatment phase in which subjects who were abstinent at Week 12 were randomized to either varenicline 1 mg BID or placebo (Weeks 13 – 24); and a nontreatment follow-up phase to Week 52. Subjects who were abstinent during the last week of the open-label treatment period (i.e., reported they had not smoked over the past 7 days and had an end-expired CO ≤ 10 ppm at the Week 12 visit) were eligible to enter the double-blind treatment phase. In the summary, the applicant reported that

Approximately 64% (1236/1927) of subjects met the 7-day point prevalence abstinence criteria at the end of the open-label varenicline phase; of these, 1206 (602 varenicline, 604 placebo) were randomized to and received double-blind treatment. As shown in Table 6, the varenicline group demonstrated significantly higher (p < 0.0001) CA rates at the primary efficacy endpoint (Weeks 13 – 24) than the placebo group. The odds of maintained abstinence at Week 24 (following 12 weeks additional treatment with varenicline) were 2.47 times those for placebo. At Week 52 (i.e. after a 28-week

nontreatment follow-up period), the CA rate remained significantly higher ($p = 0.0126$) in the varenicline group than in the placebo group. LTQR results (not shown) were similar to the CA rate from Week 13 through Week 52.

Table 6: Continuous Abstinence for Weeks 13 – 24 and Weeks 13 - 52): Maintenance Study A3051035

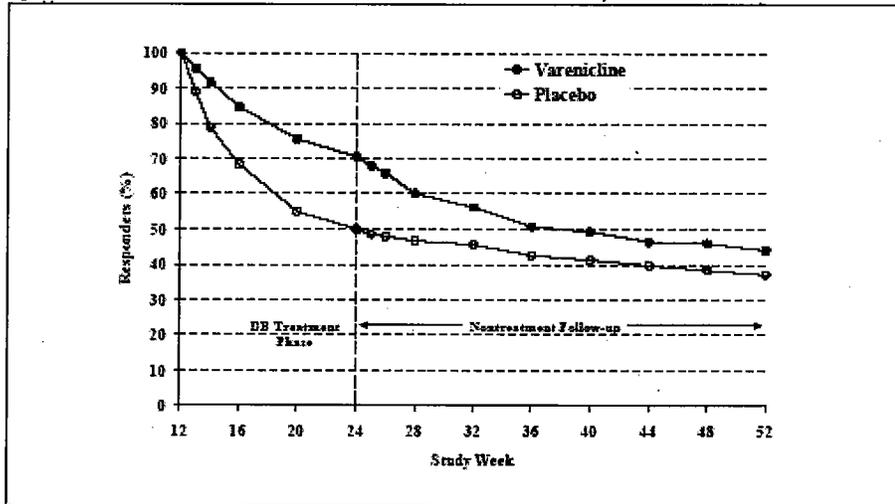
Treatment	n/N	%	Odds Ratio (95% CI)	P value
CA from Week 13 through Week 24				
OL Var/DB Var	425/602	70.6	2.47 (1.95-3.15)	<0.0001
OL Var/DB Pbo	301/604	49.8		
CA from Week 13 through Week 52				
OL Var/DB Var	265/602	44.0	1.35 (1.07-1.70)	0.0126
OL Var/DB Pbo	224/604	37.1		

Source: Clinical Study Report A3051035 Tables 13.4.2.1 and 13.4.3.1

Study A3051035 tested the hypothesis that subjects who abstained from smoking during at least the last week of a 12-week treatment period would be less likely to relapse if treated with varenicline for an additional 12 weeks. Figure 3 shows the continuous abstinence rate by visit during the double-blind treatment (Weeks 13 – 24) and nontreatment follow-up phases (Weeks 25 – 52). Only those subjects who entered the double-blind treatment phase are included in calculation of the abstinence (responder) rates. Subjects in both treatment groups relapsed over time. The extent of relapse may reflect the fact that subjects were not required to demonstrate stable (i.e., four continuous weeks) abstinence during the open-label period prior to randomization. The additional 12 weeks treatment with varenicline reduced the initial rate of relapse compared with the placebo group. As a result, the abstinence rate in the varenicline group was 70.6% compared with 49.8% in the placebo group at Week 24, the primary endpoint. The varenicline group showed an increased rate of relapse at the end-of-treatment transition (between Weeks 25 and 28) then stabilized with the abstinence rate approximately 7 percentage points higher than placebo for the remainder of the study (44.0% versus 37.1% at Week 52).

These data demonstrate that 12 additional weeks of treatment improves long-term abstinence rates compared with placebo.

Figure 3: Continuous Abstinence from Week 13: Maintenance Study A3051035



Source: Clinical Study Report A3051035 Table 13.4.3.1

Note: The 100% response rate at Week 12 represents the proportion of subjects who met the Week 12 point prevalence criterion for continuation in the study and who were randomized and received treatment in the double-blind phase.

3.1.2.4 Applicant's Efficacy Conclusion

According to the applicant, varenicline at the recommended dosing regimen (1 mg BID for 12 weeks) is superior to placebo for smoking cessation at the end of treatment period and at one year from the start of treatment.

The weight of evidence indicates that varenicline is similarly superior to Zyban. In subjects who stopped smoking at the end of 12 weeks, an additional 12 weeks of treatment was more beneficial than placebo in maintaining abstinence to the end of treatment and to one year from the start of treatment.

Across the Phase 3 studies, compared with placebo, varenicline significantly reduced craving; withdrawal symptoms of negative affect (depressed mood, irritability, frustration, or anger, anxiety, difficulty concentrating); and the reinforcing effects of smoking. Taken together, efficacy data from the Phase 2/3 program support the use of varenicline at 1 mg BID for 12 weeks for smoking cessation. An additional 12 weeks treatment is recommended for patients who stopped smoking at the end of the first 12 weeks.

In their proposed product labeling, they claim that

[

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[

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In both studies, the key secondary endpoints were protocol specified as continuous abstinence rate (CA) and long term quit rate (LTQR) at 52 weeks.

[

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They also claim that

[

]

3.1.3 REVIEWER'S OPINION ON SMOKING CESSATION AND MAINTENANCE OF ABSTINENCE CLAIM

The applicant is seeking approval to market CHANTIX™ as an aid to smoking cessation and maintenance of abstinence. In the following sections, I will discuss whether the labeling claims abovementioned are appropriate.

3.1.3.1 Study 28 and Study 36 (Phase III Zyban Comparator Studies)

Studies 28 and 36 were identical 12-week Zyban comparator trials in which the applicant was able to demonstrate the efficacy of varenicline 1.0 mg BID compared to placebo and compared to Zyban on abstinence from tobacco use in cigarette smokers. Not only do the demographic and baseline characteristics appear to be comparable, but the efficacy results between these two studies are more similar than would be expected statistically. This caused some concern which the medical reviewers and I resolved by consulting with the Division of Scientific Investigations (DSI). Several sites in each study were investigated by the DSI. I generated efficacy data from the Nicotine Inventory Use for each of these sites. The DSI investigator compared these data with the case report forms at the sites. Based on the preliminary results from the investigation, it appears that the data from the two studies were accurate. Subjects who were randomly chosen and contacted by the DSI investigators confirmed their existence and the data reported on their study records were correct.

Re-analyzing the applicant's data using their definition of CO-confirmed four-week abstinence and imputation rule, I found that the CO-confirmed four-week Continuous Quit Rate (CQR) from Week 9 through Week 12 was significantly higher for varenicline than for placebo in both studies (Study 28: Odds ratio = 3.9, 95% CI 2.7 to 5.6, $p < 0.0001$; Study 36: OR=3.9, 95% CI 2.7 to 5.6, $p < 0.0001$).

The CO-confirmed four-Week CQR for varenicline was also significantly higher than for Zyban (odds ratio = 2.0, 95% CI 1.4 to 2.7, $p < 0.0001$). A slightly higher rate of four-week abstinence with varenicline compared to placebo was observed in patients in the evaluable population and completer population (OR = 4.1 and OR = 4.4, respectively, Table 7).

Because of our concern with the imputation method the applicant used, I re-analyzed the data using the imputation rule from the Phase 2 studies, Study 07 and Study 16. Only four subjects did not meet the criteria of four-week abstinence when the Phase 2 imputation rule is applied in Study 28 (3 in varenicline and 1 in placebo). Only two subjects did not meet the criteria in Study 36 (1 in varenicline, 1 in Zyban). The overall conclusion did not change (Table 8).

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Table 7: Primary Efficacy Criterion - Four-Week Abstinence Rates

	Study 28			Study 36		
	Varenicline	Placebo	Zyban	Varenicline	Placebo	Zyban
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 (varenicline vs.)		3.9 (2.7, 5.6)	2.0 (1.4, 2.7)		3.8 (2.7, 5.5)	1.9 (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 (varenicline vs.)		4.1 (2.9, 6.0)	1.9 (1.3, 2.6)		4.1 (2.8, 5.8)	1.9 (1.4, 2.7)
p-value (varenicline vs.)		<0.0001	0.0004		<0.0001	0.0001
Completer	N=244	N=202	N=211	N=239	N=209	N=225
Abstinent (%)	147 (60%)	57 (28%)	90 (43%)	140 (59%)	54 (26%)	98 (44%)
Odds ratio (varenicline vs.)		4.4 (2.9, 6.7)	2.1 (1.4, 3.2)		4.3 (2.8, 6.4)	1.9 (1.3, 2.8)
p-value (varenicline vs.)		<0.0001	0.0001		<0.0001	0.0008

Table 8: Re-analysis of the Primary Efficacy Criterion - Four-Week Abstinence Rates

	Study 28			Study 36		
	Varenicline	Placebo	Zyban	Varenicline	Placebo	Zyban
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 (varenicline vs.)		3.9 (2.7, 5.5)	1.9 (1.4, 2.6)		3.8 (2.7, 5.4)	1.9 (1.4, 2.6)
p-value (varenicline vs.)		<0.0001	0.0001		<0.0001	0.0001

As requested by the clinical reviewers, I also looked at the CO-confirmed continuous abstinence rate from Weeks 3 to 12 to assess the efficacy of varenicline compared to placebo and to Zyban with a shorter grace period, instead of nine weeks before efficacy is assessed. In exploratory analyses in both studies 28 and 36, significantly higher rates of continuous abstinence from Weeks 3 to 12 with varenicline (29%) compared to placebo (12%) were observed (OR=3.2 and OR=3.5, respectively) (Table 9). There is also evidence that continuous abstinence rates for varenicline were numerically higher compared to Zyban in both studies (Study 28: Varenicline 29%, Zyban 23%; Study 1036: Varenicline 29%, Zyban 21%). Analyses of continuous abstinence rates from Weeks 4, 5, 6, 7, 8 and 9 to Week 12 suggest similar findings (Table 10).

Table 9: Continuous Abstinence Rates from Week 3 to 12

	Study 28			Study 36		
	Varenicline	Placebo	Zyban	Varenicline	Placebo	Zyban
ITT Subjects	N=349	N=344	N=329	N=343	N=340	N=340
Abstinent (%)	102 (29%)	41 (12%)	77 (23%)	101 (29%)	38 (12%)	71 (21%)
Odds ratio (varenicline vs.)		3.2 (2.1, 4.8)	1.4 (1.0, 2.0)		3.5 (2.3, 5.3)	1.6 (1.1, 2.3)
p-value (varenicline vs.)		<0.0001	0.0800		<0.0001	0.0079

Table 10: Continuous Abstinence Rate from Weeks 3 through Timepoints – Number (%) of Subjects (Study 28 and Study 36)

	Varenicline N=349	Placebo N=344	OR Varenicline vs. Study 28	p-value	Zyban N=329	OR Varenicline vs. Study 36	p-value
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
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

There were two secondary endpoints in the study: continuous abstinence rate from week 9 to 52, and the long term quit rate at Week 52. The rate of Continuous Abstinence from Week 9 through Week 52, was significantly higher for varenicline (22%) than for placebo (8%, $p < 0.0001$) (Table 11). The rate of Continuous Abstinence through Week 52 for varenicline was also higher than for Zyban (16%, $p = 0.0640$). Re-analysis of the continuous abstinence rate using the Phase 2 imputation rule (see Reviewer's Table 11 and Table 12) did not change the overall conclusion.

Table 11: Continuous Abstinence Rate – Number (%) of Subjects (Study 28)

	Sponsor's			Reviewer's		
	Varenicline N=349	Placebo N=344	Zyban N=329	Varenicline N=349	Placebo N=344	Zyban N=329
Week 13	145 (42%)	59 (17%)	93 (28%)	142 (41%)	57 (17%)	93 (28%)
Week 16	133 (38%)	49 (14%)	86 (26%)	123 (35%)	42 (12%)	75 (23%)
Week 20	122 (35%)	44 (13%)	79 (24%)	112 (32%)	38 (11%)	69 (21%)
Week 24	104 (30%)	36 (11%)	68 (21%)	100 (29%)	34 (10%)	64 (19%)
Week 28	101 (29%)	33 (10%)	65 (20%)	94 (27%)	32 (9%)	59 (18%)
Week 32	97 (28%)	33 (10%)	64 (20%)	90 (26%)	31 (9%)	58 (18%)
Week 36	88 (25%)	31 (9%)	58 (18%)	82 (24%)	28 (8%)	56 (17%)
Week 40	88 (25%)	31 (9%)	58 (18%)	82 (24%)	28 (8%)	56 (17%)
Week 44	82 (24%)	31 (9%)	55 (17%)	79 (23%)	28 (8%)	52 (16%)
Week 48	80 (23%)	31 (9%)	55 (17%)	77 (22%)	28 (8%)	52 (16%)
Week 52	77 (22%)	29 (8%)	54 (16%)	74 (21%)	27 (8%)	52 (16%)

Table 12: Continuous Abstinence Rate – Number (%) of Subjects (Study 36)

	Sponsor's			Reviewer's		
	Varenicline N=343	Placebo N=340	Zyban N=340	Varenicline N=343	Placebo N=340	Zyban N=340
Week 13	140 (41%)	59 (17%)	98 (29%)	140 (41%)	59 (17%)	96 (28%)
Week 16	133 (39%)	54 (16%)	94 (28%)	127 (37%)	52 (15%)	91 (27%)
Week 20	121 (35%)	50 (15%)	83 (24%)	115 (34%)	49 (14%)	80 (24%)
Week 24	102 (30%)	45 (13%)	69 (20%)	98 (29%)	44 (13%)	67 (20%)
Week 28	98 (29%)	44 (13%)	66 (19%)	93 (27%)	43 (13%)	64 (19%)
Week 32	94 (27%)	41 (12%)	65 (19%)	89 (26%)	40 (12%)	63 (19%)
Week 36	87 (25%)	39 (12%)	58 (17%)	83 (24%)	38 (11%)	56 (16%)
Week 40	87 (25%)	38 (11%)	57 (17%)	81 (24%)	37 (11%)	55 (16%)
Week 44	83 (24%)	35 (10%)	54 (16%)	78 (23%)	34 (10%)	52 (15%)
Week 48	83 (24%)	35 (10%)	52 (15%)	78 (23%)	34 (10%)	50 (15%)
Week 52	79 (23%)	35 (10%)	51 (15%)	74 (22%)	34 (10%)	49 (14%)

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Figure 4: Continuous Abstinence Rate from Week 9 to Week 52 – Reviewer's (28)

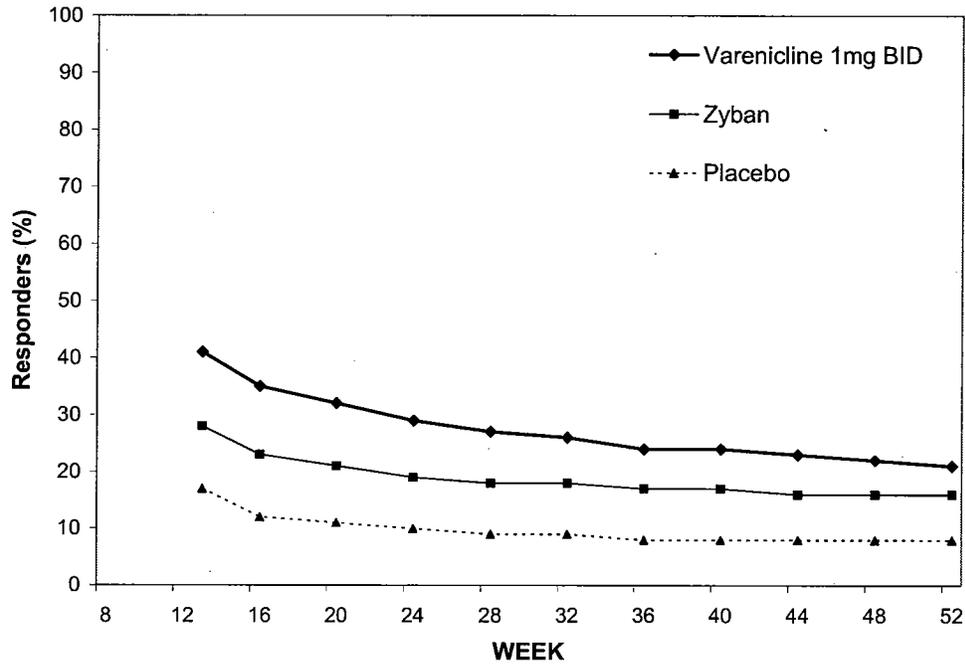
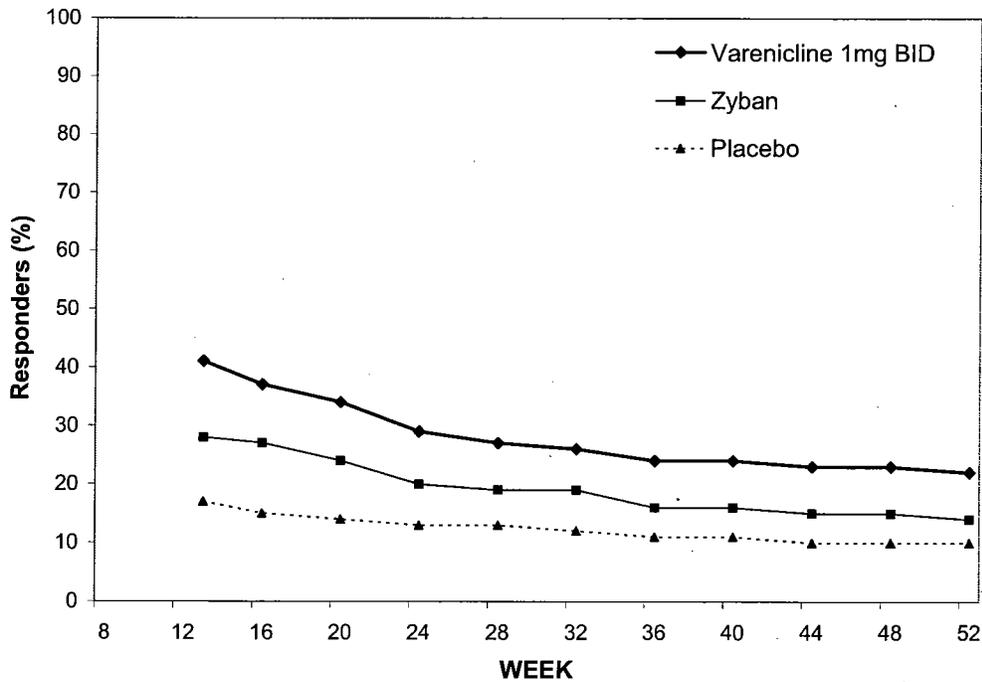


Figure 5: Continuous Abstinence Rate from Week 9 to Week 52 – Reviewer's (36)



As mentioned in Section 3.1.1, although the applicant prespecified a step-down procedure in order to preserve the family-wise type I error rate for multiple contrasts, this procedure is only employed within each endpoint. There is no prespecification on how type I error rate could be preserved in testing of multiple endpoints. Because the rate of continuous abstinence through week 52 for varenicline was not statistically significant different from Zyban, comparison of other secondary endpoints with regards to treatment difference between varenicline and Zyban should not be included in the label. With that said, the Long-Term Quit Rate (LTQR) at Week 52, was significantly higher for varenicline (26%) compared with placebo (10%, $p < 0.0001$) (Table 13). The LTQR at Week 52 for varenicline was also numerically higher than for Zyban (18%, $p = 0.0161$). Re-analysis of the LTQR applying the applicant's criteria for imputation (see Reviewer's results Table 13 and Table 14) and using the Phase 2 imputation rule (not provided) did not change the overall conclusion.

Table 13: Long Term Quit Rate – All Subjects (Study 28)

	Sponsor's			Reviewer's		
	Varenicline N=349	Placebo N=344	Zyban N=329	Varenicline N=349	Placebo N=344	Zyban N=329
Week 13	153 (44%)	61 (18%)	95 (29%)	153 (44%)	61 (18%)	95 (29%)
Week 16	146 (42%)	58 (17%)	94 (29%)	146 (42%)	58 (17%)	94 (29%)
Week 20	134 (38%)	52 (15%)	86 (26%)	134 (38%)	52 (15%)	86 (26%)
Week 24	119 (34%)	44 (13%)	76 (23%)	119 (34%)	44 (13%)	76 (23%)
Week 28	114 (33%)	40 (12%)	72 (22%)	114 (33%)	40 (12%)	72 (22%)
Week 32	107 (31%)	39 (11%)	70 (21%)	107 (31%)	38 (11%)	70 (21%)
Week 36	101 (29%)	35 (10%)	65 (20%)	101 (29%)	34 (10%)	64 (19%)
Week 40	100 (29%)	35 (10%)	64 (20%)	100 (29%)	34 (10%)	63 (19%)
Week 44	94 (27%)	35 (10%)	63 (19%)	93 (27%)	34 (10%)	61 (19%)
Week 48	91 (26%)	35 (10%)	61 (19%)	90 (26%)	34 (10%)	59 (18%)
Week 52	89 (26%)	33 (10%)	59 (18%)	88 (25%)	32 (9%)	57 (17%)

Table 14: Long Term Quit Rate – All Subjects (Study 36)

	Sponsor's			Reviewer's		
	Varenicline N=343	Placebo N=340	Zyban N=340	Varenicline N=343	Placebo N=340	Zyban N=340
Week 13	149 (43%)	60 (18%)	100 (29%)	149 (43%)	60 (18%)	100 (29%)
Week 16	142 (41%)	58 (17%)	100 (29%)	142 (41%)	58 (17%)	100 (29%)
Week 20	131 (38%)	56 (17%)	92 (27%)	131 (38%)	56 (17%)	92 (27%)
Week 24	115 (34%)	52 (15%)	82 (24%)	115 (34%)	52 (15%)	82 (24%)
Week 28	109 (32%)	50 (15%)	80 (24%)	109 (32%)	50 (15%)	80 (24%)
Week 32	102 (30%)	48 (14%)	78 (23%)	102 (30%)	48 (14%)	78 (23%)
Week 36	97 (28%)	46 (14%)	72 (21%)	97 (28%)	46 (14%)	71 (21%)
Week 40	96 (28%)	46 (14%)	70 (21%)	96 (28%)	46 (14%)	69 (20%)
Week 44	92 (27%)	43 (13%)	66 (19%)	90 (26%)	43 (13%)	65 (19%)
Week 48	92 (27%)	43 (13%)	64 (19%)	90 (26%)	43 (13%)	63 (19%)
Week 52	87 (25%)	43 (13%)	62 (18%)	86 (25%)	43 (13%)	61 (18%)

Three aspects of smoking cessation to address the objective of comparing varenicline to placebo were investigated by the applicant using Patient Reported Outcomes questionnaires. They claim that the following were validated: Craving, measured by Brief Questionnaire of Smoking Urges (QSU-Brief) and Minnesota Nicotine Withdrawal Scale (MNWS) Urge to Smoke item; Withdrawal, measured by 4 MNWS subscales; and Reinforcing Effects of Smoking, measured by five Modified Cigarette Evaluation Questionnaire (mCEQ)

subscales. Similar to the multiplicity problem in the key secondary endpoints, the applicant failed to specify how type I error rate could be preserved in testing these multiple endpoints, even though the comparison is only between varenicline and placebo. Furthermore, according to the findings of Dr. Jane Scott (Study Endpoints and Label Development or SEALD reviewer),

The concept “urge to smoke” is more appropriate for labeling than the term “craving. Furthermore, 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.

Therefore, the claims of “craving reduction”, “symptoms of withdrawal” and/or “reduction of reinforcing effects of smoking” should not be granted. In my opinion, a claim about “urge to smoke” is appropriate for labeling only if there are consistent findings. As seen in the next two tables (Table 15 and Table 16), it appears that there is in fact consistent evidence that varenicline is more effective than placebo in reducing the “urge to smoke.”

Table 15: Secondary Endpoints – All Subjects (Study 28)

	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)	(-0.4, -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)			
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)	(-0.3, -0.1)	0.0002
Placebo	0.8 (0.03)	(0.7, 0.8)			
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)	(-0.2, 0.0)	0.0841
Placebo	0.8 (0.04)	(0.8, 0.9)			
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)	(-0.4, -0.1)	0.0038
Placebo	2.5 (0.06)	(2.4, 2.7)			

^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 16: Secondary Endpoints – All Subjects (Study 36)

	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)	(-0.5, -0.3)	<0.0001
Placebo	1.7 (0.04)	(1.6, 1.8)			
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)	(-0.5, -0.2)	<0.0001
Placebo	2.2 (0.05)	(2.1, 2.3)			
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)	(-0.2, -0.1)	0.0014
Placebo	0.7 (0.03)	(0.7, 0.8)			
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)	(-0.5, -0.2)	0.0003
Placebo	3.2 (0.06)	(3.1, 3.3)			
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)	(-0.4, -0.1)	0.0003
Placebo	2.5 (0.05)	(2.4, 2.6)			

^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.

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3.1.3.2 Study 35 Maintenance of Efficacy

Study 35 is a 52-week multicenter study evaluating the safety and efficacy of varenicline for the maintenance of smoking cessation.

Re-analyzing the applicant's data, I found that the continuous abstinence rate from Week 13 through Week 24 was significantly higher for subjects randomized to double-blind varenicline (71%) than for subjects randomized to double-blind placebo (50%) (Odds ratio = 2.5, 95% CI 2.0 to 3.2, p <0.0001).

Table 17: Primary Efficacy Criterion – Continuous Abstinence Rate from Week 13 Through Week 24

	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

Because of our concern with the imputation method the applicant used, I re-analyzed the data using the imputation rule from the Phase 2 studies, 07 and 16. Only five subjects (all in varenicline group) did not meet the criteria of continuous abstinence from Week 13 to 24 when the Phase 2 imputation rule is applied. The overall conclusion did not change (Table 18).

Table 18: Re-analysis - Continuous Abstinence Rate from Week 13 Through Week 24

	Double-Blind Varenicline	Double-Blind Placebo
ITT Subjects	N=601	N=603
Abstinent (%)	420 (70%)	301 (50%)
Odds ratio (95% CI) vs. placebo		2.4 (1.9, 3.0)
p-value vs. placebo		<0.0001
Evaluable	N=574	N=574
Abstinent (%)	415 (72%)	299 (52%)
Odds ratio (95% CI) vs. placebo		2.5 (1.9, 3.2)
p-value vs. placebo		<0.0001
Completer	N=494	N=474
Abstinent (%)	382 (77%)	284 (60%)
Odds ratio (95% CI) vs. placebo		2.3 (1.7, 3.1)
p-value vs. placebo		<0.0001

Like Studies 28 and 36, there were two secondary endpoints in the study: continuous abstinence rate from week 13 to 52, and the long term quit rate at Week 52. The rate of Continuous Abstinence from Week 13 through Week 52, was significantly higher for varenicline (44%) than for placebo (37%, p=0.0123) (Table 19). Although numerically the completer population supports the efficacy in terms of continuous abstinence rate for the all subject population, this did not achieve statistical significance. Moreover, re-analysis of the continuous abstinence rate using the Phase 2 imputation rule made the difference in continuous abstinence rate between varenicline and placebo smaller (see Re-analysis Table 19) even when it did not change the overall conclusion for the all subject population.

Table 19: Secondary – Continuous Abstinence Rate from Week 13 Through Week 52

	Treated		Re-analysis	
	Double-Blind Varenicline	Double-Blind Placebo	Double-Blind Varenicline	Double-Blind Placebo
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
Completer	N=494	N=474	N=494	N=474
Abstinent (%)	246 (50%)	211 (45%)	231 (47%)	204 (43%)
Odds ratio (95% CI) vs. placebo		1.2 (1.0, 1.6)		1.2 (0.9, 1.5)
p-value vs. placebo		0.1033		0.2443

The proportion of subjects who were four-week CO-confirmed abstinent during the last five weeks of the open-label phase (Weeks 8 – 12) was 51% (Table 20). This result independently substantiates the numerically high proportion of subjects who were four-week CO-confirmed abstinent taking varenicline 1.0 mg BID found in Study 28 and Study 36, which was around 44%. Unlike Study 28 and Study 36, data were only available for Weeks 1 – 8, 10 and 12 in this open-label treatment phase, therefore, data for Weeks 8, 10 and 12 were used to calculate the CO-confirmed continuous abstinence, instead of the “last four weeks” or Weeks 9 – 12. Furthermore, 64% were abstinent during the last seven days of the open-label treatment phase, and 61% were reported abstinent during the last reported visit of the open-label treatment phase.

Table 20: Continuous Abstinence Rate (Open-Label Treatment Phase)

	Open-Label	Double-Blind Varenicline	Double-Blind Placebo	Total
	N=717	N=603	N=607	N=1927
Weeks 8 – 12	21 (3%)	492 (82%)	479 (79%)	992 (51%)
Last 7 day (Week 12)	31 (4%)	602 (100%)	606 (100%)	1239 (64%)
Last Visit (Week 12)	30 (4%)	574 (95%)	581 (96%)	1185 (61%)

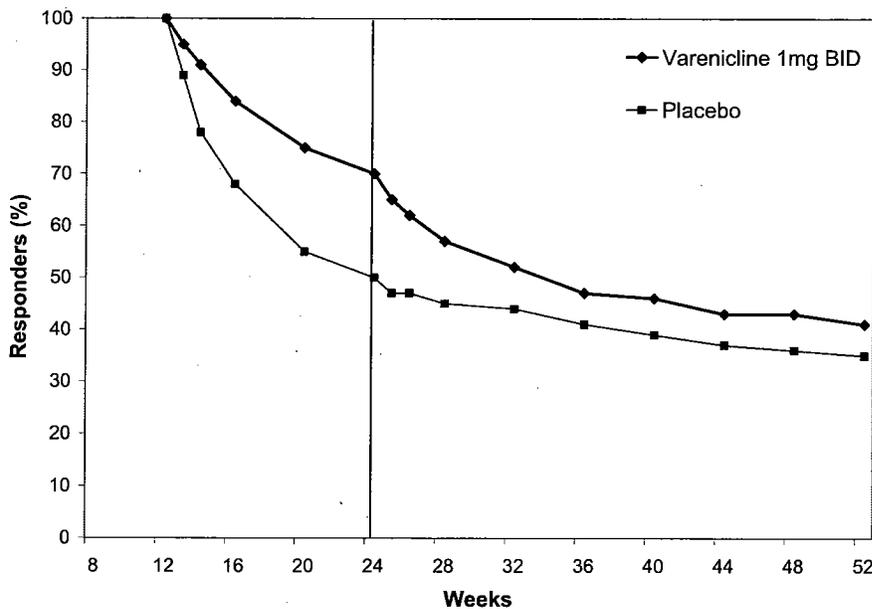
Continuous abstinence rates from Week 13 through each timepoints suggest that subjects who were randomized to the placebo group in the double-blind phase (from open-label varenicline) had a faster and sharper decline in staying abstinent during the double-blind treatment phase (39% drop, Week 13: 89% to Week 24: 50%) compared to the varenicline group (25% drop, Week 13: 95% to Week 24: 70%). While the

decline continued in both treatment groups, a sharper decline occurred after the non-treatment phase among the varenicline-treated group between Weeks 24 to 36. Nonetheless, the difference in the continuous abstinence rate remains in favor of the varenicline-treated group (Table 21 and Figure 6).

Table 21: Continuous Abstinence Rate from Week 13 Through Each Timepoints

	Treated		Re-analysis	
	Double-Blind Varenicline N=601	Double-Blind Placebo N=603	Double-Blind Varenicline N=601	Double-Blind Placebo N=603
Double-Blind Treatment Phase				
Week 13	575 (96%)	537 (89%)	573 (95%)	534 (89%)
Week 14	550 (92%)	476 (79%)	545 (91%)	473 (78%)
Week 16	509 (85%)	413 (68%)	505 (84%)	410 (68%)
Week 20	454 (75%)	331 (55%)	450 (75%)	330 (55%)
Week 24	425 (71%)	301 (50%)	420 (70%)	301 (50%)
Non-Treatment Follow-up Phase				
Week 25	408 (68%)	293 (49%)	389 (65%)	286 (47%)
Week 26	396 (66%)	290 (48%)	370 (62%)	281 (47%)
Week 28	361 (60%)	282 (47%)	340 (57%)	274 (45%)
Week 32	338 (56%)	275 (46%)	311 (52%)	264 (44%)
Week 36	306 (51%)	257 (43%)	285 (47%)	246 (41%)
Week 40	296 (49%)	249 (41%)	276 (46%)	235 (39%)
Week 44	280 (47%)	239 (40%)	259 (43%)	226 (37%)
Week 48	277 (46%)	232 (38%)	256 (43%)	220 (36%)
Week 52	265 (44%)	224 (37%)	247 (41%)	214 (35%)

Figure 6: Continuous Abstinence Rate from Week 13 to Week 52 – Reviewer’s (35)



Like Studies 28 and 36, although the applicant prespecified a step-down procedure in order to preserve the family-wise type I error rate for multiple contrasts, this procedure is only employed within each endpoint. There is no prespecification on how type I error rate could be preserved in testing of multiple endpoints. With that said, the Long-Term Quit Rate (LTQR) at Week 52, was significantly higher for varenicline (25.5%) compared with placebo (9.6%, $p < 0.0001$) (Table 22). Re-analysis of the LTQR applying the applicant's criteria for imputation (see Re-analysis results Table 22) and using the Phase 2 imputation rule (Table 23) did not change the overall conclusion.

Table 22: Long Term Quit Rate – All Subjects (Study 35)

	Treated		Re-analysis	
	Double-Blind Varenicline N=601	Double-Blind Placebo N=603	Double-Blind Varenicline N=601	Double-Blind Placebo N=603
Week 25	421 (70%)	297 (49%)	421 (70%)	297 (49%)
Week 26	415 (69%)	294 (49%)	415 (69%)	293 (49%)
Week 28	394 (66%)	290 (48%)	394 (66%)	289 (48%)
Week 32	374 (62%)	289 (48%)	374 (62%)	288 (48%)
Week 36	348 (58%)	275 (46%)	348 (58%)	274 (45%)
Week 40	333 (55%)	266 (44%)	332 (55%)	265 (44%)
Week 44	311 (52%)	260 (43%)	310 (52%)	259 (43%)
Week 48	302 (50%)	254 (42%)	301 (50%)	253 (42%)
Week 52	288 (48%)	246 (41%)	287 (48%)	245 (41%)
OR (vs. placebo)		1.3 (1.1, 1.7)		1.3 (1.1, 1.7)
p-value vs. placebo		0.0119		0.0114

Table 23: Long Term Quit Rate using Phase 2 Imputation Rule for CQR – All Subjects (Study 35)

	Double-Blind Varenicline N=601	Double-Blind Placebo N=603
Week 25	403 (67%)	290 (48%)
Week 26	397 (66%)	285 (47%)
Week 28	374 (62%)	282 (47%)
Week 32	355 (59%)	281 (47%)
Week 36	327 (54%)	264 (44%)
Week 40	313 (52%)	253 (42%)
Week 44	289 (48%)	247 (41%)
Week 48	280 (47%)	240 (40%)
Week 52	269 (45%)	234 (39%)
OR (vs. placebo)		1.3 (1.0, 1.6)
p-value vs. placebo		0.0320

3.1.3.3 Study 07/18 Phase II Study

Study 07 is one of the three Phase 2 studies that examined the efficacy of varenicline at different doses, treatment durations and dosing regimens. According to the applicant, in all three Phase 2 studies, varenicline-treated subjects demonstrated significantly higher-end-of-treatment four-week continuous quit rate (at >0.3 mg QD) and Week 52 continuous abstinence rates (at BID doses of at least 0.5 mg and flexible dosing) than subjects receiving placebo. Although the applicant proposed that the “recommended” dose of CHANTIX (varenicline) is 1 mg twice daily following a one-week titration (0.5 mg QD × 3 days followed by 0.5 mg BID × 4 days), there was some evidence in this study (07) that nausea incidence, as well as treatment discontinuations due to nausea, were higher with varenicline 1.0 mg BID (titrated or nontitrated) compared to varenicline 0.5 mg BID (titrated or nontitrated), see Table 24 and Table 25. The majority of all incidences of nausea were reported to be mild in severity, and only four episodes of severe nausea were reported. Furthermore, according to the applicant, varenicline was safe and well tolerated at dosages of 0.5 mg BID and 1.0 mg BID (titrated or nontitrated). Nonetheless, I believe it is important to review this study, as well as the 40-week extension study (18), and to confirm whether initial dose titration improved the tolerability of varenicline or whether varenicline 0.5 mg BID could serve as an alternative dosing regimen for subjects who can not tolerate the 1.0 mg BID.

Table 24: Nausea: Incidence and Treatment Discontinuations – Study 07

	CP-526,555				
	0.5 mg BID nontitrated N = 124	0.5 mg BID titrated N = 129	1.0 mg BID nontitrated N = 124	1.0 mg BID titrated N = 129	Placebo N = 121
	Incidence of Nausea				
All reports	28 (22.6)	21 (16.3)	52 (41.9)	45 (34.9)	18 (14.9)
Severe nausea	0 (0.0)	1 (0.8)	0 (0.0)	2 (1.6)	1 (0.8)
Treatment Discontinuation due to nausea					
	2 (1.6)	0 (0.0)	6 (4.8)	5 (3.9)	3 (2.5)

Source: Study Report 07 page 12

Table 25: Treatment-Emergent Adverse Events: Incidence and Discontinuations of Study Medication – Study 07

	CP-526,555				
	0.5 mg BID nontitrated N = 124	0.5 mg BID titrated N = 129	1.0 mg BID nontitrated N = 124	1.0 mg BID titrated N = 129	Placebo N = 121
	Incidence of Adverse Events				
	107 (86.3)	105 (81.4)	112 (90.3)	110 (85.3)	96 (79.3)
Treatment Discontinuations					
	9 (7.3)	18 (14.0)	17 (13.7)	28 (21.7)	21 (17.4)

Source: Study Report 07 page 12

Study 07 is a 12-week double-blind, placebo-controlled, randomized, multicenter study evaluating the safety and efficacy of four dosing strategies for varenicline (0.5 mg BID, titrated 0.5 mg BID, 1 mg BID, and titrated 1 mg BID) in smoking cessation. In order to measure the long-term efficacy of varenicline following 12 weeks of treatment in Study 07, the applicant conducted a forty-week, double-blind, multicenter, nontreatment extension (Study 18). Therefore, Week13 is 13 weeks after Baseline in Study 07, and one week after entry into the follow-up Study 18.

Before I discuss the efficacy results, it is important to note that the applicant performed interim analysis on the primary efficacy endpoints four-week CO-confirmed abstinence at Weeks 9 -12 and Weeks 4 – 7 such that adjustments were made to the final type I error rate to account for the interim analysis, and thus the primary analysis used an α of 0.049 (0.05 minus 0.001) at the end of the study.

Re-analyzing the applicant's submitted data, I find that the CO-confirmed four-week CQR was significantly higher for both the varenicline 0.5 mg BID- and 1.0 mg BID-treated groups than for the placebo-treated group ($p < 0.0001$) in both the Weeks 4 – 7 and the Weeks 9 – 12 even after re-analyses. Results of the analyses for the Evaluable and Completer population supported these findings (Table 26). When comparisons were done separately for each of the four titrated and nontitrated varenicline dosage groups versus placebo, statistically significant differences from placebo were maintained for all active treatment groups at both timepoints. For all four varenicline dosage groups, response rates for Weeks 9 – 12 were numerically greater than those for the Weeks 4 – 7 timepoint; while for placebo, response rates were similar for the two timepoints (Table 27 and Table 28). Like the pooled population, results of the analyses for the Evaluable and Completer population supported these findings (Table 27 and Table 28).

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Table 26: Re-analysis Primary Efficacy Criterion: Protocol-Specified Analyses – Study 07

	Weeks 4 – 7				Weeks 9 – 12			
	Varenicline		Varenicline		Varenicline		Varenicline	
	0.5 mg BID	1.0 mg BID	Placebo	Placebo	0.5 mg BID	1.0 mg BID	Placebo	
ITT Subjects	N=253	N=253	N=121	N=121	N=253	N=253	N=121	
Abstinent (%)	94 (37%)	102 (40%)	14 (12%)	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=104	N=231	N=235	N=104	
Abstinent (%)	91 (39%)	102 (43%)	14 (13%)	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=66	N=169	N=162	N=66	
Abstinent (%)	84 (50%)	82 (51%)	12 (18%)	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		

Table 27: Primary Efficacy Criterion: Non-Pooled Analyses (Weeks 4 – 7) – Study 07

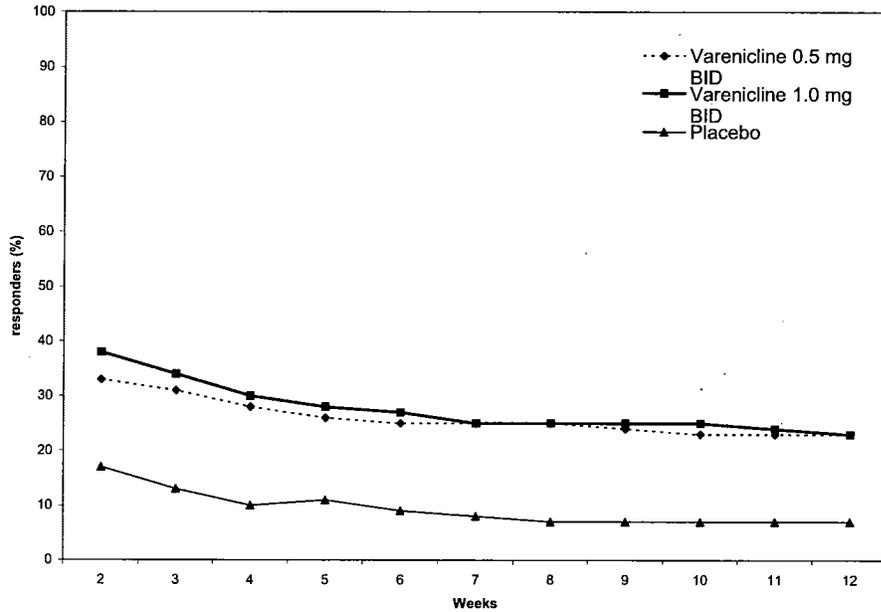
	Varenicline			
	0.5 mg BID Nonitrated	0.5 mg BID Titrated	1.0 mg BID Nonitrated	1.0 mg BID Titrated
ITT Subjects	N=124	N=129	N=124	N=121
Abstinent (%)	48 (39%)	46 (36%)	50 (40%)	52 (40%)
Odds ratio (95% CI) vs. placebo	5.0 (2.6, 9.9)	4.6 (2.3, 8.8)	5.5 (2.8, 10.8)	5.6 (2.8, 10.9)
p-value vs. placebo	<0.0001	<0.0001	<0.0001	<0.0001
Evaluable	N=113	N=118	N=114	N=121
Abstinent (%)	47 (42%)	44 (37%)	50 (44%)	52 (43%)
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
Completer	N=88	N=81	N=84	N=78
Abstinent (%)	43 (49%)	41 (51%)	42 (50%)	40 (51%)
Odds ratio (95% CI) vs. placebo	4.6 (2.1, 9.9)	4.6 (2.1, 10.1)	4.7 (2.2, 10.2)	4.8 (2.2, 10.6)
p-value vs. placebo	0.0001	0.0001	<0.0001	<0.0001
				Placebo N=121 14 (12%)

Table 28: Primary Efficacy Criterion: Non-Pooled Analyses (Weeks 9 – 12) – Study 07

	Varenicline			
	0.5 mg BID Nontitrated	0.5 mg BID Titrated	1.0 mg BID Nontitrated	1.0 mg BID Titrated
ITT Subjects	N=124	N=129	N=124	N=121
Abstinent (%)	61 (49%)	53 (41%)	57 (46%)	71 (55%)
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
Abstinent (%)	60 (53%)	52 (44%)	57 (50%)	71 (59%)
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
Completer	N=88	N=81	N=84	N=78
Abstinent (%)	57 (65%)	48 (59%)	52 (62%)	56 (72%)
Odds ratio (95% CI) vs. placebo	7.7 (3.6, 16.6)	5.9 (2.8, 12.7)	6.4 (3.0, 13.7)	10.1 (4.6, 22.4)
p-value vs. placebo	<0.0001	<0.0001	<0.0001	<0.0001
				Placebo N=121 15 (12%)

For the All Subjects analyses, the CO-confirmed rate of continuous abstinence from the target quit date (starting at Week 2) to Week 12 was also higher for both the varenicline-treated groups compared to the placebo. At the Week 12 timepoint, the rates were approximately 20% to 25% for the varenicline-treated groups compared to a rate of 7% for the placebo (Figure 7).

Figure 7: Continuous Abstinence Rate from Week 2 to Week 12 – (Study 07)



Like the two Phase 3 studies, I also looked at the CO-confirmed continuous abstinence rate from Weeks 3 to 12 to assess the efficacy of varenicline compared to placebo after a shorter grace period. Numerically higher rates of continuous abstinence from Weeks 3 to 12 for both varenicline 0.5 mg BID- and 1.0 mg BID-treated groups (32% and 33%, respectively) compared to placebo (9%) were observed (Table 29). Analyses of continuous abstinence rates from Weeks 4, 5, 6, 7, 8 and 9 to Week 12 led to similar conclusions.

Table 29: Continuous Abstinence Rate from Weeks 3 through Timepoints – (Study 07)

	Varenicline 0.5 mg BID N=253	Varenicline 1.0 mg BID N=253	Placebo N=121
Week 3 – 12	79 (31%)	79 (31%)	10 (8%)
Week 4 – 12	82 (32%)	92 (36%)	11 (9%)
Week 5 – 12	89 (35%)	105 (42%)	12 (10%)
Week 6 – 12	96 (38%)	113 (45%)	12 (10%)
Week 7 – 12	99 (39%)	115 (45%)	13 (11%)
Week 8 – 12	106 (42%)	122 (48%)	15 (12%)
Week 9 – 12 *	114 (45%)	128 (51%)	15 (12%)

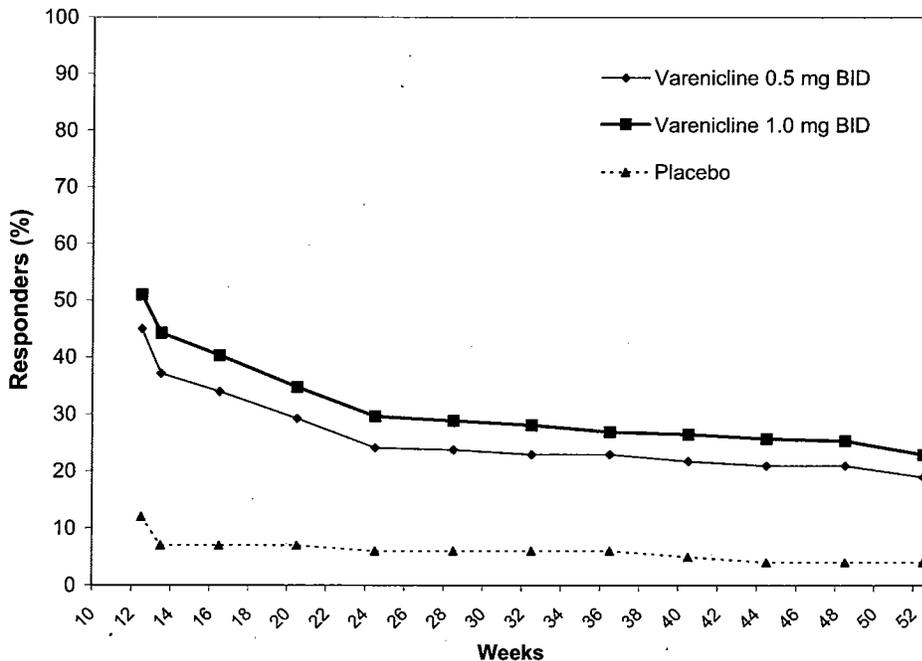
* Primary Efficacy Criterion

I also find that the CO-confirmed rate of continuous abstinence from Week 9 to Week 52 (primary efficacy parameter in Study 18) was significantly higher for both the varenicline 0.5 mg BID- and 1.0 mg BID-treated groups (19% and 23%, respectively) compared to the placebo (4%, $p < 0.0001$). The CO-confirmed rate of continuous abstinence from Week 9 to Week 24 was also significantly higher for both varenicline-treated groups compared to the placebo (24% and 30%, respectively versus 6%, $p < 0.0001$) (Table 30 and Figure 8).

Table 30: Continuous Abstinence Rate from Week 9 Through Each Timepoints (Study 07/18)

	Varenicline		Placebo N=121
	0.5 mg BID N=253	1.0 mg BID N=253	
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%)

Figure 8: Continuous Abstinence Rate from Week 9 to Week 52 – (Study 07/18)



3.1.3.4 Study 16/19 Phase II Study

This is another Phase 2 study that could provide us with information about the efficacy of 0.5 mg BID. Study 16 is a 12-week, double-blind, placebo-controlled, randomized, multicenter study evaluating the safety and efficacy of a flexible-dosing strategy for Varenicline (0.5 mg to 2.0 mg total daily dose, administered BID) in smoking cessation. In order to measure the long-term efficacy of varenicline following 12 weeks of treatment in Study 16, the applicant conducted a forty-week, double-blind, multicenter, nontreatment extension (Study 19). Therefore, Week 13 is 13 weeks after Baseline in Study 16, and one week after entry into the follow-up Study 19. In this study, the dosing regimen is as follows:

Study Medication

Test Product/Strength	FID #	Lot #
CP-526,555 (0.5 mg tablet)	G02306AA	ED-G-286-701
Placebo (0 mg tablet)	G02328AA	ED-G-106-301

Dosing: CP-526,555: 0.5 mg QD for 3 days, followed by 0.5 mg BID for 4 days; after Day 7, dosing schedule was flexible (minimum of 0.5 mg QD, maximum of 1.0 mg BID)
Placebo: one tablet QD for 3 days, followed by one tablet BID for 4 days; after Day 7, dosing schedule was flexible (minimum of one tablet QD, maximum of 2 tablets BID)

Duration: 12 weeks for CP-526,555 and placebo

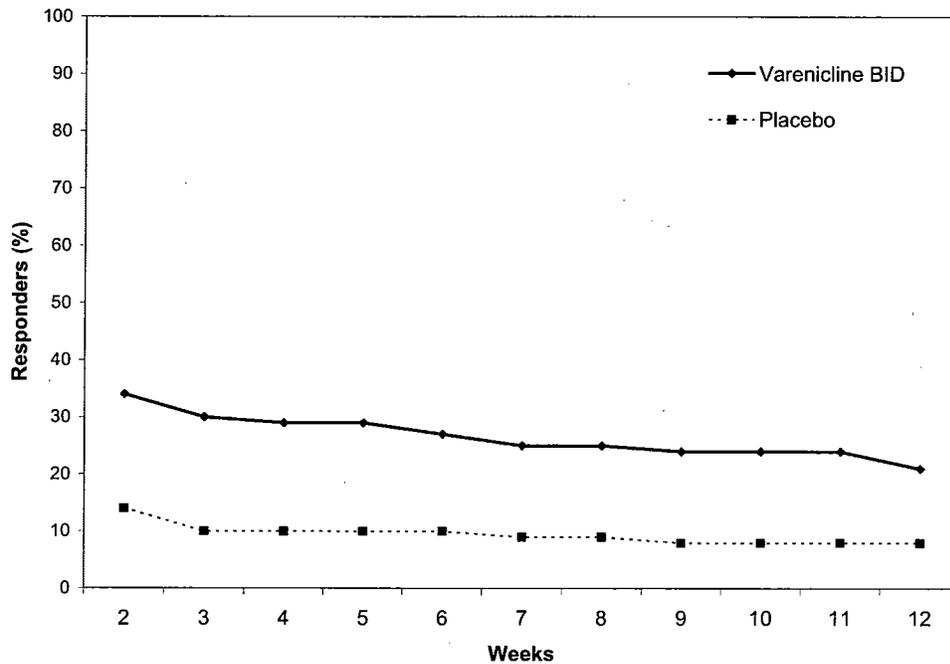
I find that after re-analyzing the applicant's data, the CO-confirmed four-week CQR was significantly higher for the varenicline-treated group than for the placebo-treated group ($p < 0.0001$) in both the Weeks 4 – 7 and the Weeks 9 – 12 analyses. Results of the analyses for the Evaluable and Completer population supported these findings (Table 31).

Table 31: Primary Efficacy Criterion – 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 (12%)
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
Completer	N=109	N=102	N=109	N=102
Abstinent (%)	52 (48%)	14 (14%)	56 (51%)	13 (13%)
p-value vs. placebo		<0.0001		<0.0001

For the All Subjects analyses, the CO-confirmed rate of continuous abstinence from the target quit date (starting at Week 2) to Week 12 was also higher for the varenicline-treated group compared to the placebo. At the Week 12 timepoint, the rate was 21% for varenicline and 8% for placebo (Figure 9).

Figure 9: Continuous Abstinence Rate from Week 2 to Week 12 – (Study 16)



Like the two Phase 3 studies, I also looked at the CO-confirmed continuous abstinence rate from Weeks 3 to 12 to assess the efficacy of varenicline compared to placebo after a shorter grace period. Numerically higher rates of continuous abstinence from Weeks 3 to 12 with varenicline (29%) compared to placebo (9%) were observed (Table 32). Analyses of continuous abstinence rates from Weeks 4, 5, 6, 7, 8 and 9 to Week 12 lead to similar conclusions.

Table 32: Continuous Abstinence Rate from Weeks 3 through Timepoints – Number (%) of Subjects (Study 16)

	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

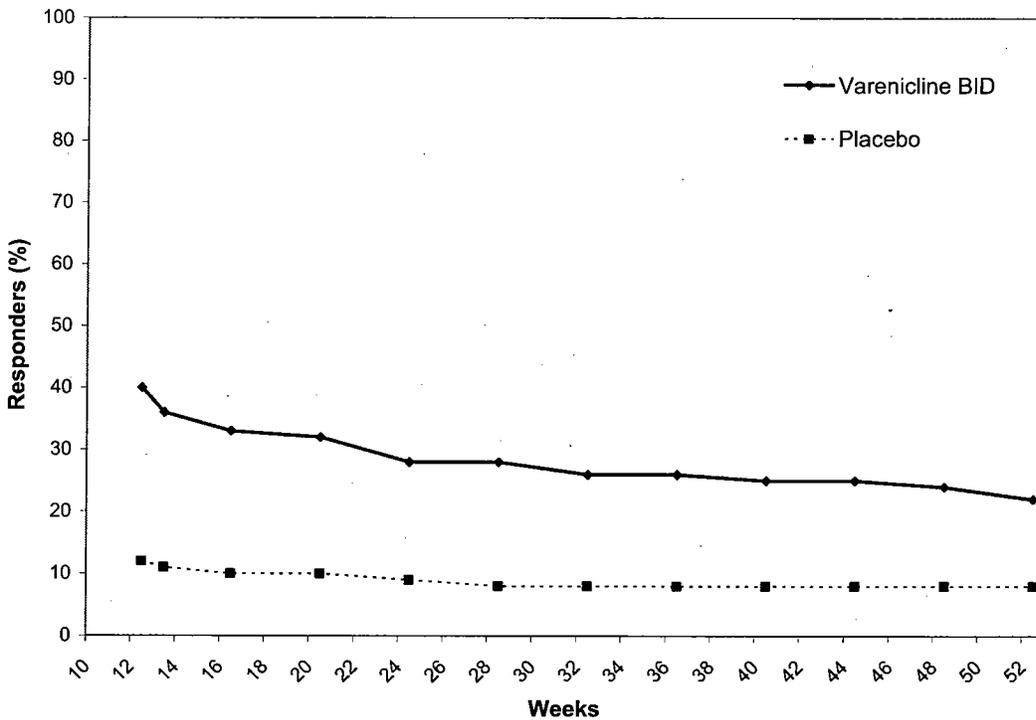
I also find that the CO-confirmed rate of continuous abstinence from Week 9 to Week 52 (primary efficacy parameter in Study 19) was significantly higher for the varenicline-treated group (22%) compared to the placebo (8%, p=0.0001). The CO-confirmed rate of continuous abstinence from Week 9 to Week 24 was also

significantly higher for the varenicline-treated group compared to the placebo (28% versus 9%, $p < 0.0001$) (Table 33 and Figure 10).

Table 33: Continuous Abstinence Rate from Week 9 Through Each Timepoints (Study 16/19)

	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%)

Figure 10: Continuous Abstinence Rate from Week 9 to Week 52 – (16/19)



3.1.4 SUMMARY OF THE REVIEWER'S RESULTS

Like the applicant's, my analysis of the three principal smoking cessation studies (Studies 28, 36 and 07), showed that the four-week continuous quit rate (Weeks 9 – 12) for subjects receiving varenicline 1.0 mg BID were significantly higher than those of the corresponding placebo-treated subjects (Table 34). The four-week continuous quit rate (Weeks 9 – 12) in Study 07 for subjects receiving varenicline 0.5 mg BID was also significantly higher than the placebo-treated group. In the Zyban comparator studies (28 and 36), the two trials demonstrated the superiority of varenicline 1.0 mg BID versus Zyban for smoking cessation as measured by the four-week continuous quit rate (Weeks 9 – 12).

In terms of maintenance of abstinence (Study 35), the continuous abstinence rates at Weeks 13 – 24 (primary efficacy endpoint) for subjects receiving varenicline 1.0 mg BID-treated group were significantly higher compared to the placebo group. The odds of maintained abstinence at Week 24 (following 12 weeks additional treatment with varenicline) were 2.5 times those for placebo. At week 52 (i.e. after a 28-week nontreatment follow-up period), the continuous abstinence rate remained significantly higher in the varenicline-treated group compared to the placebo group (Table 35).

An additional Phase 2 study (16) was also reviewed. This study was conducted to assess the efficacy of flexible dosing (0.5 mg to 2.0 mg total daily dose administered BID) of varenicline over placebo. Like Studies 28, 36 and 07, the CO-confirmed four-week continuous quit rate (Weeks 9 – 12) for subjects receiving varenicline were significantly higher than those of the corresponding placebo-treated subjects (Table 34). Studies 07 and 16 imply that varenicline 0.5 mg BID works as well as varenicline 1.0 mg BID, so that subjects who cannot tolerate varenicline 1.0 mg BID should take varenicline 0.5 mg BID. However, these studies do not support a comparative claim to Zyban at the lower dose of varenicline 0.5 mg BID.

Table 34: Primary Efficacy Criterion – Four-Week Continuous Quit Rate

	Varenicline 0.5 mg BID	Varenicline 1.0 mg BID	Varenicline Flexible	Zyban	Placebo
Study 28 (%) OR (95% CI) varenicline vs.		44%		30%	17%
				1.9 (1.4, 2.6)	3.9 (2.7, 5.5)
Study 36 (%) OR (95% CI) varenicline vs.		44%		30%	18%
				1.9 (1.4, 2.6)	3.8 (2.7, 5.4)
Study 35 (%)		51%*			
Study 07 (%) OR (95%) vs. placebo	45%	51%			12%
	6.1 (3.3, 11.1)	7.8 (4.3, 14.3)			
Study 16 (%) OR (95%) vs. placebo			40%		12%
			5.7 (3.1, 10.4)		

* Post-hoc calculation based on Weeks 8 – 12 data during the open-label phase of Study 35.

There were two secondary endpoints in all the studies (except Study 16) which the applicant described as "key": continuous abstinence rate from week 9 to 52 (in Study 35, continuous abstinence rate is from Week 13 to 52), and the long term quit rate at Week 52. These two endpoints were included in the label. Although it is not unusual to include secondary endpoints in the label, there are reasons why LTQR should not be in the label. According to the Draft Guidance on Labeling, there should be a well-documented, statistically and clinically meaningful effect on prospectively defined endpoint. The applicant described the assessment of LTQR in the nontreatment follow-up phase as the proportion of all subjects treated who (1) were responders

for the four-week continuous quit rate (Weeks 9 – 12) in the treatment phase; and (2) had no more than six days of cigarette smoking during the nontreatment phase. The second item is where the problem lies. In the nontreatment phase, subjects returned for visits to the clinic at Weeks 13, 24, 36, 44, and 52; and received telephone call at Weeks 16, 20, 28, 32, 40 and 48. The number of days the subject smoked cigarettes was determined at each contact after Week 12 by the subject's response to the question on the "Nicotine Use Inventory." Thus, there is a four-week interval for subject to recall the number of days they smoked cigarettes, leading to possible recall bias. Furthermore, as mentioned in Section 3.1.1, although the applicant prespecified a step-down procedure in order to preserve the family-wise type I error rate for multiple contrasts, this procedure is only employed within each endpoint (see Studies 28, 36 and 35). There is no prespecification on how type I error rate could be preserved in testing of multiple endpoints (i.e. key secondary endpoints). Thus, the endpoint LTQR does not qualify to be in the label. On the other hand, continuous abstinence rate from Week 9 – 52 (or Week 13 – 52) was clearly defined, and the results were statistically and clinically meaningful, therefore in my opinion appropriate for labeling.

The rate of Continuous Abstinence from Week 9 through Week 52 was significantly higher for both the varenicline 0.5 mg BID and 1.0 mg BID compared to placebo in studies 28, 36 and 07. Analysis of continuous abstinence rate at Week 9 to 52 in study 16 also suggest significantly higher continuous abstinence rate in the flexible dose varenicline compared to placebo. In the Zyban comparator studies, the rate of Continuous Abstinence through Week 52 for varenicline was also higher than for Zyban (Table 35). In Study 35, the rate of Continuous Abstinence from Week 13 through Week 52, was also significantly higher for varenicline than for placebo.

In Studies 28 and 36, because the rate of continuous abstinence through week 52 for varenicline was not statistically significant different from Zyban, comparison of other secondary endpoints with regards to treatment difference between varenicline and Zyban will not be considered conclusive evidence. Instead, the comparison of other secondary endpoints with regards to treatment difference between varenicline and Zyban will only be considered supportive evidence. With that said, in all studies, the Long-Term Quit Rate (LTQR) at Week 52, was significantly higher for varenicline (either 0.5 mg BID, 1.0 mg BID, or flexible dose) compared to placebo (Table 36). Although LTQR at Week 52 for varenicline was also significantly higher than for Zyban, this will only be considered supportive evidence of the efficacy of varenicline over Zyban.

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Table 35: Continuous Abstinence Rates across different studies

	Varenicline 0.5 mg BID	Varenicline 1.0 mg BID Weeks 9 – 52	Varenicline Flexible	Zyban	Placebo
Study 28 (%)		21%		16%	8%
Study 36 (%)		22%		14%	10%
Study 35 (%)*		41%			35%
Study 07/18 (%)	19%	23%			4%
Study 16/19 (%)			22%		8%
Weeks 9 – 24					
Study 28 (%)		29%		19%	10%
Study 36 (%)		29%		20%	13%
Study 35 (%)*		70%			50%
Study 07/18 (%)	24%	30%			6%
Study 16/19 (%)			28%		9%

* Continuous abstinence rate from Week 13 to Week 52 and from Week 13 to Week 24 data during the nontreatment phase of Study 35.

Table 36: Long Term Quit Rate at Week 52 across different studies

	Varenicline 0.5 mg BID	Varenicline 1.0 mg BID LTQR at Week 52	Varenicline Flexible	Zyban	Placebo
Study 28 (%)		25%		17%	9%
Study 36 (%)		25%		18%	13%
Study 35 (%)		48%			41%
Study 07/18 (%)	22%	27%			4%
Study 16/19 (%)			26%		8%

Three aspects of smoking cessation to address the objective of comparing varenicline to placebo were investigated by the applicant using Patient Reported Outcomes questionnaires. Similar to the multiplicity problem in the secondary endpoints, the applicant failed to specify how type I error rate could be preserved in testing these multiple endpoints, even though the comparison is only between varenicline and placebo.

Furthermore, according to the findings of Dr. Jane Scott (Study Endpoints and Label Development reviewer), the content validity of both the “symptoms of withdrawal” and the “reinforcing effects of smoking” measures have not been adequately documented. Therefore, the claims of “symptoms of withdrawal” and/or “reduction of reinforcing effects of smoking” will not be granted. However, because there are consistent and compelling findings to suggest a reduction in the “urge to smoke”, this claim is appropriate for labeling.

3.2 EVALUATION OF SAFETY

Dr. Josefberg has reviewed the safety of varenicline in detail. He found no issues requiring statistical evaluation.

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

4.1 SEX, RACE AND AGE

The applicant conducted post hoc subgroup analyses based on gender, age, race, and baseline smoking characteristics (i.e. total Fagerstrom score and average number of cigarettes smoked during the month prior to study enrollment) using pooled data from Studies 28, 36, and 1 mg BID arm of Study 07. In their analysis, they split the age into <45 and ≥45 years because they claim that the small number of subjects ≥65 years (2%) precluded a meaningful analysis based on the age groups designated in ICH-E7. There were no remarkable effects of age, gender or baseline smoking characteristics on either four-week continuous quit rate (Weeks 9 – 12) or continuous abstinence (Weeks 9 – 52). They claimed that in the by-race analysis, the small number of non-white subjects limits the ability to estimate precisely the treatment effect in these subpopulations. Nonetheless, it appears that the weeks 9 – 12 CQRs and the CA rates from Weeks 9 – 24 and Weeks 9 – 52 were similar in Whites and Other races. Varenicline also increased the rate of smoking cessation in Blacks, however, the CQR and CA rates from Weeks 9 – 24 and Weeks 9 – 52 were lower than those of the Whites and Other races, and the treatment effects were smaller (Blacks OR = 1.72 versus White OR = 4.57 and Other OR=4.08). The applicant claimed that this finding of a smaller treatment effect in Blacks is consistent with published survey data for the United States showing that fewer Blacks than Whites or Hispanics remained abstinent for at least one month.

When subgroup analyses were conducted separately for each of the five studies reviewed, there were no remarkable effects of age, gender, or baseline smoking characteristics on four-week continuous quit rate between varenicline 1.0 mg BID and placebo, except on Study 07 (gender). Because nearly all subjects in each study were white, it is impossible to distinguish the possible treatment effects of race on the four-week continuous quit rate (Table 39 to Table 43).

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Table 37: Weeks 9 – 12 CQR and Continuous Abstinence (Weeks 9 – 24 and Weeks 9 – 52) by Age, Gender, Race: Pooled Principal Smoking Cessation Studies

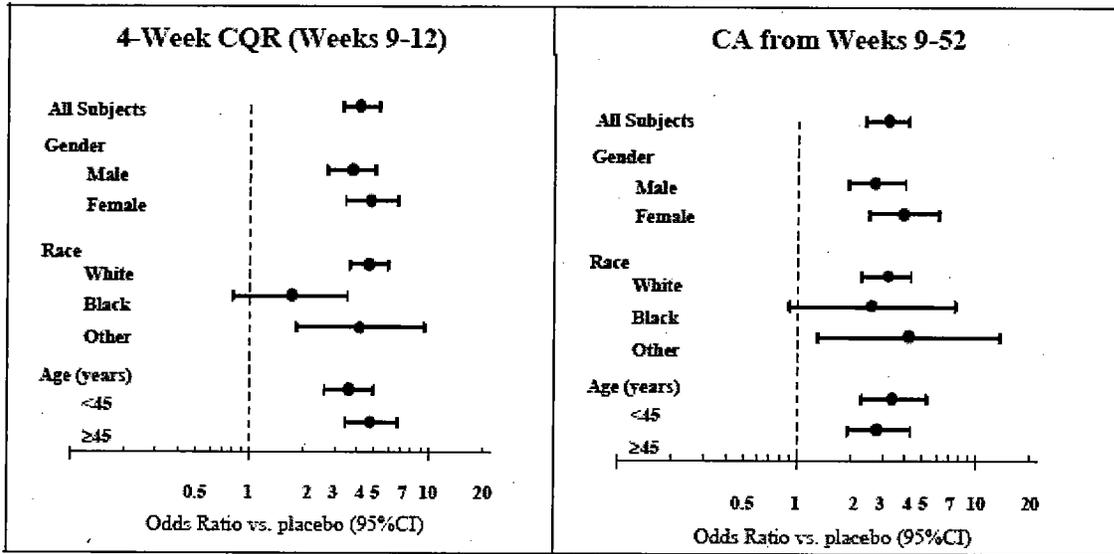
	Responders n/N (%)	OR (95% CI) vs. placebo	p-value vs. Pbo	Responders n/N (%)	OR (95% CI) vs. placebo	p-value vs. Pbo
				<u><45 years</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	205/496 (41.3)	3.58 (2.63, 4.86)	<0.0001	229/449 (51.0)	4.67 (3.40, 6.66)	<0.0001
Placebo	76/467 (16.3)	--	--	60/338 (17.8)	--	--
Continuous Abstinence Weeks 9-24						
Varenicline	130/496 (26.2)	3.27 (2.27, 4.72)	<0.0001	151/449 (33.6)	3.68 (2.51, 5.40)	<0.0001
Placebo	47/467 (10.1)	--	--	41/338 (12.1)	--	--
Continuous Abstinence Weeks 9-52						
Varenicline	101/496 (20.4)	3.43 (2.25, 5.23)	<0.0001	113/449 (25.2)	2.83 (1.88, 4.25)	<0.0001
Placebo	33/467 (7.1)	--	--	36/338 (10.7)	--	--
				<u>Male</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	220/489 (45.0)	3.69 (2.73, 5.00)	<0.0001	214/456 (46.9)	4.74 (3.36, 6.67)	<0.0001
Placebo	80/448 (17.9)	--	--	56/357 (15.7)	--	--
Continuous Abstinence Weeks 9-24						
Varenicline	148/489 (30.3)	3.06 (2.17, 4.32)	<0.0001	133/456 (29.2)	4.29 (2.82, 6.52)	<0.0001
Placebo	56/448 (12.5)	--	--	32/357 (9.0)	--	--
Continuous Abstinence Weeks 9-52						
Varenicline	109/489 (22.3)	2.73 (1.86, 4.01)	<0.0001	105/456 (23.0)	3.87 (2.45, 6.12)	<0.0001
Placebo	43/448 (9.6)	--	--	26/357 (7.3)	--	--
				<u>Female</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	381/782 (48.7)	4.57 (3.55, 5.87)	<0.0001	26/97 (26.8)	1.72 (0.84, 3.50)	0.1347
Placebo	110/637 (17.3)	--	--	16/99 (16.2)	--	--
Continuous Abstinence Weeks 9-24						
Varenicline	248/782 (31.7)	3.57 (2.68, 4.76)	<0.0001	14/97 (14.4)	2.04 (0.77, 5.27)	0.1396
Placebo	76/637 (11.9)	--	--	7/99 (7.1)	--	--
Continuous Abstinence Weeks 9-52						
Varenicline	189/782 (24.2)	3.15 (2.30, 4.32)	<0.0001	12/97 (12.4)	2.56 (0.86, 7.63)	0.0800
Placebo	60/637 (9.4)	--	--	5/99 (5.1)	--	--
				<u>White</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	27/66 (40.9)	4.08 (1.76, 9.50)	0.0006			
Placebo	10/69 (14.5)	--	--			
Continuous Abstinence Weeks 9-24						
Varenicline	19/66 (28.8)	5.36 (1.83, 15.7)	0.0008			
Placebo	5/69 (7.2)	--	--			
Continuous Abstinence Weeks 9-52						
Varenicline	13/66 (19.7)	4.15 (1.27, 13.6)	0.0111			
Placebo	4/69 (5.8)	--	--			
				<u>Black</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	27/66 (40.9)	4.08 (1.76, 9.50)	0.0006			
Placebo	10/69 (14.5)	--	--			
Continuous Abstinence Weeks 9-24						
Varenicline	19/66 (28.8)	5.36 (1.83, 15.7)	0.0008			
Placebo	5/69 (7.2)	--	--			
Continuous Abstinence Weeks 9-52						
Varenicline	13/66 (19.7)	4.15 (1.27, 13.6)	0.0111			
Placebo	4/69 (5.8)	--	--			
				<u>Other</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	27/66 (40.9)	4.08 (1.76, 9.50)	0.0006			
Placebo	10/69 (14.5)	--	--			
Continuous Abstinence Weeks 9-24						
Varenicline	19/66 (28.8)	5.36 (1.83, 15.7)	0.0008			
Placebo	5/69 (7.2)	--	--			
Continuous Abstinence Weeks 9-52						
Varenicline	13/66 (19.7)	4.15 (1.27, 13.6)	0.0111			
Placebo	4/69 (5.8)	--	--			

Sources: Section 2.7.3 Tables A13.1, A25.1, A14.1, A26.1, Tables A13.3, A25.3, A14.3, A26.3, Tables A13.2, A25.2, A14.2, A26.2

OR (95% CI)= Odds ratio (95% Confidence Interval)

Source: Summary of Clinical Efficacy Smoking Cessation, page 72

Figure 11: Treatment Effect (as Odds Ratio) for four-week CQR and CA from Weeks 9 – 52 by Gender, Race, and Age: Pooled Principal Smoking Cessation Studies



Sources: Section 2.7.3 Tables A7.1, A8.1, A13.1, A13.2, A13.3, A14.1, A14.2, A14.3

Source: Summary of Clinical Efficacy Smoking Cessation, page 73

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Table 38: Weeks 9 – 12 CQR and Continuous Abstinence (Weeks 9 – 24 and Weeks 9 – 52) by Number of cigarettes smoked per day in the past month and Fagerstrom total score: Pooled Principal Smoking Cessation Studies

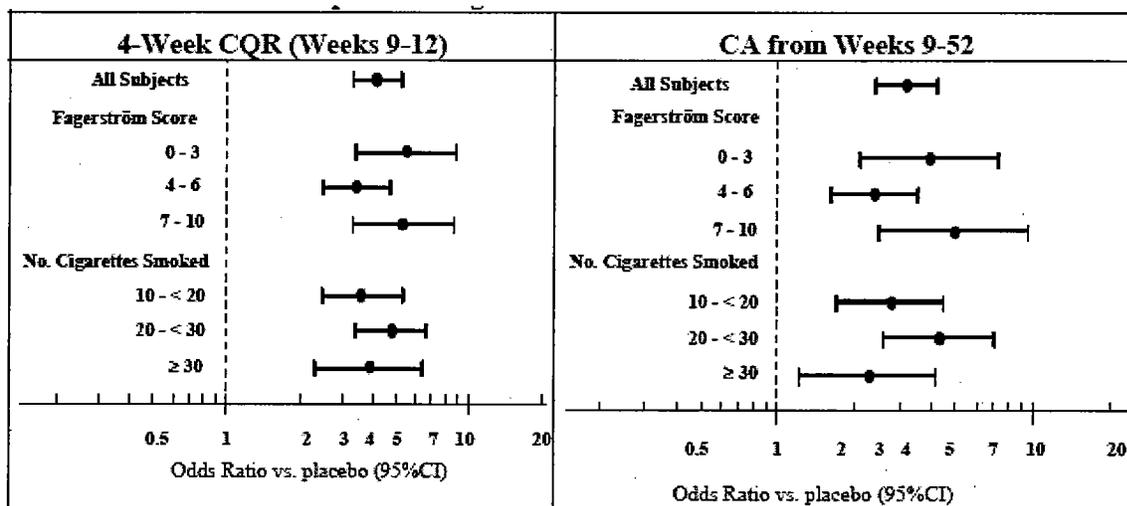
	Responders n/N (%)	OR (95% CI) vs. placebo	p-value vs. Pbo	Responders n/N (%)	OR (95% CI) vs. placebo	p-value vs. Pbo
				<u>10-<20 cigarettes/day</u>		
				<u>Fagerström Total Score 0-3 (mild)</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	157/301 (52.2)	3.64 (2.49, 5.32)	<0.0001	108/196 (55.1)	5.49 (3.38, 8.93)	<0.0001
Placebo	55/241 (22.8)	--	--	32/169 (18.9)	--	--
Continuous Abstinence Weeks 9-24						
Varenicline	101/301 (33.6)	2.81 (1.83, 4.31)	<0.0001	71/196 (36.2)	4.30 (2.47, 7.46)	<0.0001
Placebo	37/241 (15.4)	--	--	21/169 (12.4)	--	--
Continuous Abstinence Weeks 9-52						
Varenicline	84/301 (27.9)	2.77 (1.73, 4.41)	<0.0001	54/196 (27.6)	3.94 (2.12, 7.34)	<0.0001
Placebo	29/241 (12.0)	--	--	15/169 (8.9)	--	--
				<u>20-<30 cigarettes/day</u>		
				<u>Fagerström Total Score 4-6 (moderate)</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	192/428 (44.9)	4.76 (3.37, 6.62)	<0.0001	217/448 (48.4)	3.42 (2.50, 4.67)	<0.0001
Placebo	56/388 (14.4)	--	--	79/381 (20.7)	--	--
Continuous Abstinence Weeks 9-24						
Varenicline	126/428 (29.4)	5.16 (3.35, 7.94)	<0.0001	139/448 (31.0)	3.00 (2.09, 4.31)	<0.0001
Placebo	30/388 (7.7)	--	--	50/381 (13.1)	--	--
Continuous Abstinence Weeks 9-52						
Varenicline	86/428 (20.1)	4.31 (2.62, 7.07)	<0.0001	103/448 (23.0)	2.39 (1.61, 3.53)	<0.0001
Placebo	22/388 (5.7)	--	--	43/381 (11.3)	--	--
				<u>≥30 cigarettes/day</u>		
				<u>Fagerström Total Score 7-10 (severe)</u>		
4-Week CQR (Weeks 9-12)						
Varenicline	85/215 (39.5)	3.85 (2.32, 6.38)	<0.0001	107/298 (35.9)	5.28 (3.25, 8.59)	<0.0001
Placebo	25/175 (14.3)	--	--	24/250 (9.6)	--	--
Continuous Abstinence Weeks 9-24						
Varenicline	54/215 (25.1)	2.4 (1.38, 4.18)	0.0013	69/298 (23.2)	4.33 (2.43, 7.71)	<0.0001
Placebo	21/175 (12.0)	--	--	16/250 (6.4)	--	--
Continuous Abstinence Weeks 9-52						
Varenicline	44/215 (20.5)	2.25 (1.24, 4.08)	0.0059	56/298 (18.8)	4.91 (2.50, 9.64)	<0.0001
Placebo	18/175 (10.3)	--	--	11/250 (4.4)	--	--

Sources: Section 2.7.3 Tables A7.1, A8.1, A13.4, A25.4, A14.4, A26.4, A13.5, A25.5, A14.5, A26.5
 OR (95% CI)= Odds ratio (95% Confidence Interval)

Source: Summary of Clinical Efficacy Smoking Cessation, page 74

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Figure 12: Treatment Effect (as Odds Ratio) for four-week CQR and CA from Weeks 9 – 52 by Number of cigarettes smoked per day in the past month and Fagerstrom total score: Pooled Principal Smoking Cessation Studies



Sources: Section 2.7.3 Tables A7.1, A8.1, A13.4, A13.5, A14.4, A14.5

Source: Summary of Clinical Efficacy Smoking Cessation, page 75

Table 39: 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)

Table 40: 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)

Table 41: Weeks 9 – 12 CQR by Age, Gender, Race, and Baseline Smoking Characteristics – Study 07

	Varenicline 0.5 mg BID % (n/N)	OR (95% CI) p-value	Varenicline 1.0 mg BID % (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)

Table 42: 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)	-

Table 43: 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)

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

There are no major statistical issues in this NDA submission that could not be handled by recoding and re-analyzing the data. Examples of these issues are the missing data imputation used by the applicant regarding the carbon monoxide measurements and on responders (abstinence) in the Phase 3 studies (28, 36 and 35), as well as the lack of prespecified procedure in handling multiple endpoints.

As mentioned, the claims of “craving reduction”, “symptoms of withdrawal” and/or “reduction of reinforcing effects of smoking” should not be granted because according to Jane Scott, the content validity of both the “symptoms of withdrawal” and the “reduction of reinforcing effects of smoking” are not well documented, and the concept of “urge to smoke” is more appropriate for labeling compared to “craving reduction”.

Lastly, because the results in both study 28 and 36 were so similar, we felt the need to investigate whether the data submitted for the two studies were accurate. Based on the preliminary results from the investigation, it appears that the data from the two studies were accurate. Subjects who were randomly chosen and contacted by the DSI investigators confirmed their existence and the data reported on their study records were correct.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Varenicline at the recommended dosing of 1.0 mg BID for 12 weeks appears to be superior to placebo for smoking cessation at the end of the treatment period, and at one year from the start of the treatment.. There is evidence that varenicline is superior to Zyban.

In subjects who stopped smoking at the end of 12 weeks, an additional 12 weeks of treatment appears to be more beneficial than placebo in maintaining abstinence to the end of treatment and to one year from the start of treatment.

Furthermore, based on Studies 07 and 16, varenicline 0.5 mg BID appears to work as well as varenicline 1.0 mg BID, so that subjects who cannot tolerate varenicline 1.0 mg BID should take varenicline 0.5 mg BID.

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6 LABELING

Below is a portion of the proposed draft label. The first part is the original version taken from the proposed draft label, and the second part is the corrected version Dr. Winchell and I worked on during the review process. We made the changes because the applicant did not include all the relevant Phase 2 studies in the original version. We believe it is important to discuss these Phase 2 studies because these studies provided additional efficacy information about the study drug that are going to be helpful to the prescribing physician including the dosage (e.g. 0.5 mg BID is also superior to placebo) and administration of the study drug (i.e. fixed dose versus flexible dose). Patients who are taking a fixed dose of 1.0 mg BID and who could not tolerate the dose can down-titrate to 0.5 mg BID based on the results of these additional studies. Furthermore, as discussed in my review, there were some claims made by the applicant that were not appropriate for labeling (e.g. the long term quit rates, and the claims of withdrawal symptom and reinforcing effects of smoking)

6.1 ORIGINAL VERSION

CLINICAL STUDIES

[

]

COMPARATIVE CLINICAL STUDIES

[

]

6.2 CORRECTED VERSION

The efficacy of CHANTIX in smoking cessation was demonstrated in six clinical trials in which a total of 3659 chronic cigarette smokers (≤ 10 cigarettes per day) were treated with varenicline. In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide ($CO \leq 10$ ppm) at weekly visits. Among the varenicline-treated patients enrolled in these studies, the completion rate was 65%. Except for the initial Phase 2 study (Study 1) and the maintenance of abstinence study (Study 6), patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. Most subjects enrolled in these trials were white (79% - 96%). All studies enrolled almost equal numbers of men and women. The average age of subjects in these studies was 43 years. Subjects on average had smoked about 21 cigarettes per day for an average of approximately 25 years.

In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines. Patients set a date to stop smoking (target quit date, TQD) with dosing starting 1-2 weeks before this date.

INITIATION OF ABSTINENCE

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

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

with full dosage achieved starting with the second week of dosing. The titrated and nontitrated groups were pooled for efficacy analysis.

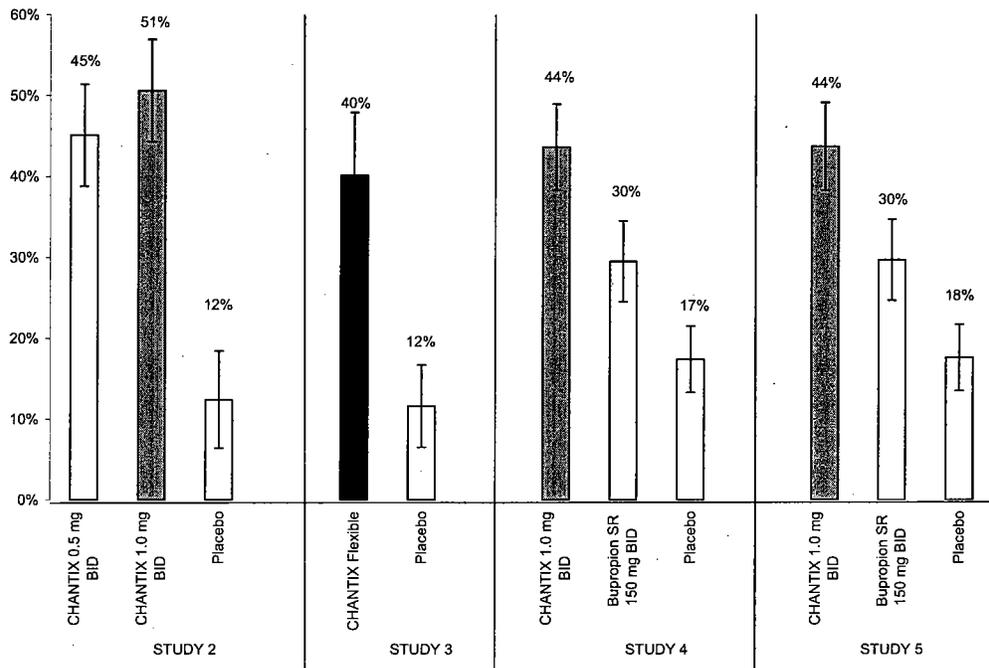
Forty five percent of subjects receiving CHANTIX 1 mg per day (0.5 mg BID) and 51% subjects receiving 2 mg per day (1 mg BID) had CO-confirmed continuous abstinence between weeks 9 to 12 compared to 12% subjects in the placebo group, (Figure 7). In addition, 31% of the 1 mg per day group and 31% of the 2 mg per day group were continuously abstinent from one week after TQD through the end of treatment as compared to 8% of the placebo group.

Study 3: This flexible-dosing study of 312 subjects examined the effect of a patient-directed dosing strategy of CHANTIX or placebo. After an initial one-week titration to a dose of 0.5 mg BID, subjects could adjust their dosage as often as they wished between 0.5 mg QD to 1 mg BID per day. 69% patients titrated to the maximum allowable dose at any time during the study []

Of the subjects treated with CHANTIX, 40% had CO-confirmed four-week continuous abstinence [] weeks 9 to 12 compared to 15% in the placebo group. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 9% of the placebo group.

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

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URGE TO SMOKE

Based on responses to the Brief Questionnaire on Smoking Urges and the Minnesota Nicotine Withdrawal scale “Urge to Smoke” item, CHANTIX reduced urge to smoke compared to placebo in all studies.

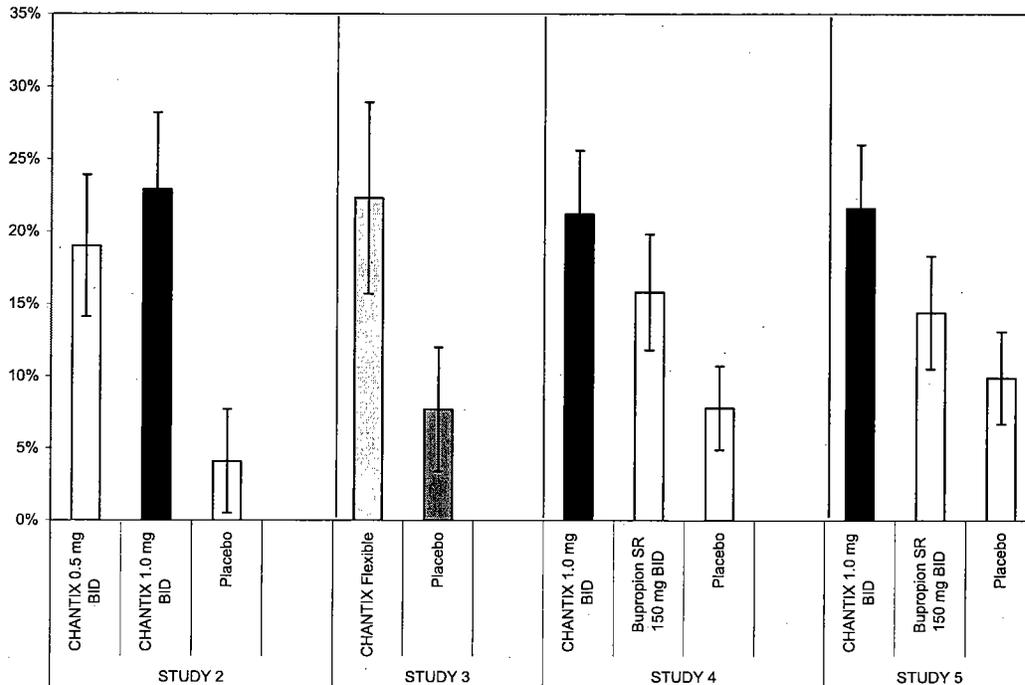
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Studies 1 through 5 included 40 weeks of post-treatment follow-up. In each study, CHANTIX-treated patients were more likely to maintain abstinence throughout the follow-up period than were patients treated with placebo (Table —

[] Continuous Abstinence — Weeks 9 – 52, []

	Varenicline 0.5 mg BID	Varenicline 1.0 mg BID	Varenicline Flexible	Bupropion SR	Placebo
Study 2					
Study 3					
Study 4					
Study 5					

Continuous Abstinence Weeks 9 to 52

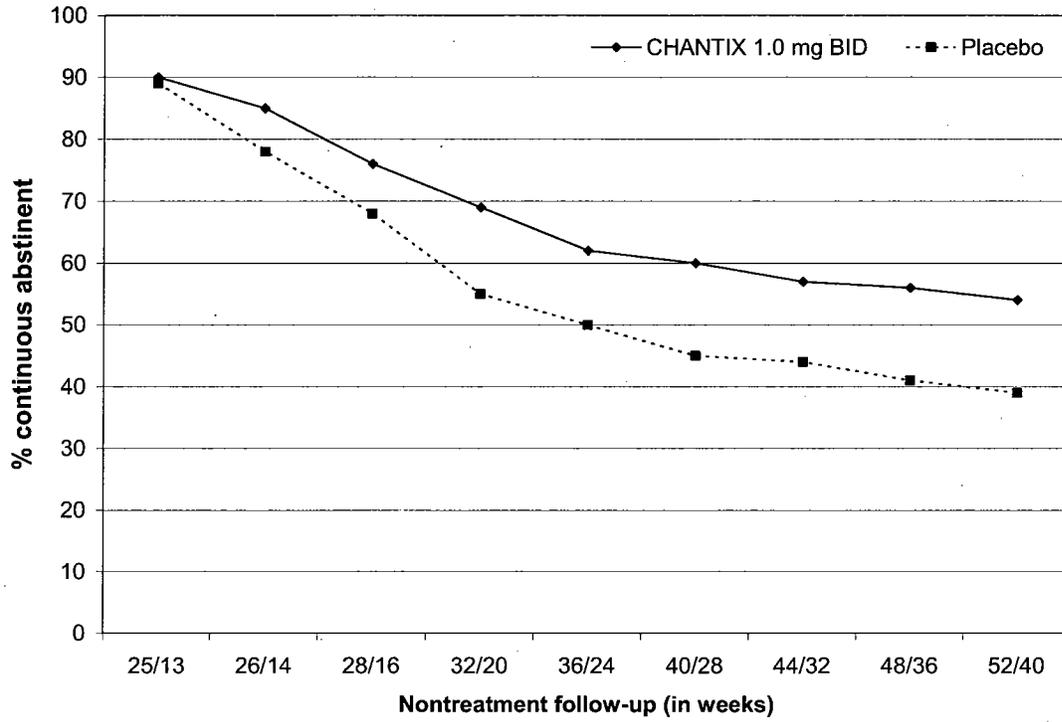


Study 6: This study assessed the effect of an additional 12 weeks of CHANTIX therapy on the likelihood of long-term abstinence. Patients in this study (n=1927) were treated with open-label CHANTIX 1 mg BID for 12 weeks. Patients who had stopped smoking by Week 12 were then randomized to double-blind treatment with CHANTIX (1 mg BID) or placebo for an additional 12 weeks and then followed for 28 weeks post-treatment.

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

In the figure below, the x-axis represents the study week for each observation allowing a comparison of groups at similar times after discontinuation of CHANTIX. Post-CHANTIX follow-up begins at Week 13 for the placebo group and Week 1 for the CHANTIX group. The y-axis represents the percent of subjects who had been abstinent for the last week of CHANTIX treatment and remained abstinent at the given timepoint.

Figure 1 Continuous Abstinence Rate during nontreatment follow-up



7 APPENDIX

Table 7.1: Subject Disposition – Studies 28 and 36

	Study 28			Study 36		
	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
Evaluable Population ^b	309 (89%)	275 (84%)	302 (88%)	310 (90%)	295 (87%)	304 (89%)
Completer Population ^c	244 (70%)	211 (64%)	202 (59%)	239 (70%)	225 (66%)	209 (62%)
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	34	24	14	16	13
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	31	42	28	31	51
Lost to follow-up	43	36	49	33	39	43
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%)

^aTreated: All randomized subjects who took at least one dose of study medication

^bEvaluated: Subset of the All Subjects population who received at least 14 days of study medication in the first 21 days of the study.

^cCompleter: 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.

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Table 7.2: Subject Disposition – Studies 35

	Open-Label	Double-Blind	
	Varenicline	Varenicline	Placebo
Screened	2416		
Assigned to Treatment	1928	603	607
All Subjects (Treated) ^a	1927	601	603
Completed the Study	1210 (63%)	493 (82%)	463 (77%)
Discontinued Study	717 (37%)	108 (18%)	140 (23%)
During the treatment Phase		47 (8%)	93 (15%)
Adverse Events	200	8	8
Lack of Efficacy	29	4	5
Protocol Deviations	71	3	2
Pregnancy	1	0	0
Refusal to participate further	150	19	44
Lost to follow-up	132	12	30
Other	134	1	4
During the non-treatment Phase		61 (10%)	47 (8%)
Subject Died		2	0
Adverse Events		2	1
Lack of Efficacy		0	2
Protocol Deviations		0	0
Pregnancy		0	0
Refusal to participate further		27	19
Lost to follow-up		28	24
Other		2	1
Evaluable Population ^b		574 (96%)	574 (95%)
Completer Population ^c		494 (83%)	474 (79%)
Protocol Deviations	44 (6%)	15 (3%)	28 (5%)

^aTreated: All randomized subjects who took at least one dose of study medication

^bEvaluated: Subset of the All Subjects population who received at least 14 days of study medication in the first 21 days of the study.

^cCompleter: 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.

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Table 7.3: Subject Disposition – Studies 07/18

	Varenicline				Placebo
	0.5 mg BID nontitrated	0.5 mg BID titrated	1.0 mg BID nontitrated	1.0 mg BID titrated	
Screened	980				
	Treatment Phase (STUDY 07)				
Assigned to Treatment	129	130	129	130	129
All Subjects (Treated) ^a	124	129	124	129	121
Evaluable Population ^b	113 (91%)	118 (92%)	114 (92%)	121 (94%)	104 (86%)
Completed the Study	96 (77%)	92 (71%)	95 (77%)	100 (78%)	72 (60%)
Discontinued Study	28 (23%)	37 (29%)	29 (23%)	29 (23%)	49 (41%)
Discontinuation by Reason:					
Adverse Events ^c	4	7	8	6	9
Lack of Efficacy	0	2	2	0	4
Subject Defaulted ^d	23	27	16	16	31
Other ^e	1	1	3	7	5
Completer Population ^f	88 (71%)	81 (63%)	84 (68%)	78 (61%)	66 (55%)
Discontinued Study Treatment	36 (29%)	48 (37%)	40 (32%)	51 (40%)	55 (45%)
Discontinuation by Reason:					
Adverse Events ^c	9	19	18	28	22
Lack of Efficacy	0	2	2	0	4
Subject Defaulted ^d	21	25	16	13	23
Other ^e	6	2	8	10	6
Protocol Deviations	18	17	15	19	21
	Nontreatment Phase (STUDY 18)				
Entered ^g	88 (71%)	77 (60%)	86 (69%)	93 (72%)	54 (45%)
Completed	63 (51%)	60 (47%)	69 (56%)	77 (60%)	40 (33%)
Discontinued (Subject Defaulted)	25 (20%)	17 (13%)	17 (14%)	16 (12%)	14 (12%)

^aTreated: All randomized subjects who took at least one dose of study medication

^bEvaluated: Subset of the All Subjects population who received at least 14 days of study medication in the first 21 days of the study.

^cAdverse event includes laboratory abnormalities

^dSubject defaulted = subject withdrew consent or was lost to follow-up

^eOther includes: protocol violations, subject did not meet entry criteria, noncompliance, and personal reasons.

^fCompleter: 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.

^gDenominator, N, in the number of subjects treated in Study 07.

Table 7.4: Subject Disposition – Studies 16/19

	Varenicline 0.5 mg BID nontitrated	Placebo
Screened	434	
Treatment Phase (16)		
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%)
Discontinuation by Reason:		
Adverse Events ^c	7	2
Lack of Efficacy	0	7
Subject Defaulted ^d	24	34
Other ^e	4	2
Completer Population ^f	109 (69%)	102 (66%)
Discontinued Study Treatment	48 (31%)	53 (34%)
Discontinuation by Reason:		
Adverse Events ^c	11	7
Lack of Efficacy	0	7
Subject Defaulted ^d	23	33
Other ^e	14	6
Protocol Deviations	13	24
Nontreatment Phase (19)		
Entered ^g	120 (76%)	100 (65%)
Completed	100 (64%)	40 (33%)
Discontinued	20 (13%)	11 (7%)
Subject Defaulted	18	11
Other	2	0

^aTreated: All randomized subjects who took at least one dose of study medication

^bEvaluated: Subset of the All Subjects population who received at least 14 days of study medication in the first 21 days of the study.

^cAdverse event includes laboratory abnormalities

^dSubject defaulted = subject withdrew consent or was lost to follow-up

^eOther includes: protocol violations, subject did not meet entry criteria, noncompliance, and personal reasons.

^fCompleter: 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.

^gDenominator, N, in the number of subjects treated in Study 07.

Table 7.5: Demographic and Baseline Characteristics – Studies 28 and 36

	Study 28			Study 36		
	Varenicline N=349	Zyban N=329	Placebo N=344	Varenicline N=343	Zyban N=340	Placebo N=340
Sex (Male), n(%)	175 (50%)	192 (58%)	186 (54%)	189 (55%)	206 (61%)	198 (58%)
Mean Age (SD), y	43 (11)	42 (12)	43 (12)	45 (12)	43 (12)	43 (12)
Range	18 – 75	18 – 75	18 – 73	18 – 75	18 – 73	19 – 75
Race, n(%)						
White	278 (80%)	264 (80%)	262 (76%)	294 (86%)	281 (83%)	289 (85%)
Black	35 (10%)	28 (9%)	49 (14%)	30 (9%)	36 (11%)	26 (8%)
Asian	4 (1%)	5 (2%)	9 (3%)	8 (2%)	4 (1%)	6 (2%)
Other	32 (9%)	32 (10%)	24 (7%)	11 (3%)	19 (6%)	19 (6%)
	N=348	N=329	N=343	N=343	N=340	N=340
Number of years subject smoked						
Mean	24	24	25	27	26	24
Range	2 – 56	2 – 61	1 – 61	2 – 59	2 – 57	2 – 60
Number of cigarettes per day over past month						
Mean	21	21	22	23	22	22
Range	10 – 70	10 – 65	10 – 80	10 – 60	10 – 60	10 – 60
Previous Serious quit attempt						
None	53 (15%)	45 (14%)	55 (16%)	53 (15%)	46 (14%)	45 (13%)
>1	295 (85%)	284 (86%)	288 (84%)	290 (85%)	294 (86%)	295 (87%)
Longest period of abstinence in past year, d						
Mean	5.0	5.8	5.6	6.3	7.6	8.0
Range	0 – 90	0 – 90	0 – 97	0 – 90	0 – 90	0 – 180
Fagerstrom Test for Nicotine Dependence Score ^a						
N	347	329	342	342	339	338
Mean (SD)	5.2 (2.2)	5.2 (2.1)	5.4 (2.0)	5.4 (2.2)	5.4 (2.2)	5.2 (2.2)

^a Fagerstrom score can range from 0 to 10, with higher scores indicating greater nicotine dependence.

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Table 7.6: Duration of Treatment – Number (%) of Subjects (Study 28)

	Varenicline N = 349	Zyban N = 329	Placebo N = 344
Duration (Days)^a			
≥1	349 (100.0)	329 (100.0)	344 (100.0)
Unknown ^b	6 (1.7)	9 (2.7)	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

Source: Table 13.3.1

^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.

Source: Clinical Study Report 28 page 62

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Table 7.7: Duration of Treatment – Number (%) of Subjects (Study 36)

	Varenicline N = 343	Zyban N = 340	Placebo N = 340
Duration (Days)^a			
≥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	1 - 102	1 - 100	3 - 133

Source: Table 13.3.1

^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.

Source: Clinical Study Report 36 page 60

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Table 7.8: Demographic and Baseline Characteristics – Studies 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.

Source: Study Report 35 page 57

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Table 7.9: Demographic and Baseline Characteristics – Studies 07

	CP-526,555				
	0.5 mg BID nontitrated N = 124	0.5 mg BID titrated N = 129	1.0 mg BID nontitrated N = 124	1.0 mg BID 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)	96 (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	20.3	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 Nicotine Dependence Score*					
N	122	129	124	129	120
Mean	5.47	5.43	5.58	5.35	5.77

Source: Tables 2.1, 2.2.1, 2.2.2

*Fagerström score²⁴ can range from 0 to 10, with higher scores indicating greater nicotine dependence.

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Table 7.10: Demographic and Baseline Characteristics – Studies 16

	CP-526,555 N = 157	Placebo N = 155
Sex [n (%)]		
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 Score ^a		
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 (days)		
Mean	8.38	8.59
Range	0-90	0-90

Source: Tables 2.1, 2.2.1, 2.2.2

SD = standard deviation

^a Fagerström score¹⁴ can range from 0 to 10, with higher scores indicating greater nicotine dependence.

Source: Clinical Study Report 16, page 34

Table 7.11: Modal Daily Dose (mg or mg Equivalents) by Week – Study 16

	CP-526,555			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	

Source: Tables 3.1.1 and 3.1.2

Source: Clinical Study Report 16, page 36

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/s/

Joan Buenconsejo
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Thomas Permutt
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S. Edward Nevius
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U.S. Department of Health and Human Services
Food and Drug Administration

Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA: 21928

Drug Name: CHAMPIX™ (Varenicline Tartrate) Tablets

Applicant: Pfizer Inc.

Indication: Smoking cessation

Biometrics Division: Biometrics Division 2

Statistical Reviewer: Moh-Jee Ng, M.S. (HFD-715)

Concurring Reviewers: Karl Lin, Ph.D. (HFD-715)

Medical Division: Division of Anesthetic, Critical Care and Addiction Drug Products

Pharmacologist: Mamata De, Ph.D. (HFD-170)

Keywords: NDA review, carcinogenicity

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Executive Summary

Statistical analyses of 2-year carcinogenicity studies of varenicline in rats and mice showed no statistically significant, positive dose-response relationships in the incidence of any tumors in either sex and in either species. There were two vehicle control groups and three treated groups. Rats received varenicline at dose levels of 1, 5, or 15 mg/kg/day, and mice received at dose levels of 1, 5, or 20 mg/kg/day. In mice, but not in rats, both sexes showed statistically significant, dose-related increases in mortality ($p < 0.05$). The high-dose male and female rats show significant change in mean body weight reduction (more than 10% reduction in mean body weight relative to the control group). The high-dose male mice had a 1% increase and the high-dose female mice had 3% increase in mean body weight relative to the control group. The survival data show that they were sufficient numbers of animals living long enough to be at risk of late-developing tumor. The body weight data of the rat study show that the high dose is close to MTD. However, analyses of the body weight and survival data can't reach a conclusion on the appropriateness of the high dose used in mouse studies. Other information such as if the animals exhibit clinical signs and histopathological toxic effects that was attributed to the dosed drug should be used for the evaluation of the appropriateness of the high dose.

Introduction

The objective of this review is to evaluate the oncogenic potential of varenicline (also referred to as CP-526,555) when administered by oral gavage daily to rats and mice for two years. There were two vehicle control groups (CD) and three treated groups, namely low dose (LD), medium dose (MD), and high dose (HD). Animals in the two control groups were administered the vehicle (distilled water) at a dose volume of 10 mg/kg/day. For rats, the dose levels for the three treatment groups were 1, 5, and 15 mg/kg/day for LD, MD, and HD groups, respectively. For mice, the dose levels for the three treatment groups were 1, 5, and 20 mg/kg/day for LD, MD, and HD groups, respectively. Due to excessive mortality, the HD males were terminated after 93 weeks of treatment, and the rest were terminally sacrificed at 104 weeks. There were 65 animals of each sex in each treatment group for both rats and mice. The study design is summarized in Table 1.

Table 1: Overall designs of 2-year carcinogenicity study of varenicline in rats and mice

Species	Rat	Mice
Strain	CD [®] (SD)IGS BR	:CD-1 [®] (ICR)BR
Route of Administration	Oral	Oral
Dose Unit	mg/kg/day	mg/kg/day
Varenicline (mg/kg/day)	0 (Vehicle Control 1) 0 (Vehicle Control 2) 1 (Low) 5 (Med) 15 (High)	0 (Vehicle Control 1) 0 (Vehicle Control 2) 1 (Low) 5 (Med) 20 ^a (High)
Number of Animals/sex/	65/sex/dose	65/sex/dose
Length of Study	105 weeks	104 weeks except 93 weeks for HD males

^a : Dose levels and concentrations decreased at week 22

Reviewer's Analyses

Analyses of survival and neoplastic data were done on using the programs written by Dr. Ted Guo of

Division of Biostatistics II. The test for carcinogenic potential is based on the principles outlined in the Food and Drug Administration's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceutical (May 2001).

Survival. Homogeneity and trend tests are used to examine the dose-related in mortality. Different in survival distributions among the treatment groups is tested by homogeneity test. A positive trend in the proportion of deaths with respect to the dose levels is tested by trend test. Tests for homogeneity and dose-mortality trends were conducted via the Cox test¹ and the Kruskal-Wallis test². Tables A1-A4 include the numbers of animals at risk, the numbers of animals at deaths, the numbers of animals alive, the cumulative percentages of survival, and the cumulative percentages of deaths by treatment and time intervals. The time intervals used were 0-52, 53-78, 79-91, 93-103 weeks, and the terminal-sacrifice. The two vehicle controls groups were combined in all analyses. The actual doses were used as weights. Figures 1-4 present the plots of Kaplan-Meier estimates of the survival distributions of the treatment groups. Tables B1-B4 present results of the dose-mortality trends.

Neoplastic Data. To determine if there is a positive trend in the proportions of a selected tumor type in a selected organ/tissue with respect to the dose levels. The tumors were classified as either fatal and incidental and were analyzed using the death-rate method³, and the prevalence method, respectively. A combined test was utilized to analyze tumors classified as both fatal and incidental. Multiplicity was addressed employing a decision rule proposed in the guidance. Specifically, positive trends in incidence rates of rare and common tumors were tested at the 0.025 and 0.005 level of significance, respectively. Rare and common tumors were defined based on the tumor rate in the control group. If the tumor rate in the control group was less than 1%, the tumor was classified as rare. Otherwise, the tumor was classified as common. In all analyses, male and female data were analyzed separately, and the two vehicle control groups were combined and treated as a single group. Tables C1-C5 present results of the dose-tumor trends.

Lastly, to further validate results of negative studies, this reviewer evaluated the number of animals at risk in relation to the adequacy of exposure. Per the guidance document, "a 50% survival rate of the 50 initial animals in any treatment group between weeks 80-90 of a two year study may be considered as a sufficient number and adequate exposure". In addition, this reviewer examined the adequacy of the doses to see if they present a reasonable tumor challenge to the animals. This evaluation was conducted utilizing criteria outlined by Chu, Cueto, and Ward⁴. Under the criteria, a dose may be considered adequate "if there is a detachable loss in weight gain of up to 10% in a dosed group relative to the controls" and "if dosed animals show a slight increased mortality compared to the control."

¹ Cox, DR: "regression Models and Lfe tables" *Journal of the Toyal Staastistical Society, Series B*, 34, 187-220, 1972.

² Gehan, EA: "A Generalized Wilcoxon Test for Comparing K Samoles Subject to Unequal Patterns of Censorship" *Biometrika*, 52, 203-223, 1965

³ Peto, R, MC Pike, NE Day, RG Gray, PN Lee, S Parish, J Peto, S Richards, and J Wahrendorf: "Guidelines for Simple Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments" *In Long-term and Short-term Screening Assayss for Carcinogens: A critical Prrraisal*, World Health Organization 1980

⁴ Chu C, C Cueto, and JM Ward: "Factors in the evaluation of 200 National Cancer Institute Carcinogen Bioassays" *Journal of Toxicology and Environmental Health*, 8, 251-280,

Analysis of the Rat Data

Survival. The dose-mortality trend was not statistically significant using the Cox test (male $p=0.0777$, female $p=0.1857$) and the Kruskal-Wallis test (male $p=0.1205$, female $p=0.1789$) (see appendix Tables B1-B2). Table 5 summarizes the accumulative mortality of the study. The respective accumulative mortality rates at the end of the treatment for the CD, LD, MD, and HD group were 51, 52, 54, and 63% in the males, and 58, 55, 65, and 48% in the females. Figures 1 and 2 (see appendix) present the survival curve as a function of time for males and females. Each group had at least 23 rats surviving to the scheduled sacrifice at week 104 (see Table 3). The sufficient numbers of rats survived the treatment to the end of the study to provide a strong evidence of adequate exposure of the drug to the animals.

Table 2: Accumulative Mortality (%) presented for Rats

Sex varenicline (mg/kg/day)	Male				Female			
	CD 0	LD 1	MD 5	HD 15	CD 0	LD 1	MD 5	HD 15
Weeks 0 - 52	8.5	10.8	9.2	3.1	4.6	7.7	3.1	4.6
53-78	17.7	30.8	15.4	30.8	23.1	24.6	21.5	12.3
79-91	32.3	38.5	30.8	43.1	39.2	44.6	41.5	35.4
92-103	50.8	52.3	53.8	63.1	58.3	55.4	64.6	47.7

Table 3: Number of Rats Survived the Treatment at week 104

Sex varenicline (mg/kg/day)	CD 0	LD 1	MD 5	HD 15
Male	64	31	30	24
Female	54	29	23	34

Neoplastic Findings: No statistical significance in incidence for any tumor types tested was detected in either sex. Tables C1-C2 (see appendix) list the incidence rates of tumors with p-values in testing positive linear dose-tumor trends. Table 4 below provides an additional statistical analysis in combining benign and malignant hibernomas in throat for males. No statistically significant positive dose-response and pairwise comparisons were detected when combining hibernomas ($p=0.0271$, the sponsor's reported p-value is 0.0253). There is no incidence occurs in females.

Table 4: Results of Trend Tests in Combining Hibernomas for Male Rats

Tumor	Number of animals with tumor/number of animals examined					P-values
	0 mg/kd/day (control)	1 mg/kg/day (low)	5 mg/kg/day (mid-low)	10 mg/kg/day (mid-high)	15 mg/kg/day (high)	
b-hibernoma	0/130	0/65	0/65	1/65	0/65	0.4351
m-hibernoma	0/130	0/65	0/65	0/65	2/65	0.0034
b & m-hibernoma	0/130	0/65	0/65	1/65	2/65	0.0271*

Source data: dataset received on 11/9/2005, analysis data R4M21928

*: The combined tumor type should be tested at 0.025 significant level

There were no statistically significance dose-related increases in mortality and positive-response relationship in the incidence of any tumor in either sex. Table 5 summarizes the survival data for the HD at weeks 52, 91, and the end of the study. More than 50% of the male and female animals were alive at the end of week 91. This suggests a sufficient number of animals with adequate exposure.

Table 5: Survival data for the High Doses of Male and Female Rats

Sex	End of 52 Weeks	End of 91 Weeks	End of Study at week 103
Male	97%	57%	37%
Female	95%	65%	52%

To evaluate adequacy of dose levels, a summary of the body weight data was generated and displayed in Table 6. The HD male and female rats had a 17% and 16% reduction in mean weight gain relative to the control group, respectively. The body weight data suggest that the HD rats reached the maximum tolerated dose (MTD)⁴.

Table 6: Mean Body Weight (%) for Rats

	Dose Groups	Mean Body Weight (grams)		Mean Body Weight Gain (MBWG)	% Differences in MBWG
		Beginning Study (week 1)	End of Study (week 105)		
Male	0 mg/kg/day	158.5	602	443.5	
	1 mg/kg/day	158	558	400	-10
	5 mg/kg/day	158	543	385	-13
	15mg/kg/day	157	523	366	-17
Female	0 mg/kg/day	143.5	409.5	266	
	1 mg/kg/day	143	418	275	4
	5 mg/kg/day	143	404	261	-2
	15mg/kg/day	142	365	223	-16

Source: Adapted from final report, text table 4, pages 61-67/2727

Conclusion of the Rat Study

In the 2-year study, rats received varenicline at dose levels of 1, 5, or 15 mg/kg/day, and there were 2 vehicle control groups. No significant positive dose-reponse relationships in tumor incidence rate were detected in either sex. The dose-mortality trend was not statistically significant using the Cox test (male $p=0.0777$, female $p=0.1857$) nor was the Kruskal-Wallis test (male $p=0.1205$, female $p=0.1789$). The respective cumulative mortality rates at the time of terminal sacrifice for the CD, LD, MD, and HD group were 51, 52, 54, and 63% in the males, and 58, 55, 65, and 48% in the females. Each group has at least 23 rats surviving to the scheduled sacrifice. A sufficient number of rats survived long enough to be at risk of late developing tumors. The HD male and female rats show significant reduction in mean body weight reduction (17% and 16% reduced in mean weight gain relative to the control group, respectively). In this reviewer's opinion, this 2-year carcinogenicity study in rats was a valid study because an MTD was reached.

Analysis of the Mice Study

Survival. The dose-mortality trend was statistically significant in both male and female mice using the Cox test (male $p=0.0001$, female $p=0.0158$) and the Kruskal-Wallis test (male $p < 0.0001$, female $p=0.0204$) (see appendix Tables B3-B4). Table 7 summarizes the accumulative mortality of the study. The respective accumulative mortality rates at the end of the treatment for the CD, LD, MD, and HD group were 60, 51, 59, and 75 % in the male, and 50, 57, 48, and 34% in the females. The mortality rate of the HD group in the males, however, was higher than in females. Only 16 (25%) HD male mice survived to the scheduled termination (week 104), and the rest of the treatments have sufficient numbers of mice survived to provide adequate exposure (see Table 8). Figures 3 and 4 (see appendix

present the survival curve as a function of time for males and females.

Table 7: Accumulative Mortality (%) presented for Mice

Sex varenicline (mg/kg/day)	Male				Female			
	CD 0	LD 1	MD 5	HD 20	CD 0	LD 1	MD 5	HD 20
Weeks 0 - 52	8	2	5	25	5	3	.	2
53-78	25	22	31	49	17	25	23	9
79-91	40	32	45	68	32	31	40	22
92-103	60	51	59	75	50	57	48	34

Table 8: Number of Mice that Survived the Treatment at week 104

Sex varenicline (mg/kg/day)	CD 0	LD 1	MD 5	HD 20
Male	52	32	27	16
Female	65	28	34	43

Neoplastic Findings: No significantly positive dose-response relationships in incidence for any tumor types were detected in either sex. Tables C3-C4 (see appendix) list the incidence rates of tumors with p-values in testing positive linear dose-tumor trends. Due to excessive mortality of the HD males, this reviewer performed an additional statistical analysis excluding the HD group (see appendix Table C5). It also showed no significant dose-response relationship in incidence for any tumor types in males.

Table 9 summarizes the survival data for the HD groups at weeks 52, 91, and the end of the study. The survival rates at week 91 for male and females in the HD group were 32% and 78%, respectively. Less than 50% of the HD males were alive at the end of week 91 suggesting a slightly low sufficient number of animals with adequate exposure.

Table 9: Survival data for the High Doses of Male and Female Mice

Sex	End of 52 Weeks	End of 91 Weeks	End of Study at week 103
Male	75%	32%	25%
Female	98%	78%	66%

To evaluate adequacy of doses, a summary of the body weight data was generated and displayed in Table 10. The HD males and females had a 1% and 3% increase in mean body weight gain, respectively. Although magnitude of gain as apparently below MTD according to the criterion proposed by Chu, Cueto, and Ward (1981)⁴. However, the high-dose group had significantly higher mortality than the CD group indicating that the high dose is over MTD. The above evaluation of validity of the study design was based on the mortality and body weight information contained in the electronic database. Information about clinical signs and histopathologic effects attributed to the drug should also be included in the final evaluation of the appropriateness of the doses used.

Table 10: Mean Body Weight (%) for Mice

	Dose Groups	Mean Body Weight (grams)		Mean Body Weight Gain (MBWG)	% Differences in MBWG
		Beginning Study (week 1)	End of Study (week 105)		
Male	0 mg/kg/day	29.6	40.2	10.6	
	1 mg/kg/day	29.3	39.8	10.5	-1
	5 mg/kg/day	29.0	40.1	11.1	5
	20 mg/kg/day	28.9	39.6	10.7	1
Female	0 mg/kg/day	22.25	34.7	12.45	
	1 mg/kg/day	22.2	34.9	12.7	2
	5 mg/kg/day	21.9	35.8	13.9	12
	20mg/kg/day	22.2	35.0	12.8	3

Source: Adapted from final report, text table 8, page 92-103

Conclusion of Mouse Study

In the 2-year study, mice received varenicline at dose levels of 1, 5, or 20 mg/kg/day, and there were 2 vehicle control groups. No significant positive dose-reponse relationships in tumor incidence rate for any tumor types were detected in either sex. The dose-mortality trend was statistically significant in both sexes using the Cox test (male $p=0.0001$, female $p=0.0158$) and the Kruskal-Wallis test (male $p < 0.0001$, female $p=0.0204$). The respective cumulative mortality rates at the end of the treatment for the CD, LD, MD, and HD group were 60, 51, 59, and 75 % in the males, and 50, 57, 48, and 34% in the females. The survival rates at week 91 for males and females in the HD group were 32% and 78%, respectively. Less than 50% of the HD males were alive at the end of week 91. Only 16 (25%) HD male mice survived to the scheduled termination. There was a slightly low sufficient animals living long enough at risk of late-developed tumors. The HD males and females had a 1% and 3% increase in mean body weight gain, respectively. However, the high-dose group had significantly higher mortality than the CD group indicating that the high dose is over MTD. The above evaluation of validity of the study design was based on the mortality and body weight information contained in the electronic database. Information about clinical signs and histopathologic effects attributed to the drug should also be included in the final evaluation of the appropriateness of the doses used.

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Appendices

Table A1: Analysis of Mortality Data for Male Rats by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
Combined 2 Vehicle Control Groups 0 mg/kg/day	0-52	130	11	119	91.5	8.5
	53-78	119	12	107	82.3	17.7
	79-91	107	19	88	67.7	32.3
	92-103	88	24	64	49.2	50.8
	TERMINAL SACRIFICE	64	64	0		
Low 1 Mg/kg/day	0-52	65	7	58	89.2	10.8
	53-78	58	13	45	69.2	30.8
	79-91	45	5	40	61.5	38.5
	92-103	40	9	31	47.7	52.3
	TERMINAL SACRIFICE	31	31	0		
MED 5 mg/kg/day	0-52	65	6	59	90.8	9.2
	53-78	59	4	55	84.6	15.4
	79-91	55	10	45	69.2	30.8
	92-103	45	15	30	46.2	53.8
	TERMINAL SACRIFICE	30	30	0		
HIGH 15 mg/kg/day	0-52	65	2	63	96.9	3.1
	53-78	63	18	45	69.2	30.8
	79-91	45	8	37	56.9	43.1
	92-103	37	13	24	36.9	63.1
	TERMINAL SACRIFICE	24	24	0		

Source data: dataset received on 11/9/2005, analysis data R1M21928

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Table A2: Analysis of Mortality Data for Female Rats by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
Combined 2 Vehicle Control Groups	0-52	130	6	124	95.4	4.6
	53-78	124	24	100	76.9	23.1
	79-91	100	21	79	60.8	39.2
	92-103	79	25	54	41.5	58.5
	TERMINAL SACRIFICE	54	54	0		
Low 1 Mg/kg/day	0-52	65	5	60	92.3	7.7
	53-78	60	11	49	75.4	24.6
	79-91	49	13	36	55.4	44.6
	92-103	36	7	29	44.6	55.4
	TERMINAL SACRIFICE	29	29	0		
MED 5 mg/kg/day	0-52	65	2	63	96.9	3.1
	53-78	63	12	51	78.5	21.5
	79-91	51	13	38	58.5	41.5
	92-103	38	15	23	35.4	64.6
	TERMINAL SACRIFICE	23	23	0		
HIGH 15 mg/kg/day	0-52	65	3	62	95.4	4.6
	53-78	62	5	57	87.7	12.3
	79-91	57	15	42	64.6	35.4
	92-103	42	8	34	52.3	47.7
	TERMINAL SACRIFICE	34	34	0		

Source data: dataset received on 11/9/2005, analysis data RIF21928

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Table A3: Analysis of Mortality Data for Male Mice by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
Combined 2 Vehicle Control Groups	0-52	130	10	120	92.3	7.7
	53-78	120	22	98	75.4	24.6
	79-91	98	20	78	60.0	40.0
	92-103	78	26	52	40.0	60.0
	TERMINAL SACRIFICE	52	52	0		
Low 1 Mg/kg/day	0-52	65	1	64	98.5	1.5
	53-78	64	13	51	78.5	21.5
	79-91	51	7	44	67.7	32.3
	92-103	44	12	32	49.2	50.8
	TERMINAL SACRIFICE	32	32	0		
MED 5 mg/kg/day	0-52	65	3	62	95.4	4.6
	53-78	62	17	45	69.2	30.8
	79-91	45	9	36	55.4	44.6
	92-103	36	9	27	41.5	58.5
	TERMINAL SACRIFICE	27	27	0		
HIGH 20 mg/kg/day	0-52	65	16	49	75.4	24.6
	53-78	49	16	33	50.8	49.2
	79-91	33	12	21	32.3	67.7
	92-103	21	5	16	24.6	75.4
	TERMINAL SACRIFICE	16	16	0		

Source data: dataset received on 11/9/2005, analysis data M1M21928

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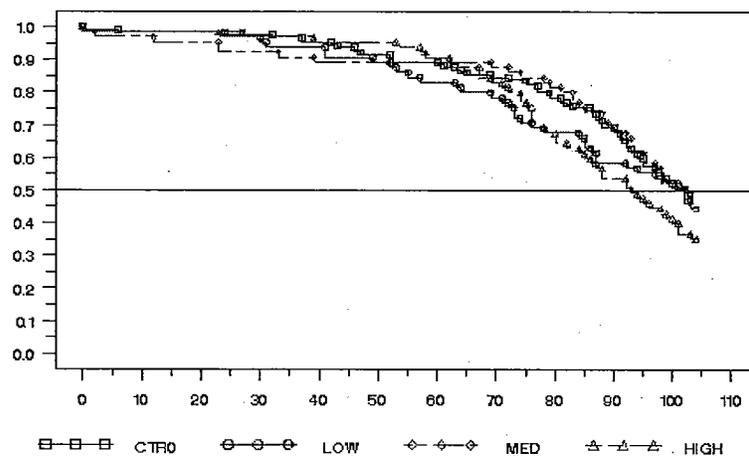
Table A4: Analysis of Mortality Data for Female Mice by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
Combined 2 Vehicle Control Groups	0-52	130	6	124	95.4	4.6
	53-78	124	16	108	83.1	16.9
	79-91	108	20	88	67.7	32.3
	92-103	88	23	65	50.0	50.0
	TERMINAL SACRIFICE	65	65	0		
Low 1 Mg/kg/day	0-52	65	2	63	96.9	3.1
	53-78	63	14	49	75.4	24.6
	79-91	49	4	45	69.2	30.8
	92-103	45	17	28	43.1	56.9
	TERMINAL SACRIFICE	28	28	0		
MED 5 mg/kg/day	53-78	65	15	50	76.9	23.1
	79-91	50	11	39	60.0	40.0
	92-103	39	5	34	52.3	47.7
	TERMINAL SACRIFICE	34	34	0		
	HIGH 20 mg/kg/day	0-52	65	1	64	98.5
53-78		64	5	59	90.8	9.2
79-91		59	8	51	78.5	21.5
92-103		51	8	43	66.2	33.8
TERMINAL SACRIFICE		43	43	0		

Source data: dataset received on 11/9/2005, analysis data M1F21928

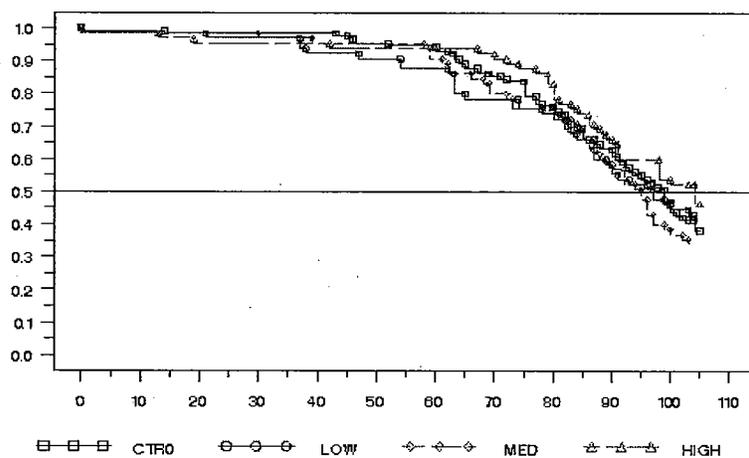
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Figure 1: Kaplan-Meier Survival Curve of the 2-year oral carcinogenicity Study of Champix in Male Rats



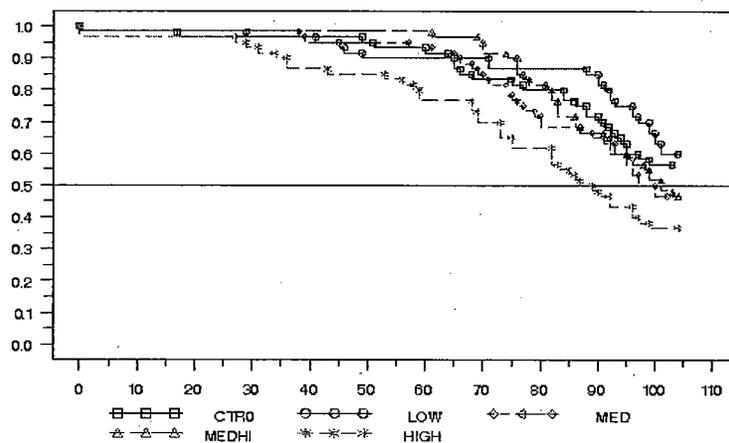
Source data: dataset received on 11/9/2005, analysis data R1M21928

Figure 2: Kaplan-Meier Survival Curve of the 2-year oral carcinogenicity Study of Champix in Female Rats



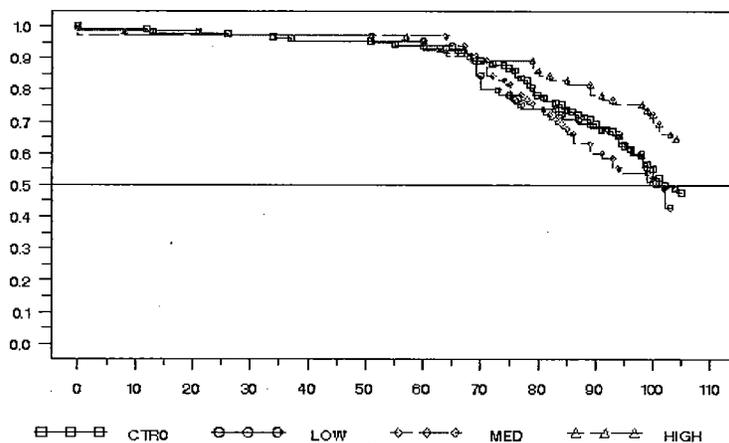
Source data: dataset received on 11/9/2005, analysis data R1F21928

Figure 3: Kaplan-Meier Survival Functions for Male Mice



Source data: dataset received on 11/9/2005, analysis data M1M21928

Figure 4: Kaplan-Meier Survival Functions for Female Mice



Source data: dataset received on 11/9/2005, analysis data M1F21928

Table B1: Analysis of Dose-Mortality Trend for Male Rats

Time-Adjusted Trend Test	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Dose-Mortality Trend	3.1122	0.0777	2.4109	0.1205
Homogeneity	3.7764	0.2866	3.6633	0.3002

Source data: dataset received on 11/9/2005, analysis data R1M21928

Table B2: Analysis of Dose-Mortality Trend for Female Rats

Time-Adjusted Trend Test	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Dose-Mortality Trend	1.7517	0.1857	1.8070	0.1789
Homogeneity	3.6285	0.3045	3.2560	0.3538

Source data: dataset received on 11/9/2005, analysis data R1F21928

Table B3: Analysis of Dose-Mortality Trend for Male Mice

Time-Adjusted Trend Test	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Dose-Mortality Trend	16.1799	0.0001	22.3148	0.0000
Homogeneity	18.3421	0.0004	24.2555	0.0000

Source data: dataset received on 11/9/2005, analysis data M1M21928

Bold areas showed statistically significant at 0.05 level.

Table B4: Analysis of Dose-Mortality Trend for Female Mice

Time-Adjusted Trend Test	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Dose-Mortality Trend	5.8294	0.0158	5.3769	0.0204
Homogeneity	6.7260	0.0812	6.2890	0.0984

Source data: dataset received on 11/9/2005, analysis data M1F21928

Bold areas showed statistically significant at 0.05 level.

Table C1: Report on Test for Positive Linear Dose-Tumor Trends in Male Rats

Organ Name	Tumor Name	CTR0	LOW	MED	HIGH	P-Value
	*B-HIBERNOMA	0	0	1	0	0.3624
	†M-HIBERNOMA	0	0	0	2	0.0349
Harderian gland	M-CARCINOMA, SQUAMOUS CELL	2	0	0	0	0.8599
Adrenal	B-ADENOMA, CORTICAL	1	0	0	1	0.2527
Adrenal	B-NEOPLASM, MEDULLARY, BENIGN	13	3	3	2	0.9251
Adrenal	M-NEOPLASM, MEDULLARY, MALIGNANT	1	1	0	0	0.8220
Heart	M-MESOTHELIOMA, ATRIOCAVAL, MA	0	0	0	1	0.1611
Heart	M-SCHWANNOMA, ENDOCARDIAL, MAL	1	0	0	0	1.0000
Kidney	M-LIPOSARCOMA	1	0	0	0	1.0000
Liver	B-ADENOMA, HEPATOCELLULAR	0	0	1	0	0.3624
Liver	M-CARCINOMA, HEPATOCELLULAR	0	1	0	1	0.1849
Liver	X-NEOPLASM, METASTATIC	0	0	0	1	0.2131
Lymphoreticular	M-SARCOMA, HISTIOCYTIC	3	1	2	2	0.2700
Lymphoreticular	M-LYMPHOMA, MALIGNANT	1	0	2	0	0.6000
Mammary gland	B-FIBROADENOMA	1	0	1	1	0.2870
Pancreas	B-ADENOMA, ISLET CELL	5	0	2	1	0.7200
Pancreas	M-CARCINOMA, ISLET CELL	2	0	2	0	0.6643
Pituitary	I-SCHWANNOMA, MALIGNANT	0	0	0	1	0.2131
Pituitary	B-ADENOMA, PARS DISTALIS	57	29	36	32	0.0562
Pituitary	B-ASTROCYTOMA, PARS NERVOSA	2	0	0	0	1.0000
Salivary gland	B-SCHWANNOMA	1	0	0	0	1.0000
Skin and adnexa	B-PAPILLOMA, SQUAMOUS CELL	0	1	1	0	0.4209
Skin and adnexa	B-LIPOMA, SUBCUTANEOUS TISSUE	4	2	0	0	0.9783
Skin and adnexa	B-FIBROMA	9	1	0	4	0.3526
Skin and adnexa	B-HEMANGIOMA	1	1	0	0	0.8057
Skin and adnexa	M-CARCINOMA, SQUAMOUS CELL	0	2	1	0	0.7225
Skin and adnexa	M-CARCINOMA, BASAL CELL	0	1	0	0	0.6066
Skin and adnexa	M-MELANOMA, MALIGNANT	0	1	0	0	0.5705
Skin and adnexa	M-SCHWANNOMA, MALIGNANT	0	0	1	0	0.3624
Skin and adnexa	B-KERATOACANTHOMA	2	1	0	3	0.0592
Spleen	M-HEMANGIOSARCOMA	0	0	0	1	0.2131
Spleen	B-HEMANGIOMA	0	0	0	1	0.1611
Testis	M-MESOTHELIOMA, MALIGNANT	0	0	1	0	0.4590
Testis	B-ADENOMA, INTERSTITIAL CELL	7	3	4	3	0.4182
Thyroid	B-ADENOMA, FOLLICULAR CELL	8	0	1	0	0.9939
Thyroid	M-CARCINOMA, C-CELL	0	2	1	0	0.7293
Thyroid	B-ADENOMA, C-CELL	6	3	4	5	0.1110
Thyroid	M-ADENOCARCINOMA, FOLLICULAR C	0	1	1	0	0.4130
Brain	M-SCHWANNOMA, MALIGNANT	0	0	0	1	0.1646
Brain	M-ASTROCYTOMA, MALIGNANT	3	3	1	0	0.9166
Brain	B-NEOPLASM, GRANULAR CELL, BEN	1	1	1	0	0.6463

Source data: dataset received on 11/9/2005, analysis data R2M21928

*B: Benign
†M: Malignant

Table C2: Report on Test for Positive Linear Dose-Tumor Trends in Female Rats

Organ Name	Tumor Name	CTR0	LOW	MED	HIGH	P-Value
Cervix	*M-SCHWANNOMA	1	0	0	0	1.0000
Cervix	†B-POLYP, ENDOMETRIAL STROMAL	1	1	1	1	0.4159
Cervix	M-LEIOMYOSARCOMA	0	1	0	0	0.6000
Adrenal	B-ADENOMA, CORTICAL	1	0	2	1	0.3058
Adrenal	B-NEOPLASM, MEDULLARY, BENIGN	4	2	1	0	0.9585
Adrenal	M-CARCINOMA, CORTICAL	0	1	0	0	0.6143
Kidney	B-LIPOMA	1	0	0	0	1.0000
Kidney	M-CARCINOMA, TRANSITIONAL CELL	0	1	0	0	0.6143
Kidney	M-CARCINOMA, SQUAMOUS CELL	1	0	0	0	1.0000
Kidney	M-RENAL MESENCHYMAL TUMOR, MAL	0	1	0	0	0.6613
Liver	B-ADENOMA, HEPATOCELLULAR	1	0	0	1	0.4281
Liver	M-HEMANGIOSARCOMA	1	0	0	0	1.0000
Lymphoreticular	M-SARCOMA, HISTIOCYTIC	1	1	3	0	0.7055
Lymphoreticular	M-LYMPHOMA, MALIGNANT	1	1	1	2	0.1631
Mammary gland	B-FIBROADENOMA	51	22	13	18	0.9697
Mammary gland	M-ADENOCARCINOMA	26	21	5	12	0.8968
Mammary gland	B-MAMMARY MASS, NOT OTHERWISE	0	0	0	1	0.2429
Mammary gland	B-ADENOMA	0	1	0	1	0.2394
Mouth	M-CARCINOMA, SQUAMOUS CELL	1	0	0	0	1.0000
Ovary	B-NEOPLASM, SEX CORD STROMAL,	1	0	0	0	1.0000
Ovary	B-LUTEOMA, BENIGN	0	0	0	1	0.2429
Ovary	M-NEOPLASM, GRANULOSA CELL, MA	0	0	0	1	0.2429
Ovary	B-LEIOMYOMA	0	1	0	0	0.6143
Pancreas	B-ADENOMA, ISLET CELL	1	0	1	1	0.3105
Pituitary	M-CARCINOMA, PARS DISTALIS	3	1	0	0	0.9756
Pituitary	B-ADENOMA, PARS DISTALIS	106	48	54	49	0.8984
Skin and adnexa	B-PAPILLOMA, SQUAMOUS CELL	2	0	0	0	1.0000
Skin and adnexa	B-LIPOMA, SUBCUTANEOUS TISSUE	1	1	0	1	0.4603
Skin and adnexa	B-FIBROMA	2	3	0	1	0.7202
Skin and adnexa	M-CARCINOMA, BASAL CELL	0	0	0	1	0.2407
Skin and adnexa	M-SCHWANNOMA, MALIGNANT	1	0	0	0	1.0000
Skin and adnexa	M-FIBROSARCOMA	1	0	0	0	1.0000
Skin and adnexa	M-CARCINOMA, SEBACEOUS	1	0	0	0	1.0000
Thymus	B-THYMOMA, BENIGN	1	1	0	0	0.8889
Thymus	M-THYMOMA, MALIGNANT	1	0	0	0	1.0000
Bone, unspec.	B-OSTEOMA	0	1	0	0	0.6143
Thyroid	B-ADENOMA, FOLLICULAR CELL	1	0	0	0	1.0000
Thyroid	M-CARCINOMA, C-CELL	1	0	0	1	0.4281
Thyroid	B-ADENOMA, C-CELL	8	5	6	5	0.3928
Thyroid	M-ADENOCARCINOMA, FOLLICULAR C	3	1	0	0	0.9754
Urinary bladder	M-CARCINOMA, TRANSITIONAL CELL	0	1	0	0	0.5975
Uterus	B-POLYP, ENDOMETRIAL STROMAL	3	0	4	1	0.5084
Uterus	M-ADENOCARCINOMA	0	0	0	1	0.2429
Uterus	M-SARCOMA, ENDOMETRIAL STROMAL	0	0	1	0	0.4259
Vagina	B-POLYP, STROMAL	1	2	0	1	0.4959
Brain	M-ASTROCYTOMA, MALIGNANT	2	1	0	0	0.9572
Brain	M-OLIGODENDROGLIOMA, MALIGNANT	1	0	0	0	1.0000

*B: Benign †M: Malignant

Table C3: Report on Test for Positive Linear Dose-Tumor Trends in Male Mice

Organ Name	Tumor Name	CTRO	LOW	MED	HIGH	P-Value
Epididymis	B-ADENOMA, LEYDIG CELL	0	0	1	0	0.2692
Adrenal	M-NEOPLASM, MEDULLARY, MALIGNA	1	0	0	0	1.0000
Adrenal	B-ADENOMA, SUBCAPSULAR CELLS	2	2	0	0	0.9023
Harderian gland	B-ADENOMA	12	5	5	2	0.8080
Harderian gland	M-ADENOCARCINOMA	0	0	1	0	0.3386
Ileum	M-ADENOCARCINOMA	1	0	0	0	1.0000
Jejunum	M-ADENOCARCINOMA	1	0	0	0	1.0000
Kidney	M-CARCINOMA	1	0	0	0	1.0000
Kidney	B-ADENOMA	0	2	0	0	0.6263
Liver	M-CARCINOMA, HEPATOCELLULAR	9	0	0	2	0.6703
Liver	M-HEMANGIOSARCOMA	3	3	0	1	0.6355
Liver	B-ADENOMA, HEPATOCELLULAR	11	6	2	1	0.9535
Liver	B-HEMANGIOMA	1	0	1	0	0.5643
Lung	M-CARCINOMA, BRONCHIOLO-ALVEOL	15	1	2	3	0.7394
Lung	B-ADENOMA, BRONCHIOLO-ALVEOLAR	11	7	10	4	0.6567
Lymphoreticular	M-SARCOMA, HISTIOCYTIC	1	1	0	0	0.8237
Lymphoreticular	M-LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.1593
Lymphoreticular	M-LYMPHOMA, MALIGNANT	11	4	8	2	0.7175
Mesenteric node	M-HEMANGIOSARCOMA	0	0	0	1	0.1290
Pituitary	B-ADENOMA, PARS INTERMEDIA	1	0	0	0	1.0000
Seminal vesicle	M-LEIOMYOSARCOMA	1	0	0	0	1.0000
Skin and adnexa	B-HEMANGIOMA	1	1	0	0	0.8343
Skin and adnexa	M-HISTIOCYTOMA, FIBROUS, MALIG	1	0	0	0	1.0000
Skin and adnexa	M-FIBROSARCOMA	2	2	2	1	0.3522
Spleen	M-HEMANGIOSARCOMA	4	1	0	1	0.6255
Stomach	M-ADENOCARCINOMA	0	0	1	0	0.3386
Testis	B-ADENOMA, LEYDIG CELL	1	3	3	1	0.3087
Testis	B-ADENOMA, RETE TESTIS	0	0	1	0	0.2745
Thyroid	B-ADENOMA, FOLLICULAR CELL	1	0	0	0	1.0000

Source data: dataset received on 8/14/2004, analysis data M1M21928

*B: Benign

†M: Malignant

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Table C4: Report on Test for Positive Linear Dose-Tumor Trends in Female Mice

	Tumor Name	CTR0	LOW	MED	HIGH	P-Value
Cervix	*M-LEIOMYOSARCOMA	4	0	0	1	0.7491
Cervix	*B-LEIOMYOMA	6	0	0	4	0.2575
Cervix	B-POLYP, ENDOMETRIAL STROMAL	2	0	0	0	1.0000
Cervix	M-ADENOCARCINOMA	0	1	2	1	0.3572
Cervix	B-NEOPLASM, GRANULAR CELL, BEN	1	0	0	0	1.0000
Cervix	M-SARCOMA, STROMAL	1	0	0	0	1.0000
Adrenal	B-ADENOMA, SUBCAPSULAR CELLS	0	1	0	1	0.2514
Harderian gland	B-ADENOMA	6	4	7	3	0.6744
Jejunum	M-ADENOCARCINOMA	0	0	1	0	0.4529
Liver	M-CARCINOMA, HEPATOCELLULAR	0	1	0	0	0.6027
Liver	M-HEMANGIOSARCOMA	4	0	1	2	0.3997
Liver	B-ADENOMA, HEPATOCELLULAR	0	3	2	2	0.2473
Liver	B-HEMANGIOMA	0	2	0	0	0.7179
Lung	M-CARCINOMA, BRONCHIOLO-ALVEOL	5	3	3	2	0.7519
Lung	B-ADENOMA, BRONCHIOLO-ALVEOLAR	14	9	6	8	0.5579
Lymphoreticular	M-SARCOMA, HISTIOCYTIC	5	3	3	0	0.9644
Lymphoreticular	M-NEOPLASM, MAST CELL, MALIGNA	0	0	1	0	0.4018
Lymphoreticular	M-LEUKEMIA, GRANULOCYTIC	3	1	0	0	0.9132
Lymphoreticular	M-LYMPHOMA, MALIGNANT	18	9	7	6	0.9260
Mammary gland	M-ADENOCARCINOMA	3	0	0	0	0.8995
Mammary gland	B-FIBROADENOMA	1	0	0	0	1.0000
Ovary	B-CYSTADENOMA	2	2	3	3	0.1970
Ovary	B-NEOPLASM, GRANULOSA CELL, BE	6	0	0	2	0.6221
Ovary	B-LUTEOMA, BENIGN	6	0	3	1	0.8198
Ovary	B-THECOMA, BENIGN	1	0	0	0	1.0000
Ovary	M-CARCINOMA, NOS	0	0	0	1	0.2500
Oviduct	M-LEIOMYOSARCOMA	1	0	0	0	1.0000
Pancreas	B-NEOPLASM, ISLET CELL, BENIGN	0	1	0	0	0.6176
Pituitary	B-ADENOMA, PARS INTERMEDIA	1	0	1	0	0.6492
Pituitary	M-CARCINOMA, PARS DISTALIS	1	0	0	0	1.0000
Pituitary	B-ADENOMA, PARS DISTALIS	2	0	1	1	0.3564
Pituitary	M-SCHWANNOMA, MALIGNANT	1	0	0	0	1.0000
Skeletal muscle	M-FIBROSARCOMA	1	0	0	0	1.0000
Skin and adnexa	M-FIBROSARCOMA	3	1	3	1	0.6137
Skin and adnexa	M-HEMANGIOSARCOMA	2	0	0	0	1.0000
Skin and adnexa	B-PAPILLOMA, SQUAMOUS CELL	0	0	1	0	0.4529
Skin and adnexa	M-CARCINOMA, BASAL CELL	0	1	0	0	0.6046
Spleen	M-HEMANGIOSARCOMA	3	2	1	0	0.9425
Spleen	B-HEMANGIOMA	1	0	1	0	0.5871
Bone, unspec.	M-OSTEOSARCOMA	1	1	1	0	0.6913
Thorax	M-CARCINOMA, SQUAMOUS CELL, ME	1	0	0	0	1.0000
Thyroid	B-ADENOMA, FOLLICULAR CELL	3	0	1	0	0.9092
Thyroid	B-ADENOMA, C-CELL	0	1	0	0	0.6213
Uterus	M-HEMANGIOSARCOMA	3	0	2	0	0.8412
Uterus	B-HEMANGIOMA	1	2	1	0	0.7158
Uterus	B-POLYP, ENDOMETRIAL STROMAL	9	2	6	4	0.4962
Uterus	M-LEIOMYOSARCOMA	2	0	2	0	0.7817
Uterus	M-SARCOMA, ENDOMETRIAL STROMAL	3	0	0	0	0.8816

Uterus	B-LEIOMYOMA	2	0	1	1	0.4191
Uterus	M-ADENOCARCINOMA	1	0	0	1	0.4275
Uterus	B-ADENOMA	1	1	0	0	0.8341
Vagina	M-CARCINOMA, SQUAMOUS CELL	1	0	0	0	1.0000
Vagina	M-LEIOMYOSARCOMA	0	0	1	0	0.4036
Vagina	B-POLYP, STROMAL	0	2	1	0	0.7613
Vagina	M-CARCINOMA, BASAL CELL	1	0	0	0	1.0000

Source data: dataset received on 9/6/2005, analysis data M2F21928

*B: Benign

*M: Malignant

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**Table C5: Report on Test for Positive Linear Dose-Tumor Trends in Male Mice
(excluded the high dose group)**

Organ Name	Tumor Name	CTR0	LOW	MED	P-Value
Epididymis	*B-ADENOMA, LEYDIG CELL	0	0	1	0.1915
Adrenal	[†] M-NEOPLASM, MEDULLARY, MALIGNA	1	0	0	1.0000
Adrenal	B-ADENOMA, SUBCAPSULAR CELLS	2	2	0	0.8367
Harderian gland	B-ADENOMA	12	5	5	0.5957
Harderian gland	M-ADENOCARCINOMA	0	0	1	0.2432
Ileum	M-ADENOCARCINOMA	1	0	0	1.0000
Jejunum	M-ADENOCARCINOMA	1	0	0	1.0000
Kidney	M-CARCINOMA	1	0	0	1.0000
Kidney	B-ADENOMA	0	2	0	0.5102
Liver	M-CARCINOMA, HEPATOCELLULAR	9	0	0	0.9915
Liver	M-HEMANGIOSARCOMA	3	3	0	0.8925
Liver	B-ADENOMA, HEPATOCELLULAR	11	6	2	0.9330
Liver	B-HEMANGIOMA	1	0	1	0.4290
Lung	M-CARCINOMA, BRONCHIOLO-ALVEOL	15	1	2	0.9720
Lung	B-ADENOMA, BRONCHIOLO-ALVEOLAR	11	7	10	0.1035
Lymphoreticular	M-SARCOMA, HISTIOCYTIC	1	1	0	0.7286
Lymphoreticular	M-LYMPHOMA, MALIGNANT	11	4	8	0.1580
Pituitary	B-ADENOMA, PARS INTERMEDIA	1	0	0	1.0000
Seminal vesicle	M-LEIOMYOSARCOMA	1	0	0	1.0000
Skin and adnexa	B-HEMANGIOMA	1	1	0	0.7828
Skin and adnexa	M-HISTIOCYTOMA, FIBROUS, MALIG	1	0	0	1.0000
Skin and adnexa	M-FIBROSARCOMA	2	2	2	0.2761
Spleen	M-HEMANGIOSARCOMA	4	1	0	0.9335
Stomach	M-ADENOCARCINOMA	0	0	1	0.2432
Testis	B-ADENOMA, LEYDIG CELL	1	3	3	0.0684
Testis	B-ADENOMA, RETE TESTIS	0	0	1	0.1957
Thyroid	B-ADENOMA, FOLLICULAR CELL	1	0	0	1.0000

*B: Benign

[†]M: Malignant

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Concur with review