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**PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Champix®/Varenicline Tartrate**

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** Aid to smoking cessation treatment

**NCT NO.:** NCT00463918

**PROTOCOL NO.**: A3051070

**PROTOCOL TITLE**: Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Multiple-Dose Pharmacokinetics, Safety and Tolerability of Varenicline in Healthy Adolescent Smokers

**Study Centers**: United Kingdom (1), United States (16)

**Study Initiation and Completion Dates:** 23 May 2007 to 01 December 2007

**Phase of Development**: Phase 1

**Study Objective(s):**

Primary objective: To characterize the multiple-dose pharmacokinetics (PK) of varenicline in adolescent male and female smoking subjects

Secondary objective: To evaluate the safety and tolerability of varenicline in adolescent male and female smoking subjects

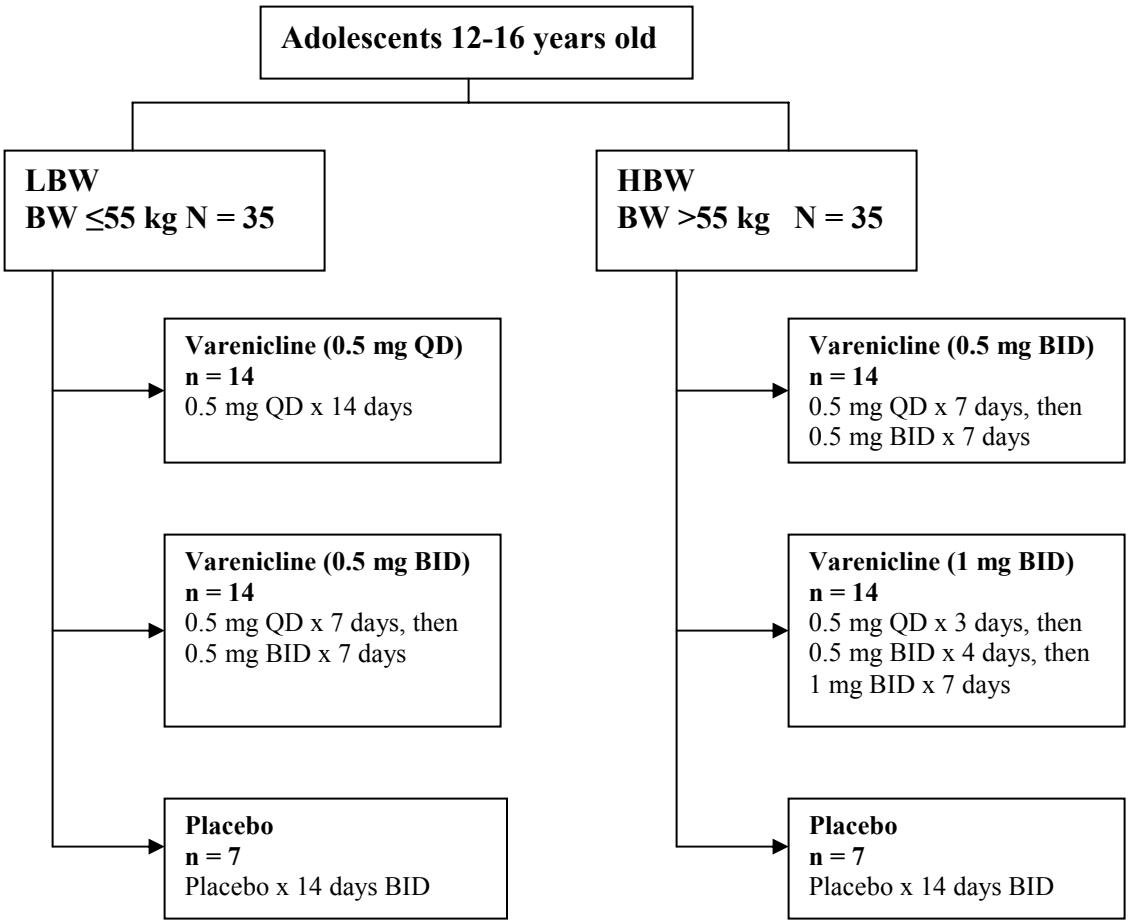
**METHODS**

**Study Design:** This was a double-blind, randomized, parallel group, placebo-controlled study. Subjects were allowed to continue smoking at will during the course of the study, although they were offered smoking cessation counseling at the end of the study.

After obtaining informed consent from the parent(s)/legal guardian(s) for their minor child, subjects were enrolled in 2 groups of approximately 35 subjects each, depending on body weight (BW). Subjects in the low body weight (LBW) group weighed ≤55 kg, whereas those in the high body weight (HBW) weighed >55 kg. An attempt was to be made to evenly distribute males and females between both BW groups. Efforts were made to enroll a minimum of 6 young females (12 to 13 years of age) in the LBW group. Within each group,

subjects were randomized to a higher dose of varenicline, a lower dose of varenicline, or placebo using a 2:2:1 randomization scheme (Figure S1). Subjects in the LBW group had their varenicline dose strengths adjusted to half those in the HBW group. Varenicline or placebo was administered in a double-blind fashion.

**Figure S1. Overview of Study Design**




All subjects were at their target dose by Day 8.
Abbreviations: BID = twice daily, QD = once daily; N (n) = number of subjects, BW = body weight, HBW = high body weight, LBW = low body weight

Subjects in the 0.5 mg twice daily (BID) and 1.0 mg BID treatment groups were titrated to the target dose over a 1-week titration phase. All subjects were at their target dose by Day 8. The last dose of study drug was administered on the morning of Day 14. Study drug was administered after a standardized non-high fat meal in both weight groups. Subjects were admitted to the clinical research unit (CRU) on Days 1, 8 and 14 for dosing, PK sampling and safety evaluations. Subjects returned to the CRU for drug dispensing and adverse event

(AE)/concomitant drug monitoring on Day 3. Pharmacodynamic (PD) assessments were based on the number of cigarettes smoked per day, as entered in subjects' smoking logs.

**Number of Subjects (Planned and Analyzed):** 70 healthy adolescents were planned and 72 subjects were dosed. Data from each of the 57 subjects who received at least 1 dose of varenicline, and the 15 subjects who received at least 1 dose of placebo (72 subjects overall), were included in the PD and safety analyses. Data from the 57 subjects who received at least 1 dose of varenicline were included in the population PK analysis.

**Diagnosis and Main Criteria for Inclusion:** Subjects were healthy male and female adolescents between 12 and 16 years of age; they were regular smokers (smoking on a daily basis for at least the previous 3 months) who smoked an average of at least 3 cigarettes per day over the 4 weeks before enrollment. To qualify for enrollment, subjects weighed at least 30 kg and had a body mass index (BMI) no greater than 30.0 $kg/m^2$.

**Study Treatment:** Varenicline tartrate 0.5 mg film coated tablets and matching placebo, and varenicline tartrate 1.0 mg film coated tablets and matching placebo were supplied to the CRU.

Study medication was administered with 240 mL ambient temperature water. All subjects received study medication in the morning on Days 1 to 3, in the morning and evening on Days 4 to 13, and in the morning of Day 14. Treatments were administered in a double dummy fashion.

While in house, CRU staff administered study medication at approximately 0800 hours and 1800 hours, within 5 minutes after a standardized non-high fat breakfast and dinner, respectively. During the outpatient period, subjects were to make every attempt to self administer study medication within 5 minutes after breakfast and dinner at approximately 0800 hours and 1800 hours.

**Efficacy Evaluations:** No efficacy evaluations were done.

**Pharmacokinetic Evaluations:** Blood samples were collected into appropriately labeled tubes containing sodium heparin before each dose (0 hour) and at the following times: Day 1 at 1.5, 3, 6, and 10 hours postdose; Day 8 at 0 hour and 3 hours postdose; Day 14 at 0 hour and 1.5, 3, 6, and 10 hours postdose, and within 48 to 84 hours after the last dose of study medication.

Samples were analyzed for varenicline plasma concentrations using a validated assay employing liquid-liquid extraction followed by high performance liquid chromatography/mass spectroscopy/mass spectroscopy. Concentration-time data were analyzed using a nonlinear mixed-effects population analysis approach with the NONMEM software system, Version V, Level 1.1 (ICON Development Solutions, Ellicott City, MD). Models were developed to characterize the PK of varenicline in adolescents. Estimates of varenicline population PK parameters (typical values, intersubject variability and residual variability) for apparent plasma clearance (CL/F) and volume of distribution (V/F), and relationships between PK parameters and various (demographic or physiologic) covariate

factors were explored. Analyses were conducted using the first-order conditional estimation method with η–ε interaction.

Additionally, individual predicted estimates of maximum observed plasma concentrations ($C_{max}$) and area under the curve from time 0 to 24 hours ($AUC_{ss[0-24]}$) on Day 14 (steady state) were derived using the final PK model and individual post-hoc estimates of the PK parameters.

**Pharmacodynamic Evaluations:** The number of cigarettes smoked per day, Days 1 through follow-up (48 to 84 hours post last dose), for each treatment group was estimated from subject-maintained daily cigarette smoking logs.

**Safety Evaluations:** Safety evaluations included clinical monitoring for AEs, vital signs (heart rate, blood pressure), 12-lead electrocardiograms (ECGs), and safety laboratory tests.

**Statistical Methods:** Safety parameters were summarized by BW group and treatment regimen using descriptive statistics. The daily number of cigarettes smoked was summarized through data tabulations and descriptive statistics.

## RESULTS

**Subject Disposition and Demography:** Subject disposition is summarized in Table S1. Thirty-seven subjects were randomized and treated in the LBW group and 35 subjects were randomized and treated in the HBW group. Seventy subjects completed the study, and 2 treated subjects discontinued the study: One subject (0.5 mg QD, LBW) was withdrawn due to lack of compliance and 1 subject (placebo, LBW) withdrew consent. Discontinued subjects were not replaced.

**Table S1. Subject Disposition**

| | Low Body Weight | | | | High Body Weight | | |
|---|---|---|---|---|---|---|---|
| | Varenicline | | Placebo | Not Dosed[a] | Varenicline | | Placebo |
| | 0.5 mg QD | 0.5 mg BID | | | 0.5 mg BID | 1 mg BID | |
| Number of Subjects Assigned to Study Treatment | 15 | 14 | 8 | 1 | 14 | 14 | 7 |
| Treated | 15 | 14 | 8 | 0 | 14 | 14 | 7 |
| Completed | 14 | 14 | 7 | 0 | 14 | 14 | 7 |
| Discontinued | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Analyzed for Pharmacokinetics: | | | | | | | |
| Pharmacokinetics | 15 | 14 | 0 | 0 | 14 | 14 | 0 |
| Analyzed for Pharmacodynamics: | | | | | | | |
| Pharmacodynamics | 15 | 14 | 8 | 0 | 14 | 14 | 7 |
| Analyzed for Safety: | | | | 0 | | | |
| Adverse events | 15 | 14 | 8 | 0 | 14 | 14 | 7 |
| Laboratory data | 14 | 14 | 8 | 0 | 14 | 14 | 7 |

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
Abbreviations: BID = twice daily, QD = once daily, N/A = not applicable
[a]One subject in the LBW group was withdrawn after randomization but before dosing because he did not meet Entrance Criterion No. 1. This subject had been randomized to placebo.



Fourteen subjects enrolled in the study were 12 and 13 years old (8 females and 6 males). All three 12-year-olds were in the LBW group, and of the eleven 13-year-olds, 9 were in the LBW group and 2 were in the HBW group. While the overall proportion of males and females was nearly equivalent for the entire study population (35 females, 37 males), more females (n=23) than males (n=14) were enrolled in the LBW group and more males (n=23) than females (n=12) were enrolled in the HBW group. Most subjects were White (45 of 72 subjects) or Hispanic (21 of 72 subjects). Ten subjects were in the United Kingdom, and the remaining 62 subjects were in the United States. Within each BW group, the 3 treatment groups were balanced with respect to BW and/or BMI. On average, subjects in the LBW group had been smoking for slightly fewer years and smoked fewer cigarettes per day than those in the HBW group.

**Efficacy Results:** No efficacy evaluation was done.

**Pharmacokinetic Results:** An open one-compartment model with first-order absorption and elimination adequately described the plasma concentration-time profile of varenicline in adolescent smokers. This model was parameterized in terms of CL/F, V/F, and first-order absorption rate-constant (Ka). The effect of body size was investigated as a potential predictor for CL/F and V/F and described as a function of total BW, normalized by the reference weight of 70 kg to facilitate comparison to historical adult data. The final forms of the equation for the model are given below:

$$Ka = \theta_1$$

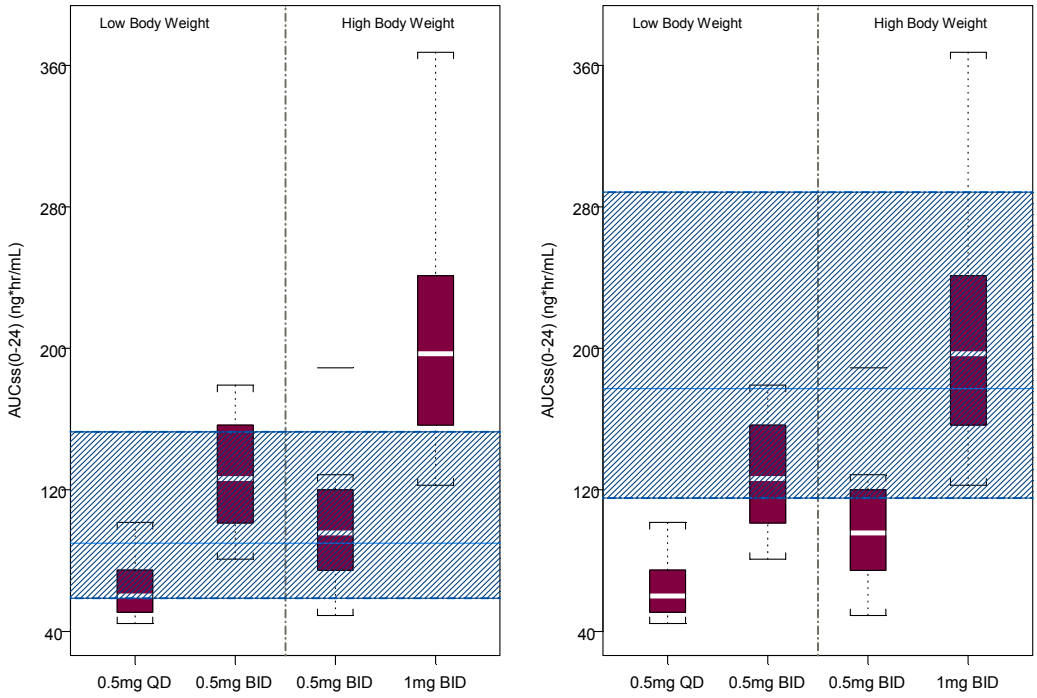
$$\frac{CL}{F} = \theta_2 \cdot \left(\frac{WT_i}{70}\right)^{\theta_{WT}}$$

$$\frac{V}{F} = \theta_3 \cdot \left(\frac{WT_i}{70}\right)^{\theta_{WT}}$$

The typical population PK parameter estimates and their 95% confidence intervals (CIs [obtained from 1000 stratified non-parametric bootstrap replicates]) for the final varenicline model were 10.4 L/hr [9.2-11.5] for CL/F, 215 L [204-238] for V/F, and 1.13 hr-1 [0.94-1.51] for Ka. These estimates were similar to those obtained with the base model. Typical value parameters for V/F, CL/F, and Ka were estimated with good precision (most with % relative standard error [RSE] values of <10% and all with %RSE <25%). Unexplained random interindividual variances were: 29% CV (Ka), 30% CV (CL/F), and 18% CV (V/F) with terms describing the correlation between these parameters. A combined additive and constant coefficient of variation model was utilized for residual intraindividual variability. The proportional residual variance was estimated to be 28% CV. The observed BW covariate factor in the final PK model described a large fraction of the total observed interindividual variability [calculated as ($\omega^2_{\text{base model}}$ - $\omega^2_{\text{full model}}$)/ $\omega^2_{\text{base model}}$ %] in the V/F (64.3%) for varenicline, whereas its influence on CL/F (18.9%) was relatively minimal. The average (and %RSE) population estimate for the effect of BW on V/F was 1.07 (13 %RSE). In healthy young subjects, interindividual variability in varenicline CL/F was to some extent related to body size; the average population estimate for the effect of BW on CL/F was 0.72 (28 %RSE). The 95% CIs around the BW covariate effects did not include zero. V/F was estimated to decrease, on average, approximately 21% between a typical HBW adolescent weighing 66 kg (V/F = 202 L) and a typical LBW individual weighing 53 kg (V/F = 160 L). As a result, there was an approximate 30% increase in median Cmax in subjects with low BW (6.34 ng/mL) as compared to the high BW group (4.85 ng/mL) for the same total daily dose of 1 mg per day (0.5 mg BID).

Figure S2 presents the final model distributions for $AUC_{ss(0-24)}$ by BW and treatment groups. Results are shown as box and whisker plots by total daily dose group. The box represents the inter-quartile distance with the median indicated by a dotted line in the center of the box; whiskers represent data less than or equal to 1.5 times the inter-quartile range and outliers are represented by single solid lines outside of the whiskers. The crosshatched areas are the 95% prediction intervals for the population distribution of adult exposures at the 0.5 mg BID (left panel) and 1 mg BID (right panel) dose regimens.

**Figure S2. Final Model Distributions of Individual Predicted Steady-State 24-hour Varenicline Plasma $AUC_{ss(0-24)}$ by Body Weight and Treatment Group**




Abbreviations: $AUC_{ss(0-24)}$ = area under the curve at steady-state, BID = twice daily, QD = once daily

Predicted steady state median exposures ($AUC_{ss[0-24]}$) in adolescents weighing > 55 kg were 95.7 ng.h/mL (49.0-189) and 197 ng.h/mL (123-367) for 0.5 mg BID and 1 mg BID, respectively. Similarly in adolescents of LBW, median exposures were 60.1 ng.h/mL (44.4-102) and 126 ng.h/mL (128-179) after administration of 0.5 mg once or twice daily, respectively.

**Pharmacodynamic Results:** In the LBW subjects, the mean reduction in daily cigarettes smoked was similar in all 3 dose groups. On average, these subjects were smoking fewer cigarettes per day at baseline than the HBW subjects, with the lowest smoking level in the placebo group. In the HBW subjects there was a dose-related trend in cigarette reduction over the course of the study with the greatest effect in subjects who received 1 mg BID varenicline. HBW subjects who received placebo showed little mean change in daily cigarettes smoked.

**Safety Results:** There were no deaths, serious adverse events (SAEs), or withdrawals due to AEs reported in this study. One SAE was reported before randomization.

AEs reported by 31 of the 38 subjects were considered treatment-related (Table S2).

## Table S2. Treatment-Emergent AEs (All Causalities and Treatment-Related)

| | Low Body Weight | | | High Body Weight | | | |
|---|---|---|---|---|---|---|---|
| | Varenicline | | Placebo | Varenicline | | Placebo | |
| | 0.5 mg QD N=15 | 0.5 mg BID N=14 | N=8 | 0.5 mg BID N=14 | 1 mg BID N=14 | N=7 | Total |
| Subjects evaluable for AEs | 15 | 14 | 8 | 14 | 14 | 7 | 72 |
| All causality AEs | | | | | | | |
| Subjects with AEs | 11 | 9 | 1 | 8 | 8 | 1 | 38 |
| Subjects with severe AEs | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Number of AEs | 28 | 21 | 3 | 13 | 16 | 1 | 82 |
| Treatment-related AEs | | | | | | | |
| Subjects with AEs | 10 | 8 | 1 | 6 | 6 | 0 | 31 |
| Subjects with severe AEs | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Number of AEs | 22 | 17 | 3 | 7 | 11 | 0 | 60 |

Abbreviations: AEs = adverse events, BID = twice daily, QD = once daily, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects per dosing regimen
Includes all data collected since the first dose of study drug. This table presents discrete treatment-emergent AEs.
Except for the number of AEs, subjects are counted only once per treatment in each row.
Severe AEs - according to the investigator's assessment.
MedDRA (version 10.1) coding dictionary applied.



Most subjects had mild AEs, fewer had moderate AEs, and 1 subject had a single severe AE (nausea) (Table S3). Most AEs resolved during the study, and most were judged to be treatment-related. Treatment-related AEs were more frequently reported in active- versus placebo-treated subjects. Treatment-emergent AEs of all causalities that occurred in >2 subjects are presented in Table S3.

## Table S3. AEs (All Causalities) Reported by >2 Subjects in LBW or HBW Treatment Groups

| | Low Body Weight | | | High Body Weight | | |
|---|---|---|---|---|---|---|
| | Varenicline | | Placebo | Varenicline | | Placebo |
| MedDRA[a] Preferred Term | 0.5 mg QD N=15 | 0.5 mg BID N=14 | N=8 | 0.5 mg BID N=14 | 1 mg BID N=14 | N=7 |
| Nausea | 6 (1 sev) | 5 (2 mod) | 1 | 2 (1 mod) | 2 (2 mod) | 0 |
| Headache | 2 | 3 | 1 | 3 (1 mod) | 1 | 0 |
| Vomiting | 2 (2 mod) | 3 (1 mod) | 0 | 1 | 2 (1 mod) | 0 |
| Dizziness | 2 | 2 | 1 | 1 | 0 | 0 |
| Pharyngolaryngeal pain | 2 (1 mod) | 1 | 0 | 1 (1 mod) | 0 | 0 |
| Abdominal pain upper | 1 (1 mod) | 0 | 0 | 0 | 2 | 0 |
| Anorexia | 3 | 0 | 0 | 0 | 0 | 0 |
| Flatulence | 0 | 0 | 0 | 0 | 3 | 0 |
| Fatigue | 2 (1 mod) | 0 | 0 | 0 | 0 | 0 |

AEs without severity indicated were all mild
Abbreviations: AE = adverse event, BID = twice daily, QD = once daily, MedDRA = Medical Dictionary for Regulatory Activities, mod = moderate, sev = severe, N = number of subjects per dosing regimen,
[a]Version 10.1

The most frequently reported treatment-emergent AEs were nausea, headache, and vomiting. Nausea and vomiting were more frequent in females than in males. Overall, frequently reported AEs were more frequent in the LBW group. Within the LBW group, more AEs occurred in subjects who received varenicline 0.5 mg QD than in those who received 0.5 mg BID. The single severe instance of nausea occurred in 1 female in the LBW group.

Two subjects in the LBW group and 3 subjects in the HBW group experienced mood-related and psychiatric AEs (abnormal dreams [2 subjects], anger, irritability, and mood swings). The irritability and mood swings were considered not treatment-related by the investigator.

One subject in the LBW group experienced markedly elevated liver function test values at the end of the treatment period judged related to 0.5 mg BID varenicline. The subject was experiencing lymphadenopathy at the time. The values returned to normal range without concomitant treatment.

No vital signs results or ECG results were of clinical concern.

**CONCLUSIONS:**

- A one-compartment model with first-order absorption and elimination adequately described the multiple-dose pharmacokinetics of varenicline in adolescent smokers. BW was an important predictor of the interindividual variability in varenicline volume of distribution.

- Steady-state exposures in adolescents weighing >55 kg were consistent with those previously reported in adult smokers at an equivalent daily dose.

- Results also showed that the pharmacokinetics of varenicline in adolescents was dose-proportional across the 0.5 mg to 2 mg daily dose range.

- The effect of BW on varenicline adolescent pharmacokinetics, which resulted in higher exposures in individuals of smaller body size, was adequately adjusted by halving the total daily dose of varenicline; 55 kg appears to be an appropriate threshold for adjusting varenicline dose levels in adolescent subjects. Adjusting the dose to half in adolescents ≤55 kg results in predicted exposures at the lower end of the range observed in adults.

- Varenicline at both dose levels examined (1 mg BID and 0.5 mg BID in subjects >55 kg, and 0.5 mg BID and 0.5 mg QD in subjects ≤55 kg) was well tolerated in this healthy (but smoking) adolescent population. However, subjects ≤55 kg reported more adverse events than subjects >55 kg.