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PROPRIETARY DRUG NAME/GENERIC DRUG NAME: Chantix™/Varenicline

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: *A3051016*: 00150228

A3051019: Not available

PROTOCOL NO.: A3051016 and A3051019

PROTOCOL TITLE:

A3051016: A Twelve-week, Double-Blind, Placebo-controlled, Randomized, Multicenter Study Evaluating the Safety and Efficacy of a Flexible-Dosing Strategy for CP-526,555 (0.5 mg to 2.0 mg Total Daily Dose) in Smoking Cessation

A3051019: A Forty-week, Double-blind, Multicenter, Nontreatment Extension to Study A3051016 Evaluating the Efficacy of a Flexible-dosing Strategy (0.5 to 2.0 mg Total Daily Dose) in Smoking Cessation

Study Center(s): Five (5) study centers in the United States enrolled subjects.

Study Initiation and Completion Dates:

A3051016: 26 December 2001 to 18 September 2002

A3051019: 19 March 2002 to 24 June 2003

Phase of Development: Phase 2

Study Objective(s):

A3051016: The purpose of this study was to measure the safety and efficacy of CP-526,555 (administered in a flexible dosing strategy within the range of 0.5 mg to 2.0 mg daily) for smoking cessation in a population of healthy smokers.

A3051019: The purpose of this study was to measure the long-term efficacy of CP-526,555 for smoking cessation following 12 weeks of treatment with CP-526,555 (flexible dose 0.5 to

2.0 mg daily) or placebo in Study A3051016. As this was a non-treatment protocol, safety was not assessed.

METHODS

Study Design:

This was a 12-week, multicenter, randomized, double-blind, placebo-controlled study. Subjects who qualified at the screening visit were scheduled to return for a baseline visit, at which time they were randomized to CP-526,555 or to placebo. The total daily dose ranged from 0.5 to 2.0 mg CP-526,555, administered BID (or placebo equivalent), and study medication was administered for 12 weeks. Subjects who discontinued study medication prematurely could remain in the study, attending the remaining visits and completing all assessments. Beginning on the day of the baseline visit and throughout the 12-week study, subjects maintained a daily smoking diary in which they recorded the number of cigarettes smoked each day. Subjects were advised to take study medication for 1 week before attempting to quit smoking. Starting on the day of the Week 1 visit, subjects attempted to remain abstinent from smoking and other nicotine use. Subjects attended weekly clinic visits at which efficacy and safety were assessed. Samples were collected for pharmacometric analyses.

After completing the 12-week treatment phase, subjects continued in a 40-week a double-blind, non-treatment protocol, Study A3051019, in which long-term abstinence from smoking was assessed. Week designators in Study A3051019 refer to the total time in the 12-week Study A3051016 and A3051019 combined. Thus, Week 13 is 13 weeks after baseline in Study A3051016 and 1 week after entry into follow-up Study A3051019. Subjects had visits in an outpatient clinic setting at Weeks 13, 24, and 52 at which assessments were performed. Telephone visits were conducted at Weeks 16, 20, 28, 32, 36, 40, 44, and 48. Only efficacy assessments were conducted in Study A3051019.

At baseline, subjects were given an educational booklet on smoking cessation to review (“Clearing the Air: How to Quit Smoking...and Quit for Keeps”, National Cancer Institute Publication 95-1647). At all clinic visits except screening subjects received up to 10 minutes of brief counseling regarding smoking cessation in accordance with AHCPR guidelines (“Smoking Cessation: Quick Reference Guide for Smoking Cessation Specialists”, AHCPR Publication No. 96-0694).

Number of Subjects (Planned and Analyzed):

Planned: The planned sample size for A3051016 was approximately 300 subjects or 150 subjects per treatment group.

Analyzed: In Study A3051016, 320 subjects were randomized (160 per treatment group) and 312 were treated (157 in the CP-526,555 group and 155 in the placebo group). A total of 220 subjects from Study A3051016 (120 in the CP-526,555 group and 100 in the placebo group) continued in Study A3051019.

Diagnosis and Main Criteria for Inclusion:

Subjects in A3051016 were healthy male or female cigarette smokers, between the ages of 18 and 65 years, who, during the past year, had smoked an average of at least 10 cigarettes per day with no period of abstinence greater than 3 months. Eligible subjects for Study A3051019 were those who had completed Study A3051016 (whether or not they had quit smoking), and signed a Study A3051019 Informed Consent Form.

Study Treatment:

- *A3051016 Dosage:*
 - CP-526,555: 0.5 mg QD for 3 days, followed by 0.5 mg BID for 4 days; after Day 7, dosing schedule was flexible (minimum of 0.5 mg QD, maximum of 1.0 mg BID)
 - Placebo: One tablet QD for 3 days, followed by 1 tablet BID for 4 days; after Day 7, dosing schedule was flexible (minimum of one tablet QD, maximum of 2 tablets BID)

- *A3051016 Duration:* 12 weeks for CP-526,555 and placebo

No study medication was administered in Study A3051019.

Efficacy Evaluations:

Smoking status assessments at each clinic visit included smoking diary collection (in Study A3051016) and oral self-reporting of smoking or use of other nicotine-containing products (yes, no), confirmed by quantification of exhaled carbon monoxide (CO) ≤ 10 ppm.

A3051016:

Primary:

The primary efficacy measure was the CO-confirmed 4-week continuous quit rate (CQR) for Weeks 9-12 and Weeks 4-7, defined as the proportion of subjects abstaining from smoking during the specified 4-week periods, based on subject oral self-report of smoking or other nicotine use since the last study visit.

Secondary:

Secondary endpoints included the rate of CO-confirmed continuous abstinence from the target quit date to Week 12, the CO-confirmed 7-day point prevalence of abstinence and the number of cigarettes smoked per day.

In addition, subjects completed the following self-administered rating scales: the Minnesota Nicotine Withdrawal Scale (MNWS), from which 2 scores were derived: a nicotine craving

score (Item 1); and a composite score of withdrawal symptoms (sum of Items 2 through 9); and the Smoking Effects Inventory (SEI) that assessed the degree to which subjects experienced both desirable and aversive effects from smoking (administered only to subjects who had smoked since the previous assessment). Body weight was assessed at each visit.

A3051019:

Primary: The primary efficacy parameter in this study was the rate of CO-confirmed continuous abstinence from Week 9 of Study A3051016 through Week 52 of Study A3051019.

Secondary: Secondary efficacy parameters included: the rate of CO-confirmed continuous abstinence from Week 9 of Study A3051016 through Week 24; the Long-Term Quit Rate (LTQR) at Week 52 (defined as the proportion of subjects who had abstained from smoking during Weeks 9 through 12 of Study A3051016 and had no more than 6 days of smoking during the non-treatment follow-up from the end of Week 12 through Week 52); and the CO-confirmed 7-day point prevalence of smoking cessation at Weeks 24 and 52.

In addition, subjects completed the Minnesota Nicotine Withdrawal Scale (MNWS) at Week 13 to assess whether stopping study medication resulted in withdrawal symptoms and the Smoking Cessation Quality of Life (SCQoL) questionnaire at Weeks 24 and 52. Changes in body weight were assessed at each clinic visit.

Pharmacokinetic Evaluations:

In Study A3051016, plasma samples (minimum of 4 mL) for pharmacokinetic assay were obtained at the Week 1, 2, 4, and 12 visits.

Safety Evaluations:

For Study A3051016, information on adverse events (AEs) was collected at each study visit. All observed or volunteered AEs, regardless of suspected causal relationship to study drug, were recorded on an electronic case report form (eCRF) AE page. Other safety assessments included AEs, clinical laboratory values, vital signs, 12-lead electrocardiograms (ECGs) and physical examinations. No safety evaluations were performed for Study A3051019.

Statistical Methods:

The All Subjects population, defined as those subjects who received at least 1 dose of study medication was considered the primary population for all efficacy and safety analyses for Study A3051016. For Study A3051019, abstinence analyses were based on the All Subjects population from A3051016.

Efficacy:

Evaluations compared data for active treatment versus placebo. All significance tests were 2-tailed using an overall level of significance of $\alpha = 0.05$. A step-down procedure was used for the primary endpoint (Week 9 – 12 CQR, followed by Week 4 – 7 CQR) in order to preserve the family-wise error rate, $\alpha = 0.05$. Binary data (i.e., 4-week CQRs, long term quit rate and rate of continuous abstinence), were analyzed using a logistic regression model

including treatment and center. Testing was carried out using the likelihood ratio chi-squared test statistic. In all assessments of abstinence, subjects who withdrew from the study and were lost to follow-up for subsequent visits were considered to be smokers from the day of withdrawal through the end of the non-treatment phase, regardless of their smoking status at the last recorded visit.

For the self-administered rating scales MNWS and SEI in Study 3051016, inferential statistics were carried out using an Analysis of Variance (ANOVA) model including the fixed effects of treatment and center. For Study A3051019, no inferential statistics were conducted on MNWS, SCQoL or weight change. These were summarized using descriptive statistics.

Safety:

For Study A3051016, AEs were summarized using COSTART terminology. Descriptive statistics and frequency tabulations were used to evaluate the safety data. There were no safety evaluations for Study A3051019.

RESULTS

Subject Disposition and Demography:

A total of 434 subjects were screened and 320 were randomized. Eight subjects who were assigned to treatment did not take any study medication (3 subjects were randomized to CP-526,555 and 5 subjects were randomized to placebo). Thus, a total of 312 subjects took study medication and were evaluated for safety and efficacy.

Subject disposition is summarized in Table S1.

Table S1 Subject Disposition

	CP-526,555 n (%)	Placebo n (%)
<i>Study A3051016</i>		
Number Screened= 434		
Assigned to treatment	160	160
Treated ^a	157	155
Completed study	122 (77.7)	110 (71.0)
Discontinued study	35 (22.3)	45 (29.0)
Adverse events ^b	7 (4.5)	2 (1.3)
Lack of efficacy	0 (0.0)	7 (4.5)
Subject defaulted ^c	24 (15.3)	34 (21.9)
Other ^d	4 (2.5)	2 (1.3)
<i>Study A3051019^e</i>		
Entered	120 (76.4)	100 (64.5)
Completed	100 (63.7)	89 (57.4)
Discontinued	20 (12.7)	11 (7.1)
Subject defaulted	18 (11.5)	11 (7.1)
Other	2 (1.3)	0 (0)

^aPercentages based on number of subjects treated

^bIncludes laboratory abnormalities

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

^d“Other” includes the following: protocol violations and non-compliance.

^eDenominator, N, is the number of subjects treated in Study A3051016.

For both studies, approximately 91% of subjects were white. Slightly more than half (52%) were male, and the mean age was approximately 42 years (range 18 – 65). Subjects represented a population of smokers who, on average, had smoked about 20 cigarettes per day for an average of approximately 25 years. More than half of the subjects in each treatment group had made at least 3 prior attempts to quit smoking.

Efficacy Results:

Primary:

A3051016: Results for the primary efficacy measure are presented in Table S2.

Table S2 CO-confirmed 4-week Continuous Quit Rate (A3051016)

	Weeks 4 – 7			Weeks 9 – 12		
	Responder Rate		p-value vs Placebo	Responder Rate		p-value vs Placebo
	n/N	Percent		n/N	Percent	
CP-526,555	60/157	38.2	<0.0001	63/157	40.1	<0.0001
Placebo	18/155	11.6		18/155	11.6	

A3051019: Results for primary efficacy measure are shown in Table S3.

Table S3 CO-Confirmed Rates of Continuous Abstinence from Week 9 (A3051019)

Week	CP-526,555	Placebo	p-Value
	N= 157	N= 155	
	n (%)	n (%)	
24	44 (28.0)	14 (9.0)	<0.0001
52	35 (22.3)	12 (7.7)	0.0001

^aDenominator is N, number of subjects treated in Study A3051016.

Secondary: Because some secondary endpoints were examined in both Study A3051016 and Study A3051019, the secondary endpoint results from both studies are presented in the same section below. For each table or data presentation, the study that the results are derived is noted.

Long Term Quit Rate (A3051019): Long Term Quit Rate is shown in Table S4.

Table S4 Long Term Quit Rate (A3051019)

	CP-526,555	Placebo	p-Value
	N= 157	N= 155	
	n ^a (%) ^b	n ^a (%) ^b	
Week 52	40 (25.5)	12 (7.7)	<0.0001

^aDetermined as the number of subjects who were abstinent from Weeks 9 through 12 (inclusive) in A3051016 and reported no more than 6 days of smoking during the 40-week nontreatment follow-up.

^bDenominator is number of subjects treated in A3051016.

Rates of CO-confirmed Continuous Abstinence from Target Quit Date to Week 12 in Study A3051016: Data for this endpoint are shown in Table S5.

Table S5 Rate of CO-confirmed Continuous Abstinence from Target Quit Date^a (A3051016)

	CP-526,555 N= 157 n (%)	Placebo N= 155 n (%)	P-value
Week 12	33 (21.0)	13 (8.39)	0.0007

^aThe percentage of subjects with a CO-confirmed report of no cigarette or nicotine use from the day of the Week 1 visit (coincident with the target quit date) through the Week 12 visit.

CO-confirmed 7-day) Point Prevalence: Data for this endpoint is shown in Table S6 (Studies A3051016 and A3051019).

Table S6 CO-confirmed Weekly (7-day) Point Prevalence^a of Abstinence (A3051016 and A3051019)

Week	CP-526,555 N= 157 n (%)	Placebo N= 155 n (%)	P-value
12	73 (46.5)	22 (14.1)	<0.0001
24	51 (32.5)	21 (13.5)	<0.0001
52	44 (28.0)	21 (13.5)	0.0011

^aDetermined at each visit as number (%) of subjects with a CO-confirmed report of no cigarette or nicotine use in the previous 7 days.

Mean Number of Cigarettes per Smoker per Day (Study A3051016): The mean number of daily cigarettes per smoker is shown in Table S7.

Table S7 Mean Number of Cigarettes per Smoker per Day (A3051016)

	Baseline		Week 2		Week 12	
	n	Mean ^a	n	Mean ^a	n	Mean ^a
CP-526,555	157	19.9	97	5.3	45	6.4
Placebo	155	20.6	119	9.3	86	10.8

^aMean value calculations include data only for subjects who smoked during the given week (i.e., subjects smoking 0 cigarettes are not included in the denominator.)

Minnesota Nicotine Withdrawal Scale: In study A3051016, CP-526,555 reduced craving (Question 1) significantly more than placebo at every weekly time point assessed (Weeks 1 through 7, and Week 12; $p \leq 0.0075$). The composite score for withdrawal effects (sum of Questions 2 – 9) showed that, for both treatment groups, withdrawal symptoms peaked at Week 2 and declined steadily thereafter, but did not return to baseline. (Data for the MNWS change from baseline to Week 12 are shown in Table S8.)

Table S8 Minnesota Nicotine Withdrawal Scale Change from Baseline to Week 12 (A3051016)

Treatment Group	Statistic	Q1	Sum Q2 to Q9
CP-526,555	Mean	1.1	4.5
	Mean Change	-1.5	0.2
	Standard Error	0.11	0.44
	N	119	117
	LSMean	-1.70	1.29
	P-value ^a	<0.0001	0.0790
Placebo	Mean	1.7	5.4
	Mean Change	-0.9	1.2
	Standard Error	0.09	0.48
	N	110	107
	LSMean	-1.16	2.48

Q1= Urge to smoke; Q2= Depressed mood; Q3= Irritability, frustration, or anger; Q4= Anxiety; Q5= Difficulty concentrating; Q6= Restlessness; Q7= Increased appetite; Q8= Difficulty going to sleep; Q9= Difficulty staying asleep.

Individual scores range from 0 to 4, where 0= not at all, 1= slight, 2= moderate, 3= quite a bit and 4= extreme
^aP-value is a pairwise comparison versus placebo obtained from an analysis of variance model including the fixed effects of treatment and center.

For Study A3051019, results of the MNWS indicate no evidence of withdrawal symptoms following cessation of CP-526,555 therapy. Comparison of mean scores for individual items of the MNWS at Week 12 (Study A3051016) and Week 13 (Study A3051019) indicate no clinically meaningful increases in craving or withdrawal symptoms for the CP-526,555 group compared with placebo.

Smoking Effects Inventory: At the primary time point in Study A3051016 (Week 1 visit), there were no significant treatment differences for any of the SEI subscales. Starting at Week 2, Satisfaction subscale scores showed there was a trend for CP-526,555 to be more effective than placebo in reducing the satisfying effects of smoking ($p < 0.05$ at Weeks 2, 3, 4, and 5). In addition, based on scores for the Craving subscale, there was a trend for CP-526,555 to reduce craving to a greater extent than placebo. This finding was consistent for all weeks from Week 2 through Week 7, although treatment differences were not statistically significant.

Smoking Cessation Quality of Life (SCQoL): Results for the SCQoL were summarized separately for abstinent subjects and for smokers. In general, there were no consistent patterns of results for self-reported functional status (SF-36 and cessation-targeted subscales) for either Study A3051016 or A3051019.

Weight Change: Weight change for Study A3051016 is summarized in Table S9.

Table S9 Weight Change (kg) from Baseline to Weeks 7 and 12

	Cessators ^a		Smokers	
	n	Mean change (SE)	n	Mean Change (SE)
Week 7				
CP-526,555	39	2.4 (0.45)	85	1.3 (0.24)
Placebo	13	3.2 (0.49)	96	0.7 (0.23)
Week 12				
CP-526,555	32	4.0 (0.79)	78	1.9 (0.33)
Placebo	9	3.8 (0.64)	91	0.4 (0.30)

^aCessators are defined as subjects who abstained from smoking from their target quit date to the day of the measurement.

For Study A3051019, weight gain was also somewhat greater among Cessators for both CP-526-,555 and placebo-treated subjects; no statistical analyses were conducted.

Pharmacokinetic Results: Pharmacokinetic results were incorporated in pharmacometric population analyses.

Safety Results: Frequent AEs for Study A3051016 are shown in Table S10.

Table S10 Most Frequent Treatment-emergent Adverse Events (All Causalities)

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

^aTreatment-emergent AEs occurring in $\geq 3\%$ of subjects in either treatment group

Adverse events for Study A3051016 leading to discontinuation are shown in Table S11.

Table S11 Treatment-emergent Adverse Events Contributing to Discontinuation^a of Study Drug

COSTART Preferred Term	CP-526,555 N= 157 n (%)	Placebo N= 155 n (%)
Headache	2 (1.3)	1 (0.6)
Nausea	2 (1.3)	0 (0.0)
Insomnia	2 (1.3)	0 (0.0)
Chest pain	2 (1.3)	2 (1.3)
Thinking abnormal	1 (0.6)	1 (0.6)
Myasthenia	1 (0.6)	0 (0.0)
Neck pain	1 (0.6)	0 (0.0)
Abnormal dreams	1 (0.6)	0 (0.0)
Respiratory disorder	1 (0.6)	0 (0.0)
Depression	1 (0.6)	0 (0.0)
SGOT increased	1 (0.6)	1 (0.6)
SGPT increased	1 (0.6)	2 (1.3)
Lactate dehydrogenase increased	1 (0.6)	0 (0.0)
Creatine phosphokinase increased	1 (0.6)	0 (0.0)
Breast pain	0 (0.0)	1 (0.6)
Hypertension	0 (0.0)	1 (0.6)
Pain	0 (0.0)	1 (0.6)
Increased appetite	0 (0.0)	1 (0.6)
Agitation	0 (0.0)	1 (0.6)

^aTreatment discontinuation in a given subject could be attributed to a single AE or to multiple events. SGOT (AST)= serum glutamic-oxaloacetic transaminase (aspartate aminotransferase), SGPT (ALT)= serum glutamic-pyruvic transaminase (alanine aminotransferase)

Overall, the frequency of clinically significant laboratory test abnormalities in Study A3051016 was low, similar for both treatment groups, and did not indicate any issues of concern. Treatment-emergent increases in hepatic enzymes (serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic-pyruvic transaminase [SGPT], or lactate dehydrogenase [LDH] increased) contributed to discontinuation of treatment in 2 subjects treated with CP-526,555 and in 2 subjects treated with placebo. One additional placebo-treated subject had a clinically significant elevation in SGOT that did not result in discontinuation of study medication.

No subjects experienced events meeting the predefined criteria for a serious adverse event (SAE) during treatment in Study A3051016, although 3 subjects treated with CP-526,555 experienced SAEs within 30 days of the last dose of study medication. None of these events was considered related to study medication. No SAEs were reported for any subject in the placebo treatment group.

There were no deaths during Study A3051016.

Median changes in blood pressure and heart rate from baseline to last observation were small and indicated no differences between treatment groups. The ECG data collected in this study did not suggest any clinically significant effect of study medication on the PR interval or the

QT interval and revealed no clinically significant concerns. Vital signs data also indicated no concerns.

No safety evaluations were performed in Study A3051019.

CONCLUSION(S):

- CP-526,555, administered in a flexible, self-regulated dosing regimen of 0.5 to 2.0 mg daily for 12 weeks, was efficacious in promoting abstinence from smoking for 1 year and also reduced craving and smoking satisfaction.
- CP-526,555 was safe and well tolerated when administered in a flexible dosing regimen of 0.5 to 2.0 mg daily.