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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-928

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-928	Submission Date(s): 11/10/05
Brand Name	Champix®
Generic Name	Varenicline Tartarate Tablets
Reviewer(s)	Srikanth C. Nallani, Ph.D.
	Lei K. Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewer	Jenny J. Zheng, Ph.D.
Pharmacometrics Team Leader	Jogarao Gobburu, Ph.D.
OCPB Division	Division of Clinical Pharmacology and Biopharmaceutics – 2
ORM Division	Division of Anesthesia, Analgesia, and Rheumatology Products
Sponsor	Pfizer Inc., New London, CT 06320
Relevant IND(s)	58,994 (Immediate Release)
Submission Type; Code	1(New Chemical Entity); P (Priority review)
Formulation; Strength(s)	Film Coated Tablet; 0.5 & 1 mg
Indication	Smoking Cessation
Dosage form	0.5 mg and 1 mg immediate release tablet;
Proposed Dosing Regimen	Days 1 – 3: 0.5 mg once daily; Days 4 – 7: 0.5 mg twice daily Day 8 – End of treatment (upto 12 weeks): 1 mg twice daily. Subjects who are able to successfully quit can continue to take 1 mg twice daily for additional 12 weeks to maintain abstinence.

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1 Executive Summary

1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of CPB Findings

Background: Varenicline tartarate (CHAMPIX^{TM}), subject of NDA 21-928, is a new chemical entity developed by Pfizer Inc., for the indication of smoking cessation. Approved for the same indication, there are several over-the-counter and prescription nicotine replacement products such as nicorette gum, transdermal patches, Nicotrol nasal spray and Nicotrol inhaler. The only non-nicotine containing product approved for this indication is the prescription medication Zyban (bupropion extended release 150 mg oral tablet). Priority review status was awarded to this 505(b)(1) application based on the assessment that if approved, varenicline would be a significant improvement compared to currently available therapy.

Champix is currently under consideration for the same indication by the European Medicines Agency (EMEA).

Mechanism of action: It is proposed that by means of its partial agonist activity at the $\alpha4\beta2$ neuronal nicotinic acetylcholine receptors, varenicline decreases the effects of nicotine observed following smoking tobacco.

Clinical Pharmacology : Twenty five Clinical Pharmacology and Biopharmaceutics Studies support dosing or other claims:

1. Exposure-Response Analysis:

Based on the observations from different Phase 1 studies, dose-limiting nausea and vomiting was most frequent with single dose of 3 mg or multiple doses of 2 mg QD varenicline. Tolerability was improved with the titration of varenicline when administering doses above 1 mg BID for several days.

Pharmacokinetic assessments were made in Phase 2a, Phase 2b and Phase 3 clinical studies evaluating the safety and efficacy of varenicline. A population PK/PD analysis was submitted to support the dosing regimen. Apart from confirmation of the exposure-response analysis, independent analyses were conducted by the pharmacometrician to identify possible lower doses that would achieve acceptable safety profile of the drug without compromising the efficacy of the drug. The Exposure-Response of varenicline is discussed in reference to the following:

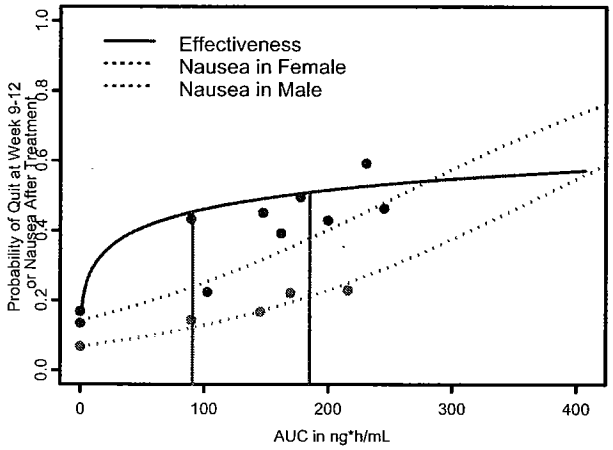
a) *Efficacy & tolerability in the Population PK/PD report, and*

b) *Cardiac QT intervals in the Cardiovascular Report*

a) *Efficacy & tolerability in the Population PK/PD report:* Exposure – Response analysis demonstrates relationship between varenicline exposure and primary efficacy measure (4-week Continuous Quit Rate (CQR)). Initial results from study A3051002 demonstrated that a clear and robust varenicline exposure-response relationship exists for the probability of Week 4-7 CQR across all doses (0.3 mg QD to 1 mg BID). In confirmation, week 4-7 CQR was reproduced in study # A3051007/1018 employing 0.5 mg BID and 1 mg BID, with the additional demonstration of significant quit in terms of primary efficacy measure of weeks 9-12 CQR. Upon inclusion of pivotal clinical trials using Zyban as comparators (study A3051028 and A3051036) along with the Study # A3051007 in the exposure-response analysis, the following observations were made:

- *Efficacy endpoint:* Increasing dose from 0.5 mg BID to 1 mg BID, the probability of quitting increases, but to a minimal extent, from 45% to 51%. There is no difference in efficacy with respect to gender.

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



- *Tolerability Endpoints:* The incidence of tolerability endpoint, nausea, is related to the varenicline exposure especially in women. At proposed dose regimen of 1.0 mg BID, the nausea incidence could be as high as 40% in women. Additionally, some gastrointestinal and psychiatric adverse events appear to increase with dose.

    1. The predicted nausea rates in placebo group are 0.07 and 0.14 in male and female, indicating a two-fold nausea incidence in females.

    2. For males, the predicted average incidence of nausea are about 0.07, 0.12, and 0.21 in placebo, 0.5 mg BID and 1 mg BID treatment, respectively.

    3. For females, the predicted nausea incidence are about 0.14, 0.23, and 0.38 in placebo, 0.5 mg BID, and 1mg BID treatment, respectively.

In light of the observed exposure-response noted with respect to achieving of efficacy and improving tolerability the following dosing regimen is recommended for the treatment of smoking cessation with Champix:

The patient should set a date to stop smoking. CHAMPIX dosing should start 1–2 weeks before this date.

The recommended dose of CHAMPIX is 0.5 mg to 1 mg twice daily following titration as follows:

Days 1 – 3: 0.5 mg once daily

Days 4 – [ ] 0.5 mg twice daily

[ ] - End of treatment:

[

]

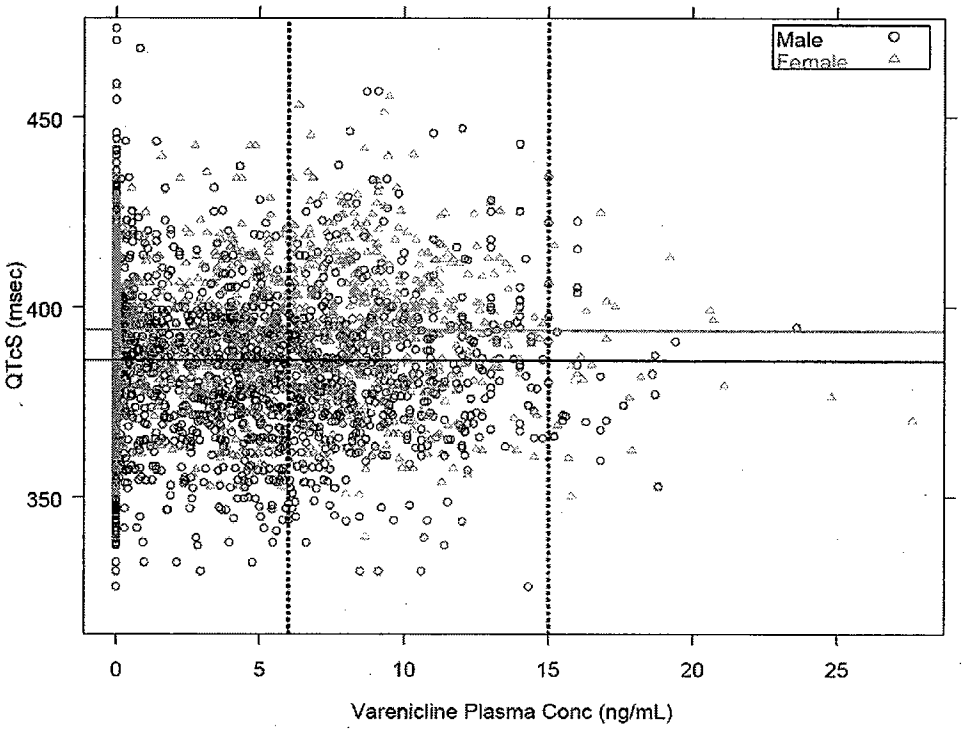
Patients should be treated with CHAMPIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX at 1 mg twice daily is recommended to further increase the likelihood of long-term abstinence.

b. *Varenicline exposure in reference to Cardiac QT intervals in the Cardiovascular Report*

The sponsor provided a report of preclinical studies and clinical observations of cardiac QT interval changes observed in different phase 1/2/3 clinical trials in lieu of a thorough QT prolongation study. At concentrations of ~ 100-fold compared to clinically observed plasma levels, varenicline treatment did not result in significant observations in *in vitro* HERG inhibition assay and Action potential assay in isolated canine Purkinje fibers. Since dogs did not tolerate the human equivalent doses of varenicline due to vomiting, Effect of single and multiple doses of varenicline on cardiovascular effects were assessed in conscious monkeys at doses upto 1.2 mg/kg/day. There were no significant changes in vital signs or electrocardiograms. Plasma concentrations ($C_{max\text{-}ss}$ ~ 155 ng/mL, AUCss 2550 ng.h/mL) observed in these studies are above and beyond those observed clinically.

PK/PD analysis of pooled data from Phase 1 studies looking at the changes in QT interval corrected by a study specific-correction factor over a range of plasma levels was submitted. Significant QT prolongation signal was not observed in the clinically observed plasma concentration range.

Study-Specific QTcS Interval vs. Varenicline Plasma Concentration Following Oral Administration of Varenicline in Adult Male and Female Subjects



2. Pharmacokinetics of Varenicline:

Eighteen clinical PK/PD studies and seven *in vitro* studies evaluated the absorption, distribution, metabolism, and excretion (ADME) aspects of varenicline.

Varenicline tartarate is the salt of a week organic base with highly soluble and permeable characteristics (Biopharmaceutics Classification System – 1 drug). The immediate release tablet exhibits rapid dissolution characteristics *in vitro* [ ] dissolution in < 15 minutes). Pharmacokinetics of varenicline are linear and dose-proportional in the range of 0.3 – 2 mg single and multiple doses (QD or BID). Compared to single dose, Cmax and AUC were ~ 3-fold (accumulation) higher at steady-state. Administration of varenicline with food does not change its bioavailability. Varenicline is absorbed with a Tmax of ~ 3 hours and exhibits very low plasma protein binding (10-20 %). It is secreted into saliva in humans and distribution into brain and melanin-rich tissues was noted in preclinical studies. Varenicline undergoes very little metabolism (<10%) and is excreted predominantly by renal route with a small role for renal hOCT-2 in active secretion. Pharmacokinetics of varenicline are similar irrespective of the time of administration (AM vs PM). The elimination half-life of varenicline is generally 20 hours.

Intrinsic Factors: Pharmacokinetics of varenicline were studied in subjects of different age (adolescents, young adults and elderly) and race (Caucasian and Japanese). Population pharmacokinetic analysis of Phase 1 PK studies was conducted to explain the variability of varenicline pharmacokinetics with respect to demographic factors. Dose adjustment is not required with respect to the intrinsic factors such as age, gender, race,

body weight and hepatic dysfunction as variability in pharmacokinetics is not explained by these covariates in population pharmacokinetic analysis.

Dose adjustment is recommended in subjects with severe and end-stage renal disease: In renal impairment PK study # A3051008, increase in Cmax and AUC was noted in moderate (1.5-fold), severe (2-fold) and end-stage (2.7-fold) renal disease patients compared to healthy subjects at steady-state. In addition, population pharmacokinetic analysis identified glomerular filtration rate as the major factor contributing to the variability of varenicline pharmacokinetics. A 0.5 mg QD regimen is recommended in severe renal impaired subjects. The 1 mg QD regimen can be considered if the effectiveness of varenicline treatment is lacking. The ESRD subjects received underwent a four-hour long hemodialysis session atleast three times a week. At steady-state, plasma levels in subjects with end-state renal disease receiving 0.5 mg QD comparable to those observed for the efficacious dose 0.5 mg BID in healthy subjects. In this study, significant extraction (~ 0.2- 0.3 mg) of varenicline was noted following a 3-hour dialysis. If smoking cessation treatment in ESRD subjects is necessary, varenicline should be used with caution at a dose of 0.5 mg once daily.

Extrinsic Factors: Clinical drug interactions were conducted with drugs of different classes with the potential for coadministration in smokers.

a. Narrow-therapeutic index drugs:

   Pharmacokinetic or pharmacodynamic changes were not noted with the coadministration of multiple doses of varenicline with multiple doses of either digoxin or warfarin.

b. Other Smoking cessation Products:

   Nicotine-replacement therapy: Twenty four subjects were randomized to receive both NRT + varenicline and NRT + placebo. However, pharmacokinetics of nicotine was studied in twelve subjects who received both treatments and five subjects receiving only NRT + Placebo. Within the subjects receiving both treatments, there was no clear trend toward change in plasma nicotine levels (Cmax and AUC0-τ). Increase in treatment-related adverse events in subjects receiving NRT + varenicline (total 124 AEs in 18 of 22 exposed subjects) was noted compared to NRT administered with placebo (total 71 AEs in 15 of 17 exposed subjects). There were 8 discontinuations (36%) due to adverse events associated with the nicotine + varenicline regimen, 1 associated with the nicotine + placebo regimen, and none associated with the nicotine alone regimen.

   Zyban (Bupropion): Pharmacokinetics of bupropion or varenicline did not change with the coadministration of the multiple doses of these drugs. While the total number of adverse events and discontinuations was similar in the two treatment groups, incidence of nausea and constipation was higher in Zyban + varenicline group compared to Zyban + placebo.

c. Drugs that are excreted by renal hOCT-2 transporter:

Cimetidine: Although statistically significant, the 29% increase in exposure of varenicline noted with coadministration of multiple doses of cimetidine does not required dose adjustment.

Metformin: There is no change in pharmacokinetics of varenicline or metformin following multiple dose administration of varenicline (1 mg BID for 7 days) and metformin (500 mg BID for 7 days).

Biopharmaceutics: The sponsor requested waiver of BE studies based on the argument that

a) Varenicline is a Biopharmaceutics Classification System (BCS) class 1 drug.

b) Champix drug product is rapidly soluble (dissolution in < 15 minutes)

Varenicline tartarate is a Biopharmaceutics Classification System type I class drug due to its high solubility and permeability characteristics.

Varenicline tartarate is highly soluble in aqueous solutions of different pH values (pH 1.2, 4.5 6.8). Clinical mass balance study # A305104 revealed that following administration of [14C] varenicline, most of the recovered radioactivity (~88%) was in urine (>98%).

Individual Excretion Data for Six Healthy Human Subjects after Oral Administration of 1 mg [^{14}C]Varenicline

	Recovery	% of recovered dose in:	
Subject	(% of Dose)	Urine	Feces
smoker			
smoker			
smoker			
nonsmoker			
nonsmoker			
nonsmoker			

In addition, the registration batch film-coated varenicline tartarate tablets and the developmental uncoated tablets exhibit rapid dissolution characteristics (in 15 minutes) at different pH conditions (pH 1.2, 4.5 and 6.8).

The BCS committee assessed the available data in this regard and concluded that this product fits the criteria of BCS Class I designation.

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

Bioequivalence Studies with Varenicline Tablet Formulations: Studies A3051030, A3051026, and A3051006

Pharmacokinetic Parameter	Adjusted Geometric Mean		Statistical Comparison	
	Test	Reference	Ratio (Test/Ref, %)	90% Confidence Interval (%)
Study # A3051030	Commercial Image Tartrate Tablets 1 x 1.0 mg N = 11	Phase 3 Tartrate Tablets 2 x 0.5 mg N = 12		
AUC(0-∞) (ng·hr/mL)	101.1	103.9	97.26	91.73-103.12
AUC(0-tlast) (ng·hr/mL)	96.6	95.2	101.43	94.17-109.26
Cmax (ng/mL)	4.0	4.3	93.05	89.13-97.15
	Commercial Image Tartrate Tablets 1 x 1.0 mg N = 11	Phase 2b Tartrate Tablets 2 x 0.5 mg N = 12		
AUC(0-∞) (ng·hr/mL)	101.1	101.1	99.98	94.30-106.01
AUC(0-tlast) (ng·hr/mL)	96.6	97.1	99.45	92.32-107.12
Cmax (ng/mL)	4.0	4.0	99.90	95.69-104.29
Study # A3051026	Phase 3 Tartrate Tablets 2 x 0.5 mg [a] N = 12	Phase 2b Tartrate Tablets 1 x 1.0 mg [a] N = 12		
AUC(0-∞) (ng·hr/mL)	49.87 [b]	49.25 [c]	101.26	94.61-108.38
AUC(0-tlast) (ng·hr/mL)	44.40	44.61	99.51	90.23-109.75
Cmax (ng/mL)	2.36	2.24	105.59	100.38-111.08
Study # A3051006	Phase 2b Tartrate Tablets 1 x 1.0 mg N = 15	Phase 2a Succinate Tablets 1 x 1.0 mg N = 15		
AUC(0-∞) (ng·hr/mL)	127.76	124.96	102.24	93.86-111.38
AUC(0-tlast) (ng·hr/mL)	115.53	112.56	102.64	94.56-111.41
Cmax (ng/mL)	4.22	4.16	101.53	97.15-106.10

Overall, the Clinical Pharmacology and Biopharmaceutics submission is acceptable.

2 QBR

2.1 General Attributes

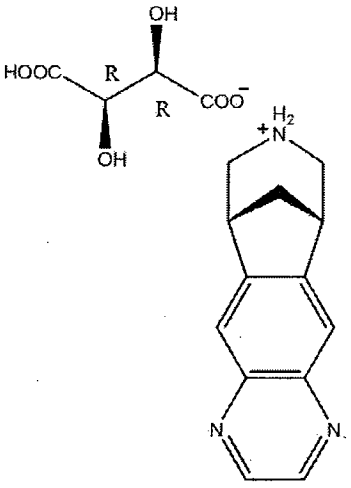
1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Varenicline tartarate (CHAMPIX™), the subject of NDA 21-928, is a new chemical entity developed by Pfizer Inc., for the indication of smoking cessation. Approved for the same indication, there are several over-the-counter and prescription nicotine replacement products such as Nicorette gum, Nicotrol nasal spray, Nicotrol inhaler, and several transdermal patches. The only non-nicotine containing product approved for this indication is the prescription medication Zyban (bupropion extended release 150 mg oral tablet). Priority review status was awarded to this 505(b)(1) application based on the assessment that if approved, varenicline would be a significant improvement compared to currently available therapy.

Priority review status was awarded to this 505(b)(1) application based on the overview of varenicline's safety and efficacy profile in comparison with the currently available therapy of smoking cessation using Zyban.

Pfizer submitted a marketing authorization application to the European Medicines Agency (EMEA) on November 2nd, 2005.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?



Chemical Name (IUPAC): 7,8,9,10-tetrahydro-6,10-methano-6*H*-azepino[4,5-*g*]quinoxaline (2*R*,3*R*)-tartrate.

Alternate Name: CP-526,555

Varenicline tartarate is a weak base with a pKa of 9.2. It is highly soluble in aqueous solutions in the pH range of 1.1 – 12.

Varenicline tartarate is formulated as film-coated, capsular biconvex immediate release tablet. The 0.5 mg and 1 mg strength tablets are compositionally proportional.

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Therapeutic Indication: Varenicline tartarate (CHAMPIX) is indicated for smoking cessation.

Proposed Mechanism of action: It is proposed that by means of its partial agonist activity at the α4β2 neuronal nicotinic acetylcholine receptors, varenicline decreases the effects of nicotine observed following smoking tobacco.

It is hypothesized that nicotine stimulates the central nervous mesolimbic dopamine system which results in the reinforcement and reward experienced upon smoking tobacco. It is proposed that varenicline blocks the ability of nicotine to activate the $\alpha_4\beta_2$ nicotinic acetylcholine receptor. In addition, varenicline being a partial agonist stimulates the $\alpha_4\beta_2$ receptor-mediated activity at a significantly lower level than nicotine.

4. What are the proposed dosage(s) and route(s) of administration?

Film coated varenicline tartarate oral tablets are available in 0.5 mg and 1 mg strengths. The recommended dose of CHAMPIX is 1 mg twice daily following a 1-week titration as follows:
Days 1 – 3: 0.5 mg once daily
Days 4 – 7: 0.5 mg twice daily
Day 8 – End of treatment: 1 mg twice daily

2.2 General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical Pharmacology Studies that support dosing or other claims are noted below:

- Clinical PK studies of the absorption, distribution, metabolism, and excretion (ADME) of varenicline in
    - special populations (Elderly - A3051009, Renal Impairment -A3051008)
- Pharmacodynamics (PD) studies investigating varenicline's tolerability and its effects on abstinence-induced craving/withdrawal
- Studies of varenicline's potential for drug-drug interactions

In addition, varenicline exposure is discussed with reference to

- Efficacy & tolerability in the Population PK/PD report, and
- Cardiac QT intervals in the Cardiovascular Report

Clinical studies conducted to support dosing or claims include:

- *Smoking cessation*: The goal of varenicline treatment in these trials was to achieve complete abstinence during the last 4 weeks of 12-week treatment and during the subsequent nontreatment follow-up phase (40 weeks). The primary endpoint used was "4-week continuous quit rate". Two study groupings are presented:
    - Principal Smoking Cessation Studies: with placebo as comparator A3051007/1018, with Zyban as comparator (A3051028, A3051036)
    - Supportive Phase 2 Studies: A3501002, A3051016/1019
- *Maintenance of abstinence*: The goal of varenicline treatment in this study (A3051035) was to maintain continuous abstinence from smoking during Weeks 13 to 24 and during the subsequent non-treatment follow-up phase in subjects

responding to an initial 12-week course of smoking cessation therapy with varenicline. This study forms the basis for a continuation of dosing for 12 extra weeks in responders.

Assessments of Smoking Status

- Smoking status was based on self-reports obtained by interviewing the subject about cigarette and nicotine use at each visit/contact using a standard set of questions.
- Exhaled carbon monoxide (CO) was measured at each clinic visit. Any subject with a CO>10 ppm during treatment or in the non-treatment follow-up was considered to be a smoker, irrespective of questionnaire responses.

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Society for Research on Nicotine and Tobacco recommends the use of the 4-Week CQR and continuous abstinence as the primary and secondary efficacy endpoints, respectively (Hughes et. al. Nicotine & Tobacco Research (2003) 5, 13-25). In addition, the above mentioned response endpoints were employed in the Zyban (bupropion) registration trials.

Smoking cessation endpoints used in prospectively designing the phase 2/3 clinical studies are as follows:

Primary Efficacy Endpoint:

- 4-Week Continuous Quit Rate (CQR): defined as the proportion of subjects who maintained complete abstinence from cigarette smoking and other nicotine use for a protocol-specified consecutive 4 weeks of treatment (Studies A3051002 assessed continuous quit for weeks 4-7, Studies A3051007/1018, A3051028, and A3051036 assessed continuous quit for weeks 9-12).

Secondary Efficacy Endpoints:

- Continuous Abstinence (CA) Rate: defined as the proportion of subjects who maintained complete abstinence from cigarette smoking and other tobacco use for a specified time period (week 9- 12).
- Long-term Quit Rate (LTQR): defined as the proportion of subjects who successfully stopped smoking at the end of the treatment phase and had ≤6 days of smoking during non-treatment phase.
- Point Prevalence (PP) Abstinence (7 days): defined as the proportion of subjects who were abstinent for the preceding 7 days.

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to II. F, Analytical Section; if no, describe the reasons)

Yes. Please refer to the Analytical Section below for details of validation for the method used in analyzing varenicline in plasma.

4. Exposure-response

a) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Population PK/PD analysis of phase 2 (A3051002 and A3051007/1018) and three Phase 3 clinical studies (A3051028, A3051036 and A3051037) revealed strong relationship between primary efficacy endpoint, 4-week quit rate, and dose/exposure (AUC) of varenicline.

Using as reference, subjects who responds to the Fagerstrom question 1 saying that he/she can hold for 6 – 30 min without smoking after waking up in the morning,

- a 45 year old subject has an average probability of continuous abstinence of smoking from week 9 -12 were as follows:
    - 0.17 for Placebo
    - 0.46 for 0.5 mg BID regimen (using mean AUC=87.55 ng*h/mL) and
    - 0.52 for 1 mg BID regimen (using mean AUC=185.24 ng*h/mL)
- At 1 mg BID regimen, as the degree of addiction increases the predicted average probability of quit decreased from 0.70 (FSQ1(>60min)) to 0.43 (FSQ1(<5min))

Reference Subject's response to Fagerstrom Question 1: How soon after you wake up do you smoke your first cigarette?

- ☐ within 5 minutes
- ☐ **6-30 minutes**
- ☐ 31-60 minutes
- ☐ after 60 minutes

- At 1 mg BID regimen, the predicted probability of quit increases from 0.39 to 0.66 for subjects with increasing age from 18 to 75 year old.
- Gender had no effect on the 4-Week CQR endpoint.

Additional comments about the nature of the exposure-response relationship for efficacy:

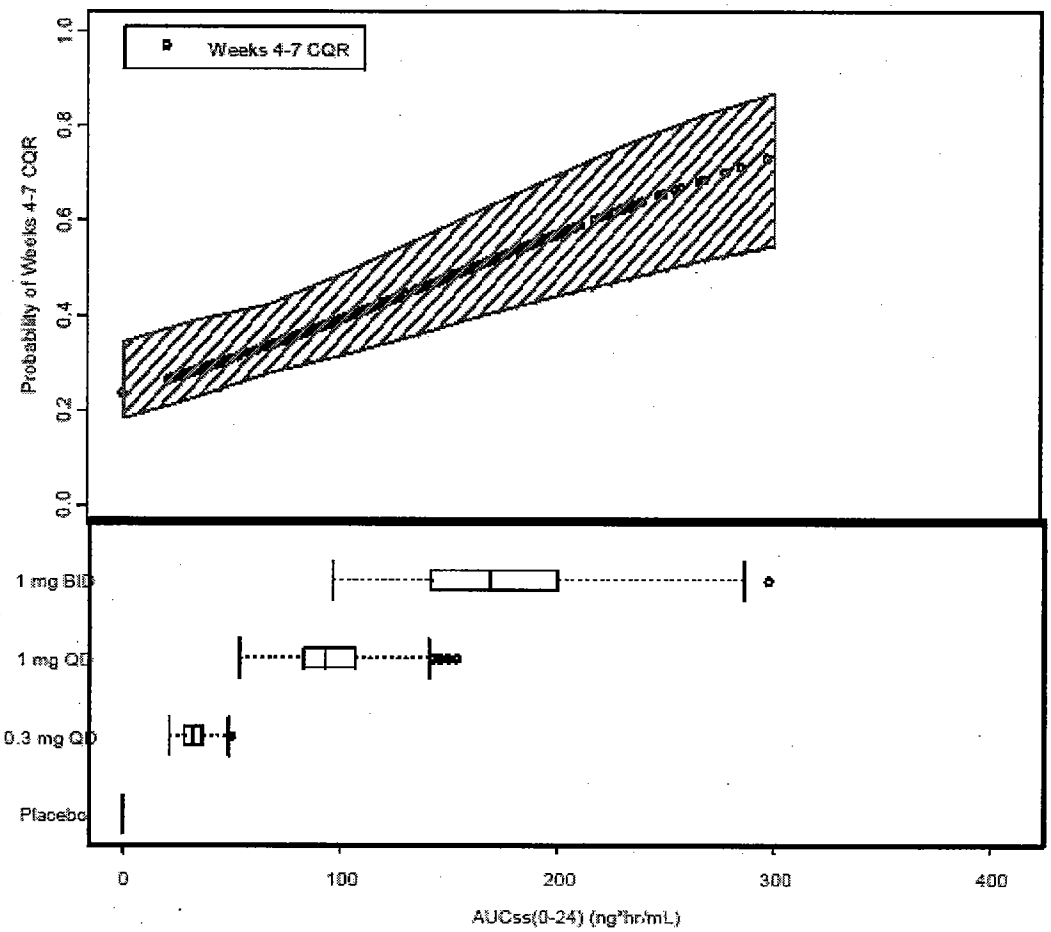
The study design, study population, and timing of blood samples varied between the five clinical studies used in the exposure-response analysis. Varenicline (succinate or tartrate salt) doses were given orally as immediate-release tablets. Doses ranged from 0.3 to 2 mg/day given orally once (QD) or twice (BID) daily.

Based on data from the Phase 2/3 clinical trials the following aspects of smoking cessation treatment with varenicline were observed:

Exposure – Response between varenicline exposure and primary efficacy measure (4-week CQR):

Phase 2a study A3051002 is a seven-week, double-blind, placebo-controlled, randomized, multicenter study evaluating the safety and efficacy of three doses of

varenicline (0.3 mg qd, 1 mg qd, and 1 mg BID) in comparison with Zyban® in smoking cessation. The primary efficacy endpoint employed in this study, CQR between weeks 4 -7, was different from the Weeks 9-12 CQR in phase 2b and Phase 3 clinical trials.



Reflect population (not individual) exposure-response relationship for reference population of White, Male, 45 yrs old, Fagerström Question 1(6-30min); predicted probability ± bootstrapped 95% CI. The box and whisker plots at the bottom describe the distribution of the exposure data. The box and whisker plots in the bottom panel of each plot, describe the distribution of the predicted exposure data. The box itself indicates the difference between the first and third quartiles of the data, showing the spread of the data. The solid line in the middle of the box is the median value and the "whiskers" indicate the range of the data or 1.5 x the inter-quartile distance, whichever is less.

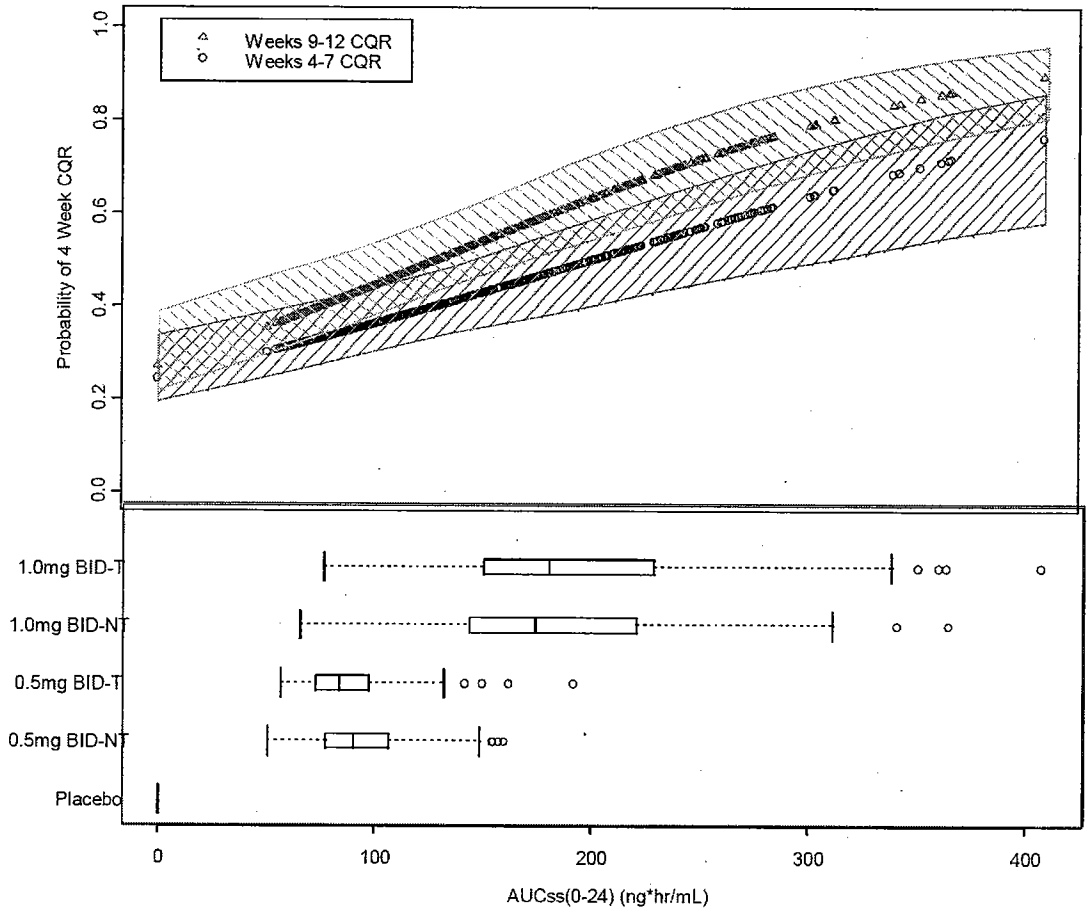
Although there was some overlap in the ranges of $AUC_{(0\text{-}24)ss}$ due to the known variability in the varenicline plasma concentrations, dose separation was generally observed between the various varenicline-treated groups. Increased probability of quit was related to greater varenicline steady-state exposure.

2. Exposure-Response and Duration of treatment for smoking cessation with varenicline:

Study # A3051007 is a twelve-week, double-blind, placebo controlled, randomized, multicenter study evaluating the safety and efficacy of four dosing strategies for cp-

526,555 (0.5 mg BID, titrated 0.5 mg BID, 1 mg BID, and titrated 1 mg BID) in smoking cessation. Since both the Weeks 4-7 and Weeks 9-12 CQR endpoints were available, population exposure-response relationships were compared. Extending the duration of the treatment period to 12 weeks resulted in a steeper slope for response, whereby a greater probability of quit was reached at the higher exposures associated with 1 mg BID.

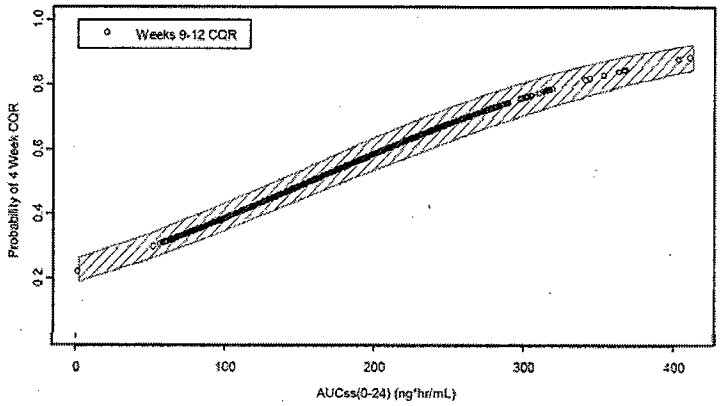
Exposure-Response Relationships for the Weeks 4-7 and Weeks 9-12 CQR in Study A3051007/1018



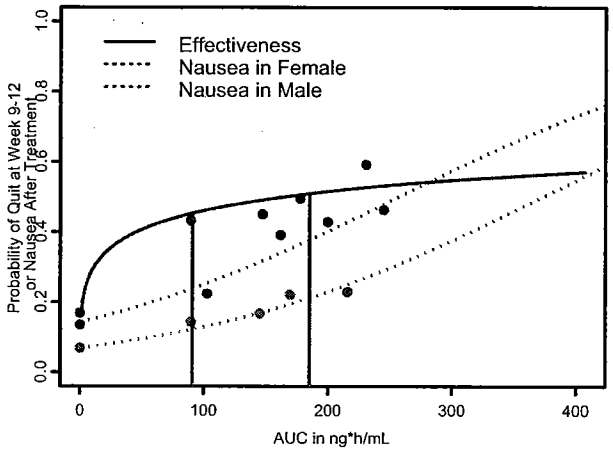
Reflect population (not individual) exposure-response relationship for reference population of White, Male, 45 yrs old, Fagerström Question 1(6-30min); predicted probability ± bootstrapped 95% CI. The box and whisker plots at the bottom describe the distribution of the exposure data. The box itself indicates the difference between the first and third quartiles of the data, showing the spread of the data. The solid line in the middle of the box is the median value and the "whiskers" indicate the range of the data or 1.5 x the inter-quartile distance, whichever is less; if the data are normally distributed, approximately 99.3% of the data fall within these whiskers. Open circles plotted outside the whiskers exceed these limits and may be considered outliers. T= titrated; NT= nontitrated.

Pooling data from the above Phase 2 (A3051007) and two Phase 3 clinical trials (A3051028, A3051036) the previously described exposure-response relationship was

Exposure-Response Relationships for the Weeks 9-12 CQR for the combined Phase 2/3 Studies



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



confirmed (See Figure below).

In addition, the pharmacometrics reviewer Dr. Jenny J. Zheng noted that the analyses suggest with an increase of dose from 0.5 mg BID to 1 mg BID, the probability of quitting increases, but to a minimal extent, from 45% to 51%. The observed and model predicted response rate in combined dataset from Study 1007, 1028 and 1036 are presented in Table below. The results show that the predicted response rate is very similar to the observed response rate except that the response rate is slightly higher than observed response rate at 1.0 mg BID.

Observed and Predicted Response Rate across Treatments (Combined dataset from Study 1007, 1028, and 1036)

	Observed Response rate (# of responder/# of total patients)	Model Predicted [c]
Placebo	**17%** (136/806)	**17%**
0.5 mg BID [a]	**45%** (114/253)	**45%**
1.0 mg BID [b]	**46%** (434/949)	**51%**

a: including both non-titrate (0.5mg tablets BID for 12 weeks) and titrated (0.5mg tablets QD for 7 days followed by 0.5mg BID for 11 weeks) regimens in Study 1007.

b: including both non-titrated (1mg tablet BID for 12 weeks) and titrated (0.5 mg tablets QD for 3 days, then 0.5mg BID for 4 days followed by 1 mg BID for 11 weeks) in Study 1007, 1028, and 1036.

c: the mean model predicted response rate for pooled data from study 1007, 1028 and 1036

b) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The incidence of tolerability endpoint, nausea, is related to the varenicline exposure especially in women. At proposed dose regimen of 1.0 mg BID, the nausea incidence

could be as high as 40% in women. Additionally, some gastrointestinal and psychiatric adverse events appear to increase with dose.

General comments on tolerability: Nausea and vomiting were the dose-limiting side-effects in Phase 1 and Phase 2 clinical studies. Single dose of varenicline was generally well tolerated upto 1 mg in smokers and non-smokers (Study # 305-001). Two out of four non-smokers at single dose of 3 mg & all four smokers at single dose of 10 mg had vomited. Varenicline dose of 3 mg QD regimen (Study 305-001) was not well tolerated beyond 8 days in all four subjects studied and multiple dosing was discontinued. Nausea and vomiting were the dose-limiting side effects. One subject receiving 2 mg QD was discontinued due to three episodes of vomiting on three consecutive days (Days 9, 10 and 11). In order to improve tolerability, later multiple dose PK and clinical studies were conducted following a titration scheme for 1mg BID and above.

Pharmacometrics reviewer made the following observations: Using the pooled data from clinical studies A3051007, A3051028, A3051036, and A3051037, the exposure response analysis showed that the incidence of nausea was related to gender and the varenicline exposure.

- The predicted nausea rates in placebo group are 0.07 and 0.14 in male and female, indicating a two-fold nausea incidence in females.
- For males, the predicted average incidence of nausea are about 0.07, 0.12, and 0.21 in placebo, 0.5 mg BID and 1 mg BID treatment, respectively.
- For females, the predicted nausea incidence are about 0.14, 0.23, and 0.38 in placebo, 0.5 mg BID, and 1mg BID treatment, respectively.

The observed and model predicted incidence of nausea between male and female in combined dataset from Study 1007, 1028, 1036 and 1037 are presented in Table below. The results show that the model predicted incidences of nausea are similar to observed incidence of nausea.

Observed and Predicted Incidence of Nausea between Male and Female (Combined dataset from Study 1007, 1028, 1036 and 1037)

		Observed rate % (# of subjects with nausea/ # total patients)	**Model Predicted [c]**
Placebo	Female	13% (57/423)	14%
	Male	7% (35/509)	7%
0.5 mg BID [a]	Female	18% (23/130)	25%
	Male	10% (13/123)	12%
1.0 mg BID [b]	Female	42% (242/582)	40%
	Male	22% (133/618)	20%

a: including both non-titrated (0.5mg tablets BID for 12 weeks) and titrated (0.5mg tablets QD for 7 days followed by 0.5mg BID for 11 weeks) regimens in Study 1007.
b: including both non-titrated (1mg tablet BID for 12 weeks) and titrated (0.5 mg tablets QD for 3 days, then 0.5mg BID for 4 days followed by 1 mg BID for 11 weeks) in Study 1007, 1028, and 1036.
c = the mean model predicted response rate for pooled data from study 1007, 1028 and 1036

Dose-related changes in the side-effects:

Exposure-response analysis was not done with respect to other varied side-effects as they were not the cause for drop-out in the clinical trials. However, dose-related changes in side-effects in different Phase 2 and Phase 3 clinical trials are discussed.

Study A3051002 is a Phase 2a seven-week, double-blind, placebo-controlled, randomized, multicenter study evaluating the safety and efficacy of three doses of varenicline (0.3 mg qd, 1 mg qd, and 1 mg BID) in comparison with Zyban® in smoking cessation. In general, a) the order of incidence of side-effects is Zyban > varenicline > placebo; b) increased incidence of different side-effects was noted with increase in dose.

Safety Results
AC & T-R AEs ≥5% and > placebo (%)[b]
Discontinuations (%)
Deaths (number of subjects)
SAEs (number of subjects)[c]

	Varenicline				
SOC	0.3 mg QD	1 mg QD	1 mg BID	Zyban	Pbo
MedDRA term	(N=126)	(N=126)	(N=125)	(N=126)	(N=123)
Treatment Related					
Gastrointestinal Disorders					
Abd pain upper	5.6	0.8	3.2	0	2.4
Constipation	4.0	4.8	5.6	8.7	2.4
Dry mouth	3.2	8.7	5.6	11.9	5.7
Flatulence	4.0	4.0	6.4	0	0.8
Nausea	16.7	36.5	49.6	19.0	15.4
Nervous System Disorders					
Disturbance in att.	4.8	6.3	4.0	4.8	2.4
Dsygeusia	8.7	12.7	15.2	11.1	7.3
Headache	9.5	15.9	13.6	15.9	9.8
Psychiatric Disorders					
Anxiety	2.4	7.1	3.2	7.1	3.3
Abnormal dreams	6.3	10.3	12.0	11.1	5.7
Insomnia	10.3	15.9	15.2	26.2	9.8
Irritability	7.9	4.0	3.2	4.8	4.9
Sleep disorder	2.4	4.0	8.8	7.1	0.8
Other SOCs					
Fatigue	7.9	7.1	7.2	4.8	2.4
Discontinuation from treatment					
All AEs/labs	14.3	13.5	12.0	16.7	9.8
T-R AEs/labs	10.3	11.1	10.4	13.5	8.1
Deaths (none)					
SAEs (total)	1	2	4	4	1

Study # A3051007 is a twelve-week, double-blind, placebo controlled, randomized, multicenter study evaluating the safety and efficacy of four dosing strategies for cp-526,555 (0.5 mg BID titrated (T), 0.5 mg BID non-titrated (NT), 1 mg BID non-titrated (NT), and titrated 1 mg BID (T)) in smoking cessation. In general, a) the order of incidence of side-effects is varenicline 1 mg BID NT > 1 mg BID T > 0.5 mg BID NT > 0.5 mg BID T > Placebo; b) the order of % subjects discontinuing due to treatment emergent adverse events is 1 mg BID T> Placebo > 1 mg BID NT> 0.5 mg BID T > 0.5 mg BID NT.

Safety Results
AC & T-R AEs ≥5% and > placebo (%)[b]
Discontinuations (%)
Deaths (number of subjects)
SAEs (number of subjects)[c]

Varenicline SOC / AE name (MedDRA)	0.5 mg NT N = 124	0.5 mg T N = 129	1.0 mg NT N = 124	1.0 mg T N = 129	Pbo N = 121
Treatment Related					
Gastrointestinal Disorders					
Constipation	4.8	3.9	8.9	7.8	0.8
Dyspepsia	5.6	2.3	4.0	4.7	2.5
Flatulence	14.5	8.5	9.7	7.8	5.0
Nausea	21.0	14.0	38.7	31.0	12.4
Nervous System Disorders					
Disturb attent	3.2	3.1	8.1	3.9	2.5
Dysgeusia	14.5	6.2	12.9	11.6	4.1
Headache	8.1	9.3	10.5	7.0	5.8
Somnolence	3.2	2.3	6.5	6.2	1.7
Psychiatric Disorders					
Abnormal dreams	13.7	7.8	11.3	17.8	4.1
Insomnia	16.1	14.0	12.9	19.4	7.4
Discontinuations from treatment					
All AEs/labs	7.3	14.7	14.5	21.7	18.2
T-R AEs/labs	4.8	6.2	12.1	17.8	15.7
Deaths (none)					
SAEs (total)	1	5	2	3	2

c) Does this drug prolong the QT or QTc interval?

Based on the preclinical and clinical PK/PD cardiovascular safety observations there does not appear to be an obvious signal for QT prolongation potential of varenicline.

In lieu of a prospectively designed thorough QT prolongation study, a report was submitted summarizing preclinical, clinical and PK/PD assessments to support cardiovascular safety of varenicline.

Preclinical observations: At concentrations of ~ 100-fold compared to clinically observed plasma levels, varenicline treatment did not result in significant observations in *in vitro* HERG inhibition assay and Action potential assay in isolated canine Purkinje fibers. Since dogs did not tolerate the human equivalent doses of varenicline due to vomiting, effect of single and multiple doses of varenicline on cardiovascular effects were assessed in conscious monkeys at doses upto 1.2 mg/kg/day. There were no significant changes in vital signs or electrocardiograms. Plasma concentrations ($C_{max\text{-}ss}$ ~ 155 ng/mL, AUCss 2550 ng.h/mL) observed in these studies are above and beyond those observed clinically.

Clinical observations: Electrocardiograms were collected from eight Phase 2/3 efficacy safety studies and 24 phase 1 studies. A categorical summary of post-baseline ECG data was presented separately for Phase 1, Phase 2/3 clinical studies with regard to dose.

Categorical Summary of Post-Baseline Electrocardiogram Data – All Completed Phase 1/2/3 Studies

ECG Measurementa	Varenicline (N=4452)[a]		Placebo (N=1340)[a]	
	N	%	N	%
QT interval (msec)				
≥500	3	0.0	1	0.1
QTcF				
≥500	2	0.0	0	0.0
30-<60 msec increasea,	335	7.5	91	5.4
≥60 msec increasea,	5	0.1	2	0.2

all males and females combined

N= The number of subjects who had a post-baseline ECG reading which met study treatment or within 7 days after the last day of study treatment.

[a] Change from baseline (where baseline is the last ECG taken on or before the first dose of study medication).

While most of the ECGs collected were at baseline, pre-dose and T_{max} (~ 3 hours into dosing), two phase 1 studies A3051014 and A3051012 had rigorous collections of ECGs.

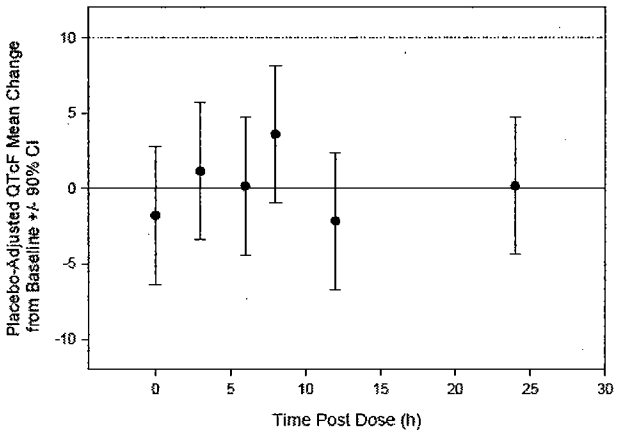
Study A3051012 was a randomized, double-blind, placebo-controlled, single dose safety, tolerability study evaluating pharmacokinetics of 2 mg immediate release and extended release formulations under development (2mg, 3 mg and 4 mg). Baseline EKG measurements were recorded on the day before first treatment to match the EKG measures at 0, 3, 6, 9, 12 and 24 hours post-dose.

Study A3051014 was a randomized, double-blind, placebo-controlled, multiple dose, parallel group study conducted in 120 subjects to examine the following three treatment regimens:

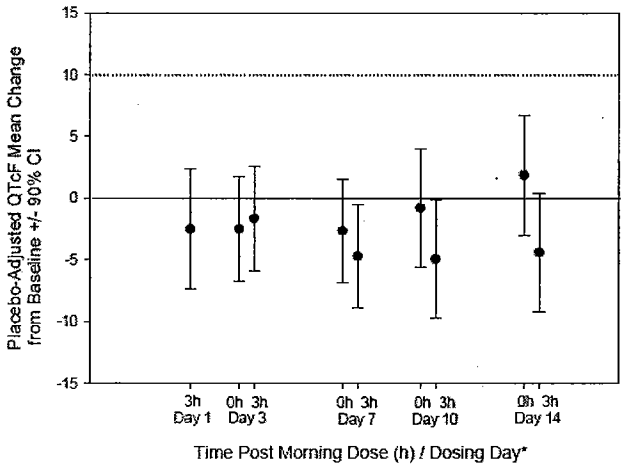
Regimen:	Week 1	Week 2	Week 3
A: titration	0.5 mg QD x 3 days, 0.5 mg BID x 4 days	1 mg BID daily	1.5 mg BID daily
B: non-titration C: positive control	1 mg BID daily placebo	1 mg BID daily placebo	placebo 1.5 mg BID daily

Placebo-adjusted QTcF over time-matched baseline observations from these two studies are presented in the figures below:

A) 2mg IR single dose; Study A3051012

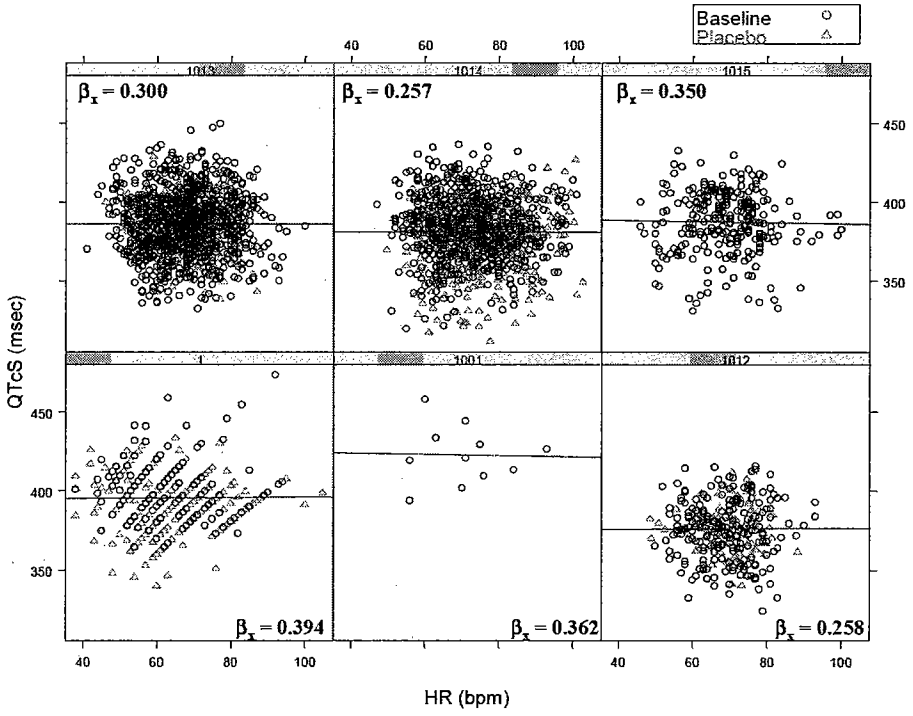


B) 0 and 3h after morning dosing, 1 mg BID; Study A3051014

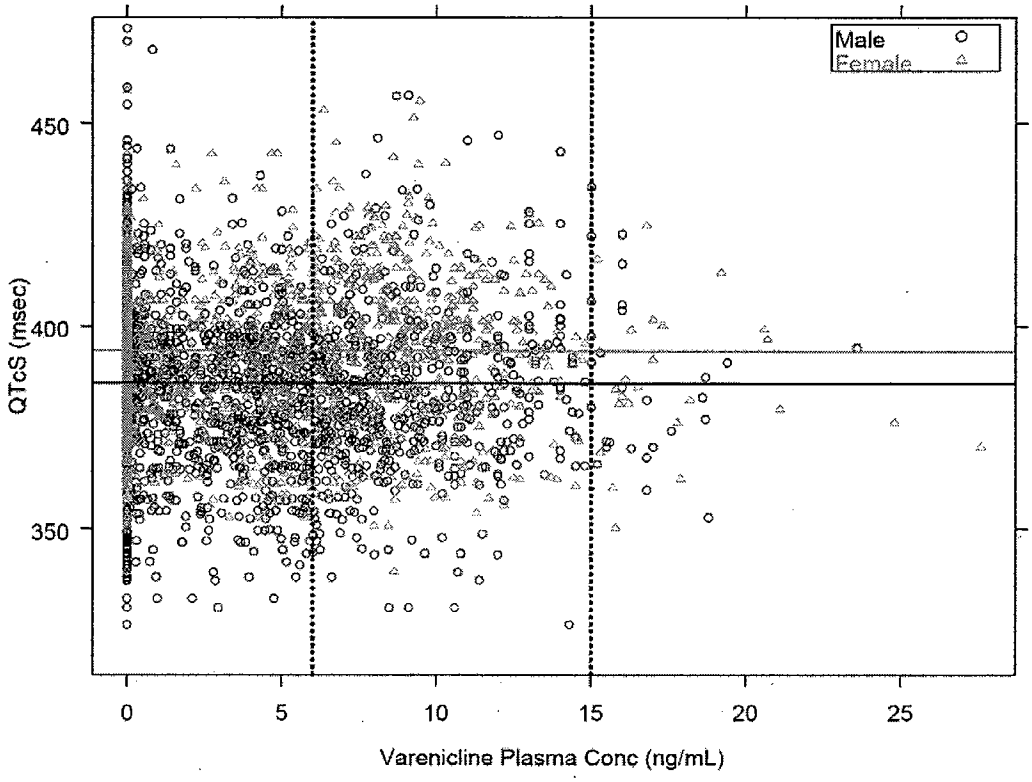


PK/PD Analysis: In addition, PK/PD analysis of pooled data from Phase 1 studies looking at the changes in QT interval corrected by a study specific-correction factor over a range of plasma levels was submitted.

QTcS (Study-specific Correction) vs. Heart Rate Obtained at Baseline or During Placebo Dosing in Normal Subjects individual study data)



Study-Specific QTcS Interval vs. Varenicline Plasma Concentration Following Oral Administration of Varenicline in Adult Male and Female Subjects (Subgroup analysis)



5. What are the PK characteristics of the drug and its major metabolite?

a) What are the single dose and multiple dose PK parameters?

Pharmacokinetics of varenicline tartarate were studied in smokers and limited number of healthy non-smokers following single and multiple dose administration of 0.01 – 10 mg (Study # 305-001). The PK data from 0.01 & 0.03 mg doses was omitted because of low plasma levels. Where possible, the data from different studies were pooled (See footnotes to the tables).

Pharmacokinetic parameters of varenicline following single dose administration.

Dose (mg)	Study	N	Smoking Status	Tmax[a] (h)	Cmax (ng/mL)	AUC(0-∞) (ng·hr/mL)	t1/2 (h)
0.1	305-001	4	smokers	1.50 [1.00-2.00]	0.468 (0.071)	9.52 (3.6)	14.8 (6.5)
	305-001	4	nonsmokers	2.00 [0.500-8.00]	0.825 (0.105)	12.6 (0.7)	13.3 (2.0)
0.3	305-001	4	smokers	1.50 [0.50-3.00]	2.35 (0.93)	37.9 (9.7)	14.4 (2.9)
	305-001	4	nonsmokers	1.00 [1.00-4.00]	1.90 (0.56)	31.4 (9.6)	12.6 (2.2)
0.5	A3051026	12	smokers	3.00 [1.00-4.00]	2.37 (0.46)	57.9 (10.0)[e]	20.1 (3.1)[e]
1	combined[b]	43	smokers	3.00 [1.00-6.00]	4.32 (0.92)	105 (18.7)	19.1 (3.34)
	combined[c]	23	nonsmokers	3.00 [0.500-8.00]	4.67 (1.13)	120 (31)	19.3 (3.16)

2	combined[d]	27	smokers	4.00 [1.00-8.00]	9.01 (1.47)	240 (61)	18.6 (4.30)
3	305-001	12	smokers	4.00 [2.00-8.00]	12.3 (3.25)	270 (55)	18.8 (5.17)
	305-001	4	smokers (SR)	3.00 [2.00-4.00]	14.0 (1.41)	288 (55)	16.5 (7.3)
	305-001	4	nonsmokers	3.00 [0.500-6.00]	10.8 (2.1)	223 (83)	20.5 (10.3)
10	305-001	4	smokers	5.00 [1.00-6.00]	13.0 (6.2)	303 (168)	19.5 (5.9)

Sources: Clinical Study Report 305-001; A3051012; A3051004; A3051026; A3051030; A3051006; A3051001; A3051042 Data are presented without regard to formulation or prandial state
N=Number of subjects in studies; NC = not calculated; SR=smoking restricted
[a] Tmax values presented as median [range]
[b] Includes Studies 305-001, A3051004, A3051026, A3051030, and A3051042
[c] Includes Studies 305-001, A3051004, and A3051006 (10 nonsmokers and 2 ex-smokers)
[d] Includes Studies A3051001 and A3051012
[e] N=5

b) How does the PK of the varenicline in healthy volunteers compare to that in patients?

The pharmacokinetics of varenicline were studied mainly in healthy smokers and a limited number of healthy non-smokers. Considering the major route of elimination and evidence from renal impairment study, only severe renal impairment affects the disposition of varenicline (see intrinsic factors) necessitating dose-adjustment.

c) What are the characteristics of drug absorption?

Varenicline is completely absorbed following oral administration. The time to achieve peak plasma concentration varied between 1 – 4 hours in different subjects. A dose-proportionate increase in C_{max} and AUC were noted following single and multiple dose administration below 3 mg dose (See table in above section).

d) What are the characteristics of drug distribution?

Varenicline does not bind to plasma proteins (~10 -20%) and distributes freely into blood (Blood/Plasma ratio is 1). Salivary secretion of varenicline in parallel to appearance of drug in plasma was noted in pharmacokinetics studies.

Preclinical observations (Study # DM2000-526555-012) suggest distribution of varenicline into $\alpha 4\beta 2$-nicotine receptor rich parts of brain. Varenicline appears to distribute to tissues with higher levels of melanin. The melanin-rich components of the eye (choroid, ciliary body, iris, and skin of the Long-Evans rats and the pigmented mice) and skin follicles contained the highest concentrations of varenicline-associated radioactivity at all sampling times upto 168 hours. The lens and vitreous body of the eye, which are devoid of melanin, were the only tissues that were devoid of varenicline-associated radioactivity. Please refer to Pharmacology/Toxicology review for preclinical ocular toxicity assessment and Medical officer review for clinical observations of any ocular toxicity.

An increase in salivary varenicline levels was noted with increasing plasma levels in human pharmacokinetics study # A3051014. Salivary levels of varenicline were variable but higher than in plasma by an average of approximately 2-fold.

e) Does the mass balance study suggest renal or hepatic as the major route of elimination?

Renal excretion appears to be the major route of varenicline elimination.

In the mass balance study # A30541004, average (+/-RSD) recovery of varenicline drug-related material in urine and feces combined was 88.0% (+/- 5.7%) of the dose with individual values ranging from [redacted] (See table below).

Summary of extent of radioactive varenicline excretion in urine and feces after single 0.5 mg dose administration in healthy volunteers

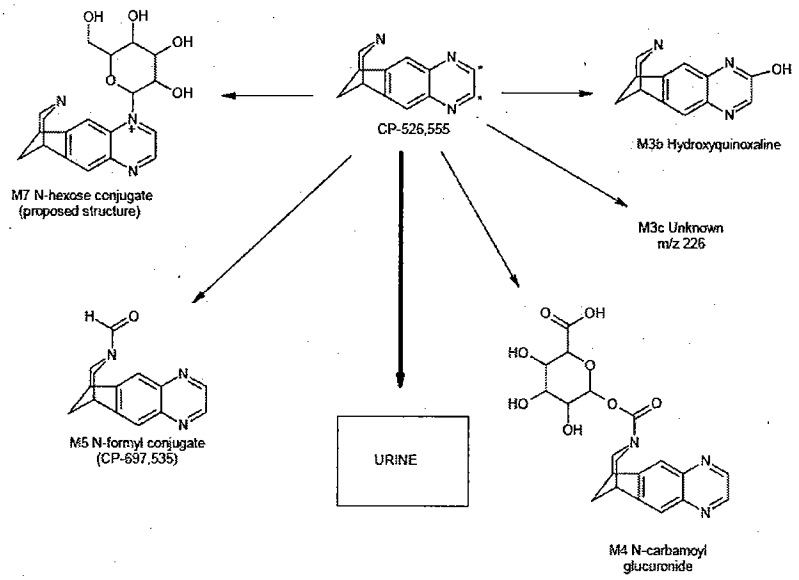
	Subject 001 Smoker	***Subject 002 Smoker***	***Subject 003 Smoker***	***Subject 007 Non-smoker***	***Subject 008 Non-smoker***	***Subject 009 Non-smoker***	***Mean***	***SD***
				Total Radioactivity Recovered in Feces				
	[redacted]					[redacted]	*0.9*	*0.5*
				Total Radioactivity Recovered in Urine				
	[redacted]					[redacted]	*87.1*	*5.5*
				Percent of Urine Radioactivity Recovered				
M3b	[redacted]					[redacted]	*3.3*	*0.9*
Varenicline	[redacted]					[redacted]	*91.6*	*1.5*
M4	[redacted]					[redacted]	*4.1*	*0.9*

f) What are the characteristics of drug metabolism?

Varenicline is not extensively metabolized. To the small extent (<10%) that is metabolized, hepatic enzymes are not involved in the metabolism of varenicline.

Varenicline was metabolically stable up on incubation with human liver microsomes for up to 20 minutes (Study # DM1998-526555-008). In the *in vivo* mass balance study, plasma samples consisted primarily of varenicline with the other four metabolites at 1.1%, 3.8%, 0.9%, and 3.5% for M3c (unidentified), M4 (N-carbamoyl glucuronide), M5 (N-formyl conjugate), and M7 (hexose conjugate), respectively (see figure below). While very little drug related material (~0.9%) was recovered in feces, urine consisted mostly (>98%) of unaltered drug and metabolites M3b (hydroxyquinoxaline ~3%) and M4 (N-carbamoylglucuronide, ~3.6%).

SUMMARY OF HUMAN METABOLISM AND EXCRETION
PATHWAYS OF CP-526,555 (Varenicline)
(STUDY - A3051004)



g) What are the characteristics of drug excretion?

Varenciline is primarily eliminated in the urine as unchanged drug with an elimination half-life of ~20 hours. The renal clearance-mediated elimination process is independent of dose regimens and was not altered with repeated dosing. Minor role for the human Organic Cation Transporter-2 (hOCT2)-mediated active secretion was noted in vitro and in vivo.

Renal clearance estimates of varenicline were obtained in healthy subjects from different studies. For the duration of urine collection (~24-48 hours), approximately 60% of the varenicline dose was recovered unchanged in the urine of subjects with normal renal function. The estimates of renal clearance are consistent across studies and treatments, and across study days. The overall mean estimate for renal clearance of varenicline in the different treatment groups (mean ~117.3 mL/min, range 88-155 mL/min) was only slightly higher than glomerular filtration rate for healthy subjects. This indicates involvement of an active secretion mechanism for renal elimination of varenicline. In vitro transporter studies (Study # DM2003-526555-052) suggest that varenicline is a low affinity substrate (Km = 366 ± 90 μM) for hOCT2, which is shown to play a role in the renal clearance of drugs that are weak organic cations.

Estimates of Renal Clearance of Varenicline in Healthy Adult smokers

Study	Dose	Day	N	Renal Clearance (mL/min)		
				Mean	SD	Range
305-001	1 mg QD	1	8	88	23	[
		14	7	92	34	
	2 mg QD	1	7	121	29	
		14	6	109	16	
	3 mg QD	1	8	155	60	]

		8	8	143	56	
	1 mg BID	1	7	101	51	
		14	6	125	54	
A3051008	0.5 mg QD	12	6	94.4	34.5	
A3051009	1 mg QD	1	8	130	45	
		7	7	92.1	27.1	
	1 mg BID	1	7	126	40	
		7	6	130	28	
A3051010	2 mg	1	12	133	36	
A3051038	1 mg BID	7	28	120	28.1	
Overall Mean				117.3		

h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

A dose-propotional increase in varenicline exposure (C_{max} and AUC) was noted following single dose (0.1- 2 mg) and multiple dose (0.5 to 1.5 mg BID) administration.

Note: Single dose of varenicline was generally well tolerated upto 1 mg in smokers and non-smokers (Study # 305-001). Nausea and vomiting were the dose-limiting side-effects, where two out of four non-smokers at single dose of 3 mg and all four smokers at single dose of 10 mg had vomited.

i) How do the PK parameters change with time following chronic dosing?

Following repeated administration (QD & BID) steady state levels of varenicline are achieved after four days with about 2.5- to 3- fold accumulation compared to single dose. The pharmacokinetic parameters C_{max} and AUC change in a linear fashion following multiple dose administration of upto 2 mg QD or BID regimen.

Doses of 3 mg QD regimen (Study 305-001) were not well tolerated beyond 8 days in all four subjects and multiple dosing was discontinued. Nausea and vomiting were the dose-limiting side effects. One subject receiving 2 mg QD was discontinued due to three episodes of vomiting on three consecutive days (Days 9, 10 and 11).

Mean (SD) PK Parameters after Single and Multiple Doses of Varenicline in Smokers: Study 305-001

Dose (mg)	Days of Dosing	N	Tmax[a] (h)	Cmax (ng/mL)	AUC(0-τ)[b] (ng·h/mL)	t1/2 (h)
1 QD	1	8	4.00 [1.00-8.00]	4.29 (0.32)	74.7 (8.2)	21.8 (2.6)
	14	7	4.00 [1.00-8.00]	7.93 (0.90)	144 (24)	23.8 (4.9)
2 QD	1	7	2.00 [2.00-4.00]	8.67 (1.59)	148 (24)	21.4 (3.4)
	14	6	2.00 [2.00-4.00]	15.1 (1.8)	280 (33)	24.8 (2.9)[d]
3 QD	1	8	4.00 [2.00-8.00]	10.8 (3.1)	187 (50)	20.9 (4.1)
	8[c]	8	4.00 [2.00-8.00]	19.8 (3.8)	352 (87)	25.2 (3.8)
1 BID	1	7	4.00 [2.00-8.00]	4.08 (0.82)	39.3 (7.3)	NA
	14	7	2.00 [1.00-4.00]	10.2 (1.0)[e]	105 (16)	31.5 (7.7)[e]

Source Clinical Study Report 305-001 Tables 5.2.2-11.
Tmax, Cmax of the first dosing interval: NA= Not available due to limited sampling period
[a]Tmax values presented as median [range]
[b]τ=dosing interval of 24 h for QD dosing, 12 h for BID
[c]3 mg dose discontinued on Study Day 11 (Day 8 of multiple dosing) due to vomiting
[d]N = 7
[e]N = 6

In order to improve tolerability, later multiple dose PK were conducted following a titration scheme for 1mg BID and above.

Mean (SD) PK Parameters in Smokers given Multiple Doses of Varenicline: Studies A3051013, A3051014, A3051015

Dose (mg)	Studies	Days of Dosing	N	Tmax[a] (h)	C_{max} (ng/mL)	AUC(0-8) (ng·h/mL)	AUC(0-24) (ng·h/mL)	t1/2 (h)
2 QD	A3051015	7 (QAM)	38	3.00 [2.00-4.00]	12.4 (1.9)		188 (31)	-
		7 (Qhs)	38	3.00 [2.00-4.00]	12.2 (2.2)		187 (38)	
1 BID	A3051013	14	18	3.00 [2.00-5.00]	10.8 (2.6)		208 (44.8)	
	A3051014	7[b]	79	3.00 [1.00-8.00]	8.79 (1.79)	61.1 (12.5)	184 (41.3)[c]	33.3 (15.4)[d]
1.5 BID	A3051014	7[e]	79	3.00 [1.00-8.00]	14.0 (3.73)	97.4 (27.7)		29.1 (7.35)[f]

Source: Clinical Study Report A3051013 Table 5.2.1; A3051014 Table 5.2.3-6, 5.2.8-11, 5.2.13-16; A3051015 Table 5.2.1

[a] Tmax values presented as median [range]

[b] Includes 79 subjects in A3051014: 40 subjects given 1 mg BID for 2 weeks then placebo for 1 week, and in 39 subjects dose was titrated from 0.5 mg QD days 1-3, 0.5 mg BID days 4-7, 1 mg BID days 8-14

[c] N=40

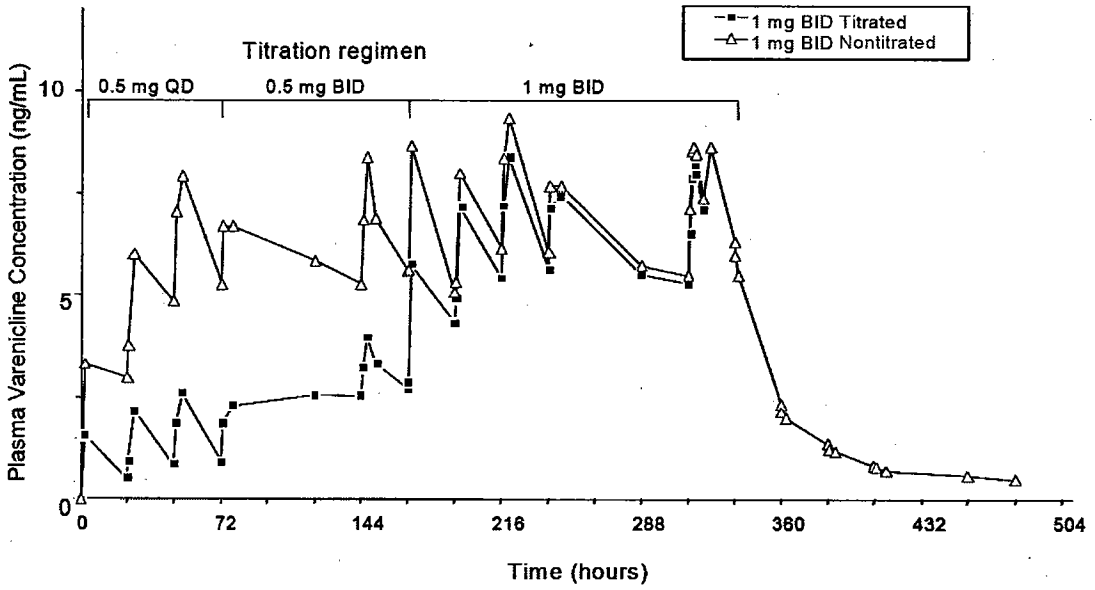
[d] N=31

[e] Includes 79 subjects in A3051014: 40 subjects given placebo BID for 2 weeks then for 1.5 mg BID for 1 week, and in 39 subjects, dose was titrated from 0.5 mg QD days 1-3, 0.5 mg BID days 4-7, 1 mg BID days 8-14, 1.5 mg BID days 15-21

[f] N=50

There was no diurnal variation in pharmacokinetics of varenicline at steady-state, as examined in study # A3051015 following 1 mg BID treatment for seven days. PK parameters Cmax and AUC of varenicline at steady-state were comparable between the second dosing interval to the first dosing interval on Day 7 (see table above; QAM, morning dosing vs Qhs, evening dosing).

Mean Plasma Concentration-Time Profiles Following Repeated Oral Administration of 1 mg BID Varenicline Using Titration and Non-titration Dosing Regimens in Healthy Adult Smokers: Study A3051014



j) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Intra-subject and inter-subject variability of < 20% was noted in pharmacokinetic parameters of C_{max} and AUC.

Data obtained from several bioequivalence studies was used in deriving the variability estimates for Cmax and AUC of varenicline. The bioequivalence studies were conducted to bridge different immediate release formulations developed and used in different stages of product development.

Variability Estimates (%CV) for Cmax and $AUC_{0-\infty}$ in Subjects Given Varenicline Tablet Formulations: Studies A3051006, A3051026, A3051030, A3051042

Study	Formulation	Inter-Subject Variability (%CV)		Intra-Subject Variability (%CV)	
		C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$
A3051006	Phase 2a, Phase 2b (fed & fasted)	18.52	15.13	7.05	13.67
A3051026	Phase 2b, Phase 3	13.4	15.9	7.2	7.3
A3051030	Phase 2b, Phase 3, Commercial Image	8.02	11.98	5.89	8.01
A30951042	Commercial Image (fed & fasted)	18.73	15.26	5.59	6.61

k) Does the drug exhibit chrono-pharmacokinetics?

Pharmacokinetics of varenicline are similar following administration in the morning or in the evening.

Study A 3051015 is a Phase 1, double-blind, randomized, multiple dose, crossover study to evaluate the nausea profile and pharmacokinetics of once daily 2 mg varenicline administered in the morning and at bedtime. No differences in oral steady-state pharmacokinetics were observed when varenicline was administered daily in the morning compared to bedtime in the fed state. Overall, the nausea profile was not different in either groups of subjects receiving the drug in the morning or in the evening.

Summary of Statistical Analysis on Day 7 Following Administration of a 2 mg Single Daily Oral Tablet Doses for 7 Days to Healthy Smokers

Pharmacokinetic Parameter	Bedtime (Test)	Morning (Reference)	Ratio (%)*	90% Confidence Interval
AUC_{0-24}(ng·h/mL)	183.7	185.8	99	(95%, 103%)
Cmax (ng/mL)	12.0	12.3	98	(94%, 102%)
* Ratio of adjusted geometric means (test/reference)				

2.3 Intrinsic Factors

1. **What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?**

Dose adjustment is required in subjects with severe impairment of renal function. Dose adjustment is not required with respect to the intrinsic factors such as age, gender, race, body weight and hepatic dysfunction as variability in pharmacokinetics is not explained by these covariates in population pharmacokinetic analysis.

Population PK analysis was conducted using plasma varenicline data pooled from four Phase 1, two Phase 2 and three Phase 3 data. A total of 954 male and 924 (49.2%) female adult smokers, of whom 81%, 12.6 %, 1.2%, and 5.2%, were Caucasian, Black, Asian, or of other ethnic origins, respectively. A total of 283 (15.1 %) subjects with mild, moderate and severe renal impairment were included in the analysis.

Summary of Baseline Demographics for the Varenicline Database (N=1878)*

Baseline Characteristic (Units)	Mean	Median	Range
Age (years)	44.0	44.2	18 - 76
Height (cm)	171	170	135 - 202
Total Body Weight (kg)	78.0	77.0	41.0 - 129
Body Mass Index (kg/m^2)	26.6	26.0	16.0 - 44.8
Estimated GFR^ (mL/min)	112	107	15.6 - 268
Sex			Males =954; Females = 924
Race			Caucasians = 81.0%; Black = 12.6%; Asian = 1.22%; Other = 5.22%

Pharmacokinetics in pediatric subjects have not been characterized. The sponsor conducted a PK study in adolescent smokers (age 12- 17 years), however that data was not included in the population PK analysis.

Varenicline undergoes negligible metabolism in humans. The effect of hepatic insufficiency on total body clearance of varenicline has not been studied but is expected to be minimal.

Variability in pharmacokinetics of varenicline is only explained by changes in renal function in terms of glomerular filtration rate (GFR). Varenicline clearance is predicted to decrease from 10.4 L/hr for a typical subject with normal renal function (estimated GFR = 100 mL/min) to 4.4 L/hr (estimated GFR = 20 mL/min) for a typical subject with severe renal impairment, thus resulting in an overall increase in daily steady-state exposure of 2.4-fold from the minimum to maximum of this renal function range.

2. **Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

Comparison of Mean (SD) PK Parameters in Adolescent, Young Adult and Elderly Smokers

Treatment Age of subjects	N	Tmax[a] (h)	C_{max} (ng/mL)	$AUC_{(0-\tau)}$[b] (ng·h/mL)	$t_{1/2}$ (h)
0.5 mg, single dose					
12-17 years old	10	3.00 [2.00-4.00]	3.01 (0.46)	50.6 (13.3)	10.9 (3.1)
18-55 years old	12	3.00 [1.00-4.00]	2.37 (0.459)	57.9 (10.0)	20.1 (3.1)
1 mg, single dose					
≥65 years old	8	3.00 [2.00-6.00]	3.86 (0.54)	55.2 (9.8)	NA
18-45 years old	8	4.00 [1.00-8.00]	4.29 (0.32)	74.7 (8.2)	21.8 (2.6)
12-17 years old	12	4.00 [2.00-4.00]	6.38 (1.50)	106 (24.3)	10.9 (1.93)
1 mg QD at steady-state[c]					
≥65 years old	8	2.50 [2.00-6.00]	7.03 (1.21)	126 (32)	27.5 (5.9)
18-45 years old	7	4.00 [1.00-8.00]	7.93 (0.90)	144 (24)	23.8 (4.9)
1 mg BID after 1stdose					
≥65 years old	8	2.50 [1.00-6.00]	3.32 (0.61)	30.4 (5.6)	NA
18-45 years old	7	4.00 [2.00-8.00]	4.08 (0.82)	39.3 (7.3)	NA
1 mg BID, at steady-state[c]					
≥65 years old	8	2.00 [1.00-3.00]	8.86 (1.8)	88.4 (19.9)	29.2 (7.9)
18-45 years old	6	2.00 [1.00-4.00]	10.2 (1.0)	105 (16)	31.5 (7.7)

Source: Clinical Study Report 305-001
Elderly data from Study A3051009; 18-45 year old data from Study 305-001; Adolescent (12- 17 yr) data from study A3051029
NA=Not available
[a] T_{max} values presented as median [range]
[b] τ = dosing interval ; ∞ or last point for single dose, 24 h for QD dosing, 12 h for BID dosing
[c] 7 days dosing in elderly, 14 days in non-elderly

a) Elderly

Dosage adjustment is not required for elderly smokers based on pharmacokinetics.

While cross study comparison of C_{max} and AUC from limited number of elderly subjects suggests lower levels in elderly compared to young adults (See Table above); population pharmacokinetic analyses of larger data set did not reveal significant effect of age on the pharmacokinetic parameters.

b) Pediatric patients; what is the status of pediatric studies and/or any pediatric plan for study?

In the pre-NDA meeting, Pfizer was advised to submit a proposal for pediatric study request after action is taken on the NDA. In an end-of-phase 2 meeting, the sponsor was also advised that it would not be acceptable to make an extrapolation of efficacy data on smoking cessation in adults to support pediatric use.

c) Gender

Dose of varenicline may be reduced to 0.5 mg BID in females who are unable to tolerate the regular dose of 1 mg BID.

Population PK analysis did not suggest differences in varenicline exposure with regard to gender. In addition, population PK/PD analysis revealed that there is no gender difference in efficacy of varenicline. However, considering greater incidence of nausea females who do not tolerate the regular dosing regimen at 1 mg BID may be administered with 0.5 mg BID regimen (see exposure-response related to tolerability).

d) Race

Dose adjustment is not required with regard to patient's race.

Population PK analysis revealed that race of a subject is not a significant covariate that would explain the variability of varenicline pharmacokinetics. Single dose (18- 35 years old subjects) and multiple dose varenicline pharmacokinetics in Japanese subjects were similar compared majority of subjects in other PK studies.

Summary of Pharmacokinetic Parameters of varencline Following Single Oral Dosing in Japanese Healthy Adult Male Volunteers (Smokers)

Pharmacokinetic parameters		Varenicline			
		0.25 mg	0.5 mg	1.0 mg	2.0 mg
		(n=12)	(n=11)	(n=12)	(n=11)
AUC_{last}(ng.h/mL)	Arithmetic Mean	23.0	46.6	101	220
	Standard Deviation	4.26	5.68	10.6	44.9
	Geometric Mean	22.7	46.2	100	217
AUC (ng.h/mL)	Arithmetic Mean	26.2	50.0	104	226
	Standard Deviation	3.88	5.88	10.8	46.9
	Geometric Mean	25.9	49.7	104	222
C_{max}(ng/mL)	Arithmetic Mean	1.32	2.45	4.97	9.96
	Standard Deviation	0.11	0.24	0.56	1.25
	Geometric Mean	1.32	2.44	4.94	9.89
T_{max}(h)	Arithmetic Mean	2.75	2.36	2.75	3.09
	Standard Deviation	1.06	0.92	0.75	1.38
$t_{1/2}$(h)	Arithmetic Mean	13.1	14.5	18.4	19.3
	Standard Deviation	2.10	2.40	3.15	2.17

Summary of plasma and urine pharmacokinetic Parameters of varenicline in Japanese male smokers following multiple oral doses

PK parameters		CP-526,555			
		0.5 mg BID group (n=8)		1.0 mg BID group (n=8)	
		Day 1	Day 14	Day 1	Day 14
AUCτ* (ng·h/mL)	Arithmetic mean	21.79	58.48	42.68	116.00
	SD	3.02	10.38	6.14	29.27
	Geometric mean	21.61	57.79	42.33	113.52
Cmax* (ng/mL)	Arithmetic mean	2.62	5.94	5.29	11.95
	SD	0.32	1.06	0.89	2.86
	Geometric mean	2.61	5.87	5.24	11.71
Tmax* (h)	Arithmetic mean	3.13	3.50	2.50	3.13
	SD	0.99	0.93	0.93	0.64
$t_{1/2}$ (h)	Arithmetic mean	-	27.98	-	24.21
	SD	-	4.52	-	3.46
Racc*	Arithmetic mean	2.700		2.697	
	SD	0.400		0.316	
CLr (mL/min)	Arithmetic mean	79.02	83.70	99.25	90.46
	SD	14.84	14.86	23.66	19.97

e) Renal impairment

Dose adjustment is necessary in subjects with severe renal impairment. Dosing should begin at 0.5 mg once daily and 0.5 mg twice daily regimen can be considered if the effectiveness of varenicline treatment is lacking with lower dose. If smoking cessation treatment in end-stage renal disease (ESRD) subjects is necessary, varenicline should be used with caution at a dose of 0.5 mg once daily.

Pharmacokinetics of varenicline (0.5 mg QD for 12 days) was studied in subjects with mild, moderate, and severe renal impairment and also in subjects with end-stage renal disease. Following twelve doses of 0.5 mg QD, compared to subjects with normal renal function, an increase in exposure of ~ 52%, 106% and 172% was noted in subjects with moderate, severe and end-stage renal disease. As noted in other PK studies, a 2-fold accumulation of drug was noted in subjects with normal, mild or moderate subjects. However, for subjects with severe and end-stage renal disease (ESRD) accumulation of drug was higher with decreased renal clearance of varenicline at steady-state.

Arithmetic Means (SD) for C_{max}, AUC, CL and T½ and Median [range] for T_{max} in subjects with mild, moderate, severe or end-stage renal disease

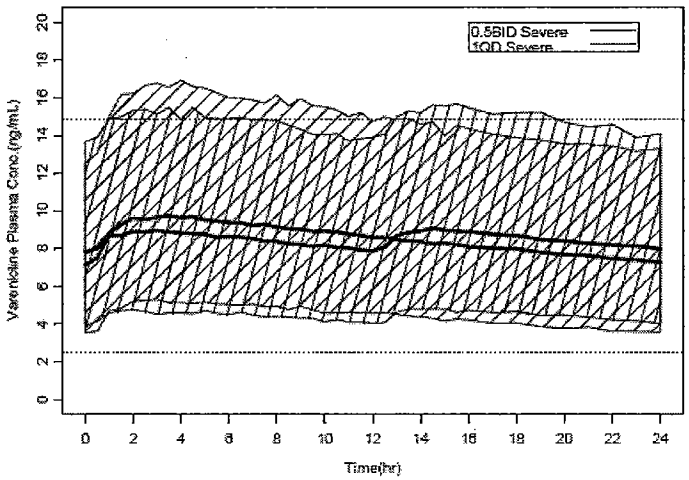
Renal Function Group	N	Day 1 C_{max} (ng/mL)	Day 1 AUC_{0-24} (ng.hr.mL)	Day 12 C_{max} (ng/mL)	Ratio (%) vs Normal	Day 12 AUC_{0-24} (ng•hr/mL)	Ratio (%) vs Normal	Tmax (hr)	T½ (hr)	CLr (mL/min)
Normal	6	2.12 (0.38)	28.7 (7.6)	4.13 (1.28)		56.8 (13.8)		1 [1-2]	34.4 (27.5)	94.4 (34.5)
Mild Impairment	6	2.12 (0.43)	30.4 (4.7)	3.83 (1.19)	92%	62.3 (23.0)	106%	3 [1-4]	32.5 (7.7)	101 (27)
Moderate Impairment	6	2.31 (0.42)	39.5 (4.1)	4.88 (0.82)	121%	85.4 (14.5)	152%	2 [2-4]	34.5 (6.5)	56.4 (11.0)
Severe Impairment	6	2.24 (0.69)	35 (11)	6.39 (2.28)	153%	122 (45)	206%	2.5 [1-6]	56.1* (14.2)	48.4 (25.0)
End-Stage Disease	6	1.85 (0.45)	34.3 (6.2)	7.46 (1.75)	183%	154 (37)	272%	3 [1-8]	78.3† (5.9)	N/A

While no dosing adjustment is necessary for patients with mild renal impairment, dose reduction may be necessary in subjects with moderate renal impairment if they do not tolerate the regular dose prescribed for healthy subjects. A reduced dosing frequency of 0.5 mg once daily is recommended for patients with severe renal impairment. Since the 0.5 mg BID regimen is found to be efficacious, the dosing recommendation for severe renal impairment is proposed accordingly to compensate for the anticipated increases in exposure for this regimen. The 0.5 mg twice regimen can be considered if the effectiveness of varenicline treatment is lacking.

In this study, ESRD subjects received underwent a four-hour long hemodialysis session atleast three times a week. At steady-state, plasma levels in subjects with end-state renal disease receiving 0.5 mg QD comparable to those observed for the efficacious dose 0.5 mg BID in healthy subjects. In this study, significant extraction (~ 27% - 66% of 0.5 mg administered) of varenicline was noted following a 3-hour dialysis. If smoking cessation treatment in ESRD subjects undergoing hemodialysis is necessary, varenicline should be used with caution at a dose of 0.5 mg once daily.

At the pre-NDA meeting the sponsor was advised to justify the dose and regimen change proposed for this special population. The sponsors' recommendation is based on the

proposed use of 1 mg BID regimen in healthy subjects. Based on population pharmacokinetic analysis, the predicted steady-state pharmacokinetic profiles of varenicline in subjects with severe renal impairment following 1 mg QD or 0.5 mg BID Varenicline are presented in the figure below.



Bold lines (black and red) are the median steady-state pharmacokinetic profiles of 0.5 mg BID and 1 mg QD, respectively; the shaded areas are the corresponding 95% prediction intervals for the population distribution. The upper and lower dotted lines are the 95% population prediction interval from Cmax to Cmin in the population with normal renal function at the 1 mg BID dose regimen.

Differences in median values for Cmax (9.1 ng/mL vs. 8.4 ng/mL) and Cmin (6.5 ng/mL vs. 7.2 ng/mL) were less than 10%, for 1 mg QD vs. 0.5 mg BID dosing, respectively. Therefore, a reduced dosing frequency of 1 mg varenicline once daily is most appropriate for subjects with severe renal insufficiency (estimated GFR<30 mL/min). Hence, a reduced dosing frequency of 1 mg varenicline once daily is recommended for patients with severe renal impairment.

f) Hepatic impairment

Dose adjustment may not be necessary in subjects with hepatic impairment, considering the low extent of metabolism and predominant renal clearance of varenicline.

g) What pharmacogenetics information is there in the application and is it important or not?

Pharmacogenetics/pharmacogenomic information is not available in this submission.

h) What pregnancy and lactation use information is there in the application?

Varenicline was not administered to pregnant and lactating women in clinical studies. Preclinical data pertaining from teratogenicity experiments was submitted. Please refer to pharmacology/toxicology review by Dr. Mamata De for detailed assessment of preclinical teratogenic effects of varenicline. It is not known if varenicline is excreted in human milk.

i) Other human factors that are important to understanding the drug's efficacy and safety

None

2.4 Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

No extrinsic factors were identified that would influence the exposure of varenicline to necessitate an adjustment in dose.

2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None

3. Drug-Drug Interactions

a) is there an in vitro basis to suspect in vivo drug-drug interactions?

There may be a small role for hOCT-2 inhibition related drug interactions.

In vitro studies suggest that varenicline is a low affinity substrate (Km = 366 ± 90 μM) for the renal human organic cation transporter-type 2. It is also shown to competitively inhibit (IC_{50} = 959 ± 557 μM) transport of coadministrated hOCT-2 substrates, albeit at concentrations very high compared those observed in clinical setting.

b) is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Varenicline is not extensively metabolized; to the extent metabolized (<10%) CYP enzymes are not involved in the metabolism of varenicline. Pharmacogenetics of varenicline metabolism may not be relevant.

c) is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro studies indicate that varenicline is not an inhibitor or inducer of major CYP enzymes.

In vitro studies demonstrated that varenicline does not inhibit cytochrome P450 enzymes (IC50 >6400 ng/mL). The P450 enzymes tested for inhibition were: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5.

Marker Substrate Activity	Enzyme	% of control at [I] = 30 μM	IC_{50} (μM) Mean ± SE
Phenacetin *O*-Deethylase	CYP1A2	100	>30
Coumarin 7-Hydroxylase	CYP2A6	110	>30
Bupropion Hydroxylase	CYP2B6	99	>30
Amodiaquine *N*-Deethylase	CYP2C8	99	>30
Diclofenac 4'-Hydroxylase	CYP2C9	93	>30
S-Mephenytoin 4'-Hydroxylase	CYP2C19	100	>30
Dextromethorphan *O*-Demethylase	CYP2D6	96	>30
Chlorzoxazone 6-Hydroxylase	CYP2E1	100	>30
Felodipine Oxidase	CYP3A	75	>30
Midazolam 1'-Hydroxylase	CYP3A	90	>30
Testosterone 6β-Hydroxylase	CYP3A	97	>30

In human hepatocytes in vitro, varenicline was shown to not induce the mRNA of CYP1A2 and CYP3A4.

	Treatment	Dose (μM)	Percent of Positive Control		Fold Induction Over DM SO		Taqman RQ	
			Mean	SD	Mean	SD	Mean	SD
CYP3A4	DM SO	0.1%	0.00	3.64	1.00	0.279	1.00	NA
	Rifampin	10.0	100	16.4	6.40	4.16	11.9	6.09
	varenicline	0.500	6.40	4.52	1.28	0.188	1.17	0.625
	varenicline	0.250	4.88	5.62	1.16	0.222	1.12	0.375
	varenicline	0.125	6.55	2.69	1.38	0.338	1.06	0.445
	varenicline	0.050	10.4	4.21	1.58	0.513	1.10	0.727
	varenicline	0.025	7.21	7.18	1.16	0.252	1.06	0.246
CYP1A2	DM SO	0.1%	0.00	0.372	1.00	0.128	1.00	NA
	Lansoprazole	10.0	100	19.4	36.0	9.93	67.7	78.4
	varenicline	0.500	0.848	0.869	1.32	0.326	1.79	0.0904
	varenicline	0.250	0.169	1.19	1.08	0.400	1.50	0.151
	varenicline	0.125	0.781	0.741	1.29	0.314	1.23	0.179
	varenicline	0.050	0.513	0.634	1.20	0.236	0.991	0.366
	varenicline	0.025	0.484	0.926	1.21	0.372	1.20	0.267

NA = Not applicable. RQ = Relative Quantitation

d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Varenciline does not appear to be a substrate for P-glycoprotein. While its potential to inhibit P-glycoprotein was not investigated in vitro, clinical drug interaction study with digoxin suggests lack of intestinal as well as renal P-gp inhibition by varenicline (See section f below).

The permeability of varenicline appears pH-dependent as with other weak organic bases. In vitro transport studies looking at absorption characteristics of varenicline indicate high permeability characteristics at intestinal pH of 7.4 (Study # DM2003-526555-052). It should be noted that the transport from apical to basolateral and vice versa in Caco-2 cells were conducted with coincubation of varenicline and metoprolol.

See discussion on clinical drug interaction study between varenicline and digoxin in section f.

e) are there other metabolic/transporter pathways that may be important?

Glucuronidation was identified as a minor metabolic pathway and several UGT enzymes were identified as capable of mediating glucuronidation of varenicline.

f) does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Varenicline may be coadministered with narrow therapeutic drugs such as digoxin and warfarin, other smoking cessation products such as nicotine replacement therapies and non-nicotine prescription drug Zyban (bupropion tablets).

The potential for drug interaction between varenicline and coadministered drugs such as digoxin, warfarin, nicotine transdermal patch and Zyban have been investigated. In addition, potential for drug interaction due to hOCT-2 transport inhibition by varenicline or coadministered drugs such as cimetidine and Metformin was also investigated.

Clinical drug interaction studies with the following drugs:

Study No, Objectives	Population	No. of Subjects[a]	Design	Dosage/ Regimen/Comparator Duration
Narrow Therapeutic Index Drugs: **Rationale:** Smokers have higher risk for heart disease and clotting disorders. Digoxin or warfarin may be likely administered medications in smokers.				
A3051031 Digoxin PK interaction	HV smokers	18	R, ISBSO, PC, 2-way XO	Lanoxicap 0.2 mg QD + 1 mg BID varenicline x 14 days Lanoxicap 0.2 mg QD + placebo
A3051032 Warfarin PK/PD interaction	HV smokers	24	R, ISBSO, PC, 2-way XO	Warfarin 25 mg SD+ 1 mg BID varenicline x 14 days Warfarin 25 mg SD + placebo
Other Smoking cessation Products: **Rationale:** Smokers might use previously approved prescription (Zyban) or over-the-counter nicotine containing products for smoking cessation.				
A3051033 NRT PK/PD (safety) interaction	HV smokers	24	R, DB, PC, 2-way XO	NRT Patch 21 mg + 1 mg BID varenicline x 14 days NRT Patch 21 mg + placebo
A3051034 Zyban PK/PD (safety) interaction	HV smokers	46	R, ISBSO, PC, 2-way XO	Zyban 150 mg BID + 1 mg BID varenicline x 14 days Zyban 150 mg BID + Placebo
Drugs that are excreted by renal hOCT-2 transporter: **Rationale:** In vitro studies suggest varenicline is substrate for the renal hOCT-2 transporter and cimetidine inhibited its transport. Varenicline is a weak inhibitor for hOCT2 and metformin is a prototypical substrate of hOCT-2.				
A3051010 Cimetidine PK interaction	HV smokers	12	OL	2 mg varenicline SD+ 300 mg QID Cimetidine x 5 days Cimetidine 300 mg QID

A3051038 Metformin PK/PD interaction	HV smokers	30	R, OL, 3-way XO	Metformin 500 mg BID + Varenicline 1mg BID x 7 days Metformin 500 mg BID Varenicline 1 mg BID

SD: Single-dose; DB: double-blind; ISBSO: investigator and subject blind, sponsor open; OL: open label; PC: placebo-controlled; XO: cross-over; HV: healthy volunteers; QD: once a day; BID: twice a day; NRT: nicotine replacement therapy
[a] Subjects randomised and received at least one dose of study drug

Narrow-therapeutic index drugs: Pharmacokinetic or pharmacodynamic changes were not noted with the coadministration of multiple doses of varenicline with multiple doses of either digoxin or warfarin.

Study (Test Drug)	Parameter	Adjusted Geometric Means: Test Drug + Placebo	Adjusted Geometric Means: Test Drug + Varenicline	Ratio [a] (%)	90% Confidence Interval
A3051031 (Digoxin)	AUC(0-24), ng·hr/mL	11.835	11.519	97.32	(87.51%, 108.24%)
	Cmin, ng/mL	0.389	0.384	98.66	(83.84%, 116.10%)
	Cmax, ng/mL	1.211	1.174	96.99	(87.53%, 107.47%)
	CLr, mL/min	115.163	128.179	111.30	(95.26%, 130.04%)
A3051032 (Warfarin)	R-Warfarin				
	Cmax, mg/L	1.07	1.07	100.69	(97.30%, 104.19%)
	AUC(0-∞), mg·hr/L	51.18	52.18	101.95	(98.03%, 106.03%)
	S-Warfarin				
	Cmax, mg/L	1.06	1.06	100.14	(96.84%, 103.54%)
	AUC(0-∞), mg·hr/L	36.54	36.81	100.76	(97.07%, 104.58%)

Pharmacodynamic Parameters (units)	N	Adjusted Geometric Means: Placebo + Warfarin (Reference)	Adjusted Geometric Means: Varenicline + Warfarin (Test)	Ratio [a] (%)	90% Confidence Interval
AUC(INR) (h)	24	161.54	160.64	99.44	(97.64%, 101.28%)
INRmax	24	1.40	1.39	99.44	(95.44%, 103.60%)

Other Smoking cessation Products:

Nicotine-replacement therapy: Twenty four subjects were randomized to receive both NRT + varenicline and NRT + placebo. However, pharmacokinetics of nicotine was studied in twelve subjects who received both treatments and five subjects receiving only NRT + Placebo. Within the subjects receiving both treatments, there was no clear trend toward change in plasma nicotine levels (Cmax and AUC0-τ). The pharmacokinetic parameters of nicotine and the descriptive statistics are listed below.

Pharmacokinetic Parameters (units)	Nicotine + Placebo (N = 17)	Nicotine + Varenicline N = 12)
AUC(0-tau) (ng•h/mL)	941 (614)	831 (616)
Cmax (ng/mL)	210 (329)	177 (291)
tmax[b](h)	1.00 (1.00-8.00)	2.00 (1.00-4.00)

AUC(0-tau) = AUC(0-24)
[a]14 days in table title refers to length of study period. Varenicline (or placebo) was received only for 12 days (Days 3 –14).
[b]Median (range)

Increase in treatment-related adverse events in subjects receiving NRT + varenicline (total 124 AEs in 18 of 22 exposed subjects) was noted compared to NRT administered with placebo (total 71 AEs in 15 of 17 exposed subjects). There were 8 discontinuations (36%) due to adverse events associated with the nicotine + varenicline regimen, 1 associated with the nicotine + placebo regimen, and none associated with the nicotine alone regimen.

Zyban (Bupropion): Pharmacokinetics of bupropion or varenicline did not change with the coadministration of the multiple doses of these drugs. While the total number of adverse events and discontinuations was similar in the two treatment groups, incidence of nausea and constipation was higher in Zyban + varenicline group compared to Zyban + placebo.

Pharmacokinetic Parameter	Adjusted Geometric Mean (N = 31)		Ratio[a] (%)	90% Confidence Interval
	Zyban + Placebo (Reference)	Zyban + Varenicline (Test)		
AUC(0-24) (ng•h/mL)	2006.6	2006.5	99.99	(96.04%, 104.10%)
Cmax (AM) (ng/mL)	143.0	143.3	100.19	(94.39%, 106.35%)
Cmax (PM) (ng/mL)	152.5	151.9	99.57	(93.95%, 105.52%)

Drugs that are excreted by renal hOCT-2 transporter:

Cimetidine: Although statistically significant, the 29% increase in exposure of varenicline does not required dose adjustment coadministration of multiple doses of cimetidine or other hOCT-2 inhibitors.

Cimetidine is a prototypical competitive inhibitor of hOCT2. Other weakly basic organic cationic drugs may compete for hOCT2 transport in kidneys. Cimetidine partially inhibited (~24% inhibition at 1mM concentration) varenicline transport by hOCT2, in vitro; a preclinical and a clinical drug interaction study was conducted to further characterize the drug interaction potential.

As shown in the table below, 29% increase in varenicline exposure was noted upon coadministration of varenicline with cimetidine. The increase in exposure may be direct

result of decrease renal clearance (25%). Over a 48 hour period, cimetidine reduced urinary varenicline excretion from 57% to 52% of dose. Elimination half-life of varenicline was prolonged by 3 to 6 hours in the majority of subjects.

Summary Statistical Analyses of CP-526,555 Pharmacokinetic Parameters Following Single Administration of 2 mg CP-526,555 Alone or in Combination with Cimetidine 300 mg QID to Healthy Adult Smokers

Parameters (units)	Adjusted Geometric Mean		Ratio[a] (%)	90% Confidence Intervals
	CP-526,555 Alone	CP-526,555 + Cimetidine		
CLr (mL/min)	96.7	129.1	74.86%	(68.29%, 82.07%)
AUC(0-inf) (ng•hr/mL)	229.0	177.6	128.99%	(121.5%, 136.9%)
Cmax (ng/mL)	7.8	7.6	102.97%	(101.2%, 104.8%)

[a] Ratio of adjusted geometric means between test (CP-526,555 + Cimetidine) and reference (CP-526,555).

Metformin: There is no change in pharmacokinetics of varenicline or metformin following multiple dose administration of varenicline (1 mg BID for 7 days) and metformin (500 mg BID for 7 days).

Parameter	Adjusted Geometric Mean		Ratio(%)	90% Confidence Interval
	Metformin (Reference)	Metformin + Varenicline (Test)		
AUC(0-τ) (ng•h/mL)	5974.3	6126.5	102.55	(99.96%, 105.20%)
Cmax (ng/mL)	942.9	940.9	99.79	(96.18%, 103.54%)
CLr (mL/minute)	471.3	477.5	101.30	(94.34%, 108.77%)
	Varenicline	Varenicline +		
	(Reference)	Metformin (Test)		
AUC(0-τ) (ng•h/mL)	87.9	90.9	103.39	(100.24%, 106.64%)
Cmax (ng/mL)	10.6	10.8	102.68	(99.80%, 105.65%)
CLr (mL/minute)	115.9	113.5	97.95	(86.64%, 110.74%)

These results are consistent with the in vitro findings that circulating varenicline concentrations (Cav,ss ~43 nM) associated with therapeutic response are substantially lower than the Km (~ 360 μM) of varenicline transport by hOCT2.

g) what other co-medications are likely to be administered to the target patient population?

Subjects taking varenicline had side-effects such as nausea, vomiting, insomnia and abnormal dreams. Medications for the management of these side-effects may be administered in subjects on smoking cessation with varenicline.

h) are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

None

i) is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Not known

j) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

None

2.5 General Biopharmaceutics

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Varenicline tartarate is a Biopharmaceutics Classification System type I class drug due to its high solubility and permeability characteristics.

Varenicline tartarate is highly soluble in aqueous solutions of different pH values (pH 1.2, 4.5 6.8). Clinical mass balance study # A305104 revealed that following administration of [14C] varenicline, most of the recovered radioactivity (~88%) was in urine (>98%). The BCS committee assessed the available data in this regard and concluded that this product fits the criteria of BCS Class I designation.

Individual Excretion Data for Six Healthy Human Subjects after Oral Administration of 1 mg [^{14}C]Varenicline

Subject	Recovery (% of Dose)	% of recovered dose in: Urine	Feces
smoker			
smoker			
smoker			
nonsmoker			
nonsmoker			
nonsmoker			

Recovery= total amount of radioactivity recovered in urine and feces compared to orally administered dose

2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The proposed to-be marketed formulation, a film-coated tablet, and the uncoated tablet formulation used in the pivotal clinical trials are bioequivalent.

Bioequivalence Studies with Varenicline Tablet Formulations: Studies A3051030, A3051026, and A3051006

Pharmacokinetic Parameter	Adjusted Geometric Mean		Statistical Comparison	
	Test	Reference	Ratio (Test/Ref, %)	90% Confidence Interval (%)
Study # A3051030	Commercial Image Tartrate Tablets 1 x 1.0 mg N = 11	Phase 3 Tartrate Tablets 2 x 0.5 mg N = 12		
AUC(0-∞) (ng·hr/mL)	101.1	103.9	97.26	91.73-103.12
AUC(0-tlast) (ng·hr/mL)	96.6	95.2	101.43	94.17-109.26
Cmax (ng/mL)	4.0	4.3	93.05	89.13-97.15
	Commercial Image Tartrate Tablets 1 x 1.0 mg N = 11	Phase 2b Tartrate Tablets 2 x 0.5 mg N = 12		
AUC(0-∞) (ng·hr/mL)	101.1	101.1	99.98	94.30-106.01
AUC(0-tlast) (ng·hr/mL)	96.6	97.1	99.45	92.32-107.12
Cmax (ng/mL)	4.0	4.0	99.90	95.69-104.29
Study # A3051026	Phase 3 Tartrate Tablets 2 x 0.5 mg[a] N = 12	Phase 2b Tartrate Tablets 1 x 1.0 mg[a] N = 12		
AUC(0-∞) (ng·hr/mL)	49.87[b]	49.25[c]	101.26	94.61-108.38
AUC(0-tlast) (ng·hr/mL)	44.40	44.61	99.51	90.23-109.75
Cmax (ng/mL)	2.36	2.24	105.59	100.38-111.08
Study # A3051006	Phase 2b Tartrate Tablets 1 x 1.0 mg N = 15	Phase 2a Succinate Tablets 1 x 1.0 mg N = 15		
AUC(0-∞) (ng·hr/mL)	127.76	124.96	102.24	93.86-111.38
AUC(0-tlast) (ng·hr/mL)	115.53	112.56	102.64	94.56-111.41
Cmax (ng/mL)	4.22	4.16	101.53	97.15-106.10

a) What data support a waiver of in vivo BE data?

The following aspects of Champix drug substance and drug product support waiver of in vivo BE studies:

a) Data indicates that varenicline tartarate is a biopharmaceutics classification system - Class 1 type drug.

b) The film-coated varenicline tablets have a rapid dissolution profile.

Hence, formulations changes are not expected to alter the bioavailability characteristics of Champix.

b) what are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable

c) if the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable

3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

High fat diet did not affect the bioavailability of varenicline tartarate and hence the drug may be taken with or with out food.

Comparison of Varenicline Tablets Administered in the Fed and Fasted State: Studies A3051042, A3051006, A3051001

	Adjusted Geometric Means		Statistical Comparison	
Pharmacokinetic Parameter	Test	Reference	Ratio (Test/Ref, %)	90% Confidence Interval (%)
A3051042: Commercial image tablet (1 x 1.0 mg)				
	Fed N = 12	Fasted N = 12		
AUC(0-∞) (ng·hr/mL)	102.7	104.1	98.62	93.92-103.57
AUC(0-tlast) (ng·hr/mL)	98.7	99.2	99.54	94.60-104.73
Cmax (ng/mL)	4.2	4.2	100.9	96.88-105.22
A3051006: Phase 2b varenicline tartrate tablet (1 x 1.0 mg)				
	Fed N = 14	Fasted N = 15		
AUC(0-∞) (ng·hr/mL)	122.79[a]	127.76	96.11	87.77-105.24
AUC(0-tlast) (ng·hr/mL)	111.08	115.53	96.14	88.35-104.63
Cmax (ng/mL)	4.34	4.22	102.76	98.19-107.54
A3051001: Varenicline succinate tablet (2 x 1.0 mg)				
	Fed N = 10	Fasted N = 10		
AUC(0-∞) (ng·hr/mL)	225.85	237.37	95.15	87.18-103.84
Cmax (ng/mL)	9.54	9.33	102.30	96.37-108.59

4. When would a fed BE study be appropriate and was one conducted?

A bioequivalence study under fed condition is not required as; (a) high fat meal did not show any effect on the exposure of varenicline, (b) varenicline tartarate is classified as a BCS class 1 drug, i.e., highly soluble and highly permeable drug.

5. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The registration batch film-coated varenicline tartarate tablets and the developmental uncoated tablets exhibit rapid dissolution characteristics (NLT [illegible]% in 30 minutes) at different pH conditions (pH 1.2, 4.5 and 6.8). The dissolution method employs Apparatus I (basket) at an agitation rate of 100 rpm in 500 mL of 0.01 N HCl.

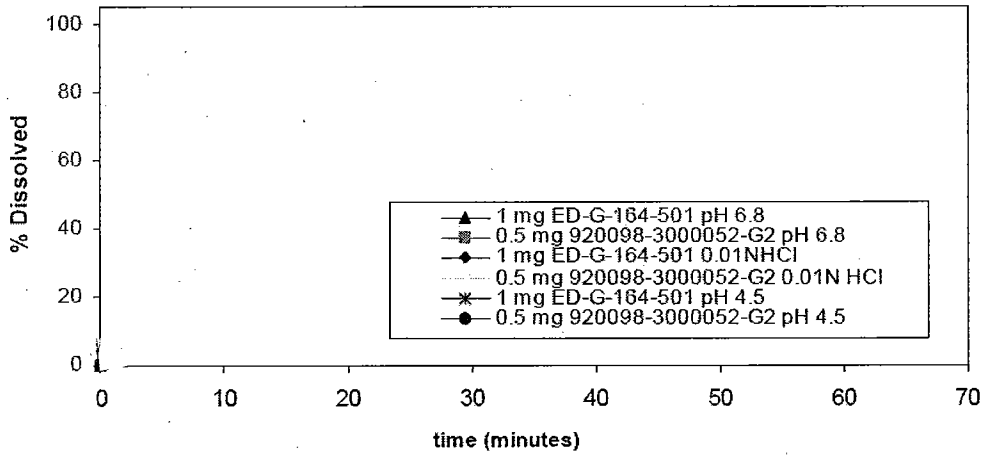
Dissolution of 0.5 mg and 1 mg strengths of varenicline tartarate film coated (commercial batch) and uncoated tablets (Phase 3 batch) were investigated in the following conditions:

Apparatus	USP <711> Dissolution Apparatus I (baskets)
Media	500 mL of 0.01N HCl 500 mL of 0.1N HCl 500 mL of USP pH 4.5 acetate buffer 500 mL of USP pH 6.8 phosphate buffer 500 mL of Water
Agitation Rate	100 rpm
# of dosage units tested per condition	12*

*For 1.0 mg tablets evaluated in water, 0.01N HCl and pH 4.5 buffer, 11 units were analyzed due to analytical equipment errors. However, the results from 11 units clearly illustrate rapid release with little variability.

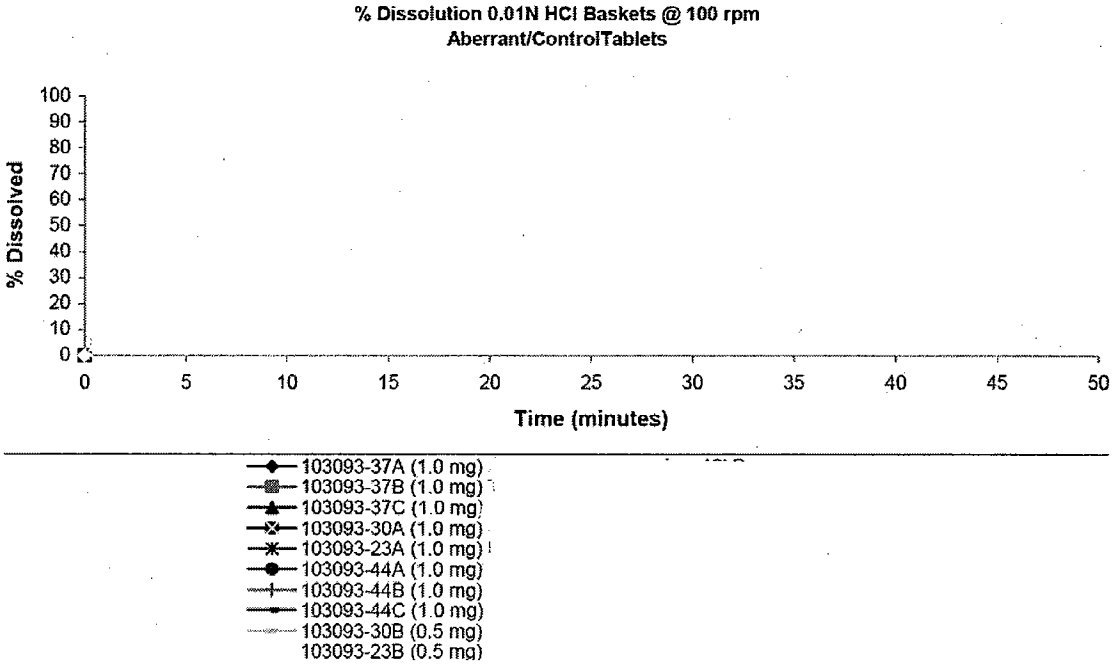
As shown in the figure below, the dissolution of varenicline in media of different pH was rapid (NLT [ ] in 30 minutes).

Varenicline Tartrate Tablet Dissolution Profiles
Baskets at 100 rpm, Multi media
(Non film-coated vs film-coated tablet)



The ability of the proposed dissolution and disintegration methods to discriminate deviations in tablet formulation and the manufacturing process was evaluated using aberrant tablet lots that were purposefully manufactured outside the proposed composition and/or manufacturing parameters.

As illustrated in the Figure below, all formulations exhibit rapid dissolution characteristics. A comparative summary of data obtained from each method indicates that the dissolution method has limited ability to detect differences in tablets manufactured under aberrant conditions.



6. If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable

7. If the NDA is for a modified release formulation of an approved immediate product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable

8. If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable

9. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None

2.6 Analytical

The sponsor employed adequately validated analytical methods for the analysis of varenicline in body fluids. All plasma samples were analyzed for varenicline concentrations using a fully validated assay employing [ ] followed by HPLC/MS/MS. The analytical method validation information is provided below:

QC Sample	Accuracy (%)	Precision (%)

Concentrations (ng/mL)	Range of Intra-Inter-assay assay Daily Mean	Mean	Range of Intra-Inter-assay assay Daily Mean	Mean
[			]	
0.2	89 - 91	91	5.4 - 5.6	5.1
16	93 - 102	97	2.2 - 7.5	6.1
40	94 - 106	100	2.4 - 4.9	6.4
[			]	
0.300	89.0 - 98.7	94.7	3.72 - 4.84	5.33
15.0	96.0 - 99.3	97.3	2.49 - 5.83	1.81
40.0	92.3 - 98.3	94.9	1.50 - 8.48	3.22

Accuracy and precision was also determined at the lower limit of quantitation (LLOQ, 0.1 ng/mL) and upper limit of quantitation (ULOQ, 50 ng/mL) at both laboratories. At the LLOQ, the mean accuracy and precision was 92% and 7.8%, respectively, at [ ] and 115% and 7.70% at [ ]. At the ULOQ, the mean accuracy and precision was 103% and 2.7%, respectively, at [ ] and 101% and 1.51% at [ ]

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____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

4.2 Individual Study Review

4.2.1 305-001: Single- and Multiple-dose PK study synopsis

CP-526,555
305-001
FINAL Clinical Study Report

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/305-001 **Phase:** 1

Title: Phase 1, Double-Blind, Placebo-Controlled Study of the Clinical Pharmacology of CP-526,555

Investigators: [redacted]

Study Publication: None at time of report issue.

Study Dates: 08 March 1999 to 07 January 2000

Study Objectives: The objectives of this study were:

A. To study the single-dose clinical pharmacology of CP-526,555 in healthy smokers and non-smokers.

1. To determine the clinical pharmacology of CP-526,555 administered under fasting conditions.
2. To determine if smoking influences the clinical pharmacology of CP-526,555.
3. To study the effect of food on the clinical pharmacology of CP-526,555.
4. To determine the clinical pharmacology of CP-526,555 administered as a tablet.
5. To determine the clinical pharmacology of CP-526,555 administered in the morning and in the evening.

B. To study the 14-day multiple-dose clinical pharmacology of CP-526,555 in healthy smokers.

Study Design: This study was comprised of 2 parts. Part 1 was a double-blind, placebo-controlled, single-dose, dose-escalation study, with subject groups for fed/fasted dosing comparisons and with subject groups for morning/evening dosing comparisons. Part 2 was a double-blind, placebo-controlled, 14-day multiple-dose, dose-escalation study, with doses administered once or twice per day (QD or BID, respectively) under fasting or fed conditions.

In the first part of the trial, blinding was achieved by having a third party prepare study medication. At a given dose level, CP-526,555 (succinate salt) given as solution (OPC) or placebo was administered in a double-blind fashion. Dose level assignment was single-blind (subject blinded only). The single-dose escalation was 0.01, 0.03, 0.1, 0.3, 1, 3 and 10 mg. Successive subject groups in the fasting solution dose-escalation sequence were studied at approximately weekly intervals. For doses larger than those administered previously, the new dose was no greater than 3.33X the preceding maximum dose.

Following completion of the initial single-dose escalation, the protocol was amended to allow administration of multiple doses of study drug. In the second part of the trial, CP-526,555 (succinate salt) given as a tablet or placebo was administered at a given dose level in a double-blind fashion, but open-labeled with respect to dose level assignment. The doses given were 1, 2 and 3 mg QD, and 1 mg BID.

Study Population and Criteria for Inclusion: Healthy, male or female, cigarette smokers (determined by cotinine levels) and non-smokers (determined by cotinine levels) between the ages of 18 and 45 years, inclusive. Females must have been of non-child-bearing potential, ie, surgically sterilized or at least 2 years postmenopausal, not breast-feeding.

Treatments:

Dosage Form	CP-526,555, Oral Powder for Constitution (Lot #ED-G-400-998) Placebo, Oral Powder for Constitution (Lot #ED-G-394-998) CP-526,555, 1.0 mg Tablet (Lot #ED-G-511-Y98) CP-526,555, 5.0 mg Tablet (Lot #ED-G-512-Y98) Placebo, Tablet (Lot #ED-G-514-Y98) Placebo, Tablet (Lot #ED-G-515-Y98)
Dosing and Duration	**Single-Dose Escalation** 0.01 mg CP-526,555, Oral Powder for Constitution, Smoker, Fasting, AM 0.03 mg CP-526,555, Oral Powder for Constitution, Smoker, Fasting, AM 0.1 mg CP-526,555, Oral Powder for Constitution, Smoker, Fasting, AM 0.3 mg CP-526,555, Oral Powder for Constitution, Smoker, Fasting, AM 1.0 mg CP-526,555, Oral Powder for Constitution, Smoker, Fasting, AM 3.0 mg CP-526,555, Oral Powder for Constitution, Smoker, Fasting, AM 3.0 mg CP-526,555, Oral Powder for Constitution, Smoker, Fed, AM 3.0 mg CP-526,555, Oral Powder for Constitution, Smoker, Fed, PM 3.0 mg CP-526,555, Oral Powder for Constitution, Restricted Smoker (no smoking from 8 hours before dosing until 4 hours after dosing), Fasting, AM 10.0 mg CP-526,555, Oral Powder for Constitution, Smoker, Fasting, AM Placebo, Oral Powder for Constitution, Smoker 0.01 mg CP-526,555, Oral Powder for Constitution, Non-Smoker, Fasting, AM 0.03 mg CP-526,555, Oral Powder for Constitution, Non-Smoker, Fasting, AM 0.1 mg CP-526,555, Oral Powder for Constitution, Non-Smoker, Fasting, AM 0.3 mg CP-526,555, Oral Powder for Constitution, Non-Smoker, Fasting, AM 1.0 mg CP-526,555, Oral Powder for Constitution, Non-Smoker, Fasting, AM 1.0 mg CP-526,555, Oral Powder for Constitution, Non-Smoker, Fed, AM 3.0 mg CP-526,555, Oral Powder for Constitution, Non-Smoker, Fasting, AM Placebo, Oral Powder for Constitution, Non-Smoker **Multiple-Dose Escalation** 1.0 mg CP-526,555, Tablet, QD, Days 1 and 4-17, Fasted and Placebo QD, Days 0, 2-3 and 18-22 2.0 mg CP-526,555, Tablet, QD, Days 1 and 4-17, Fed and Placebo QD, Days 0, 2-3 and 18-22 3.0 mg CP-526,555, Tablet, QD, Days 1 and 4-17, Fasted and Placebo QD, Days 0, 2-3 and 18-22 1.0 mg CP-526,555, Tablet, BID, Days 1-14, Fed and Placebo BID, Days 0, 15-18 and 19 AM Placebo, QD Placebo BID

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: All subjects were evaluated for safety, which was assessed by clinical observation, physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory measurements.

Pharmacokinetics: Urine (multiple-dose escalation only) and plasma samples were assayed for CP-526,555 concentrations using a [redacted] followed by HPLC/MS/MS. For plasma, the assay had a dynamic range extending from 0.100 to 50.0 ng/mL. For urine, the assay had a dynamic range of 1.00 to 500 ng/mL and a limit of quantification of 1.00 ng/mL using a 1 mL sample volume. Pharmacokinetic parameters [single-dose escalation: maximum observed concentration (Cmax), the time to Cmax (Tmax), the area under the plasma concentration-time curve (AUC; calculated by the linear trapezoidal rule), and the half-life (T½); multiple-dose escalation: Cmax, Tmax, AUC(0-inf), AUC(0-τ) and T½] were estimated from plasma concentration-time data using standard non-compartmental methods. In the multiple-dose escalation part of the study, the predicted (Rp) and observed (Ro) accumulation ratios were determined to provide an estimate of the extent of accumulation. The steady-state accumulation ratio (Rs) was assessed to evaluate time- and concentration-dependent changes in CP-526,555 pharmacokinetics following repeated administration. Renal clearance (CLr) was calculated using urinary excretion data obtained after repeat dosing, as the total amount of unchanged drug eliminated in urine (Ae) in t = 12 or 24 hours divided by plasma AUC(0-t), where t is equal to 12 or 24 hours, respectively.

Pharmacodynamics: Subjective ratings of nicotine-like effects were assessed by the Positive and Negative Affect Schedule (PANAS) scale (smokers and non-smokers), which consisted of 20 items measuring negative and positive subjective reactions on a 5 unit rating scale, by the nicotine effect questionnaire (smokers only), which consisted of 16 items measuring subjective perceptions of physiological responses to nicotine on an 11 unit rating scale and by the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami's Withdrawal Symptoms Questionnaire), which consisted of 8 items measuring withdrawal symptoms from nicotine on a 5 unit rating scale. The latter questionnaire was used only for the subjects in the multiple-dose part of the study.

Efficacy: For smokers in both the single-dose and multiple-dose groups, blood sufficient to provide a minimum of 3 mL serum (or plasma) for nicotine and cotinine was collected and expired air carbon monoxide levels were measured by a carbon monoxide analyzer at the same times as serum nicotine/cotinine levels. For smokers in the single-dose part of the study, each cigarette smoked during the study was recorded with start and end times. After smoking, each remaining cigarette was collected and weighed. The difference from the mean of the corresponding unsmoked samples was the consumed cigarette weight. For smokers dosed in the evening, each cigarette smoked during the study was recorded with start times only and the weight of the cigarettes was not measured. During the multiple-dose part of the study, each cigarette smoked during the study was recorded with start times only. The weight of the cigarettes was not measured.

Statistical Methods: No specific statistical hypothesis tests were planned. Pharmacokinetic and safety data were summarized through appropriate data tabulations, descriptive statistics and graphical presentations.

RESULTS:

Subject Disposition: In the single-dose part of the study, 102 subjects were enrolled, dosed and completed the study. All 102 subjects were assessed for safety, pharmacodynamics and efficacy. Pharmacokinetic parameters were evaluated in all 68 subjects that received CP-526,555.

In the multiple-dose part of the study, 44 subjects were enrolled and dosed. Seventeen subjects were withdrawn after dosing (6 subjects – AE; 3 subjects – withdrew consent ; 8 subjects – other: discontinuation of 3 mg and matching placebo dosing). All 44 subjects were assessed for safety, pharmacodynamics and efficacy. Pharmacokinetic parameters were evaluated in all 30 subjects that received CP-526,555.

Demographic Characteristics: In the single-dose part of the study, the different dose groups of smokers (including the restricted smokers) had a mean age ranging from 30.0 to 41.0 years, a mean height ranging from 169.0 to 186.8 cm and a mean weight ranging from 65.8 to 84.8 kg. For the non-smokers, the mean age ranged from 23.5 to 32.5 years, the mean height ranged from 170.0 to 181.5 cm and the mean weight ranged from 65.8 to 78.5 kg.

In the multiple-dose part of the study, the different dose groups (all smokers) had a mean age ranging from 26.7 to 35.3 years, a mean height ranging from 171.0 to 181.0 cm and a mean weight ranging from 67.4 to 75.3 kg.

Safety: Adverse Events: During the single-dose escalation part of the study, there were no deaths, serious adverse events (SAEs) or withdrawals due to adverse events (AEs). There were a total of 107 treatment-emergent AEs reported in 56 subjects. Seventy-seven of the treatment-emergent AEs were observed in 39 of the 68 subjects treated with CP-526,555. Thirty AEs were reported by 17 of 34 subjects receiving placebo. There appeared to be an increase in AEs seen in the 3.0 mg (fasted non-smokers and restricted smokers) and 10.0 mg (smokers) dosing groups. All AEs were mild to moderate in severity. The most frequent AEs, which showed evidence of relationship to dose, were nausea and vomiting. The nausea was dose limiting and typically occurred within 1.5 hours of dosing. There was an apparent increase in tolerability (nausea) in subjects who were smokers and in those who were dosed in the fed state. All AEs resolved without sequelae. Seventy-two of the AEs reported by 36 subjects who received CP-526,555 and 21 of the AEs observed in 12 subjects receiving placebo were considered treatment-related. All treatment-emergent AEs are summarized below.

Treatment-Emergent Adverse Events – Single-Dose Escalation

	0.01 mg OPC* NS Fast am	0.03 mg OPC NS Fast am	0.1 mg OPC NS Fast am	0.3 mg OPC NS Fast am	1.0 mg OPC NS Fed am	1.0 mg OPC NS Fast am	3.0 mg OPC NS Fast am	Pla OPC NS	0.01 mg OPC S Fast am	0.03 mg OPC S Fast am	0.1 mg OPC S Fast Am	0.3 mg OPC S Fast am	1.0 mg OPC S Fast am	3.0 mg OPC S Fast am	3.0 mg OPC S Fed am	3.0 mg OPC S Fed pm	3.0 mg OPC RS Fast am	10.0 mg OPC S Fast am	Pla OPC S
Total Number of AEs	3	3	0	3	6	4	14	9	1	5	4	1	6	2	0	3	10	12	21
Most Frequent AEs:																			
Headache	0	1	0	1	0	0	2	2	0	2	2	0	2	0	0	1	1	3	5
Nausea	1	0	0	0	2	0	3	0	0	0	0	0	0	2	0	1	3	4	0
Vomiting	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	4	1
Number of Subjects with AEs	2	2	0	2	4	2	4	5	1	4	2	1	3	2	0	2	4	4	12
Number of Subjects Exposed	4	4	4	4	4	4	4	14	4	4	4	4	4	4	4	4	4	4	20

Σεχπον 13

OPC – Oral powder for constitution; NS – non-smoker; S – smoker; RS – restricted smoker; Fast – fasted; Pla – placebo.

During the multiple-dose escalation part of the study, there were no deaths, one SAE (Placebo BID) and six withdrawals due to AEs. Five subjects (one subject – 2.0 mg CP-526,555 QD fed; 4 subjects – 3.0 mg CP-536,555 QD fasted) were withdrawn due to mild to moderate vomiting, which resolved shortly after the last dose of study medication. Nausea and vomiting showed an apparent dose-dependent increase, were decreased when given as a divided dose (1.0 mg BID vs. 2.0 mg QD) and were dose limiting. When they occurred, they were typically reported within 1.5 hours of dosing. Treatment with 3.0 mg CP-526,555 was discontinued due to the nausea and vomiting. The additional withdrawal, an SAE which was not considered related to study medication, was a perianal abscess, a post-operative wound infection and subsequent diagnosis of anal cancer. There were a total of 143 treatment-emergent AEs reported in 40 subjects. One hundred and six of the treatment-emergent AEs were observed in 28 of the 30 subjects treated with CP-526,555. Thirty-seven AEs were reported by 12 of 14 subjects receiving placebo. All AEs were mild to moderate in severity, except for the SAE. The most frequent AEs, which showed evidence of relationship to dose, were nausea and vomiting. All AEs resolved by the end of the study, except for three subjects (tooth caries – one subject; maculopapular rash – one subject; SAE [perianal abscess] – one subject). Ninety-one of the AEs reported by 26 subjects who received CP-526,555 and 26 of the AEs observed in 12 subjects receiving placebo were considered treatment-related.

Treatment –Emergent Adverse Events – Multiple-Dose Escalation

	1.0 mg Tab* QD Fast	1.0 mg Tab BID Fed	2.0 mg Tab QD Fed	3.0 mg Tab QD Fast	Pla QD	Pla BID
Total Number of AEs	34	13	32	37	30	7
Most Frequent AEs:						
Somnolence	4	2	3	3	7	0
Nausea	2	1	5	8	2	0
Number of Subjects with AEs	7	6	7	8	10	2
Number of Subjects Exposed	8	7	7	8	11	3

* Tab – tablet; QD – once per day; BID – twice per day; Fast – fasted; Pla – placebo.

Clinical Laboratory Assessments: Overall, there was no apparent effect of CP-526,555 on clinical laboratory assessments. During the single-dose part of the study, six subjects had postdose clinical laboratory assessments of potential clinical concern (increased potassium – one subject; increased glucose – one subject; decreased hemoglobin – one subject; decreased hemoglobin and hematocrit – one subject; increased WBC – one subject; increased total bilirubin – one subject). These clinical laboratory values of potential clinical concern were sporadic, asymptomatic, and considered not clinically significant by the Investigator. During the multiple-dose part of the study, three subjects had postdose clinical laboratory assessments of potential clinical concern (increased glucose – one subject; increased potassium – one subject; decreased hematocrit and increased glucose – one subject), which were asymptomatic, and considered not clinically significant by the Investigator.

Vital Signs: Overall, there was no apparent effect of CP-526,555 on vital signs (blood pressure and heart rate). During the single-dose part of the study, 61 subjects had vital signs changes of potential clinical concern during the study. These vital signs changes were considered not clinically significant by the Investigator. These vital signs changes were asymptomatic in all subjects, except for mild dizziness associated with an increased supine systolic blood pressure in one subject and mild dizziness associated with an increased supine diastolic blood pressure in one subject. In the multiple-dose part of the study, fifteen subjects had vital signs changes of potential clinical concern, which were considered not clinically significant by the Investigator. These vital signs changes were asymptomatic in all subjects, except for mild dizziness associated with a low supine diastolic blood pressure in two subjects and moderate dizziness associated with an increase in supine diastolic blood pressure. However, the last subject also had several other episodes of dizziness, which were not associated with vital signs changes of potential clinical concern.

ECGs: Overall, there was no apparent effect of CP-526,555 on QTc or ECG morphology. During the single-dose part of the study, there were 4 subjects with ECG intervals of potential clinical concern which were asymptomatic and considered not clinically significant by the Investigator. All postdose ECG morphologies were considered normal by the Investigator. An increase of QTcB and/or QTcF of greater than 60 msec was observed in one subject in each of the following groups: 0.1 mg CP-526,555 OPC (fasted smokers), 1.0 mg CP-526,555 OPC (fasted smokers), 3.0 mg CP-526,555 OPC (fasted smokers) and 10.0 mg CP-526,555 OPC (fasted smokers). However, these increases in QTc were not seen at other ECG assessments or at Tmax for CP-526,555.

During the multiple-dose part of the study, there were 2 subjects with ECG intervals (both subjects had increases in the PR interval) of potential clinical concern which were asymptomatic and considered not clinically significant by the Investigator. All postdose ECG morphologies were considered normal by the Investigator, except for both Day 1 ECGs for one subject (1.0 mg, BID, Fed). At 3 hours post morning dosing, a finding of sinus bradycardia with occasional premature ectopic complexes, possible inferior infarct age undetermined was observed. At 3 hours post evening dosing, a finding of sinus bradycardia with sinus arrhythmia was observed. These findings were asymptomatic and considered not clinically significant by the Investigator. No additional testing was performed at the time of this finding. All other postdose ECGs in this subject were considered normal by the Investigator. An increase of QTcB of greater than 60 msec was observed in one subject receiving 1.0 mg CP-526,555 Tablet BID in the fed state. This increased QTcB was observed at the Day 7 assessment, however, no other increases in QTc were observed in this subject over the course of the study.

Pharmacokinetics: In the single-dose part of the study, systemic exposure increased approximately linearly with dose over the range of 0.1 to 3.0 mg in smokers and non-smokers, and was similar for both groups. Plasma concentrations of CP-526,555 at the 0.01 dose were not quantifiable. In smokers, exposure to CP-526,555 at the 10 mg dose was similar to that at 3.0 mg. However, subjects at the 10.0 mg dose vomited shortly after dosing, which may have affected drug exposure. In non-smokers, 2 of 4 subjects at the 3.0 mg dose vomited shortly after dosing. The overall Tmax was about 2.9 hours (range in individuals 0.5 to 8 hours) in smokers and 2.6 hours (range in individuals 0.5 to 8 hours) in non-smokers. After attaining Cmax, the decline in CP-526,555 plasma concentration was monophasic. Individual T½ values ranged from 10.1 to 25.6 hours (overall mean 16.6 hours) in smokers and from 8.1 to 30.2 hours (overall mean 14.2 hours) in non-smokers. There was no food effect in either group. Smoking restriction did not affect the pharmacokinetics of CP-526,555 in smokers given the 3.0 mg dose. No marked difference in the single 3.0 mg dose pharmacokinetics of CP-526,555 was observed between morning and evening dosing. The pharmacokinetic parameters for smokers and non-smokers are summarized below.

Pharmacokinetic Parameters for CP-526,555[a] - Single-Dose Escalation, Smokers

Dose (mg)	N	Descriptive Statistic	Tmax (hr)	Cmax (ng/mL)	AUC(0-Tlast) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	Kel (hr^{-1})	T1/2 (hr)
0.01 mg	4	Mean (Arithmetic)	NC	NC	NC	NC	NC	NC
		SD (Arithmetic)	NC	NC	NC	NC	NC	NC
0.03 mg	4	Mean (Arithmetic)	0.750	0.165	0.877	NC	NC	NC
		SD (Arithmetic)	0.289	0.037	0.553	NC	NC	NC
0.1 mg	4	Mean (Arithmetic)	1.50	0.468	4.70	9.52	0.0525	14.8
		SD (Arithmetic)	0.58	0.071	1.68	3.60	0.0168	6.5
0.3 mg	4	Mean (Arithmetic)	1.63	2.35	35.1	37.9	0.0497	14.4
		SD (Arithmetic)	1.11	0.93	9.5	9.7	0.0110	2.9
1.0 mg	1		3.00	4.8	138	140	0.0342	20.2
3.0 mg	4	Mean (Arithmetic)	4.00	13.8	296	299	0.0445	16.6
		SD (Arithmetic)	2.83	2.5	51	51	0.0126	4.8
3.0 mg (Fed AM)**	4	Mean (Arithmetic)	3.75	14.5	269	273	0.0388	18.3
		SD (Arithmetic)	0.50	0.58	52	52	0.0066	3.4
3.0 mg (Fed PM)[#]	4	Mean (Arithmetic)	4.0	8.50	227	238	0.0347	21.6
		SD (Arithmetic)	1.6	1.91	51.1	57.5	0.0114	6.84
3.0 mg (SR)	4	Mean (Arithmetic)	3.00	14.0	283	288	0.0485	16.5
		SD (Arithmetic)	0.82	1.4	51	55	0.0202	7.3
10.0 mg	4	Mean (Arithmetic)	4.25	13.0	298	303	0.0383	19.5
		SD (Arithmetic)	2.36	6.2	167	168	0.0122	5.9

*OPC dosage form; **Fed – FDA high-fat breakfast; #Fed – standard meal.
NC – not calculated, as all time points were <LLOQ; SR – smoking restricted.

Pharmacokinetic Parameters for CP-526,555* – Single-Dose Escalation, Non-Smokers

Dose (mg)	N	Descriptive Statistic	Tmax (hr)	Cmax (ng/mL)	AUC(0-Tlast) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	Kel (hr^{-1})	T1/2 (hr)
0.01 mg	4	Mean (Arithmetic)	NC	NC	NC	NC	NC	NC
		SD (Arithmetic)	NC	NC	NC	NC	NC	NC
0.03 mg	4	Mean (Arithmetic)	2.00	0.135	0.545	NC	NC	NC
		SD (Arithmetic)	2.68	0.045	0.334	NC	NC	NC
0.1 mg	4	Mean (Arithmetic)	3.13	0.825	9.21	12.6	0.0530	13.3
		SD (Arithmetic)	3.42	0.105	0.54	0.7	0.0079	2.0
0.3 mg	4	Mean (Arithmetic)	1.75	1.90	28.6	31.4	0.0561	12.6
		SD (Arithmetic)	1.50	0.56	8.5	9.6	0.0099	2.2
1.0 mg	4	Mean (Arithmetic)	3.00	6.20	98.4	102	0.0579	13.6
		SD (Arithmetic)	2.16	1.10	13.6	14	0.0213	6.1
1.0 mg (Fed)	4	Mean (Arithmetic)	2.63	5.70	94.3	97.7	0.0639	11.1
		SD (Arithmetic)	1.49	0.57	11.9	11.7	0.0112	2.2
3.0 mg	4	Mean (Arithmetic)	3.13	10.8	216	223	0.0443	20.5
		SD (Arithmetic)	2.25	2.1	79	83	0.0293	10.3

*OPC dosage form; NC, not calculated, as all time points were <LLOQ; Fed – FDA high-fat breakfast.

In the multiple-dose part of the study (all smokers), systemic exposure to CP-526,555 increased proportionately with dose following single and repeat oral administration. Based on trough concentrations, steady-state was reached within 4 days of repeat dosing. The extent of accumulation in exposure of CP-526,555 at steady-sate was well predicted from the single-dose pharmacokinetic data. Once daily dosing resulted, on average, in an approximate 2-fold accumulation in exposure of CP-526,555 with the observed accumulation ratio being consistent across all three dose levels. When CP-526,555 was administered BID, exposure was increased approximately 3-fold over the 12 hour dosing interval. There was no evidence of concentration- or time-dependent changes in the pharmacokinetics of CP-526,555 upon repeat dosing. High amounts of CP-526,555 were recovered in the urine, and estimates of renal clearance were similar across treatments and study days, indicating that renal elimination of CP-526,555 was not altered upon repeat dosing. For the 1.0 mg BID group, a comparison of pharmacokinetic parameters obtained from the second (12-24 hour) and first (0-12 hour) dosing intervals on Day 14 showed no diurnal variation in the multiple-dose pharmacokinetics of CP-526,555.

Arithmetic mean (S.D.) for Cmax, AUC and T1/2 and median [range] Tmax values are summarized below.

Pharmacokinetic Parameters for CP-526,555 – Multiple-Dose Escalation, Smokers

	1 mg QD		2 mg QD		3 mg QD		1 mg BID	
Parameters (units)	Day 1 (N=8)	Day 17 (N=7)	Day 1 (N=7)	Day 17 (N=6)	Day 1 (N=8)	Day 17 (N=8)	Day 1 (N=7)	Day 14 (N=7)
AUC(0- τ) (ng.h/mL)	74.7 (8.2)	144 (24)	148 (24)	280 (33)	187 (50)	352 (87)	39.3 (7.3) 104 (16)^	105 (16) 215 (30)^
AUC(0-inf) (ng.h/mL)	139 (14)	271 (75)	280 (60)	589 (112)	334 (88)	756 (268)	n/a	504 (101)
Cmax* (ng/mL)	4.29 (0.32)	7.93 (0.90)	8.67 (1.59)	15.1 (1.8)	10.8 (3.1)	19.8 (3.8)	4.08 (0.82)	10.2 (1.0)
Tmax* (h)	4.00 [1.00-8.00]	4.00 [1.00-8.00]	2.00 [2.00-4.00]	2.00 [2.00-4.00]	4.00 [2.00-8.00]	4.00 [2.00-8.00]	4.00 [2.00-8.00]	2.00 [1.00-4.00]
T1/2 (h)	21.8 (2.6)	23.8 (4.9)	21.4 (3.4)	24.8 (2.9)	20.9 (4.1)	25.2 (3.8)	n/a	31.5 (7.7)

τ = dosing interval (QD, 24 hours) or (BID, 12 hours); ^ AUC(0-24) was also calculated after BID dosing
* Tmax, Cmax of the first dosing interval (0-12 hr postdose)
n/a – Not available; T1/2 could not be estimated, thus AUC(0-inf) not calculated due to limited sampling period

Pharmacodynamics: In the single-dose part of the study, there was no apparent change in mean mood, mean physiological response or mean urge to smoke, according to the Nicotine Effect Questionnaire (administered to smokers only). There was no apparent change in mean positive subjective reactions or mean negative subjective reactions, according to the PANAS (administered to all subjects).

In the multiple-dose part of the study, conducted in smoking subjects only, there was an apparent decrease in mean craving (approximately 50 – 95%) following administration of 2 mg QD and 1 mg BID CP-526,555, but no apparent decrease in mean withdrawal symptoms following administration of CP-526,555, according to the Minnesota Nicotine Withdrawal Scale. There was an apparent decrease in mean mood (approximately 15 – 30%), mean physiological response (approximately 20%) and mean urge to smoke (approximately 40 – 70%), according to the Nicotine Effect Questionnaire.

Efficacy: In the single-dose part of the study, there was an apparent decrease in mean plasma cotinine levels at 0.1 mg and above (approximately 10 – 60%), but no apparent decrease in mean plasma nicotine levels following administration of any dose level of CP-526,555. There was no apparent change in mean expired air carbon monoxide levels.

In the multiple-dose part of the study, there was an apparent decrease in both mean plasma cotinine (approximately 60 – 90%) and mean plasma nicotine (approximately 50 – 80%) levels following administration of the 2.0 mg and 3.0 mg QD doses and the 1.0 mg BID dose of CP-526,555. There was an apparent decrease in mean Expired Air Carbon Monoxide (approximately 50 – 80%) levels following administration of the 2.0 mg and 3.0 mg QD doses and the 1.0 mg BID dose of CP-526,555, both QD and BID. There was also an apparent decrease in the number of cigarettes smoked per day (approximately 60 – 80%) following administration of 2 mg QD, 3 mg QD and 1 mg BID CP-526,555.

CONCLUSIONS:

- Single and multiple doses of CP-526,555 were generally safe in healthy adults. However, at single and multiple doses of 3 mg and above, CP-526,555 was not well tolerated, with nausea and vomiting as the dose limiting adverse events.
- Systemic exposure to CP-526,555 increased approximately proportionately with dose following single and repeat oral administration.

- Following single-dose oral administration, systemic exposure to CP-526,555 and pharmacokinetic variability were similar between smokers and non-smokers
- Administration of CP-526,555 solution with food (high-fat breakfast) had no affect on the oral bioavailability of CP-526,555 in both smokers and non-smokers
- Smoking restriction and time of day dosing (morning vs evening) did not affect the pharmacokinetics of CP-526,555 in smokers treated with the 3.0 mg dose
- The extent of the accumulation in exposure to CP-526,555 following repeat dose administration was well predicted from the single-dose pharmacokinetic data. There was no evidence of concentration- or time-dependent changes in the pharmacokinetics of CP-526,555 upon repeat dosing.

CP-526,555
A3051001
FINAL Clinical Study Report

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051001 **Phase: 1**

Title: PHASE I OPEN RANDOMIZED CROSSOVER PILOT STUDY EVALUATING THE PHARMACOKINETICS OF CP-526,555 FOLLOWING SINGLE DOSE ADMINISTRATION IN THE MORNING UNDER FASTING AND FED CONDITIONS AND IN THE EVENING IN HEALTHY SMOKERS

Investigator: C)

Study Publication: None at time of report issue.

Study Dates: 04 October 1999 to 22 November 1999

Study Objectives: The purpose of this pilot study was to compare the single dose pharmacokinetics of CP-526,555 administered in different dosage forms (formulated as succinate salt) or at different times to healthy adult smokers:

- When administered as a tablet and as an oral solution in the fasted state in the morning.
- When administered in the fed and fasted state as a tablet in the morning.
- When administered in the morning and in the evening as a tablet in the fasted state.

Study Design: This was a randomized, open-label, 4-way crossover study of a single oral dose of 2 mg CP-526,555 administered in different dosage forms (formulated as a succinate salt) to healthy adult smokers. Each subject received:

A = 2 mg CP-526,555 as an aqueous solution in the morning (0800 hours) in the fasting state
B = 2 mg CP-526,555 as two 1 mg tablets in the morning (0800 hours) in the fasting state
C = 2 mg CP-526,555 as two 1 mg tablets in the morning (0800 hours) in the fed state
D = 2 mg CP-526,555 as two 1 mg tablets in the evening (2000 hours) in the fasting state

in one of the following sequences:

1. ADBC
2. BACD
3. CBDA
4. DCAB

Dosing occurred approximately every 7 days (Days 1, 8, 15 and 22). There was at least a 6-day washout period between each dosing day.

Study Population and Criteria for Inclusion: Subjects were healthy male or female cigarette smokers between the ages of 18 and 50 years, inclusive. Females were of non-child-bearing potential, (i.e., surgically sterilized or at least two years post-menopausal and not breast feeding). They smoked at least 20 cigarettes per day.

Treatments:

All CP-526,555 formulations were administered as the succinate salt.

Dosage Form	CP-526,555, oral powder for constitution, 2 mg (Pfizer, G01573AA-B)
	CP-526,555, tablet, 2 x 1mg (Pfizer, G01691AA)

Dosing and Duration	2 mg CP-526,555 oral solution, PO, Dosed one time in the morning in the fasting state
	2 mg CP-526,555 tablet, PO, Dosed one time in the morning in the fasting state
	2 mg CP-526,555 tablet, PO, Dosed one time in the morning in the fed state
	2 mg CP-526,555 tablet, PO, Dosed one time in the evening in the fasted state

PO = orally administered

CRITERIA FOR EVALUATION AND METHODOLOGY: The following safety and pharmacokinetic endpoints were assessed during this study.

Safety: Safety evaluations included clinical monitoring, vital signs (blood pressure, pulse rate, oral temperature, respiration rate and weight), 12-lead electrocardiographs (ECGs), safety laboratory tests, physical examinations and the reporting of adverse events.

Pharmacokinetics: On Days 1, 8, 15 and 22, blood sufficient to provide a minimum of 3 mL plasma for CP-526,555 pharmacokinetics was collected in heparinized tubes at the following times: 0 (just prior to dosing), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours after drug administration. Plasma samples were analyzed for CP-526,555 using [ ] followed by HPLC/MS/MS analysis. The following pharmacokinetic parameters for CP-526,555, Cmax and Tmax, were obtained directly from the data profiles, whereas AUC(0-inf) and t½ were estimated using non-compartmental methods.

Statistical Methods: Log-transformed AUC, log-transformed Cmax and untransformed Tmax and t½ were analyzed by an analysis of variance appropriate for a 4-period, 4-treatment crossover design.

After constructing 90% confidence intervals for log AUC and log Cmax, the anti-log was taken on the confidence limits to obtain the corresponding confidence intervals for the ratio.

RESULTS:

Subject Disposition:

Eleven subjects entered the study and ten subjects completed the study.

Table SA Subject Disposition

	Total	Regimen A	Regimen B	Regimen C	Regimen D
Total Planned	Up to 12	Up to 12	Up to 12	Up to 12	Up to 12
Total Number Enrolled	11	11	11	11	11
Total Number Dosed	11	10	10	11	10
Total Withdrawn After Dosing	1	0	0	1	0
Due to Adverse Event	1	0	0	1	0
Number Completed	10	10	10	10	10
Assessed for Safety	11	10	10	11	10
Adverse Events	11	10	10	11	10
Laboratory Tests	11	10	10	11	10
Number Evaluated	10	10	10	10	10
Pharmacokinetics	10	10	10	10	10

Regimen A: 2 mg CP-526,555 solution, fasted, AM
Regimen B: 2 mg CP-526,555 succinate tablet, fasted, AM
Regimen C: 2 mg CP-526,555 succinate tablet, fed, AM
Regimen D: 2 mg CP-526,555 succinate tablet, fasted PM

Demographic Characteristics: Demographic characteristics for enrolled subjects are displayed in the table below.

Table SB Demographic Characteristics of the Study Population

Group	Parameter	Age (years)	Weight (kg)	Height (cm)
All subjects n = 11	**Mean**	35.2	72.1	167.9
	SD	10.2	7.9	6.8
	Range	19.0-50.0	64.0-89.0	155.0-178.0
Males n = 5	**Mean**	30.2	73.8	173.4
	SD	10.8	11.1	3.6
	Range	19.0-42.0	64.0-89.0	168.0-178.0
Females n = 6	**Mean**	39.3	70.7	163.3
	SD	8.4	4.4	5.1
	Range	28.0-50.0	66.0-78.0	155.0-168.0

18.2% Black; 9.1% White; 72.7% Hispanic; 45.5% Male, 54.5% Female

Safety: There were no deaths or other serious adverse events reported during this study. One subject was withdrawn from the study due to mild headache, nausea and vomiting after treatment with 2 mg CP-526,555, succinate tablet, fed. These adverse events (AEs) were considered related to the study medication by the investigator and resolved by 32.5 hours after onset. Twenty-five adverse events in 9 subjects were reported during the study. Six AEs in 5 subjects occurred after the morning administration of the aqueous solution in the fasting state. Eleven AEs in 5 subjects occurred after the morning administration of tablets in the fasted state. Six AEs in 3 subjects occurred after the morning administration of tablets in the fed state. Two AEs in one subject occurred after the evening administration of tablets in the fasted state. All AEs were mild in severity and resolved before the completion of the study. The most common AEs were nausea and headache. Twenty-one of the 25 AEs were considered related to the study medication by the investigator. All treatment-emergent AEs are summarized in the table below.

Table SC Adverse Events

Adverse Event (Preferred Term)	Number of Subjects Regimen				
	A	B	C	D	Total
Most Frequent AEs (nausea/headache)	**3/2**	**1/1**	**2/1**	**1/0**	**5/4**
Total Number of AEs	**6**	**11**	**6**	**2**	**25**
Number of Subjects with AEs	**5**	**5**	**3**	**1**	**9**
Number of Subjects Exposed	**10**	**10**	**11**	**10**	**11**

A = 2 mg CP-526,555 as an aqueous solution in the morning in the fasting state
B = 2 mg CP-526,555 as two 1 mg tablets in the morning in the fasting state
C = 2 mg CP-526,555 as two 1 mg tablets in the morning in the fed state
D = 2 mg CP-526,555 as two 1 mg tablets in the evening in the fasting state

Clinical laboratory measurements of potential clinical concern were asymptomatic, sporadic, transient and appeared to be unrelated to the study medication. Two female subjects had laboratory values of potential clinical concern (elevated urine red blood cells) during the study. Two subjects had a vital signs change of potential clinical concern during the study, one of which was most likely due to an isolated increased baseline measurement. Both changes were asymptomatic and considered not clinically significant by the investigator. Two subjects had QTcB increases of 30 to <60 msec during the study. No subjects had increases of potential clinical concern in QTcF. One subject had an enlarged thyroid at screening that was subsequently diagnosed as hyperthyroidism.

Pharmacokinetics: The rate and extent of absorption of CP-526,555 following the tablet treatments in the fasted state were generally similar to those observed following the solution treatment in the fasted state in the morning. There was no effect of food or time-of-dosing on the pharmacokinetics of CP-526,555.

Table SD Summary of Mean (SD) Pharmacokinetic Parameters of CP-526,555 Following Administration of the Solution and Tablet Formations to Healthy Smokers

Parameter	Treatment			
	Solution AM Fasted	**Tablets AM Fasted**	**Tablets PM Fasted**	**Tablets AM Fed**
AUC(0-inf) (ng*h/mL)	264 (70)	242 (60)	247 (61)	231 (51)
Cmax (ng/mL)	9.61 (1.37)	9.37 (1.25)	9.22 (0.96)	9.60 (1.09)
Tmax (h)	4.2 (1.6)	3.6 (0.5)	3.8 (0.4)	3.8 (0.9)
t½ (h)	17.3 (4.3)	17.8 (3.8)	19.0 (5.3)	16.2 (3.3)

The results demonstrated that CP-526,555 was completely available in the tablet formulation relative to the solution. The mean relative bioavailability of the tablet formulation [as assessed by AUC(0-inf)] was on average 93% compared with the solution formulation. The complete oral bioavailability of the tablet formulation in the fed state relative to the fasting condition suggested the absence of food effect. The mean relative bioavailability of the tablet formulation in the fed state [as assessed by AUC(0-inf)] was on average 95% compared with the fasting condition. Also, there was no effect of time of day of dosing on the single dose pharmacokinetics of the CP-526,555 tablet formulation observed. The mean relative bioavailability of the tablet formulation administered in the fasted state, PM [as assessed by AUC(0-inf)] was on average 101% when compared with the AM

administration. For all three comparisons, the bounds of 90% confidence limits for both Cmax and AUC(0-inf) fell well within the bioequivalence limits (80%,125%). The point estimates and confidence intervals (CIs) for the treatment comparisons are shown in the table below.

Table SE Pairwise Comparisons of Tablets Vs. Solution, Tablets in the Fasted State Vs. Fasted State and Tablets Administered in the PM Vs. AM

Pharmacokinetic Parameter	Treatment Comparison	Ratio[a]	90% Confidence Intervals
AUC(0-inf) (ng'h/mL)	**Tablets AM Fasted vs. Solution AM Fasted**	**93%**	**(85%,101%)**
	Tablets AM Fed vs. Tablets AM Fasted	**95%**	**(87%,104%)**
	Tablets PM Fasted vs. Tablets AM Fasted	**101%**	**(92%, 110%)**
Cmax (ng/mL)	**Tablets AM Fasted vs. Solution AM Fasted**	**97%**	**(91%,103%)**
	Tablets AM Fed vs. Tablets AM Fasted	**102%**	**(96%,109%)**
	Tablets PM Fasted vs. Tablets AM Fasted	**99%**	**(93%, 105%)**

[a]Ratio of adjusted geometric means (Test/Reference)

CONCLUSIONS: The results of this study demonstrated similar oral bioavailability of CP-526,555 following single oral doses between

- tablets and solution administered in the morning in the fasted state,
- tablets administered in the morning and in the evening in the fasted state and
- tablets administered in the morning in the fed and fasted states.

The comparisons indicated a high relative bioavailability of the tablet formulation compared with the solution and no effect of food or time of dosing on the single dose pharmacokinetics of the CP-526,555 tablet formulation. There were no safety or tolerability issues raised with the succinate salt solution and tablet formulations used in this study. There were no apparent differences in the safety or tolerability between formulations.

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051004 **Phase: 1**

Title: PHASE I OPEN STUDY TO EXAMINE THE METABOLISM AND EXCRETION OF ORALLY ADMINISTERED [^{14}C]CP-526,555 IN HEALTHY SMOKING AND NON-SMOKING MALE SUBJECTS

Investigator: [redacted]

Study Publication: None at time of report issue

Study Dates: 10 July 2000 to 04 August 2000

Study Objectives: To evaluate the metabolic profile and the route(s) of elimination of CP-526,555 following oral administration of a single dose of [^{14}C]CP-526,555 in healthy smoking and non-smoking male subjects.

Study Design: This was a non-randomized, open-label, single-dose study of CP-526,555. Subjects received a single 1 mg oral dose of CP-526,555 containing 100 µCi of [^{14}C]CP-526,555 on Day 1.

Study Population and Criteria for Inclusion: Three healthy smoking male subjects and 3 healthy non-smoking male subjects between the ages of 18 and 55 years, inclusive, were enrolled and dosed in this study. All 6 subjects completed the study.

Treatments:

Dosage Form	[^{14}C]CP-526,555 oral powder for constitution, 1 mg, (Pfizer, ED-G-213-600)

Dosing and Duration	Single, 1 mg dose, PO, Day 1.

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: Safety evaluations included clinical monitoring, vital signs (blood pressure, pulse rate), oral temperature, safety laboratory tests, physical examinations and the reporting of adverse events. ECGs were performed at screening only.

Pharmacokinetics: Blood samples sufficient to provide a minimum of 6 mL plasma (3 mL for plasma total radioactivity measurement and 3 mL for plasma CP-526,555 concentrations) were collected in heparinized tubes at 0 hr (prior to dosing) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168 and 192 hrs post-dose. An additional blood samples was collected at 216 hr post-dose for Subject 008. Blood sufficient to provide a minimum of 20 mL plasma for CP-526,555 metabolite identification was collected 1, 4, 8, 12, and 24 hours after drug administration.

Urine samples for the analysis of CP-526,555, for the isolation and identification of metabolites, and for measurement of total radioactivity were collected. Following dosing, there were two

12-hour urine collections (0-12 hours and 12-24 hours) and six 24-hour urine collections [24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours post-dose (except Subject 002)] An additional collection occurred at the interval of 168-192 hours post-dose for Subject 008.

Feces for the analysis of CP-526,555, for the isolation and identification of metabolites, and for measurement of total radioactivity were collected prior to dosing were collected prior to dosing ("blank"), and at intervals of 0-24, 24-48, 48-72 and 72-96 hours after drug administration.

Twenty-four hour urine and daily fecal specimens were collected beyond 96 hours (in 24 hour intervals) until samples from 2 consecutive days had radioactivity levels less than 1% of the total administered radioactivity.

The data collected on plasma concentrations of CP-526,555, and total radioactivity were analyzed to estimate the maximum observed concentration (Cmax), the time to the first occurrence of Cmax (Tmax) and the area under the plasma concentration-time curve (AUC). The elimination half-lives of CP-526,555, and total radioactivity were also determined whenever possible.

Statistical Methods: No specific statistical hypotheses were tested. Data are presented in descriptive form only.

RESULTS:

Subject Disposition: Subject disposition is summarized in the table below.

Table SA Subject Disposition

	[^{14}C]CP-526,555		
	Smokers	**Non-smokers**	**Total**
Total Planned	3	3	6
Total Number Enrolled	3	3	6
Total Number Dosed	3	3	6
Total Withdrawn After Dosing	0	0	0
Number Completed	3	3	6
Assessed for Safety	3	3	6
Adverse Events	3	3	6
Laboratory Tests	3	3	6
Number Evaluated	3	3	6
Pharmacokinetics	3	3	6

Demographic Characteristics:

Table SB Demographic Characteristics of Study Population

Group	Parameter	Age (years)	Weight (kg)	Height (cm)
Smokers n = 3	**Mean**	30	77.0	176
	SD	15	5.7	3
	Range	20-48	73.0-83.5	172-179
Non-smokers n = 3	**Mean**	27	83.7	179
	SD	4.6	7.9	5.6
	Range	23-32	74.8-89.7	174-185
All Subjects n = 6	**Mean**	29	80.3	178
	SD	10	7.2	5
	Range	20-48	73.0-89.7	172-185

100% White; 100% male

Safety: There were no deaths, serious adverse events, or withdrawals due to adverse events (AEs) reported during this study. One subject reported two adverse events (moderate nausea and moderate vomiting) following the administration of 1 mg [^{14}C]CP-526,555 (2 hours and 4 hours post-dose, respectively). The AEs were considered unrelated to the study medication (attributed to phlebotomy) by the investigator and resolved without sequelae or treatment. No laboratory abnormalities of potential clinical concern were reported during this study. There were no clinically significant changes in physical examinations or vital signs during the study. ECGs were performed at screening only.

Pharmacokinetics: The mean overall recovery of CP-526,555 drug-related material was 88.0% of the dose with values for individuals that ranged from [ ] Material was almost completely excreted in urine (87.1% of dose; 99% of the recovered dose) with < 1% in feces. The presence of almost all radioactivity in urine and almost none in feces as unchanged drug (80.5% of the dose; 91.6 % of the recovered dose) indicates that CP-526,555 is virtually completely absorbed after oral administration.

Plasma CP-526,555 concentrations rose to a mean C_{max} of 4.01 ng/mL at a mean T_{max} of 4.3 hours post-dose. This was followed by a mono-exponential decline in concentrations with a mean $t_{1/2}$ of 16.7 hr. The pharmacokinetics of total drug-related material, as assessed by liquid scintillation counting, showed that the mean $t_{1/2}$ was 17.4 hours, which was 1.04 times that of the parent drug. The mean C_{max} and mean T_{max} values for total drug-related material were 4.57 ng-eq/mL and 2.8 hours, respectively. The percentage of AUC(0-inf) of total drug-related material that is represented by unchanged CP-526,555 was 75.7%.

CP-526,555 was the predominant drug-related entity in both circulation (90.8%) and urine (91.6%). Metabolites in human circulation included the N-carbamoyl glucuronide (M4, 3.8% of recovered radioactivity in plasma), N-formyl conjugate (M5, 0.9%), and putative N-hexose conjugate (M7, 3.5%), as well as a minor unidentified metabolite M3c (1.1%, putatively assigned as a carbonyl metabolite because the molecular weight was 14 mass units greater than CP-526,555). The only two metabolites excreted in urine in humans were the hydroxyquinoxaline (M3b, 3.3% vs. 2.9% of dose) and N-carbamoyl glucuronide (M4, 4.1% of recovered radioactivity in urine vs. 3.6% of dose).

There were no remarkable differences in the metabolism or excretion of CP-526,555 between smokers and nonsmokers.

CONCLUSIONS: The major mechanism of excretion of CP-526,555 is via the urine as unchanged drug, and almost no drug-related material is excreted in the feces. CP-526,555 undergoes four minor routes of metabolism: N-carbamoyl glucuronidation, N-formylation, conjugation with an hexose sugar and oxidation. The presence of almost all radioactivity in urine as unchanged drug with the remaining material eliminated in the urine as metabolites indicates that CP-526,555 is virtually completely absorbed with high systemic availability after oral administration. Single doses of 1 mg [^{14}C]CP-526,555 were generally safe and well-tolerated in healthy young male smokers and non-smokers.

CP-526,555
A3051005
FINAL Clinical Study Report

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051005 **Phase:** 1

Title: A SINGLE DOSE DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO CHARACTERIZE THE EFFECT OF CP-526,555 ON NICOTINE CRAVING IN HEALTHY SMOKERS

Investigator: [ ]

Study Publication: None at time of report issue.

Study Dates: 09 November 2000 - 12 April 2001

Study Objective: This study was intended to measure the effect of CP-526,555 on ameliorating abstinence- and cue-induced nicotine craving/withdrawal symptoms in a population of healthy smokers not currently intending to quit.

Study Design: This was a randomized, double-blind, placebo-controlled, single dose, crossover study comparing CP-526,555 with placebo in relief of cigarette craving. The study was conducted at a single center and consisted of a screening visit, 2 one-day treatment visits separated by a 7-day washout period, and a closeout (follow-up) visit, 1 week after the second treatment visit. Subjects were randomly assigned to receive a single dose of either CP-526,555 2 mg (2 x 1 mg) tablets, or placebo in a crossover design, as illustrated in the following schematic.

	Screen Visit	Visit 1	Washout ≥7 days	Visit 2	Closeout Visit (1 week post Visit 2)
Treatment	None	Active or Placebo	Crossover	Placebo or Active	None

Subjects were also to be randomized to a cue sequence that would assign them to either an Active-Neutral or Neutral-Active cue sequence. The sequence was to be preserved for use in the cue reactivity session at each of the 2 treatment visits (active cue: subject held and lit a personally preferred brand of cigarette without smoking it; neutral cue: subject held and sharpened a pencil). However, due to an error at the site, instead of subjects being randomized to cue sequence, they were assigned to cue sequence at screening.

Study Population and Criteria for Inclusion: Forty healthy male and female smokers between the ages of 18 and 65, and not currently intending to quit smoking, were enrolled in this study. Subjects were required to be in good health as determined by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate, a 12-lead electrocardiogram (ECG), and clinical laboratory tests. Subjects were to weigh ≥100 pounds (45.5 kg) with a body mass index (BMI) ≥15 and ≤35, in accordance with the BMI Table. In addition, subjects were to have smoked, on average during the past year, either a minimum of 20 cigarettes per day or between 11 and 19 (inclusive) cigarettes per day with the first cigarette of the day smoked within 30 minutes of waking, and to have an exhaled carbon monoxide (CO) level of ≥15 ppm. Subjects were also to be willing to refrain from smoking for a specified 8-hour period during each of the 2 study treatment days while in the clinical research unit (CRU).

Treatments: Pfizer Global Research and Development (PGRD) supplied study medication as follows:

Table S-1. Drug Administration:

Test Product	Appearance	Formulation	Strength	FID	Lot
CP-526,555	Off-white, round	Tablets	1.0 mg	G01691AA	ED-G-283-800
Placebo	Off-white, round	Tablets	NA	G01905AA	ED-O-284-800

Dosing: CP-526,555, 2.0 mg (2 x 1.0 mg tablets) or 2 placebo tablets with 240 mL of water in a crossover manner after the ingestion of the FDA standard meal.

Duration: A single oral dose in each period of the crossover.

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: The CRU staff assessed the safety and tolerability of the study medication by clinical observation, querying subjects for adverse effects, and spontaneous reports of adverse events (AE) by subjects. In addition, BP and pulse rate were measured and a 12-lead ECG was obtained on each treatment day, at baseline (t = 0 hours), just prior to dosing, and at specified post-dose times throughout the study. Additional measurements collected to fully characterize the clinical pharmacology of CP-526,555, the Smoking Urges Scale,[1,2] MNWS,[3,4] and PANAS[5]), were evaluated in a manner different from that used for observed or volunteered adverse events. No attempt was made to resolve any apparent discrepancies between the number of AEs reported through the questionnaires and the total number of AEs reported.

Efficacy: The primary outcome of interest in this study was the treatment effect of CP-526,555 compared to placebo in reduction of craving in response to smoking-related cues during a specific cue reactivity session conducted four hours after drug dosing. The craving response was assessed by the self-reported responses of subjects on the Smoking Urges Scale questionnaire. During the one-hour cue reactivity session, subjects were exposed to one active cue and one neutral cue in an assigned sequence of either: Active-Neutral or Neutral-Active. The sequence was preserved for the one cue reactivity session that subjects were to have at each treatment visit.

The self-reported questionnaires: the Smoking Urges Scale,[1,2] the Minnesota Nicotine Withdrawal Scale (MNWS),[3,4] and the Positive Affect/ Negative Affect Scale (PANAS)[5] were used to assess the secondary measures, affect and withdrawal symptoms, in response to each cue and compared to pre-drug baseline. These same questionnaires were used to assess the additional secondary measures, self-reported urge and affect and withdrawal symptom levels evaluated as a function of time before and after drug dosing. These were also to be compared with plasma levels of CP-526,555 measured concomitantly at 4 hours post dose, the start of the cue exposure.

Pharmacokinetics: Plasma samples were assayed for CP-526,555 concentrations by [redacted] using a validated liquid chromatography, tandem mass spectrometry (LC/MS/MS) assay in compliance with Pfizer standard operating procedures. The dynamic range of the assay extended from 0.10 to 50.0 ng/mL.

Pharmacokinetics/Pharmacodynamics: Concentration-time data for CP-526,555 were analyzed (Cmax, Tmax) by non-compartmental techniques. Population pharmacokinetics (PK) and PK-pharmacodynamic (PD) models were then developed via nonlinear mixed effects (NONMEM)[6] modeling to explore the concentration-response relationship for the effect of CP-526,555 (2 mg) on reduction of cigarette craving. A two-compartment PK model and population parameters were developed using data from 4 previous clinical studies to serve as prior information for a MAP Bayesian analysis of the limited pharmacokinetic data from study A3051005. Individual PK parameters were estimated, given the population priors, and individual concentrations were then predicted for all actual PD observation times. The primary PD endpoint was the mean of questions 1 to 5 from the Smoking Urges Scale; secondary endpoints included mean of questions 2 through 9 (Q2-Q9, withdrawal) and question 1 (Q1, craving) of the Minnesota Nicotine Withdrawal Scale. The PK-PD analysis used data from the 4-hour abstinence period post dosing of both the placebo and active drug periods. PK-PD data after the cue session, which followed the 4-hour sampling time, were omitted from the PK-PD modeling effort because of possible confounding and a lack of recorded cue session times.

Statistical Methods: Two models were used in the statistical analysis: 1) For data collected during the cue sessions, a repeated measures analysis of variance (ANOVA) model containing sequence, subject within sequence, period, treatment, cue and repeat effects, was used; 2) For data collected prior to the cue sessions, an ANOVA model containing sequence, subject within sequence, period, and treatment was used. Pre-cue session data was averaged over the 4 hours preceding the cue session and used as the response in the latter model. The analysis set consisted of subjects who completed both periods of the crossover.

Laboratory and other safety data were summarized by appropriate descriptive statistics.

RESULTS:

Subject Disposition: Forty subjects were enrolled and dosed in this study. Two subjects were discontinued from the study after completing only 1 treatment period and were excluded from the efficacy analyses. Subject 50150018 withdrew consent after receiving a single dose of placebo. Subject 50150021 stopped smoking during the washout period between visits after receiving a single 2 mg dose of CP-526,555. A summarization of subject evaluation groups is presented below in Table S-2.

Table S-2. Subject Evaluation Groups

Total Number Enrolled (N=40)	CP-526,555 (2 mg)	Placebo
Total Number Dosed	39	39
Withdrawn After Dosing	1	1
-Deviation from Protocol	1	
-Other (Subject defaulted.)		1
Number Completed	38	38
Assessed for Safety		
Adverse Events	39	39
Laboratory Tests[a]	13	11
Evaluated for Efficacy[b]		
Smoking Urges Scale	39	39
MNWS	39	39
PANAS	39	39
Number Evaluated		
Pharmacokinetics	39	NA

[a]Per protocol, postdose laboratory tests were performed after the second treatment phase only. Thus, much of the laboratory test data was excluded, since the window for collecting laboratory test result data excluded tests conducted >8 days after the last dose of either CP-526,555 or placebo.
[b]For each dosing group, 39 subjects were evaluated for efficacy, eg, completed questionnaires, but data for only 38 subjects were included in the efficacy analyses since 1 subject in each group discontinued after completing only 1 treatment.

Demographic Characteristics: Subjects smoked approximately 21 cigarettes per day and on average had been smoking since age 17. Demographic characteristics are presented below in Table S-3.

Table S-3. Characteristics of Study Population

All Subjects (N=40)	Parameter	Age (years)	Weight (kg)
Males	**Mean**	34.0	76.6
N=21	**SD**	13.7	9.2
	Range	18-56	59- 95
Females	**Mean**	39.0	71.8
N=19	**SD**	15.7	10.5
	Range	18-63	58-90

2.5% Black; 97.5% White; 0% Other
N = number of subjects. SD = standard deviation.

Efficacy: A single 2 mg oral dose of CP-526,555 significantly decreased nicotine craving and withdrawal symptoms in smokers who refrained from smoking, compared to placebo. With respect to the primary efficacy endpoint, CP-526,555 decreased craving during cue reactivity sessions 4 hours after dosing, as measured by the Smoking Urges Scale. On the Smoking Urges Scale, treatment benefit over placebo was significant for both the active and neutral cues with p-values <0.0001 and <0.0003, respectively. The craving response to the active cue was always higher than the response to the neutral cue, regardless of treatment, cue sequence, or repeat. The primary efficacy cue session analysis is presented below in Table S-4. With respect to the secondary efficacy endpoints, a trend toward significance in craving reduction appeared in the CP-526,555 treated group during the four hours prior to the cue sessions.

Table S-4. Cue Session Analysis

		ACTIVE CUES			NEUTRAL CUES		
EFFICACY SCORES:	**MEASURE**	**CP-526,555**	**PBO**	**P-VALUE**	**CP-526,555**	**PBO**	**P-VALUE**
Smoking Urges	**LSMean**	40.821	52.891	<0.0001	34.630	45.112	0.0003
	Std Err	2.06	2.06		2.05	2.05	
	N	113	113		114	114	

N= Total number of observations. Std Err = standard error

Subjects treated with CP-526,555, compared to placebo, also showed a significant decrease in craving, as measured by the MNWS, in response to both the active and neutral cues (p-values 0.0113 and 0.0006, respectively). Moreover, there was a significant decrease in withdrawal symptoms in response to both active (p-value<0.0001) and neutral (p-value <0.0001) cues. The PANAS scores, on the negative sub-scale only, revealed a significant decrease in withdrawal symptoms (p-value 0.0113) during the active cue exposure.

Safety: CP-526,555 was well-tolerated after a single 2 mg oral dose. There were no deaths, serious adverse events, or discontinuations due to adverse events in this study. In the CP-526,555-treated group, 14 of 39 subjects (36%) experienced 19 treatment-emergent AEs, 14 of which were considered treatment-related. In the placebo group, 7 of 39 subjects (18%) experienced 10 AEs, 7 of which were considered treatment-related. Headache was the most frequently reported event in both treatment groups. Six subjects (15%) in the CP-526, 555 group and 3 subjects (8%) in the placebo group reported headache. Most events were of mild severity; 4 were moderate (1 each headache, nausea, vomiting, and somnolence). None was severe. Treatment-emergent signs and symptoms are presented below in Table S-5.

Table S-5. Treatment -Emergent Signs and Symptoms (All Causalities)

Adverse Event (Preferred Term)	CP-526, 555 (2 mg)	Placebo
Headache	6	3
Bradycardia	3	3
Nausea	3	0
Tachycardia	1	0
Vomiting	1	0
Peripheral edema	1	0
Somnolence	1	1
Maculopapular rash	1	0
Fungal infection	1	0
Respiratory disorder	1	0
Diarrhea	0	1
Back pain	0	1
SGPT increased	0	1
Total Number of AEs	**19**	**10**
Number of Subjects with AEs	**14**	**7**
Number of Subjects Exposed	**39**	**39**

Pharmacokinetics: PK data were characterized by a mean Cmax of 8.27 ng/mL (geometric mean = 8.14 ng/mL) with SD = 1.47 and a mean Tmax of 3.25 hours with SD = 1.13.

Pharmacokinetics/Pharmacodynamics: The PK/PD analysis using nonlinear-mixed effects modeling of the relationship between cigarette craving and exposure to CP-526,555 showed the following results:

- CP-526,555 significantly decreased craving (mean of questions 1-5 of the Smoking Urges Scale) when compared to placebo and the magnitude of this response was related to plasma CP-526,555 concentration.
- The time course and magnitude of both placebo and CP-526,555 craving responses were characterized by a large degree of random, unexplained variability. Attempts to explain random variability by inclusion of covariate factors did not reveal any significant relationships. In addition, there was no significant correlation between baseline craving and magnitude of drug response. Because of this, a priori prediction of individual craving response is expected to be poor. Simulations indicate that although there was a treatment response, separation of active drug response from placebo response at a given point in time following dosing may be difficult with a small study such as this one.
- In addition to the craving data from the Smoking Urges Scale, a significant concentration-response trend was identified for question 1 (Q1) of the Minnesota Nicotine Withdrawal Scale (MNWS). Questions 2 through 9 (Q2-Q9) of the MNWS were also explored and although a trend towards a significant concentration-response relationship was observed, model convergence problems prevented this trend from being characterized definitively.

CONCLUSIONS:

- CP-526,555 significantly decreased craving and withdrawal symptoms compared to placebo in smokers who refrained from smoking. CP-526,555 ameliorated both cue-stimulated craving and withdrawal responses in the cue reactivity sessions (begun 4 hours after dosing) and in self-reported craving and withdrawal symptoms during the 4-hour post-dose period that preceded the cue reactivity sessions.

- The PK-PD modeling of the 4-hour abstinence period post dosing resulted in a significant active drug treatment effect when compared to placebo. The magnitude of the reduction in cigarette craving, as measured by the Smoking Urges Scale, was related to plasma CP-526,555 concentrations.

- There were no safety concerns in this study. CP-526,555 was well tolerated.

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051006 **Phase: 1**

Title: PHASE I RANDOMIZED, OPEN-LABELED, CROSSOVER STUDY TO EVALUATE THE PHARMACOKINETICS OF CP-526,555 FOLLOWING A SINGLE DOSE OF TARTRATE SALT TABLET DOSAGE FORM UNDER FED AND FASTED CONDITIONS IN COMPARISON WITH THE SUCCINATE SALT

Investigator: [ ]

Study Publication: None at time of report issue

Study Dates: 26 October 2000 to 08 December 2000

Study Objectives: The objective of this study was to compare the pharmacokinetics of a single 1 mg oral dose of CP-526,555 in healthy subjects

a. administered as the tartrate salt tablet under fasted conditions vs. the succinate salt tablet under fasted conditions
b. administered as the tartrate salt tablet under fed vs. fasted conditions

Data were collected to allow for evaluation of the safety and tolerability of single doses of the tartrate and succinate salt tablets.

Study Design: This was a randomized, open-label, three-way crossover study of a single-dose of CP-526,555. CP-526,555, 1 mg, was administered as a tartrate salt tablet to 15 subjects under fasted and fed (standard FDA high fat breakfast) conditions and as a succinate salt tablet to the same subjects under fasted conditions. A washout period of seven days separated each treatment.

Study Population and Criteria for Inclusion: Fifteen healthy male (n = 12) and female (n = 3) subjects between the ages of 18 and 55 years, inclusive, participated in the study.

Treatments:

Dosage Form	CP-526,555, tartrate salt tablet, 1 mg, (Pfizer, Batch/Lot Number ED-G-310-900, FID G02222AA)
	CP-526,555, succinate salt tablet, 1 mg (Pfizer, Batch/Lot Number ED-G-283-800, FID G01691AA)

Dosing and Duration	1 mg CP-526,555 tartrate salt tablet, PO, fasting
	1 mg CP-526,555 tartrate salt tablet, PO, fed
	1 mg CP-526,555 succinate salt tablet, PO, fasting
	Single doses were given with a washout period of 7 days between treatments.

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: Safety evaluations included clinical monitoring, vital signs (blood pressure, pulse rate and weight), 12-lead ECGs, safety laboratory tests, physical examinations and the reporting of adverse events.

Pharmacokinetics: On each treatment day (Days 1, 8 and 15), blood was collected from each subject to provide plasma for pharmacokinetic analysis of CP-526,555 at the following times: 0 (just prior to dosing), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 hours after dosing. Plasma samples were analyzed for CP-526,555 using [ ] followed by HPLC/MS/MS analysis.

For each subject and on each treatment day, plasma CP-526,555 concentration-time data were analyzed by non-compartmental techniques and the following pharmacokinetic parameters were estimated: Cmax, Tmax, AUC(0-Tlast), AUC(0-inf) and terminal phase half-life (t½).

Statistical Methods: Bioequivalence was evaluated between CP-526,555 administered as tartrate and succinate formulations under fasted conditions, and between fasted and fed conditions for the tartrate formulation. The criteria for bioequivalence was that the 90% confidence interval for the ratio of treatment means must have been entirely within the interval 80% to 125% for both AUC and Cmax, when data were analyzed on the natural log scale. The analysis of variance included terms for sequence, subject, treatment and period. LSMEANS were calculated for each treatment, and 90% confidence intervals comparing the treatments listed above were calculated. For AUC and Cmax the anti-log of the difference between treatments and for the confidence interval was calculated to obtain the ratio of the treatments and confidence limit for the ratio. Untransformed Tmax and half-life were analyzed similarly, and estimates of the difference between treatments and the 90% confidence interval for the difference were calculated.

RESULTS:

Subject Disposition:

Fifteen healthy male and female subjects between the ages of 18 and 55 years, inclusive, were enrolled and dosed in the study.

Table SA Subject Disposition

		1 mg CP-526,555		
	Total	**Tartrate salt tablet, fasting**	**Tartrate salt tablet, fed**	**Succinate salt tablet, fasting**
Total Planned	15	15	15	15
Total Number Enrolled	15	15	15	15
Total Number Dosed	15	15	14	15
Total Withdrawn After Dosing	1	0	0	1
Due to Adverse Event	1	0	0	1
Number Completed	14	15	14	14
Assessed for Safety	15	15	14	15
Adverse Events	15	15	14	15
Laboratory Tests	15	15	14	15
Number Evaluated – Pharmacokinetics	15	15	14	15

Demographic Characteristics

Demographic characteristics for all enrolled subjects are displayed in the table below. Smoking status was not specified for inclusion into this study, but smoking status data was collected (3 smokers, 2 ex-smokers, 10 never smoked).

Table SB Demographic Characteristics of the Study Population

Group	Parameter	Age (years)	Height (cm)	Weight (kg)
All Subjects N = 15	**Mean**	37.9	174	79.6
	SD	8.9	8.8	9.7
	Range	21.0-51.0	158-185	56.7-91.7

6.7% Black; 86.7% White; 6.7% Hispanic (Percentages do not add up to 100% due to rounding.)

Safety: There were no deaths or serious adverse events reported in this study. One subject (Subject 011) was withdrawn due to an adverse event (AE), mild chest pain, that was considered unrelated to the study medication by the investigator. The event was treated and resolved. There were 82 AEs reported during the study. The most common AEs reported during this study were dizziness and nausea. Seventy-three AEs were considered related to the study medication by the investigator. All AEs resolved before the completion of the study.

Table SC Adverse Events

	Regimen			
	Tartrate, Fed	**Tartrate, Fasted**	**Succinate, Fasted**	**Total**
Total Number of AEs	23	30	29	82
Number of Subjects with AEs	12	14	14	15
Total Number of Treatment-Related AEs	21	27	25	73
Number of Subjects with Treatment-Related AEs	12	13	14	14
Number of Subjects Exposed	14	15	15	15

No ECG intervals of clinical significance were noted during this study. There were no significant changes in physical exams from screening to the final visit.

Pharmacokinetics:

No differences in the single dose pharmacokinetics of CP-526,555 were observed between the tartrate and succinate treatments in the fasted state and between the tartrate treatments in the fed and fasted state. The latter comparison indicated the absence of a food effect. Mean (SD) pharmacokinetic parameters of CP-526,555 were similar among all three treatments, as depicted in the table below.

Table SD Mean (SD) Pharmacokinetic Parameters of CP-526,555 Following Administration of a 1 mg Single Oral Dose of a Succinate or Tartrate Salt Tablet to Healthy Subjects

Pharmacokinetic Parameter	**Treatment**		
	Succinate Fasted	**Tartrate Fasted**	**Tartrate Fed**
AUC(0-Tlast) (ng*hr/mL)	115 (29)	117 (26)	113 (28)
AUC(0-inf) (ng*hr/mL)	127 (30)	130 (30)	124 (32)
Cmax (ng/mL)	4.23 (1.00)	4.28 (0.88)	4.44 (1.08)
Tmax* (hr)	3.0 [2.0-8.0]	4.0 [1.0-8.0]	4.0 [3.0-6.0]
T1/2 (hr)	19.9 (2.6)	19.8 (4.0)	18.0 (2.3)

*Tmax presented as median [range]

The point estimates and confidence intervals (CIs) for comparisons of interest are shown in the table below. There were no statistically significant period or sequence effects.

Table SE Summary of the Statistical Analysis of the Pairwise Comparisons of Interest

Pharmacokinetic Parameter	Treatment Comparison	N	Ratio*	90% Confidence Intervals
AUC(0-Tlast) (ng*h/mL)	Tartrate Fasted vs. Succinate Fasted	15 15	102%	(94%,111%)
	Tartrate Fed vs. Tartrate Fasted	14 15	96%	(88%,105%)
AUC(0-inf) (ng*h/mL)	Tartrate Fasted vs. Succinate Fasted	15 15	103%	(95%,111%)
	Tartrate Fed vs. Tartrate Fasted	13‡ 15	96%	(88%,105%)
Cmax (ng/mL)	Tartrate Fasted vs. Succinate Fasted	15 15	102%	(97%,106%)
	Tartrate Fed vs. Tartrate Fasted	14 15	103%	(98%,108%)

*Ratio of adjusted geometric means (Test/Reference)
‡AUC(0-inf) was not calculated for Subject 007 following the Tartrate Fed treatment (elimination phase was not defined)

Mean relative oral bioavailability values, based on AUC(0-inf), were 102% for the tartrate formulation relative to the succinate formulation in the fasted state and 96% for the tartrate formulation in the fed state relative to the fasting condition. For AUC(0-Tlast), AUC(0-inf) and Cmax, the bounds of the 90% CI were completely contained within the established bioequivalence limits (80% and 125%). Tmax and half-life values also did not differ significantly (90% CIs included 0) between all three treatments.

CONCLUSIONS: Bioequivalence was established between the tartrate and succinate salt tablet formulations of CP-526,555 administered in the fasted state. The absence of food effect was demonstrated for the tartrate salt tablet. There were no safety or tolerability issues raised with the tartrate or succinate formulations of CP-526,555 used in this study.

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051008 **Phase:** 1

Title: Phase I Open Multiple Dose Study Designed to Evaluate the Effects of Varying Degrees of Renal Function on the Safety, Toleration, and Pharmacokinetics of CP-526,555

Investigator(s): [redacted]

Study Publication: None at time of report issue.

Study Dates: 10 July 2001 to 25 June 2002

Study Objectives: The objectives of this study were to investigate the effect of varying degrees of renal function on the multiple dose pharmacokinetics, safety, and toleration of CP 526,555 and to determine the fraction of CP-526,555 excreted by dialysis.

Study Design: This was a non-randomized, open-label, parallel group study of multiple doses (0.5 mg QD) of CP-526,555. Five groups of subjects (up to 12 subjects/group) with varying degrees of renal impairment (ie, ranging from normal renal function to end-stage renal disease [ESRD]) were to be evaluated. The severity of renal impairment was based on the subjects' estimated creatinine clearance using the Cockroft-Gault formula and any requirement for hemodialysis at Screening. Note: While the protocol used the term of creatinine clearance for assessing renal function, this report uses the more appropriate terminology of estimated glomerular filtration rate (GFR), when calculated from a serum creatinine concentration with the use of the Cockcroft and Gault equation that accounts for the influence of weight, age, and gender on creatinine production.[1] From this point forward, estimated GFR will be used in place of estimated creatinine clearance. Subjects were to be admitted to the clinical research unit (CRU) at least 24 hours prior to the Day 1 dosing and be confined from Day 0 to Day 14. Each subject was to receive a 0.5 mg dose of CP-526,555 once daily under fasted conditions for 12 days (Days 1-12). The duration of the study (exclusive of the screening period) was approximately 20 days including the pharmacokinetic (PK) follow-up period following the last dose of medication.

Study Population and Criteria for Inclusion: Male or female subjects between the ages of 18 and 64 years (inclusive) who met the renal function criteria described below.

Table S-A. Renal Function of Study Population

Group	Renal Impairment	Estimated Glomerular Filtration Rate*
1	None (Normal)	>80 mL/min
2	Mild	50 <estimated GFR ≤80 mL/min
3	Moderate	30 ≤ estimated GFR ≤50 mL/min
4	Severe	Estimated GFR <30 mL/min
5	ESRD	Requiring regular hemodialysis, 3 times/week

* Glomerular filtration rate (GFR) is the standard indicator of renal function; estimated from a serum creatinine concentration using the Cockcroft and Gault formula.[1]

All subjects having renal impairment (estimated GFR ≤80 mL/min) had to have stable renal function for the previous 2 months. Female subjects were either not of childbearing potential or practiced successful contraception or practiced sexual abstinence for at least 3 months prior to entry into the study.

Treatments: The Pharmacy Operations department at Pfizer Global Research & Development (PGRD) supplied study medication as follows:

Table S-B. Study Medication

Study Drugs	Appearance	Formulation	Dose Unit	Batch/Lot Numbers	FID*
CP-526,555-18	White, round	Tablet	0.500 mg	ED-G-072-201	G02306AA
CP-526,555-18	White, round	Tablet	0.500 mg	ED-G-166-501	G02306AA

*FID=formulation identification

Subjects in each group received a 0.5 mg tablet of CP-526,555 once daily on Days 1-12.

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: All subjects were evaluated for safety by clinical observations and querying for adverse events, physical examinations, vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

Pharmacokinetics: On Days 1 and 12, blood was collected at specified intervals from 0 (just prior to morning dose) up to 16 hours on Day 1 and up to 192 hours following dosing on Day 12. In addition, subjects who underwent hemodialysis had multiple blood samples obtained (just prior to dosing and up to 16 hours following dosing) on the day of hemodialysis (Day 11). A validated [ ] procedure followed by HPLC/MS/MS was used to determine CP-526,555 plasma concentration levels. The primary PK study endpoints were the Day 12 parameters $AUC_{(0-\tau)}$, (area under the curve from time 0 to the end of the dosing interval on Day 12 where τ is the dosing interval time equal to 24 hours), C_{max} (maximum observed serum concentration), and CL/F (apparent plasma clearance).

Statistical Methods:

Safety: Demographic and safety data were summarized through data tabulations and descriptive statistics. ECG interval parameters (PR, QT, heart rate, QTc, and QRS) and vital sign parameters were summarized by renal function group using descriptive statistics (n, mean, mean change from baseline, and standard deviation). Categorical summarization of post baseline ECG intervals and vital sign parameters were performed.

For Groups 1-4, log-transformed AUC(0-24), Cmax, and untransformed T½ were analyzed using one-way analysis of variance (ANOVA). For AUC(0-24), Cmax, and T½, each of Groups 2, 3, and 4 were compared to subjects with normal renal function (Group 1); ratios of AUC(0-24), Cmax Geometric Means, and difference of adjusted arithmetic means of T½ were estimated and 90% confidence intervals for these differences were calculated. Only PK data obtained from Day 12 was used for this analysis. To provide a quantitative basis for dose recommendation for subjects with renal impairment, linear regression models were fitted to address the relationship between the AUC(0-24), Cmax, apparent plasma clearance (CL/F), and subject's estimated GFR. AUC, Cmax, and CL/F were the response variables. Estimated GFR was the independent variable.

RESULTS:

Subject Disposition: Thirty subjects entered and completed the study.

Table S-C. Subject Disposition

	Renal Impairment of Subjects Evaluated				
	None	**Mild**	**Moderate**	**Severe**	**ESRD**
Total Planned 60 (up to 12/group)					
Total Number Enrolled	6	6	6	6	6
Total Number Dosed	6	6	6	6	6
Total Withdrawn After Dosing	0	0	0	0	0
Number Completed	6	6	6	6	6
Assessed for Safety					
Adverse Events	6	6	6	6	6
Laboratory Tests	6	6	6	6	6
Number Evaluated for Pharmacokinetics					
AUC, Cmax, T½, CL/F	6	6	6	6	6

None=normal renal function (estimated GFR >80 mL/min)
Mild=mild renal impairment (50 <estimated GFR <80 mL/min)
Moderate=moderate renal impairment (30 ≤ estimated GFR ≤ 50 mL/min)
Severe=severe renal impairment (estimated GFR <30 mL/min)
ESRD=end-stage renal disease (requiring regular hemodialysis, 3 times/week)

Demographic Characteristics: Subjects were between 24 and 64 years of age. The majority of the subjects (24 out of 30) were nonsmokers (ie, 14 had never smoked, and 10 were ex-smokers). Of the 6 subjects who were current smokers, 5 were in the ESRD group.

Table S-D. Demographic Characteristics

	Renal Impairment of Subjects Evaluated				
	None	**Mild**	**Moderate**	**Severe**	**ESRD**
Age (years)					
Mean	48.7	52.2	46.7	50.0	46.8
SD	5.0	11.1	9.2	11.6	13.0
Range	44-57	35-64	33-60	33-61	24-64
Race					
White	3	6	6	4	2
Black	1	0	0	1	4
Hispanic	1	0	0	1	0
Other	1	0	0	0	0
Weight (kg)					
Mean	78.5	77.0	71.8	77.5	70.5
SD	4.9	13.8	7.9	16.7	10.4
Range	70-84	60-99	58-80	51-102	61-89
N	6	6	6	6	6
Body Mass Index (kg/m2)					
Mean	27.3	25.7	25.1	25.9	24.7
SD	2.9	5.5	3.4	5.7	4.0
Range	25-33	22-36	22-30	19-34	22-32
N	6	6	6	6	6
Height (cm)					
Mean	170.2	173.3	169.5	173.2	169.2
SD	9.6	5.5	9.7	9.9	5.5
Range	157-185	166-178	157-185	165-187	163-178
N	6	6	6	6	6

Body mass index = weight/(height × 0.01)^2
None=normal renal function (estimated GFR >80 mL/min)
Mild=mild renal impairment (50 <estimated GFR <80 mL/min)
Moderate=moderate renal impairment (30 ≤ estimated GFR ≤ 50 mL/min)
Severe=severe renal impairment (estimated GFR <30 mL/min)
ESRD=end-stage renal disease (requiring regular hemodialysis, 3 times/week)

Safety: There were no deaths, dose reductions, or temporary or permanent withdrawals due to AEs reported in the study. A total of 57 treatment-emergent AEs were reported in 24 subjects (80%). Nausea (7 subjects) was the most frequently reported adverse event followed by headache and dizziness (5 subjects each). All cases of nausea and dizziness were considered to be mild by the investigator. Dizziness was attributed to reasons other than the study medication. Three subjects had serious adverse events which included coronary artery bypass graft and cardiac catheterization attributed to subject's underlying pathology of coronary artery disease, lung cancer, and congestive heart failure. None of these events were considered by the investigator to be related to treatment.

There were 4 subjects who had a postdose clinical laboratory value exceeding the clinical concern threshold. The majority of these changes appeared to be related to the subjects' renal disease state (3 out of 4 subjects were ESRD subjects). None of the laboratory abnormalities were reported as clinically significant adverse events.

None of the changes in vital signs, ECGs, or physical examinations were of clinical concern.

Pharmacokinetics: Pharmacokinetic results from this study clearly indicated that renal impairment had an effect on the elimination process of CP-526,555. Decreases in oral clearance of CP-526,555 correlated well with its decreasing renal clearance, and increases in CP-526,555 systemic exposure showed an evident dependence with the degree of renal impairment. Mean AUC(0-τ) values ranged from 55.5 ng•h/mL in subjects with normal renal function to 151 ng•h/mL in subjects with ESRD, representing a 2.7-fold increase in steady-state exposure with decreasing kidney function (Table S-E).

Table S-E. Summary of Statistical Comparisons (one-way ANOVA) of CP-526,555 PK Parameters in Subjects with Varying Degrees of Renal Impairment

Parameters (units)	Test	Reference	Geometric Mean LSMean 1	Geometric Mean LSMean 2	Ratio* (%)	90% Confidence Intervals
AUC(0-τ) (ng•h/mL)	Mild	Normal	58.7	55.6	105.6	(79.4, 140.7)
	Moderate	Normal	84.4	55.6	151.9	(114.1, 202.3)
	Severe	Normal	114.9	55.6	206.9	(155.4, 275.4)
	ESRD	Normal	150.8	55.6	271.5	(203.9, 361.4)
Cmax (ng/mL)	Mild	Normal	3.7	4.0	91.9	(70.3, 120.2)
	Moderate	Normal	4.8	4.0	121.0	(92.6, 158.1)
	Severe	Normal	6.1	4.0	153.0	(117.0, 199.9)
	ESRD	Normal	7.3	4.0	183.0	(140.0, 239.2)
			Arithmetic Mean LSMean 1	Arithmetic Mean LSMean 2	Difference†	90% Confidence Intervals
T½ (hr)	Mild	Normal	33.1	34.4	-1.3	(-16.8, 14.1)
	Moderate	Normal	34.5	34.4	0.1	(-15.4, 15.5)
	Severe	Normal	56.1	34.4	21.7	(5.5, 37.9)
	ESRD	Normal	78.3	34.4	43.9	(25.0, 62.8)

AUC(0-τ) = AUC(0-24) for QD dosing
ESRD = End-stage renal disease
LSMean = Least Squares Mean
* Ratio of adjusted geometric means between Mean 1 (test) and Mean 2 (reference)
† Difference of adjusted arithmetic means between Mean 1 (test) and Mean 2 (reference)

As expected for CP-526,555, a drug almost exclusively excreted in the urine, there was a strong correlation between CL/F and renal function, as measured by estimated GFR (Cockcroft and Gault method). For the regression analysis, the incorporation of ideal body weight (utilized as an index of muscle mass) into the equation effectively reduced the curvilinear shape between CL/F and estimated GFR. The estimated slope of 0.92 indicates that oral clearance of CP-526,555 decreases proportionately with each decrement of 1 mL/min in GFR.

Evidence for a significant secretory component to the renal elimination of CP-526,555 was provided by the positive intercept (~ 44 mL/min) obtained from the linear relationship between CP-526,555 renal clearance and the subject's GFR estimate. The mean excretion ratio of 1.19 in normal subjects increased progressively with mild (mean 1.92), moderate (mean 2.15), and severe (mean 2.81) renal impairment, respectively indicating that the contribution by secretion to renal elimination of CP-526,555 increases with declining renal function.

The investigations on the dialysability of CP-526,555 showed that hemodialysis appeared to be almost as efficient as renal function in healthy subjects in the removal of varenicline. After a single 3-hour session, the hemodialysis clearance was on average 210 mL/min (range 146-244 mL/min) with a mean extraction coefficient of 0.440 (range 0.205-0.687).

CONCLUSIONS:

Comparison of steady-state PK data between subjects having normal renal function and subjects with impaired renal function showed that renal impairment had no effect on the pharmacokinetics of CP-526,555 in mildly impaired subjects, while systemic exposure of CP-526,555 increased in subjects with moderate (1.5-fold normal AUC) and severe (2.1-fold normal AUC) renal impairment, and subjects with ESRD (2.7-fold normal AUC). Consequently, dose adjustment may be warranted in subjects with marked renal insufficiency.

There were no safety issues raised in this study.

CP-526,555
A3051009
FINAL Clinical Study Report

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051009 **Phase: 1**

Title: Phase 1, Randomized, Double-Blind, Placebo Controlled Study Designed to Evaluate the Safety, Toleration and Single and Multiple Dose Pharmacokinetics of CP-526,555 in Elderly Subjects Who are Smokers

Investigators:
[ ]

Study Publication: None at time of report issue

Study Dates: 23 May 2001 to 08 May 2002

Study Objectives: 1) to investigate the single and multiple dose pharmacokinetics of CP-526,555 in elderly male and female smokers; 2) to evaluate the safety and toleration of CP-526,555 in elderly male and female smokers following oral dosing.

Study Design: This was a double-blind, randomized study evaluating two dose levels of CP-526,555. At each dose level, 8 subjects were randomized to CP-526,555 and 4 to placebo. Group 1: received CP-526,555 1 mg once daily (QD) or placebo administered on Days 1-7. Group 2: received CP-526,555 1 mg twice daily (BID) or placebo administered on Days 1-6 with a single dose on Day 7. All doses were administered in a fasting state.

Study Population and Criteria for Inclusion: Subjects screened for this study were healthy adult smokers of any race who were at least 65 years of age, weighed no more than 200 lbs, and were within 30% of the recommended weight range based on age, gender, height, and body frame as established in the "1983 Metropolitan Life Insurance Height and Weight Tables." Enrolled subjects were required to be in good health as determined by a detailed medical history, full physical examination [including blood pressure (BP) and heart rate (HR) measurements], 12-lead electrocardiogram (ECG), and clinical laboratory tests.

Treatments: Pfizer Global Research & Development supplied study medication as follows:

Table S-A Study Medication Used

Study Drugs	Appearance	Formulation	Dose Unit	Batch/Lot Numbers	FID#
CP-526,555-18	Off-white, round	Tablets	1.0 mg	ED-G-164-501 ED-G-100-301	G02222AA G02222AA
Placebo	Off-white, round	Tablets	NA	ED-G-107-301	G02329AA

FID = Formulation identification.

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: Safety and tolerability of study medication was assessed by physician observation and spontaneous reporting of adverse events (AEs) by subjects. In addition, routine vital sign measurements, 12-lead ECG, and safety laboratory tests were performed.

Pharmacokinetics: Plasma samples were assayed for CP-526,555 concentrations by [ ] and [ ] using a validated assay in compliance with Pfizer standard operating procedures. Samples were analyzed using a [ ] followed by LC/MS/MS. The following pharmacokinetic parameters, Cmax, Tmax, and AUC(0-τ) for CP-526,555 were determined using non-compartmental methods following dosing on Days 1 and 7. The terminal phase half-life was only determined following Day 7 dosing. Observed accumulation of CP-526,555 was assessed by the ratios of AUC(0-τ) and Cmax following repeat administration (Day 7) relative to single dosing (Day 1). The attainment of CP-526,555 steady-state was evaluated from plasma trough concentration data.

Statistical Methods: Demographics and safety data were summarized through data tabulations and descriptive statistics. ECG interval parameters (PR, QT, HR, QTc, and QRS) were summarized by treatment group using descriptive statistics (n, mean, mean change from baseline, stderr, min, max). QTc was also descriptively summarized using the categories in the CPMP Points to Consider CPMP/986/96, namely normal/borderline/prolonged (males ≤430/431-450/>450 msec and females ≤450/451-470/>470 msec) and whether changes in QTc were <30, 30-60 and >60 msec.

RESULTS:

Twenty–four healthy male and female smokers, 65 to 75 years of age, were enrolled in and completed this study. All subjects were evaluable for pharmacokinetic and safety analyses. Subject demographics are summarized in the following table:

Table S-B Demographic Characteristics

	CP-526,555 1 mg QD			CP-526,555 1 mg BID			Placebo		
Group	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Number of Subjects	7	1	8	6	2	8	4	4	8
Age (years)									
65-74	6	1	7	5	2	7	4	4	8
75-84	1	0	1	1	0	1	0	0	0
Mean	69.4	67.0	69.1	68.8	66.0	68.1	68.8	67.0	67.9
SD	4.0	0	3.8	3.5	0	3.3	3.9	1.8	2.9
Range	65-75	67	65-75	66-75	66	66-75	65-74	65-69	65-74
Race									
Black	1	0	1	0	0	0	0	0	0
Hispanic	2	0	2	3	1	4	4	1	5
White	4	1	5	3	1	4	0	3	3
Weight (kg)									
Mean	75.1	69.0		86.0	88.0		88.0	76.3	
SD	10.6	0		14.0	1.4		6.5	13.0	
Range	64-90	69		71-109	87-89		81-94	64-88	
Height (cm)									
Mean	172.9	161.0		175.2	161.5		174.0	164.5	
SD	4.0	0		5.5	2.1		6.2	1.0	
Range	168-179	161		169-183	160-163		165-178	163-165	

Safety: No deaths, serious AEs (SAEs) or withdrawals due to AEs were reported during this study. AEs were reported by 4 (50%) subjects in the CP-526,555 1 mg QD group, 3 (38%) in the CP-526,555 1 mg BID group, and 5 (62%) in the Placebo group. The most common AE across the treatment groups was nausea (12-25%). The majority (50-75%) of the AEs were considered treatment related. All of the AEs in this study were of mild to moderate intensity.

In general, vital sign values, identified as being of potential clinical concern in this study, were sporadic, transient, and appeared unrelated to study drug. There were no clinically significant changes in laboratory values. No clinically significant changes were observed in mean baseline and mean changes from baseline for QTc.

Pharmacokinetics: There was no evidence of concentration- or time-dependent changes in the pharmacokinetics of CP-526,555 upon repeat dosing in healthy elderly smokers. Consistent with a mean elimination half-life of approximately 28 hours, steady-state appeared to be reached within 4 days of repeat administration of CP-526,555. QD and BID dosing resulted on average, in an approximate 2- and 3-fold accumulation in systemic exposure, respectively. Overall, exposure to CP-526,555 and pharmacokinetic variability at

steady-state in healthy elderly smokers were comparable to those obtained in the young smoking population observed in previous studies.

Arithmetic mean (SD) for Cmax, AUC and t1/2 and median [range] Tmax values are presented for each dosing regimen following single (Day 1) and repeat (Day 7) dosing in the table below:

Table S-C Arithmetic Mean (SD) for Pharmacokinetic Parameters Following Single and Repeat Oral Doses of 1 mg CP-526,555 Given QD or BID to Healthy Elderly Smokers

	1 mg CP-526,555 QD		1 mg CP-526,555 BID	
Parameters (units)	**Day 1**	**Day 7**	**Day 1**	**Day 7**
	(N=8)	(N=8)	(N=8)	(N=8)
AUC(0-τ) (ng·h/mL)	55.2 (9.8)	126 (32)	30.4 (5.6)	88.4 (19.9)
Cmax[a] (ng/mL)	3.86 (0.54)	7.03 (1.21)	3.32 (0.61)	8.86 (1.79)
Tmax[a,b] (h) [range]	3.00 [2.00-6.00]	2.50 [2.00-6.00]	2.50 [1.00-6.00]	2.00 [1.00-3.00]
t1/2 (h)	NA	27.5 (5.9)[c]	NA	29.2 (7.9)

τ = dosing interval (QD, 24 hours) or (BID, 12 hours); NA – Not available
[a] Tmax, Cmax of the first dosing interval (0-12 hr) for BID regimen; [b]Tmax presented as median [range]; [c](N=7).

CONCLUSIONS:

- There was no evidence of concentration- or time-dependent changes in the pharmacokinetics of CP-526,555 upon repeat dosing in healthy elderly smokers.
- Systemic exposure in elderly smokers, based on Cmax and AUC, was comparable to that observed previously in the young smoking population following single and multiple dose administration of 1 mg CP-526,555 once or twice-a-day.
- There were no safety or unique tolerability issues raised in this study.
- CP-526,555 may be administered to elderly patients with normal renal function at the same daily dose as for younger subjects.

CP-526,555
A3051010
FINAL Clinical Study Report

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051010 **Phase: 1**

Title: Phase 1, Open-Label, Fixed Sequence, Study Evaluating the Effects of Steady-State Cimetidine on the Pharmacokinetics of a Single Dose of CP-526,555 in Healthy Smoking Subjects

Investigator: [redacted]

Study Publication: None at time of report issue

Study Dates: 12 August 2002 to 23 September 2002

Study Objectives: Primary objective: to characterize the effects of steady-state cimetidine on the renal clearance (CLr) of a single 2 mg dose of CP-526,555 in healthy adult smokers; Secondary objectives: to evaluate the effects of steady-state cimetidine on the pharmacokinetics (AUC and Cmax) of a single 2 mg dose of CP-526,555 and to evaluate the safety and toleration of CP-526,555 when co-administered with steady-state cimetidine in healthy adult smokers.

Study Design: This was a non-randomized, open-label, fixed sequence study to evaluate the effects of cimetidine on the renal clearance of CP-526,555 in a single group of 12 healthy smokers. All subjects received study medication as follows: Period 1, single dose of 2 mg CP-526,555 on Day 1; Period 2, 300 mg cimetidine QID [four times a day, (at meals and at bedtime)] on Days 1-5; single dose of 2 mg CP-526,555 on Day 2. There was a washout period of at least 7 days between study Period 1 and study Period 2. All doses were administered in a fed state (standard non-high fat diet).

Study Population and Criteria for Inclusion: Subjects screened for this study were healthy adult, male and female smokers of any race between 18 to 55 years of age with a Body Mass Index (BMI) between 18-30 kg/m^2, inclusive; and a total body weight >50 kg (110 lbs). Enrolled subjects were required to be in good health as determined by a detailed medical history, full physical examination (including blood pressure and heart rate measurements), 12-lead electrocardiogram (ECG), and clinical laboratory tests.

Treatments: Commercially available cimetidine tablets (300 mg, Tagamet, Lot # 11T13) were supplied by the investigator. Pfizer Global Research & Development supplied study medication as follows:

Table S-A: Study Medication Used

Study Drugs	Appearance	Formulation	Dose Unit	Batch/Lot Numbers	FID#
CP-526,555-18	Off-white, round	Tablets	1 mg	ED-G-164-501	G02222AA

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: Safety and tolerability of study medication was assessed by physician observation and spontaneous reporting of adverse events (AE) by subjects. In addition, routine vital sign measurements, 12-lead ECG, and safety laboratory tests were performed.

Pharmacokinetics: In Period 1 (Day 1) and Period 2 (Day 2), blood samples were collected serially up to 96 hours (h) postdose. Plasma samples were assayed for CP-526,555 concentrations by [ ] using a validated assay in compliance with Pfizer standard operating procedures. Samples were analyzed using a [ ] followed by LC/MS/MS. The following pharmacokinetic parameters, Cmax, Tmax, AUC, and renal clearance (CLr) were determined using non-compartmental methods. In addition, blood samples were collected predose (time 0) on Days 2, 3, and 4 to assess steady-state attainment of cimetidine during Period 2. Plasma samples were assayed for cimetidine concentrations by [ ]

Statistical Methods: Demographics and safety data were summarized through data tabulations and descriptive statistics. For QT interval measurements, descriptive statistics (n,mean, standard deviation, min, and max) were calculated at each time point for the change from baseline between the single postdose measurement at 0, 3, and 24 hours after dosing with CP-526,555 during Periods 1 and 2 and the predose measurements taken on Period 1, Day 0. QTc was also descriptively summarized using the categories in the CPMP Points to Consider CPMP/986/96, namely normal/borderline/prolonged (males ≤430/431-450/>450 msec and females ≤450/451-470/>470 msec) and whether changes in QTc were <30, 30-60 and >60 msec.

The AUC, Cmax, and CLr for the single dose of CP-526, 555 were compared with CP-526,555 co-administered with steady-state cimetidine. The 90% confidence interval was calculated for difference of the log-transformed AUC, Cmax and untransformed CLr for the single dose CP-526, 555 with and without steady-state cimetidine co-administered. Cimetidine predose concentrations were used to document, via visual inspection, the attainment and maintenance of steady state during the blood sampling and urine collection procedures for CP-526,555 concentrations.

RESULTS:

Subject Disposition: Twelve (12) healthy male and female smokers, aged 19 to 41 were enrolled in and completed this study.

Table S-B: Subject Disposition

	Number of Subjects			
		CP-526,555 2 mg	Cimetidine 1200 mg	CP-526,555 + Cimetidine
Total Planned	12			
Total Number Enrolled	12			
Total Number Dosed		12	12	12
Total Withdrawn After Dosing		0	0	0
Number Completed		12	12	12
Assessed for Safety				
Adverse Events		12	12	12
Laboratory Tests		12	0	12
Number Evaluated				
Pharmacokinetics		12	12	12

Table S-C: Demographic Characteristics

	All Subjects		
Group	**Male**	**Female**	**Total**
Number of Subjects	8	4	12
Age (years)			
Mean	27.3	24.3	26.3
SD	7.6	6.1	7.0
Range	20-41	19-30	19-41
Race			
Asian	1	0	1
White	7	4	11
Weight (kg)			
Mean	81.4	67.6	76.8
SD	12.1	6.5	12.3
Range	70.3-100.2	62.1-76.2	62.1-100.2
BMI (kg/m^2)			
Mean	24.6	25.6	24.9
SD	3.5	2.8	3.2
Range	20-30	24-30	20-30
Height (cm)			
Mean	181.9	162.6	175.5
SD	4.9	5.5	10.7
Range	175.3-190.5	157.5-170.2	157.5-190.5

Safety: No deaths, SAE or withdrawals due to AE were reported during this study. Adverse events were reported by 8 (67%) subjects following receipt of CP-526,555 2 mg alone, 3 (25%) following receipt of cimetidine alone (Period 2, Day 1), and 8 (67%) following receipt of CP-526,555 plus cimetidine. The most common AE in subjects who received CP-526,555 either alone or with cimetidine were headache (17-25%) and nausea (33%). There was no obvious difference in nausea incidence between administration of CP-526,555 alone or CP-526,555 plus cimetidine. Neither AE occurred in subjects receiving cimetidine alone. Dizziness, which was not associated with clinically significant vital sign changes, was reported in one subject receiving CP-526,555 2 mg (Subject 0008). Less than 50% of the adverse events in all treatment groups were considered treatment-related. There were no AE of severe intensity in this study

In general, clinical laboratory measurements and vital sign values, identified as being of potential clinical concern in this study, were sporadic, transient, and appeared unrelated to study drug. No clinically significant changes were observed in mean baseline and mean changes from baseline for QTc.

Pharmacokinetics: Co-administration of cimetidine (300 mg QID) and CP-526,555 (2 mg) increased the plasma systemic exposure, based on Cmax and AUC(0-inf), of CP-526,555 by an average of 2.97% and 28.9%, respectively, and reduced its overall renal clearance over 48 hours by approximately 25%. None of the 90% CIs for the treatment ratios included 100%.

A summary of the point estimates, mean ratios and associated 90% confidence intervals for the comparisons of interest are presented in the table below.

Table S-D Summary Statistical Analyses of CP-526,555 Pharmacokinetic Parameters Following Single Administration of 2 mg CP-526,555 Alone or in Combination with Cimetidine 300 mg QID to Healthy Adult Smokers

Parameters (units)	Adjusted Geometric Mean		Ratio[a] (%)	90% Confidence Intervals
	CP-526,555 + Cimetidine	CP-526,555 Alone		
CLr (mL/min)	96.7	129.1	74.86%	(68.29%, 82.07%)
AUC(0-inf) (ng•hr/mL)	229.0	177.6	128.99%	(121.5%, 136.9%)
Cmax (ng/mL)	7.8	7.6	102.97%	(101.2%, 104.8%)

[a] Ratio of adjusted geometric means between test (CP-526,555 + Cimetidine) and reference (CP-526,555).

Examination of the cimetidine predose concentration-time data obtained on Days 2 to 4 showed that steady-state conditions of cimetidine 300 mg given four times daily were generally reached by Day 2 and maintained during the study period.

CONCLUSIONS:

- Co-administration of cimetidine (300 mg QID) and CP-526,555 (2 mg) resulted in increased plasma systemic exposure of CP-526,555 by an average of 29% due to a reduction in its renal clearance. This suggests that cimetidine competes with CP-526,555 for the human proximal renal tubular secretion system.

- There were no safety issues raised in this study.

9 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051014 **Phase:** 1

Title: PHASE 1 DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE NAUSEA PROFILE, SAFETY AND PHARMACOKINETICS OF CP-526,555 GIVEN BY TITRATION AND NON-TITRATION DOSING REGIMENS

Investigator: [

Study Publication: None at time of report issue

Study Dates: 31 October 2001 to 12-March 2002

Study Objectives: 1) to evaluate the safety, tolerability, and pharmacokinetics of CP-526,555 given by titration and non-titration regimens; 2) to compare nausea incidence, onset, and duration in healthy adult smokers of titration and non-titration dosing regimens of CP-526,555; 3) to evaluate the pharmacokinetic and pharmacodynamic relationships for nausea seen with CP-526,555 in healthy adult smokers.

Study Design: This was a randomized, double-blind, parallel group study of CP-526,555 in healthy male and female smokers. Three treatment groups (Dose Titration, Non-Titration, and Positive Control) were each given CP-526,555 or placebo for 21 days. All doses were administered in a fed state (following standard meals). A follow up safety visit occurred 7 to 10 days after the last dose of study medication.

Regimen A - **Dose Titration Group**: 0.5 mg QD of CP-526,555 a.m. and placebo p.m. for 3 days, 0.5 mg BID of CP-526,555 for 4 days, 1 mg BID of CP-526,555 for 1 week and then 1.5 mg BID of CP-526,555 for 1 week

Regimen B – **Non-Titration Group**: 1 mg BID of CP-526,555 for 2 weeks and then placebo BID for 1 week

Regimen C – **Positive Control Group**: Placebo BID for 2 weeks and then 1.5 mg BID of CP-526,555 for 1 week.

Study Population and Criteria for Inclusion: Subjects screened for this study were healthy adult smokers of any race between 18 to 55 years of age and within 25% of the recommended weight range based on age, gender, height, and body frame as established in the "1999 Metropolitan Life Insurance Height and Weight Tables." Enrolled subjects were required to be in good health as determined by a detailed medical history, full physical examination [including blood pressure (BP) and heart rate (HR) measurement], 12-lead electrocardiogram (ECG), and clinical laboratory tests.

Treatments: Pfizer Global Research & Development supplied study medication as follows:

Table S-A Study Medication Used

Study Drugs	Appearance	Formulation	Dose Unit	Batch/Lot Numbers	FID#
CP-526,555	Off white round	Tablets	0.5 mg	ED-G-166-501	G02306AA
Placebo	Off white, round	Tablets	NA	ED-G-106-301	G02328AA

FID = Formulation identification.

Study medication was administered with 240 mL of water at approximately 0800 and 1800 hours. The morning dose was administered immediately (within 5 minutes) after breakfast and the evening dose was administered immediately (within 5 minutes) after dinner. Each subject received a total of three tablets at the administration of each dose.

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: Safety and tolerability of study medication was assessed by physician observation and spontaneous reporting of adverse events (AE) by subjects. Routine vital sign measurements, 12-lead ECG, and safety laboratory tests were also performed. In addition to recording observed or volunteered AE, the Clinical Research Unit staff solicited specific nausea data from subjects in this study to more fully characterize the clinical pharmacology of CP-526,555. These data included the onset, intensity and duration of nausea as assessed by subject Self-Reported Nausea Profiles. The Self-Reported Nausea Profile was filled out at the onset of any nausea episode, at any change in the intensity of the nausea and at the end of the episode. All subjects, regardless of whether or not they had nausea that day, filled out a daily Impact of Nausea on Functioning questionnaire.

Subjects in the Placebo-treatment weeks of the Positive Control group are listed separately in safety listing because they were not exposed to study medication during the first two weeks of treatment. Non-Titration subjects, who were on placebo during the third week (Days 15-21), are not included in the placebo group because of their previous (within 7 days) exposure to study medication.

Pharmacokinetics: Plasma, urine and saliva samples were assayed for CP-526,555 concentrations by [ ] using a validated assay in compliance with Pfizer standard operating procedures. Samples were analyzed using a [ ] followed by [ ] The following pharmacokinetic parameters, Cmax, Tmax, AUC(0-Tlast) and t1/2 for CP-526,555 were determined using non-compartmental methods.

Other Assessments: A Stated Preference Exercise was completed on Day 22 to gather information concerning potential acceptable trade-offs between nausea severity and amount of symptom relief from individuals who received CP-526,555.

Statistical Methods: ECG interval parameters (PR, QT, HR, QTc, and QRS) were summarized, by treatment group, using descriptive statistics (n, mean, mean change from baseline, stderr, min, max). QTc was also descriptively summarized using the categories in the CPMP Points to Consider CPMP/986/96, i.e., normal/borderline/prolonged (males ≤430/431-450/>450 msec and females ≤450/451-470/>470 msec) and whether changes in QTc were <30, 30-60 and >60 msec. Nausea rates (proportion of randomized and treated subjects that experienced nausea at least once were compared using a two-sided Fisher's

exact test (alpha=0.05). Asymptotic 95% confidence intervals for the odds ratios were also computed. The primary comparison was all three weeks of the Titration group versus all three weeks of Positive Control group. For subjects who experienced nausea at least once, the onset, duration, AUC of intensity, for the first episode of nausea, and the total duration, maximum intensity and AUC of intensity of all nausea events, for each subject during the treatment period were summarized by treatment group using descriptive statistics. The severity scores for each of the 13 individual questions, as well as the composite severity scores for the Nicotine Evaluation Questionnaire (NEQ) physiological subscale items and the composite severity scores for gastrointestinal (GI) distress categories were summarized using descriptive statistics. The maximum score was selected for subjects experiencing more than one nausea episode within a treatment period. Maximum severity scores were summarized by treatment group. The results of the impact of nausea on functioning questionnaires were tabulated.

Demographics and safety data were summarized through data tabulations and descriptive statistics.

RESULTS:

Subject Disposition: One hundred and twenty healthy male and female smokers were enrolled in this study and randomized to three treatment groups: Titration, Non-Titration, and Positive-Control. During first two weeks of treatment 40 subjects in the Positive-Control group received placebo BID. These same 40 subjects received CP-526,555 1.5 mg BID for the third week of treatment. Non-Titration subjects, who were on placebo during the third week of treatment, are not included in the placebo group because of their previous (within 7 days) exposure to study medication.

Table S-B Subject Disposition

	Number of Subjects				
		Titration	Non-Titration[a]	Positive Control[b]	
				Placebo	1.5 mg
Total Planned	120				
Total Number Enrolled	120				
Total Number Dosed		40	40	40	40
Total Withdrawn After Dosing		0	0	0	0
Number Completed		40	40	40	40
Assessed for Safety					
Adverse Events		40	40	40	40
Laboratory Tests		40	40	40	40
Number Evaluated					
Pharmacokinetics		39	40	39	39

[a] Non-Titration: subjects were on placebo during the third week (Days 15-21). [b] Subjects in the Positive Control Group received placebo bid for the first two weeks [Positive Control (Placebo)] and then received CP-526,555 1.5 mg BID for the 3rd week only (Positive Control).

Demographic Characteristics: One hundred and twenty healthy male and female smokers, aged 20 to 55 were enrolled in and completed this study.

Table S-C Demographic Characteristics

	Titration			Non-Titration			Positive Control		
Group	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
No. of Subjects	20	20	40	20	20	40	20	20	40
Age (years)									
18-44	13	17	30	17	15	32	16	16	32
45-65	7	3	10	3	5	8	4	4	8
Mean	41.0	33.7	37.3	38.6	36.3	37.4	37.1	38.3	37.7
SD	7.3	8.9	8.9	7.7	9.5	8.6	8.7	7.9	8.2
Range	30-55	20-52	20-55	24-53	21-51	21-53	20-50	20-51	20-51
Race									
Black	16	13	29	12	10	22	15	16	31
White	4	7	11	8	10	18	5	3	8
Other	0	0	0	0	0	0	0	1	1
Weight (kg)									
Mean	77.5	73.0		78.4	74.6		81.3	77.7	
SD	10.7	9.0		9.2	11.2		11.2	10.0	
Range	67-106	54-90		68-104	57-98		62-104	60-98	
Height (cm)									
Mean	175.6	163.3		180.2	165.5		175.8	163.9	
SD	7.9	4.2		7.4	6.4		7.0	7.7	
Range	157-188	152-170		168-193	157-183		163-191	152-178	

Safety: No deaths, serious adverse events, or withdrawals due to adverse events were reported during this study. Adverse events were reported by 27 subjects in the Titration group, 27 subjects in the Non-Titration group, 15 subjects in the Positive Control group, and 19 subjects in the Placebo-treatment weeks of the Positive Control group. The most common AE across the treatment groups were headache (18-58%), nausea (15-30%), and vomiting (5-25%). Greater than 90% of the adverse events in all treatment groups were considered treatment-related. Most (60-90%) of the adverse events in this study were of mild to moderate intensity. Adverse events of severe intensity were reported by 2 subjects in the Titration group, 6 subjects in the Non-Titration group, 7 subjects in the Positive Control group, and 3 subjects in the Placebo-treatment weeks of Positive Control group. Nausea and/or vomiting were reported as the severe AE in 15 of the 18 (83%) subjects who had an AE of severe intensity.

There were no clinically significant changes from baseline in laboratory, vital sign, and ECG values in any treatment group. Some subjects had transient laboratory, vital sign, and ECG values that met the threshold for potential clinical concern. None of these values were considered to be medically significant.

The nausea incidence rates over the entire three weeks were 27.5% for the Titration group, 22.5% for the Non-Titration group, and 42.5% for the Positive Control group. These differences were not statistically significant. There were statistically significant differences in the nausea incidence rates during the third week only between the Titration group (titrated to 1.5 mg BID) and the Positive Control group (1.5 mg BID) and between the Non-Titration group, who were treated with placebo during the third week, and Positive Control group.

The incidence rates were 10% for the Titration group, 5% for the Non-Titration group, and 30% for the Positive Control group.

For the first episode of nausea in the all three-weeks assessment, the lowest AUC for intensity was observed in the Titration group compared to the other groups. The AUC of intensity takes into account the intensity and duration of the first nausea event, both of which were slightly higher for the Non-Titration and Positive control groups. Similar results were seen combining all episodes. For the first two weeks of treatment, smaller mean values of duration, intensity, and AUC of intensity for the first episode of nausea, and smaller mean values of total duration, total AUC of intensity, and maximum intensity for all episodes of nausea were observed for the Titration (titrated to 1-mg CP-526,555 BID) group compared to the Non-Titration group (1-mg CP-526,555 BID).

There was a smaller number of subjects in the Titration group than in the Positive Control group who reported that the nausea/vomiting they experienced had caused mild, moderate or a lot of distress, discomfort or interfered with their daily life. This was seen in both the all three weeks assessment and in the third week only assessment. Similar results were seen with the response to whether the nausea/vomiting experienced had an impact on their ability to drink or eat.

Pharmacokinetics: The oral steady-state pharmacokinetics of CP-526,555 was comparable between the titration and non-titration dosing regimens.

In the Titration Group, approximate dose-proportional increases in Cmax and AUC values were observed in all subjects between the 1 mg BID and 1.5 mg BID. Maximum plasma concentration was achieved typically within 3 to 4 hours postdose following multiple doses of CP-526,555. For the same total daily dose steady-state exposures to CP-526,555 were consistent between the titration and non-titration dosing regimens. Most subjects attained steady-state conditions within 3 to 4 days.

Arithmetic mean (SD) for Cmax, AUC and t1/2 and median [range] Tmax values following administration of CP-526,555 given by titration and non-titration dosing regimens are presented in Table S-D.

Table S-D Arithmetic mean (SD) for Pharmacokinetic Parameters Following Administration of CP-526,555 Given by Titration and Non-Titration Dosing Regimens

	Dose-Titration		Non-Titration	Positive Control
Parameters (units)	**1 mg BID (N=39)**	**1.5 mg BID (N=39)**	**1 mg BID (N=40)**	**1.5 mg BID (N=39)**
	Day 14	Day 21	Day 14	Day 21
AUC(0-Tlast) AUC(0-8) (ng·h/mL)	- 59.3 (10.7)	418 (113) 96.9 (24.6)	- 62.9 (14.0)	427 (163) 97.9 (30.9)
Cmax (ng/mL)	8.54 (1.51)	13.9 (3.3)	9.04 (2.01)	14.2 (4.1)
Tmax (h)	3.00 [1.00-8.00]	3.00 [1.00-4.00]	3.00 [1.00-4.00]	3.00 [2.00-8.00]
t1/2 (h)	NA [a]	27.3 (8.5) [b]	33.3 (15.4) [c]	30.1 (6.4) [c]

Cmax, Tmax of the first dosing interval. Tmax values presented as median (range).
[a] NA- t1/2 not available due to limited sampling period [range]. [b] (N=19). [c] (N=31).

Optimal characterization of the pharmacokinetic-pharmacodynamic relationship between plasma exposure to CP-526,555 and nausea incidence rates requires additional data and thus will be done in subsequent population pharmacokinetic-pharmacodynamic meta-analyses via nonlinear mixed effects modeling.

Other Assessments: The results of the analysis of the Stated Preference Exercise indicate that for all study subjects (across treatment groups), in general, craving relief was the most important treatment attribute. While subjects would prefer a product that was not associated with nausea, the most important aspect about nausea was its intensity rather than its frequency. Subjects were prepared to tolerate an effective smoking cessation treatment (i.e., moderate as opposed to complete craving and withdrawal relief) that caused daily nausea as long as the intensity of nausea remained mild.

CONCLUSIONS:

- There were no safety issues raised in this study.
- The nausea incidence rates over the entire three weeks were 27.5% for the Titration group, 22.5% for the Non-Titration group, and 42.5% for the Positive Control group. These differences were not statistically significant.
- For all three-weeks, subjects in the Titration group demonstrated a shorter duration of nausea, a lower maximum intensity, and lower AUC of intensity compared to subjects in both the Non-Titration and the Positive Control groups. These results suggest that titration may improve tolerability of CP-526,555
- The oral steady-state pharmacokinetics of CP-526,555 was comparable between the titration and non-titration dosing regimens. Systemic exposure to CP-526,555 in plasma increased approximately proportionately with escalating doses up to 1.5 mg BID.

CP-526,555
A3051015
FINAL Clinical Study Report

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051015 **Phase:** 1

Title: Phase 1, Double-Blind, Randomized, Multiple Dose, Crossover Study to Evaluate the Nausea Profile and Pharmacokinetics of CP-526,555 Administered in the Morning and at Bedtime

Investigator: [ ]

Study Publication: None at time of report issue

Study Dates: 22 October 2001 to 28 January 2002

Study Objectives: There were two objectives:

1) To evaluate the nausea profile of morning (AM) and bedtime (QHS) multiple doses of CP-526,555 via a comparison of the nausea incidence rate.
2) To compare the relative bioavailability of morning (AM) and bedtime (QHS) multiple doses of CP-526,555 at steady state.

Study Design: This was a double-blind, randomized, multiple dose, crossover study of CP-526,555, administered as 2 x 1 mg immediate release (IR) tablets. Subjects received each of the following treatment regimens according to a computer-generated randomization (A→B or B→A): A = CP-526,555 2 mg daily in the morning and placebo daily at bedtime, for 7 days; and B = CP-526,555 2 mg daily at bedtime and placebo daily in the morning, for 7 days. All study medication was administered to subjects with breakfast and an evening snack. There was a washout period of at least 7 days between each dosing regimen and a follow up safety visit 7 to 10 days after the last dose of study medication.

Study Population: The study population was to consist of enough subjects to ensure that 40 healthy adult smokers (approximately 50% male, 50% female) between 18-55 years inclusive completed the study. Subjects were to weigh no less than 110 pounds (50 kg), and be within 25% of the recommended weight range for age, gender, height, and frame as established in the "1999 Metropolitan Life Insurance Height and Weight Tables." Subjects were required to be in good health as determined by a detailed medical history, a full physical examination including vital signs, a 12-lead resting electrocardiogram (ECG), and clinical laboratory evaluations. In addition, smokers were to be subjects smoking an average of at least 10 cigarettes per day, with no period of abstinence greater than 3 months in the past year.

Treatments:

The Pharmacy Operations department at Pfizer Global Research and Development (PGRD) supplied study medication as follows:

Table S-A. Study Medication

Study Drugs	Appearance	Formulation	Dose Unit	Duration	Lot Number	FID Number
CP-526,555 (IR)	Off-white, round	Tablets	2 X 1 mg	Once daily X 7 days / regimen	ED-G-164-501	G02222AA
Placebo (IR match)	Off-white, round	Tablets	NA	Once daily X 7 days / regimen	ED-G-107-301	G02329AA

Study Endpoints for Evaluation:

Safety: All subjects were evaluated for safety, which was assessed by clinical observations, querying for adverse events (AEs), physical examination, vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

Nausea Profiles: The severity of nausea and its associated symptoms were evaluated by the Self-Reported Nausea Profile, a visual analog scale used to evaluate the onset, intensity, and duration of each nausea episode that occurred while the subject was in the Clinical Research Unit (CRU). In addition, the Impact of Nausea on Functioning Questionnaire was collected just prior to the bedtime snack and evening dosing on Days 1 through 6, regardless of whether or not subjects had experienced nausea that day.

Pharmacokinetics: On Day 7 of each study period, blood was collected at specified intervals from 0 (just prior to morning dosing) to 38 hours after morning dosing. A validated [redacted] assay was used to determine CP-526,555 plasma concentration levels. The primary pharmacokinetic (PK) study endpoints were $AUC_{0\text{-}24}$ (area under the plasma concentration time-curve from time 0 to 24 hours after study drug administration), Cmax (maximum observed plasma concentration), and Tmax (time to maximum observed plasma concentration) of CP-526,555 following administration of a 2 mg dose either in the morning or at bedtime.

Statistical Methods:

Sample Size: A sample size of 40 pairs (40 individual subjects with 2 periods of nausea assessment) would have 80% power to detect a difference in proportions of subjects experiencing nausea of 0.250 when the proportion of discordant pairs was expected to be 0.360.

Safety and Nausea Profiles: One of the primary questions of interest was whether there was a significant difference in nausea incidence rates between the AM and QHS dosing of CP-525, 555. McNemar's test for matched pairs and SAS PROC FREQ were used to test for differences in nausea rates.

Nausea incidence rates, intensity of the first episode of nausea, and number of episodes were obtained from the Self-Reported Nausea Profile Questionnaire data

and were summarized by treatment regimen using descriptive statistics. For subjects who experienced nausea at least once, the onset (time elapsed from the first dose time to start of nausea episode), duration, intensity, and AUC of intensity were summarized for the first nausea episode of each subject within a treatment. For all nausea episodes, the total duration, total AUC of intensity, and the maximum intensity of all nausea episodes were summarized by treatment group using descriptive statistics.

Demographics and safety data were summarized through data tabulations and descriptive statistics. The results of the exhaled CO and time of each cigarette were tabulated. No formal analyses were performed.

Pharmacokinetic: Natural log-transformed CP-526,555 AUC_{0-24} and Cmax and untransformed Tmax were analyzed using a mixed effects model containing fixed effects for sequence, period, and treatment, and random effects for subjects (within sequence). Compound symmetry was assumed, and Restricted Maximum Likelihood Estimates (REML) were used. Estimates of the adjusted mean differences between treatments, and 90% confidence intervals (CIs) around the differences were calculated. For AUC_{0-24} and Cmax, the anti-log (exponent) of the differences and confidence limits were taken to estimate the ratios between treatments and the CIs of the ratios. For Tmax, the confidence intervals on the mean differences were calculated. Geometric means were provided for AUC_{0-24} and Cmax. Arithmetic means were provided for Tmax. The comparison was 2 mg morning dosing versus 2 mg bedtime dosing. Morning dosing was the reference. SAS procedure PROC MIXED was used for these analyses.

Results:

Subject Disposition: The study population consisted of 44 healthy adult smokers (21 males, 23 females), between 18-49 years inclusive. Of the 44 enrolled subjects, 5 (1 male and 4 females) chose not to continue due to personal reasons (not treatment-related) after the first regimen of study drug, and 1 female subject discontinued after the second dosing regimen due to AEs. Despite the discontinuations, AEs and laboratory safety data were collected for 43 subjects in the AM dosing regimen and 40 subjects in the QHS dosing regimen. Thirty-eight (38) subjects were evaluable for PK in each treatment group. Summary demographic information is displayed below.

Table S-B. Demographic Characteristics of Study Population

		All Subjects		
		Male	Female	Total
Number of Subjects		21	23	44
Age	Mean	29	25	27
	SD	11	8	10
	Range	18-49	19-44	18-49
Race	White	21	21	42
	Asian	0	1	1
	Hispanic	0	1	1
Weight	Mean	77.5	66.7	71.8
	SD	12.4	7.9	11.6
	Range	57.0-104.0	54.0-83.0	54.0-104.0
Height	Mean	174.1	163.9	168.8
	SD	6.9	4.4	7.6
	Range	157.0-188.0	157.0-175.0	157.0-188.0

Safety:

There were no deaths, serious adverse events, or adverse events of severe intensity in this study. There were no safety concerns based on analysis of clinical laboratory data, physical exams, ECGs, or vital signs. There was one withdrawal due to adverse events. Subject #31 was a 28 year old white female who discontinued treatment after reporting recurring episodes of nausea and vomiting (both of mild intensity) on Days 4-7 following CP-526,555 2 mg QHS treatment (Period 1) and on Days 3-8 following CP-526,555 2 mg AM treatment (Period 2).

Most of the adverse events reported were treatment-related and of mild intensity. Thirty (30) of the 43 subjects receiving CP-526,555 2 mg AM dose reported a total of 70 adverse events. Twenty-five (25) of the 40 subjects receiving CP-526,555 2 mg QHS dose reported a total of 45 AEs. The most frequent AEs reported were related to the gastrointestinal system, particularly nausea and vomiting.

There was no evidence of significant differences in nausea incidence rates between the two dosing groups. Subjects in the AM dosing group reported a nausea incidence rate of 53.8% from spontaneous AEs and 47.4% from the nausea self report profiles. Subjects in the QHS dosing group reported a nausea incidence rate of 46.2% from spontaneous AEs and 36.8% from the nausea self report profiles. The reported p-value for the two-sided McNemar's test was 0.366 based on all reported nausea events from spontaneous AE report and 0.248 for nausea reported in nausea profile filled by subjects while they were in the CRU.

Pharmacokinetics: No differences in oral steady-state pharmacokinetics were observed when CP-526,555 was administered daily in the morning compared to bedtime in the fed state.

Mean relative oral bioavailability values, based on AUC0-24, were ≈100% for the bedtime dosing relative to the morning dosing. For AUC0-24 and Cmax, the bounds of the 90% CI were completely contained within the established bioequivalence limits (80, 125%).

Table S-C. Summary of Statistical Analysis on Day 7 Following Administration of a 2 mg Single Daily Oral Tablet Doses for 7 Days to Healthy Smokers

Pharmacokinetic Parameter	Bedtime (Test)	Morning (Reference)	Ratio (%)*	90% Confidence Interval
AUC0-24 (ng·h/mL)	183.7	185.8	99	(95%, 103%)
Cmax (ng/mL)	12.0	12.3	98	(94%, 102%)

* Ratio of adjusted geometric means (test/reference)

The within-subject variability (coefficient of variation within subjects - CV%) was 10%, 10%, and 21% for AUC0-24, Cmax, and Tmax, respectively.

CONCLUSIONS:

The observed nausea incidence rates for the AM group (53.8%, spontaneous AEs; 47.4% self report profiles) were not statistically significantly different than those for the QHS dosing group (46.2%, AEs; 36.8%, self report profiles).

There were no safety concerns in this study.

There was no effect of time-of-day dosing on the steady-state pharmacokinetics of 2 mg CP-526,555 when administered daily in the morning compared with bedtime dosing.

Results suggest that CP-526,555 may be given without regard to time of day.

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051026 **Phase: 1**

Title: Phase 1, Open-Label, Randomized, Three-Way Crossover Study to Establish the Bioequivalence of a 1 mg Single Dose of CP-526,555 Administered as 2 x 0.5 mg Phase 3 Immediate Release (IR) Tablet Formulation Versus the 1 mg Phase 2 IR Tablet Formulation and to Evaluate the Pharmacokinetic Performance of the 0.5 mg Phase 3 IR Tablet Under Fed Conditions in Healthy Adult Smokers

Investigator: [ ]

Study Publication: None at time of report issue.

Study Dates: 5 November 2002 to 27 January 2003

Study Objectives: 1) To establish the bioequivalence of a 1 mg dose of CP-526,555 (given as 2 x 0.5 mg tablets) of the Phase 3 IR formulation of CP-526,555 and the 1 mg Phase 2 IR tablet formulation, under fed conditions in healthy adult smokers. 2) To explore the dose proportionality of 2 x 0.5 mg tablets of the Phase 3 IR formulation relative to 1 x 0.5 mg tablet of the Phase 3 IR formulation of CP-526,555. 3) To evaluate the safety and tolerability of a 1 mg dose (2 x 0.5 mg) of the Phase 3 IR formulation of CP-526,555 in healthy smokers.

Study Design: This was an open-label, randomized, six sequence, three-way crossover single dose study of CP-526,555 in healthy adult smokers. CP-526,555 was administered orally as either the Phase 3 or Phase 2 immediate-release (IR) tablet formulation. Subjects received one of the following in each session:

Table S-A Treatment Regimens

Regimen	Study Medication(s)
A	CP-526,555 1 mg Phase 2 IR tablet administered as a single oral dose under fed conditions
B	CP-526,555 1 mg (2 x 0.5 mg Phase 3 IR tablets) administered as a single oral dose under fed conditions
C	CP-526,555 0.5 mg Phase 3 IR tablet administered as a single oral dose under fed conditions

Subjects were randomized to one of six sequences of administration of each of the three treatment regimens:

Table S-B Randomization Sequences

A)	A → B → C	D)	B → C → A
B)	A → C → B	E)	C → A → B
C)	B → A → C	F)	C → B → A

The total duration of the study was approximately 3 weeks with a 7-day washout between administrations of doses. A follow-up safety visit occurred on Day 5 of Dosing Period 3.

Study Population and Criteria for Inclusion: Subjects screened for this study were healthy adult smokers of any sex and race between 18 to 55 years of age with a Body Mass Index (BMI) between 18-30 kg/m^2, inclusive; and a total body weight >50 kg (110 lbs). Enrolled subjects were required to be in good health as determined by a detailed medical history, full physical examination (including blood pressure and heart rate measurement), 12-lead electrocardiogram (ECG), and clinical laboratory tests.

Treatments: Pfizer Global Research & Development supplied study medication as follows:

Table S-C Study Medication Used

Study Drugs	Appearance	Formulation	Dose Unit	Batch/Lot Numbers	FID#
CP-526,555-18	White round	Tablets	0.5 mg	920098-3000052-G2	G02610AA
CP-526,555-18	Off white, round	Tablets	1.0 mg	ED-G-164-501	G02222AA

Study medication was administered with 240 mL of water at approximately 0800 hours. All dosing was performed in the fed state (standard, not high-fat, meal) immediately (within 5 minutes) after breakfast. Subjects were assigned a subject number in the order of their acceptance into the study.

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: Safety and tolerability of study medication were assessed by physician observation and spontaneous reporting of adverse events (AEs) by subjects. Routine vital sign measurements, 12-lead electrocardiogram (ECG), and safety laboratory tests were also performed.

Pharmacokinetics: Plasma samples were assayed for CP-526,555 concentrations by [ ] using a validated assay in compliance with Pfizer standard operating procedures. Samples were analyzed using a [ ] followed by LC/MS/MS. The following pharmacokinetic parameters, Cmax, Tmax, AUC(0-Tlast), AUC(0-inf) and t1/2 for CP-526,555 were determined using non-compartmental methods.

Statistical Methods: Demographics and safety data were summarized through data tabulations and descriptive statistics. ECG interval parameters (PR, QT, heart rate, QTc, and QRS) were summarized by treatment group using descriptive statistics (n, mean, mean change from baseline, stderr, min, max). QTc was also descriptively summarized using the categories in the Committee for Proprietary Medicinal Products (CPMP) Points to Consider CPMP/986/96, i.e., normal/borderline/prolonged (males ≤430/431-450/>450 msec and females ≤450/451-470/ >470 msec) and whether changes in QTc were <30, 30-60 and >60 msec.

Natural log-transformed CP-526,555 AUC(0-inf), AUC(0-Tlast) and Cmax were analyzed using a mixed effects model containing fixed effects for sequence, period, and treatment and a random effect for subjects (within sequence). The AUC(0-inf), AUC(0-Tlast) and Cmax values for the 1 x 1 mg Phase 2 IR tablet and 2 x 0.5 mg Phase 3 IR tablet treatments were dose normalized to 0.5 mg prior to the log-transformation and analysis. The bioequivalence of the 2 x 0.5 mg Phase 3 and 1 x 1 mg Phase 2 IR tablet formulations was declared if the 90% confidence

intervals of the AUC(0-inf), AUC(0-Tlast) and Cmax ratios fell entirely within the bioequivalence limits of 80-125%. Dose proportionality of the 1 x 0.5 mg and 2 x 0.5 mg Phase 3 IR tablets was established if the 90% confidence intervals of the AUC(0-inf), AUC(0-Tlast) and the Cmax ratios fell entirely within the bioequivalence limits of 80-125%.

RESULTS:

Subject Disposition: Fourteen (14) healthy male and female smokers, aged 18 to 48 were enrolled in this study.

Table S-D Subject Disposition

		Number of Subjects		
		1 x 1 mg Phase 2 IR Tablet	2 x 0.5 mg Phase 3 IR Tablet	1 x 0.5 mg Phase 3 IR Tablet
Total Planned	12			
Total Number Enrolled	14			
Total Number Dosed		14	13	12
Total Withdrawn After Dosing		2	0	0
Number Completed		12	13	12
Assessed for Safety				
Adverse Events		14	13	12
Laboratory Tests		13	13	12
Number Evaluated				
Pharmacokinetics		14	13	12

Two subjects discontinued from the study due to events considered not related to study drug. Subject 10011002, a 21-year old male, was discontinued on Day 14 after treatment with the CP-526,555 1 mg Phase 2 IR formulation due to noncompliance with study procedures that resulted in laboratory abnormalities [creatine phosphokinase (CK), aspartate aminotransferase (AST)] at 7 days post Day 1 dosing that were considered to be unrelated to study medication (see details below). Subject 10011011, a 22-year old male was no longer willing to participate in the study (defaulted) for personal reasons (non-study drug related).

Demographic Characteristics:

Table S-E Demographic Characteristics

	All Subjects		
Group	**Male**	**Female**	**Total**
Number of Subjects	8	6	14
Age (years)			
18-44	8	4	12
45-64	0	2	2
Mean	22.0	31.0	25.9
SD	3.5	13.4	9.8
Range	18-28	19-48	18-48
Race			
Asian	1	0	1
White	7	6	13
Weight (kg)			
Mean	73.8	64.3	69.7
SD	13.1	7.4	11.7
Range	62-104	51-73	51-104
BMI (kg/m^2)			
Mean	22.9	23.5	23.2
SD	3.2	2.0	2.7
Range	20.0-29.4	19.9-25.3	19.9-29.4
Height (cm)			
Mean	179.1	165.2	173.1
SD	7.4	4.1	9.3
Range	168-191	160-170	160-191

Safety: No deaths, serious adverse events, or withdrawals due to AEs were reported during this study. Adverse events were reported by 5 (36%) subjects in the 1 mg Phase 2 IR group, 4 (31%) subjects in the 2 x 0.5 mg Phase 3 IR group, and 3 (25%) subjects in the 1 x 0.5 mg Phase 3 IR group. The most common AE across the treatment groups was headache (14-17%). Less than 35% of the AEs were considered treatment-related. All of the AEs in this study were of mild to moderate intensity.

Subject 10011002, a 21-year old male, was discontinued on Day 14 after treatment with the CP-526,555 1 mg Phase 2 IR formulation due to noncompliance with study procedures [lifted weights at approximately 10:30 am on study Day 7 (7 days post Day 1 dosing), the day of return to the CRU for Period 2] resulting in a laboratory abnormality considered unrelated to study medication. This subject's creatine phosphokinase values were within normal range at study entry (135 IU/L) increased to values exceeding the clinical concern threshold (10890 IU/L) by Day 7, and decreased to a non-clinically significant value (216 IU/L) by Day 15. The decision was subsequently made by the Sponsor to not dose this individual and to withdraw the subject from the study due to noncompliance with study procedures.

In general, clinical laboratory measurements, identified as being of potential clinical concern in this study, were sporadic, transient, and appeared unrelated to study drug. There were no

clinically significant changes in sitting Diastolic and Systolic BP and HR. No clinically significant changes were observed in mean baseline and mean changes from baseline for QTc.

Pharmacokinetics: Based on the 90% confidence intervals for Cmax, AUC(0-inf) and AUC(0-Tlast), a 1 mg dose of the Phase 3 IR tablet formulation was bioequivalent to a 1 mg dose of the Phase 2 IR tablet, used in previous Phase 2 studies under fed conditions (standard meal). Results also demonstrated that the observed increases in Cmax and AUC values were dose-proportional between the 0.5 and 1 mg dose levels of the Phase 3 IR tablet.

A summary of the point estimates, mean ratios and associated 90% confidence intervals (CI) for the comparisons of interest are presented in the table below.

Table S-F Summary Statistical Analyses of CP-526,555 Pharmacokinetic Parameters Following Single Oral Doses of CP-526,555 Given as the Phase 2 and Phase 3 IR Tablet Formulations to Healthy Adult Smokers

			Adjusted Geometric Means			
Parameter (units)	**Test**	**Reference**	**Test**	**Reference**	**Ratio[a] (%)**	**90% Confidence Interval**
AUC(0-inf)[b] (ng·h/mL)	2 x 0.5 mg Phase 3 IR Tablet	1 x 1 mg Phase 2 IR Tablet	49.87	49.25	101.26	94.61, 108.38
	2 x 0.5 mg Phase 3 IR Tablet	1 x 0.5 mg Phase 3 IR Tablet	49.87	52.08	95.75	87.64, 104.61
AUC(0-Tlast)[b] (ng·h/mL)	2 x 0.5 mg Phase 3 IR Tablet	1 x 1 mg Phase 2 IR Tablet	44.40	44.61	99.51	90.23, 109.75
	2 x 0.5 mg Phase 3 IR Tablet	1 x 0.5 mg Phase 3 IR Tablet	44.40	43.49	102.08	92.56, 112.58
C(max)[b] (ng/mL)	2 x 0.5 mg Phase 3 IR Tablet	1 x 1 mg Phase 2 IR Tablet	2.36	2.24	105.59	100.38, 111.08
	2 x 0.5 mg Phase 3 IR Tablet	1 x 0.5 mg Phase 3 IR Tablet	2.36	2.34	101.21	96.21, 106.47

[a] Ratio of dose-normalized adjusted geometric means [Mean 1(test) /Mean 2(reference)].
[b] 1 x 1 mg Phase 2 IR tablet values and 2 x 0.5 mg Phase 3 tablet values were dose normalized to 0.5 mg prior to analysis.

CONCLUSIONS:

- Bioequivalence was established between the Phase 2 and Phase 3 IR tablet formulations of CP-526,555 administered in the fed state.
- Dose-proportional increase in plasma systemic exposure to CP-526,555 was demonstrated between the 1 x 0.5 mg and 2 x 0.5 mg dose levels of the new Phase 3 IR tablet.
- There were no safety issues raised in this study.

CP-526,555
A3051027
Final Clinical Study Report

REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/ A3051027 **Phase: 1**

Title: PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE ESCALATING STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY AND SINGLE ORAL DOSE PHARMACOKINETICS OF CP-526,555 (A PARTIAL AGONIST FOR THE NICOTINIC RECEPTOR $\alpha_4\beta_2$) IN JAPANESE HEALTHY ADULT MALE SMOKERS

Principal Investigator: [redacted]

Study Publication: None at time of report issue

Study Dates: 12 March 2003 to 27 May 2003

Study Objectives: To evaluate the safety, tolerability, and pharmacokinetics of single oral doses of CP-526,555 in Japanese healthy adult male volunteers

Study Design: This was a 4-way crossover study in Japanese subjects (smokers) and drug administration in each period was conducted in a double-blind, placebo-controlled manner. Subjects were to receive CP-526,555 (0.25 mg, 0.5, 1.0, 2.0 mg) or placebo, from Period I (0.25 mg administration) to Period IV (2.0 mg administration), at an interval of approximately 2 weeks.

Each subject was administered with the study drug throughout the 4 periods. Subjects were moved to the next period after principal investigator and study sponsor had confirmed their safety and made the conclusion, by fully taking subjects' health conditions and results of interview and examinations by principal investigator (sub-investigator) into account.

Sequence	Subjects	Period I	Period II	Period III	Period IV
A	6	0.25 mg	0.5 mg	1.0 mg	2.0 mg
B	2	0.25 mg	0.5 mg	1.0 mg	Placebo
C	2	0.25 mg	0.5 mg	Placebo	2.0 mg
D	2	0.25 mg	Placebo	1.0 mg	2.0 mg
E	2	Placebo	0.5 mg	1.0 mg	2.0 mg

<Randomization of subjects>

Volunteers who were considered eligible to this study by screening were admitted as candidates. After the subjects received regulated tests at admission (Day 0), and their eligibility was finally confirmed, the subjects were randomly allocated to study drug or placebo with sequence of A to E at a ratio of 3:1:1:1:1, on the date of drug administration (Day 1).

Study Population and Criteria for Inclusion: Japanese healthy adult male volunteers aged 20 to 55, who are smokers, were willing to give their consent to participate in the study and considered suitable to participate in this study by the principal investigator (sub-investigator), based on the results of observation and examination of the subject background, physical examination, vital signs (body temperature, blood pressure, pulse rate), ECG, laboratory tests that were conducted at screening by the principal investigator (sub-investigator).

Treatments:

Study Medication:

Study Drugs	Formulation	Dose Unit	Lot Number	FID Number
CP-526,555-18[+] tablet 0.25 mg		0.25 mg	ED-G-252-802	G02691AA
CP-526,555-18 tablet 0.5 mg		0.5 mg	920098-3000052-G1	G02610AA
CP-526,555-18 tablet 1.0 mg		1.0 mg	920108-3000052-G1	G02611AA
Matching placebo of CP-526,555-18 tablet 0.25 mg *	FC Tablets[++]	0 mg	ED-G-254-802	G02693AA
Matching placebo of CP-526,555-18 tablet 0.5 mg*		0 mg	ED-G-310-902	G02613AA
Matching placebo of CP-526,555-18 tablet 1.0 mg*		0 mg	ED-O-155-502	G02615AA

[+]L-tartrate salt
[++]Film-coated tablets
*Indistinguishable from CP-526,555-18 in their appearance

Dosing: 0.25, 0.5, 1.0 and 2.0 mg of CP-526,555 and matching placebo
The study drug was swallowed as it was with 200 mL water within 5 minutes after breakfast (standard non-high-fat meal).

Duration: Single-dose

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: As to safety evaluations, adverse events, subjective symptoms/objective findings, laboratory tests, measurement of body temperature, blood pressure, and pulse rate and ECG data assessment were included.

Pharmacokinetics: CP-526,555 plasma concentrations were analyzed by non-compartment model and the following pharmacokinetic parameters were estimated.

Plasma concentrations of CP-526,555: C_{max}, AUC_{last}, AUC, T_{max}, k_{el}, $t_{1/2}$, CL_R

Urinary concentrations of CP-526,555 were analysed and the following pharmacokinetic parameters were estimated.

Urinary concentrations of CP-526,555: urinary excretion amount and percent dose of CP-526,555 excreted unchanged, and accumulative urinary excretion amount and

accumulative percent dose of CP-526,555 excreted unchanged at each measurement time.

Pharmacodynamics:

1. Incidence of nausea
2. Onset time (hours after dosing) and duration of the first episode of nausea
3. Mean duration of nausea
4. Severity scores on "Self-Reported Nausea and Vomiting Profile"
5. Composite severity scores for NEQ (Nicotine Effect Questionnaire)
6. Composite severity scores for GI distress
7. Impact of Nausea or Vomiting on Functioning Questionnaire
8. The number of cigarette smoked

Statistical Methods:

Pharmacokinetics: For plasma concentrations at each sampling point, the arithmetic mean, standard deviation, and coefficient of variation (CV) were calculated. In this calculation, 0 was entered for concentrations below the limit of quantification; and when the drug concentrations in the majority of the subjects were below the limit of quantification, the mean, standard deviation, and CV were not calculated. Summary statistics (arithmetic mean, standard deviation, range and CV) for all pharmacokinetic parameters were calculated by treatment group. In addition, geometric mean for C_{max}, AUC_{last}, and AUC, and the harmonic mean for k_{el} were calculated. Regarding urinary concentrations, the arithmetic mean, standard deviation, and coefficient of variation (CV) were calculated for urinary excretion amount, % of dose excreted unchanged, and renal clearance.

Pharmacodynamics: Incidence of nausea, onset time (hours after administration) and duration of first episode, and mean duration of nausea observed in each period were calculated. Also severity scores of each item on "Self-Reported Nausea and Vomiting Profile", composite severity scores for NEQ, composite severity scores for GI distress, and the number of cigarette smoked, the basic statistics were calculated. For impact of nausea or vomiting on functioning, results that summarized by question item were shown in a table.

Safety: A summary and list of safety data (adverse events, laboratory tests, blood pressure, pulse rate, body temperature, ECG findings, etc.) were prepared according to the "Worldwide Safety Standards for Clinical Trials, Release 3.0 (WSS 3.0)," a Pfizer's in house standard, and clinical evaluation was performed. As to 12-lead ECG, heart rate, PR interval, QRS interval, QT interval, QTcB interval, and QTcF interval were calculated.

RESULTS:

Subject Disposition: Although 14 subjects were enrolled in this study, one subject was discontinued from the study due to respiratory tract infection (treatment-related treatment-emergent adverse event, Investigator term : common cold) after Period I. Therefore, this study was conducted with 13 subjects after Period II.

Subject disposition were summarized in the table below.

Subject Disposition by Treatment Regimen

		CP-526,555				
		0.25 mg	0.5 mg	1.0 mg	2.0 mg	Placebo
Total Number of Screened	14					
Total Number Enrolled	14					
Total Number Dosed		12	11	12	11	7
Number Completed		11	11	12	11	7
Total Withdrawn Post-Dose		1	0	0	0	0
Evaluated for Pharmacokinetics		12	11	12	11	7
Assessed for Safety						
Adverse Events		12	11	12	11	7
Laboratory Tests		12	11	12	11	7

Source: Table 1.1

Demographic Characteristics:

Background Factors	Sequence A (n=6)	B (n=2)	C (n=2)	D (n=2)	E (n=2)
Age (years):					
Mean	27.3	23.0	28.5	21.5	25.0
SD	3.3	1.4	7.8	2.1	2.8
Range	22-32	22-24	23-34	20-23	23-27
Weight (kg):					
Mean	61.3	59.1	63.0	55.6	71.6
SD	4.5	9.5	2.9	1.1	5.4
Range	55.1 - 65.8	52.3 - 65.8	60.9 - 65.0	54.8 - 56.3	67.7 - 75.4
BMI(kg/m^2) :					
Mean	21.5	21.4	20.4	19.6	23.0
SD	1.6	1.4	1.3	0.7	0.7
Range	19.7 - 23.5	20.4 - 22.3	19.5 - 21.3	19.1 - 20.2	22.5 - 23.5

Source:Table 2.1

Safety: No deaths, serious adverse events or discontinuation due to treatment-emergent adverse events (AEs) which observed within lag period (7 days) were reported during this study. One of subjects (ID: 1001 111) discontinued the study on Day 15 due to respiratory tract infection (Investigator term: common cold, All causality) which was reported on Day 10 after Period I (0.25 mg).

Three AEs were reported in 3 subjects among 12 subjects in the 0.25 mg regimen, 3 events were reported in 3 subjects among 12 subjects in the 1.0 mg regimen, and 5 events were reported in 2 subjects among 11 subjects in the 2.0 mg regimen. There was no report about AEs in 11 and 7 subjects in the 0.5 mg and placebo regimens, respectively. All AEs were mild in severity. The disposition of treatment-related AEs were as follows; 2 events in the 0.25 mg regimen were headache and retinal disorder, 1 event in the 1.0 mg regimen was diarrhea, and 5 events in the 2.0 mg regimen were abdominal pain, dyspepsia, and nausea in one subject, and abdominal pain and dyspepsia in one subject.

The funduscopy result of a subject (ID: 1001 106) showed retinal disorder (treatment-related AE, investigator term: soft retinal exudate) on 48 hr after the dosing of 0.25 mg. This AE was not observed on 168 hr after this dosing nor was it observed upon administration of higher dosages. There were no other subjective and objective symptoms in this subject.

AEs (all causality) were shown in the table below.

Treatment-emergent Signs and Symptoms (All Causalities)

	CP-526,555				Placebo
	0.25 mg	0.5 mg	1.0 mg	2.0 mg	
Number of adverse events (AEs)	3	0	3	5	0
Number of subjects with AEs	3	0	3	2	0
Number of subjects evaluable for AEs	12	11	12	11	7
Abdominal pain	0	0	0	2	0
Headache	1	0	0	0	0
Pain	0	0	1	0	0
Diarrhea	0	0	1	0	0
Dyspepsia	0	0	0	2	0
Nausea	0	0	0	1	0
Vertigo	0	0	1	0	0
Rhinitis	1	0	0	0	0
Retinal disorder	1	0	0	0	0

Source:Table 6.1.1, 6.1.2, 6.1.3

Clinical laboratory evaluation: Without regard to baseline, Eosinophils increased (ID: 1001 112) was observed in 0.5 mg treatment group, the others were observed in one subject (ID: 1001 109). There was no adverse event out of these abnormalities.

Clinical laboratory evaluation

Item of abnormal changes	CP-526,555				Placebo
	0.25 mg	0.5 mg	1.0 mg	2.0 mg	
# of subjects evaluable for	12	11	12	11	7
Eosinophils	1	2	0	1	0
Urine occult blood	1	1	0	1	0

Source:Table 7.3

Vital sign: No abnormal changes in vital signs (body temperature, blood pressure, pulse rate) were reported.

Electrocardiogram: There was no clinically significant change in ECG. For both Bazett and Fridericia post-dose QTc intervals, there were no subjects with QTc intervals ≥450 msec or QTc increase from baseline ≥60 msec. In addition, there were no subjects with QT intervals ≥500 msec or QRS interval changes ≥25%.

Summary of Post-Dose ECG Intervals Exceeding Categories for Clinical Significance

ECG Interval	Category	CP-526,555				Placebo
		0.25mg	0.5mg	1.0mg	2.0mg	
Number of Subjects		12	11	12	11	7
Bazett QTc	30 to 60msec increase	0	1	4	0	0
	≥60msec increase	0	0	0	0	0
Fridericia QTc	30 to 60msec increase	0	0	0	0	0
	≥60msec increase	0	0	0	0	0
PR	≥25% increase	1	0	0	0	0

Source:Table 9.3

Pharmacokinetics: The results showed that C_{max}, AUC_{last} and AUC values of CP-526,555, the parameters of plasma pharmacokinetics, increased approximately proportionately with escalating doses. The mean value of T_{max} was about 3 hours at all doses. The mean $t_{1/2}$ ranged from 13.1 to 19.3 hours across all four doses. Total percent dose of CP-526,555 excreted unchanged in the urine after single dose of 0.25, 0.5, 1.0, and 2.0 mg CP-526,555 were 70.3, 63.7, 63.5, and 68.4 %, respectively. Pharmacokinetic parameters of CP-526, 555 are summarized in the table below.

Summary of Pharmacokinetic Parameters of CP-526,555 Following Single Oral Dosing in Japanese Healthy Adult Male Volunteers (Smokers)

Pharmacokinetic parameters		CP-526,555 0.25 mg (n=12)	0.5 mg (n=11)	1.0 mg (n=12)	2.0 mg (n=11)
AUC_{last} (ng.h/mL)	Arithmetic Mean	23.0	46.6	101	220
	Standard Deviation	4.26	5.68	10.6	44.9
	Geometric Mean	22.7	46.2	100	217
AUC (ng.h/mL)	Arithmetic Mean	26.2	50.0	104	226
	Standard Deviation	3.88	5.88	10.8	46.9
	Geometric Mean	25.9	49.7	104	222
C_{max} (ng/mL)	Arithmetic Mean	1.32	2.45	4.97	9.96
	Standard Deviation	0.11	0.24	0.56	1.25
	Geometric Mean	1.32	2.44	4.94	9.89
T_{max} (h)	Arithmetic Mean	2.75	2.36	2.75	3.09
	Standard Deviation	1.06	0.92	0.75	1.38
$t_{1/2}$ (h)	Arithmetic Mean	13.1	14.5	18.4	19.3
	Standard Deviation	2.10	2.40	3.15	2.17

Sourse:Table 5.1

Pharmacodynamics: Nausea was seen in only one subject (ID 1001 108) in the 2.0 mg regimen. The onset time of the first episode of nausea was 26 min after administration of CP-526,555 and the duration time of it was 190 min. This episode of nausea was a 2 (mild) on a scale of one to ten in severity (1; extremely mild, 10; serious), with associated symptoms of heartburn and dyspesia and the intensity of these symptoms was 2. The NEQ score (mean) of 2.0 mg regimen was 0.3 and the GI score (mean) was 0.8.

This subject commented on impact of nausea on functioning as follows; felt mild distress which caused discomfort but did not interfere with normal daily life; no impact on eating/drinking; experienced in the morning (the time of gets up-12:00)

As this subject did not have an episode of vomiting there were no responses to the summary of impact of vomiting on functioning questionnaire.

The mean value of the number of cigarette smoked per day from admission until discharge each period was shown below. It should be noted that the time for smoking was limited in Day 3 because subjects were released from unit on Day 3.

Number of cigarette smoked per day [Mean value (SD)]

Day	CP-526,555				Placebo
	0.25 mg	0.5 mg	1.0 mg	2.0 mg	
Number of evaluation	12	11	12	11	7
Pre-dose day (admission)	15.1(5.2)	16.9(8.2)	13.8(8.1)	13.6(6.3)	14.6(5.5)
Day 1 (day of drug administration)	21.4(8.5)	23.1(10.9)	18.6(9.3)	16.0(5.5)	23.0(11.8)
Day 2	21.4(8.9)	24.3(10.8)	22.3(9.7)	18.7(7.7)	22.3(11.3)
Day 3* (discharge)	4.7(2.6)	3.5(3.6)	5.3(3.0)	3.5(2.3)	6.3(4.3)

Source:Table 5.6

* Time for smoking was limited in Day 3 because subjects were released from unit on Day 3

CONCLUSIONS:

The single oral doses of CP-526,555 were administered in Japanese healthy adult male smokers at the dose of 0.25 to 2.0 mg, safety and pharmacokinetic following single dosing were evaluated.

There were no issues on safety and tolerability raised in this study.

C_{max}, AUC_{last} and AUC values of CP-526,555, increased approximately proportionately with escalating (0.25 to 2 mg) doses. There was no obvious difference in percentage of urinary excretion amount among treatment groups.

CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A3051029

Protocol Title: Phase 1, Randomized, Sponsor-Open, Investigator- and Subject-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Single-Dose Pharmacokinetics, Safety, and Tolerability of Varenicline in Healthy Adolescent Smokers

Investigator: C J

Study Center(s): 1 center in the United States

Publications Based on the Study: None

Study Initiation and Completion Dates: 16 September 2004 to 05 December 2004

Phase of Development: Phase 1

Study Objectives:

- Primary: To evaluate the single-dose pharmacokinetics of varenicline at 0.5 and 1 mg in adolescent smoking subjects
- Secondary: To evaluate the safety and tolerability of varenicline in adolescent smoking subjects.

METHODS

Study Design: This was a sponsor-open, investigator- and subject-blind, randomized, parallel-group, placebo-controlled study of male and female adolescent smokers. There were 3 parallel treatment groups. Thirty subjects were to be randomized to receive either a single oral dose of 0.5 mg varenicline (n = 12), a single oral dose of 1 mg varenicline (n = 12), or a single oral dose of matching placebo (n = 6). Subject enrollment within both varenicline and placebo dose groups was stratified by age groups: 12 - 13, 14 - 15, and 16 - 17 year-olds.

Diagnosis and Main Criteria for Inclusion: Healthy male and female adolescent smokers between the ages of 12 and 17 years were enrolled. A total body weight of ≥40 kg (88 lb) and a Body Mass Index (BMI) ≤30 kg/m^2 were required.

Study Treatment: Table S1 below summarizes study treatments provided by Pfizer Global Research and Development (PGRD).

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Lot and Formulation Identification (FID) Numbers

Study Drug	Dosage Form	Lot Number	Formulation Identification Number
CP-526,555-18 (varenicline tartrate)	0.5 mg tablet	920098-3000052-G4	G02610AA
Placebo	0 mg tablet	ED-G-310-902	G02613AA

Subjects were to receive trial medication on the morning of Day 1 within 5 minutes of completing a standardized (non–high-fat) meal. Investigator site personnel were to administer trial medication with 240 mL ambient temperature water. Subjects were to swallow the trial medication whole, without chewing the medication prior to swallowing.

Pharmacokinetic Evaluations: Blood samples to provide plasma for PK analysis of varenicline were collected into appropriately labeled tubes containing sodium heparin at the following nominal times: 0 hour (just prior to dosing), and 1, 2, 3, 4, 8, 12, 24, and 48 hours after morning dosing on Day 1.

Beginning on Day 1, a complete 48-hour urine collection was obtained for analysis of varenicline. Urine was collected over the 3 intervals of 0 - 12,12 – 24, and 24 - 48 hours after drug administration.

Plasma and urine samples were analyzed for varenicline concentrations using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay.

Individual plasma concentration-time data for varenicline were analyzed by standard noncompartmental approaches, and the following pharmacokinetic parameters were estimated: maximum observed concentration (Cmax), the time to Cmax (tmax), the area under the plasma concentration-time curve (AUC) from time 0 to the last time (tlast) with a quantifiable concentration (AUC[0-tlast]), AUC from time 0 to infinity (AUC[0-inf]) and the apparent terminal half-life (t1/2). Renal clearance (CLr) and the percent amount of varenicline excreted unchanged in the urine (%Ae) relative to dose, were derived using the 48-hour urinary excretion data.

No pharmacodynamic evaluations were done in this study.

Safety Evaluations: Safety evaluations included reports of adverse events, vital signs (heart rate [HR], blood pressure [BP]), 12-lead electrocardiograms (ECGs), physical examinations, and safety laboratory tests.

Statistical Methods: BP, HR, and safety laboratory data were reviewed on an ongoing basis during the trial to evaluate the safety of subjects. Treatment-emergent AEs were summarized. QT interval measurements had descriptive statistics (n, mean, standard deviation, minimum, and maximum) calculated at each time point for the change from baseline. The descriptive statistics were calculated for each dose level and the pooled placebo subjects. QTc was descriptively summarized using the borderline and prolonged categories defined in the protocol.

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RESULTS

Subject Disposition and Demography: Twenty-seven subjects were randomized. Ten subjects were treated in the 0.5 mg varenicline group, 12 were treated in the 1 mg varenicline group, and 5 received placebo. There were no discontinuations. All treated subjects were evaluated for safety (AE and laboratory) and PK parameters. Demographic characteristics are summarized in Table S2 below.

Table S2. Demographic Characteristics

		0.5 mg Varenicline	1 mg Varenicline	Placebo
Number of Subjects/ (Male, Female)		10 (6 males, 4 females)	12 (7 males, 5 females)	5 (1 male, 4 females)
Age (years)	12 - 13	2	4	1
	14 - 15	4	4	2
	16 - 17	4	4	2
	Mean	15.1	14.3	15.0
	SD	1.7	1.7	1.6
	Range	12 - 17	12 - 17	13 - 17
Race	White	1	2	0
	Black	9	10	5
Weight (kg)	Mean	64.4	66.3	72.2
	SD	12.4	13.8	4.5
	Range	46.0 - 78.0	45.0 - 95.0	68.0 - 79.0
Body Mass Index (kg/m^2)	Mean	22.7	23.4	26.7
	SD	4.1	3.6	2.9
	Range	17.3 - 29.4	18.4 - 29.8	23.5 - 29.6

Pharmacokinetic Results: Single-dose pharmacokinetics of varenicline were approximately dose proportional between the 0.5 mg and 1 mg doses in adolescent smokers. Varenicline systemic exposure, as assessed by AUC(0-inf), and renal elimination of varenicline were comparable to those of an adult population.

Varenicline exhibited approximately dose-proportional pharmacokinetics over the 0.5 mg to 1 mg dosing range in adolescent smokers. Mean plasma peak concentrations occurred typically within 3 - 4 hours after single oral administration. Varenicline concentrations declined mono-exponentially in a parallel fashion and were quantifiable in plasma up to 48 hours after dosing.

Arithmetic means (SD) for Cmax, AUC, t1/2, and CLr, and median (range) for tmax values are given in Table S3 below.

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Table S3. Mean (SD) Varenicline Pharmacokinetic Parameters Following Single Oral Doses of 0.5 mg and 1 mg of Varenicline to Healthy Adolescent Smokers

Pharmacokinetic Parameters (units)	Varenicline 0.5 mg (N=10)	Varenicline 1 mg (N=12)
AUC(0-inf) (ng•h/mL)	50.6 (13.3)	106 (24.3)
Cmax (ng/mL)	3.01 (0.460)	6.38 (1.50)
tmax[a](h)	3.00 (2.00 - 4.00)	4.00 (2.00 - 4.00)
t1/2 (h)	10.9 (3.11)	10.9 (1.93)
CLr (mL/min)	116 (42.8)	103 (39.8)

[a]Median (range)

High amounts of varenicline were recovered in the urine of healthy adolescent subjects over the first 48 hours. On average, 61 ± 15% and 59 ± 19% of the 0.5 mg and 1 mg doses, respectively, were excreted unchanged via the kidney.

Safety Results: There were no deaths, SAEs, or withdrawals due to AEs reported for this study. Dizziness was reported by 1 subject in the 0.5 mg varenicline group and by 2 subjects in the 1 mg varenicline group. Abdominal pain was reported by 1 subject in the placebo group. All AEs were classified as mild.

There were no laboratory tests that exceeded the criteria of potential clinical concern defined in the protocol. There were no notable trends noted in mean change from baseline for supine HR or BP values. Some subjects had values meeting protocol-specified criteria of potential concern for changes in systolic or diastolic BP; however, these changes were asymptomatic and were not deemed clinically significant by the investigator.

There were no notable trends noted in mean change from baseline for ECG values. There were no PR or QRS values that met criteria for potential clinical concern defined in the protocol. One subject had a QT value of 504 msec at 24 hours postdose, with a heart rate of 43 bpm, which was asymptomatic and was not deemed clinically significant by the investigator. Associated QTcF and QTcB values were 451 msec and 427 msec, respectively.

Conclusions:

- Varenicline systemic exposure, as assessed by AUC(0-inf), and renal clearance of varenicline were comparable to those of an adult population. The results also suggest that the single-dose pharmacokinetics of varenicline were approximately dose proportional between the 0.5 mg and 1 mg doses in adolescent smokers.
- Single doses of 0.5 mg and 1 mg varenicline were safe and well tolerated when administered to an adolescent population (12 – 17 years of age).

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REPORT SYNOPSIS

Compound/Protocol Number: CP-526,555/A3051015 **Phase:** 1

Title: Phase 1, Double-Blind, Randomized, Multiple Dose, Crossover Study to Evaluate the Nausea Profile and Pharmacokinetics of CP-526,555 Administered in the Morning and at Bedtime

Investigator: [redacted]

Study Publication: None at time of report issue

Study Dates: 22 October 2001 to 28 January 2002

Study Objectives: There were two objectives:

1) To evaluate the nausea profile of morning (AM) and bedtime (QHS) multiple doses of CP-526,555 via a comparison of the nausea incidence rate.
2) To compare the relative bioavailability of morning (AM) and bedtime (QHS) multiple doses of CP-526,555 at steady state.

Study Design: This was a double-blind, randomized, multiple dose, crossover study of CP-526,555, administered as 2 x 1 mg immediate release (IR) tablets. Subjects received each of the following treatment regimens according to a computer-generated randomization (A→B or B→A): A = CP-526,555 2 mg daily in the morning and placebo daily at bedtime, for 7 days; and B = CP-526,555 2 mg daily at bedtime and placebo daily in the morning, for 7 days. All study medication was administered to subjects with breakfast and an evening snack. There was a washout period of at least 7 days between each dosing regimen and a follow up safety visit 7 to 10 days after the last dose of study medication.

Study Population: The study population was to consist of enough subjects to ensure that 40 healthy adult smokers (approximately 50% male, 50% female) between 18-55 years inclusive completed the study. Subjects were to weigh no less than 110 pounds (50 kg), and be within 25% of the recommended weight range for age, gender, height, and frame as established in the "1999 Metropolitan Life Insurance Height and Weight Tables." Subjects were required to be in good health as determined by a detailed medical history, a full physical examination including vital signs, a 12-lead resting electrocardiogram (ECG), and clinical laboratory evaluations. In addition, smokers were to be subjects smoking an average of at least 10 cigarettes per day, with no period of abstinence greater than 3 months in the past year.

Treatments:

The Pharmacy Operations department at Pfizer Global Research and Development (PGRD) supplied study medication as follows:

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Table S-A. Study Medication

Study Drugs	Appearance	Formulation	Dose Unit	Duration	Lot Number	FID Number
CP-526,555 (IR)	Off-white, round	Tablets	2 X 1 mg	Once daily X 7 days / regimen	ED-G-164-501	G02222AA
Placebo (IR match)	Off-white, round	Tablets	NA	Once daily X 7 days / regimen	ED-G-107-301	G02329AA

Study Endpoints for Evaluation:

Safety: All subjects were evaluated for safety, which was assessed by clinical observations, querying for adverse events (AEs), physical examination, vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

Nausea Profiles: The severity of nausea and its associated symptoms were evaluated by the Self-Reported Nausea Profile, a visual analog scale used to evaluate the onset, intensity, and duration of each nausea episode that occurred while the subject was in the Clinical Research Unit (CRU). In addition, the Impact of Nausea on Functioning Questionnaire was collected just prior to the bedtime snack and evening dosing on Days 1 through 6, regardless of whether or not subjects had experienced nausea that day.

Pharmacokinetics: On Day 7 of each study period, blood was collected at specified intervals from 0 (just prior to morning dosing) to 38 hours after morning dosing. A validated [redacted] assay was used to determine CP-526,555 plasma concentration levels. The primary pharmacokinetic (PK) study endpoints were AUC_{0-24} (area under the plasma concentration time-curve from time 0 to 24 hours after study drug administration), Cmax (maximum observed plasma concentration), and Tmax (time to maximum observed plasma concentration) of CP-526,555 following administration of a 2 mg dose either in the morning or at bedtime.

Statistical Methods:

Sample Size: A sample size of 40 pairs (40 individual subjects with 2 periods of nausea assessment) would have 80% power to detect a difference in proportions of subjects experiencing nausea of 0.250 when the proportion of discordant pairs was expected to be 0.360.

Safety and Nausea Profiles: One of the primary questions of interest was whether there was a significant difference in nausea incidence rates between the AM and QHS dosing of CP-525, 555. McNemar's test for matched pairs and SAS PROC FREQ were used to test for differences in nausea rates.

Nausea incidence rates, intensity of the first episode of nausea, and number of episodes were obtained from the Self-Reported Nausea Profile Questionnaire data

and were summarized by treatment regimen using descriptive statistics. For subjects who experienced nausea at least once, the onset (time elapsed from the first dose time to start of nausea episode), duration, intensity, and AUC of intensity were summarized for the first nausea episode of each subject within a treatment. For all nausea episodes, the total duration, total AUC of intensity, and the maximum intensity of all nausea episodes were summarized by treatment group using descriptive statistics.

Demographics and safety data were summarized through data tabulations and descriptive statistics. The results of the exhaled CO and time of each cigarette were tabulated. No formal analyses were performed.

Pharmacokinetic: Natural log-transformed CP-526,555 AUC0-24 and Cmax and untransformed Tmax were analyzed using a mixed effects model containing fixed effects for sequence, period, and treatment, and random effects for subjects (within sequence). Compound symmetry was assumed, and Restricted Maximum Likelihood Estimates (REML) were used. Estimates of the adjusted mean differences between treatments, and 90% confidence intervals (CIs) around the differences were calculated. For AUC0-24 and Cmax, the anti-log (exponent) of the differences and confidence limits were taken to estimate the ratios between treatments and the CIs of the ratios. For Tmax, the confidence intervals on the mean differences were calculated. Geometric means were provided for AUC0-24 and Cmax. Arithmetic means were provided for Tmax. The comparison was 2 mg morning dosing versus 2 mg bedtime dosing. Morning dosing was the reference. SAS procedure PROC MIXED was used for these analyses.

Results:

Subject Disposition: The study population consisted of 44 healthy adult smokers (21 males, 23 females), between 18-49 years inclusive. Of the 44 enrolled subjects, 5 (1 male and 4 females) chose not to continue due to personal reasons (not treatment-related) after the first regimen of study drug, and 1 female subject discontinued after the second dosing regimen due to AEs. Despite the discontinuations, AEs and laboratory safety data were collected for 43 subjects in the AM dosing regimen and 40 subjects in the QHS dosing regimen. Thirty-eight (38) subjects were evaluable for PK in each treatment group. Summary demographic information is displayed below.

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Table S-B. Demographic Characteristics of Study Population

		All Subjects		
		Male	Female	Total
Number of Subjects		21	23	44
Age	Mean	29	25	27
	SD	11	8	10
	Range	18-49	19-44	18-49
Race	White	21	21	42
	Asian	0	1	1
	Hispanic	0	1	1
Weight	Mean	77.5	66.7	71.8
	SD	12.4	7.9	11.6
	Range	57.0-104.0	54.0-83.0	54.0-104.0
Height	Mean	174.1	163.9	168.8
	SD	6.9	4.4	7.6
	Range	157.0-188.0	157.0-175.0	157.0-188.0

Safety:

There were no deaths, serious adverse events, or adverse events of severe intensity in this study. There were no safety concerns based on analysis of clinical laboratory data, physical exams, ECGs, or vital signs. There was one withdrawal due to adverse events. Subject #31 was a 28 year old white female who discontinued treatment after reporting recurring episodes of nausea and vomiting (both of mild intensity) on Days 4-7 following CP-526,555 2 mg QHS treatment (Period 1) and on Days 3-8 following CP-526,555 2 mg AM treatment (Period 2).

Most of the adverse events reported were treatment-related and of mild intensity. Thirty (30) of the 43 subjects receiving CP-526,555 2 mg AM dose reported a total of 70 adverse events. Twenty-five (25) of the 40 subjects receiving CP-526,555 2 mg QHS dose reported a total of 45 AEs. The most frequent AEs reported were related to the gastrointestinal system, particularly nausea and vomiting.

There was no evidence of significant differences in nausea incidence rates between the two dosing groups. Subjects in the AM dosing group reported a nausea incidence rate of 53.8% from spontaneous AEs and 47.4% from the nausea self report profiles. Subjects in the QHS dosing group reported a nausea incidence rate of 46.2% from spontaneous AEs and 36.8% from the nausea self report profiles. The reported p-value for the two-sided McNemar's test was 0.366 based on all reported nausea events from spontaneous AE report and 0.248 for nausea reported in nausea profile filled by subjects while they were in the CRU.

Pharmacokinetics: No differences in oral steady-state pharmacokinetics were observed when CP-526,555 was administered daily in the morning compared to bedtime in the fed state.

Mean relative oral bioavailability values, based on AUC0-24, were ≈100% for the bedtime dosing relative to the morning dosing. For AUC0-24 and Cmax, the bounds of the 90% CI were completely contained within the established bioequivalence limits (80, 125%).

Table S-C. Summary of Statistical Analysis on Day 7 Following Administration of a 2 mg Single Daily Oral Tablet Doses for 7 Days to Healthy Smokers

Pharmacokinetic Parameter	Bedtime (Test)	Morning (Reference)	Ratio (%)*	90% Confidence Interval
AUC0-24 (ng·h/mL)	183.7	185.8	99	(95%, 103%)
Cmax (ng/mL)	12.0	12.3	98	(94%, 102%)

* Ratio of adjusted geometric means (test/reference)

The within-subject variability (coefficient of variation within subjects - CV%) was 10%, 10%, and 21% for AUC0-24, Cmax, and Tmax, respectively.

CONCLUSIONS:

The observed nausea incidence rates for the AM group (53.8%, spontaneous AEs; 47.4% self report profiles) were not statistically significantly different than those for the QHS dosing group (46.2%, AEs; 36.8%, self report profiles).

There were no safety concerns in this study.

There was no effect of time-of-day dosing on the steady-state pharmacokinetics of 2 mg CP-526,555 when administered daily in the morning compared with bedtime dosing.

Results suggest that CP-526,555 may be given without regard to time of day.

CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A3051033

Protocol Title: Phase 1, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Study to Evaluate the Effect of Varenicline on the Safety and Tolerability of Transdermal Nicotine Replacement Therapy in Healthy Smoking Subjects

Investigator: [ ]

Study Center: 1 center, United States

Publications Based on the Study: None

Study Initiation and Completion Dates: 30 October 2003 to 15 January 2004

Phase of Development: Phase 1

Study Objectives:

1. To estimate the effect on cardiovascular measures, including blood pressure and heart rate, of nicotine replacement therapy (nicotine patch) administered concurrently with varenicline in healthy adult smokers

2. To evaluate the general safety and tolerability of nicotine replacement therapy (nicotine patch) administered concurrently with varenicline in health adult smokers

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, crossover design study. All subjects were to have a nicotine transdermal patch (Nicoderm® 21 mg/24 hour) applied daily for 14 days during each study period. Subjects were randomly assigned to receive 1 of the regimens depicted in Table S1 below (beginning on Day 3) during each period.

Table S1. Study Regimens

Regimen	Study Medication(s)
A	Varenicline 0.5 mg QD x 3 days, 0.5 mg BID x 4 days, 1 mg BID x 5 days
B	Placebo: 1 tablet QD x 3 days, 1 tablet BID x 4 days, 2 tablets BID x 5 days

Diagnosis and Main Criteria for Inclusion: Healthy male and/or female smokers between the ages of 18 and 55 years, inclusive, were enrolled. Subjects were current smokers and were required to have smoked an average of at least 10 cigarettes per day during the past year, with no period of abstinence greater than 3 months continuous in the past year. Body Mass Index (BMI) between 18 to 30 kg/m^2, inclusive, and a total body weight >50 kg (110 lb) were required.

Study Treatment: Pfizer Global Research and Development (PGRD) supplied varenicline and matching placebo, as described in Table S2 below.

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Table S2. Lot and Formulation Identification (FID) Numbers

Study Drug	Dosage Form	Lot Number	FID Number
Varenicline (CP-526,555-18)	Tablet	03-003794	G02610AA
Placebo	Tablet	03-001746	G02613AA

The study center supplied Nicoderm® CQ (lot numbers 3E2702 and 3F1302).

After completion of breakfast on Days 1 – 2 (both study periods), subjects had a nicotine transdermal patch applied at approximately 0800 hours. After completion of breakfast beginning on Day 3 (both study periods), subjects had a nicotine transdermal patch applied and received varenicline or placebo with 240 mL of ambient temperature water at approximately 0800 hours.

Table S3 below shows the titration schedule for varenicline and matching placebo.

Table S3. Varenicline/Placebo Dosing Schedule

Study Day	Varenicline Treatment Period	Placebo Treatment Period
	Varenicline 0.5 mg Tablet	Placebo Tablet
Days 3-5	1 tablet in the morning	1 tablet in the morning
Days 6-9	1 tablet in the morning 1 tablet in the evening	1 tablet in the morning 1 tablet in the evening
Days 10-14	2 tablets in the morning 2 tablets in the evening	2 tablets in the morning 2 tablets in the evening

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: During each study period, blood samples for plasma varenicline concentrations were collected just prior to morning dosing on Days 12, 13, and 14. Blood samples for plasma nicotine and cotinine concentrations were also collected just prior to morning dosing on Days 12 and 13. Samples for nicotine and cotinine were also collected on Day 14 up to 24 hours after patch application.

Plasma samples were analyzed for varenicline concentrations using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay. The dynamic range of the assay was 0.100 - 50.0 ng/mL. The lower limit of quantitation (LLOQ) was 0.100 ng/mL. Plasma samples were analyzed for plasma nicotine and cotinine concentrations using validated LC/MS/MS methods. The LLOQs for these assays were 1.00 ng/mL and 10.0 ng/mL, respectively.

Individual plasma concentration-time data for nicotine and cotinine on Day 14 were analyzed by standard noncompartmental methods. Maximum observed plasma concentrations (Cmax) of nicotine and cotinine were estimated directly from the experimental data. Tmax was defined as the time of the first occurrence of Cmax. Areas under the plasma nicotine and cotinine concentration-time curve from time zero to the end of the dosing interval on Day 14 [AUC(0-tau), where tau is the dosing interval equal to 24 hours, were determined using the linear-log trapezoidal rule.

The PD analysis focused on systolic BP (SBP). On Day 14 of each period, 9 times during the 24 hours after dosing (1, 2, 3, 4, 5, 6, 8, 10 and 24 hours after dosing), triplicate measures of SBP were made.

In addition, the time of each cigarette smoked, while the subject was in the CRU, was to be recorded. This information was collected with the intent that it could aid in the interpretation of the nicotine/cotinine concentration data.

There were no PK/PD analyses planned or performed for this study.

Safety Evaluations: All subjects were evaluated for safety by clinical observations and querying for adverse events (AEs), conducting physical examinations and obtaining vital sign measurements, electrocardiograms (ECGs), and clinical laboratory tests.

Statistical Methods: Raw SBP data were analyzed using a mixed effects model and Restricted Maximum Likelihood Estimates (REML). Compound symmetry was assumed.

The average of the 3 SBP values in each triplicate set were calculated to obtain an average value for each of the 9 times triplicate sets were measured. The mean of these 9 values was denoted as SBP14. The maximum of these 9 values was denoted as maxSBP14.

For each study period each evaluable subject had a value of SBP14 and of max SBP14 on Day 14. Each of the endpoints, SBP14 and maxSBP14, were analyzed with a mixed effects model, with sequence, treatment, and period effects considered fixed and subjects (within sequence) considered random. Least squares means were calculated for nicotine + placebo (reference; REF) and nicotine + varenicline (TEST), and 90% confidence limits for the difference, TEST – REF, were calculated.

BP, HR, ECG, and safety laboratory data were reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Safety data were summarized descriptively.

RESULTS

Subject Disposition and Demography: All 24 subjects who received study drug were evaluated for safety (AEs and laboratory data). For the pharmacodynamic (SBP) analysis and for the PK evaluation, 12 subjects who received nicotine + varenicline were analyzed, and 17 subjects who received nicotine + placebo were analyzed. Subject disposition is further summarized in Table S4 below.

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Table S4. Subject Disposition

Number of Subjects		Nicotine Alone[a]	Nicotine + Varenicline	Nicotine + Placebo
Total randomized	24			
Treated		24	22	17
Completed		24	12	15
Discontinued		0	10	2
due to:				
Adverse event		0	8	1
Other		0	1[b]	1[c]
Subject defaulted		0	1[d]	0

N/A = not applicable.
[a]Pooled data from days of each study period when nicotine patch was given alone (Days 1 – 2) before varenicline or placebo was initiated.
[b]Subject taken into police custody.
[c]Subject had protocol deviation: positive drug screen at check-in for Period 2.
[d]Subject no longer willing to participate in study.

Fifteen male subjects and 9 female subjects were randomized. All subjects were white. Table S5 below summarizes demographic information for these subjects.

Table S5. Demographic Characteristics

Age (years)	Mean	32.9
	SD	9.1
	Range	19-50
Weight (kg)	Mean	72.1
	SD	10.0
	Range	51.8 - 97.6
Body Mass Index (kg/m^2)	Mean	24.3
	SD	2.6
	Range	20.0-29.2
Height (cm)	Mean	172.2
	SD	8.2
	Range	160.0 - 188.0

Pharmacokinetic and Pharmacodynamic Results:

Pharmacokinetic Results: Coadministration of varenicline 1 mg BID with transdermal nicotine (Nicoderm®CQ 21 mg/24 hours) resulted in no clinically relevant effect on the steady-state pharmacokinetics of nicotine or its major metabolite, cotinine, in healthy adult smokers.

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Relevant PK parameters and associated summary statistics of nicotine administered concomitantly with multiple doses of varenicline were estimated. Arithmetic means (SD) for Cmax, AUC(0-tau), and median (range) for tmax values are given in Table S6 below.

Table S6. Mean (SD) Pharmacokinetic Parameters of Nicotine Following Multiple Oral Doses of Nicoderm®CQ 21 mg/24 hours Alone or with Varenicline 1 mg BID for 14 Days in Healthy Adult Smokers[a]

Pharmacokinetic Parameters (units)	Nicotine + Placebo (N = 17)	Nicotine + Varenicline N = 12)
AUC(0-tau) (ng•h/mL)	941 (614)	831 (616)
Cmax (ng/mL)	210 (329)	177 (291)
tmax[b] (h)	1.00 (1.00-8.00)	2.00 (1.00-4.00)

AUC(0-tau) = AUC(0-24)
[a]14 days in table title refers to length of study period. Varenicline (or placebo) was received only for 12 days (Days 3 –14).
[b]Median (range)

Relevant PK parameters and associated summary statistics of cotinine administered concomitantly with multiple doses of varenicline were estimated. Arithmetic means (SD) for Cmax, AUC(0-tau), and median (range) for tmax values are given in Table S7 below.

Table S7. Mean (SD) Pharmacokinetic Parameters of Cotinine Following Multiple Oral Doses of Nicoderm® CQ 21 mg/24 hours Alone or with Varenicline 1 mg BID for 14 Days in Healthy Adult Smokers[a]

Pharmacokinetic Parameters (units)	Nicotine + Placebo (N = 17)	Nicotine + Varenicline (N = 12)
AUC(0-tau) (ng•h/mL)	10800 (2580)	10300 (2940)
Cmax (ng/mL)	485 (111)	463 (120)
tmax[b] (h)	4.00 (3.00-10.00)	4.00 (3.00-24.00)

AUC(0-tau) = AUC(0-24)
[a]14 days in table title refers to length of study period. Varenicline (or placebo) was received only for 12 days (Days 3 –14).
[b]Median (range)

There was no apparent difference in the mean ratio of the cotinine-to-nicotine AUC values for the Nicoderm® system at steady state, thus suggesting that metabolism of nicotine was not altered in the presence of varenicline.

Visual inspection of mean and individual plasma trough concentration-time profiles showed that all subjects attained steady-state conditions for varenicline by Day 12.

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Pharmacodynamic Results: Average SBP as measured on Day 14 (SBP14) was 111.6 mm Hg and 114.1 mm Hg, for nicotine + varenicline and nicotine + placebo, respectively. The estimated mean difference between varenicline and placebo (in mm Hg) for SBP14 was–2.6 [90% CI : (-4.3, -0.8)]. Maximum SBP as measured on Day 14 (maxSBP14) was 119.0 mm Hg and 121.8 mm Hg, for nicotine + varenicline and nicotine + placebo, respectively. The estimated mean difference (in mm Hg) for maxSBP14, between varenicline and placebo was found to be –2.9 [90% CI:(-6.4, 0.7)].

For the analysis of SBP14 for as measured on Day 14 of this study, the 90% CI did not include 0. Therefore a marginal but statistically significant decrease in SBP noted for nicotine + varenicline. The data are statistically compatible with a true difference between treatments as large as -4.3 mm Hg or as small as -0.8 mm Hg.

There was however, no discernable treatment effect on maxSBP14 (90% CI included 0). The data are statistically compatible with a true difference between treatments as large as -6.4 mm Hg or a true difference as large as 0.7 mm Hg.

Safety Results: Fourteen subjects in the nicotine alone regimen experienced 37 AEs. Eighteen subjects in the nicotine + Varenicline regimen experienced 135 AEs. Fifteen subjects in the nicotine + placebo regimen experienced 81 AEs. There were 9 permanent discontinuations due to AEs (8 in nicotine + varenicline regimen, 1 in nicotine + placebo regimen. There were no SAEs associated with this study.

All AEs were mild to moderate in severity. Most AEs were judged by the investigator to be treatment related.

Gastrointestinal and nervous system disorders were the most frequent types of AEs reported. Nausea, headache, fatigue, vomiting, and dizziness were the most frequently occurring AEs in this study. All of these AEs occurred were notably more frequent in the nicotine + varenicline regimen. Dyspepsia was also most frequent in the nicotine + varenicline regimen. Five subjects discontinued from the study due to nausea or vomiting AEs on the nicotine + varenicline regimen. Changes in vital signs and ECGs were isolated events with no indication of a consistent drug effect over the dosing period. A marginal decrease in SBP14 noted for the nicotine + varenicline regimen on statistical analysis is considered clinically unimportant. Laboratory values identified as potentially significant were isolated.

Conclusion(s):

- There was a small but statistically significant decrease of average systolic blood pressure as measured on Day 14 (SBP14) for nicotine + varenicline versus nicotine + placebo. This observed decrease in SBP for the combination is considered to be clinically unimportant. There was no discernable treatment effect on maximum SBP as measured on Day 14 (maxSBP14).
- No effect was noted on diastolic BP or heart rate during nicotine + varenicline treatment.

- Nicotine replacement therapy (21 mg Nicoderm®CQ) and varenicline (up to 1 mg BID) were safe when administered concurrently in healthy adult smokers. Nausea, headache, fatigue, vomiting, dizziness, and dyspepsia were notably more frequent with concurrent administration.
- Steady-state varenicline had no clinically relevant effect on the multiple-dose pharmacokinetics of transdermal nicotine (21 mg-Nicoderm®CQ) in healthy adult smokers.

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CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A3051034

Protocol Title: A Phase 1, Randomized, Investigator and Subject Blind, Two-Way Crossover Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Co-Administration of Varenicline and Zyban® in Healthy Adult Smokers

Investigator: [redacted]

Study Center(s): 1

Publications Based on the Study: None

Study Initiation and Completion Dates: 22 September 2003 to 08 January 2004

Phase of Development: Phase 1

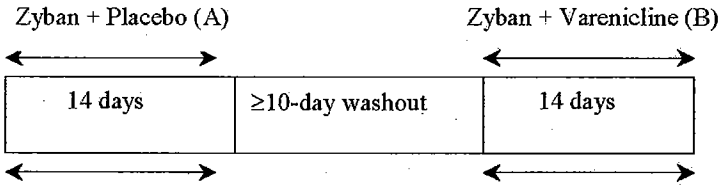
Study Objective(s):

1. To evaluate the safety and tolerability of varenicline and Zyban when administered together in healthy adult smokers
2. To evaluate the effect of chronic administration of varenicline on Zyban pharmacokinetics in healthy adult smokers

Study Design: This was an investigator-blind, subject-blind, sponsor-open, randomized, 2-way crossover, multiple-dose study in healthy adult smokers. The total duration of this study was approximately 7 weeks, including at least a 10-day washout period between dosing periods and a follow-up visit 7 – 10 days after Period 2. Subjects were to be randomized to receive 1 of the 2 treatment sequences shown in Figure S1 below.

Figure S1. Treatment Sequences

Sequence 1



Sequence 2

Zyban + Varenicline (B) Zyban + Placebo (A)

Subjects were to stay in the Clinical Research Unit (CRU) for an approximate total of 30 days (two 15-day confinements separated by at least 10 days).

CLINICAL STUDY REPORT SYNOPSIS

Number of Subjects: At least 42 healthy adult smokers were planned for enrollment. Table S1 below summarizes subject disposition and subjects evaluated/analyzed.

Table S1. Subject Disposition

Number of Subjects		Zyban + Varenicline	Zyban + Placebo
Total randomized	46		
Treated		41	41
Completed		33	34
Discontinued		8	7
due to:			
Adverse event		6	6
Other		1[a]	1[c]
Subject defaulted		1[b]	0
Evaluated for safety (adverse events/ laboratory data)		41	41
Statistical Analysis of Pharmacokinetic Parameters [AUC(0-24) and Cmax]		31	31

[a]Subject withdrew consent.
[b]Subject did not return for Period 2.
[c]Subject failed drug screen prior to Period 2.

Diagnosis and Main Criteria for Inclusion: Subjects were to be healthy male and/or female smokers between the ages of 18 and 55 years, inclusive. Body Mass Index (BMI) between 18 to 30 kg/m^2, inclusive, and a total body weight >50 kg were required.

Study Treatment: The identity of study treatments supplied by Pfizer Global Research and Development (PGRD) is shown in Table S2 below.

Table S2. Lot and Formulation Identification (FID) Numbers

Study Drug	Dosage Form	Lot Number	FID Number
CP-526555-18	0.5 mg tablets	920098-3000052-G3	G02610AA
Placebo	tablets	ED-G-310-902	G02613AA

The 1.0 mg varenicline or placebo doses were to be achieved through administering 2 x 0.5 mg varenicline or matching placebo tablets. Zyban (150 mg tablets; lot number 3ZP0625) was purchased by the CRU. Subjects were to be dosed/titrated as shown in Table S3 below.

CLINICAL STUDY REPORT SYNOPSIS

Table S3. Dose Titration

Regimen	Dose Titration Scheme
A	**Zyban:** 150 mg tablet QD Days 1 - 3, followed by 150 mg BID Days 4 - 14
	Placebo: 1 tablet QD Days 1 - 3, followed by 1 tablet BID Days 4 - 7, followed by 2 tablets BID Days 8 - 14
B	**Zyban:** 150 mg tablet QD Days 1 - 3, followed by 150 mg BID Days 4 - 14
	Varenicline: 0.5 mg tablet QD Days 1 - 3, followed by 0.5 mg BID for Days 4 - 7, followed by 1.0 mg BID (2 x 0.5 mg tablets) Days 8 - 14

BID = twice daily; QD = once daily.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Blood samples were to be collected prior to morning dosing on Days 12 and 13 of both study periods to assess steady-state attainment. During both study periods, blood samples for varenicline and bupropion pharmacokinetic analysis were to be collected at 0 hour (just prior to morning dosing) on Day 14, and up to 24 hours after morning dosing on Day 14.

Plasma samples were analyzed for bupropion (Zyban), Zyban's major metabolite (hydroxybupropion), and varenicline concentrations using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay. The dynamic range of the assay for bupropion was 1.00 - 200 ng/mL; the dynamic range of the assay for hydroxybupropion was 5.00 - 1000 ng/mL. The dynamic range of the assay for varenicline was 0.100 – 50.0 ng/mL.

Individual plasma concentration-time data for varenicline and Zyban were analyzed by standard noncompartmental approaches. Maximum concentration (Cmax) values for varenicline and Zyban were estimated directly from the experimental data for each dosing interval; tmax was defined as the time of the first occurrence of Cmax over the dosing interval. Cmax and tmax were broken into 2 groups for analysis: AM (following morning dose) and PM (following evening dose). Areas under the plasma Zyban and varenicline concentration-time curves from time zero (0) to the end of each dosing interval on Day 14 [AUC(0-10) and AUC(10-24)] were determined using the linear trapezoidal rule up to Cmax and the log trapezoidal rule for each trapezoid post Cmax within each dosing interval. AUC(0-24) was defined as the sum of AUC(0-10) and AUC(10-24) based on the aforementioned linear-log trapezoidal analysis.

Attainment of steady-state conditions was confirmed by visual inspection of the graphical representations of plasma predose concentrations of Zyban and varenicline measured immediately prior to dosing on Days 12, 13, 14, and 15 (ie, 24 hours after dosing on Day 14).

Pharmacodynamic and pharmacokinetic/pharmacodynamic evaluations were not part of this study.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead electrocardiograms (ECGs), adverse events (AEs), and safety laboratory tests.

CLINICAL STUDY REPORT SYNOPSIS

Statistical Methods: A sample size of 42 subjects (21 subjects per sequence) was selected empirically to evaluate the safety and tolerability of co-administration of varenicline and Zyban in healthy adult smokers. With 21 subjects per sequence, the study had 90% power to detect equivalence in AUC or Cmax for Zyban pharmacokinetics, with an equivalence range of (80%, 125%). The assumed ratio of 100% and assumed within-subject coefficient of variation (CV) of 30% were used for the power computation.

Natural log-transformed Zyban AUC(0-24), Cmax (AM), and Cmax (PM) were analyzed using a mixed effects model containing fixed effects for sequence, period, and treatment and a random effect for subjects (within sequence). The SAS procedure MIXED was used for these analyses, with the assumption of compound symmetry. Restricted Maximum Likelihood Estimates (REML) were used. The least squares means, their standard errors, and covariances were used to obtain estimates of the adjusted mean differences between treatments, and 90% confidence intervals (CIs) around the differences. For log-transformed AUC(0-24), Cmax (AM), and Cmax (PM), the anti-log (exponent) of the differences and confidence limits were used to estimate the ratios of means between treatments and the CIs of the ratios. Geometric means were provided for each parameter. The conclusion was that there was no effect of varenicline on the pharmacokinetics of Zyban if the 90% CIs for the ratios for both AUC and Cmax fell entirely within the (80%, 125%) range

Safety data are presented in tabular and/or graphical format and summarized descriptively. The morphology and the calculated values of all ECG intervals were reported. QTc was descriptively summarized using the categories delineated in the protocol.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: Steady state plasma concentrations of varenicline (1 mg BID) had no effect on the pharmacokinetics of Zyban (150 mg BID) administered as multiple oral doses. The 90% CIs for AUC(0-24) and Cmax were within the equivalence limits of (80%, 125%) for Zyban.

Visual inspection of mean and individual plasma trough concentration-time profiles showed that all subjects attained steady-state conditions for Zyban when co-administered with either 1 mg BID varenicline or placebo by Day 14. In addition, no consistent increase or decreases were observed in varenicline steady-state plasma concentrations, thus indicating that steady state was achieved by Day 12.

A summary of point estimates, mean ratios, and 90% CIs for Zyban in the presence and absence of varenicline, following natural log-transformation and analysis using a mixed effects model, is shown in Table S4 below.

CLINICAL STUDY REPORT SYNOPSIS

Table S4. Summary Results of Statistical Analyses of Zyban Pharmacokinetic Parameters When Co-administered with 1 mg BID Varenicline or Placebo in Healthy Adult Smokers

Pharmacokinetic Parameters (units)	Adjusted Geometric Mean (N = 31)		Ratio (%)[a]	90% Confidence Intervals
	Zyban + Placebo (Reference)	Zyban + Varenicline (Test)		
AUC(0-24) (ng•h/mL)	2006.6	2006.5	99.99	(96.04, 104.10)
Cmax (AM) (ng/mL)	143.0	143.3	100.19	(94.39, 106.35)
Cmax (PM) (ng/mL)	152.5	151.9	99.57	(93.95, 105.52)

[a]Ratio between Mean 1 (test) and Mean 2 (reference)
AM, PM =morning and evening dosing, respectively

Safety Results: There were no deaths or SAEs associated with this study. There were 12 withdrawals due to AEs (6 per treatment group). In the Zyban + placebo regimen, 211 AEs were reported by 35/41 subjects. In the Zyban + varenicline regimen, 245 AEs were reported by 38/41 subjects. The majority of AEs in both treatment regimens were judged by the investigator to be treatment related. All AEs were classified as mild in intensity.

The body systems most frequently affected by AEs were the body as a whole, nervous, and digestive systems. Headache, insomnia, and pruritus were the most frequently reported AEs. The number of headaches was comparable for both regimens. Insomnia and pruritus were experienced by comparable or equal numbers of subjects in each treatment group.

Nausea was noted to be more than twice as frequent for the Zyban + varenicline regimen, compared with the Zyban + placebo regimen. This was an expected outcome, as nausea has been one of the most frequently reported treatment-related adverse events in varenicline-treated subjects to date. All cases of nausea (both regimens) were mild in intensity. While subjects on both regimens exhibited several skin AEs (rash, urticaria, and maculopapular rash), it was noted that the frequency was greater for the Zyban + placebo regimen than for the Zyban + varenicline regimen.

Four subjects receiving the Zyban + varenicline regimen and 3 subjects receiving the Zyban + placebo regimen were discontinued related to skin AEs. Two subjects receiving the Zyban + placebo regimen were discontinued due to elevated SGOT and/or SGPT (recorded in Period 2 admission laboratory values, >168 hours after last dose of Zyban + placebo regimen); no subjects receiving the Zyban + varenicline regimen were discontinued related to elevated SGOT and/or SGPT.

There were no laboratory or vital sign values of significant concern identified in this study. Two male subjects had transient, asymptomatic QTcB/QTcF prolongations ≥450 msec. One subject was assigned Zyban + placebo; the other Zyban + varenicline. A female subject assigned to Zyban + varenicline was discontinued from the study due to mild, asymptomatic second-degree atrioventricular block, which was attributed by the investigator to illness/preexisting condition. There were no other notable ECG values.

Conclusion(s):

- The combined administration of varenicline 1 mg BID with Zyban 150 mg BID was safe and tolerated when administered in healthy adult smokers.
- Steady-state administration of varenicline has no clinically relevant effect on the multiple dose pharmacokinetics of Zyban in healthy adult smokers.

CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A3051038

Protocol Title: Phase 1, Randomized, Open-label, Multiple-Dose Study to Evaluate the Effect of Varenicline on the Pharmacokinetics and Safety of Multiple Dose Metformin in Healthy Smoking Subjects

Investigator: [ ]

Study Center: The study was conducted at 1 center in the United States.

Publications Based on the Study: None

Study Initiation and Completion Dates: 27 October 2003 to 06 January 2004

Phase of Development: Phase 1

Study Objective(s):

1. To estimate the effect of steady-state varenicline on the multiple dose pharmacokinetics of metformin
2. To estimate the effect of steady-state metformin on the multiple dose pharmacokinetics of varenicline
3. To evaluate the safety of multiple doses of metformin and varenicline when administered concurrently

METHODS

Study Design: This was a randomized, open-label, 3-period, 6-sequence, crossover design study. During each study period subjects were to receive 1 of 3 treatments (metformin 500 mg twice daily [BID], varenicline 1 mg BID, metformin 500 mg BID + varenicline 1 mg BID). Subjects were to be dosed for 7 days in each study period. Blood samples were collected serially following Day 7 dosing for determination of metformin and varenicline concentrations. Urine was collected at 2 intervals postdose on Day 7 in each study period (0 - 6 and 6 - 10 h) for determination of metformin and varenicline renal clearance. There was a minimum 1-week washout required between study periods.

Diagnosis and Main Criteria for Inclusion: Healthy male and female smokers between the ages of 18 and 55 years, inclusive, were enrolled. Healthy was defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure [BP] and heart rate [HR] measurement, 12-lead electrocardiogram (ECG), and clinical laboratory tests. A Body Mass Index (BMI) between 18 to 30 kg/m^2, inclusive, and a total body weight >50 kg (110 lb) were required. Smokers were to have smoked an average of at least 10 cigarettes per day during the past year, with no period of abstinence greater than 3 months continuous in the past year.

Study Treatment: On Days 1 – 7 of each study period, subjects were to receive assigned study medication from study personnel at approximately 0800 hours following consumption of a

standard breakfast. A second dose of assigned study medication was administered following the evening meal (approximately 10 hours after morning dosing), except on Day 7. For each varenicline dose 2 × 0.5 mg tablets were to be dispensed. For each metformin dose 1 × 500 mg tablet was to be dispensed.

Varenicline was provided by Pfizer Global Research and Development. Details are provided in Table S1 below.

Table S1. Lot and Formulation Identification (FID) Numbers for Varenicline Tartrate

Study Drug	Dosage Form	Lot Number	Formulation Identification Number
CP-526,555-18	0.5 mg Tablet	920098- 3000052- G4	G02610AA

The study center supplied metformin (lot number IM44988).

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: On Days 5 and 6 of each study period, a blood sample was collected prior to morning dosing for determination of varenicline or metformin concentrations. On Day 7, serial blood samples for varenicline or metformin pharmacokinetic (PK) analysis were collected over the dosing interval from 0 hours (just prior to dosing) and at intervals up to 10 hours after the morning dose. Validated assays for varenicline and metformin plasma samples were performed using liquid chromatography/tandem mass spectrometry (LC/MS/MS).

Urine was also collected during each study period, on Day 7 for intervals of 0 to 6 hours and 6 to 10 hours postdose. Validated assays were performed for varenicline (LC/MS/MS) and metformin (LC with ultraviolet detection).

Individual plasma concentration-time data for metformin and varenicline were analyzed by standard noncompartmental approaches. Maximum observed concentration (Cmax) values for metformin and varenicline were estimated directly from the experimental data for each dosing interval. Tmax was defined as the time of the first occurrence of Cmax over the dosing interval. Areas under the plasma metformin and varenicline concentration-time curve from time zero (0) to the end of the dosing interval on Day 7 [AUC(0-tau), where tau equals 10 hours] were determined using the linear trapezoidal rule up to Cmax and the log trapezoidal rule for each trapezoid post Cmax within each dosing interval. Metformin and varenicline renal clearance (CLr) were calculated as the total amount of unchanged drug eliminated in urine (Ae) divided by plasma AUC(0-10) during the 0-10 hour dosing interval.

Attainment of steady-state conditions was confirmed by visual inspection of the graphical representations of plasma predose concentrations of metformin and varenicline measured immediately prior to dosing on Days 5, 6, and 7.

Pharmacodynamic evaluations were not planned for this study.

Safety Evaluations: All subjects were evaluated for safety by clinical observations and querying for adverse events (AEs), conducting physical examinations, and obtaining vital sign measurements, ECGs, and clinical laboratory tests.

Statistical Methods: For the analysis of the primary PK parameters, AUC and Cmax, the least squares means were calculated for the metformin treatment (REF) and the metformin + varenicline treatment (TEST). Also, least squares means were calculated for the varenicline treatment (REF) and the metformin + varenicline treatment (TEST). Then 90% confidence limits for each of the 2 ratios, TEST/REF, were calculated with the intent of estimating the effects of varenicline on metformin PK and metformin on varenicline PK. Two separate mixed-effects models were run, one model using the metformin PK data comparing metformin to the combination treatment and another model using the varenicline PK data comparing varenicline to the combination treatment. The least squares means were obtained from a mixed-effects model with sequence, treatment, and period effects considered fixed and subject (within sequence) considered random. The log-transformed data were analyzed using a mixed-effects model and Restricted Maximum Likelihood Estimates (REML). Compound symmetry was assumed.

For both metformin and varenicline the secondary PK parameter (CLr), was evaluated in a manner similar to the primary analysis. In particular, from least squares means obtained from a mixed-effects model, a 90% CI for each of the 2 ratios was computed to estimate the size of the effect on this clearance parameter. This 90% CI was only used to describe and to interpret results. No hypothesis was tested.

Safety data, including QTc data, were reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects.

RESULTS

Subject Disposition and Demography: Approximately 30 healthy male/female subjects were planned for enrollment, in order to provide 24 completers. Table S2 below summarizes subject disposition.

Table S2. Subject Disposition

Number of Subjects	Metformin 500 mg BID	Varenicline 1 mg BID	Metformin 500 mg BID + Varenicline 1 mg BID
Randomized	30	30	30
Treated	29	29	29
Completed	29	28	28
Discontinued due to:	0	1	1
Adverse event	0	1[a]	0
Defaulted	0	0	1
Evaluated for safety: AEs and laboratory data	29	29	29
Analyzed for PK: AUC(0-tau), Cmax, CLr	29	29	29

[a]Increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
AUC(0-tau) = AUC(0-10)

Subject demographic characteristics are summarized in Table S3 below.

Table S3. Demographic Characteristics

		All Treatments		
		Male	Female	Total
Age (years)	Mean	30.1	31.7	30.6
	SD	10.7	12.2	11.1
	Range	18 - 53	19 - 47	18 - 53
Race	White	17	10	27
	Black	1	0	1
	Other	2	0	2
Weight (kg)	Mean	77.9	72.5	76.1
	SD	12.1	9.8	11.5
	Range	59.5 - 103.1	54.9 - 82.6	54.9 - 103.1
Body Mass Index (kg/m^2)	Mean	24.8	26.4	25.3
	SD	3.3	3.6	3.5
	Range	17.6 - 30.0	20.2 - 29.9	17.6 - 30.0
Height (cm)	Mean	177.2	166.1	173.5
	SD	7.3	7.0	8.9
	Range	165.1 - 198.1	149.9 – 177.8	149.9 – 198.1

SD = standard deviation

Pharmacokinetic, Pharmacodynamic, and/or Other Results: Co-administration of varenicline (1 mg BID) and metformin (500 mg BID) had no clinically relevant effects on the steady-state pharmacokinetics of either varenicline or metformin. The bounds of the 90% CIs

for the primary endpoints, AUC(0-tau) and Cmax, were well within the equivalence limits of (80%-125%) for both varenicline and metformin.

Visual inspection of mean and individual plasma trough concentration-time profiles showed that all 29 subjects attained steady-state conditions for metformin by Day 5. Following multiple doses of 500 mg BID metformin with and without varenicline, plasma peak concentrations of metformin occurred at approximately 4 hours after dosing. Plasma steady-state exposure to metformin, as assessed by Cmax and AUC(0-tau), was nearly identical when metformin was administered alone and in combination with varenicline. Consistent with this, renal excretion of metformin remained unchanged in the presence of varenicline. For these comparisons, the bounds of the 90% CI were well within the (80%-125%) equivalence limits.

A summary of point estimates, mean ratios, and 90% CIs for metformin in the presence and absence of varenicline, following natural log-transformation and analysis using a mixed-effects model, is shown in Table S4 below.

Table S4. Summary Results of Statistical Analyses of Metformin Pharmacokinetic Parameters When Co-administered with 1 mg BID Varenicline in Healthy Adult Smokers

	Adjusted Geometric Mean (N=29)			
Pharmacokinetic Parameters (units)	**Metformin (Reference)**	**Metformin + Varenicline (Test)**	**Ratio (%)[a]**	**90% Confidence Intervals**
AUC(0-tau) (ng•h/mL)	5974.3	6126.5	102.55	(99.96,105.20)
Cmax (ng/mL)	942.9	940.9	99.79	(96.18,103.54)
CLr (mL/minute)	471.3	477.5	101.30	(94.34,108.77)

[a]Ratio between metformin + varenicline (test) and metformin (reference)

Varenicline plasma concentrations measured on Days 5, 6, and 7 averaged (± SD) 7.65 ± 1.46 ng/mL, 8.04± 1.64 ng/mL, and 7.48 ± 1.49 ng/mL, indicating that steady state for varenicline given BID appeared to have been reached in all subjects by Day 5.

There were no marked changes in the steady-state pharmacokinetics of varenicline administered alone or in combination with 500 mg BID metformin. Plasma peak concentrations of varenicline occurred at approximately 3 hours after dosing. Consistent with this, renal excretion of varenicline remained unchanged in the presence of metformin. For these comparisons, the bounds of the 90% confidence interval (CI) were well within the (80%-125%) equivalence limits.

A summary of point estimates, mean ratios, and 90% CIs for varenicline in the presence and absence of metformin, following natural log-transformation and analysis using a mixed-effects model, is shown in Table S5 below.

CLINICAL STUDY REPORT SYNOPSIS

Table S5. Summary Results of Statistical Analyses of Varenicline Pharmacokinetic Parameters When Co-administered with Metformin 500 mg BID in Healthy Adult Smokers

Pharmacokinetic Parameters (units)	Adjusted Geometric Mean (N = 29)		Ratio (%)[a]	90% Confidence Intervals
	Varenicline (Reference)	Varenicline + Metformin (Test)		
AUC(0-tau) (ng•h/mL)	87.9	90.9	103.39	(100.24,106.64)
Cmax (ng/mL)	10.6	10.8	102.68	(99.80,105.65)
CLr (mL/minute)	115.9	113.5	97.95	(86.64,110.74)

[a]Ratio between varenicline + metformin (test) and varenicline (reference)

Pharmacodynamic and pharmacokinetic/pharmacodynamic evaluations were not planned or performed for this study.

Safety Results: Fifteen subjects in the metformin alone regimen experienced 26 AEs. Twelve subjects in the varenicline alone regimen experienced 19 AEs. Eighteen subjects in the metformin + varenicline regimen experienced 39 AEs. One subject was permanently discontinued from the study due to an AE of mild increased ALT and AST levels that started on Day 8 (1 day after the last dose in the varenicline 1 mg BID regimen) and lasted until Day 27 (20 days after the last dose of study drug). The baseline ALT and AST values were 35 IU/L and 50 IU/L, respectively. The ALT and AST values on Day 7 (last day of treatment) were 56 IU/L and 77 IU/L, respectively. These elevated values did not meet the criteria for laboratory values of potential clinical concern (>3 × ULN), but were identified as clinically significant (AEs) and treatment related by the investigator. There were no SAEs associated with this study.

All AEs were mild to moderate in severity. Most AEs were judged by the investigator to be treatment related.

Gastrointestinal and nervous system disorders were the most frequent types of AEs reported. Headache, nausea, abdominal pain, dyspepsia, and vomiting were the most frequently occurring AEs in this study. In general, the types of AEs and the number of subjects experiencing each type of AE were similar across the 3 treatment groups, with the exception of abdominal pain, nausea, dyspepsia, and vomiting. Abdominal pain and dyspepsia were most frequent in the metformin + varenicline regimen. The incidence of nausea was similar in the metformin+ varenicline and the metformin alone regimens, and higher for these regimens compared with the varenicline alone regimen. Vomiting occurred exclusively in the metformin + varenicline regimen.

Laboratory values of potential clinical concern were sporadic and asymptomatic. There were no notable apparent differences between treatment regimens in mean change from baseline for heart rate or for PR, QRS, QT, QTcB, or QTcF intervals. No other trends were noted in mean change from baseline for ECG intervals. There were no subjects with ECG values that exceeded the Criteria for Potential Clinical Concern. There were no subjects with prolonged QTc values.

Conclusions:

- Co-administration of metformin (500 mg BID) and varenicline (1 mg BID) resulted in no clinically relevant effects on the oral multiple-dose pharmacokinetics of either varenicline or metformin in healthy adult smokers.
- Multiple doses of metformin and varenicline were safe and tolerated when administered concurrently.

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CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A3051039

Protocol Title: Phase I, randomized, double-blind, placebo-controlled, double-dummy, single-dose, crossover study to evaluate physiologic, subjective and reinforcing effects on varenicline

Investigator: [redacted]

Study Center: One study center in Toronto, Canada

Publications Based on the Study: None

Study Initiation and Completion Dates: 05 January 2005 to 27 March 2005

Phase of Development: Phase 1

Study Objective: To evaluate the abuse liability of varenicline relative to placebo through comparison of the acute physiologic, subjective, and reinforcing effects of each agent.

METHODS

Study Design: This was a randomized, double-blind, 5-period, placebo-controlled, double-dummy, crossover design study. Subjects were enrolled in the study only after satisfying all inclusion and exclusion criteria and undergoing an amphetamine qualification procedure. Separate randomizations were used for smokers and non-smokers. During each of the 5 study periods, subjects received a single oral dose of one of the study medications described in Table S1 below, according to a randomly assigned treatment sequence. All study medications were administered as a single dose under fed conditions. Subjects were required to stay in the Clinical Research Unit (CRU) for approximately 36 hours each study period. Each period was separated from the preceding one by at least 7 days.

Table S1. Summary of Study Treatments

Treatment	Study Drug
A	Amphetamine 15 mg
B	Amphetamine 30 mg
C	Varenicline 1 mg
D	Varenicline 3 mg
E	Placebo

Evaluation of the pharmacodynamic effects of the study medication was determined serially by: Visual Analogue Scales (VAS), Addiction Research Center Inventory (ARCI/Cole version), and Multiple Choice/Subjective Price Monetary Value Procedure (MCP).

Diagnosis and Main Criteria for Inclusion: Healthy male and/or female subjects, both smokers and nonsmokers, ages 18 through 55 years (inclusive) were enrolled. All subjects were to be non-therapeutic poly-drug stimulant users, defined as individuals who recreationally used

amphetamine (or a pharmacologically similar drug such as methamphetamine) and additionally 1 other drug (not including alcohol) they liked to use recreationally on a minimum of 5 occasions within the past year.

Study Treatment: For each study period, subjects in a fed state were to receive a single oral dose of study medication, with at least 7 days between study periods. Study medication was to be administered with 240 mL ambient temperature water. Table S2 summarizes study medications supplied to the study center.

Table S2. Study Medications Supplied

Study Drug	Formulation	Dose Unit	Formulation Identification Number	Lot Number
CP-526,555-18 (varenicline tartrate)	Film-coated Tablets	0.5 mg	G02610AA	920098-3000052-G4
Dextroamphetamine sulfate (amphetamine)	Capsules	5 mg	D0401174	PCS0419
Dextroamphetamine sulfate (amphetamine)	Capsules	10 mg	D0401175	PCS0420
Placebo (for varenicline tartrate)	Film-coated Tablets	N/A	G02613AA	ED-G-310-902
Placebo for 5 mg dextroamphetamine	Capsules	N/A	D0401131	PCS0418
Placebo for 10 mg dextroamphetamine	Capsules	N/A	G02580AA	B03484

Pharmacodynamic Evaluations: Subjective and mood effects were evaluated by questionnaires completed by the subjects, predose and 1, 2, 3, 4, 6, 8, and 24 hours postdose (all time points for Visual Analog Scales [VAS] and Addiction Research Center Inventory [ARCI]; only 8 hours postdose for the Monetary Value procedure [MCP]). The following is a brief summary of each pharmacodynamic measure.

VAS: consisted of a series of 10 horizontal lines, displayed one at a time, each labeled above the line with a word or phrase (eg, "I can feel a drug effect", "I am feeling high", etc). All scales and the middle (bipolar scales only) were also marked with anchors (eg, "not at all" and "extremely" for some unipolar scales). Subjects were instructed to indicate along each line how they felt at the moment. Each scale was scored as an integer from 0 to 100, representing the position at the time the response was indicated.

ARCI (ARCI/Cole version): Cole et al (1982) used a different subset of the shortened version of the ARCI scale (Martin et al, 1971), which overlapped the shortened version and provided 7 additional scales including Sedation-Motor, Sedation-Mental, Unpleasantness-Physical, Unpleasantness-Dysphoria, Stimulation-Euphoria, Stimulation-Motor, and Abuse Potential.

A 57-question subset of the 2 combined instruments was used in this study, allowing scoring on 8 relevant scales.

Multiple Choice/Subjective Price Monetary Value Procedure (MCP): This procedure was a series of independent, theoretical forced choices between the drug administered and different money values. Subjects had to choose between receiving another dose of the same drug to take home or an envelope containing a specified amount of money. Depending on the answer to each question, the next monetary value was either higher or lower. At the end of the 6 questions, the procedure had estimated the crossover point at which the subject was indifferent between choosing drug (as would be done for all smaller values) and choosing money (as would be done for all larger values). The crossover point was the proxy index of reinforcing efficacy that was used as an outcome measure for estimating the abuse liability of varenicline relative to placebo and d-amphetamine. The subjects never received either the drug or the money described in the choices.

Safety Evaluations: All subjects were evaluated for safety by clinical observations and querying for adverse events (AEs), conducting physical examinations and obtaining vital sign measurements, electrocardiograms (ECGs), pulse oximetry, and clinical laboratory tests.

Statistical Methods: There were 4 primary endpoints: the maximum values over the 8 hours postdose measurements of Drug High, Drug Liking scores in the Visual Analog Scales (VAS), the abuse potential score in the Addiction Research Center Inventory (ARCI/Cole) scales, and the 8 hours postdose measurement of the dollar value at crossover from the MCP.

Secondary endpoints included the remaining visual analog scales (Any Effects, Good Effects, Bad Effects, Nausea, Energized, Fatigue, Pleasant Mental State, Pleasant Physical State), the ARCI/Cole scales (Unpleasantness-Physical, Unpleasantness-Dysphoria, Stimulation-Motor, Stimulation-Euphoria, Amphetamine, Benzedrine Group, LSD) and the physiologic measures (BP, HR, respiratory rate, and pulse oximetry).

All analyses for abuse potential assessment were performed on subjects who had completed at least 1 period of the study. All analyses were performed separately for smokers and nonsmokers. The study objective for each stratum was addressed by the following treatment comparisons:

(1) comparing 30 mg amphetamine versus placebo
(2) comparing 15 mg amphetamine versus placebo
(3) comparing 1 mg varenicline versus placebo and 3 mg varenicline versus placebo
(4) comparing 1 mg varenicline versus 30 mg amphetamine and 3 mg varenicline versus 30 mg amphetamine

The analyses were based on models for a multivariate outcome consisting of these 4 primary endpoints. Amphetamine was the positive control for abuse potential testing and has an established and known pattern of drug abuse. A significant 30 mg amphetamine treatment difference from placebo for the multivariate outcome consisting of the 4 primary endpoints, ie, the first comparison above, would thus establish the validity of the study. If the validity test failed, then the subsequent comparisons were not to be done. The second treatment comparison between 15 mg amphetamine and placebo provided context for the amphetamine dose response.

The comparison of the 2 doses of varenicline versus placebo (third comparison) estimated the drug abuse potential of varenicline relative to placebo. The comparison of the 2 doses of varenicline versus 30 mg amphetamine estimated the drug abuse potential of varenicline relative to 30 mg amphetamine.

Each of the treatment effect differences for comparisons (1) – (4) above were tested for statistical significance with a 4 degrees of freedom likelihood ratio test, ie, simultaneous testing of 4 primary outcomes. Separately for smokers and nonsmokers, the 4 primary endpoints were analyzed using a mixed effects model for a multivariate outcome consisting of the 4 endpoints. The model contained baseline score as a covariate as appropriate (ie, for VAS Drug High and ARCI/Cole Abuse Potential only), fixed effects for sequence, period, and treatment, and a random effect for subjects (within sequence) for each of the 4 outcomes. The baseline score was the predose score from each study period.

A complementary analysis was conducted using the standardized outcomes to test each of the treatments for homogeneity of effect across the standardized outcomes using a 3 degrees of freedom likelihood ratio test for each. This was followed by a global homogeneity test for all treatments simultaneously, based on a 12 degrees of freedom likelihood ratio test.

Complete time course data were plotted. Descriptive statistics are provided for all endpoints, separately for smokers and nonsmokers by treatment. For secondary endpoints, only descriptive statistics were provided.

RESULTS

Subject Disposition and Demography: Forty-five subjects (23 smokers and 22 nonsmokers) were assigned to treatment. Subject disposition is summarized by treatment group in Table S3 below. Subject demography is summarized in Table S4 below.

Table S3. Subject Disposition

		Smokers					Nonsmokers				
		Placebo	Amphetamine		Varenicline		Placebo	Amphetamine		Varenicline	
			15 mg	30 mg[c]	1 mg	3 mg		15 mg	30 mg	1 mg	3 mg
Assigned to Treatment	45										
Treated		21	21	21	20	20	21	21	20	21	22
Completed		20	20	21	20	19	21	21	20	21	20
Discontinued due to		1	1	0	0	1	0	0	0	0	2
Adverse event		1[a]	0	0	0	0	0	0	0	0	1[d]
Other		0	1[b]	0	0	1[b]	0	0	0	0	1[e]

[a]Bronchitis
[b]Unable to complete study within timeline as per sponsor (subjects missed several scheduled visits).
[c]One subject received a second amphetamine 30 mg dose in Period 4 instead of the assigned varenicline 3 mg dose, due to center error. The subject was analyzed as treated.
[d]Multiple events: see SAE description in Safety Results below
[e]Subject defaulted (no longer willing to participate in study).

Table S4. Subject Demographics

		Smokers (Male 16/Female 7)			Nonsmokers (Male 20/Female 2)		
		Male	**Female**	**Total**	**Male**	**Female**	**Total**
Age	Mean	29.9	25.7	28.7	30.1	32.5	30.3
	SD	9.0	5.9	8.3	8.2	3.5	7.9
	Range	18 - 47	20 - 34	18 - 47	20 - 51	30 - 35	20 - 51
Race	White	11	6	17	9	2	11
	Black	4	0	4	2	0	2
	Asian	1	0	1	2	0	2
	Other	0	1	1	7	0	7
Weight (kg)	Mean	73.5	60.2	69.5	75.9	59.7	74.5
	SD	11.6	5.7	11.8	9.4	0.4	10.1
	Range	49.8 - 99.5	54.0 - 70.7	49.8 - 99.5	60.8 - 91.9	59.4 - 59.9	59.4 - 91.9
Body Mass Index (kg/m^2)	Mean	24.4	22.4	23.8	24.3	21.4	24.0
	SD	3.0	2.0	2.9	3.5	0.5	3.5
	Range	20.3 - 31.2	20.1 - 24.9	20.1 - 31.2	19.0 - 30.2	21.0 - 21.7	19.0 - 30.2
Height (cm)	Mean	173.6	164.1	170.7	177.1	167.0	176.2
	SD	9.3	6.6	9.5	6.0	1.4	6.4
	Range	154.0 - 194.0	154.0 - 174.0	154.0 - 194.0	168.0 - 187.0	166.0 - 168.0	166.0 - 187.0

Pharmacodynamic Results: For both smoking and nonsmoking cohorts, study validity was achieved and the results of the multivariate analysis of primary endpoints were echoed consistently by the univariate analysis of the individual endpoints and the analysis of the secondary endpoints.

Smokers who received 1 mg varenicline did not differ significantly from placebo for any of the 4 scale scores. Smokers who received 3 mg varenicline had VAS Drug Liking scale scores significantly lower than scores for placebo-treated subjects, while the other 3 primary scales were not significantly different from placebo. At the 1 mg dose level, varenicline was perceived by subjects to be similar to placebo and very different from 15 mg amphetamine, a drug of known abuse potential. At varenicline 3 mg, the sensation of being on an active drug was offset by the dysphoric effects and discomfort (subjective ratings and AEs) it induced. The dose response for varenicline was nil or in the inverse direction on all scales, dissimilar to amphetamine in this study and to the typical behavior of drugs of abuse in general. For 3 mg varenicline, Drug Liking scale scores were significantly lower than scores for placebo.

Nonsmokers who received 1 mg varenicline reported a significantly increased mean drug effect (as measured by the VAS High scale peak score) and a significantly higher ARCI Abuse Potential peak score as compared with placebo. Examination of the secondary endpoints elucidated this multivariate finding. At 1 to 2 hours post dose, the 1 mg varenicline means were elevated relative to placebo for VAS High, VAS Good Effects, ARCI/Cole Abuse Potential,

ARCI/Cole Stimulation-Euphoria, VAS Energized, ARCI/Cole Stimulation-Motor, and ARCI/Cole Amphetamine scales. Simultaneously, the 1 mg varenicline means were elevated relative to placebo for the ARCI/Cole Unpleasantness-Physical, VAS Nausea, and ARCI/Cole LSD scales. Together, these effects offset each other, as evidenced by the mean for VAS Drug Liking scale score for this time period, which was comparable to that for placebo and far below the neutral score of 50 for 1 mg varenicline nonsmokers. Thus the elevation of mean VAS Drug High captured the sensation of being on an active drug, but subjects disliked this sensation, especially compared with their liking of amphetamine. For nonsmokers, dose responses were inverted on positive measures, while the reverse was true for negative measures, suggesting that dose escalation is unlikely. Nonsmokers who received 3 mg varenicline did not differ significantly from placebo for any of the 4 primary scale scores. As with smokers, the pattern for nonsmokers was dissimilar to the dose response exhibited by amphetamine.

In summary, the pattern for both smokers and nonsmokers in this study is consistent with the profile of a drug that has some known action but has a dose-response profile unlike drugs of abuse, as defined by a multivariate analysis of primary measures of abuse potential and echoed by univariate analysis of the individual endpoints and further evaluation of secondary parameters, including physiological effects. The subjective experience of similarity to placebo and/or unpleasant effects, in combination with the higher rate of headache, nausea, and vomiting (see Safety Results, below), precludes the potential for abuse. Finally, subjects who received varenicline exhibited no significant difference from placebo on the MCP; therefore, no reinforcing effects were identified for varenicline.

Safety Results: There were no deaths associated with this study. Most AEs were classified as mild or moderate and treatment related. There were 2 discontinuations due to AEs. One male smoker (placebo) was discontinued from the study due to moderate bronchitis. A second male nonsmoker (3 mg varenicline) was discontinued from the study due to SAEs of nausea, tachycardia, tachypnea, numbness of lower extremities, numbness of upper extremities, and numbness facial, as well as AEs of lightheadedness, headache, lower abdominal cramping, mild chills, and vomiting at the time of the AEs that led to discontinuation. Several of these SAEs/AEs were moderate to severe in intensity. In the opinion of the investigator, the SAEs were related to varenicline. Review by the sponsor concluded that a possible relationship between these AEs and varenicline could not be excluded.

In smokers headache, nausea, euphoric mood, dry mouth, and vomiting were the most frequent AEs reported across all treatments. Nausea, headache, and vomiting occurred most frequently in the varenicline 3 mg regimen. Dry mouth and euphoric mood were only experienced in the amphetamine groups.

In nonsmokers headache, nausea, vomiting, euphoric mood, and dizziness were the most frequent AEs reported across all treatments. Headache, nausea, vomiting, and dizziness occurred most frequently in the 3 mg regimen. Euphoric mood was seen across all dose groups, with an increased frequency in the amphetamine 30 mg group (6 AEs; 4 mild, 2 moderate). The incidence of euphoria in the varenicline 1 mg (2 mild AEs), varenicline 3 mg (1 mild, 1 moderate AE), and amphetamine 15 mg (2 mild AEs) groups was not appreciably different from placebo.

There were no laboratory findings, vital signs, ECG results, or pulse oximetry readings associated with varenicline that were identified as being of clinical concern by the investigator.

Conclusions:

- The results of this study suggest that varenicline is unlikely to be abused.
- Based on the results of multivariate primary analyses varenicline has significantly less abuse potential than amphetamine.
- The negative dose response profile on positive scales and the positive dose response on negative scales exhibited by varenicline is notably different from the expected dose-response profile for known drugs of abuse.
- There were no reinforcing effects for smokers or nonsmokers identified for either dose of varenicline, as indicated by no significant differences versus placebo in MCP scores.
- Varenicline was safe and tolerated at single doses of 1 mg. Varenicline 3 mg single doses were safe but not well tolerated, as evidenced by an increased frequency of headache, nausea, and vomiting AEs and an SAE of nausea that contributed to discontinuation of varenicline for 1 subject.

REPORT SYNOPSIS

Compound/Protocol Number: **CP-526,555/A3051041** **Phase:** **1**

Title: **PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE ORAL DOSES OF CP-526,555 (A PARTIAL AGONIST OF THE $\alpha_4\beta_2$ NICOTINIC RECEPTOR) IN JAPANESE HEALTHY ADULT MALE SMOKERS**

Principal Investigator: [ ]

Study Publication: None at time of report issue

Study Dates: 16 September 2003 to 15 December 2003

Study Objectives: To evaluate the safety, tolerability, and pharmacokinetics of multiple oral doses of CP-526,555 in Japanese healthy adult male volunteers

Study Design: This study was an ascending dose, parallel-group, double-blind, placebo-controlled, randomized study of multiple oral doses of CP-526, 555 in Japanese healthy adult male smokers.

This study consisted of two cohorts with different treatments, Cohort 1 (received CP-526,555 0.5 mg or placebo twice a day) and Cohort 2 (received CP-526,555 1.0 mg or placebo twice a day). Volunteers who were judged appropriate to participate in this study after screening were admitted to the study site in the evening 2 days prior to dosing for standard tests, conducted on the day before treatment, to confirm their eligibility. Eligible subjects participated in either Cohort 1 or Cohort 2, and were allocated either to active drug or to placebo as follows:

Cohort 1: Japanese healthy male subjects (smokers) were given a CP-526,555 0.5 mg tablet or a placebo tablet, orally, twice a day (after breakfast and dinner) for 14 days (the "0.5 mg group" and the "placebo group" hereafter).

Cohort 2: Japanese healthy male subjects (smokers) were given a CP-526,555 1.0 mg tablet or a placebo tablet, orally, twice a day (after breakfast and dinner) for 14 days (the "1.0 mg group" and the "placebo group" hereafter).

Cohort	Dosage	Number of Subjects
Cohort 1	CP-526,555 0.5 mg	8
	Placebo	4
Cohort 2	CP-526,555 1.0 mg	8
	Placebo	4

Cohort 2 was conducted after the study had been completed in the Cohort 1 subjects, and their safety confirmation was done as specified in the study protocol.

Study Population and Criteria for Inclusion: Japanese healthy adult male smokers (aged 20 to 55), who had given consent and considered suitable to participate in this study by the principal investigator (sub-investigator), based on the screening results of observation and

examination of the subject background, physical examination, vital signs [body temperature, blood pressure (BP), pulse rate], electrocardiogram (ECG), laboratory tests.

Treatments:

Study Medications:

Study Drugs	Formulation	Dose Unit	Batch/Lot Numbers	FID#
CP-526,555-18 0.5 mg tablets[#]	FC tablets[$]	0.5 mg	920098-3000052-G1	G02610AA
CP-526,555-18 1.0 mg tablets[##]		1.0 mg	920108-3000052-G1	G02611AA
CP-526,555-18 0.5 mg tablets placebo*		0 mg	ED-G-310-902	G02613AA
CP-526,555-18 1.0 mg tablets placebo*		0 mg	ED-O-155-502	G02615AA

[#]: Each tablet contains CP-526,555 (L-tartrate) equivalent to 0.5 mg of CP-526,555
[##]: Each tablet contains CP-526,555 (L-tartrate) equivalent to 1.0 mg of CP-526,555
[$]: Film-coated tablets
*: Externally indistinguishable from the corresponding active drug tablets

Dosing:

Cohort 1: CP-526,555 0.5 mg or placebo was administered orally with 200 mL water within 5 minutes after breakfast and dinner without chewing.

Cohort 2: CP-526,555 1.0 mg or placebo was administered orally with 200 mL water within 5 minutes after breakfast and dinner without chewing.

Duration: 14 days

CRITERIA FOR EVALUATION AND METHODOLOGY:

Safety: Subjects were evaluated by clinical observation, querying for adverse events (AEs) and by body temperature, BP, pulse rate, 12-lead ECG, funduscopy and visual acuity test, and clinical laboratory tests measurements.

Pharmacokinetics: Plasma CP-526,555 concentrations on Day 1 and Day 14; AUC_τ [area under plasma concentration-time curve at dosing intervals (0 to 12 hours and 12 to 24 hours after dosing)], $AUC_{(0\text{-}24)}$ (area under plasma concentration-time curve of 0 to 24 hours after dosing), C_{max} (maximum plasma concentration), C_{min} (minimum plasma concentration, Day 1-Day 14), Tmax (time to maximum plasma concentration), CLR (renal clearance), $t_{1/2}$ (elimination half life, Day 14 only), kel (elimination rate constant, Day 14 only), PTR (Peak: Trough Ratio), Rac (accumulation ratio)

CP-526,555 Concentration in Urine; Ae_τ (amount excreted in urine) and the percent dose of CP-526,555 excreted unchanged at each interval of urine collection (0 to 12 and 12 to 24 hours after CP-526,555 dosing on Day 1 and Day 14)

Pharmacodynamics: The number of cigarettes smoked by each subject per day from admission to discharge of each cohort

Statistical Methods:

Safety: A summary and overview of safety data (adverse events, body temperature, laboratory tests, blood pressure, pulse rate, funduscopy and visual acuity test, and ECG findings) and the other observation items (background and composition of subjects, physical findings, etc.) had been prepared according to the form and algorithms specified in "Worldwide Safety Standards for Clinical Trials Release 3.0 (WSS 3.0)", and then clinical evaluation was performed. Heart rate, PR interval, QRS interval, QT interval, QTcB and QTcF intervals were calculated from 12-lead ECG.

Pharmacokinetic: For CP-526,555 plasma concentrations at each sampling point, the arithmetic mean, standard deviation, and coefficient of variation (CV) were calculated. In this calculation, 0 was entered for concentrations below the limit of quantification (<0.100 ng/mL); and when the drug concentrations in the majority of the subjects were below the limit of quantification, the arithmetic mean, standard deviation, and CV were not reported. Summary statistics (the number of subjects, arithmetic mean, standard deviation, range and CV) were calculated by dose, for AUCτ, $AUC_{(0-24)}$, C_{max}, Tmax, and $t_{1/2}$ out of all pharmacokinetic parameters. In addition, the geometric means for C_{max}, AUCτ, and $AUC_{(0-24)}$ were calculated. Also the number of subjects, arithmetic mean, harmonic mean, standard deviation, CV, for k_el were calculated. Number of subjects, arithmetic mean, standard deviation, and CV were calculated for PTR and Rac. For CP-526,555 urinary concentrations, the urinary excretion amount, and for percent dose excreted unchanged and renal clearance, the arithmetic mean, standard deviation, and CV were calculated.

The comparison of pharmacokinetics among treatment groups was conducted in descriptive statistics of the measured plasma drug concentration levels and the calculated pharmacokinetic parameters.

Pharmacodynamic: The numbers of cigarettes smoked were summarized by treatment groups descriptively (number of subjects, mean, median, standard deviation, minimum, maximum).

RESULTS: Twelve subjects per each cohort (Active: 8 subjects, Placebo: 4 subjects) were enrolled, and all subjects completed the study as planned. Subject disposition is summarized in the table below.

Subject Disposition

		CP-526,555		Placebo group
		0.5 mg group	1.0 mg group	
Total Number of Screened	24			
Total Number of Enrolled		8	8	8
Total Number of Dosed		8	8	8
Total Number of Completed		8	8	8
Total Withdrawn Post-Dose		0	0	0
Evaluated for Pharmacokinetics		8	8	8
Assessed for Safety				
Adverse Events		8	8	8
Laboratory Tests		8	8	8

Demographic Characteristics

Background Factors	CP-526,555		Placebo group
	0.5 mg group	1.0 mg group	
Number of subjects	8	8	8
Age (years):			
Mean	22.5	25.4	23.8
SD	2.2	3.4	2.6
Range	20-27	22-32	21-29
Weight (kg):			
Mean	63.0	65.2	59.1
SD	10.8	7.2	3.7
Range	51.3-75.4	55.0-78.9	54.1-65.7
BMI (kg/m^2):			
Mean	22.0	21.5	20.1
SD	3.0	2.1	1.3
Range	18.2-27.1	19.0-24.3	18.6-22.5

Safety:

No deaths, serious adverse events, or discontinuations were reported during this study. There were 5 AEs in 3 subjects in the 0.5 mg group, 2 of which were considered treatment-related, 9 AEs in 4 subjects in the 1.0 mg group, 4 of which were considered treatment-related, and 10 AEs in 5 subjects in the placebo group, 4 of which were considered treatment-related. All AEs were mild in severity, and all were resolved. The most frequent AEs occurred in the digestive system (diarrhea, nausea, stools loose). In previous Western studies, nausea was considered a dose limiting event. In this study, nausea was observed in 2 subjects in the 1.0 mg group. One subject experienced nausea five times (once each on Days 1, 2, 4, 6, and 8 of dosing), and it was concluded to be treatment-related adverse events. The nausea in this subject was always within 1 hour after dosing of the study drug and was always resolved on the day it appeared. The other subject experienced nausea once on Day 9 of dosing, but this was attributed to stress as a result of environmental changes, and it was not concluded to be treatment-related.

AEs (all causality) were shown in the table below.

Treatment -Emergent Adverse Events

	CP-526,555		Placebo group
	0.5 mg group	1.0 mg group	
Number of subjects per group	8	8	8
Number of subjects who experienced AEs (%)	3(37.5)	4(50.0)	5(62.5)
Total Number of Episodes	5	9	10
Name of AEs			
Body As a Whole			
Abdominal pain	1	0	0
Chest pain	0	1	0
Headache	1	1	0
Malaise	1	0	0
Digestive			
Diarrhea	0	1	2
Nausea	0	2	0
Stools loose	0	1	2
Hemic and Lymphatic			
Hypochromic anemia	0	1	1
Metabolic and Nutritional			
SGOT increased	1	0	0
SGPT increased	1	0	0
Respiratory			
Pharyngitis	0	0	2
Respiratory tract infection	0	2	2
Special Sense			
Eye hemorrhage	0	0	1

Clinical laboratory evaluation: With normal baseline, one laboratory abnormality (urine specific gravity) was in one subject in the 0.5 mg group. This abnormality was not reported as an adverse event. With abnormal baseline, there was no laboratory abnormality.

Vital signs (blood pressure, pulse rate, and body temperature): There were no clinically abnormal changes in sitting systolic blood pressure, diastolic blood pressure, or pulse rate. There were no special changes in the body temperature.

Electrocardiogram: There were no clinically abnormal changes in ECG

Pharmacokinetics: The mean C_{max} and AUC_{τ} on Day 1 and Day14 increased in an approximate proportional manner with dose after multiple oral dosing of 0.5 or 1.0 mg CP-526,555 twice a day. Based on the plasma trough concentration-time data, steady-state exposure to CP-526,555 appeared to have been reached after 4 days of twice-daily dosing. The elimination half-life of CP-526,555 estimated on Day 14 was on average 27.98 hours (range: 19.2 to 34.5 hours) and 24.21 hours (range: 20.1 to 31.2 hours) in the 0.5 and 1.0 mg BID groups, respectively. Mean Tmax (arithmetic mean) in the 0.5 mg group was 3.13 hours (range: 1.0 to 4.0 hours) and 3.50 hours (range: 2.0 to 4.0 hours) on Days 1 and 14, respectively, and in the 1.0 mg group, 2.50 hours (range: 1.0 to 4.0 hours) and 3.13 hours (range: 2.0 to 4.0 hours) on Days 1 and 14, respectively. Mean observed accumulation (Rac) obtained from the AUCτ at the first dosing interval (0 to 12 hours) on Days 1 and 14 was 2.7 in both dosing groups. On Day 14, AUCτ at the first dosing interval (0 to 12 hours) and the AUCτ at the second dosing interval (12 to 24 hours) were comparable in both groups.

Renal clearance estimates were similar across doses and study days. Plasma and urine pharmacokinetic parameters of CP-526,555 were summarized in the table below.

Summary of plasma and urine pharmacokinetic Parameters of CP-526,555 in Japanese male smokers following multiple oral doses

PK parameters		CP-526,555			
		0.5 mg BID group (n=8)		1.0 mg BID group (n=8)	
		Day 1	Day 14	Day 1	Day 14
AUCτ* (ng·h/mL)	Arithmetic mean	21.79	58.48	42.68	116.00
	SD	3.02	10.38	6.14	29.27
	Geometric mean	21.61	57.79	42.33	113.52
Cmax* (ng/mL)	Arithmetic mean	2.62	5.94	5.29	11.95
	SD	0.32	1.06	0.89	2.86
	Geometric mean	2.61	5.87	5.24	11.71
Tmax* (h)	Arithmetic mean	3.13	3.50	2.50	3.13
	SD	0.99	0.93	0.93	0.64
$t_{1/2}$ (h)	Arithmetic mean	-	27.98	-	24.21
	SD	-	4.52	-	3.46
Racτ*	Arithmetic mean	2.700		2.697	
	SD	0.400		0.316	
CLr (mL/min)	Arithmetic mean	79.02	83.70	99.25	90.46
	SD	14.84	14.86	23.66	19.97

*: Data of 0-12 hours after dosing
–: Not calculated

Pharmacodynamics: The mean number of cigarettes smoked in the 1.0 mg BID group decreased markedly compared to that of the 0.5 mg BID and placebo groups, although there were no marked difference in the number of cigarettes smoked between the 0.5 mg BID group and the placebo group. The mean number of cigarettes smoked on Day 0 in placebo, the 0.5 mg BID, and the 1.0 mg BID groups were 20.1, 18.4, and 20.1, respectively. The mean number of cigarettes smoked on Day 14 in placebo, the 0.5 mg BID, and the 1.0 mg BID groups were 19.4, 14.9, and 4.9, respectively. The substantial decrease of mean number of cigarettes smoked was observed after 5 days of multiple doses in the 1.0 mg BID group. And in 4 subjects, half of the total subjects of the1.0 mg group, no smoking day(s) were observed from the Day 5.

CONCLUSIONS: This study was conducted to evaluate the safety, tolerability, and pharmacokinetics after 14 days of multiple oral administrations of 0.5 or 1.0 mg CP-526,555 tablets twice a day (after breakfast and dinner) to Japanese healthy adult male smokers.

Multiple oral doses of CP-526,555 for 14 days were well tolerated in Japanese healthy adult male smokers up to 1.0 mg twice a day.

The mean C_{max} and AUC_{τ} on Day 1 and Day14 increased in an approximate proportional manner with dose after multiple oral dosing of 0.5 or 1.0 mg CP-526,555 twice a day. CP-526,555 plasma concentration reached steady state after 4 days of dosing. There was no

evidence of concentration- or time-dependent changes in the pharmacokinetics of CP-526,555 upon repeat dosing and the observed drug accumulation at steady-state was well predicted from the single dose pharmacokinetic data in Japanese smokers.

There was a substantial decrease in the number of cigarettes smoked in the1.0 mg BID group compared to the 0.5 mg BID and placebo groups. The substantial decrease of mean number of cigarettes smoked was observed on the 5th day of dosing in the 1.0 mg BID group. Since the CP-526,555 plasma concentration reached steady state after Day 4 of multiple dosing, these results suggested the possibility that the CP-526,555 plasma concentration had an effect on the number of cigarettes smoked.

CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A3051042

Protocol Title: Phase I, Open-Label, Randomized, Two-Way Crossover, Single Dose Study to Estimate the Pharmacokinetics of a 1 mg Commercial Image Immediate Release (IR) Tablet Formulation of Varenicline Under Fed and Fasted Conditions in Healthy Adult Smokers

Investigator: [redacted]

Study Center: 1 center in the United States

Publications Based on the Study: None

Study Initiation and Completion Dates: 24 September 2004 to 26 October 2004

Phase of Development: Phase 1

Study Objective: To estimate the oral bioavailability of a 1 mg (1 x 1 mg) commercial image formulation of varenicline, administered as a single oral tablet under fed conditions with a standard FDA high-fat breakfast, relative to the formulation administered under fasted conditions.

METHODS

Study Design: This was an open-label, randomized, 2-sequence, 2-way crossover, single-dose study of 12 healthy adult smokers. During one period subjects received a single dose of varenicline under fed (standard FDA high-fat breakfast) conditions. During the other period subjects received a single dose of varenicline under fasted conditions. The duration of the study was approximately 2 weeks, including a 7-day washout period between administrations of doses.

Diagnosis and Main Criteria for Inclusion: Healthy male and/or female subjects between the ages of 18 and 55 years, inclusive, were enrolled in the study. A Body Mass Index (BMI) of approximately 18 to 30 kg/m^2 and a total body weight >50 kg (110 lb) were required. Subjects were to be current smokers and were required to have smoked an average of at least 10 cigarettes per day during the past year, with no period of abstinence >3 months continuous in the past year.

Study Treatment: Each subject received 1 orally administered tablet of the 1 mg commercial image formulation during each study period. During the fed period, in which subjects ingested a high-fat meal (approximately 150 protein calories, 250 carbohydrate calories, and 500 - 600 fat calories), dosing was to occur immediately after completion of breakfast. Fasting subjects received study medication following a 10-hour fast, at approximately 0800 hours.

PGRD provided 1 mg varenicline tablets to the study center (lot number 963138-3001064; formulation identification (FID) number 963138).

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: During each study period, blood samples to provide plasma for pharmacokinetic (PK) analysis of varenicline were collected into appropriately labeled tubes containing sodium heparin up to 96 hours postdose.

CLINICAL STUDY REPORT SYNOPSIS

Plasma samples were assayed for varenicline concentrations using a validated liquid chromatography/tandem mass spectrometry assay. The dynamic range of the assay was 0.100 – 50.0 ng/mL.

Individual plasma concentration-time data for varenicline were analyzed by non-compartmental methods. Maximum observed plasma concentration (Cmax) of varenicline was estimated directly from experimental data, with time to maximum concentration (tmax) defined as the time of the first occurrence of Cmax. Area under the plasma concentration-time curve from time zero to the last time (tlast) with a quantifiable concentration [AUC(0-tlast)] and AUC extrapolated to infinity [AUC(0-inf)] were derived using the linear-log trapezoidal rule. The apparent terminal phase half-life (t1/2) was calculated as ln(2)/Kel.

Pharmacodynamic (PD) and PK/PD evaluations were not planned or performed for this study.

Safety Evaluations: Safety evaluations included reports of adverse events, vital signs (heart rate, blood pressure), 12-lead ECGs, , physical examinations, and safety laboratory tests.

Statistical Methods: Log-transformed (natural log) AUC(0-inf), AUC(0-tlast), and Cmax were analyzed using a mixed-effects model containing fixed effects for sequence, period, and treatment, and random effects for subjects (within sequence). Restricted Maximum Likelihood estimates (REML) were utilized and compound symmetry was assumed. The Satterthwaite algorithm for estimation of degrees of freedom was employed.

Estimates of adjusted mean differences (Fed-Fasted) and corresponding 90% confidence intervals were estimated from this model. The estimated difference and 90% confidence limits for the true difference were exponentiated to derive estimates of the ratio (Fed/Fasted) of adjusted geometric means and the 90% confidence interval for the true ratio.

Safety laboratory data was reviewed and summarized to evaluate the safety of subjects.

RESULTS

Subject Disposition and Demography: Twelve subjects were treated in the study as planned. All subjects completed the study (no discontinuations). All subjects were analyzed for pharmacokinetics, as well as for safety (AEs and laboratory data).

Table S1 below summarizes demographic data of the study population.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Demographic Characteristics

		Total
Age (years)	Mean	35.0
	SD	11.1
	Range	20 - 52
Weight (kg)	Mean	71.6
	SD	10.8
	Range	57.8 - 94.0
Body Mass Index (kg/m^2)	Mean	24.4
	SD	3.2
	Range	20.0 – 29.0

8 male subjects, 4 female subjects.
Race: All subjects were white.
SD = standard deviation

Pharmacokinetic Results: The oral bioavailability of the 1 mg commercial image tablet formulation of varenicline was not affected by food. For these comparisons, the bounds of the 90% confidence interval for AUC(0-inf), AUC(0-tlast), and Cmax were completely contained within the established bioequivalence limits (80%, 125%).

A summary of the point estimates, mean ratios, and associated 90% confidence intervals (CIs) for the comparisons of interest, fed versus fasted, is presented in Table S2 below.

Table S2. Summary Results of Statistical Analyses of Varenicline Following Single Oral Doses of Varenicline Given as the 1 mg Commercial Image Immediate Release (IR) Tablet to Healthy Adult Smokers Under Fed and Fasted Conditions

	Adjusted Geometric Mean (N = 12)			
Pharmacokinetic Parameters (units)	**Varenicline 1 mg Fasted (Reference)**	**Varenicline 1 mg Fed (Test)**	**Ratio (%)[a]**	**90 % Confidence Intervals**
AUC(0-inf) (ng•h/mL)	104.1	102.7	98.62	(93.92, 103.57)
AUC(0-tlast) (ng•h/mL)	99.2	98.7	99.54	(94.60, 104.73)
Cmax (ng/mL)	4.2	4.2	100.96	(96.88, 105.22)

[a]Ratio of varenicline 1 mg fed (test) over varenicline 1 mg fasted (reference) × 100.

CLINICAL STUDY REPORT SYNOPSIS

Safety Results: There were no deaths, SAEs, or withdrawals due to AEs associated with this study. Three treatment-emergent AEs (1 treatment related) were reported by 3 subjects receiving varenicline 1 mg fasted, and 3 treatment-emergent (1 treatment related) AEs were reported by 3 subjects receiving varenicline 1 mg fed. One treatment-emergent AE was considered severe (headache, attributed to caffeine). All other AEs were mild to moderate.

Table S3 below summarizes AEs by treatment regimen.

Table S3. Treatment-Emergent Signs and Symptoms

MedDRA Preferred Term	Number of Subjects All Causality (Treatment Related)	
	Varenicline 1 mg Fasted	Varenicline 1 mg Fed
Headache	1 (0)	2 (1)
Contusion	1 (0)	1 (0)
Nausea	1 (1)	0
Number of Adverse Events	3 (1)	3 (1)
Number of Subjects with AEs	3	3
Number of Subjects Exposed	12	12

There were no laboratory, vital sign, or ECG values of clinical concern identified in this study.

Conclusion(s):

- The oral bioavailability of the 1 mg commercial image tablet formulation of varenicline was not affected by food.
- Varenicline administered as a single-dose, 1 mg tablet (immediate release, commercial image formulation) was safe and well tolerated.

Substrate Disappearance Studies of CP-526,555 in Rat, Dog, Monkey and Human Hepatic Microsomes

1.0 SUMMARY

CP-526,555 was incubated with rat, dog, monkey or human hepatic microsomes and the loss of parent drug from the incubations was measured. No time-dependent loss of CP-526,555 was detected in any of the species tested. This suggested that CP-526,555 was stable to metabolism by hepatic microsomal cytochrome P450 enzymes.

2.0 OBJECTIVE

To assess the metabolism of CP-526,555 (substrate consumption) in rat, dog, monkey and human hepatic microsomes.

3.0 METHODS

3.1 Incubation conditions and assay conditions (rat, dog and human experiment)

Samples were prepared on ice to contain rat (RL126), dog (DL121) or human (HL-Mix 11) microsomes (1 µM total cytochrome P450), potassium phosphate buffer (100 mM, pH 7.4) and 10 µM CP-526,555-01. The final volume was 1.5 ml. Each tube was then preincubated in a shaking water bath at 37°C for 3 minutes. The reaction was started by the addition of NADPH (50 µM), then 200 µl aliquots were withdrawn at 0, 2, 5, 10 and 20 min and dispensed into tubes containing 4 ml of acetonitrile. Protein precipitate was removed by centrifugation [ ] Fifty microliters of supernatant was analyzed by [ ] HPLC. The HPLC conditions were as follows: [ ] CP-526,555 eluted at 5 minutes and the percent remaining was determined by comparing peak heights to the time zero sample. Data are recorded in Laboratory Notebook [ ]

3.2 Incubation and assay conditions (rat and monkey experiment)

A second experiment was conducted to evaluate and compare the metabolism of CP-526,555 in rat and monkey microsomes. Samples were prepared on ice to contain rat (RL127) or monkey (MKL 114) microsomes (0.2 µM total cytochrome P450), potassium phosphate buffer (100 mM, pH 7.4) and 1.0 µM CP-526,555-01. The final volume was 3 ml. Each tube was then preincubated in a shaking water bath at 37°C for 3 minutes. The reaction was started by the addition of NADPH (50 µM), then 200 µl aliquots were withdrawn at 0, 2, 5, 10 and 20 and 35 min and dispensed into tubes containing an equal volume of ice-cold methanol. Protein precipitate was removed by centrifugation [ ]. The samples were then stored at -70°C until processed and analyzed. Prior to processing the frozen samples were thawed to room temperature. Fifty microliters of a 1 µg/ml stock solution of internal standard (CP-532,543) and 100 µl of a 1 M sodium hydroxide solution was added to a 150 µl aliquot of each sample. Each sample was extracted with 5 ml of N-butyl chloride and the phases were then separated

by centrifugation [ ] The aqueous phase was frozen in a bath with solid carbon dioxide in acetone and the organic phase was decanted into a clean tube. The solvent was then evaporated to dryness at 40°C [ ] Each sample was reconstituted in 150 µl of acetonitrile and analyzed by LC/MS using the [ ] The analyte and internal standard were eluted from a [ ]. Solvent A consisted of 0.5% formic acid in water and solvent B was 0.5% formic acid in acetonitrile. The solvent composition at initial conditions was 8% A and 92% B, held for 0.5 minutes followed by a linear gradient to 80% A and 20% B at 3.5 minutes. The flow rate was maintained at 0.4 ml/min. Parent ions were monitored for CP-532,543 and CP-526,555 which eluted at 3.5 (233.2 m/z) and 3.5 minutes (212.2 m/z), respectively. The peak area ratios of analyte/internal standard were compared to standards prepared in the range of 5-500 ng/ml and extracted from solutions containing 50% methanol in 100 mM phosphate buffer which modeled the microsomal incubations. Data are recorded in Laboratory Notebook [ ]

4.0 RESULTS AND DISCUSSION

The disappearance of CP-526,555 rat, dog and human microsomes is presented in Table 1 and Figure 1. The results showed that under the conditions evaluated there was no loss of CP-526,555 from rat, dog or human microsomes that could be considered time-dependent given the variability in the data. The possibility did exist that the metabolites cochromatographed with the parent drug which would have been detected as parent by UV absorbance. In a subsequent experiment rat and monkey hepatic microsomes were tested for their ability to metabolize CP-526,555. A more sensitive and selective analytical method was used for this experiment (LC/MS) which allowed a 10-fold lower substrate concentration to be used and was selective for the protonated molecular ion of the parent drug. The results confirmed that rat microsomes did not catalyze the disappearance of CP-526,555 from microsomal incubations, even at a substrate concentration of 1 µM. In addition, no loss of CP-526,555 was detected from monkey hepatic microsomal incubations. In conclusion, hepatic microsomes from a number of species did not appear to metabolize CP-526,555 as assessed through substrate depletion studies. This suggests that the cytochromes P450 in humans and animal species probably contribute little to the in vivo metabolism and clearance of CP-526,555.

5. TABLES

Table 1: Effect of Incubation Time on the Percent of CP-526,555 (10 μM) Remaining in Rat, Dog or Human Microsomal Incubations (1 μM Cytochrome P450).

Incubation Time (min)	Percent Remaining		
	Rat	Dog	Human
0	100	100	100
2	81.4	107.2	95.3
5	79.4	115.9	98.9
10	83.7	100.2	112
20	94.9	109.4	107

Table 2: Effect of Incubation Time on the Percent of CP-526,555 (1.0 μM) Remaining in Rat or Monkey Microsomal Incubations (0.2 μM Cytochrome P450).

Incubation Time (min)	Rat	Monkey
0	100.0	100.0
2	81.7	101.0
5	102.7	91.1
10	114.7	102.9
20	100.5	103.2
35	173.0	110.0

6. FIGURES

Figure 1: Substrate Disappearance Plots for CP-526,555 (10 μM) Following Incubation With Rat, Dog or Human Hepatic Microsomes (1 μM Cytochrome P450).

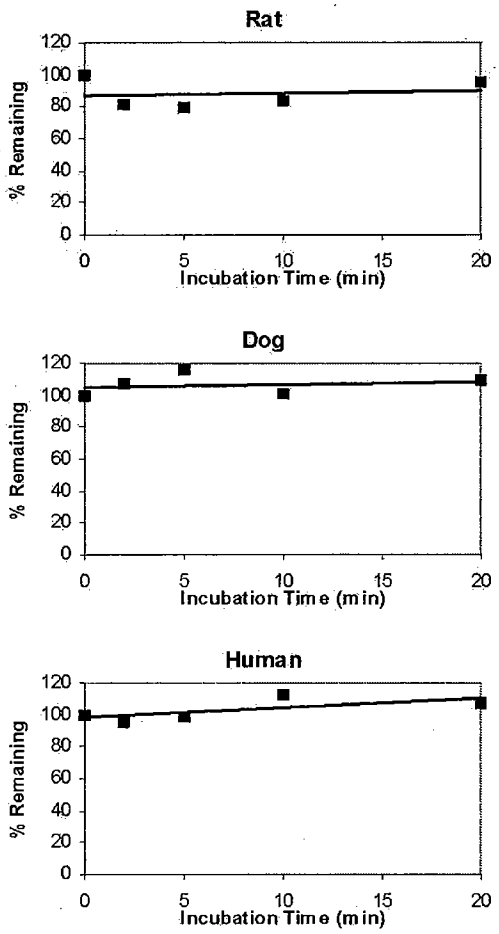
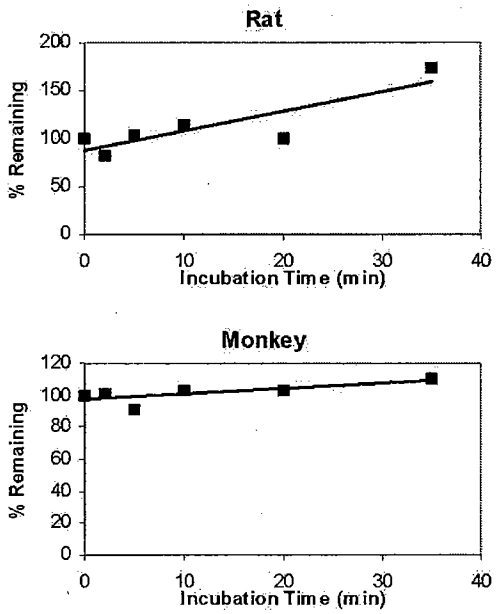


Figure 2: Substrate Disappearance Plots for CP-526,555 (1.0 μM) Following Incubation With Rat or Monkey Hepatic Microsomes (0.2 μM Cytochrome P450).



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Effect of CP-526,555 on Human Drug Metabolizing Enzymes *In Vitro*

DM Study Number: DM2001-526555-045

1. OBJECTIVE

The objective of these experiments is to determine the potential for CP-526,555 to inhibit human drug metabolizing enzymes *in vitro*.

2. METHODS

2.1 Incubation Procedures: IC_{50} Determinations

Standard marker activity substrates were incubated with pooled human liver microsomes (HL-MIX-13) in the presence of NADPH (1.3 mM;) in 100 mM KH_2PO_4, pH 7.4 containing 3.3 mM $MgCl_2$ at 37°C open to air. The incubation volume was 0.2 mL. Microsomal protein concentrations, substrate concentrations, incubation times, and reaction termination solvents for each activity are described in Appendix 1. Substrate concentrations utilized were near K_m values that had been previously determined and incubation times were selected based on previous determinations of reaction velocity linearity. (Refer to laboratory notebooks [ ]). CP-526,555-18 (lot #50452-17-5MS) was tested at 0 (control), 0.30, 3.0, and 30 µM, in duplicate for percent inhibition experiments (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A) and at 0 (control), 0.0952, 0.301, 0.951, 3, 9.49, and 30 µM in duplicate for IC_{50} determinations (CYP2A6, CYP2C8, CYP2E1). CP-526,555 was delivered to the incubation mixtures in 2 µL of 50/50 CH_3CN/H_2O. Incubations were commenced with the addition of NADPH. At the end of the incubation period, termination solvent containing internal standard was added and, except for felodipine oxidase evaluations, the terminated incubation mixture was typically filtered using [ ] to remove microsomal protein. Samples were directly injected on the HPLC/MS/MS system.

2.2 Sample Analysis

Filtered terminated incubation mixtures were analyzed by HPLC-MS/MS using a [ ] The HPLC system consisted of [ ] Summaries of each analytical procedure and assay performance values are listed in Appendix 2. Assay procedures are described in detail in validation reports for each analyte.

2.3 Calculations
Reaction velocities were calculated as:

$$\text{Reaction Velocity} = \frac{\text{nmol product formed}}{\text{incubation time} \times \text{microsomal protein concentration}}$$

% Control activities were calculated as:

$$\%\,\text{Control Activity} = 100 \times \left(\frac{\text{Avg (N = 2) metabolite formed with inhibitor}}{\text{Avg (N = 2) metabolite formed w/o inhibitor}} \right)$$

3. RESULTS

3.1 IC_{50} Determination
CP-526,555 was examined for effects on several drug metabolizing enzyme activities in pooled human liver microsomes. A summary of percentage inhibition (30μM) values are listed in Table 1. CP-526,555 demonstrated little or no inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A (felodipine oxidase, midazolam 1'-hydroxylase, testosterone 6β-hydroxylase) activities. IC_{50} values could not be calculated since CP-526,555 did not inhibit any activity more than 25%.

4. INTERPRETATION

Based on these in vitro data, CP-526,555 should not demonstrate pharmacokinetic drug interactions with compounds for which CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A mediated metabolism constitutes the primary mechanism of clearance.

5. TABLES

Table 1.

Effect of CP-526,555 on Human Drug Metabolizing Enzymes *In Vitro*

DM Study Number: DM2001-526555-045

Summary of IC_{50} Data for CP-526,555 in Human Liver Microsomes

Marker Substrate Activity	Enzyme	% of control at [I] = 30 μM	IC_{50} (μM) Mean ± SE
Phenacetin *O*-Deethylase	CYP1A2	100	>30
Coumarin 7-Hydroxylase	CYP2A6	110	>30
Bupropion Hydroxylase	CYP2B6	99	>30
Amodiaquine *N*-Deethylase	CYP2C8	99	>30
Diclofenac 4'-Hydroxylase	CYP2C9	93	>30
S-Mephenytoin 4'-Hydroxylase	CYP2C19	100	>30
Dextromethorphan *O*-Demethylase	CYP2D6	96	>30
Chlorzoxazone 6-Hydroxylase	CYP2E1	100	>30
Felodipine Oxidase	CYP3A	75	>30
Midazolam 1'-Hydroxylase	CYP3A	90	>30
Testosterone 6β-Hydroxylase	CYP3A	97	>30

6. APPENDICES

Appendix 1.

Effect of CP-526,555 on Human Drug Metabolizing Enzymes *In Vitro*

DM Study Number: DM2001-526555-045

Summary of Incubation Conditions: IC_{50} Determination

Marker Substrate Activity	Enzyme	Substrate Concentration (μM)	Microsomal Protein Concentration (mg/mL)	Incubation Time (min)	Termination Solvent
Phenacetin *O*-Deethylase	CYP1A2	50 μM	0.03	30	5/92/3
Coumarin 7-Hydroxylase	CYP2A6	1.0 μM	0.025	6	5/92/3
Bupropion Hydroxylase	CYP2B6	80 μM	0.05	20	5/92/3
Amodiaquine *N*-Deethylase	CYP2C8	1.9 μM	0.025	10	5/92/3
Diclofenac 4'-Hydroxylase	CYP2C9	4 μM	0.03	10	5/92/3
S-Mephenytoin 4'-Hydroxylase	CYP2C19	60 μM	0.2	40	5/92/3
Dextromethorphan *O*-Demethylase	CYP2D6	5 μM	0.03	10	5/92/3
Chlorzoxazone 6-Hydroxylase	CYP2E1	75 μM	0.05	20	5/92/3
Felodipine Oxidase	CYP3A	5 μM	0.01	10	50/47/3
Midazolam 1'-Hydroxylase	CYP3A	2.5 μM	0.03	4	92/5/3
Testosterone 6β-Hydroxylase	CYP3A	50 μM	0.03	10	5/92/3

Termination solvent ratio = Acetonitrile/Water/Formic Acid

4.2.24 Review of five In vitro and In vivo drug transporter drug interaction studies:
DM2003-526555-053: In vitro Caco-2 permeability studies;
DM1998-526555-006: Assessment of Blood Cell Partitioning and Plasma Protein;
DM2003-526555-052: In Vitro Transport of CP-526,555;
A3051031: Digoxin-varenicline PK drug interaction study;
A3051032: Warfarin-varenicline PK drug interaction study

NDA: 21-928	Submission Date: November 10, 2005
Brand Name	Champix®
Generic Name	Varenicline Tartrate
Reviewers	Srikanth Nallani, Ph.D, Primary Reviewer Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
Formulation; Strength(s)	Film Coated Tablet; 0.5 & 1 mg
Indication	Smoking Cessation

Summary of Review (5 studies)

Reviewer's Note: CP-526,555 and varenicline were used interchangeably in this review.

In Vitro Studies:

DM2003-526555-053
Title: In Vitro Assessment of Human Intestinal Permeation of CP-526,555 Using Caco-2 Cells Monolayers

OBJECTIVES: The objective of this study was to determine the permeation (and mechanisms that determine the permeation) of CP-526,555 (varenicline) using the Caco-2 cell monolayer, an in vitro tissue culture model of human intestinal epithelium.

Studies Conducted:
A→B and B→A assay with 5, 15 and 50 □M CP-526,555 co-incubated with 25 □M metoprolol and 0.1 mg/mL lucifer yellow; pH 6.5/7.4.
A→B and B→A assay with 5, 15 and 50 □M CP-526,555 co-incubated with 25 □M metoprolol and 0.1 mg/mL lucifer yellow; pH 7.4/7.4.
A→B and B→A assay with 5, 15, and 50 □M CP-526,555 co-incubated with 1 □M mannitol and 0.1 mg/mL lucifer yellow; pH 6.5/7.4.
A→B and B→A assay with 1 □M Acyclovir, Methotrexate, Verapamil, Caffeine, Doxorubicin, Erythromycin, each co-incubated with 0.1 mg/ml lucifer yellow; pH 6.5/7.4.

Results:
Data are shown in Tables 1 and 2.

The apparent permeability (Papp,a-b) of varenicline across Caco-2 cell monolayers was determined in the presence of 25 uM metoprolol. The permeability was pH-dependent.

At pH 7.4/7.4, Papp was 19.8-23.9 $X10^{-6}$ cm/sec and at pH 6.5/7.4, Papp,a-b was 7.31-9.18 $X10^{-6}$ cm/sec. pH-dependency in the permeability is possibly due to changes in the ionization state of CP-526,555 under different pH. The permeability data for varenicline at both pH conditions were similar to those obtained for metoprolol.

Varenicline permeation was independent of concentration (5-50 uM).

Table 1. CP-526,555 P_{app} values (A→B and B→A) and Efflux Ratios Determined Using Caco-2 Cells Under Various Experimental Conditions

			P_{app} (X 10^{-6} cm/sec)		
			$P_{app,A\rightarrow B}$	$P_{app,B\rightarrow A}$	
CP-526,555 (μM)	pH (A/B)	Co-Incubation[1]	Mean ± SD	Mean ± SD	Efflux Ratio
5.0	6.5/7.4	metoprolol	9.18 ± 2.25	53.1 ± 5.33	5.8
15	6.5/7.4	metoprolol	9.11 ± 0.43	50.6 ± 2.27	5.6
50	6.5/7.4	metoprolol	7.31 ± 0.53	48.2 ± 2.37	6.6
5.0	7.4/7.4	metoprolol	23.9 ± 1.34	35.6 ± 1.85	1.5
15	7.4/7.4	metoprolol	19.8 ± 1.21	35.8 ± 0.92	1.8
50	7.4/7.4	metoprolol	20.4 ± 0.95	33.7 ± 1.75	1.6
5.0	6.5/7.4	mannitol	8.48 ± 0.83	40.2 ± 9.86	4.7
15	6.5/7.4	mannitol	8.62 ± 1.20	29.9 ± 2.11	3.5
50	6.5/7.4	mannitol	8.51 ± 0.28	28.2 ± 5.46	3.3

[1] Co-incubation with 25 μM metoprolol or 1 μM mannitol
NA = Not Applicable

Table 2. Control Compound P_{app} values (A→B and B→A) and Efflux Ratios Determined Using Caco-2 Cells Under Various Experimental Conditions

			P_{app} (X 10^{-6} cm/sec)		
			$P_{app,A\rightarrow B}$	$P_{app,B\rightarrow A}$	
Compound[1]	pH (A/B)	Co-Incubation	Mean ± SD	Mean ± SD	Efflux Ratio
metoprolol	6.5/7.4	5 μM CP-526,555	2.25 ± 0.71	40.0 ± 10.6	7.6
metoprolol	6.5/7.4	15 μM CP-526,555	5.61 ± 1.42	35.3 ± 1.87	6.3
metoprolol	6.5/7.4	50 μM CP-526,555	5.15 ± 0.30	32.2 ± 1.89	6.3
metoprolol	7.4/7.4	5 μM CP-526,555	16.3 ± 1.22	25.0 ± 0.32	1.5
metoprolol	7.4/7.4	15 μM CP-526,555	13.5 ± 0.57	26.1 ± 2.23	1.9
metoprolol	7.4/7.4	50 μM CP-526,555	14.8 ± 2.73	24.3 ± 0.35	1.6
mannitol	6.5/7.4	5 μM CP-526,555	2.37 ± 0.97	4.85 ± 1.08	2.0
mannitol	6.5/7.4	15 μM CP-526,555	2.42 ± 0.82	6.63 ± 0.60	2.7
mannitol	6.5/7.4	50 μM CP-526,555	2.29 ± 1.05	5.10 ± 3.73	2.2
acyclovir	6.5/7.4	none	2.36 ± 0.42	3.08 ± 0.52	1.3
methotrexate	6.5/7.4	none	2.19 ± 0.32	4.42 ± 0.39	2.0
Verapamil[2]	6.5/7.4	none	9.23 ± 1.38	13.6 ± 4.06	1.5
caffeine	6.5/7.4	none	31.3 ± 3.67	55.1 ± 3.84	1.8
doxorubicin	6.5/7.4	none	1.37 ± 0.43	3.25 ± 0.46	2.4
erythromycin	6.5/7.4	none	1.36 ± 0.22	12.3 ± 1.81	9.0

[1] Each compound was assayed at 1 μM except metoprolol which was assayed at 25 μM
[2] Recovery for verapamil A→B and B→A assays was determined to be 71% and 59%, respectively

Discussion:

In this study, varenicline was co-incubated with internal standards for high (metoprolol) and low (mannitol) permeation and monolayer integrity (lucifer yellow) as recommended by the FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Because both varenicline and metoprolol are organic cations, potential interaction at the transport level exists. Co-incubation may not be appropriate. Data from Table 1 suggest that such interaction may be minimal under the experimental conditions because permeability data for varenicline under pH 6.5/7.4 were similar when varenilcine was co-incubated with metoprolol or mannitol (not expect to interact with varenicline).

The concentrations of varenicline (5,15 and 50 uM) tested in the Caco-2 study is higher than its clinical concentrations. C_{max} for varenicline at clinical doses (1 mg BID) is about 10 ng/mL (0.03 uM).

DM1998-526555-006
Title: Assessment of Blood Cell Partitioning and Plasma Protein Binding of CP-526,555 in Rat, Dog and Human Blood

OBJECTIVES
To characterize and compare the plasma protein binding and blood cell partitioning of CP-526,555 in rat, dog and human blood.

Results:
In human blood, the blood/plasma (B/P) ratio of varenicline was 1.0 at both 100 ng/mL and 400 ng/mL. In human plasma, the amount of drug bound to plasma proteins was 20.3% at100 ng/mL.

Discussion:
The protein binding data was determined from one individual using ultrafiltration method at 100 ng/mL. The concentrations of varenicline (100 ng/mL) tested in this study is much higher than its clinical concentrations (~10 ng/mL). It is not clear whether the protein binding is concentration-dependent. Protein binding of varenicline ranged between 10-20% as determined from ex-vivo samples.

Protein Binding of Varenicline in Healthy Adult Smokers, Subjects with Varying Degrees of Renal Function, and in the Elderly: Studies A3051010, A3051008, A3051009

Study Group	Dose	N	Fu (%) Mean (SD)	Fu (%) Range
A3051010				
Healthy Adult Smokers	2 mg single dose	12	93.5 (7.7)	
A3051008				
Normal Renal Function	0.5 mg QD	6	87.9 (16.7)	
Mild Renal Impairment	0.5 mg QD	6	88.6 (10.7)	
Moderate Renal Impairment	0.5 mg QD	6	85.3 (18.7)	
Severe Renal Impairment	0.5 mg QD	6	89.2 (3.8)	
End Stage Renal Disease	0.5 mg QD	5	87.1 (20.4)	
A3051009				
Healthy Elderly Smokers	1 mg QD	8	91.6 (4.6)	
Healthy Elderly Smokers	1 mg BID	8	90.4 (6.6)	

Source: Clinical Study Report A3051008, Section 13 Table 2.16; A3051009, Section 13 Table 2.8; A3051010, Section 13 Table 2.4
Plasma samples obtained at Tmax (2-4 hr post dose) and 24 hr after a single dose in study A3051010, 3 hr after the Day 12 dose in A3051008, and 3 hr after a single dose in A3051009.

DM2003-526555-052
Title: In Vitro Transport of CP-526,555

OBJECTIVE
The objective of these experiments is to determine the mechanism of renal clearance of CP-526,555 *in vitro*.

(Abbreviations: OCT: organic cation transporter; OAT: organic anion transporter; TEA: tetraethyl ammonium; PAH: p-aminohippuric acid)

Studies conducted:
CP-526,555 was screened by a panel of transporter inhibition assays (with HEK 293-transfected cells): hOCT2 inhibition assay using tetraethyl ammonium (TEA) as a substrate, hOAT1 inhibition assay using p-aminohippuric acid (PAH) as a substrate, hOAT3 inhibition assay using estrone sulfate as a substrate, hOCTN1 inhibition assay using TEA as a substrate and hOCTN2 inhibition assay using L-carnitine as a substrate. Three concentrations of CP-526,555, 0.5 mM, 1 mM and 5 mM, were evaluated in duplicate.

IC50 of varenicline in inhibiting hOCT2 was determined with TEA as substrate (50 uM). Kinetic parameters (Km and Vmax) of varennicline as a substrate for hOCT2 was determined. Interaction of cimetidine with varenicline was determined in vitro.

Results:
Inhibition assays indicated that this compound inhibits substrate uptake by hOCT2 with an IC_{50} of 959 ± 557 uM, but it has no or very weak interactions with other renal transporters (Table 1).

Varenicline is also a substrate for hOCT2. The apparent Km and Vmax values were 366 ± 90 μM and 1.74 ± 0.15 nmol/5 min/well (Figure 1).

Cimetidine, a known inhibitor of hOCT2, at 1 mM partially inhibits CP-526,555 uptake by HEK cells expressing hOCT2 (Figure 2).

Table 1.

Study DM2003-526555-052

Summary of Inhibition of Transporter Activities by CP-526,555 (1.0 mM) and Positive Control Inhibitors (1.0 mM).

		% Inhibition (Mean)	
Transporter	Positive Control Inhibitor	Positive Control	CP-526,555
hOCT2	Cimetidine	76.5	50.5
hOAT1	Probenecid	96.8	21.4
hOAT3	Probenecid	69.6	8.10
hOCTN1	Quinidine	77.2	ND
hOCTN2	Cimetidine	55.2	ND

HOCT2 inhibition assay using TEA (50 μM) as a substrate, hOAT1 inhibition assay using PAH (2 μM) as a substrate, hOAT3 inhibition assay using estrone sulfate (100 nM) as a substrate, hOCTN1 inhibition assay using TEA (100 μM) as a substrate and hOCTN2 inhibition assay using L-carnitine (200 nM) as a substrate . ND= not detectable.

Figure 1

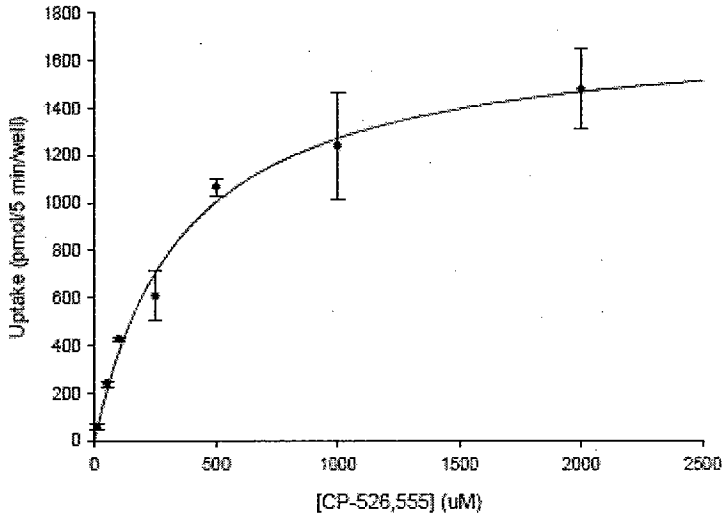
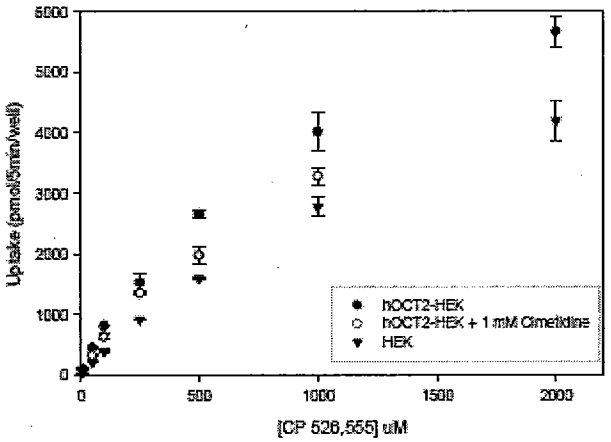


Figure 2



Discussion:

Varenicline is primarily eliminated via renal excretion. Comparing unbound renal clearance (~140 mL/min) to GFR (120 mL/min) indicates that active secretion is involved although may not be significant. The current *in vitro* transporter studies suggest that varenicline is a substrate for hOCT2 which likely plays a role in the renal secretion of varenicline in humans. Km is substantially greater than circulating concentrations associated with efficacy indicating that the transport process will not be saturated in the clinical settings. It is expected that renal clearance of varenicline would decrease if it is co-administered with a hOCT2 inhibitor. Theoretically, extent of inhibition would depend on the inhibition potency and the circulating level of the inhibitor. Extent of increase in exposure for varenicline due to transport inhibition would also depend on the percentage of renal clearance mediated by transport.

Cimetidine does not appear to be a potent inhibitor for hOCT2 from the *in vitro* study. At 1 mM, it only partially inhibits varenicline transport mediated by hOCT2. *In vivo* interaction study with cimetidine (300 mg QID) showed a 29% increase in exposure for varenicline and reduced renal clearance by an average of 25.1% (-33 mL/min on average) and brought the renal clearance close to GFR (Study A3051010). It appears that cimetidine, although is not a potent inhibitor for hOCT2 *in vitro*, almost completely inhibits the active transport component of varenicline *in vivo* if assuming little reabsorption is involved. It is possible that besides hOCT2, there is other transporter(s) in the kidney transports varenicline which are inhibitable by cimetidine.

Varenicline is a weak inhibitor for hOCT2 and even weaker inhibitor for OAT1, OAT3, OCTN1 and OCTN2. At therapeutic concentrations, varenicline is unlikely to inhibit drugs (e.g., metaformin, cisplatin, etc.) that are transported by hOCT2.

In Vivo Drug Interaction Studies:

Study A3051031
Title: Phase 1, Randomized, Investigator and Subject Blind, Sponsor Open, Placebo-Controlled, Multiple-Dose Study to Evaluate the Effect of Varenicline on the Safety, Tolerability and Multiple Dose Pharmacokinetics of Digoxin

Dates of Conduct: 10 July 2003 to 4 September 2003

Study Objectives:
To evaluate the effect of multiple dose administration of varenicline on the steady-state pharmacokinetics of digoxin in healthy adult smokers
To evaluate the safety and tolerability of digoxin administered at steady state concurrently with varenicline in healthy adult smokers

(Reviwer's Note: There is no obvious in vitro basis to suspect a potential interaction between varenicline and digoxin. The study was conducted because digoxin is a narrow therapeutic index drug and these two drugs are likely to be co-administered.)

Overall Study Design and Plan: Randomized, investigator- and subject-blind, sponsor-open, placebo-controlled, crossover design study. Subjects were to receive digoxin 0.2 mg once daily (QD) as Lanoxicaps for a total of 28 days (two 14-day periods) with a 7-day intervening washout. Varenicline or placebo was to be administered according to random assignment during the first period. Subjects were then to be crossed over to receive placebo or varenicline in the second period. All study medications were to be administered under fed conditions (standard meals). Subjects were to remain in the Clinical Research Unit (CRU) for approximately 15 days for each study period.

Regimen A: Digoxin 0.2 mg QD plus Varenicline 0.5 mg QD x 3 days followed by 0.5 mg twice daily (BID) x 4 days followed by 1 mg BID x 7 days administered as an oral dose under fed conditions

Regimen B: Digoxin 0.2 mg QD plus Placebo QD x 3 days followed by BID x 11 days administered as an oral dose under fed conditions

The 1 mg BID dose of varenicline used in this study represented the clinically relevant dose.

The dose of digoxin to be administered in this study (0.2 mg once daily [QD]) was selected based on precedent in literature and projection of serum concentrations associated with this dose.

Eighteen healthy male (n = 16) /female (n = 2) subjects between the ages of 18 and 55 years, inclusive, who were smoking currently and had smoked an average of at least 10 cigarettes per day during the past year (with no period of abstinence >3 months

continuous in the past year) were enrolled in the study. Body Mass Index (BMI) between 18 to 30 kg/m2, inclusive, and a total body weight >50 kg (110 lbs) were required.

Eighteen subjects were randomized as planned (see Table S-C below), and 18 subjects completed treatment in each regimen. All subjects were assessed for safety (AEs and laboratory tests). One subject (Subject 10011020) was not included in the PK analysis for CLr of digoxin as the subject's CLr was abnormally high (~ 450 mL/min) following digoxin + varenicline administration that is inconsistent with the corresponding digoxin plasma concentrations. The PK profiles in Periods 1 and 2 were similar.

(Reviewer's Note: It would be preferable to include CLr data analysis with and without Subject 10011020 to determine impact of data exclusion. However, because we would rely on the plasma data for comparison, it is acceptable to exclude the aberrantly high CLr value from the analysis.)

Table S-C. Demographic Characteristics of Study Population

Parameter	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Mean	44.7	175.2	75.0	24.5
SD	4.9	6.5	8.1	2.5
Range	37 - 55	163.0 – 191.0	60.0 – 93.0	18.5 – 29.4

N = 18 (16 males, 2 females)
50% White, 50% Black
SD = standard deviation

On Day 14 of each study period, blood samples to provide plasma for determination of varenicline plasma concentrations were to be collected at 0 hour (just prior to morning dosing), and serially up to 24 hours after morning dosing during each study period. Similarly, blood samples to provide plasma for digoxin pharmacokinetic (PK) analysis were to be collected on Day 14 at 0 hour (just prior to dosing) and serially up to 24 hours after dosing during each study period. Additionally, on Days 12 and 13 of each study period one sample was to be collected prior to administration of the morning doses of varenicline and digoxin to confirm steady-state attainment.

On Day 14 of each study period, a complete 24-hour urine collection was obtained for analysis of digoxin.

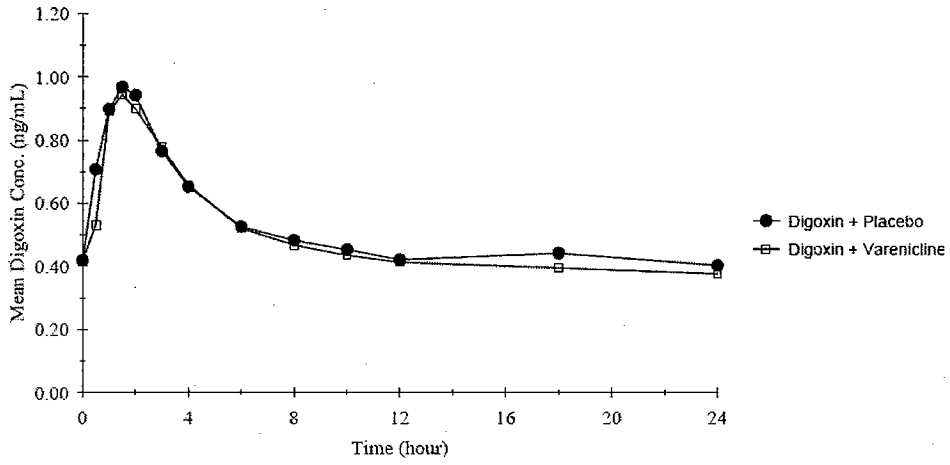
Samples were assayed for varenicline using liquid-liquid extraction followed by high performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) (LOQ 0.1 ng/mL). Samples were assayed for digoxin in both urine and plasma using a [redacted] radioimmunoassay method (LOQ 1 ng/mL and 0.15 ng/mL, respectively).

Results:
Twice daily administration of varenicline had no effect on steady-state digoxin plasma concentrations (Figure 1.1). The 90% CIs for the ratios of AUC(0-24) and Cmin values, based on log transformation, were contained within the established bioequivalence limits

of 80% -125% (Table R). A 11.3% increase in digoxin CLr occurred during concomitant varenicline administration but had no impact on systemic digoxin exposure. The 90% CI for the ratio of the CLr means was (95.26%, 130.04%) and included 100%. Given that digoxin plasma parameters were based on multiple concentration measurements while urinary parameters were based on a single 0 - 24 hour clearance measurement, plasma data would tend to be a more reliable outcome.

There was no obvious trend in the individual data towards increasing or decreasing exposures to digoxin when co-administered with steady-state varenicline (Figures 1.2 and 1.3).

Figure 1.1
CP-526,555 Protocol A3051031
Mean Plasma Digoxin Concentration-Time Profiles (Linear scale) After Multiple Oral Doses of 0.20 mg QD Digoxin Administered Alone or in Combination with Varenicline 1mg BID in Eighteen Healthy Smokers.



Source Data: Section 13. Table 2.2

Figure 1.2
CP-526,555 Protocol A3051031
Individual Digoxin Steady-State AUC(0-t) Values Following Multiple Oral Doses of 0.20 mg QD Dig Administered Alone or in Combination with Varenicline 1 mg BID in Healthy Smokers

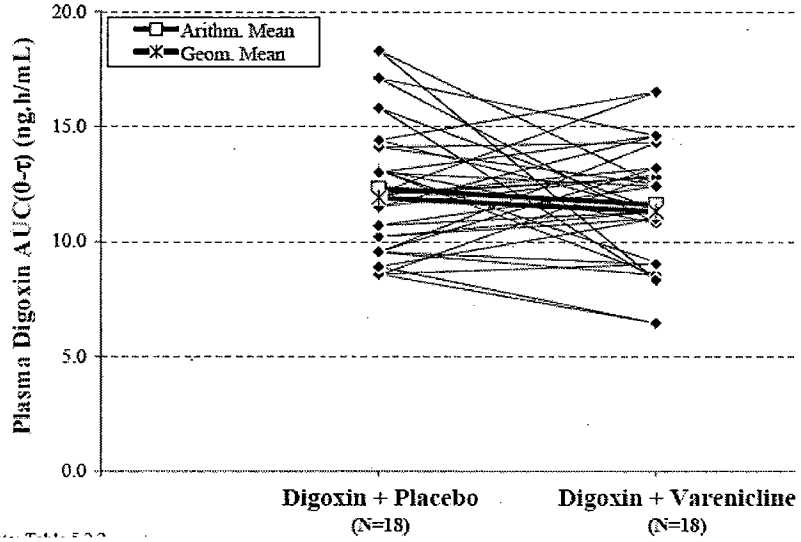
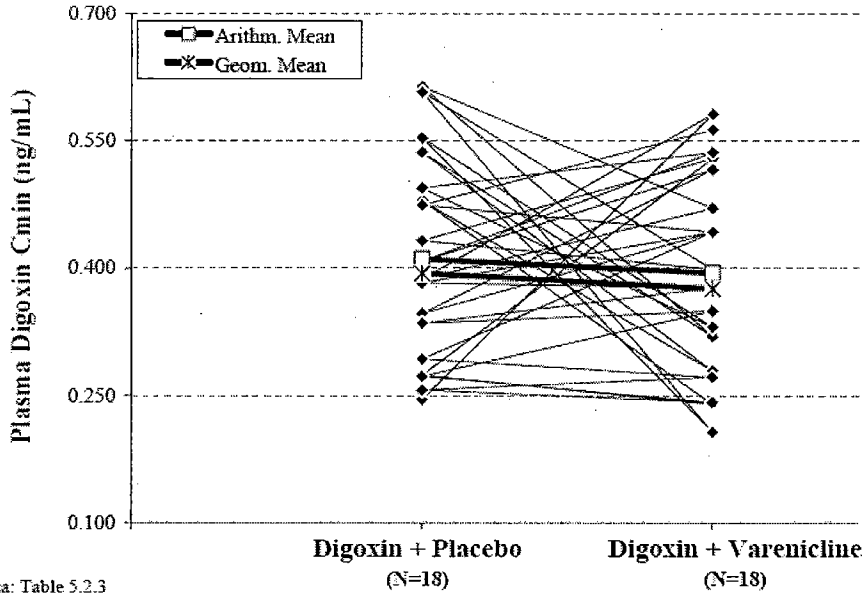


Figure 1.3
CP-526,555 Protocol A3051031
Individual Digoxin Steady-State Cmin Values Following Multiple Oral Doses of 0.20 mg QD Digoxin Administered Alone or in Combination with Varenicline 1 mg BID in Healthy Smokers



Source Data: Table 5.2.3
Date of Generation: 01/29/2004

Table Q. Summary (Mean ± SD) Pharmacokinetic Parameters for Digoxin

Treatment Period	N	AUC(0-τ) (ng•h/mL)	Cmin (ng/mL)	Cmax (ng/mL)	tmax[a] (h)	CLr (mL/min)
Digoxin + Placebo	18	12.3 ± 2.91	0.411 ± 0.120	1.25 ± 0.351	1.25 (0.50-2.00)	120 ± 35
Digoxin + Varenicline	18	11.6 ± 2.62	0.394 ± 0.121	1.19 ± 0.251	1.50 (0.50-3.00)	133 ± 33[b]

τ = dosing interval equal to 24 hours
[a]tmax presented as median (range)
[b]N=17; 1 subject excluded from PK and statistical analyses of CLr as digoxin CLr could not be adequately estimated (see Section 5.7.1.2)

Table R. Results of Statistical Analyses of Digoxin + Varenicline (Test) + Digoxin + Placebo (Reference) Pharmacokinetic Parameters

Parameters (units)	Adjusted Geometric Mean		Ratio[s] (%)	90% Confidence Intervals
	Digoxin + Varenicline	Digoxin + Placebo		
AUC(0-24) (ng·h/mL)	11.519	11.835	97.32	(87.51, 108.24)
Cmin (ng/mL)	0.384	0.389	98.66	(83.84, 116.10)
Cmax (ng/mL)	1.174	1.211	96.99	(87.53, 107.47)
CLr (mL/min)	128.179	115.163	111.30	(95.26, 130.04)

[s]Ratio of adjusted geometric means between test (digoxin + varenicline) and reference (digoxin + placebo)
AUC(0-24), Cmax, Cmin, and CLr were analyzed on the log scale.

Administration of digoxin concurrent with varenicline was generally well tolerated. Somnolence and headache were the most frequently reported AEs for both the digoxin + varenicline and
digoxin + placebo regimens.

Conclusion:
Multiple dose administration of varenicline (1 mg BID) had no effect on the steady-state pharmacokinetics of digoxin in healthy smokers. Therefore, digoxin doses do not need to be adjusted when administering concurrently with varenicline.

Study A3051032

Title: Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Dose Warfarin upon Co-administration with Varenicline in Healthy Adult Smokers

Dates of Conduct: 25 September 2003 to 12 November 2003

Study Objective(s):
Primary: to evaluate the pharmacokinetics of a single dose of warfarin in the absence and presence of steady state varenicline in healthy adult smokers.
Secondary: to describe the pharmacodynamics of a single dose of warfarin in the absence and presence of steady state varenicline in healthy adult smokers

(Reviwer's Note: There is no obvious in vitro basis to suspect a potential interaction between varenicline and warfarin. Varenicline is a low (<20%) protein-bound compound primarily excreted unchanged in the urine. In human hepatic microsomes, varenicline showed little or no inhibitory activity (IC50 >30 uM, 6.4 ug/mL) of the major cytochrome P450 enzymes. The study was conducted because warfarin is a narrow therapeutic index drug that is likely to be co-administered with varenicline.)

Overall Study Design and Plan: This was a subject- and investigator-blind, sponsor-open, randomized, 2-period, 2-sequence, placebo-controlled, crossover study. During the first study period subjects were to receive varenicline 1 mg twice daily (BID) or placebo with standard meals (8 AM, 6 PM) for 13 days. During the second study period subjects were to be crossed over to receive the remaining study medication. All subjects were to receive a single 25 mg dose of warfarin on Day 8 of each study period. Subjects were required to stay in the Clinical Research Unit (CRU) for approximately 14 days during each study period. There was to be sufficient washout such that there was a minimum 3-week interval between doses of warfarin.

Regimen A: Varenicline 1 mg BID x 13 days plus a single 25 mg dose of warfarin at approximately 0800 hours on Day 8 under fed conditions

Regimen B: Placebo BID x 13 days plus a single 25 mg dose of warfarin at approximately 0800 hours on Day 8 under fed conditions

The 1 mg BID dose of varenicline used in this study represented the clinically relevant dose.

As the aim of this study was to confirm *in vitro* predictions that varenicline would not affect the pharmacokinetics and pharmacodynamics of either enantiomer of warfarin, the single dose paradigm was used to minimize the operational complexity of the study. A single 25 mg
warfarin dose was selected as being sufficient to allow for evaluation of the pharmacokinetics of warfarin as well as increase in the prothrombin time by 20 - 25 seconds, thereby allowing for evaluation of the secondary PD endpoints using

international normalized ratio (INR). A 3-week interval between warfarin doses was selected based on precedent in the literature as being sufficient for the return of PD response to baseline conditions.

Healthy male and female smokers between 18 and 55 years of age, inclusive, who smoked an average of at least 10 cigarettes per day during the past year, with no period of abstinence greater than 3 months in the past year, were to be enrolled. Body Mass Index (BMI) between 18 to 30 kg/m2, inclusive, and a total body weight >50 kg were required. In order to have at least 16 evaluable subjects, 24 subjects were enrolled in the study (Table 9). All subjects were included in the safety and tolerability analyses as well as the pharmacokinetic/pharmacodynamic (PK/PD) analyses.

Table 9. Demographic Characteristics of Study Population

Parameter	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Mean	40.1	175.3	77.7	25.3
SD	7.7	6.9	11.4	3.1
Range	20 - 50	162.6 - 188	61.2 – 95.7	20.2 – 29.5

N = 24 (22 males, 2 females)
21% White, 79% Black

Blood samples for determination of (R)-warfarin and (S)-warfarin plasma concentrations were to be obtained prior to and after administration of the warfarin dose up to 144 hours. Blood samples for determination of prothrombin time (reported as International Normalized Ratio; INR) were to be obtained prior to and after administration of the warfarin dose up to 144 hours. In addition, on Days 6, 7, 8, and 9 blood samples for varenicline predose concentrations were to be collected just prior to administration of the morning dose to assess attainment and maintenance of varenicline steady state.

Plasma samples were analyzed for varenicline concentrations using a validated C

J assay. The dynamic range of the assay was 0.100 – 50.0 ng/mL. Plasma samples were analyzed for (R)-warfarin and (S)-warfarin concentrations using a validated stereoselective LC/MS/MS assay. The dynamic range of this assay was 5.00– 1000 ng/mL.

Pharmacokinetic Results:
Steady-state plasma concentrations of varenicline (1 mg BID) had no effect on the pharmacokinetics of both (R)- and (S)-enantiomers of warfarin administered as a single 25 mg oral dose (Figures 2 and 3). The mean ratios for AUC(0-inf) and Cmax of both (R)- and (S)-enantiomers were approximately 100% with the bounds of the 90% CI contained within the predefined limits for equivalence (80%, 125%) (Table 11).

Figure 2. Mean (R)-Warfarin Plasma Concentration-Time Profiles Following Multiple Oral Doses of Varenicline 1 mg BID or Placebo for 13 Days and a Single Dose of Warfarin 25 mg on Day 8 in 24 Healthy Adult Smokers

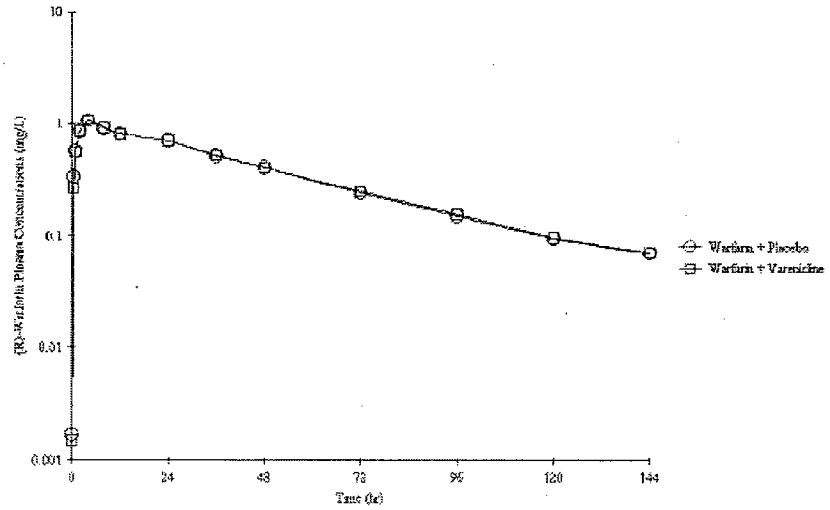
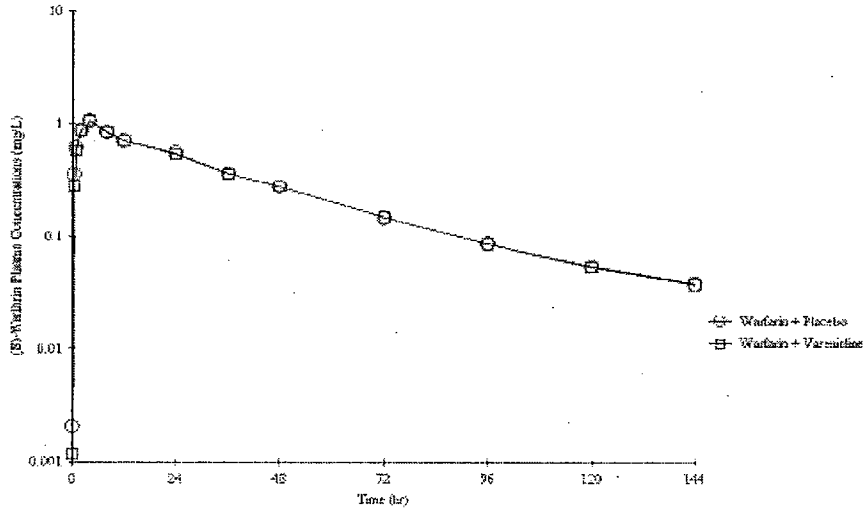
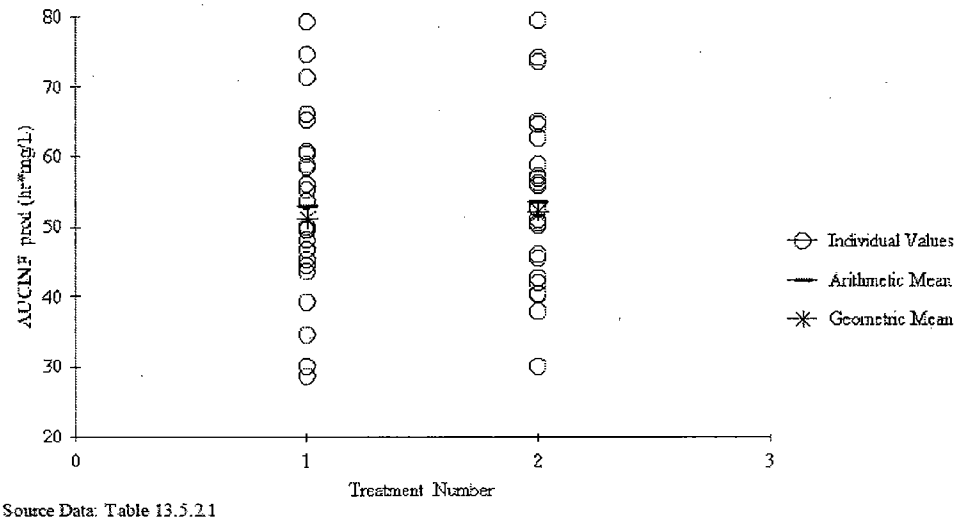


Figure 3. Mean (S)-Warfarin Plasma Concentration-Time Profiles Following Multiple Oral Doses of Varenicline 1 mg BID or Placebo for 13 Days and a Single Dose of Warfarin 25 mg on Day 8 in 24 Healthy Adult Smokers



There was no obvious trend in the individual data towards increasing or decreasing exposures (AUC and Cmax) to R- or S-warfarin when co-administered with steady-state varenicline (Figures 14.1.3 and 14.1.5 show AUC data).

Figure 14.1.3
CP-526,555 Protocol A3051032
Treatment Comparison of Individual and Mean AUC(0-INF) Values of (R)-Warfarin Following Multiple Oral Doses of Varenicline 1 mg BID (Treatment 2) or Placebo (Treatment 1) for 13 Days and a Single Dose of Warfarin 25 mg on Day 8 in Healthy Adult Smokers.



Source Data: Table 13.5.2.1
Date of Generation:21Apr04

Figure 14.1.5
CP-526,555 Protocol A3051032
Treatment Comparison of Individual and Mean AUC(0-INF) Values of (S)-Warfarin Following Multiple Oral Doses of Varenicline 1 mg BID (Treatment 2) or Placebo (Treatment 1) for 13 Days and a Single Dose of Warfarin 25 mg on Day 8 in Healthy Adult Smokers.

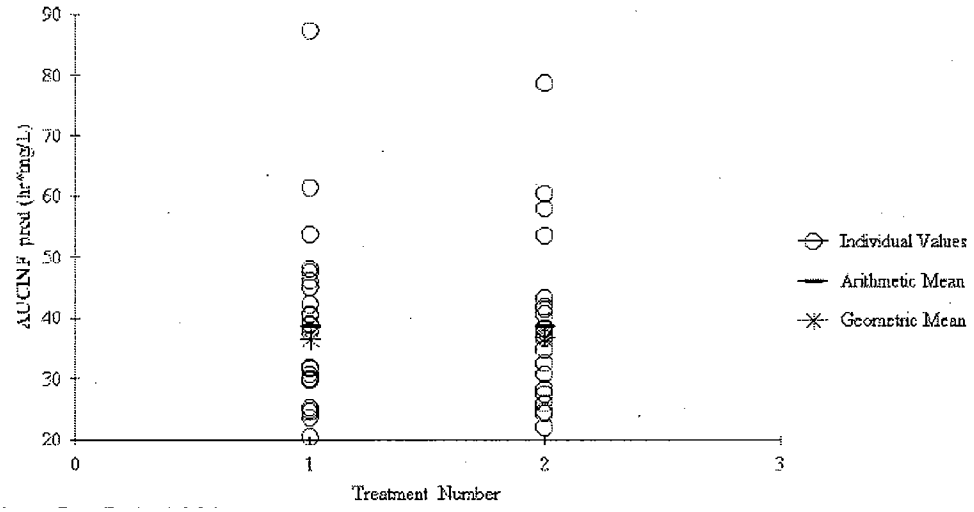


Table 10. Mean (SD) Pharmacokinetic Parameters of (R)- and (S)-Warfarin Following Multiple Oral Doses of Varenicline 1 mg BID or Placebo for 13 Days and a Single Dose of Warfarin 25 mg on Day 8 in Healthy Adult Smokers

	(R)-Warfarin (N = 24)		(S)-Warfarin (N = 24)	
Pharmacokinetic Parameters (units)	Placebo + Warfarin	Varenicline + Warfarin	Placebo + Warfarin	Varenicline + Warfarin
AUC(0-inf) (mg•h/L)	52.8 (13.2)	53.5 (12.2)	38.7 (14.6)	38.7 (13.2)
Cmax (mg/L)	1.08 (0.175)	1.09 (0.180)	1.08 (0.185)	1.07 (0.159)
tmax[a] (h)	4.00 (1.00 - 8.00)	4.00 (2.00 - 4.00)	4.00 (1.00 - 8.00)	4.00 (2.00 - 4.00)
t1/2 (h)	36.7 (7.10)	36.4 (6.62)	31.6 (6.63)	30.9 (7.21)

Source: Tables 13.5.2.1, 13.5.2.3 - 13.5.2.6 and 13.5.2.8 - 13.5.2.10
[a]Median (range)

Table 11. Summary Results of Statistical Analyses of Warfarin Pharmacokinetic Parameters When Co-administered with 1 mg BID Varenicline or Placebo in Healthy Adult Smokers

	Adjusted Geometric Means		Ratio*	90 % Confidence Intervals
Pharmacokinetic Parameters (units)	Placebo + Warfarin (Reference)	Varenicline + Warfarin (Test)		
(R)-Warfarin (N=24)				
AUC(0-inf) (mg•h/L)	51.18	52.18	101.95	(98.03,106.03)
Cmax (mg/L)	1.07	1.07	100.69	(97.30,104.19)
(S)-Warfarin (N=24)				
AUC(0-inf) (mg•h/L)	36.54	36.81	100.76	(97.07,104.58)
Cmax (mg/L)	1.06	1.06	100.14	(96.84,103.54)

*Ratio between Mean 1 (test) and Mean 2 (reference)
Source: Tables 13.5.3.1 - 13.5.3.2

Pharmacodynamic Results:
Steady-state plasma concentrations of varenicline (1 mg BID) had no effect on the pharmacodynamics of racemic warfarin (Figure 4). The mean ratios for INRmax and AUC(INR) were approximately 99% with the bound of the 90% CI contained within the (80%, 125%) equivalence range (Table 12). In addition, there was no marked change in tmax(INR) between both treatment periods.

Figure 4. Mean (SD) Pharmacodynamic Effect of Racemic Warfarin on Prothrombin Time Reported as INR Following Multiple Oral Doses of Varenicline 1 mg BID or Placebo for 13 Days and a Single Dose of Warfarin 25 mg on Day 8 in 24 Healthy Adult Smokers

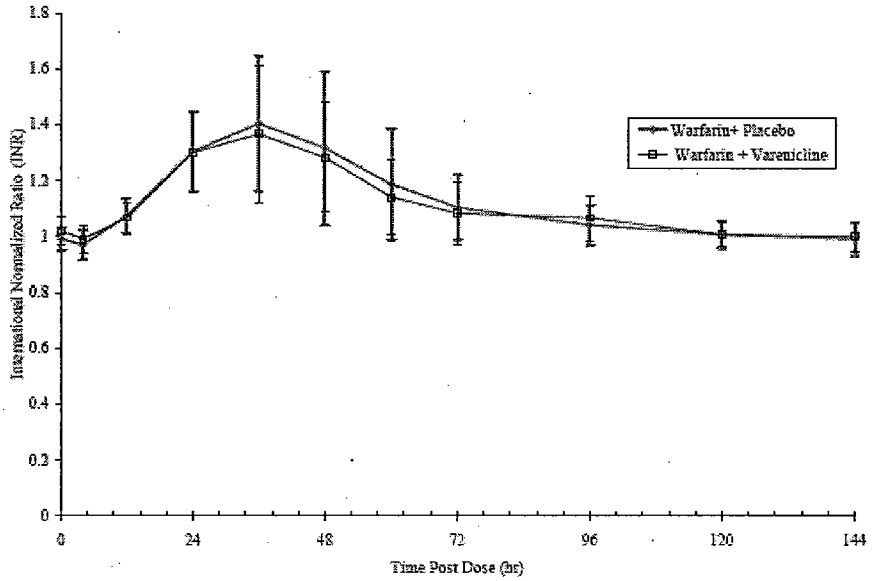


Table 12. Summary Results of Statistical Analyses of Racemic Warfarin Pharmacodynamic Parameters When Co-administered with Varenicline or Placebo

Pharmacodynamic Parameters (units)	N	Adjusted Geometric Means		Ratio*	90 % Confidence Intervals
		Placebo + Warfarin (Reference)	Varenicline + Warfarin (Test)		
AUC(INR) (h)	24	161.54	160.64	99.44	(97.64,101.28)
INRmax	24	1.40	1.39	99.44	(95.44,103.60)

*Ratio between Mean 1 (test) and Mean 2 (reference)
Source: Table 13.5.4

Observed within-subject variability for primary PD endpoints was <5% for AUC(INR) and <10% for INRmax.

Conclusion:
Multiple dose administration of varenicline has no effect on the single-dose pharmacokinetics and pharmacodynamics of racemic warfarin in healthy smokers. Administration of a single 25 mg dose of warfarin with varenicline 1 mg BID was safe and well tolerated. Effect of varenicline on PK and PD of multiple dose warfarin is unknown.

PHARMACOMETRICS REVIEW

NDA number:	21-928
Submission date:	November 9, 2005
Generic name:	varenicline tartrate
Sponsor:	Pfizer, Inc.
Type of submission:	New Drug Application
Indication:	Smoke Cessation
Primary Reviewer:	Srikanth Nallani, Ph.D.
PM reviewers	Jenny J Zheng, Ph.D.

Data Files:
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EXECUTIVE SUMMARY

The sponsor has conducted a population pharmacokinetic (PPK) analysis and the pharmacokinetic pharmacodynamic (PK/PD) analyses to support the application.

The PPK analysis showed renal function has the greatest effect on the pharmacokinetics of varenicline. Varenicline clearance is 10.4 L/hr in subjects with normal renal function and 4.4 L/hr in severe renal impaired (GFR = 20 mL/min). This 2.4-fold change in clearance also results in an increased elimination half-life of varenicline. Based on this model, simulation was conducted to evaluate a reduced dosing frequency from twice a day (bid) to varenicline once daily (qd) in patients with severe renal impairment. The results showed that the average concentrations are similar between healthy subjects who receive 1 mg varenicline bid and severer renal impaired subjects who receive 1 mg varenicline qd.

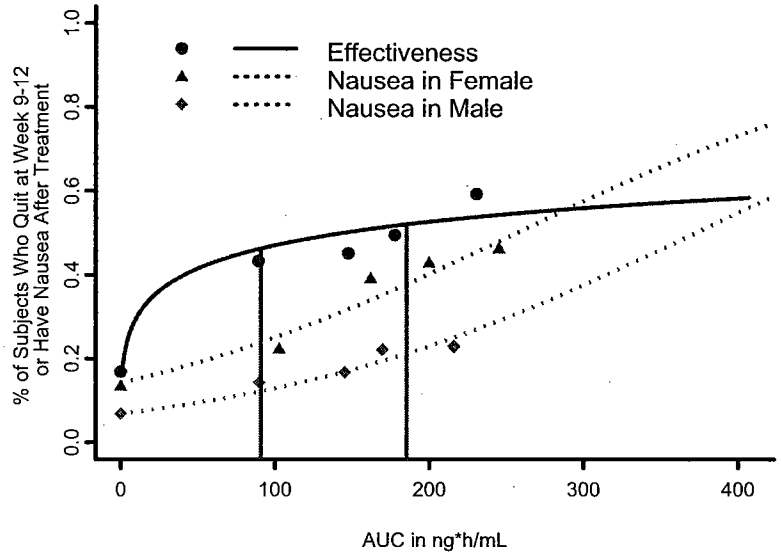
A PK/PD analysis showed that the probability of continuous abstaining from smoking at week 9-12 after the treatment, which is the primary effectiveness end point, is related to varenicline exposure, baseline smoking status measured by Fagerstrom Questions 1 (FSQ1): how soon do you want to smoke after wake up in the morning: < 5 mins, 6-30 mins, 31-60 mins, and >61 mins, and age. The relationship between effectiveness of varenicline treatment and the varenicline exposures is presented in Figure 1.

- Using a 45 years old and $FSQ1_{(6\text{-}30min)}$ subject as a reference, the probability of abstaining smoking from week 9-12 were 17%, 46% and 52% for placebo, 0.5 mg bid regimen, and 1 mg bid regimen, respectively. The mean daily steady state AUC ($AUC_{0\text{-}24,ss}$) are 87.55 ng·h/mL and 185.24 ng·h/mL after 0.5 mg bid and 1.0 mg bid, respectively.
- The PK/PD relationship for effectiveness was not different between male and female.
- At 1 mg bid regimen, the predicted probability to quit for a 45 year old, decreased from 0.70 (FSQ1(>60min)) to 0.43 (FSQ1(<5min)) as the degree of addiction increases.
- At 1 mg bid regimen, the probability to quit increases from 0.39 to 0.66 for $FSQ1_{(6\text{-}30min)}$ subjects increasing age from 18 to 75 year old.

The PK/PD analysis also showed that the incidence of nausea was related to gender and the varenicline exposure (Figure 1).

- The nausea rates in placebo group are 7% and 14% in male and female, indicating a two-fold higher incidence in females.
- For males, the incidences of nausea are about 7%, 12%, and 21% in placebo, 0.5 mg bid and 1 mg bid treatment, respectively.
- For females, the incidences of nausea are about 14%, 23%, and 38% in placebo, 0.5 mg bid, and 1mg bid treatment, respectively.

Figure 1. The Relationship of Effectiveness of Varenicline Treatment or the Incidences of Nausea and Varenicline Exposure



The blue solid line represents the relationship between probability of continuous abstaining from smoking at week 9-12 and varenicline exposure;
The two dashed lines represent the relationships between probability of nausea in female (red) and male (green) and varenicline exposure;
Two vertical brown lines represent the mean varenicline daily steady state AUC after 0.5 mg bid and 1 mg bid;
The solid cycles, triangles, and diamonds represent the observed response rates, nausea incidence rates in females, and nausea incidence rates in males of placebo group and other four varenicline treatment groups according to the AUC values: subjects with AUC in 1) 0-25% percentile; 2) 26%-50% percentile ; 3) 51-75% percentile; and 76% to 100 percentile;

In conclusion, the effectiveness of varenicline is supported by the exposure response analysis. The probability of abstaining from smoking at week 9-12 after treatment increased from placebo to 0.5 mg bid to 1 mg bid. However, the incidence of nausea is also related to the varenicline exposure especially in women. At proposed dose regimen of 1.0 mg bid, the nausea incidence could be as high as 40% in women.

RECOMMENDATIONS:
The exposure response analyses support the effectiveness of varenicline. However, both effectiveness, measured as continuous quitting rate at week 9-12 after treatment, and incidence of nausea are related to varenicline exposure. The analyses suggest that increasing dose from 0.5 mg bid to 1 mg bid, the probability of quitting increases to a nominal extent, from 45% to 51%. However, when dose is increased from 0.5 mg bid to

1 mg bid, the probability of nausea is increased more significantly from 25% to 40% in female and from 12% to 20% in males. Based on these analyses, it is recommended that:

1. Varenicline treatment need to be started at 0.5 mg qd for the first three days and increased to 0.5 mg bid for 12 weeks. 1.0 mg bid could be considered for the subjects from whom the effectiveness of the treatment is lacking.
2. Since the varenicline exposure was increased by 2 fold in severe renal impaired subjects (CLcr<30mL/min) as compared with the exposure in normal renal function subjects, a 0.5 mg qd regimen is recommended in severe renal impaired subjects. 1 mg qd regimen can be considered if the effectiveness of varenicline treatment is lacking.
3. Labeling changes are recommended in three sections:
    a. A pharmacodynamic section is recommended to be included in the Clinical Pharmacology Section of the labeling;
    b. A 0.5 mg bid dose is recommended in Dosage Administration Section;
    c. A 0.5 mg qd dose is recommended, for severe renal impaired, in Dosage Administration Section;

The deletions are read as strikethroughs and additions are read as underlines

Usual Dosage For Adults

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support.

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

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Days 8 – End of treatment:	0.5 twice daily or 1.0 mg twice daily

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

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Dose tapering of CHAMPIX is not required at the end of treatment.

Special Populations

Patients With Impaired Renal Function

No dosage adjustment is necessary for patients with mild to moderate renal impairment.

For patients with severe renal impairment, the recommended dose of CHAMPIX is 0.5 mg once daily.

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Division of Pharmaceutical Evaluation III

INTRODUCTION

Varenicline is being developed for smoking cessation based on its properties as a partial agonist at α4β2 subtype neuronal nicotinic acetylcholine receptors. It is expected that a partial agonist of the α4β2 nicotinic receptor should provide relief from craving and withdrawal symptoms and, in addition, through its receptor antagonism, reduce the psychogenic reward associated with smoking.

The sponsor has conducted a population pharmacokinetic (PPK) analysis and a pharmacokinetic pharmacodynamic (PK/PD) analysis to support the application. The PPK analysis was used to identify significant covariates for the PK of varenicline and to estimate the varenicline exposures for the patients in phase 2 and 3 studies for the exposure response analysis. In addition, the results from PPK analysis were used to explore an adequate dose regimen for severe renal impaired subjects. PK/PD analysis was conducted to characterize the quantitative relationship between varenicline exposure and effectiveness and tolerability of the drug. In addition, the effects of other baseline characteristic such as age, gender, race and smoking status (baseline CO, Fagerstrom Questions 1 and 4) on the probability of quit were also examined.

METHODS:

The data for PPK analysis were obtained from four phase 1 studies (Study 1008, 1009, 1014, and 1015), two phase 2 studies (Study 1002 and 1007), and three phase 3 studies (Study 1028, 1036, and 1037). The data from phase 1 studies, in which intensive sampling scheme was used, are needed to define the structure model of varenicline since the data from phase 2 or 3 studies, in which sparse sampling scheme was used, are not sufficient. The non-linear mixed effect model implemented by NONMEM was used in the analysis. Rather than step wise search for covariates, the pre-defined covariates relationship was identified based on exploratory graphics, scientific interest, and mechanistic plausibility of prior knowledge. The PPK model was evaluated by bootstrapping and posterior predictive check.

The data for PK/PD analysis were obtained from phase 2 and 3 studies. For effectiveness analysis, the data from one phase 2 (Study 1007) and two phase 3 studies (Study 1028 and 1036) were pooled. For safety analysis, specifically, the incidence of nausea and the time when nausea occurred, the data from one phase 2 (Study 1007) and three phase 3 studies (Study 1028, 1036, and 1037) were pooled. A logistic regression analysis was used for analyzing the incidence of nausea and non-linear mixed effect model was used for analyzing the data of time when nausea occurred since more than one observation would be obtained from each patients.

RESULTS:

The PPK analysis showed that a two-compartment model can best describe the pharmacokinetic of varenicline. The relationship between covariate and PK parameters are described in the following equations and the parameter estimates for the final model are presented in Table 1.

$CL/F = \theta_{CL/F} \cdot \theta_{Black} \cdot \theta_{Other} \cdot (CRCL/100)^{\theta_{CRCL}}$

$V2/F = \theta_{V2/F} \cdot \theta_{Black} \cdot \theta_{Other} \cdot (WT/70)^{\theta_{WT}} \cdot (AGE/45)^{\theta_{AGE}}$

$V3/F = \theta_{V3/F} \cdot (WT/70)^{1}$

$Q/F = \theta_{Q/F} \cdot (WT/70)^{0.75}$

The PPK analysis identified that renal function has the greatest effect on the pharmacokinetics of varenicline. Varenicline clearance is predicted to decrease from 10.4 L/hr for a typical subject with normal renal function (estimated GFR = 100 mL/min) to 4.4 L/hr (estimated GFR = 20 mL/min) for a typical subject with severe renal impairment, thus resulting in an overall increase in daily steady-state exposure of 2.4-fold from the minimum to maximum of this renal function range. This change in clearance also results in an increased elimination half-life of varenicline. Based on this model, simulation was conducted to evaluate a reduced dosing frequency of 1 mg varenicline once daily or 0.5 mg bid in patients with severe renal impairment. The results are presented in Figure 2. The bold lines (black and red) are the median steady-state pharmacokinetic profiles of 0.5 mg BID and 1 mg QD, respectively and the shaded areas are the corresponding 95% prediction intervals for the population distribution. The upper and lower dotted lines are the 95% population prediction interval from Cmax to Cmin in the population with normal renal function at the 1 mg BID dose regimen. The simulation shows the both 1 mg QD or 0.5 mg BID in severe renal impaired subjects are within the concentration ranges in healthy subjects at 1 mg BID.

Figure 2. Predicted Steady-State Pharmacokinetic Profiles of Varenicline in Subjects with Severe Renal Impairment Following 1 mg QD or 0.5 mg BID Varenicline

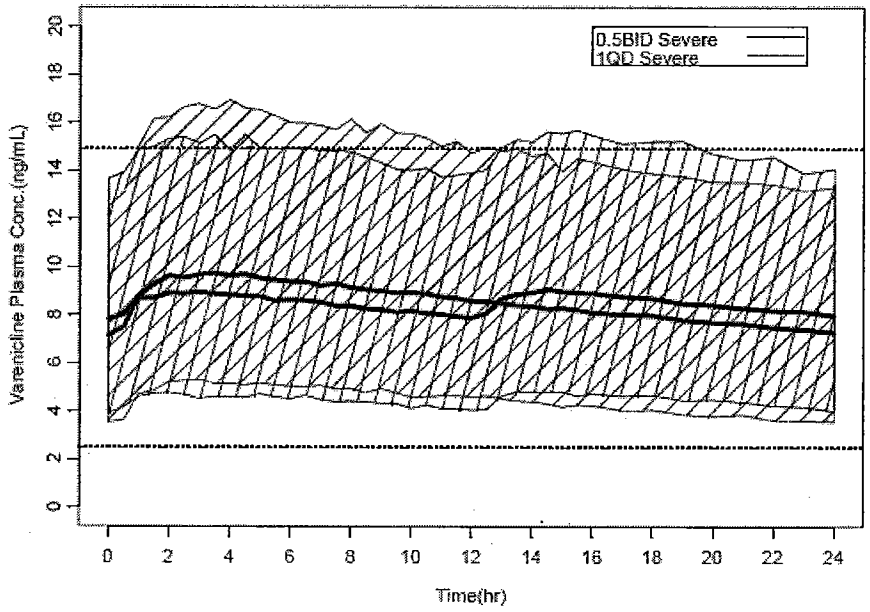


Table 1. Final Model Population Pharmacokinetic Parameter Estimates for Varenicline

Pharmacokinetic Parameter	Estimate	%RSE*	Bootstrapped 95% CI ** (lower, upper)
CL/F (L/hr)			
θ_{CL}	**10.4**	0.9%	(10.2 - 10.6)
θ_{CRCL}	0.54	5.6%	(0.48 - 0.59)
θ_{Black}	1.16	2.1%	(1.11 - 1.21)
θ_{Other}	1.11	3.3%	(1.04 - 1.18)
V2/F (L)			
θ_{V2}	**337**	4.4%	(309 - 364)
θ_{WT}	0.77	18.7%	(0.50 - 1.05)
θ_{AGE}	0.13	54.1%	(-0.01 - 0.30)
θ_{Black}	0.92	4.6%	(0.83 - 1.00)
θ_{Other}	0.71	10.4%	(0.58 - 0.89)
V3/F (L)			
θ_{V3}	**78.1**	12.7%	(61.9 - 98.9)
θ_{WT}	1 (Fixed)	--	--
Q/F (L/hr)			
θ_{Q}	**2.08**	22.2%	(1.39 - 3.79)
θ_{WT}	0.75 (Fixed)	--	--
Ka (hr-1)			
θ_{Ka}	**1.69**	9.2%	(1.27 - 2.00)
Alag (hr)			
θ_{Alag}	**0.43**	4.6%	(0.37 - 0.46)
Interindividual Variance			
ω^2_{CL}	0.061 (24.7% CV)	6.7%	(0.054 - 0.069)
ω^2_{V2}	0.25 (50.0% CV)	25.3%	(0.15 - 0.40)
ω^2_{Ka}	0.49 (70.1% CV)	38.9%	(0.23 - 0.97)
Cov_{Ka-V2}	0.24 (r = 0.67)	54.0%	(-0.05 - 0.53)
Cov_{CL-V2}	0.006 (r = 0.05)	133%	(-0.013 - 0.021)
Cov_{Ka-CL}	-0.009 (r = -0.05)	186%	(-0.045 - 0.040)
ω^2_{V3}	0 (Fixed)	-	-
ω^2_{Q}	0 (Fixed)	--	--
Residual Variance σ^2 **add** σ^2 **prop**	0.28 (SD = 0.5) 0.030 (17.2% CV)	23.5% 10.7%	(0.155 - 0.358) (0.024 - 0.036)
σ^2 add P3 σ^2 prop, P3	4.38 (SD = 2.1) 0.046 (21.5% CV)	21.0% 29.3%	(0.047 - 5.89) (0.025 - 0.128)

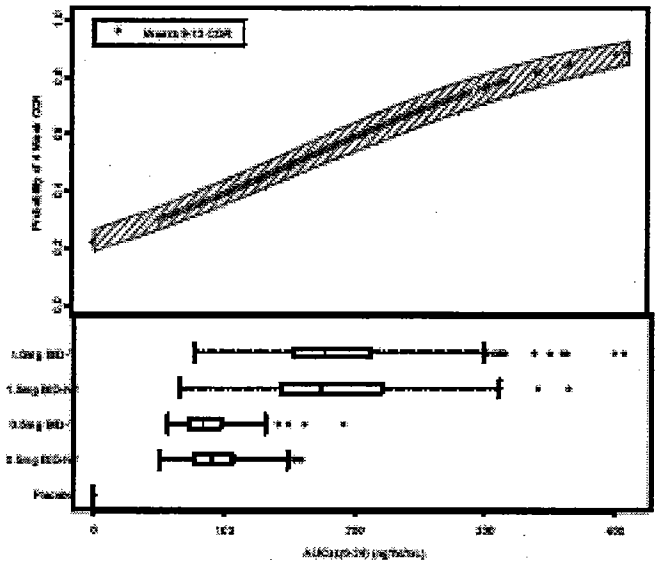
*%RSE: percent relative standard error of the estimate = SE/|parameter estimate| * 100
** 95% confidence interval (CI) of the parameter estimate derived from a nonparametric bootstrap analysis

The PK/PD analysis showed that both effectiveness end points and incidence of nausea are related to varenicline exposure. The individual varenicline exposures used in the analysis were the steady state daily area under the curve (AUC(0-24,ss)) and obtained from the aforementioned PPK analysis. The responses include both effectiveness and safety end point. Effectiveness end points are 1) continuous quit rate (CQR), defined as the proportion of subjects abstaining from smoking during the 4-week periods, week 9-12 after treatment (primary end point used in clinical study); 2) CQR during the week 4-7 after treatment; and 3) continuous abstinence (CA) from week 9-24 and 9-52. The safety end points include the incidence of nausea and the time course of nausea. Only the results of CQR at week 9-12 weeks are presented in this section and the results on CQR at week 4-7 and CA from week 9-24 and 9-52 can be found in detailed review included in appendix.

CQR from week 9-12:
The results showed that the probability of abstaining from smoking form week 9-12 after the treatment are related to drug exposure, the degree of addiction measured by the FSQ1, a question about how soon a subject wants to smoke after weak up in the morning: 0-5 minute, 6-30 minute, 31-60 minutes, or >60 minute, and age.

Using the typical smoking population (White, Male, 45 years old and FSQ1(6-30min)) as reference, the relationship between probability of Weeks 9-12 CQR and the bootstrapped 95% interval and the AUC(0-24,ss) is presented in Figure 3. The solid line represents the predicted exposure-response relationship for typical 45 yrs old, Fagerström Question 1 (6-30min) subject. The shaded area represents the bootstrapped 95% CI. The box and whisker plots at the bottom describe the distribution of the exposure data. T=titrated; NT= non-titrated

Figure 3. Exposure-Response Relationships for the Weeks 9-12 CQR for the Combined Phase 2/3 Studies



T=titrated; NT= non-titrated

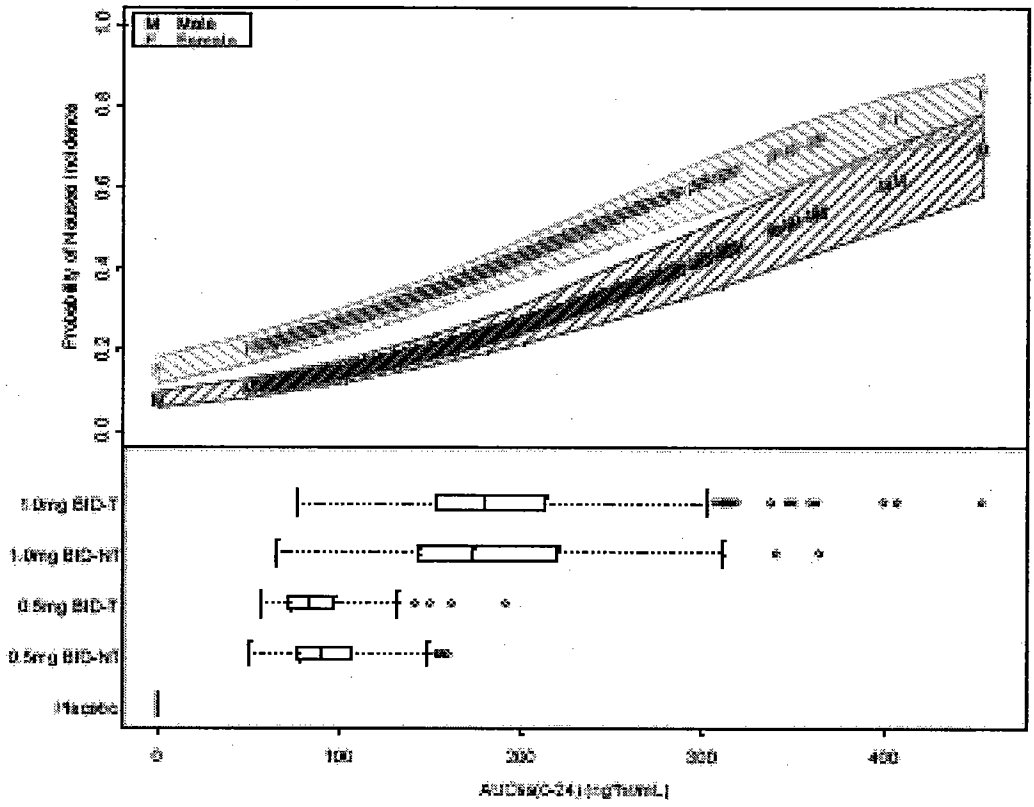
This analysis showed that:

- For a White, 45 years old and $FSQ1_{(6\text{-}30min)}$ subject, the average probability of quitting smoking from week 9-12 [bootstrapped 95% CI] increased from 0.22 [0.19-0.26] (Placebo) to 0.38 [0.34-0.42] (0.5 mg BID, mean AUC(0-24)ss = 94 ng·h/mL) and to 0.56 [0.51-0.61] (1 mg BID, mean AUC(0-24)ss = 186 ng·h/mL).
- The probability of quit decreased from 0.70 (FSQ1(>60min)) to 0.45 (FSQ1(<5min)) as the degree of addiction increases (based on FSQ1).
- The predicted probability of quit increases from 0.35 to 0.64 with increasing age across the 18 to 75 year old range.

Incidence of Nausea:

The analysis found that the probability of a nausea event to occur were positively related to varenicline exposure and associated with gender (Figure 4). In this figure, the solid red and black lines represent the predicted exposure-response relationship for typical female and male population of White, 45 yrs old, Fagerström Question 1(6-30min). The shaded area represents the bootstrapped 95% CI. The box and whisker plots at the bottom describe the distribution of the exposure data. The box itself indicates the difference between the first and third quartiles of the data, showing the spread of the data.

Figure 4. The Relationship between Probability of Nausea Incidence and Varenicline Exposure



T=titrated; NT= non-titrated

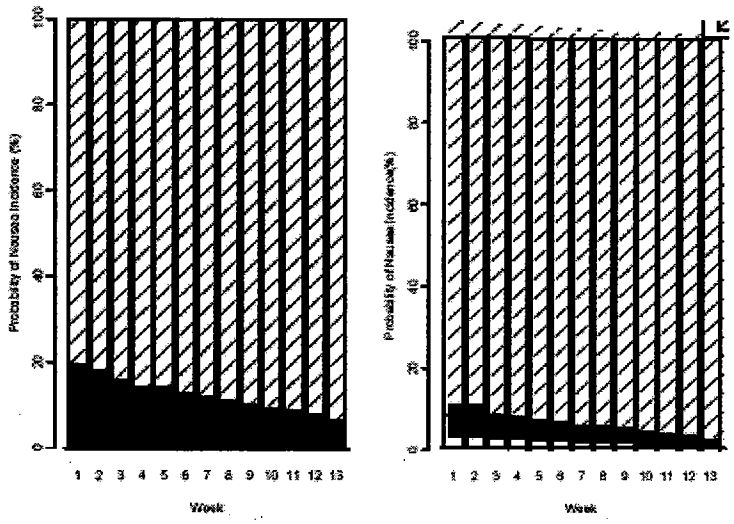
The results show that:

- The predicted nausea rates in placebo group are 0.07 and 0.14 in male and female, indicating a two-fold nausea incidence in females.
- For males, the predicted average incidence of nausea are about 0.07, 0.12, and 0.24 in placebo, 0.5 mg bid and 1 mg bid treatment, respectively.
- For females, the predicted nausea incidence are about 0.14, 0.25, and 0.40 in placebo, 0.5 mg bid, and 1mg bid treatment, respectively.

Time of Nausea Occurred

Nausea incidence in each week for 13 weeks in both female (left panel, Figure 5) and males (right panel, Figure 5) were summarized and presented in Figure 5. For subjects whose nausea event lasted more than one week, the nausea incidence was documented in each observed week interval. As shown in Figure 4, both male and female population exhibited a decrease in their weekly nausea incidence probability. Nausea incidence was highest at Week 1 with a rate of 13.5%, which decreased continuously over time to a rate of 4.1% at Week 13 in the overall smoking population.

Figure 5. Nausea Incidence in Each Week in Female and Male



CONCLUSION:

The population PK-PD analyses provided an integrated understanding of dose, exposure, response and relevant patient covariates for the effectiveness and tolerability of varenicline for smoking cessation. A clear varenicline exposure-response relationship was demonstrated for the probability of cessation.

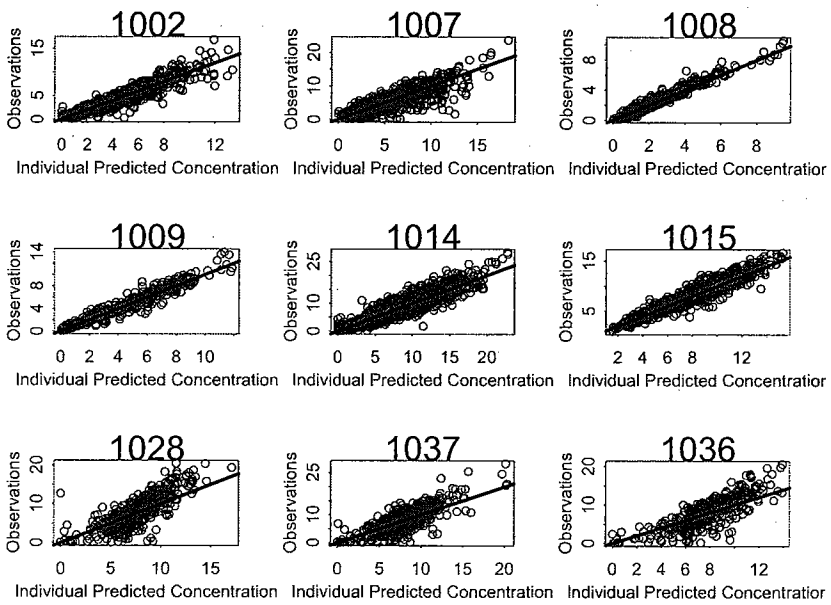
In addition, this analysis found that the most frequent adverse event with varenicline, nausea, is positively associated with drug exposure and female gender. A trend towards decreasing probability of nausea incidence with time was evident.

FDA'S EVALUATION:

The sponsor analysis was evaluated by FDA reviewer. The assessments of the analysis are described in section below:

1) Since the PPK analysis was conducted by combining phase 1, phase 2 and phase 3 studies. The predictions of phase 2 or 3 concentrations, which were sparse, may significantly be driven by the rich phase 1 concentrations. The plots of predicted individual concentrations vs individual observations by each study are presented in Figure 6. As shown in the figure, the predictions in phase 2/3 studies are reasonable and are considered acceptable for the further PK/PD analysis.

Figure 6. Individual Predictions vs Observations in Each Study



2) The relationship between CQR at week 9-12 after treatment or the nausea of incidence and the varenicline exposure was re-analyzed by FDA reviewer with the intension of confirming sponsor's analysis. The datasets, nmpd3 and nmpk5 used in the sponsor's analysis were used in this analysis. The exposures used in the analysis are $AUC_{(0\text{-}24,ss)}$. Logistic regression analysis implemented in Splus was used.

In the dataset used for PK/PD analysis (nmpd3), the mean $AUC_{(0\text{-}24,ss)}$ (range) at 0.5 mg bid and 1 mg bid are 90.93 (50.40-191) ng*h/mL and 185.24 (65.55-407.11) ng*h/mL, respectively.

CQR at week 9-12 after treatment:

To examine if it is acceptable to combine the data from different studies, the response rate in each treatment group across studies was summarized in Table 2.

It shows that the response rate in 1 mg bid non-titrate group of phase 2 study was similar to that in phase 3 studies but the response rate in 1 mg bid titrate group of phase 2 study was slightly higher as compared with the response rate in phase 3 studies.

Table 2. Summaries of Response Rate across Treatments and Studies

	# responder/# of total subjects (%)		
Study	**1007**	**1028**	**1036**
Placebo	15/121 (12%)	61/344 (18%)	60/341 (18%)
0.5 mg bid non-titrate [a]	61/124 (49%)	NA	NA
0.5 mg bid titrate [b]	53/129 (41%)	NA	NA
1.0 mg bid non-titrate [c]	57/124 (46%)	NA	NA
1.0 mg bid titrate [d]	71/129 (55%)	155/352 (44%)	151/344 (44%)
Zyban	NA	97/329 (29%)	102/342 (30%)

a = 0.5 mg BID (0.5mg tablets BID for 12 weeks)
b = 0.5 mg BID titrated (0.5mg tablets QD for 7 days followed by 0.5mg BID for 11 weeks)
c = 1 mg BID (1mg tablet BID for 12 weeks)
d = 1 mg BID titrated (0.5 mg tablets QD for 3 days, then 0.5mg BID for 4 days followed by 1 mg BID for 11 weeks)

The logistic regression analysis was conducted using varenicline $AUC_{(0\text{-}24,ss)}$, FSQ1, and age as predictors. The analysis also suggested that probability of quitting smoking at week 9-12 after the treatment are related to varenicline $AUC_{(0\text{-}24,ss)}$, FSQ1, and age. Another model, in which a log transformed $AUC_{(0\text{-}24,ss)}$ (logAUC) replace the $AUC_{(0\text{-}24,ss)}$ as the exposure measure. The predicted probability of quitting smoking vs AUC by these two models in 45 years old, FSQ1(31-60 minute) subject are presented in Figure 6 and Figure 7, respectively. The observed individuals are divided into five groups according to $AUC_{(0\text{-}24,ss)}$: 0 (placebo), 0-25 percentile, 26-50 percentile, 51-75 percentile, and 76 to 100 percentile of the population. The response rate in each group at the median $AUC_{(0\text{-}24,ss)}$ of the group is shown as point in Figure 7 and 8. As shown in the figures, the model in which $AUC_{(0\text{-}24,ss)}$ is used as predictor underestimates the response rate for the individuals with $AUC_{(0\text{-}24,ss)}$ in 0-25 percentile of the population. However, the model in which log(AUC) is used appears under estimate the response rate in the individuals with $AUC_{(0\text{-}24,ss)}$ in 76-100 percentile of the population. Since the same dataset and the number of predictors were used in both models, the second model resulted in 15 less of residual deviances than the first model, suggesting the model in which log(AUC) was used might be more reasonable. The probabilities of quitting smoking at week 9-12 after the treatment for individuals in the dataset are predicted by these two models. The mean of predicted response rates by both models are calculated and compared with observed response rates in placebo, 0.5 mg bid, and 1.0 mg bid group (Table 3). In this calculation, for Study 1007, patients in non-titrate and titrate groups at 0.5 mg bid and 1.0 mg bid are

combined. As shown in the table, the response rate was underestimated for 0.5 mg bid group (45% observed vs 34% predicted) by the first model, but are well predicted by the second model (45% observed vs 46% predicted).

Figure 7. Probability of Quitting Smoking at Week 9-12 vs $AUC_{(0\text{-}24,ss)}$ ($AUC_{(0\text{-}24,ss)}$ Used as Exposures in the Model)

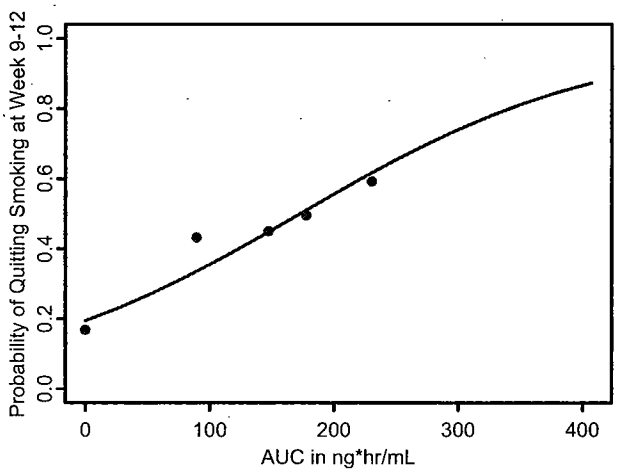


Figure 8. Probability of Quitting Smoking at Week 9-12 vs $AUC_{(0\text{-}24,ss)}$ ($\log(AUC_{(0\text{-}24,ss)})$ Used as Exposures in the Model)

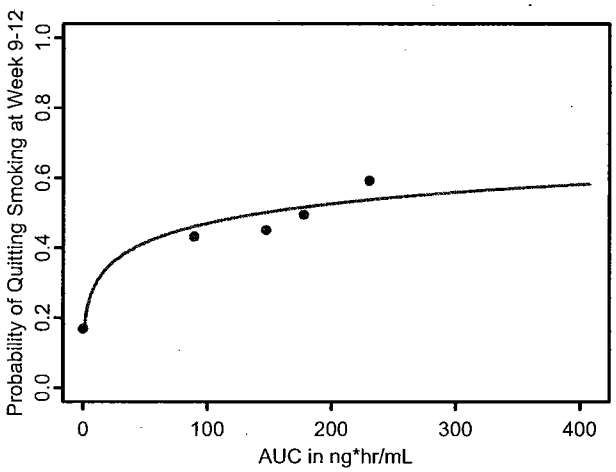


Table 3: Observed and Predicted Response Rate across Treatments (Combined dataset from Study 1007, 1028, and 1036)

	Observed Response Rate (# of responder/# of total patients)	Model Predicted [c]	Model Predicted [d]
Placebo	**17%** (136/806)	**19%**	**17%**
0.5 mg bid [a]	**45%** (114/253)	**34%**	**46%**
1.0 mg bid [b]	**46%** (434/949)	**51%**	**51%**

a: including both non-titrate (0.5mg tablets BID for 12 weeks) and titrated (0.5mg tablets QD for 7 days followed by 0.5mg BID for 11 weeks) regimens in Study 1007.

b: including both non-titrated (1mg tablet BID for 12 weeks) and titrated (0.5 mg tablets QD for 3 days, then 0.5mg BID for 4 days followed by 1 mg BID for 11 weeks) in Study 1007, 1028, and 1036.

c = the mean model predicted response rate for pooled data from study 1007, 1028 and 1036; a AUC(0-24,ss) is used in the model as exposures

d = the mean model predicted response rate for pooled data from study 1007, 1028 and 1036; a log(AUC(0-24,ss)) is used in the model as exposures

Incidence of Nausea:

The mean (range) of $AUC_{(0\text{-}24,ss)}$ in male for this dataset is 85.94 ng*h/mL and 175.83 ng*h/mL for 0.5 mg bid and 1 mg bid, respectively. The mean (range) of $AUC_{(0\text{-}24,ss)}$ in female for this dataset is 100.05 ng*h/mL and 199.17 ng*h/mL for 0.5 mg bid and 1 mg bid, respectively. The incidence of nausea across treatments by gender in each study was summarized in Table 4. It appears that the incidence of nausea was higher in females than males; in non-titrated group than titrate groups at both 0.5 mg bid and 1.0 mg bid; in 1 mg bid than 0.5 mg bid groups.

The logistic regression analysis was conducted using the data the sponsor provided. The predicted relationships between probability of nausea incidence and $AUC_{(0\text{-}24,ss)}$ in female and male are presented in Figure 9. This model is very similar to the sponsor's model. Using the predicted probability for individuals by this model, the mean nausea incidence rate in males and females was calculated for placebo, 0.5 mg bid, and 1.0 mg bid group and compared with corresponding observed the nausea incidence rate (Table 5). The results showed that model reasonable predicted the nausea incidence rate observed in the trial. The predicted nausea incidence rates (90% CI) in males are 7% (5%-8%), 12% (10%-14%), 20% (18%-22%) for placebo, 0.5 mg bid, and 1.0 mg bid, respectively. The predicted nausea incidence rates (90% CI) in females are 14% (13%-16%), 25% (23%-27%), 40% (37%-43%) for placebo, 0.5 mg bid, and 1.0 mg bid, respectively. The results are very similar to the predictions of sponsor's model.

Figure 9. The Probability of Nausea Incidence in Males and Females

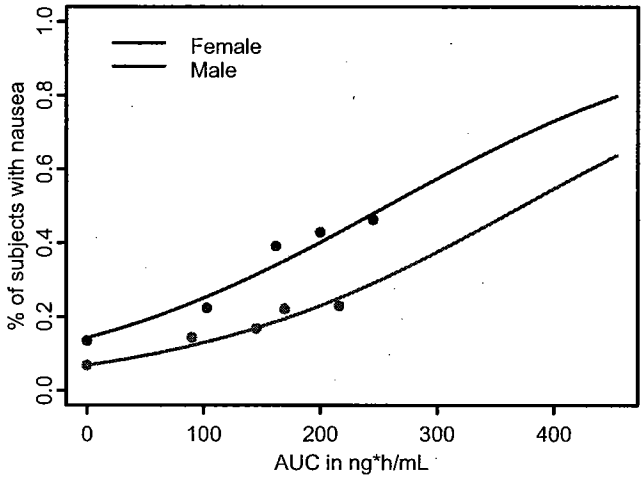


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Table 4. The Summaries of Incidence of Nausea across Treatment by Gender in Each Study

		# of subjects with nausea/# of patient in total (%)			
Study		**1007**	**1028**	**1036**	**1037**
Placebo	Female	9/57 (16%)	19/158 (12%)	24/143 (17%)	5/65 (8%)
	Male	5/64 (8%)	13/186 (7%)	13/198 (7 %)	4/61 (6%)
	Total	14/121 (12%)	32/344 (9%)	37/341 (11%)	9/126 (7%)
0.5 mg bid non-titrate [a]	Female	16/70 (23%)	NA	NA	NA
	Male	7/54 (13%)			
	Total	23/124 (19%)			
0.5 mg bid titrate [b]	Female	7/60 (12%)	NA	NA	NA
	Male	6/69 (9%)			
	Total	13/129 (10%)			
1.0 mg bid non-titrate [c]	Female	28/61 (46%)	NA	NA	NA
	Male	16/63 (25%)			
	Total	44/124 (35%)			
1.0 mg bid titrate [d]	Female	18/67 (27%)	70/176 (40%)	61/154 (40%)	65/124 (52%)
	Male	8/62 (13%)	33/176 (19%)	44/190 (23%)	32/127 (25%)
	Total	26/129 (20%)	103/352 (29%)	105/344 (31%)	97/251 (39%)
Zyban	Female	NA	26/137 (19%)	20/136 (15%)	NA
	Male		21/192 (11%)	12/206 (6%)	
	Total		47/329 (14%)	32/342 (9%)	

a = 0.5 mg BID (0.5mg tablets BID for 12 weeks)
b = 0.5 mg BID titrated (0.5mg tablets QD for 7 days followed by 0.5mg BID for 11 weeks)
c = 1 mg BID (1mg tablet BID for 12 weeks)
d = 1 mg BID titrated (0.5 mg tablets QD for 3 days, then 0.5mg BID for 4 days followed by 1 mg BID for 11 weeks)

Table 5: Observed and Predicted Nausea Incidence Rate between Male and Female (Combined dataset from Study 1007, 1028, 1036 and 1037)

		Observed	Model Predicted [c]
Placebo	Female	57/423 (13%)	14%
	Male	35/509 (7%)	7%
0.5 mg bid [a]	Female	23/130 (18%)	25%
	Male	13/123 (10%)	12%
1.0 mg bid [b]	Female	242/582 (42%)	40%
	Male	133/618 (22%)	20%

a: including both non-titrate (0.5mg tablets BID for 12 weeks) and titrated (0.5mg tablets QD for 7 days followed by 0.5mg BID for 11 weeks) regimens in Study 1007.
b: including both non-titrated (1mg tablet BID for 12 weeks) and titrated (0.5 mg tablets QD for 3 days, then 0.5mg BID for 4 days followed by 1 mg BID for 11 weeks) in Study 1007, 1028, and 1036.
c = the mean model predicted response rate for pooled data from study 1007, 1028 and 1036

CONCLUSIONS:

- The PK/PD analysis suggested that probability of quitting smoking from week 9-12 after the treatment are related to varenicline exposure, the baseline addictedness measured by FSQ1 question, and age. For a typical smoker (45 years old and FSQ1 (30-60 minutes)), the mean probability of quitting smoking from week 9-12 after varenicline treatment increased from 46% to 51% when dose is increased from 0.5 mg bid to 1 mg bid.
- The probability of nausea after varenicline treatment is related to varenicline exposure and gender. The incidence of nausea in females is about two times of that in males. Increasing dose from 0.5 mg bid to 1 mg bid, the probability of nausea incidence is increased from 12% to 20% in males and 25% to 40% in females.
- It is recommended that to minimize the probability of nausea incidence, the treatment could be started at 0.5 mg bid and titrated to 1 mg bid if the effectiveness of the treatment is not observed.

Population Pharmacokinetic Model

Title of Study: Population Pharmacokinetic Analysis of Varenicline in Adult Smokers

Objective:

- The objective of this population pharmacokinetic (PK) analysis was to describe the pharmacokinetics of varenicline following single and multiple doses in male and female adult smokers using nonlinear mixed effects modeling.
- This investigation examined primarily the effects of selected demographic or physiologic factors (age, weight, gender, race and renal function) on inter-individual differences in varenicline pharmacokinetics.
- Pharmacokinetic information generated in this analysis was utilized in subsequent population pharmacokinetic-pharmacodynamic (PK-PD) analyses of tolerability and efficacy measures.

Data: Data collected from four Phase 1 studies, and two Phase 2 and three Phase 3 clinical trials were pooled for the population pharmacokinetic analysis. The study design, study population, and timing of blood samples varied between the 9 clinical studies. Varenicline (succinate or tartrate salt) doses were given orally as immediate-release tablets. Doses ranged from 0.3 to 3 mg/day given orally once (QD) or twice (BID) daily. Dose and sampling times for the Phase 1 studies were pre-specified in the protocols. For the Phase 2 and Phase 3 protocols, the investigators were asked to document the date and time of the most recent doses and of sample collection. The study design of those studies is summarized in Table 6. The phase 1 studies were selected to include the pharmacokinetic information in special population such as renal impairment (Study 1008) subjects and elderly (Study 1009) and the occurrence of nausea in study 1014 and 1015.

Data Analysis:

Plasma concentration vs. time data were analyzed using a nonlinear mixed-effects modeling approach with the NONMEM software system, version V level 1.1(GloboMax LLC, Hanover, MD) and the NM-TRAN subroutines version III level 1.1, and the PREDPP model library, version IV level 1.1. Data analyses were performed on Intel-based PC Workstations running Intel-based PC Workstation running Red Hat Linux (3.2.3-34) operating system and GNU Fortran compiler (GCC 3.2.3 20030502). Analyses were conducted using the first-order conditional estimation with interaction (FOCE-INT) method.

Model building process:

Goodness of fit criteria:
Assessment of model adequacy was driven by the data and guided by goodness-of-fit criteria, (i) visual inspection of diagnostic scatter plots such as population and individual predicted vs. observed concentrations, residual/ weighted residual vs. predicted concentrations, plots of random effects and weighted residuals vs. covariate factors, histograms of random effects; (ii) successful minimization of the objective function with

at least 2 significant digits in parameters estimates; (iii) the AIC, change in the objective function relative to the change in number of parameters; (iv) the magnitude and precision of the parameter estimates; and (v) correlation between model parameters estimation errors <0.95.

A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for the varenicline population PK analysis. The steps of covariate analysis are the as follows:

1. Identification of pre-defined covariate-parameter relationships based on exploratory graphics, scientific interest, or prior knowledge
2. Construction of a full model based on the results of step 1 with care to avoid collinearity in predictors. Population parameters, including fixed effects parameters (covariate coefficients and model structural parameters), and random effects parameters were estimated.
3. Graphical exploration of all remaining covariate effects (plots of MAP Bayes estimates of individual random effects (□i) and/or weighted residuals (WRES) from the full model vs. covariates). Inferences about clinical relevance of parameters were based on the resulting parameter estimates of the full model and measures of estimation precision (asymptotic standard errors, bootstrap 95% confidence intervals or log-likelihood profile).

Fixed effects (Structure Model):
Initial modeling was conducted using a two-compartment pharmacokinetic model (ADVAN 4, TRANS 4).

Random effects:
Inter-subject variability in the pharmacokinetic parameters (e.g., CL/F, V2/F, V3/F, Q/F and Ka) was modeled using an exponential error model, or log-normal parameter distribution. An attempt was made to define a full block covariance matrix for the inter-individual random effects (Ω) when possible.
Residual variability was described as a combined additive and proportional error model.

Covariates:
Continuous covariates were normalized on a typical reference value (approximately the population median) and included in the model using a power function, while the effect of categorical covariates was introduced into model as percent of change. Multiple covariates are introduced into the model in a multiplicative manner described as the equation below:

$$TVP = \theta_n \cdot \prod_{1}^{m} \left(\frac{cov_{mi}}{ref_m} \right)^{\theta_{(m+n)}} \cdot \prod_{1}^{p} \theta_{(p+m+n)}^{cov_{pi}}$$

where: the typical value of a model parameter (TVP) will be described as a function of m individual continuous covariates (covmi) and p individual categorical (0-1) covariates (covpi) such that θn is an estimated parameter describing the typical PK parameter value for an individual with covariates equal to the reference covariate values (covmi =refm , covpi = 0), θ (m+n) and θ (p+m+n) are estimated parameters describing the magnitude of the covariate-parameter relationship.

Evaluation of Full Model

Bootstrap:
The precision of model parameters was investigated by performing a stratified non-parametric bootstrap procedure. One thousand replicate data sets were generated by random sampling with replacement and were stratified by race (White, Black and Other) and renal function (CRCL<30 mL/min, 30□□CRCL<50 mL/min, 50□□CRCL<80 mL/min, 80 □□CRCL□□120 mL/min, and 120<CRCL□□150 mL/min) using the individual as the sampling unit. Population parameters for each data set were subsequently estimated using the final model. This resulted in a distribution of approximately 1000 estimates for each population model parameter. Parameter uncertainty was then expressed as a 95% confidence intervals (CI) about the estimate, by observing the 0.025th and 0.975th quantiles of the resulting parameter distributions for those bootstrap runs with successful convergence.

Predictive check:
The varenicline population PK model was used to perform Monte Carlo simulations with the final model and parameter estimates (including inter-individual and residual random effects). Five-hundred Monte-Carlo simulation replicates of the renal impairment and Phase 3 subsets of the population PK database were generated and distributions of simulated concentrations were compared to observed data distributions using exploratory graphics (quantile-quantile plots and histograms). The characteristic of interest was the average of observed plasma varenicline concentrations across all data points within each individual (approximately Cav,ss). This characteristic was also summarized across all simulation replicates as the population first quartile, median, and third quartile values. For each summary statistic, the fraction of simulated values that were greater than the observed value for that statistic was calculated. This fraction defined the probability that the simulated data (under the model and parameter point estimates) could be more extreme than the observed data. Any fractions more extreme than 0.01 or 0.99 or any problems evident by visual inspection of exploratory graphics were investigated and further model development was conducted as necessary.

Results:

A total of 1878 adult smokers (954 (50.8%) males; 924 (49.2%) females) receiving varenicline contributed plasma drug concentration data for the population pharmacokinetic analysis. The characteristics of the population studied are summarized in Table 7.

Base Model:
The base model was first developed using phase 1 and phases 2 data. Various random effect models including adding between subject variability on V3/F and Q, estimating covariance between parameters using BLOCK feature in NONMEM, were examined and it was found a 2 compartment model with no inter-individual variability on V3/F and Q/F, and with terms describing the correlation between Ka, CL/F and V2/F with a full BLOCK structure, was the best of these models, having the lowest objective function and also a successful $COV step. The parameter estimates in the base model are shown in Table 8. The inter-individual variance on CL/F was estimated with the greatest precision (6.4% RSE) while the absorption rate constant (Ka) had the largest inter-individual variability estimate with the least precision (37% RSE). V2/F and Ka inter-subject variances were highly correlated; the covariance term was estimated to be 0.44 with a correlation coefficient of 0.78. The covariance between V2/F and CL/F was only 0.04 (correlation = 0.19). The additive residual variance term (expressed as standard deviation (SD)) was estimated to be 0.46 ng/mL, while the proportional residual variance term was approximately 21%. Both terms were included in the full model, in case of changes in residual variance parameter estimates due to inclusion of covariates.

Covariate effect:
In first step, the potential covariate-parameter relationships were graphically inspected and it was found that CL/F (ETA2) and V2/F (ETA3) was related to renal function, body size (weight and height) and to some extent, age. CL/F and V2/F tended to increase with increasing body weight. CL/F also tended to decline with decreasing renal function and age. Since renal function, represented by Glomerular filtration rate (GFR) which was estimated from the Cockcroft-Gault formula using the body weight and body weight were highly correlated, GFR itself may be sufficient to explain the body weight effect on total CL/F. No obvious trends were seen with gender and race for the base model. Effects of covariates on ETA1 (ka) were not evident from the exploratory graphics and were not of clinical interest.

All potential covariates were simultaneously included in a full model. The dependence of varenicline clearance on renal function was modeled by means of an estimated power model, as function of CRCL normalized on a typical reference value of 100 mL/min. In addition, subject's glomerular filtration rate values in excess of 150 mL/min were replaced with a value of 150 mL/min, which has the effect of removing very high and physiologically improbable GFR estimates obtained using the Cockroft-Gault method. The effect of body size was investigated as a potential predictor for the central volume of distribution (V2/F) and described as a function of total body weight (WT), normalized by the typical reference weight of 70 kg. All remaining predefined covariates were included in the full model for CL/F and V2/F. Multiple covariate effects were included in the model in a multiplicative fashion. The model also contained an allometric function with an effect of observed bodyweight on V3/F and Q/F using a fixed power parameter (equals to a value of 0.75 for Q/F, and a value of 1 for V3/F). Race entered the model as power functions, with a separate dichotomous (0,1) covariate serving as an on-off switch for each category. Because the number of subjects in the Hispanic, Asian, and Other races was small these categories were grouped together in the "Other" category.

Final Model:
The results of the final model are presented in Table 9. The forms of the equation for the model are given below:

$CL/F = \theta_{CL/F} \cdot \theta_{Black} \cdot \theta_{Other} \cdot (CRCL/100)^{\theta_{CRCL}}$

$V2/F = \theta_{V2/F} \cdot \theta_{Black} \cdot \theta_{Other} \cdot (WT/70)^{\theta_{WT}} \cdot (AGE/45)^{\theta_{AGE}}$

$V3/F = \theta_{V3/F} \cdot (WT/70)^{1}$

$Q/F = \theta_{Q/F} \cdot (WT/70)^{0.75}$

The typical population pharmacokinetic parameter estimates and their 95% confidence interval [CI's, obtained from 1196 stratified non-parametric bootstrap replicates] for the final varenicline model were 10.4 L/hr [10.2-10.6] for CL/F, 337 L [309-364] for V2/F, 78.1 L [61.9-98.9] for V3/F, 2.08 L/hr [1.39-3.79] for Q/F, 1.69 hr-1 [1.27-2.00] for Ka and 0.43 hr [0.37-0.46] for Alag. These estimates are similar to those obtained with the base model. Typical value parameters for V2/F, V3/F, Q, CL/F and ka were estimated with good precision (most with %RSE <10% and all with %RSE <25%). Unexplained random inter-individual variances (expressed as % Coefficient of Variation (CV)) were for Ka (70% CV), CL/F (25% CV), and V2/F (50%CV), with terms describing the correlation between these parameters. Residual intra-individual variability was allowed to differ between Phase 1-2 and Phase 3 studies, and a combined additive and constant coefficient of variation model was utilized. Proportional residual variances were estimated to be 17% CV (Phase 1 + 2 data) and 22% CV (Phase 3 data).

The average (and %RSE) population estimate for the effect of CRCL on CL/F was 0.54 (5.6%RSE). Body weight appeared to be the most important factor of variability in the central volume of distribution; the average population estimate for the effect of weight was 0.77 (19%RSE). The 95% confidence intervals around the CRCL and WT covariate effects were relatively narrow and did not include 0. V2/F was estimated to decrease, on average approximately 35% between a typical individual weighing 70 kg (V2/F = 337 L) and one weighing 40 kg (V2/F = 219 L). This would predict an average increase of about 30% in the steady-state peak plasma concentrations in individuals with smaller body size. The estimated effect of age on V2/F was poorly defined and no conclusive trends were identified (95% CI included 0). Effects of Black and Other (Asian, Hispanic and Other) races on varenicline pharmacokinetics were well defined, but caused no clinically important changes on varenicline pharmacokinetics. On average, Blacks were estimated to have a 16% greater CL/F and 8% lower V2/F than Caucasians. There was no apparent gender effect on varenicline pharmacokinetics.

Evaluation of the Final Pharmacokinetic Model and Parameters
Nonparametric Bootstrap

The stratified non-parametric bootstrap procedure resulted in 95% confidence intervals for population PK parameter estimates, which are presented in Table 9. Confidence intervals were based on the superset of 1196 bootstrap runs (including failed convergence due to rounding errors), but confidence intervals calculated from a subset including runs with successful convergence, regardless of $COV step success (1080 runs total), or runs with successful convergence plus successful $COV step (894 runs total), yielded similar confidence intervals [results not shown]. The 2.5th and 97.5th quantiles of each of the population PK model parameter estimate distributions from the successful runs were used to construct an empirical 95% CI around the point estimate.

Predictive Check:
500 data set were simulated for two groups of patients: subjects in renal impairment study and the phase 2 and phase 3 studies. Performance of the final population PK model was assessed using the average observed steady-state concentration [Cav,ss] within each individual as the data characteristic of interest. For each of 500 simulation replicates of the original data set, the first quartile, median, and third quartile Cav,ss values were calculated across the population distribution. The ratio of simulated first quartile, median, and third quartile Cav.ss to observed first quartile, median, and third quartile Cav.ss is presented in Figure 10 for renal impairment study and the Q-Q plot between observed and simulated Cav,ss are presented in Figure 11 for renal impairment study. Similarly, the ratio of simulated first quartile, median, and third quartile Cav.ss to observed first quartile, median, and third quartile Cav.ss is presented in Figure 12 for subset population of two phase 3 studies and the Q-Q plot between observed and simulated Cav,ss for the subset of two phase 3 studies are presented in Figure 13. As shown in Figure 10-11, simulations did result in an apparently increased random deviation from the observed data at the high extremes of observed concentrations for the data in renal impairment study, as might be expected due to the heteroscedastic variance associated with drug concentration data. However, Simulations of the Phase 3 data sets also revealed a strong concordance of simulated and observed data (Figure 12-13).

Conclusions:

- A two-compartment model with first-order absorption (and a lag time) and elimination adequately described the pharmacokinetics of varenicline in adult smokers.
- There were no apparent age and gender effects on varenicline pharmacokinetics.
- Renal function has the greatest effect on the pharmacokinetics of varenicline. Varenicline clearance is predicted to decrease from 10.4 L/hr for a typical subject with normal renal function (estimated GFR = 100 mL/min) to 4.4 L/hr (estimated GFR = 20 mL/min) for a typical subject with severe renal impairment, thus resulting in an overall increase in daily steady-state exposure of 2.4-fold from the minimum to maximum of this renal function range. This change in clearance also results in an increased elimination half-life of varenicline.
- A reduced dosing frequency of 1 mg varenicline once daily is recommended for patients with severe renal impairment.

Pharmacodynamic Model

Title of Study: Population Pharmacokinetic-Pharmacodynamic Analysis of Varenicline Efficacy and Tolerability Endpoints in Adult Smokers

OBJECTIVES

- To characterize the association between varenicline exposure and the efficacy and tolerability endpoints following multiple doses of Varenicline in male and female adult smokers
- To explore other covariates such as gender, age, race, and baseline smoking status (baseline CO, Fagerström Questions 1 and 4)

METHODS

Data and the Study Design:
Data collected from two Phase 2 (A3051002 and A3051007/1018) and three Phase 3 (A3051028, A3051036 and A3051037) clinical trials were pooled for the population PK/PD analysis. The two phase 2 studies were dose ranging and the two phase 3 studies (A3051028, A3051036) included placebo, active control (Zyban) and only one varenicline arm (0.5 mg qd for first three days, followed by 0.5 mg bid, then 1 mg bid for 12 weeks) . The study designs of these studies are briefly summarized below.

Study A3051002 (N = 626 total, n=377 varenicline) was a Phase 2a dose ranging trial that compared 3 doses of varenicline succinate (0.3 mg QD, 1 mg QD, and 1 mg BID) with placebo. Zyban®150 mg BID was included as an active control. Varenicline was administered for 6 weeks, followed by a 1-week blinded placebo washout period. Subjects had a target quit date on Day 8 of the study and returned to the clinic for weekly visits through Week 7 (end of study visit). After completing the 7-week treatment phase, subjects had the option to participate in the nontreatment phase that evaluated subjects' smoking status up to 52 weeks from the start of treatment.

Study A3051007/1018 (N = 627 total, n=506 varenicline) was a double blind and placebo-controlled Phase 2b trial that extended the period of dosing with varenicline to 12 weeks and designed to assess the smoking cessation efficacy and safety of 4 varenicline dose regimens and compare the effect of dose titration on the tolerability of varenicline. Each of the two varenicline doses (0.5 mg BID and 1 mg BID) was administered by two dosing strategies: fixed dose for 12 weeks or with titration in Week 1 (0.5 mg QD for 7 days as a lead-in the 0.5 mg BID group or 0.5 mg QD for 3 days, 0.5 mg BID for 4 days as a lead-in the 1.0 mg BID group). Study A3051018 was the 40-week, double blind, non-treatment follow-up phase to Study A3051007.

Studies A3051028 (N = 1022 total, n=349 varenicline) and A3051036 (N = 1023 total, n=343 varenicline) were Phase 3 clinical trials with identical designs. These studies were randomised, double blind, placebo-controlled, parallel group studies to assess the smoking cessation efficacy and safety of 1 mg BID titrated varenicline taken for 12

weeks (0.5 mg QD for 3 days, 0.5 mg BID for 4 days, and 1 mg BID for 11 weeks). Each study also included a pre-specified comparison with Zyban® 150 mg BID taken for an equal treatment duration. These studies included a follow-up period that evaluated subjects' smoking status up to 52 weeks from the start of treatment.

Protocol A3051037 (N = 377 total, n=251 varenicline) was a one-year, double blind, placebo-controlled, randomized Phase 3 multicenter trial designed to obtain safety information on cigarette smokers treated with 52 weeks of varenicline 1 mg BID (0.5 mg QD for 3 days, 0.5 mg BID for 4 days, then 1 mg BID for 51 weeks) or placebo, regardless of smoking status

Exposures and Endpoints:
The individual exposures used in the analysis were the predicted 24-hour daily exposure estimates ($AUC_{0\text{-}24,ss}$), which were obtained from population pharmacokinetic analysis.

The primacy efficacy endpoints used in this analysis were continuous quit rate (CQR), which is defined as the proportion of subjects abstaining from smoking during specified 4-week periods. The specified 4-week period CQRs were evaluated for Weeks 4-7 (Studies A3051002 and A3051007/1018) and for Weeks 9-12 (A3051007/1018, A3051028 and A3051036).

The secondary endpoint the rates of Continuous Abstinence rate (CA), defined as the proportion of subjects treated who abstained from smoking from Week 9 through the time point of interest during the non-treatment extension phase of the study, Week 24 or Week 52 were also used to examine the existence of exposure response relationship. This endpoint was obtained from Protocols A3051007/1018, A3051028 and A3051036.

In addition to efficacy end point, the correlation between tolerability, specifically the incidence of nausea and the time course of nausea obtained from there studies and drug exposure were also examined.

The analysis was conducted using using a nonlinear mixed effects approach (NONMEM software, version V level 1.1, Globomax, Hanover, MD). Two types of population modeling approaches were considered based on the nature (single vs. repeated measures) of the PD data: a naïve pooled (NP) approach or a nonlinear mixed effects (NLME) approach.

Because each of the Pharmacodynamic (PD) endpoints (4-week CQR, CA, nausea incidence) was a dichotomous categorical variable representing the occurrence of an nausea or a successful quit (1 = yes, 0 = no), logistic regression models were used to estimate the probability of response as a function of varenicline exposure. Also, since each individual contributed only one observation for each outcome endpoint, a naïve-pooled population approach was conducted. The precision of parameter estimates and the predictive ability of models of interest were tested in a separate evaluation step. The LAPLACIAN estimation method was employed for all model runs.

The potential covariate effects on the PD endpoints were also explored. The covariates of interest were predefined and the relationships between covariate and parameters were identified based on exploratory graphics, scientific interest, mechanistic plausibility of prior knowledge. The covariates of interest include age, gender, race, and baseline smoking status (baseline carbon monoxide (CO), two Fagerström Test for Nicotine Dependence questions, FSQ1 and FSQ4):

- FSQ1: How soon after you wake up do you smoke your first cigarette? Scoring was: within 5 minutes [3]; 6-30 minutes [2]; 31-60 minutes [1]; >60 minutes [0])
- FSQ4 (How many cigarettes per day do you smoke? Scoring was: □31 [3]; 21-30 minutes [2]; 11-20 [1]; 10 or less [0].

By this approach, a full model could be constructed, with care to avoid correlation or collinearity in covariates.

The probability of quit or have nausea was described in the following equations:

$p_i = e^{\lambda_i}/(1+e^{\lambda_i})$ Probability

$\frac{p_i}{(1-p_i)} = e^{\lambda_i}$ Odds Ratio

$\log\left[\frac{p_i}{(1-p_i)}\right] = \lambda_i$ Logit

The base model is defined as $\square_i = \square_1$
The exposure ($AUC_{0\text{-}24,ss}$) effect was described as $\square_i = \square_1 + \square_\square \bullet AUC$
The covariate effects was modeled as that covariates such as gender, race, smoking status change to the baseline quit rate as described in the following equation:

$$\lambda_i = \theta_1 * \theta_n^{Cov} + \theta_2 * AUC \quad \text{Categorical}$$

$$\lambda_i = \theta_1 * \left[\frac{Cov}{Cov_{ref}}\right]^{\theta_n} + \theta_2 * AUC \quad \text{Continuous}$$

Model selection was based on goodness-of-fit criteria including diagnostic plots, convergence with at least 2 significant digits, precision of parameter estimates, and the objective function value. The precision of model parameters was investigated by performing a stratified non-parametric bootstrap procedure. One thousand replicate data sets were generated by random sampling with replacement and were stratified by dose, race (White, Black and Other) and FSQ1 (score 0 to 3) for the efficacy model, and by dose and gender for the tolerability model, using the individual as the sampling unit. Population parameters for each data set were subsequently estimated using the final model. This resulted in a distribution of approximately 1000 estimates for each population model parameter. Parameter uncertainty was then expressed as a 95% confidence intervals (CI) about the estimate, by observing the 0.025th and 0.975th quantiles of the resulting parameter distributions for those bootstrap runs with successful convergence.

Results:

Weeks 4-7 CQR

Weeks 4-7 Continuous Quit Rate (CQR) data were available from the two Phase 2 dose ranging studies, A3051002 and A3051007/1018. Logistic regression analysis was conducted for each of the two studies. A total of 490 and 609 adult smokers from A3051002 and A3051007/1018, respectively were available for the population naïve-pooled analysis. Male and female subjects were present almost equally in both PK/PD databases. The baseline demographics characteristics of the population studied are summarized in Table 10.

The results of the logistic regression analysis on the Study A3051002 and Study A3051007/1018 are presented in Table 11 and 12, respectively. The results showed that the probability of quitting smoking is associated with varenicline exposure. The rank of predictive ability of the covariates tested was determined to be FSQ1> FSQ4 > race > sex > CO > age.

An alternative model, as described in the following equation, was explored for the effect of varenicline exposure on baseline probability of quit, by including all covariates of interest. The results indicated that the Emax model did not significantly improve the goodness of fit, therefore the model in which a linear relationship is used to describe varenicline exposure's effect on the outcome is considered the final model.

$$\lambda_i = \theta_1 * \theta_3^{FSQ1(31\text{-}60min)} * \theta_4^{FSQ1(6\text{-}30min)} * \theta_5^{FSQ1(<6min)} * (AGE/45)^{\theta 6} * \theta_7^{(1-SEX)} * \theta_8^{RACE(Black)} * \theta_9^{RACE(Other)} + \theta_2 * AUC/(\theta_{10} + AUC)$$

The results from Protocols A3051002 and A3051007/1018 demonstrated a clear and robust varenicline exposure-response relationship exists for the probability of Week 4-7 CQR across all doses. Figure 14 presents the population (not individual) exposure-response relationships for the Week 4-7 CQR endpoint for the reference subject (White, Male, 45 yrs old, FSQ1(6-30min)) in the dose-ranging studies A3051002 (left panel) and A3051007/1018 (right panel).

Weeks 9-12 CQR

Data for the Weeks 9-12 Continuous Quit Rate (CQR) endpoint were available from the Phase 2 study A3051007/1018 and the two pivotal Phase 3 studies, A3051028 and A3051036. Varenicline was administered for 12 weeks.

Efficacy data along with the covariate information from these three studies were pooled together and merged with the individual varenicline steady state daily exposures, [AUC(0-24)ss] predicted from the final population pharmacokinetic model and parameter estimates. The final PK/PD model-building database consisted of 1892 adult smokers.

Table 13 summarized by protocol the baseline demographics characteristics of the population studied, which contributed data for the Weeks 9-12 CQR PK/PD database.

The results obtained from logistic regression analysis were shown in Table 14 and Figure 15. The parameter associated with AUC (□2) was well estimates across all the runs with %RSE<10%. The rank of predictive ability of the covariates tested was determined to be FSQ1> FSQ4> CO>age>race>sex> based on the precision of the parameter estimates and the diagnostic plots. It shows that a continuous relationship exists between varenicline exposure and the probability of Weeks 9-12 CQR. For the typical smoking population (White, Male, 45 years old and FSQ1(6-30min)) the predicted probability of Weeks 9-12 CQR [bootstrapped 95%CI] increased from 0.22 [0.19-0.26] (Placebo) to 0.38 [0.34-0.42] (0.5 mg BID, mean AUC(0-24)ss = 94 ng·h/mL) and to 0.56 [0.51-0.61] (1 mg BID, mean AUC(0-24)ss = 186 ng·h/mL).

Since both endpoints of week 4-7 CQR and week 9-12 CQR are available for the patients from study A3051007/1018. The results of correlation between both end points and varenicline exposure are compared and presented in Figure 16. The results showed that , interestingly, extending the duration of the treatment period to 12 weeks resulted in a steeper slope for response, whereby a greater probability of quit was reached at the higher exposures associated with 1 mg BID.

All covarites including AUC(0-24)ss, FSQ1 and FSQ4, age, gender, and race are included in the full model and the results are shown in Table 15. All effects seemed to have been reasonably estimated, evidenced by the small % RSE, which is defined as the ratio of standard error to parameter estimate.

The effects of patient population characteristics, such as baseline smoking status, age, gender and race were examined on the baseline probability of quitting, thus allowing to explore their influence on prediction of response regardless of treatment condition. Figure 17 depicts the effect of these selected covariates on the Weeks 9-12 CQR endpoint relative to the reference population of White, Male, 45 yrs and FSQ1(6-30min) at the proposed therapeutic dose of 1mg BID. Effects of the predictors were estimated with good precision (all % RSEs <27%).

The probability of quit progressively decreased from 0.70 (FSQ1(>60min)) to 0.45 (FSQ1(<5min)) as the degree of addiction increases (based on FSQ1). A slightly lower probability of quit was also observed in the Black population, when compared to Whites; however, the upper bound of the 95% CI approaches the no effect value of 1. In Other races (Hispanic, Asian and others), the predicted probability of quit was similar to the reference population (95%CI included 1, with upper and lower bounds within approximately 20% of the typical value). Age also has an influence on Weeks 9-12 CQR endpoint, whereby the predicted probability of quit increases from 0.35 to 0.64 with increasing age across the 18 to 75 year old range (Figure 17). Gender had no effect on the 4-Week CQR endpoint (95% CI included 1).

Continuous Abstinence (Weeks 9-24 & Weeks 9-52)

Continuous abstinence (CA) for Weeks 9-24 and Weeks 9-52 endpoints were available from the Phase 2 study, A3051007/1018 and the two Phase 3 studies, A3051028 and A3051036. Table 16 summarized the baseline demographics characteristics of the population studied. The subjects who lost follow up were considered non-quitter. The results of logistic analysis, as presented in Figure 18, showed that for the reference population (White, Male, 45 years old and FSQ1(6-30min)) the predicted probability [95% CI] increased from 0.15 [0.12- 0.19] (Placebo) to 0.35 [0.31-0.40] (1 mg BID) and 0.12 [0.09-0.15] (Placebo) to 0.28 [0.23-0.32] (1mg BID) for continuous abstinence from Weeks 9-24 and 9-52, respectively.

Tolerability Endpoints

Nausea was the most frequently reported adverse event in the varenicline clinical program. The reported nausea data from both Phase 2 and Phase 3 programs were characterized by evaluating (1) nausea incidence over the course of 12 weeks treatment period (one single observation per subject) using a naïve pooled analysis and (2) nausea incidence week by week (repeated observations per subject) using both mixed effects and naïve pooled analyses modeling approaches. Nausea incidence data were pooled from the Phase 2 study, A3051007/1018 and the three Phase 3 clinical trials, A3051028, A3051036 and A3051037. The baseline characteristics of the data set used in this analysis are summarized in Table 17.

For the purpose of the time-course analysis, all nausea event records were binned into 13 weeks (12 weeks of varenicline treatment + one week to account for drug washout) based upon the time of onset and the duration of the nausea event. For each individual, one or multiple nausea occurrences within a week (or 7 days) was counted as one incidence during that particular week; if the duration of the adverse event extended to the next consecutive week, the nausea event was also recorded to have occurred in that second week.

Weekly nausea incidence rates were plotted against time (Figure 19). The stacked bar plot shows an apparent trend towards decreasing probability of nausea incidence with time. The decline was modeled as an exponential function as described in equation below. In fact, this is the same model used to describe nausea incidence with an additional two parameters (□10 & □11) describing the effect of time on the baseline probability of nausea. Since repeated measures of nausea incidence data were available, the inter-individual variance term (□1) was estimated as a model parameter using NLME.
However, as part of model evaluation, naïve pooled analysis was also performed fixing □1 to 0. Data were assumed to be missing at random, and since discontinuation rates due to nausea were low (Studies A3051007/1018, A3051028 and A3051036), no measures were taken to adjust for the dropouts.

$$\lambda_i = \theta_1 * \theta_3^{FSQ1(31-60\,min)} * \theta_4^{FSQ1(6-30\,min)} * \theta_5^{FSQ1(<5\,min)} * (AGE/45)^{\theta 6} * \theta_7^{(1-SEX)}$$
$$* \theta_8^{RACE(Black)} * \theta_9^{RACE(Other)} + \theta_2 * AUC + \theta_{11} * \exp(-\theta_{10} * Week) + \eta_1$$

The histogramplot of random effects (□1) describing the inter-individual variability in the logit of probability of nausea incidence over time shows a bimodal distribution (Figure 20) indicating the inadequacy of mixed effect modeling approach for these dichotomous data. This finding has been previously described for dichotomous data by Yano *et al.* Consequently, the results from the NP model are presented in this report.

The analysis found that the probability of a nausea event to occur was positively related to varenicline exposure (Figure 21). Nausea was also associated with female gender, indicating a likelihood of nausea approximately 2-fold greater in women than in men regardless of the treatment condition. A trend towards decreasing probability of nausea incidence with time was also evident. Nausea incidence was highest at Week 1 with a rate of 12.9%, which decreased progressively over time to a rate of 5% at Week 13. Also, occurrence of nausea did not appear to be correlated to success for a given individual; in fact, 77% of the quitters and 82% of non-quitters did not have this adverse event.

Conclusions:
The population PK-PD analyses provided an integrated understanding of dose, exposure, response and relevant patient covariates for the efficacy and tolerability of varenicline for smoking cessation.

A clear varenicline exposure-response relationship was demonstrated for the probability of cessation across the dose range of 0.3 mg to 2 mg/day. An increased probability of quit at the recommended dose of 1 mg BID was reliably and reproducibly related to greater steady-state exposure to varenicline. Also, comparison of the Weeks 4-7 and Weeks 9-12 CQR endpoints confirms that the likelihood of cessation is increased when the treatment period is extended to the recommended 12 weeks.

In addition, this analysis found that the most frequent adverse event with varenicline, nausea, is positively associated with drug exposure and female gender. Most events were of mild or moderate severity, and a trend towards decreasing probability of nausea incidence with time was evident.

Appendix

Table 6. Study Design Summary

Protocol	Design	Duration	Inclusion Population	Sampling	Doses
A3051008	Phase I, Open – label	12 days	30 male (n=20) and female (n=10) subjects with various degrees of renal function (6 normal, 6 mild, 6 moderate, 6 severe and 6 end-stage renal disease)	Day 1: 0, 1, 2, 3, 4, 6, 8, 12, 16 hours post-dose Days 2, 4: 0 and Days 7, 10: 0, 3 hours post-dose Day 12: 0, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192 hours post-dose	0.5 mg QD (fasted)
A3051009	Phase I, Randomized, double blind, placebo-controlled	7 days	24 (8/group) healthy elderly (aged between 65-75 years) male (n=17) and female (n=7) smokers	QD group: Day 1: 0, 1, 2, 3, 4, 6, 8, 12, 16, 24 hours post-dose Days 4, 5, 6: 0, 3 hours post-dose BID group: Day 1: 0, 1, 2, 3, 4, 6, 8, 12 hours post-dose Day 4 (0, 3, 12, 15 hours post-dose), days 5 and 6: 0, 3 hours post-dose QD&BID groups: Day 7: 0, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168 hours post-dose	1 mg QD for 7 days 1 mg BID for 6 days + 1 mg QD on Day 7 Placebo (fasted)

A3051014	Phase I, Randomized, double-blind, placebo-controlled, parallel-group	21 days	120 (40/group) healthy male (n=60) and female(n=60) smokers	Days 1, 8 and 15: 0, 0.25 and 2 hours post-dose Days 2, 9 and 16: 0, 0.5 and 3 hours post-dose Days 3, 10 and 17: 0, 1 and 4 hours post-dose Days 4, 11 and 18: 0, 0.75 and 6 hours post-dose Days 6, 13 and 20: 0 Day 7: just prior to dosing, 1, 3 and 8 hours post-dose Day 14 at 0, 1, 2, 3, 4, 8 and 12 hours post-dose Day 21 at 0, 1, 2, 3, 4, 8, 12, 24, 48, 72 and 96 hours post-dose	Titration: 0.5 mg QD a.m. and placebo p.m. for 3 days, 0.5 mg varenicline tartrate BID for 4 days, 1 mg BID for 1 week, and then 1.5 mg BID for 1 week Nontitration: 1 mg BID for 2 weeks, then placebo BID for 1 week Positive control: placebo BID for 2 weeks and then 1.5 mg BID for 1 week Placebo (fed*)
A3051015	Phase I, Randomized, double-blind, crossover	7 days	44 healthy male (n=21) and female (n=23) smokers	Day 7: 0, 1, 2, 3, 4, 8, 10, 12, 14, 15, 16, 17, 18, 22, 24, 26 and 38 hours post-dose	2 mg QD (fed*)

Protocol	**Design**	**Duration**	**Inclusion Population**	**Sampling**	**Doses**
A3051002	Phase 2a, Randomized, double-blind, placeb-controlled parallel-group multicenter	7 weeks	626 healthy male and female smokers	Week-1, Week-2 and Week-4 concurrent with blood collection for clinical laboratory assessments	0.3 mg QD 1 mg QD 1 mg BID Zyban® SR 150 mg BID Placebo

	study				
A3051 007	Phase 2b, Randomized, double-blind, placebo-controlled parallel-group multicenter study	12 weeks	627 healthy male and female smokers	Week-1, Week-2, Week-4 and Week-12 concurrent with blood collection for clinical laboratory assessments	0.5 mg BID 0.5 mg BID titrated 1 mg BID 1 mg BID titrated Placebo
A3051 028	Phase 3, Randomized, double-blind, placebo-controlled parallel-group multicenter study	12 weeks + 40 week FU period	1022 healthy male and female smokers	Week-2 and Week-12 (or ET) concurrent with blood collection for clinical laboratory assessments	1 mg BID Zyban® 150 mg BID Placebo
A3051 036	Phase 3, Randomized, double-blind, placebo-controlled parallel-group multicenter study	12 weeks + 40 week FU period	1023 healthy male and female smokers	Week-2 and Week-12 (or ET) concurrent with blood collection for clinical laboratory assessments	1 mg BID Zyban® 150 mg BID Placebo
A3051 037	Phase 3, Randomized, double-blind, placebo-controlled parallel-group multicenter study	52 weeks	377 male and female smokers	Week-2, Week-12 and Week-24, Week-36 and Week-52 (or ET) concurrent with blood collection for clinical laboratory assessments	1 mg BID Placebo

Table 7. Summary of Baseline Demographics for the Varenicline Database (N =1878)

Baseline Characteristic (Units)	Mean	Median	Range
Age (years)	44.0	44.2	18 - 76
Height (cm)	171	170	135 - 202
Total Body Weight (kg)	78.0	77.0	41.0 - 129
Body Mass Index (kg/m2)	26.6	26.0	16.0 - 44.8
Estimated GFR^ (mL/min)	112	107	15.6 - 268
Sex	Males =954; Females = 924		
Race	Caucasians = 81.0%; Black = 12.6%; Asian = 1.22%; Other = 5.22%		

Table 8. Base Model Parameter Estimates

Parameter	Estimate	%RSE*
CL/F (L/hr)	10.9	0.9%
V2/F (L)	354	3.5%
V3/F (L)	93.2	11.5%
Q/F (L/hr)	2.28	24.0%
Ka (hr-1)	1.76	8.4%
Alag (hr)	0.412	5.5%
Inter-Individual Variance		
ω^2_{CL}	0.11 (33.2% CV)	6.4%
ω^2_{V2}	0.46 (67.8% CV)	16.2%
ω^2_{Ka}	0.71 (84.1% CV)	37.3%
Cov_{Ka-V2}	0.44 (r = 0.78)	33.6%
Cov_{CL-V2}	0.04 (r = 0.19)	31.5%
Cov_{Ka-CL}	-0.02 (r = -0.08)	83.2%
ω^2_{V3}	(0) Fixed	--
ω^2_{Q}	(0) Fixed	--
Residual Variance		
σ^2 add	0.21 (SD = 0.46)	21.8%
σ^2 prop	0.04 (20.7% CV)	7.1%

* %RSE: percent relative standard error of the estimate = SE/|parameter estimate| * 100

Table 9. Final Model Population Pharmacokinetic Parameter Estimates for Varenicline

Pharmacokinetic Parameter	Estimate	%RSE*	Bootstrapped 95% CI ** (lower, upper)
CL/F (L/hr)			
θ_{CL}	**10.4**	0.9%	(10.2 - 10.6)
θ_{CRCL}	0.54	5.6%	(0.48 - 0.59)
θ_{Black}	1.16	2.1%	(1.11 - 1.21)
θ_{Other}	1.11	3.3%	(1.04 - 1.18)
V2/F (L)			
θ_{V2}	**337**	4.4%	(309 - 364)
θ_{WT}	0.77	18.7%	(0.50 - 1.05)
θ_{AGE}	0.13	54.1%	(-0.01 - 0.30)
θ_{Black}	0.92	4.6%	(0.83 - 1.00)
θ_{Other}	0.71	10.4%	(0.58 - 0.89)
V3/F (L)			
θ_{V3}	**78.1**	12.7%	(61.9 - 98.9)
θ_{WT}	1 (Fixed)	--	--
Q/F (L/hr)			
θ_{Q}	**2.08**	22.2%	(1.39 - 3.79)
θ_{WT}	0.75 (Fixed)	--	--
Ka (hr-1)			
θ_{Ka}	**1.69**	9.2%	(1.27 - 2.00)
Alag (hr)			
θ_{Alag}	**0.43**	4.6%	(0.37 - 0.46)
Interindividual Variance			
ω^2_{CL}	0.061 (24.7% CV)	6.7%	(0.054 - 0.069)
ω^2_{V2}	0.25 (50.0% CV)	25.3%	(0.15 - 0.40)
ω^2_{Ka}	0.49 (70.1% CV)	38.9%	(0.23 - 0.97)
Cov_{Ka-V2}	0.24 (r = 0.67)	54.0%	(-0.05 - 0.53)
Cov_{CL-V2}	0.006 (r = 0.05)	133%	(-0.013 - 0.021)
Cov_{Ka-CL}	-0.009 (r = -0.05)	186%	(-0.045 - 0.040)
ω^2_{V3}	0 (Fixed)	-	-
ω^2_{Q}	0 (Fixed)	--	--
Residual Variance	0.28 (SD = 0.5)	23.5%	(0.155 - 0.358)
σ^2 add σ^2 prop	0.030 (17.2% CV)	10.7%	(0.024 - 0.036)
σ^2 add P3	4.38 (SD = 2.1)	21.0%	(0.047 - 5.89)
σ^2 prop, P3	0.046 (21.5% CV)	29.3%	(0.025 - 0.128)

Table 10. Summary of Baseline Demographics Characteristics for Studies A3051002 and A3051007/1018

Baseline Characteristic (Units)	Total number of Subjects (N)	Total number of Subjects (N)
Study Number	**A3051002**	**A3051007/1018**
Total Number of Subjects	490	609
AGE (yr)*	43 (19-66)	44 (19-65)
SEX		
Male	241	302
Female	249	307
RACE		
White	427	490
Black	33	84
Other^	30	35
FSQ1 (Time to first cigarette, min)		
<5	178	211
6-30	211	261
31-60	76	94
> 60	25	43
FSQ4 (Number of cigarette smoked/day)		
=10	16	29
11-20	248	323
21-30	160	178
>30	66	79
Carbon Monoxide (CO, ppm)*	24 (1-98)	22 (1-71)

Table 11. Study A3051002: Summary of Model Building Steps (Weeks 4-7 CQR)

Run No.	Description	OF Value	Parameter estimate (%RSE)				
			θ1	θ2	θ3	θ4	θ5
1	θ1	582.599	-0.937 (10.7)	--	--	--	--
2	θ1+ θ2* AUC	562.768	-1.44 (10.8)	0.00623 (22.5)	--	--	--
3	θ1 * (CO/20) $^{\theta 3}$+ θ2 *AUC	560.73	-1.42 (11.1)	0.00619 (22.6)	0.2 (72.0)	--	--

4	$\theta 1 * (AGE/45)^{\theta 3} + \theta 2 * AUC$	560.903	-1.5 (10.6)	0.0064 (22.0)	0.384 (75.0)	--	--
5	$\theta 1 * \theta 3_{FSQ4(1)} * \theta 4_{FSQ4(2)} * \theta 5_{FSQ4(3)} + \theta 2 * AUC$	554.252	-2.06 (31.2)	0.00618 (22.8)	0.569 (32.5)	0.792 (32.3)	0.945 (34.9)
6	$\theta 1 * \theta 3_{FSQ1(1)} * \theta 4_{FSQ1(2)} * \theta 5_{FSQ1(3)} + \theta 2 * AUC$	547.707	-1.15 (36.4)	0.00649 (22.0)	0.753 (45.9)	1.16 (37.8)	1.73 (37.0)
7	$\theta 1 * \theta 3$ Female$+ \theta 2 * AUC$	557.598	-1.25 (13.8)	0.00674 (21.1)	1.38 (14.3)	--	--
8	$\theta 1 * \theta 3_{Black} * \theta 3_{Other} + \theta 2 * AUC$	556.371	-1.37 (11.6)	0.00639 (22.4)	1.85 (22.7)	1.34 (25.6)	--

Table 12. Study A3051007/1018: Summary of Model Building Steps (Weeks 4-7 CQR)

Run No.	Description	OF Value	Parameter estimate (%RSE)				
			θ1	θ2	θ3	θ4	θ5
1	θ1	783.327	-0.649 (13.2)	--	--	--	--
2	θ1+ θ2* AUC	756.479	-1.3 (11.6)	0.00549 (19.9)	--	--	--
3	$\theta 1 * (CO/20)^{\theta 3} + \theta 2 * AUC$	753.401	-1.3 (11.8)	0.00546 (20.1)	0.238 (65.5)	--	--
4	$\theta 1 * (AGE/45)^{\theta 3} + \theta 2 * AUC$	754.281	-1.26 (12.1)	0.00546 (20.0)	-0.378 (65.1)	--	--
5	$\theta 1 * \theta 3_{FSQ4(1)} * \theta 4_{FSQ4(2)} * \theta 5_{FSQ4(3)} + \theta 2 * AUC$	749.213	-0.822 (50.0)	0.00516 (21.3)	1.34 (48.2)	1.78 (49.4)	2.04 (50.5)
6	$\theta 1 * \theta 3_{FSQ1(1)} * \theta 4_{FSQ1(2)} * \theta 5_{FSQ1(3)} + \theta 2 * AUC$	748.379	-0.779 (43.9)	0.00563 (19.7)	1.4 (46.2)	1.6 (43.3)	2.08 (43.1)
7	θ1*θ3 Female+ θ2* AUC	754.373	-1.2 (13.9)	0.00577 (19.1)	1.22 (13.3)	--	--
8	$\theta 1 * \theta 3_{Black} * \theta 3_{Other} + \theta 2 * AUC$	756.134	-1.27 (12.8)	0.00545 (20.2)	1.12 (19.1)	0.968 (30.3)	--

Table 13. Summary of Baseline Demographics Characteristics for Studies contributing to the Primary Weeks 9-12 CQR End point

Baseline Characteristic (Units)	Total number of Subjects (N)
Study number	
Phase 2 A3051007/1018	609
Phase 3 A3051028	642
Phase 3 A3051036	641
Total Number of Subjects	1892
AGE (yr)*	43 (18-75)
SEX	
Male	1003
Female	889
RACE	
White	1541
Black	210
Other^	141
FSQ1 (Time to the First cigarette, min)	
<5	636
6-30	832
31-60	284
> 60	140
FSQ4 (number of cigarette smoked/day)	
=10	109
11-20	1061
21-30	511
>30	211
Carbon Monoxide (CO, ppm) *	22 (1-81)

Table 14: Studies A3051007/1018, A3051028 and A3051036: Summary of Model Building Steps (Week 9-12 CQR)

Run No.	Description	OF Value	θ1	θ2	θ3	θ4	θ5
1	θ1	2461.849	-0.597 (8.0)	--	--	--	--
2	θ1+ θ2* AUC	2237.899	-1.43 (5.6)	0.00811 (7.1)	--	--	--
3	θ1 * (CO/20) θ3+ θ2 *AUC	2222.084	-1.46 (5.5)	0.00817 (7.1)	0.253 (27.6)	--	--
4	θ1 * (AGE/45) θ3+ θ2*AUC	2226.309	-1.37 (6.0)	0.008 (7.2)	-0.449 (29.4)	--	--
5	$\theta1 * \theta3_{FSQ4(1)} * \theta4_{FSQ4(2)} * \theta5_{FSQ4(3)} + \theta2*AUC$	2219.589	-3.11 (7.5)	0.00813 (7.1)	1.06 (7.5)	0.538 (45.7)	0.158 (177.8)
6	$\theta1 * \theta3_{FSQ1(1)} * \theta4_{FSQ1(2)} * \theta5_{FSQ1(3)} + \theta2 * AUC$	2196.795	-0.784 (23.5)	0.00836 (7.0)	1.5 (25.2)	1.76 (23.4)	2.4 (23.4)
7	θ1*θ3 Female+ θ2* AUC	2237.478	-1.41 (6.4)	0.00816 (7.0)	1.05 (7.1)	--	--
8	$\theta1 * \theta3_{Black} * \theta3_{Other} + \theta2*AUC$	2232.92	-1.38 (6.1)	0.00802 (7.1)	1.27 (10.6)	1.09 (13.3)	--

Table 15: Summary of Full Models (Weeks 9-12 CQR) with Covariate Effects

Parameters	Estimate (%RSE)
OF Value	2175.318
Intercept	-0.657 (25.7)
Effect of AUC	0.00813 (7.2)
Effect of FSQ1	
<5 min	2.59 (24.6)
6-30 min	1.92 (24.6)
31-60 min	1.54 (26.9)
Effect of age	-0.563 (24.7)
Effect of gender (female)	1.02 (7.1)
Effect of race	
Black	1.27 (10.8)
Other	1.09 (13.9)

Table 16. Summary of Baseline Demographics Characteristics for Studies A3051007/1018, A3051028 and A305103

Baseline Characteristic	Total number of Subjects (N)
(Units)	
Study number	
Phase 2 A3051007/1018	609
Phase 3 A3051028	642
Phase 3 A3051036	641
Total Number of Subjects	1892
AGE (yr)*	43 (18-75)
SEX	
Male	1003
Female	889
RACE	
White	1541
Black	210
Other^	141
FSQ1 (Time to first cigarette, min)	
<5	636
6-30	832
31-60	284
> 60	140
FSQ4 (Number of cigarette smoked/day)	
=10	109
11-20	1061
21-30	511
>30	211
Carbon Monoxide (CO, ppm)*	22 (1-81)

Table 17. Summary of Baseline Demographics Characteristics for Studies A3051007/1018, A3051028, A3051036, and A3051037

Baseline Characteristic	Nausea Incidence	Nausea Time-course
(Units)	Total number of Subjects (N)	Total number of Subjects (N)
Study Number		
Phase 2 A3051007/1018	609	609
Phase 3 A3051028	642	642
Phase 3 A3051036	641	640
Phase 3 A3051037	346	346
Total Number of Subjects	2238	2237
AGE (yr)*	44 (18-75)	44 (18-75)
SEX		
Male	1175	1175
Female	1063	1062
RACE		
White	1846	1845
Black	234	234
Others^	158	158
FSQ1 (Time to first cigarette, min)		
<5	759	759
6-30	989	988
31-60	324	324
> 60	166	166
FSQ4 (number cigarette /day)		
=10	122	122
11-20	1243	1242
21-30	606	606
>30	267	267

Figure 10. Results of Simulation Predictive Check (P-values) for Renal Impairment Subset

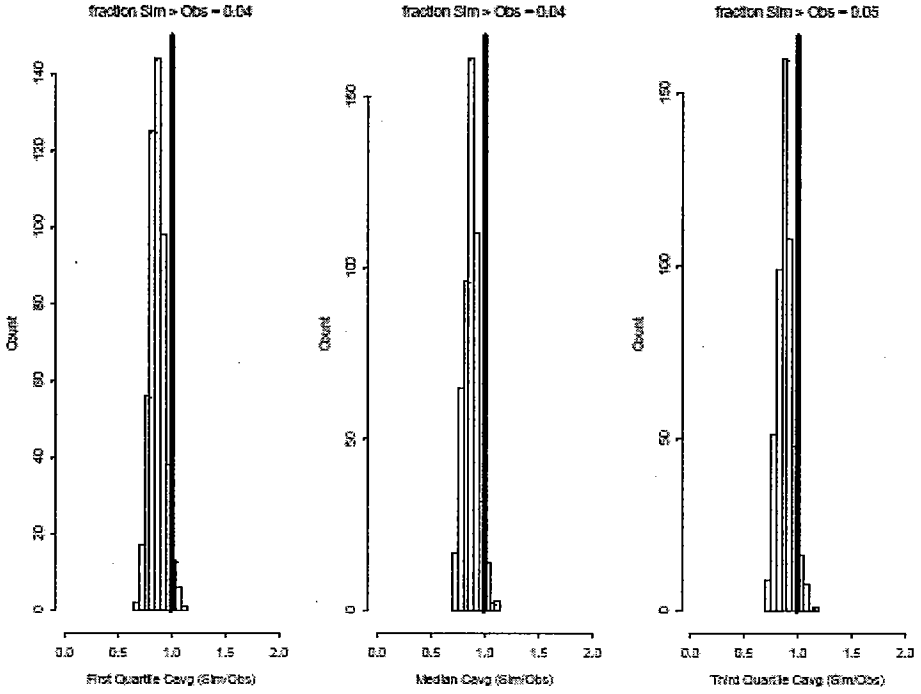

Figure 11. The Q-Q plot of simulated and observed Cavg in patients in Study 1008 (Renal Impairment) Subset of the Population PK Database

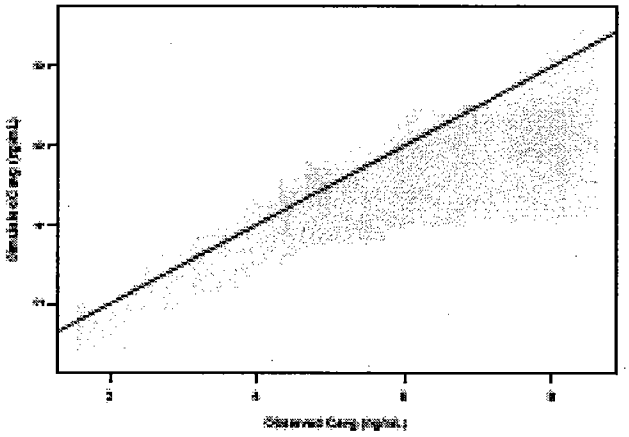

Figure 12. Results of Simulation Predictive Check (P-values) for subset of phase 3 studies (study 1028 and 1035)

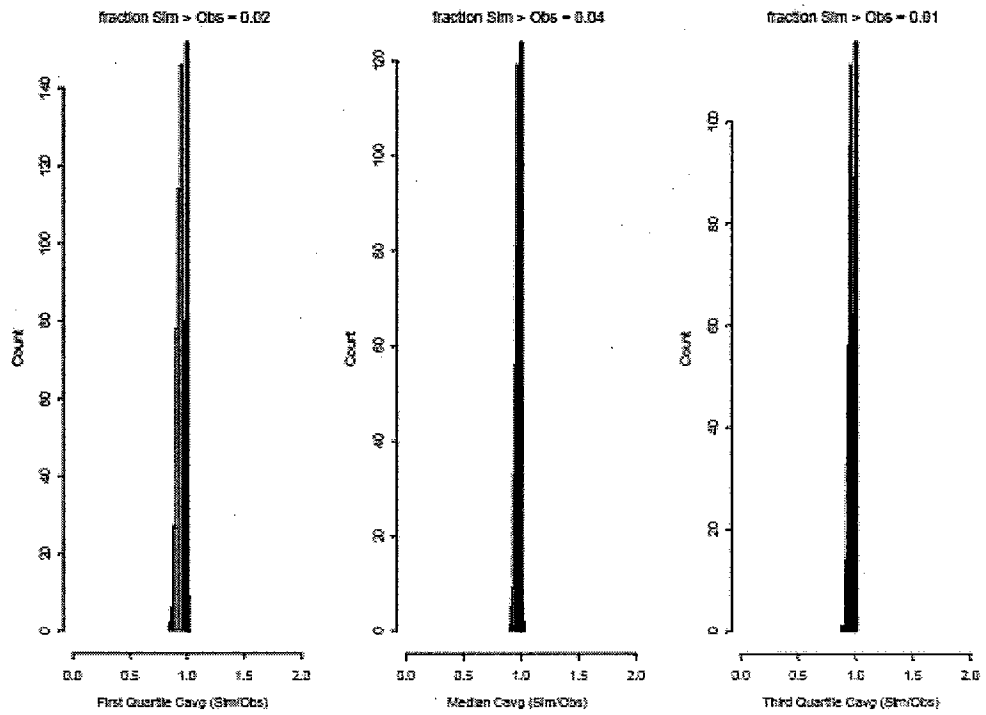

Figure 13. The Q-Q plot of simulated and observed Cavg for patients in Study 1028 and 1035

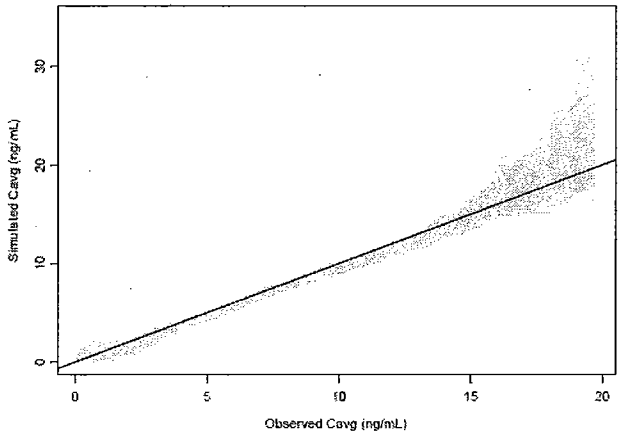

Figure 14. Predicted Varenicline Population Exposure-Response Relationships for the Weeks 4-7 CQR Endpoint in Adult Smokers

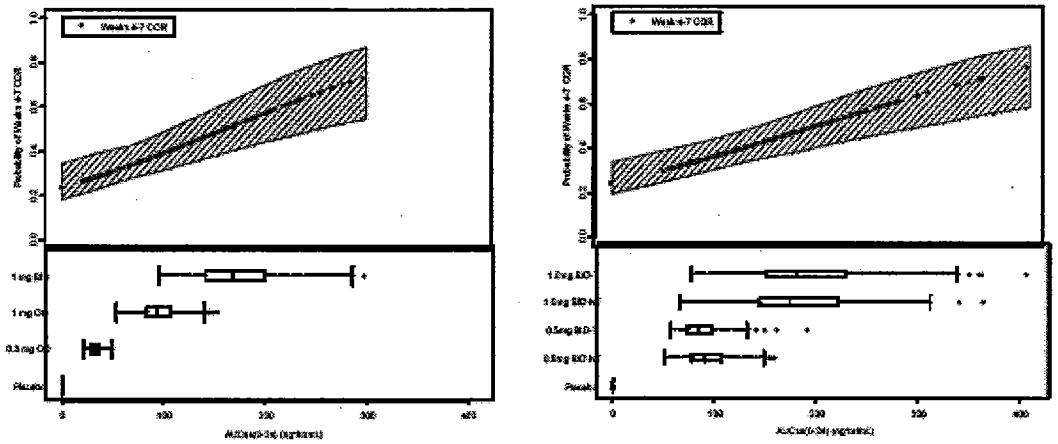

Figure 15. Exposure-Response Relationships for the Weeks 9-12 CQR for the combined Phase 2/3 Studies

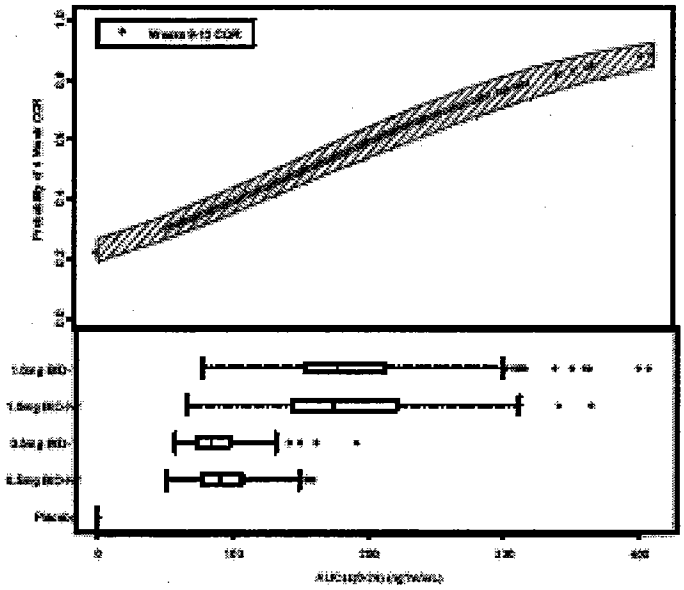

Figure 16. Exposure-Response Relationships for the Weeks 4-7 and Weeks 9-12 CQR in Study A3051007/1018

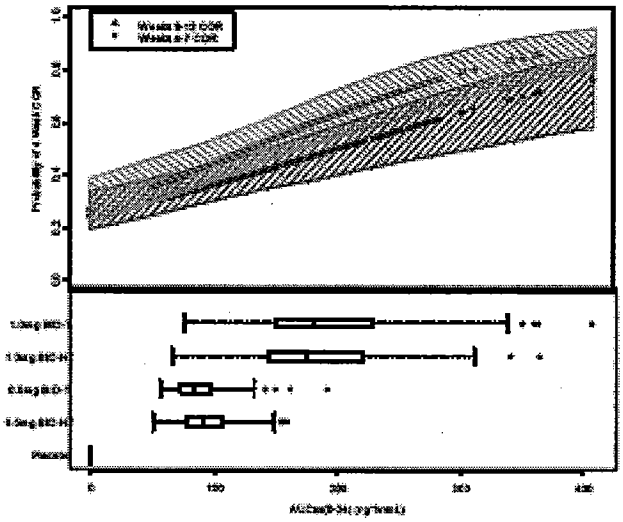

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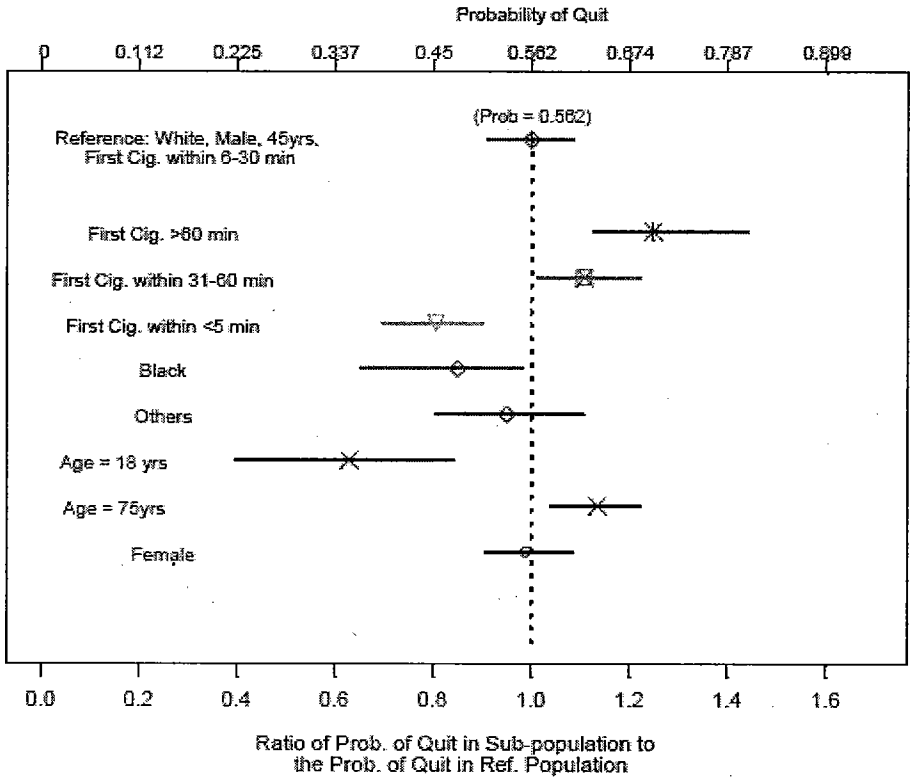
Figure 17. Effect of Age, Race, Gender and Smoking History (Fagerström Question 1) on the 4-Week CQR (Weeks 9-12) (Pooled studies A3051007/1018, A3051028 and A3051036)



Symbols represent the point estimate for the covariate effect relative to the reference population (White, Male, 45 years old, FSQ1 (6-30 min)) at the 1mg BID dose regimen; lines are the bootstrapped 95%CI. For the continuous covariate, Age, the two X symbols represent the point estimates for the effect of age on the baseline probability quit at the age of 18 and 75 years; The x-axis at the top shows the actual probabilities of quitting.

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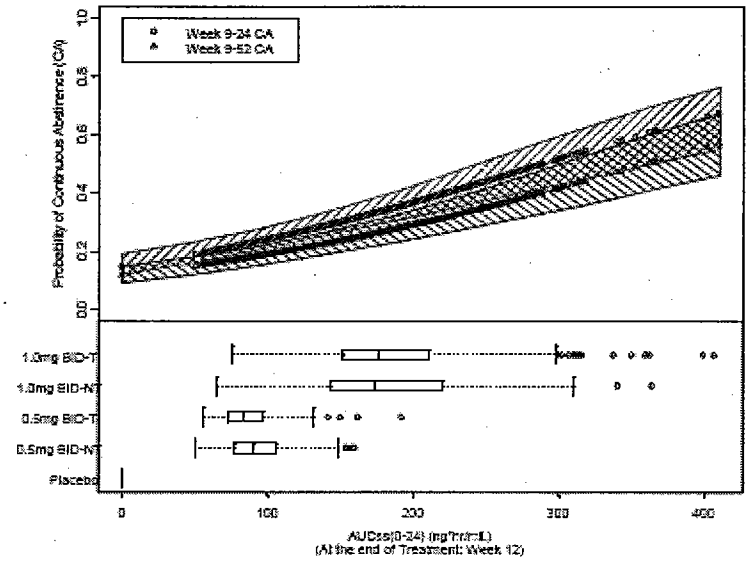
Figure 18. Predicted Varenicline Population Exposure-Response Relationships for the Weeks 9-24 and Weeks 9-52 CA Endpoints in Adult Smokers (Pooled studies A3051007/1018, A3051028 and A3051036)



Reflect population (not individual) exposure-response relationship of White, Male, 45 yrs old, Fagerström Question 1(6-30min);
predicted probability ± bootstrapped 95% CI. The box and whisker plots at the bottom describe the distribution of the exposure
data. The box itself indicates the difference between the first and third quartiles of the data, showing the spread of the data. The
solid line in the middle of the box is the median value and the "whiskers" indicate the range of the data or 1.5 x the inter-quartile
distance, whichever is less; if the data are normally distributed, approximately 99.3% of the data fall within these whiskers.
Open circles plotted outside the whiskers exceed these limits and may be considered outliers. T= titrated; NT= nontitrated

Figure 19. Observed and Model Predicted Weekly Nausea Incidence Probabilities versus Time in Adult Smokers (Pooled studies A3051007/1018, A3051028, A3051036 and A3051037)

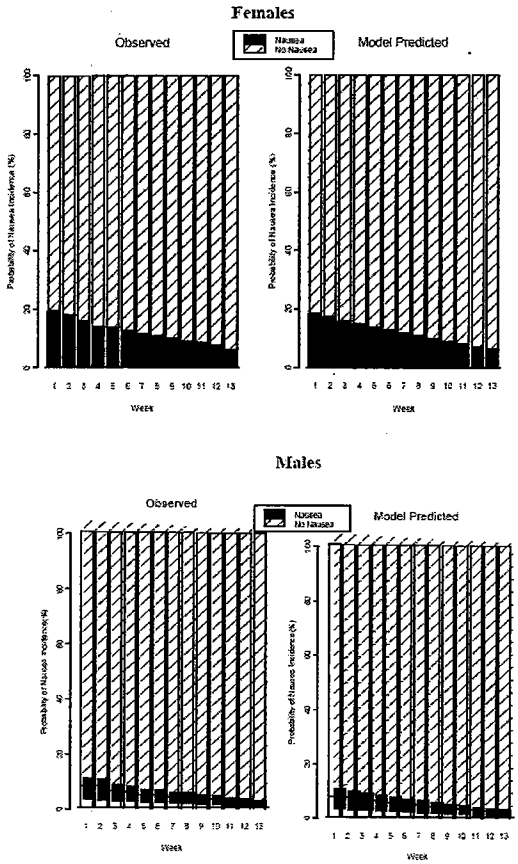


Figure 20. Distribution of Inter-Individual Variability in the Logit of Probability of Weekly Nausea Incidence (A3051007/1018, A3051028, A3051036 and A3051037) – NLME Model

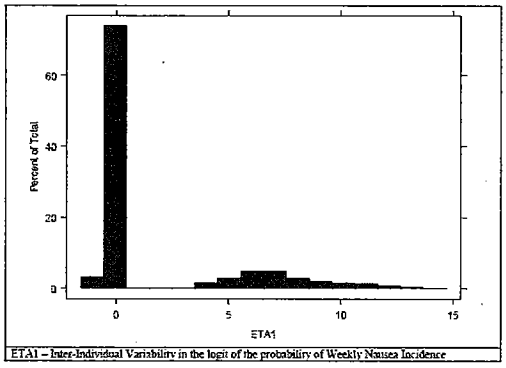


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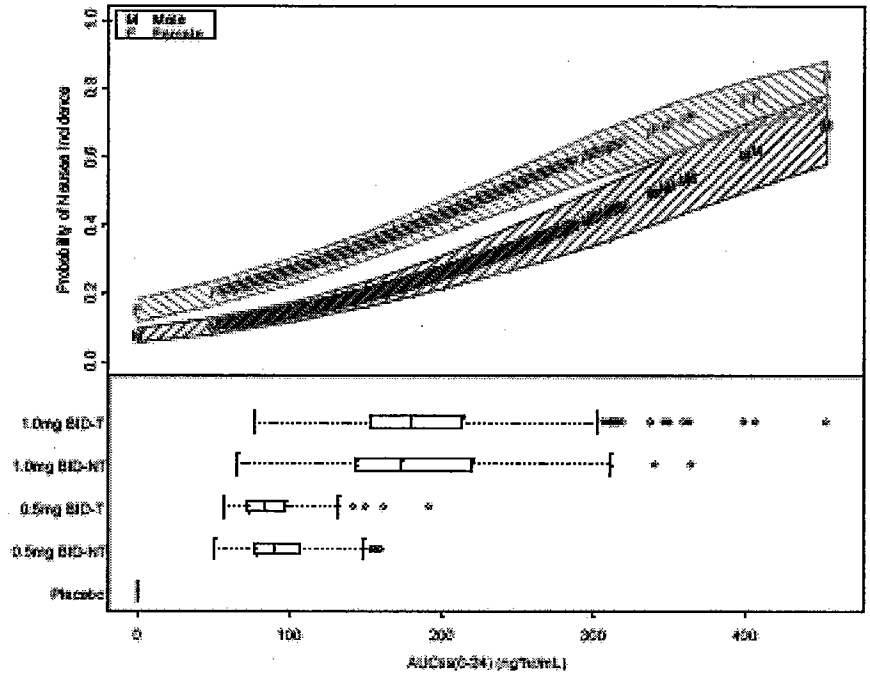
Figure 21. Predicted Varenicline Population Exposure-Response Relationships for the Nausea Incidence Rate Endpoint in Male and Female Smokers (Pooled studies A3051007/1018, A3051028, A3051036 and A3051037)



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4.2.26 Biopharmaceutics Classification committee Report

BCS Committee Meeting Minutes

When: February 2006
Where: Ad Hoc

Meeting Participants:

Mehul Mehta (Co-Chair)	Director, DPE I, OCPB
Lawrence Yu (Co-Chair)	Director for Science, OGD
Dakshina Chilukuri	Reviewer, DPE III, OCPB
Dale Conner	Director, DBE, OGD
Barbara Davit	Deputy Director, OGD
Hyojong Kwon	Reviewer, OGD
Ramana Uppoor	Team Leader, DPE I, OCPB
Jayabharathi Vaidyanathan	Reviewer, DPE II, OCPB
Donna Volpe	Team Leader, DPQR, OTR
Beth Fritsch	Executive Secretary, BCS Committee, OGD

Agenda:

BCS Classification of Varenicline Tartrate Film-Coated Tablets

Background:

Dr. Srikanth Nallani emailed a brief overview of solubility, permeability and dissolution information for Varenicline Tartrate Film-Coated Tablets.

See **Attachment I** for the background materials.

Conclusion:

Varenicline should be considered a BCS Class I drug.

Vote:

Vote: Yes (8) - Conner, Mehta, Yu, Kwon, Volpe, Uppoor, Davit and Vaidyanathan
No (1) - Chilukuri

Drafted: Beth Fritsch (02/25/06)

Comments:
M. Mehta 02/10/06
D. Conner 02/10/06
L. Yu 02/22/06
H. Kwon 02/23/06
J. Vaidyanathan 02/23/06, 03/06/06
D. Volpe 02/27/06
D. Chilukuri 02/28/06
R. Uppoor 02/28/06
B. Davit 03/03/06

V:\Division\Bio\BCS\FEB-06Minutes

ATTACHMENT I

3.2.R.5. BIOWAIVER JUSTIFICATION

Introduction

Varenicline tartrate (CP-526,555-18) is an orally administered nicotine receptor partial agonist in development for smoking cessation. This compound has high affinity for the $\alpha 4\beta 2$ neuronal nicotinic receptor subtype that mediates the reinforcing effects of nicotine. Varenicline tartrate drug product is a conventional, film-coated tablet, containing 0.5 or 1.0 mg of varenicline drug substance. The anticipated daily dose range is 0.5 to 2.0 mg.

Varenicline tartrate is a highly soluble, high permeability drug substance with rapid dissolution characteristics of the drug product. These attributes have been evaluated with reference to Guidance for Industry: *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)*. According to the biopharmaceutics classification system (BCS) criteria, a drug substance that has high solubility, high intestinal permeability, exhibits rapid in vitro dissolution in the dosage form, and is not considered a narrow therapeutic index drug, may be classified as a Class 1 compound and thereby may qualify for a BCS based waiver for in vivo BA/BE studies under certain conditions, as described in 21 CFR 320.22.

To support the BCS determination of varenicline tartrate, Pfizer has performed experiments to determine the solubility, and permeability of the drug substance and the dissolution characteristics of the film-coated tablets. At the EOPh2 meeting with FDA (09 Oct. 2003), data were presented to demonstrate that the first three criteria cited above were met. FDA agreed that solubility and dissolution data were acceptable, but asked for additional data to support the claim of high permeability[1].

Subsequent to this meeting, FDA agreed in a telecon (29 Mar. 2004) that satisfactory data from a Caco-2 study would satisfy the requirement for additional permeability data. In addition, dissolution data from tablets manufactured at the commercial facility, using the commercial formulation (including commercial shape and color) have been generated to further demonstrate that the film-coated tablets exhibit rapid release characteristics.

This submission contains data demonstrating that varenicline tartrate and varenicline tartrate film-coat tablets meet the three physiochemical criteria for BCS 1 classification. Data to demonstrate that varenicline is not a narrow therapeutic index drug will be provided pending completion of clinical studies.

[1] Meeting minutes from Varenicline (CP-526,555) Tartrate End of Phase 2 CMC Meeting with FDA, 09 Oct. 2003, 3–4 PM (Parklawn Conference Room C).

Equilibrium Solubility

Varenicline tartrate is highly soluble in aqueous solutions, >50 mg/mL over the pH range of 1 to 12 (See Section 3.2.S.1.3, General Properties). For practical considerations, instead of determining equilibrium solubility, varenicline tartrate was evaluated over a pH range of 1–7.5 at a concentration 250 times the criterion described in the FDA guidance. The amount of varenicline tartrate contained in the highest dose strength (1.7 mg) dissolved rapidly in 250 mL or less of aqueous media over the pH range of 1-7.5. The solubility study was conducted at ambient temperature. With a factor of 250, the potential solubility variations due to temperature difference are negligible. Three replicate stability determinations were made at pH = 1.0, 2.5, 4.0, 5.5, and 7.5 and verified after 3 and 7 days to demonstrate that solubility did not diminish over time. In addition, no significant degradation was observed.

Table 3.2.R.5-1. Solubility in Solutions of pH 1. 0, 2.5, 4.0, 5.5, and 7.5 at Ambient Temperature

pH Buffer	Average Solubility (n=3)			pH Verification/ %RSD (n=3)		Stability %RSD (n=3)	
	Day 0 mg/mL	Day 3 mg/mL	Day 7 mg/mL	Day 3	Day 7	Day 3	Day 7
1.0	≥1.7	≥1.7	≥1.7	1.1/2.4	1.1/1.6	ND*	ND
2.5	≥1.7	≥1.7	≥1.7	2.6/0.2	2.6/0.0	ND	ND
4.0	≥1.7	≥1.7	≥1.7	4.0/0.1	4.0/0.1	ND	ND
5.5	≥1.7	≥1.7	≥1.7	5.6/0.0	5.6/0.3	ND	ND
7.5	≥1.7	≥1.7	≥1.7	7.3/0.8	7.2/0.6	ND	ND

*ND: No degradant was detected.

The data demonstrate that varenicline tartrate is a highly soluble compound as defined by the BCS guidance[2], and that bioavailability would not be expected to be limited by the compounds solubility.

[2] *A drug substance is considered highly soluble when the highest dose is soluble in 250 mL or less of aqueous media over a pH range of 1 to 7.5.* Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System

Permeability Class Determination

Varenicline (CP-526,555), a nicotinic acetylcholine receptor partial agonist, is well-absorbed from the GI tract after oral administration in humans. Data have been generated that satisfy the permeability criterion for a BCS 1 classification. The data in support of this claim are as follows:

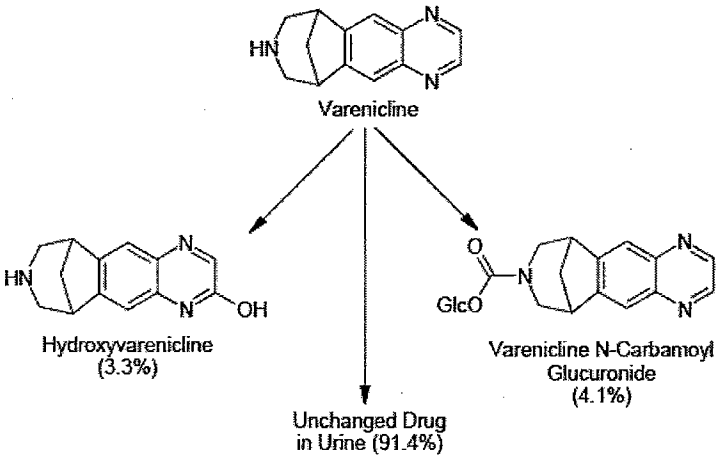
1. The excretion pattern of total radioactivity, after oral administration of [^{14}C]varenicline to healthy human subjects, demonstrates that the vast majority of recovered radioactivity was excreted in the urine (Module 4, Section 4.2.2.2, DM2000-526555-031), and
2. The permeability of [^{14}C]varenicline through the Caco-2 cell model, a well-established experimental system for assessing permeability through GI tissues, has been demonstrated to be high; consistent with highly permeable drugs (Module 4, Section 4.2.2.2, DM2003-526555-053).

A summary of the findings of these two studies and the rationale being applied to the data in support of BCS-based biowaiver status for varenicline are listed below.

Human Radiolabelled ADME Study:

Following oral administration of 1.0 mg [^{14}C] varenicline as a solution to six healthy male subjects, the mean (+/-RSD) overall recovery of varenicline drug-related material was 88.0% (+/- 5.7%) of the dose with individual values ranging from [ ] Blood samples were collected up to 192 hours after drug administration. Urine and feces collections continued until two consecutive 24-hour samples had radioactivity less than 1% of the total radioactivity administered. Material was almost all excreted in urine (87.1% of dose; 99% of the recovered dose) with < 1% in feces. In fact, the presence of almost all radioactivity in urine as unchanged drug (91.6 % of the recovered dose), with the remaining material eliminated in the urine as metabolites, indicates that varenicline is essentially completely absorbed with high systemic availability after oral administration. The metabolites observed in urine, accounting for 3–4% of recovered dose each, included a hydroxyquinoxaline and N-carbamoylglucuronide. The precise location of formation of these metabolites has not been ascertained, but both are consistent with enzymatic processes frequently encountered in the liver, suggesting that these metabolites arise post-absorption. This is shown in Figure 3.2.R.5-1.

Figure 3.2.R.5-1. Metabolite Scheme



The recommended criterion for a BCS-based biowaiver is that at least 90% of drug-related radioactivity should be recovered in urine after oral administration, and that such excretion data using radiolabelled drug can be used in support of this claim. In the case of varenicline, a mean total of 88% recovery was achieved; in which case obtaining 90% of dose in urine is not possible. However, for many possible technical reasons, excretion studies in human subjects using radiolabelled drug rarely provide "complete" mass recovery. (Such reasons can include incomplete dose administration, missed portions of excreta samples, lower limits of quantitation in radiometric analysis, etc.) The mean recovery value of 88% for varenicline is consistent with mean recovery values that we routinely measure in human mass balance studies.

In excretion studies in humans using radiolabelled drug, both urine and feces are collected. Therefore, unless excretion occurs by some highly unconventional route (e.g. exhalation) or if radiolabelled drug is metabolized in such a manner that the radioactive nucleus becomes incorporated into endogenous metabolism, the sum of urinary and fecal radioactivity after oral administration of drug can be used in the determination of the lower limit of absorption. Radioactivity in urine after oral administration of drug must arise from absorbed material. Radioactivity in feces can arise either from unabsorbed drug or from drug that was absorbed and secreted into the GI (as metabolites and/or unchanged drug). For varenicline, on average only 0.9% of the recovered drug-related material was in feces, while the other 87.1% was in urine, yielding a lower limit of absorption of 99.0%.

$$\text{absorption} \geq \frac{\text{urinary radioactivity}}{\text{urinary radioactivity} + \text{fecal radioactivity}} = \frac{87.1\%}{87.1\% + 0.9\%} = 99.0\%$$

Using this calculation for each study subject, the lower limit of absorption ranged from [ ] irrespective of the total recovery values, which ranged from [ ]
The excellent consistency for this calculation in all six subjects (98.3–99.5%) also lends

credence to the claim regarding urine as the major route of excretion of total drug related material and hence absorption that is 98% or greater. The individual results based on routes of excretion of total radioactivity are listed in Table 3.2.R.5-2. These data support that varenicline is absorbed well in excess of the recommended 90% absorption criteria for the bioequivalence waiver.

Table 3.2.R.5-2. Individual Excretion Data for Six Healthy Human Subjects after Oral Administration of 1 mg [^{14}C]Varenicline

	Recovery	% of recovered dose in:	
Subject	(% of Dose)	Urine	Feces
smoker			
smoker			
smoker			
nonsmoker			
nonsmoker			
nonsmoker			

Caco-2 Cell Monolayers Study:

Based on EOPh2 discussions with the FDA and Pfizer representatives it was agreed that Pfizer would further assess the permeability properties of varenicline tartrate through a Caco-2 cell model study. Results from this study are summarized below:

The Caco-2 study utilized cells that had been grown in culture for 21 days. A transwell assay format was utilized and varenicline, along with various control compounds, was examined in both the apical-to-basolateral (A→B) and basolateral-to-apical (B→A) directions. For weak organic bases, such as varenicline, a potential artifact can arise in transwell assays if there is a pH differential between the apical and basolateral buffers. In standard Caco-2 cell assays, a pH of 6.5 is utilized on the apical side to mimic the pH of the intestinal lumen while a pH of 7.4 is utilized on the basolateral side to mimic blood pH. Therefore, varenicline was examined under both conditions in which the pH was 6.5 or 7.4 on the apical side, and metoprolol, another weak organic base drug, was used as a positive control to account for the pH effect.

Apparent permeability flux values for varenicline in the A→B direction with equal pH on each side ranged from 19.8 to 23.9 x 10^{-6} cm/sec consistent with a high permeability. Flux values were independent of varenicline concentration through the examined range of 5.0 to 50 µM. A corresponding A→B flux value for a positive control high permeability drug, caffeine, was 31.3 x 10^{-6} cm/sec, while low permeability compounds mannitol, acyclovir and methotrexate had values that were below 3 x 10^{-6} cm/sec. Varenicline did not appear to be a substrate for uptake or efflux transporters, since the B→A/A→B ratio was below 2. (The high ratio observed under the condition of the apical side at pH 6.5 was due to a charge effect and was similarly demonstrated for metoprolol, used as a positive control for this phenomenon.) In summary, these results indicate that varenicline tartrate exhibits high permeability.

Table 3.2.R.5-3. Summary of Caco-2 Cell Permeability Data for Varenicline and Other Drugs

Compound/Condition	Absorption Characteristics	P_{app} (cm/sec) x 10^{-6} A→B	P_{app} (cm/sec) x 10^{-6} B→A	Flux Ratio
Varenicline, (pH 7.4)				
5.0 µM	High Permeability	23.9	35.6	1.5
15 µM		19.8	35.8	1.8
50 µM		20.4	33.7	1.6
Varenicline, (pH 6.5)[3]				
5.0 µM		8.83	46.7	5.3
15 µM		8.87	40.3	4.6
50 µM		7.91	38.2	5.0
Metoprolol (pH 7.4)	Control for High Permeability	14.9	25.1	1.7
Metoprolol (pH 6.5)	Control for pH Effect	4.34	35.8	6.7
Acyclovir	Control for Low Permeability	2.36	3.08	1.3
Methotrexate	Control for Low Permeability	2.19	4.42	2.0
Verapamil	Efflux Inhibitor	9.23	13.6	1.5
Caffeine	Control for High Permeability	31.3	55.1	1.8
Doxorubicin	Control for Low Permeability + Efflux Inhibitor	1.37	3.25	2.4
Erythromycin	Control for Low Permeability + Efflux Inhibitor	1.36	12.3	9.0

[3] Average of results obtained by co-incubation in (1) metoprolol and (2) mannitol.

Conclusion

Together, these two datasets support the position that varenicline is a high permeability drug that satisfies the BCS[4] classification criteria for high permeability. In humans after oral administration of radiolabelled varenicline, well over 90% of recovered radioactivity was excreted in urine indicating that varenicline is completely absorbed. This is further supported by the characterization of varenicline that was conducted in the Caco-2 cell monolayer system, a well-established model for predicting drug absorption in humans. Varenicline demonstrated flux characteristics in this system similar to other well-absorbed drugs and vastly different from those drugs that are poorly absorbed. Varenicline flux data also support that it is not actively transported across the Caco-2 monolayer.

Dissolution Rate Determination

To demonstrate the rapid dissolution of varenicline tartrate tablets, dissolution data has been generated on 0.5 and 1.0 mg varenicline tartrate film-coated tablets using the following conditions shown in Table 3.2.R.5-4.

Table 3.2.R.5-4. Dissolution Conditions

Apparatus	USP <711> Dissolution Apparatus I (baskets)
Media	500 mL of 0.01N HCl 500 mL of 0.1N HCl 500 mL of pH 4.5 buffer 500 mL of pH 6.8 buffer 500 mL of Water
Agitation Rate	100 rpm
# of dosage units tested per condition	12[5]

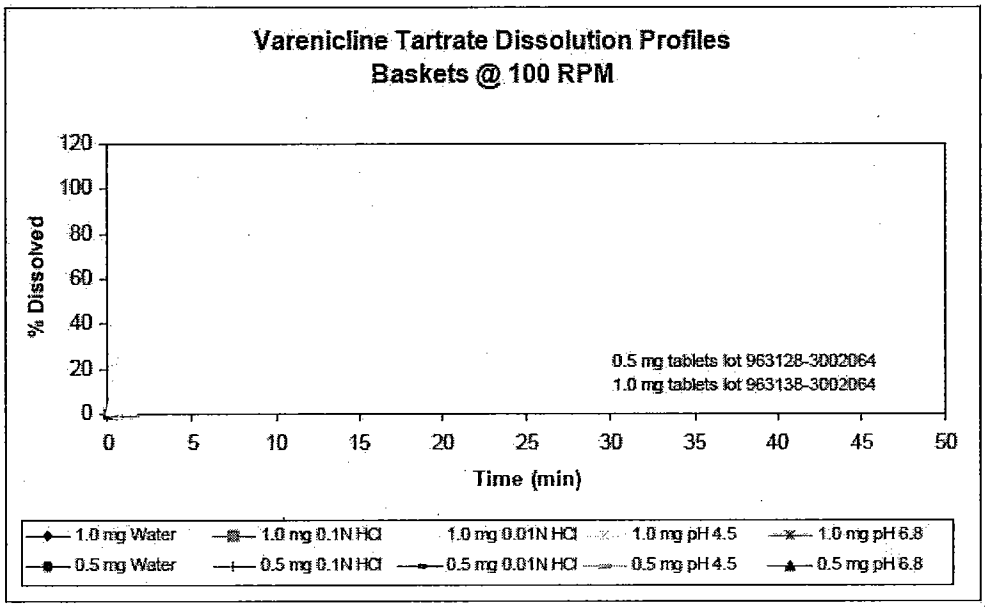
The results of these experiments are graphically depicted in Figure 3.2.R.5-2. Samples were collected at 5, 10, 15, 30 and 45 minutes. The data indicate that varenicline tartrate tablets exhibit rapid dissolution ([ ] within 15 minutes) in all media. Consequently, the dosage formulation, independent of strength, qualifies as rapidly dissolving[6] (>85% in 30 minutes) and no statistical comparison (e.g., f2 test) of dissolution profiles is necessary.

[4] Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System.

[5] For 1.0 mg tablets evaluated in water, 0.01N HCl and pH 4.5 buffer, 11 units were analyzed due to analytical equipment errors. However, the results from 11 units clearly illustrate rapid release with little variability.

[6] Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System

Figure 3.2.R.5-2. Varenicline Tartrate Dissolution Profiles, Baskets at 100 rpm



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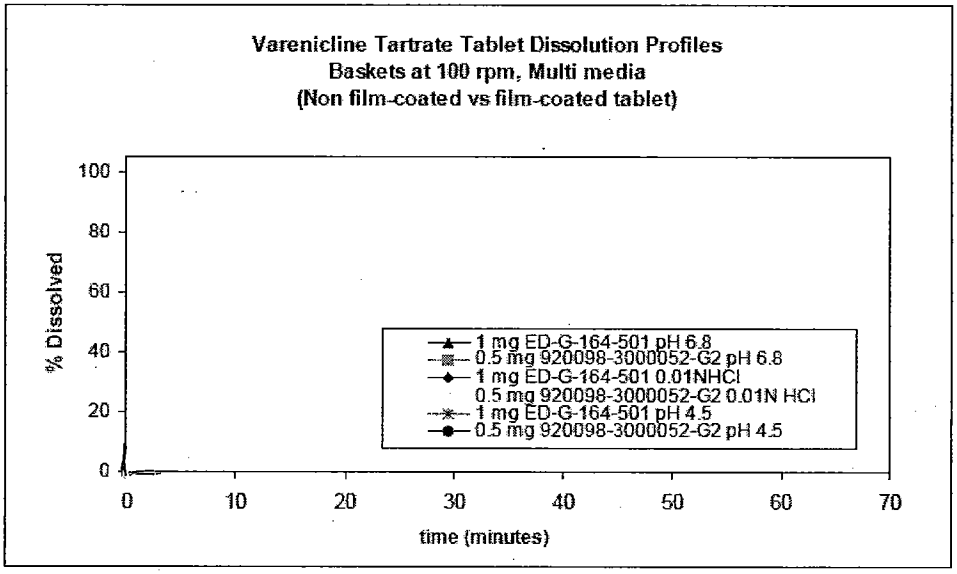
Supportive In Vitro Dissolution Studies

Supportive in-vitro dissolution studies were conducted early in development and are included to compare profiles for non-film coated tablets and film-coated tablets in multi-media studies. Dissolution testing was conducted on the 1.0 mg non-film-coated tablet and 0.5 mg film-coated tablet formulations in USP apparatus 1 (baskets) at 100 rpm in the following media: 0.01 N HCl, USP pH 4.5 acetate buffer, and USP pH 6.8 phosphate buffer. These lots were used in the BE Study # A3051026. The dissolution profiles, as illustrated in Figure 3.2.R.5-3, are essentially the same for the two formulations. The presence or absence of film-coat does not impact the rapid release of the dosage form, irrespective of the dissolution medium selected.

Figure 3.2.R.5-3. Varenicline Tartrate Tablet Dissolution Profiles, Baskets at 100 rpm, Multi-Media (Non Film-Coated vs Film-Coated Tablet)



Summary of Dissolution Methodology

A dissolution method has been validated for varenicline tartrate 0.5 and 1.0 mg film-coated tablets and is performed in accordance with the following standard USP dissolution test conditions.

Table 3.2.P.5.6-9. Standard USP Dissolution Test Conditions

Apparatus:	USP Apparatus I (baskets)
Medium:	0.01N HCl
Volume:	500 mL
Agitation Rate:	100 rpm
Analytical End Analysis:	HPLC

The dissolution conditions (medium, apparatus, and agitation rate) were selected in accordance with ICH Q6A guidance based on results from an evaluation of varenicline tartrate tablets analyzed in several dissolution conditions. The evaluation was performed on twelve units for each lot of tablets. Varenicline tartrate tablets exhibit extremely high solubility throughout the physiological pH range with rapid release characteristics ([ ] within 15 minutes) of the drug product, which are independent of medium (water, 0.1N HCl, 0.01N HCl, USP pH 4.5 and USP pH 6.8 buffers), tablet shape and tablet strength in baskets at 100 rpm. The apparatus and agitation rates were selected over paddles [

]

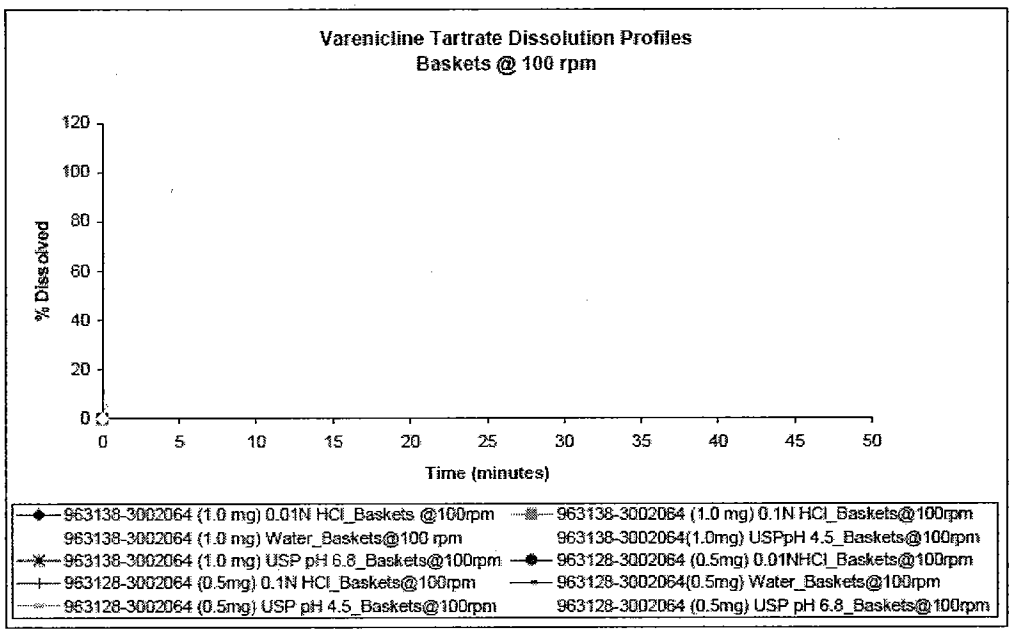
The dissolution characteristics of varenicline tartrate film-coated tablets are attributed to high solubility of the drug substance and suggest that dissolution has limited utility as an in vitro method for measuring tablet performance. Therefore, in accordance with ICH Q6A, disintegration would serve as an appropriate and adequate method for ensuring drug release. The ability of each method to discriminate for deviations in formulations or manufacturing conditions was evaluated using aberrant formulations. The following sections describe the selection of the dissolution method conditions as well as establish a relationship between disintegration and dissolution for varenicline tartrate.

Selection of Dissolution Conditions

Selection of the Medium

Standard USP media were evaluated: Water, 0.1N HCl, 0.01N HCl, USP pH 4.5 buffer, and USP pH 6.8 buffer. Dissolution profiles were obtained at 5, 10, 15, and 30-minute test intervals. An additional sample was pulled at 45 minutes for information only. The release rate profiles provided in Figure 3.2.P.5.6-1 illustrate that the formulation is a rapidly dissolving dosage form independent of medium and tablet strength. The selection of 0.01N HCl as the test medium over 0.1N HCl was made in consideration of ecological sensitivity within the context of "Green Chemistry."

Figure 3.2.P.5.6-1. Multi-Media Release Profile With Baskets at 100 rpm, 0.5 and 1.0 mg Tablet



Selection of Apparatus and Agitation Rate

USP Apparatus I (baskets) at 100 rpm was selected over USP Apparatus II (paddles)

The dissolution profiles obtained with the use of baskets, reflects the actual release properties of the formulation. Comparable results were obtained for both tablet strengths and all media evaluated (Water, 0.01N HCl, 0.1N HCl, USP pH 4.5 buffer, and USP pH 6.8 buffer). Additionally, baskets at 50 rpm provide no advantage over the mild agitation rate of 100 rpm in baskets. Higher variability is observed at five minutes with no significant differences observed at the following time points. An illustration is provided in Figure 3.2.P.5.6-6 and Figure 3.2.P.5.6-7.

Figure 3.2.P.5.6-2. Baskets at 100 rpm vs. Paddles at 50 rpm, 0.5 mg

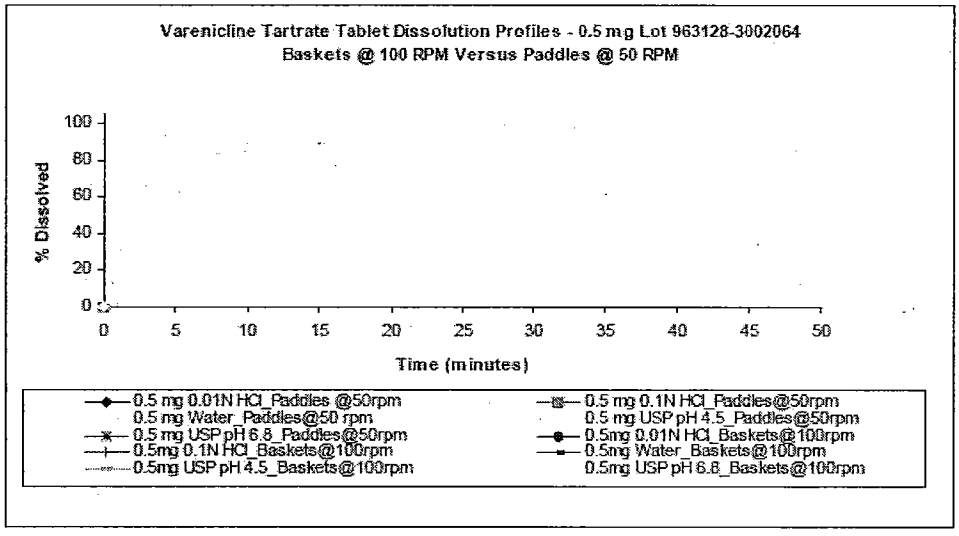


Figure 3.2.P.5.6-3. Baskets at 100 rpm vs. Paddles at 50 rpm, 1.0 mg

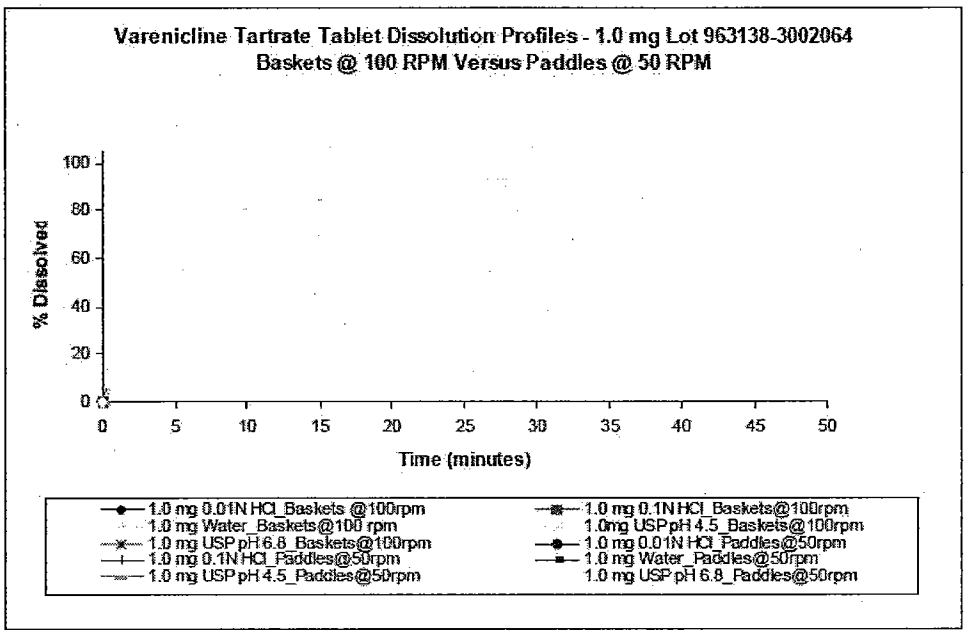


Figure 3.2.P.5.6-4. Baskets at 100 rpm vs. Paddles at 75 rpm, 0.5 mg

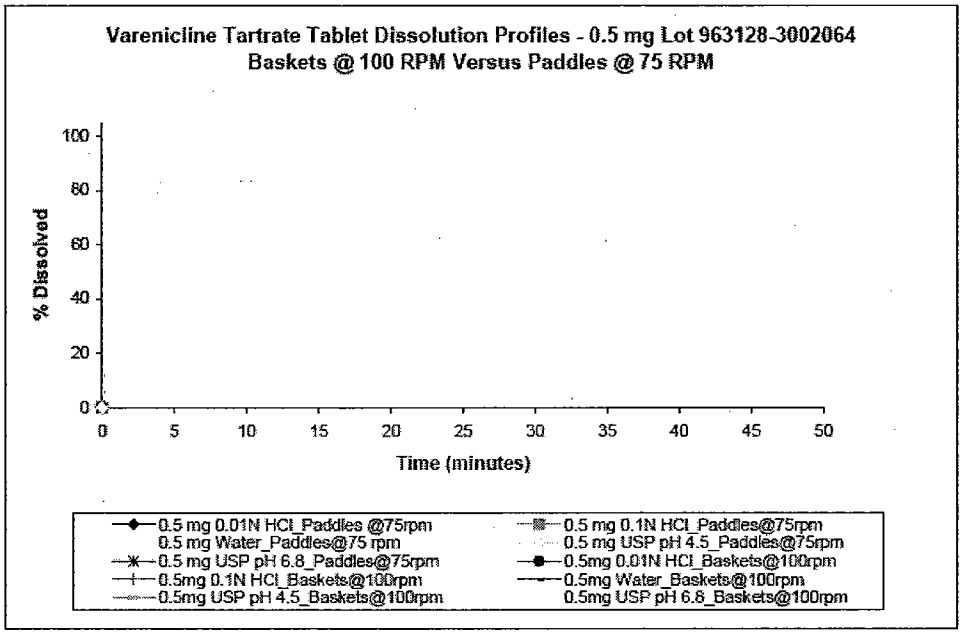


Figure 3.2.P.5.6-5. Baskets at 100 rpm vs. Paddles at 75 rpm, 1.0 mg

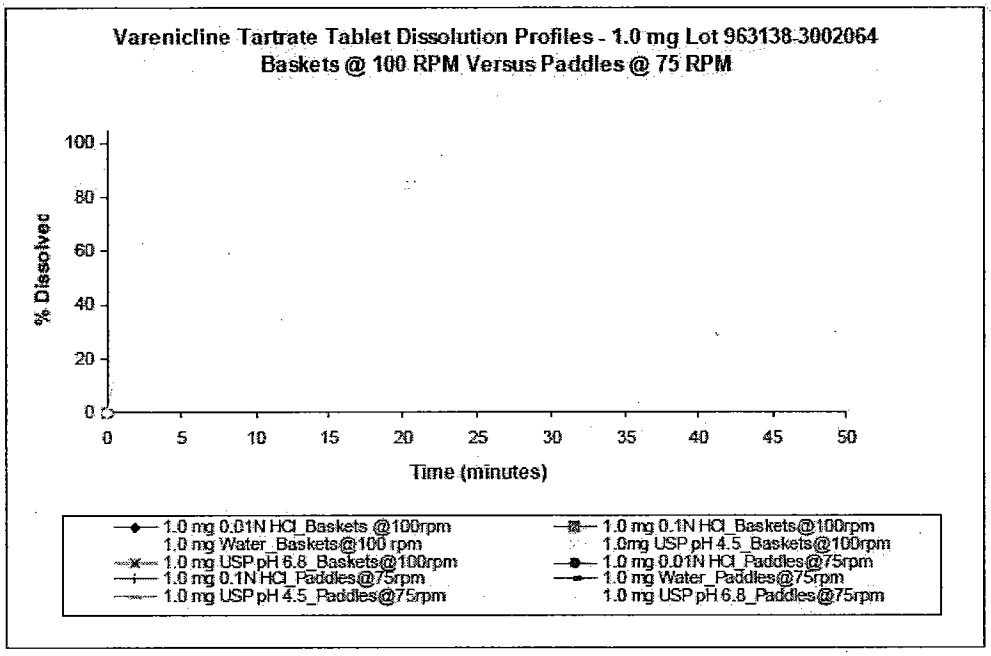


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Figure 3.2.P.5.6-6. Baskets at 100 rpm vs. Baskets at 50 rpm, 0.5 mg

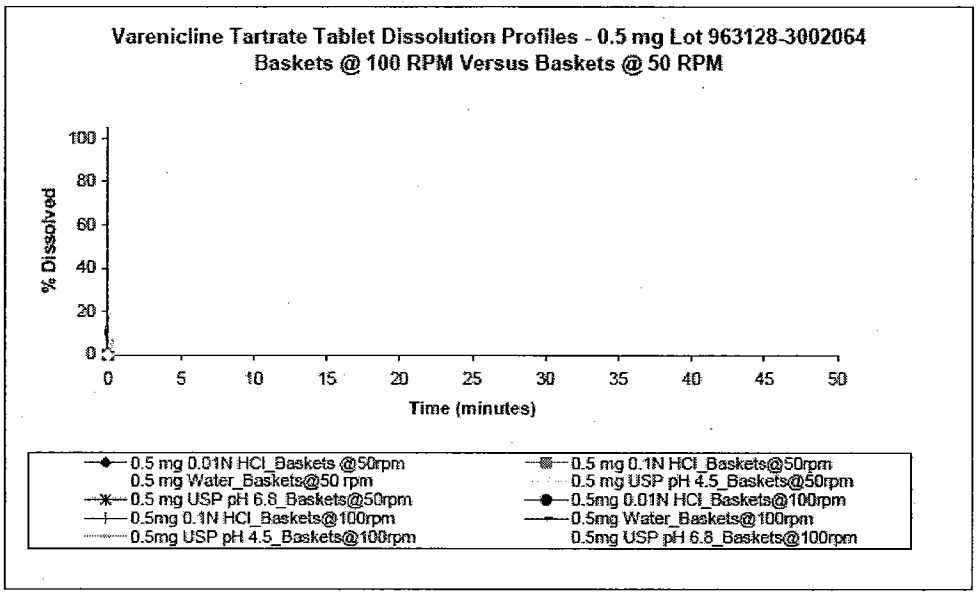

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Figure 3.2.P.5.6-7. Baskets at 100 rpm vs. Baskets at 50 rpm, 1.0 mg

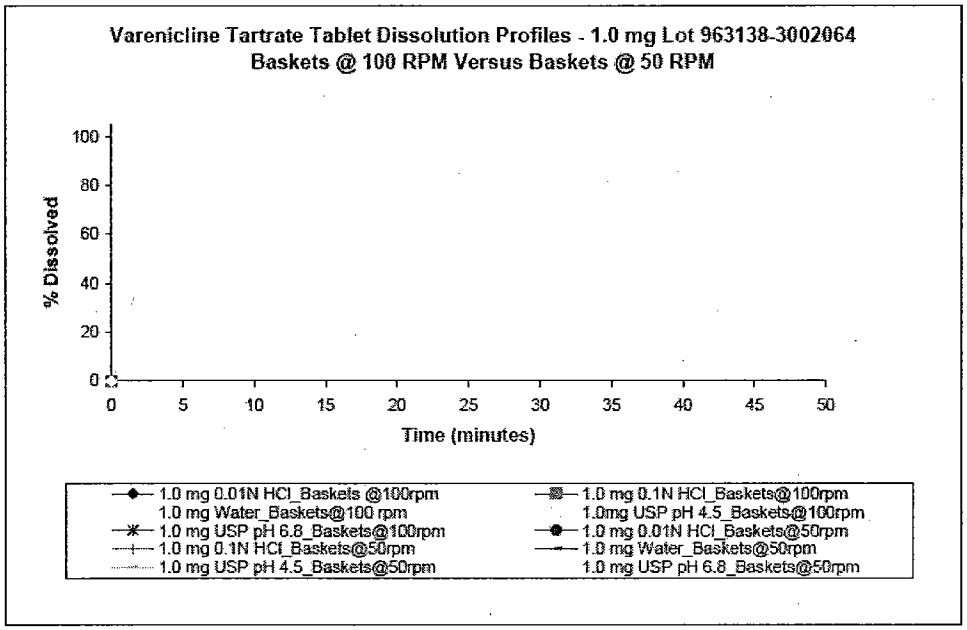

Figure 3.2.P.5.6-8. Baskets at 100 rpm vs. Paddles at 50 rpm in 0.01N HCl, 0.5 mg & 1.0 mg

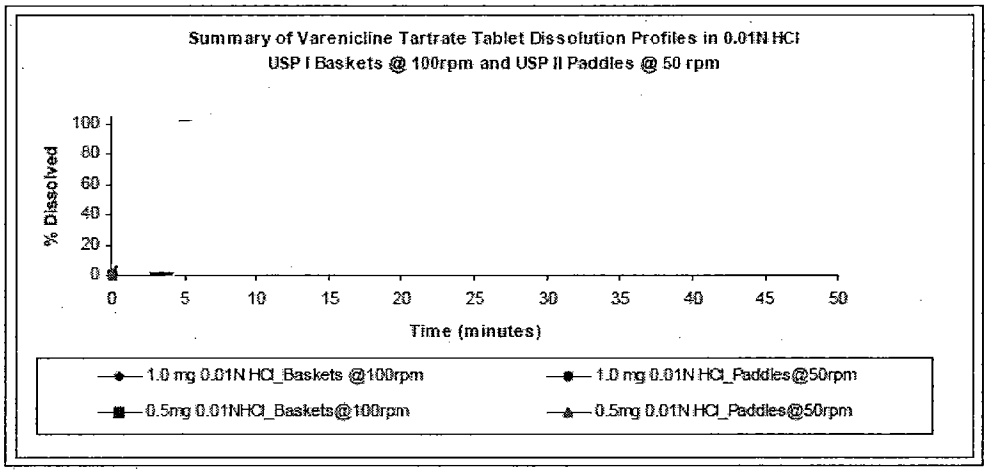

Table 7. Bioequivalence Studies with Varenicline Tablet Formulations: Studies A3051030, A3051026, and A3051006

Pharmacokinetic Parameter	Adjusted Geometric Mean		Statistical Comparison	
	Test	Reference	Ratio (Test/Ref, %)	90% Confidence Interval (%)
A3051030	Commercial Image Tartrate Tablets 1 x 1.0 mg N = 11	Phase 3 Tartrate Tablets 2 x 0.5 mg N = 12		
AUC(0-∞) (ng·hr/mL)	101.1	103.9	97.26	91.73-103.12
AUC(0-tlast) (ng·hr/mL)	96.6	95.2	101.43	94.17-109.26
Cmax (ng/mL)	4.0	4.3	93.05	89.13-97.15
	Commercial Image Tartrate Tablets 1 x 1.0 mg N = 11	Phase 2b Tartrate Tablets 2 x 0.5 mg N = 12		
AUC(0-∞) (ng·hr/mL)	101.1	101.1	99.98	94.30-106.01
AUC(0-tlast) (ng·hr/mL)	96.6	97.1	99.45	92.32-107.12
Cmax (ng/mL)	4.0	4.0	99.90	95.69-104.29
A3051026	Phase 3 Tartrate Tablets 2 x 0.5 mg[a] N = 12	Phase 2b Tartrate Tablets 1 x 1.0 mg[a] N = 12		
AUC(0-∞) (ng·hr/mL)	49.87[b]	49.25[c]	101.26	94.61-108.38
AUC(0-tlast) (ng·hr/mL)	44.40	44.61	99.51	90.23-109.75
Cmax (ng/mL)	2.36	2.24	105.59	100.38-111.08
A3051006	Phase 2b Tartrate Tablets 1 x 1.0 mg N = 15	Phase 2a Succinate Tablets 1 x 1.0 mg N = 15		
AUC(0-∞) (ng·hr/mL)	127.76	124.96	102.24	93.86-111.38
AUC(0-tlast) (ng·hr/mL)	115.53	112.56	102.64	94.56-111.41
Cmax (ng/mL)	4.22	4.16	101.53	97.15-106.10

Source: Clinical Study Report A3051030 Tables 13.5.2.1, 13.5.2.2, 13.5.2.3, 13.5.3.1, 13.5.3.2; A3051026 Tables 5.2.2, 5.2.4, 5.2.5, 5.3; A3051006 Tables 5.2.1, 5.3

Ratio = Ratio of treatment mean values, expressed as a percentage (100 x test/reference)

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percent of the reference mean.

[a] Values dose-normalized to 0.5 mg prior to analysis [b] N = 9 [c] N = 10

Variability Estimates for Exposure with Varenicline Tablets

By-study estimates for intra-subject and inter-subject variability in Cmax and AUC pharmacokinetic parameters following administration of varenicline tablets are shown below in Table 8.

Table 9. Comparison of Varenicline Tablets Administered in the Fed and Fasted State: Studies A3051042, A3051006, A3051001

Pharmacokinetic Parameter	Adjusted Geometric Means		Statistical Comparison	
	Test	Reference	Ratio (Test/Ref, %)	90% Confidence Interval (%)
A3051042: Commercial image tablet (1 x 1.0 mg)				
	Fed N = 12	Fasted N = 12		
AUC(0-∞) (ng·hr/mL)	102.7	104.1	98.62	93.92-103.57
AUC(0-tlast) (ng·hr/mL)	98.7	99.2	99.54	94.60-104.73
Cmax (ng/mL)	4.2	4.2	100.9	96.88-105.22
A3051006: Phase 2b varenicline tartrate tablet (1 x 1.0 mg)				
	Fed N = 14	Fasted N = 15		
AUC(0-∞) (ng·hr/mL)	122.79 [a]	127.76	96.11	87.77-105.24
AUC(0-tlast) (ng·hr/mL)	111.08	115.53	96.14	88.35-104.63
Cmax (ng/mL)	4.34	4.22	102.76	98.19-107.54
A3051001: Varenicline succinate tablet (2 x 1.0 mg)				
	Fed N = 10	Fasted N = 10		
AUC(0-∞) (ng·hr/mL)	225.85	237.37	95.15	87.18-103.84
Cmax (ng/mL)	9.54	9.33	102.30	96.37-108.59

Source: Clinical Study Report A3051001 Tables 5.2.2, 5.2.3, 5.3; A3051006 Tables 5.2.2, 5.2.3, 5.2.4, 5.3; A3051042 Tables 13.1.1, 13.5.3

Ratio = Ratio of adjusted geometric means, expressed as a percentage (100% x test/reference)

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percent of the reference mean.

[a] N = 13

In Study A3051001, the 90% confidence intervals of both AUC and Cmax ratios were within established BE limits (80.00%, 125.00%) for both the varenicline succinate tablet versus the OPC solution and the morning (8:00 hours) versus evening (20:00 hours) dosing comparisons (Table 10).

Hi Mehul,

Since the permeability assay data cannot be used, I am now providing the dose-proportionality info to assume passive absorption mechanism. The increase in AUC is dose-proportional upto 2 mg. At the dose of 3 mg and 10 mg because of nausea and particularly vomiting as the dose-limiting side effect the drug absorption was not complete. The proposed doses are 0.5 mg and 1 mg. Let me know if this is acceptable to the committee.

Thanks

Srikanth

Dose (mg)	Study	N	Smoking Status	Tmax [a] (h)	Cmax (ng/mL)	AUC(0-∞) (ng·hr/mL)	t1/2 (h)
0.1	305-001	4	smokers	1.50 [1.00-2.00]	0.468 (0.071)	9.52 (3.6)	14.8 (6.5)
	305-001	4	nonsmokers	2.00 [0.500-8.00]	0.825 (0.105)	12.6 (0.7)	13.3 (2.0)
0.3	305-001	4	smokers	1.50 [0.50-3.00]	2.35 (0.93)	37.9 (9.7)	14.4 (2.9)
	305-001	4	nonsmokers	1.00 [1.00-4.00]	1.90 (0.56)	31.4 (9.6)	12.6 (2.2)
0.5	A3051026	12	smokers	3.00 [1.00-4.00]	2.37 (0.46)	57.9 (10.0) [e]	20.1 (3.1) [e]
1	combined [b]	43	smokers	3.00 [1.00-6.00]	4.32 (0.92)	105 (18.7)	19.1 (3.34)
	combined [c]	23	nonsmokers	3.00 [0.500-8.00]	4.67 (1.13)	120 (31)	19.3 (3.16)
2	combined [d]	27	smokers	4.00 [1.00-8.00]	9.01 (1.47)	240 (61)	18.6 (4.30)
3	305-001	12	smokers	4.00 [2.00-8.00]	12.3 (3.25)	270 (55)	18.8 (5.17)
	305-001	4	smokers (SR)	3.00 [2.00-4.00]	14.0 (1.41)	288 (55)	16.5 (7.3)
	305-001	4	nonsmokers	3.00 [0.500-6.00]	10.8 (2.1)	223 (83)	20.5 (10.3)
10	305-001	4	smokers	5.00 [1.00-6.00]	13.0 (6.2)	303 (168)	19.5 (5.9)

4.2.27 CPB Filing Form

Office of Clinical Pharmacology and Biopharmaceutics ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		Information
NDA Number	21-928	**Brand Name**	Champix
OCPB Division	DCPB 2	**Generic Name**	Varenicline Tartarate Tablets
Medical Division	Division of Anesthesia Analgesia and Rheumatology Products	**Drug Class**	Benzazepine
OCPB Reviewer	Srikanth C. Nallani, Ph.D.	**Indication(s)**	Smoking cessation
OCPB Team Leader	Suresh Doddapaneni, Ph.D	**Dosage Form**	Oral Tablet
Date of Submission	November 9, 2005	**Dosing Regimen**	1 mg twice daily following a 1 week titration (days 1-3; 0.5 mg, days 4-7; 0.5 mg twice daily)
Estimated Due Date of OCPB Review	March 20, 2006	**Route of Administration**	Oral
PDUFA Due Date	May 9, 2006	**Sponsor**	Pfizer Inc.
Division Due Date	April 3, 2006	**Priority Classification**	Priority

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**	**1**	

Isozyme characterization:	**X**	**1**	**1**	Metabolism by UGTs (Generally not extensively metabolized)
Blood/plasma ratio:	**X**	**1**	**1**	
Plasma protein binding:	**X**	**1**	**1**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4	4	
multiple dose:	X	4	4	
Patients-				
single dose:	X	4	4	
multiple dose:	X	4	4	
Dose proportionality -				
fasting / non-fasting single dose:	X	3	3	
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3	3	DDI with Zyban, cimetidine, Metformin
In-vivo effects of primary drug:	X	3	3	DDI with digoxin, warfarin, NRT
In-vitro:	X	2	2	Effect of varenicline on Transporters, CYPs.
Subpopulation studies -				
ethnicity:	X	1	1	PK in healthy Japanese smokers
gender:	X			Subjects of either sex were included in different SD, MD PK studies
pediatrics:	X	1	1	Adolescents (12 – 17 years)
geriatrics:	X	1	1	
renal impairment:	X	1	1	
hepatic impairment:	-			Not required as drug is not extensively metabolized
PD:				
Phase 2:	**X**	**3**	**3**	
Phase 3:	**X**	**3**	**3**	
PK/PD:				

Phase 1 and/or 2, proof of concept:	X	6	6	Three Phase 1, Three Phase 2
Phase 3 clinical trial:	X	3	3	Population PK/PD analyses entailed use of data from two Phase 2 and three Phase 3 studies
Population Analyses -				
Data rich:	X	9	9	Pharmacokinetic Data from four Phase 1, two Phase 2, three Phase 3 studies was utilized
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	X	2	2	
alternate formulation as reference:	X	2	2	
Bioequivalence studies -				
traditional design; single / multi dose:	X	4	4	
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**3**	**3**	
Dissolution:	**X**	**6**	**6**	
(IVIVC):	**NA**			
Bio-wavier request based on BCS	**X**			
BCS class	**1**			Biowaiver Justification submitted
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics	**X**	**1**	**1**	
Pediatric development plan				
Literature References	**X**			
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		

Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	**NO**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What demographic factors explain the variability in pharmacokinetics of varenicline? What data supports a waiver of in vivo BE data? Does the exposure-response data justify the dose and dosing regimen employed in the pivotal clinical trials? Does varenicline has the potential to cause QT prolongation?	
Other comments or information not included above	**Pharmacometrics consult:** Review of the POP PK/PD analysis. These analyses were used to support the proposed dosing regimen and to conclude that varenicline PK does not change significantly due to covariates such as age, race, gender, etc. **BCS Biowaiver consult:** Does the BCS committee agree with the sponsor provided biowaiver justification and classification of varenicline as BCS class I drug?	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Srikanth Nallani
4/6/2006 05:30:38 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
4/7/2006 08:20:35 AM
BIOPHARMACEUTICS
Team Leader's sign off

Jogarao Gobburu
4/7/2006 09:30:33 AM
BIOPHARMACEUTICS

Lei K Zhang
4/7/2006 10:27:42 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-928	**Brand Name**	Champix
OCPB Division	DCPB 2	**Generic Name**	Varenicline Tartarate Tablets
Medical Division	Division of Anesthesia Analgesia and Rheumatology Products	**Drug Class**	Benzazepine
OCPB Reviewer	Srikanth C. Nallani, Ph.D.	**Indication(s)**	Smoking cessation
OCPB Team Leader	Suresh Doddapaneni, Ph.D	**Dosage Form**	Oral Tablet
Date of Submission	November 9, 2005	**Dosing Regimen**	1 mg twice daily following a 1 week titration (days 1-3; 0.5 mg, days 4-7; 0.5 mg twice daily)
Estimated Due Date of OCPB Review	March 20, 2006	**Route of Administration**	Oral
PDUFA Due Date	May 9, 2006	**Sponsor**	Pfizer Inc.
Division Due Date	April 3, 2006	**Priority Classification**	Priority

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
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HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		
Isozyme characterization:	**X**	**1**		Metabolism by UGTs (Generally not extensively metabolized)
Blood/plasma ratio:	**X**	**1**		
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		
multiple dose:	X	4		
Patients-				
single dose:	X	4		
multiple dose:	X	4		
Dose proportionality -				
fasting / non-fasting single dose:	X	3		
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		DDI with Zyban, cimetidine, Metformin
In-vivo effects of primary drug:	X	3		DDI with digoxin, warfarin, NRT
In-vitro:	X	2		Effect of varenicline on Transporters, CYPs.
Subpopulation studies -				
ethnicity:	X	1		PK in healthy Japanese smokers

gender:	X			Subjects of either sex were included in different SD, MD PK studies
pediatrics:	X	1		Adolescents (12 – 17 years)
geriatrics:	X	1		
renal impairment:	X	1		
hepatic impairment:	-			Not required as drug is not extensively metabolized
PD:				
Phase 2:	**X**	**3**		
Phase 3:	**X**	**3**		
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	6		Three Phase 1, Three Phase 2
Phase 3 clinical trial:	X	3		Population PK/PD analyses entailed use of data from two Phase 2 and three Phase 3 studies
Population Analyses -				
Data rich:	X	9		Pharmacokinetic Data from four Phase 1, two Phase 2, three Phase 3 studies was utilized
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**-**	**-**	-	
Relative bioavailability -				
solution as reference:	X	2		
alternate formulation as reference:	X	2		
Bioequivalence studies -				
traditional design; single / multi dose:	X	4		
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**3**		
Dissolution:	**X**	**6**		
(IVIVC):	**NA**			
Bio-wavier request based on BCS	**X**			
BCS class	**1**			Biowaiver Justification submitted
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics	**X**	**1**		
Pediatric development plan				
Literature References	**X**			
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	**NO**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What demographic factors explain the variability in pharmacokinetics of varenicline? What data supports a waiver of in vivo BE data? Does the exposure-response data justify the dose and dosing regimen employed in the pivotal clinical trials? Does varenicline has the potential to cause QT prolongation?	

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Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

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

/s/

Srikanth Nallani
2/9/2006 09:21:50 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
2/9/2006 09:26:46 AM
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