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ARTICLE

Population pharmacokinetics and exposure–response analyses of varenicline in adolescent smokers

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Abstract

Varenicline is an approved smoking cessation aid in adults. Population pharmacokinetics (popPK) and exposure–response (ER) (continuous abstinence rates [CAR] weeks 9–12 and nausea/vomiting incidence) for varenicline in adolescent smokers were characterized using data from two phase 1 and one phase 4 studies. A one-compartment popPK model with first-order absorption and elimination adequately fitted the observed data. The effect of female sex on apparent clearance was significant. Apparent volume of distribution increased with body weight and decreased by 24%, 15%, and 14% for black race, "other" race, and female sex, respectively. The observed range of exposure in the phase 4 study was consistent with that expected for each dose and body-weight group from the results obtained in adolescent PK studies, supporting that varenicline dose and administration were appropriate in the study. The relationship between CAR9–12 and varenicline area under the concentration–time curve (AUC) from 0 to 24 hours (AUC_{24}) was nonsignificant ($p = 0.303$). Nausea/vomiting incidence increased with AUC_{24} ($p < 0.001$) and was higher in females. Varenicline PK and ER for tolerability in adolescent smokers were comparable with adults, while ER for efficacy confirmed the negative results reported in the phase 4 study.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

While the pharmacokinetic (PK) and exposure–response profiles of varenicline are well characterized in adults, few studies have been conducted in adolescents.

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the population PK and varenicline exposure–response relationships for measures of efficacy (continuous abstinence rates [CAR] weeks 9–12) and tolerability (nausea/vomiting incidence) in adolescent smokers?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

For adolescent smokers, varenicline PK are generally comparable with those in adults. Nausea/vomiting increased with increasing varenicline AUC_{24}, which is also

Trial Registration: (www.clinicaltrials.gov) NCT00463918 and NCT01312909

consistent with observations in adult smokers. However, the relationship between CAR9–12 and increasing varenicline AUC_{24} was nonsignificant, which differs from studies in healthy adults showing end-of-treatment abstinence rates to increase linearly with increasing varenicline exposure.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Varenicline systemic exposure and oral clearance in adolescent and adult smokers were generally comparable and therefore cannot explain any lack of efficacy of varenicline in adolescent smokers. Researchers may need to better understand social/behavioral determinants of smoking in adolescents when considering treatment options.

INTRODUCTION

Cigarette smoking increases lifetime risk of cancers, cardiovascular, and respiratory diseases.[1] Tobacco use is the leading cause of preventable morbidity and mortality worldwide, responsible for approximately 6 million deaths each year.[2] Most adult smokers begin smoking as adolescents. In the 2019 National Youth Tobacco Survey, the US Centers for Disease Control and Prevention reported that 5.8% of US high-school students indicated current use of cigarettes (at least 1 day in the past 30 days), the lowest number recorded since the survey began in 1999, when it was 28.5%. However, the current use of any combustible tobacco product was 12.0%, and the use of any tobacco product, which includes electronic cigarettes (vaping) was 31.2%.[3] In addition, 10.8% of high-school students reported current use of two or more tobacco products, which may increase the risk of nicotine dependence and the likelihood of continued tobacco use in adulthood.[4,5]

Varenicline is a selective nicotinic acetylcholine receptor (nAChR) partial agonist approved by the US Food and Drug Administration and the European Medicines Agency as a treatment to aid smoking cessation in adults.[6,7] The efficacy of varenicline in smoking cessation is the result of varenicline's activity at α4β2 subtype of the nicotinic receptor where binding produces agonist activity while simultaneously preventing nicotine binding to these receptors.[8] These mixed agonist-antagonist properties offer the therapeutic benefit of relieving symptoms of nicotine withdrawal during abstinence, while blocking the reinforcing effects of chronic nicotine.[8]

The efficacy and safety of varenicline in adults has been demonstrated in several randomized clinical trials,[9] including two pivotal phase 3 studies[10,11] and a large phase 4 study.[12] Collectively, results have demonstrated that varenicline increases the odds of quitting smoking compared with placebo, and compared with the smoking cessation pharmacotherapies bupropion or nicotine replacement therapy.[9,12] There are currently no substantial data on varenicline and vaping. Common adverse reactions in adults receiving varenicline include nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.[6,7] Nausea is generally of mild or moderate intensity, and is often transient. Approximately 30% and 5% of smokers who received varenicline 1 mg twice daily (b.i.d.) in the phase 3 pivotal trials experienced nausea and vomiting, respectively, compared with ~10% and 2% of smokers who received placebo.[10,11] Further, the incidence of nausea associated with varenicline is dose-dependent.[9]

The approved varenicline dosing regimen for adults is 1 mg b.i.d. for 12 weeks, starting with a 1-week up-titration, prior to a predetermined target quit date.[6] Maximum plasma concentration of varenicline occurs within ~3 hours of oral administration.[13] Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine (primarily via glomerular filtration); elimination half-life is ~24 hours in plasma.[14] In adults, including the elderly, the pharmacokinetics (PK) of varenicline is linear over the recommended dose range.[14-16] Following administration of multiple oral doses of varenicline, steady-state is reached within 4 days.

Varenicline has been evaluated for PK, safety, and efficacy in adolescent smokers in three Pfizer-sponsored studies: one single-dose[14] and one multiple-dose[17] phase 1 PK study, and a phase 4 efficacy and safety study that included PK sampling.[18] In addition, results of an independent efficacy and safety study in a somewhat older adolescent population, which did not collect PK data, have been published recently.[19] The objectives of our analyses were to characterize the population PK (popPK) of varenicline using data from the three Pfizer-sponsored studies in adolescent smokers, and to explore relationships between varenicline systemic exposure and measures of efficacy and tolerability.

METHODS

Study populations

The popPK analysis was comprised of varenicline concentration–time data from two phase 1 studies and one

phase 4 study. The exposure–response (ER) analysis included smoking cessation and tolerability data from the phase 4 study only (Table 1). In all studies, subjects were randomized and received at least one dose of study drug. In the first phase 1 study (Pfizer study A3051029),[14] subjects received a single dose of varenicline 0.5 or 1 mg, or placebo. In the second phase 1 study (NCT00463918)[17] and the phase 4 study (NCT01312909),[18] subjects received 0.5 mg once daily (q.d.) or b.i.d., or 1 mg b.i.d. of varenicline based on their body weight (≤55 kg: 0.5 mg q.d. or 0.5 mg b.i.d.; >55 kg: 0.5 mg b.i.d. or 1 mg b.i.d.), or they received placebo for 14 days or 12 weeks, respectively. These studies included a 1- or 2-week titration period for subjects receiving more than 0.5 mg q.d. Both studies employed a double-dummy design to allow for multiple different doses while maintaining the blind. To ensure enrolment of nicotine-dependent subjects in the phase 4 study, study inclusion required a Fagerström Test for Nicotine Dependence (FTND)[20] score of ≥4 (moderate dependence). In addition to treatment with varenicline or placebo, subjects received brief (≤10 minutes), age-appropriate smoking cessation counseling at all study visits. Post-treatment follow-up for the phase 4 study was 40 weeks.

Sample collection and assessments

Plasma varenicline concentrations

Blood samples were collected in all studies to provide plasma for PK analysis of varenicline (Table 1). Plasma samples were analyzed for varenicline concentrations using a validated liquid chromatography/tandem mass spectrometry assay.[14] The lower limit of quantification for varenicline in plasma was 0.1 ng/mL.

TABLE 1 Summary of the studies and data used for the popPK and ER analyses in adolescents

	Study type/objectives		
	Phase 1 (study 1): PK (Pfizer study A3051029)	**Phase 1 (study 2): PK (NCT00463918)**	**Phase 4: Efficacy, safety, and PK (NCT01312909)**
Population	Healthy adolescent smokers	Healthy adolescent smokers	Nicotine-dependent adolescent smokers: FTND score ≥4
Design	Single-dose; randomized; parallel-group; placebo-controlled; investigator and subject blind, sponsor open	Multiple-dose; double-blind; parallel-group; placebo-controlled	Multiple-dose; double-blind; parallel-group; placebo-controlled
Age (years)	12–17	12–16	12–19
Number of subjects[a]	27 (22 varenicline; 5 placebo)	72 (57 varenicline; 15 placebo)	307[b] (208 varenicline; 99 placebo)
Key inclusion criteria	Total body weight ≥40 kg; current smokers (average ≥10 cigarettes per day during the past year)	Total body weight >30 kg; current smokers (≥3 cigarettes per day during the past 4 weeks)	Smokes ≥5 cigarettes per day (during the past 30 days); motivated to stop smoking; ≥1 prior, failed quit attempt
Varenicline dose and regimen	0.5 mg single dose; 1 mg single dose; or placebo single dose	BWT ≤55 kg: 0.5 mg q.d. or 0.5 mg b.i.d.[c]; BWT >55 kg: 0.5 mg b.i.d. or 1 mg b.i.d.; placebo	BWT ≤55 kg: 0.5 mg q.d. or 0.5 mg b.i.d.[d]; BWT >55 kg: 0.5 mg b.i.d. or 1 mg b.i.d.; placebo
Treatment duration	N/A	14 days	12 weeks
Blood sampling regimen	0 h (predose), 1, 2, 3, 4, 8, 12, 24, and 48 h post morning dose on day 1	0 h (predose); day 1 (1.5, 3, 6, and 10 h post morning dose); day 8 (0 and 3 h post morning dose); day 14 (0 and 1.5, 3, 6, and 10 h post morning dose), and within 48–84 h post last dose of study medication	One random time at weeks 3, 6, and 12, or at an early termination visit

Abbreviations: b.i.d., twice daily; BWT, body weight; ER, exposure–response; FTND, Fagerström Test for Nicotine Dependence; N/A, not available; PK, pharmacokinetics; popPK, population pharmacokinetics; q.d., once daily.

[a]As treated: subjects received at least one dose of varenicline.

[b]A total of 120 out of the 307 subjects were discontinued.[18]

[c]The evening dose was administered ~10 hours after the morning dose.

[d]An interval of at least 8 hours was recommended between the morning and evening dose.

Efficacy assessments

For the phase 4 study, smoking status was assessed using a standard series of questions (the nicotine use inventory), where the subject responded "Yes" or "No" to questions about cigarette or other nicotine/tobacco use since their previous visit or during the past 7 days. Smoking "even a puff" was recorded as "Yes." For subjects who responded "Yes" in the past 7 days, the number of days smoked and average number of cigarettes per day were recorded. The efficacy endpoint was the biochemically confirmed continuous abstinence rate (CAR) at weeks 9–12 (CAR9–12). Self-reported abstinence from smoking was confirmed using urine cotinine testing at weeks 9–12 during the treatment phase and at all clinic visits during follow-up. Subjects who did not complete treatment or the study were considered "nonresponders" from the point of discontinuation onward.

Tolerability assessments

The tolerability endpoint was assessed by the incidence of treatment-emergent adverse events (TEAEs). TEAEs were defined as events that began on or after the first day of study medication and until the last dose of study medication. Nausea and vomiting TEAEs were used for ER analyses.

Data analysis

The popPK and ER analyses were performed using nonlinear, log-transformed, mixed-effects modeling methodology (NONMEM version 7.3, ICON plc, Gaithersburg, MD). The final model codes are presented in Text S1 and S2. The popPK analysis used the following strategy: base structural model development (Table S1); random-effects model development; inclusion of covariates and final model development; assessment of model adequacy (goodness of fit); and assessment of final model predictive performance. The popPK analysis was conducted using the first-order conditional estimation method with interaction; the Laplacian estimation method was employed for all ER analyses. Post-processing of NONMEM output to generate goodness-of-fit plots was performed using R software (version 3.0.2 or higher). Visual predictive checks (VPCs) and bootstraps were conducted using Perl-speaks-NONMEM (PsN 4.2.0 or higher). VPCs were performed to evaluate the adequacy of the final model and parameter estimates as they provide a comprehensive evaluation of model performance by evaluating both fixed- and random-effects variance distributions. Simulation results were plotted using Xpose (version 4.4). In addition, at all stages of development, models were evaluated using goodness-of-fit criteria including: successful minimization of the objective function; visual inspection of diagnostic plots (individual predicted concentration vs. observed concentration, population predicted concentration vs. observed concentration, and conditional weighted residuals vs. time); change in objective function relative to change in the number of parameters; shrinkage of the empirical Bayes estimates; the magnitude and precision of the parameter estimates; calculation of the condition number; and changes in both inter-individual and residual variability. Diagnostic plots were stratified by study and varenicline dose to ensure the adequacy of pooling data across the different study designs and doses. Bootstrap 95% confidence intervals (CI) were used to evaluate the significance of the covariates introduced into the model based upon inclusion or exclusion of the null value.[21]

popPK analysis

Based on a prior popPK analysis that used data from the phase 1 multiple-dose study in adolescents (NCT00463918),[17] a one-compartment popPK model with first-order absorption and elimination was fitted to the observed data and parameterized as apparent clearance (CL/F), apparent volume of distribution (V/F), and first-order absorption rate constant (ka). Inter-individual variance was included on CL/F, V/F, and ka as a full block structure. Separate residual variance parameters were also incorporated for data from the phase 1 and phase 4 studies.

Baseline body weight (BWT), race, and sex were included as covariates on CL/F and V/F using the full model estimation (FME) approach.[22] With the FME approach, non-significant covariates were retained in the model to make inferences about the covariate effects of interest. Correlation of covariates was assessed to ensure that no correlated covariates with |correlation coefficient|>0.3 were added to the model. Since no highly correlated covariates were included, the FME approach was appropriate. Creatinine clearance (CrCl: based on the Cockcroft-Gault formula[23]) was not included as a covariate on CL/F since BWT and CrCl were correlated and most adolescents were expected to have normal renal function. BWT and sex were not correlated and thus were both included as covariates in model development. In addition, since BWT and age were correlated, age was not included as a covariate on CL/F or V/F. Continuous covariates were included in the model using a power function:

$$\mathrm{TVP} = P_{\mathrm{pop}} \bullet \left(\frac{\mathrm{cov}_i}{\mathrm{cov}_{\mathrm{reference}}} \right)^{\theta_S}$$

where TVP is the typical (mean) value of the PK parameter with covariate value cov_i, P_{pop} represents the population central tendency for the PK parameter TVP, $\mathrm{cov}_{\mathrm{reference}}$ represents the predefined reference value of the covariate, and θ_S represents a NONMEM-estimated scaling factor.

Considering that body weight (BWT) is an important factor for dose adjustment in adolescents and that an adequate range of body weights were present within the adolescent dataset, it was assumed that the precise relationship between BWT and CL/F could be estimated.

Categorical covariate reference values for sex and race were set to the most prevalent value in the data set (male sex and white race, respectively). In general, categorical covariate effects were parameterized as a fractional change:

$$\mathrm{TVP} = P_{\mathrm{pop}} \bullet \theta^{\mathrm{cov}_i}$$

where θ represents a NONMEM-estimated direct proportionality constant that is conditional on the covariate indicator variable cov_i (either 0 or 1).

The selection of covariates included in the final model was based upon clinical judgment, physiologic relevance, prior knowledge, and mechanistic plausibility. Covariate effects were incorporated into the final popPK model as follows:

$$\frac{\mathrm{CL}}{F} = \left[\theta_{\mathrm{TV}\frac{\mathrm{CL}}{F}} \cdot \left(\frac{\mathrm{BWT}}{70}\right)^{\theta_{\frac{\mathrm{CL}}{F}\sim\mathrm{BWT}}} \cdot \theta_{\frac{\mathrm{CL}}{F}\sim\mathrm{RACE2}} \cdot \theta_{\frac{\mathrm{CL}}{F}\sim\mathrm{RACE3}} \cdot \theta_{\frac{\mathrm{CL}}{F}\sim\mathrm{NSEX}}\right] \cdot e^{\eta_{\frac{\mathrm{CL}}{F}i}}$$

$$\frac{V}{F} = \left[\theta_{\mathrm{TV}\frac{V}{F}} \cdot \left(\frac{\mathrm{BWT}}{70}\right)^{\theta_{\frac{V}{F}\sim\mathrm{BWT}}} \cdot \theta_{\frac{V}{F}\sim\mathrm{RACE2}} \cdot \theta_{\frac{V}{F}\sim\mathrm{RACE3}} \cdot \theta_{\frac{V}{F}\sim\mathrm{NSEX}}\right] \cdot e^{\eta_{\frac{V}{F}i}}$$

where θ represents fixed-effect parameters, and empirical Bayes prediction of the inter-individual random effect (η) represents a subject-specific random effect. BWT was a continuous covariate, while categorical covariates included female sex (where NSEX describes male =0 and female =1), black (RACE2), and other (Asian, Hispanic, American Indian, and mixed race [RACE3]). The reference subject was defined as a 70 kg, white male.

ER analyses

Efficacy and tolerability data, along with covariate information, were pooled and merged with the individual varenicline area under the concentration–time curve values from 0 to 24 hours (AUC_{24}) predicted for subjects randomized to varenicline in the phase 4 study, using the parameter estimates from the final popPK model. The daily AUC_{24} was estimated from the empirical Bayes predictions of CL/F value and total daily dose for each subject. AUC_{24} was set to zero for subjects in the placebo group.

ER endpoints (a successful binary quit attempt [1 = yes, 0 = no], or the occurrence of nausea or vomiting) were dichotomous categorical variables analyzed using a logistic regression model. The predicted likelihood (l_i for individual i) of the data (y_i; 1 = yes, 0 = no) was described by a binomial probability density function. This was communicated to NONMEM software using the likelihood estimation option:

$$l_i = \left[e^{\lambda_i}/\left(1+e^{\lambda_i}\right)\right]^{y_i} \bullet \left[1/\left(1+e^{\lambda_i}\right)\right]^{1-y_i}$$

where λ_i represents the log of the odds of the probability of an event occurring vs. not occurring.

Covariate parameters including FSQ1 ("How soon after you wake up do you smoke your first cigarette?"), age, sex, and race were added to the base intercept model with AUC_{24} as a linear function using the FME approach. Baseline smoking status was set to zero for FTND score for question 1 (FSQ1), where zero was equal to >60 minutes for the time to first cigarette. The final nausea or vomiting incidence model was as follows:

$$\lambda_i = \theta_{\frac{\mathrm{Nausea}}{\mathrm{Vomiting}}} \cdot \theta_{\mathrm{FSQ1\,1}} \cdot \theta_{\mathrm{FSQ1\,2}} \cdot \theta_{\mathrm{FSQ1\,3}} \cdot \left(\frac{\mathrm{Age}}{16}\right)^{\theta_{\mathrm{Age}}} \cdot \theta_{\mathrm{NSEX}} \cdot \theta_{\mathrm{RACE2}} \cdot \theta_{\mathrm{RACE3}} + \theta_{\frac{\mathrm{Nausea}}{\mathrm{Vomiting}}\,\mathrm{AUC}_{24}} \cdot \mathrm{AUC}_{24}$$

where θ represents the fixed-effect parameters and age is a continuous covariate. Categorical covariates included time to first cigarette between 31 and 60 minutes [FSQ1 (1)], time to first cigarette between 6 and 30 minutes [FSQ1 (2)], time to first cigarette <5 minutes [FSQ1 (3)], female sex (NSEX describes male =0 and female =1), black race [RACE2], and other race [RACE3]. The reference adolescent subject was defined as a 16-year-old white male who smokes his first cigarette >60 minutes after waking up in the morning. Subjects with no measurable varenicline concentrations were excluded from the ER analyses as AUC_{24} values could not be estimated.

Ethics

All study protocols were reviewed and approved by each site's institutional review board or ethics committee and conducted in accordance with the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines. All participants aged 18 and older provided written, informed consent; subjects younger than 18 provided written assent, while their parent or other legally authorized representative provided written, informed consent.

RESULTS

Baseline demographic covariates for popPK and ER analyses

A total of 1,097 plasma varenicline concentrations from 218 subjects who received varenicline in the three studies were included in the popPK analysis (Table 2). There were <10% of PK observations below the limit

TABLE 2 Summary of baseline demographic covariates for popPK and ER (efficacy and tolerability) analyses

	popPK analysis				ER analyses (phase 4 study)
Covariate	Phase 1 study 1 (single dose)	Phase 1 study 2 (multiple dose)	Phase 4 study	Total	Total
BWT (kg), *N*	22	57	139	218	N/A
Mean (SD)	65.5 (12.9)	59.9 (14.2)	65.3 (13.1)	63.9 (13.5)	
Median	66.5	55.0	62.7	62.1	
Min, Max	45.0, 95.0	35.0, 121	35.2, 110	35.0, 121	
Age (years), *N*	22	57	139	218	238
Mean (SD)	14.7 (1.70)	14.8 (1.15)	15.8 (1.81)	15.4 (1.71)	15.8 (1.81)
Median	15.0	15.0	16.0	16.0	16.0
Min, Max	12.0, 17.0	12.0, 16.0	12.0, 20.0[a]	12.0, 20.0	12.0, 20.0
CrCl (mL/min), *N*	22	57	139	218	N/A
Mean (SD)	115 (20.7)	132 (29.6)	129 (32.7)	128 (31.1)	
Median	112	129	123	124	
Min, Max	85.3, 163	51.7, 222	53.2, 257	51.7, 257	
Sex, *N* (%)					
Male	13 (59.1)	29 (50.9)	94 (67.6)	136 (62.4)	157 (66.0)
Female	9 (40.9)	28 (49.1)	45 (32.4)	82 (37.6)	81 (34.0)
Race, *N* (%)					
White	3 (13.6)	37 (64.9)	102 (73.4)	142 (65.1)	176 (73.9)
Black	19 (86.4)	1 (1.75)	11 (7.91)	31 (14.2)	16 (6.72)
Asian	0 (0)	1 (1.75)	25 (18.0)	26 (11.9)	44 (18.5)
Other	0 (0)	18 (31.6)	1 (0.719)	19 (8.72)	2 (0.840)
FSQ1 (time to first cigarette), *N* (%)	N/A	N/A	N/A	N/A	
3 (<5 min)					98 (41.2)
2 (6–30 min)					96 (40.3)
1 (31–60 min)					39 (16.4)
0 (>60 min)					5 (2.10)

Abbreviations: BWT, baseline body weight; CrCl, creatinine clearance; ER, exposure–response; FSQ1, Fagerström Test for Nicotine Dependence score for question 1; Max, maximum; Min, minimum; N/A, not available; popPK, population pharmacokinetics; SD, standard deviation.

[a]The phase 4 study enrolled healthy adolescent smokers aged 12–19 years; however, one participant was screened 2 days after turning 20 years and was enrolled in violation of the study protocol.[18]

of quantification; therefore, it was determined that these missing values would not influence base structural model development.[24] Approximately 99% of subjects had normal renal function (CrCl >80 mL/min) while 1% had mild renal impairment (50 < CrCl ≤80 mL/min). Subjects who reported as Asian or "other" race were grouped together (and defined as "other") for the analysis, as the phase 1 studies included only one subject of Asian race vs. 18 subjects of "other" race.

For the ER analyses, 238 observations from 238 subjects in the phase 4 study, including 99 subjects who received placebo, were included. For consistency with the popPK analysis, subjects of Asian and "other" race were grouped together.

popPK analysis

The parameter estimates for the final popPK model are presented in Table 3. The population estimates of CL/F and V/F for varenicline were 12.5 L/h (95% CI 11.3–13.9) and 231 L (95% CI 199–256) for the reference subject, respectively. CL/F and V/F increased with increasing BWT (power estimate: 0.567 and 0.872), representing a <21% and <30% change relative to the reference subject, respectively. The effect of female sex on CL/F was significant, however, the magnitude of the effect was relatively small (~15% decrease in females compared with males). All other covariate effects on CL/F were not significant. The effects of black race, "other" race, and female sex on V/F were significant, causing

TABLE 3 Parameter estimates (RSE) and bootstrap median (95% CI) for the final popPK model

Parameter (unit)	Estimate	RSE, %	Median (95% CI)
CL/F (L/h)	12.5	5.06	12.4 (11.3–13.9)
Body weight	0.567	23.3	0.583 (0.317–0.904)
Black race	1.01	8.59	1.01 (0.840–1.22)
Other race	1.12	6.57	1.12 (0.982–1.31)
Female sex	0.850	5.87	0.849 (0.756–0.953)
V/F (L)	231	5.02	230 (199–256)
Body weight	0.872	10.3	0.864 (0.638–1.05)
Black race	0.757	5.46	0.754 (0.677–0.844)
Other race	0.854	4.78	0.858 (0.775–0.946)
Female sex	0.861	4.02	0.858 (0.793–0.934)
ka (h^{-1})	0.860	12.3	0.844 (0.668–1.12)
$\omega^2_{CL/F}$	0.102	26.3	0.0988 (0.0553–0.170)
$\omega^2_{V/F}$	0.0182	42.6	0.0169 (0.00371–0.0375)
ω^2_{ka}	0.174	48.5	0.182 (0.0483–0.389)
$COV_{CL/F,V/F}$	–0.00162	895	–0.000885 (–0.0369 to 0.0317)
$COV_{CL/F,ka}$	–0.0582	71.0	–0.0541 (–0.151 to 0.0306)
$COV_{V/F,ka}$	0.0307	73.3	0.0319 (–0.00836 to 0.0802)
Residual variance (σ^2)			
Phase 1 additive	0.0577 (0.240 ng/mL)[a]	51.3	0.0579 (0.00245–0.205)
Phase 1 proportional	0.0847	17.2	0.0810 (0.0455–0.114)
Phase 4 additive	0.336 (0.580 ng/mL)[a]	71.4	0.338 (0.0912–0.857)
Phase 4 proportional	0.187	14.5	0.183 (0.126–0.230)

Abbreviations: CI, confidence interval; CL/F, apparent clearance; COV, covariance; ka, absorption rate constant; popPK, population pharmacokinetics; RSE, relative standard error; V/F, apparent volume of distribution; ω^2, inter-individual variance.

[a]Standard deviations shown in parentheses; point estimates and RSEs of estimates estimated using NONMEM software; median and 95% CIs of estimates obtained from nonparametric bootstrap estimates ($N = 1{,}400$; 53 runs with minimization terminated and 284 runs with estimates near a boundary skipped when calculating bootstrap results).

an approximate decrease by 24%, 15%, and 14% relative to a white male, respectively.

All fixed-effect parameters were estimated with reasonable precision (relative standard error was <25%); condition number was 122, indicating a stable model. Inter-individual variance for CL/F, V/F, and ka (expressed as percentage coefficient of variation) was reduced from the base model (35%, 29%, and 47%, respectively) to the final model (32%, 13%, and 44%, respectively) with the inclusion of the covariate effects (BWT, race, and sex on both CL/F and V/F). The shrinkage for CL/F was 30.6%. Proportional residual error estimates were 29.1% and 43.2%, while additive residual error estimates were 0.240 ng/mL and 0.580 ng/mL for the phase 1 studies and phase 4 study, respectively. Goodness-of-fit plots, stratified by study, demonstrated an adequate fit to the varenicline plasma concentration–time data in adolescent smokers (Figure S1, S2, and S3).

Model-predictive performance was evaluated using a VPC to determine if the final model was capable of simulating data that were consistent with the observed varenicline PK measurements (Figure 1). While some time points fell outside the prediction intervals, the median and distribution of the observed data were generally contained within the 95% CI of the median of simulated data, indicating that the model adequately described the central tendency of the varenicline concentration–time profile.

The estimates of CL/F were converted to AUC_{24} and the covariate effects on AUC_{24} relative to the reference adolescent subject are presented in Figure 2.

ER analyses

The results of the logistic regression analyses for CAR9–12 and for nausea or vomiting incidence are shown in Figure 3a,b, respectively. For CAR9–12, each subject was classified as a quitter or non-quitter and hence contributed only one observation for the efficacy endpoint. However, there was no

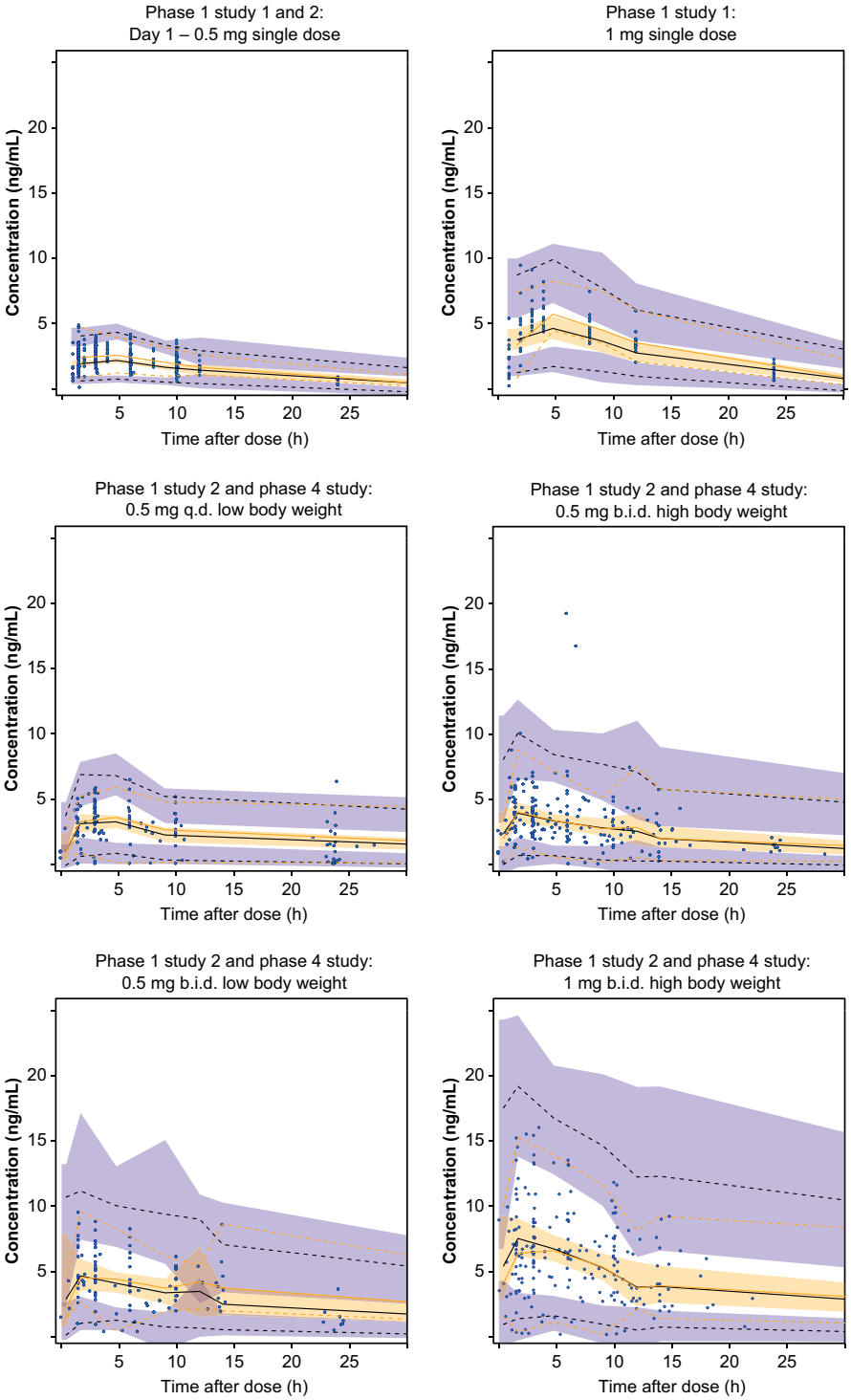

FIGURE 1 Visual predictive check. Circles represent observed plasma concentrations. Solid yellow line represents median observed plasma concentrations. Dashed yellow lines represent 2.5% and 97.5% observed percentiles. Solid black line represents simulated median. Dashed black lines represent 2.5% and 97.5% simulated percentiles. Shaded yellow area represents simulation-based 95% CI for simulated median. Shaded blue areas represent simulation-based 95% CI for 2.5% and 97.5% percentiles. b.i.d., twice daily; CI, confidence interval; q.d., once daily

statistically significant trend (slope estimate; $p = 0.303$) and no further model development was performed (Figure 3a). The reported nausea or vomiting data were characterized by evaluating incidence over the 12-week treatment period using a naïve-pooled analysis (with a single observation per subject). The addition of varenicline steady-state exposure (AUC_{24}) as a linear function resulted in an improved goodness of fit based on the objective function value, and demonstrated a statistically significant trend (slope estimate; $p < 0.001$) (Figure 3b). The final model showed that the incidence of

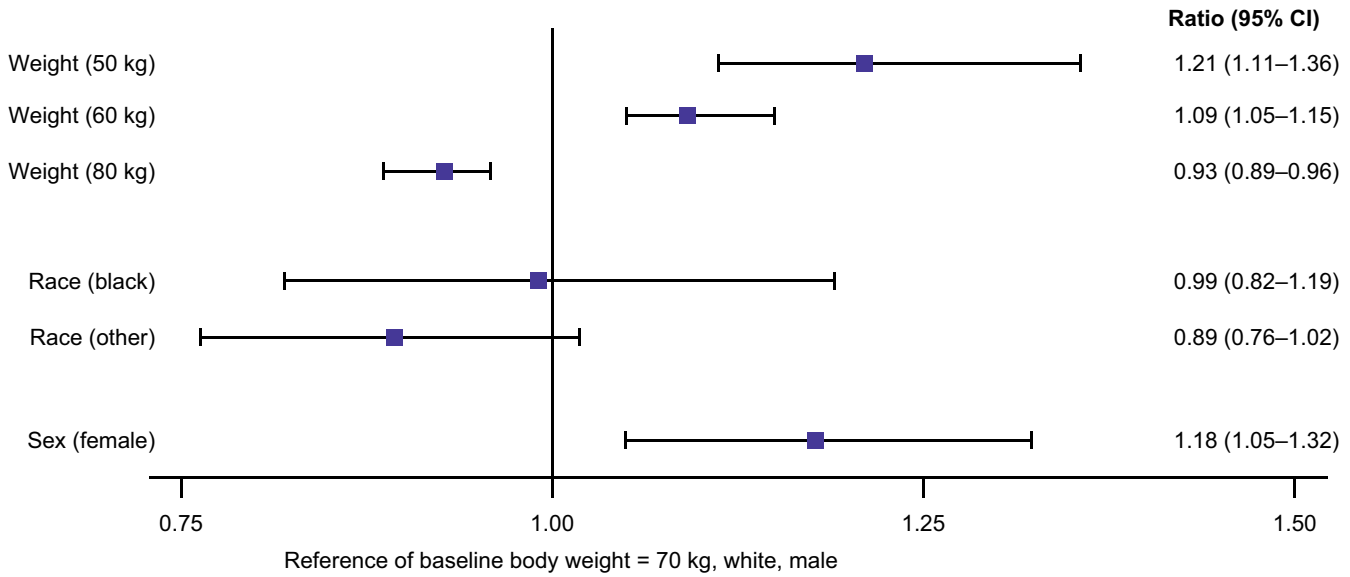

FIGURE 2 Covariate effects on AUC_{24} (95% CI). 95% CI of ratio generated from 1,400 nonparametric bootstrapped sets of population parameter values using final popPK model (50 runs with minimization terminated and 241 runs with estimates near a boundary skipped when calculating bootstrap results). AUC_{24} was derived from the final apparent clearance estimate. Solid squares represent ratio of typical predicted AUC_{24} relative to reference subject of white male weighing 70 kg. Thus, a value of 1 (1.0) represents unity or a null covariate effect. Error bars represent 95% CI of ratio. AUC_{24}, area under the concentration–time curve from 0 to 24 hours; CI, confidence interval; popPK, population pharmacokinetics

nausea or vomiting increased with increasing AUC_{24}. The parameter estimates and bootstrap median for the final nausea or vomiting incidence model are presented in Table S2.

The covariate effects of age, FSQ1 (first cigarette within 6–30 minutes), FSQ1 (first cigarette in <5 minutes), and race on nausea or vomiting incidence were not significant (based upon the CIs from the bootstrap and relative to the representative subject) (Figure 4). However, the point estimate and the bootstrapped 95% CIs for the effect of sex relative to the representative adolescent subject demonstrated a significant increase of ~86% (95% CI 17%–133%) in nausea or vomiting incidence for female smokers.

DISCUSSION

The current popPK analysis in adolescent smokers demonstrates that the varenicline PK of an adolescent population are generally comparable with those of an adult population.[14-16] Approximately 70% of subjects in the phase 4 study had at least one measurable concentration of varenicline and contributed data to the population PK analysis after being combined with data from the phase 1 studies. Varenicline PK were adequately described with a one-compartment model with first-order absorption and first-order elimination. For a reference adolescent smoker (a white male weighing 70 kg), CL/F and V/F of varenicline were estimated to be 12.5 L/h and 231 L, respectively. These estimations were approximately 20% higher and 31% lower than those characterized in adults.[15] While the higher estimation of CL/F translates to an ~17% reduction in AUC_{24}, the estimated decrease in V/F would increase maximum observed plasma concentration but would not impact AUC_{24}. Given that the efficacy and safety of varenicline has been shown to be driven by AUC in adults,[15] neither difference is considered to be clinically meaningful.

The half-life of varenicline in adolescent smokers in the phase 1 multiple-dose study was found to be shorter in adolescents compared with adults.[17] Since renal clearance was comparable for varenicline 0.5 and 1 mg single doses, and was consistent with findings in adults, the more rapid decline in plasma varenicline concentration in adolescents is considered to be due to reduced V/F following oral administration. The reason for the observed difference in distribution properties of varenicline between adolescents and adults is unclear but may be related to differential distribution patterns of lean tissue and fat mass. However, the difference is not considered to be clinically relevant as the overall varenicline exposure in adolescents was comparable to exposure in adults dosed b.i.d. The final adult popPK model included estimates of covariate effects for creatinine clearance and race on CL/F and for weight, age and race on central volume of distribution.[15] Given that sex and weight are components of the Cockcroft-Gault formula,[23] and that most adolescents had normal renal function, both sex and weight were included as covariates instead of creatinine clearance for this popPK analysis. Significant race-related changes were detected previously in adults[15]; hence the effect of race was also evaluated in this final adolescent model. Residual variability was lower in the

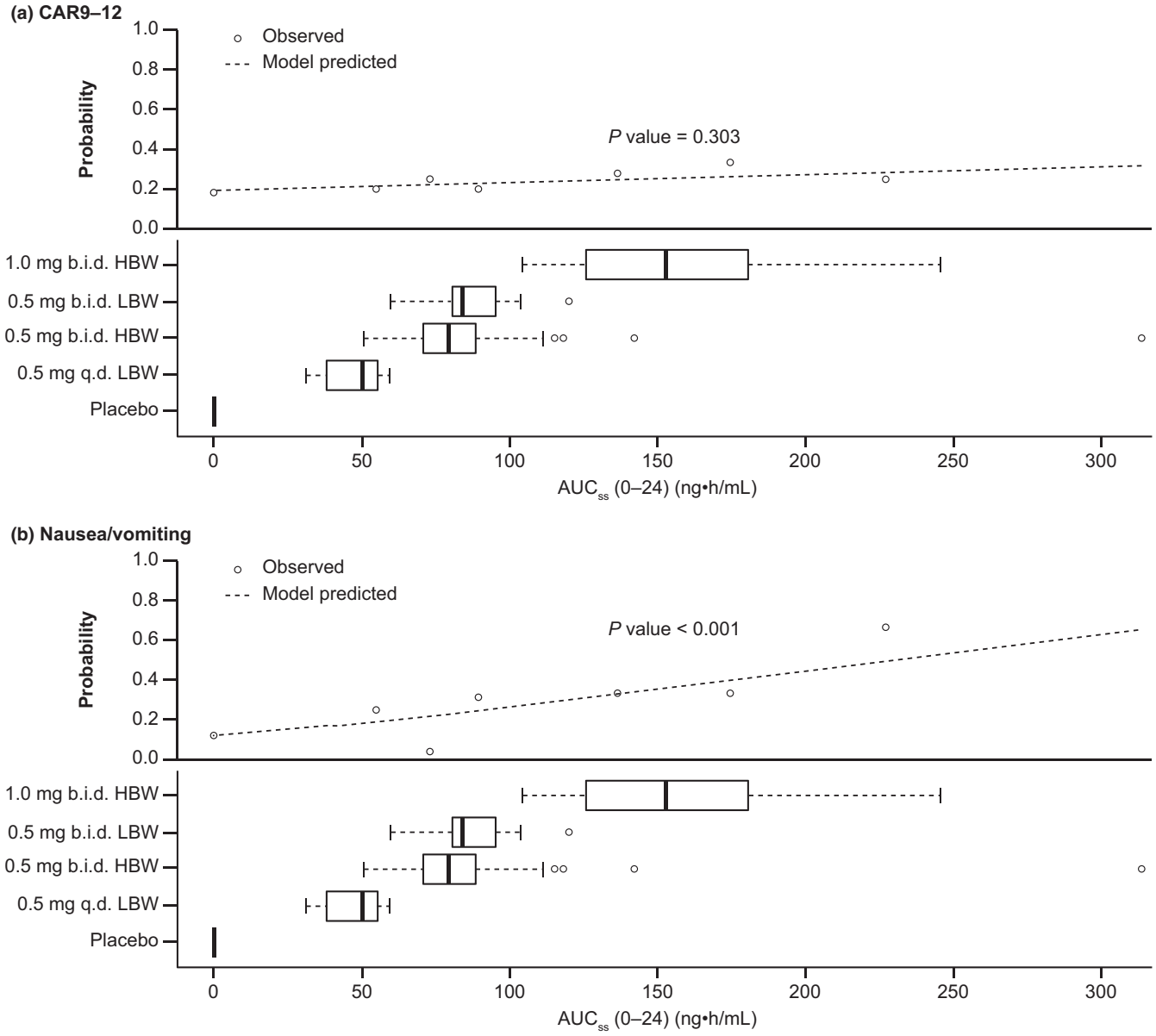

FIGURE 3 Varenicline ER relationships in adolescent smokers for (a) CAR9–12 and (b) nausea/vomiting incidence. (a) Dotted line represents predicted probability of continuous abstinence at weeks 9–12. (b) Dotted line represents predicted probability of nausea/vomiting incidence. (a and b) Circles show observed probabilities in each of the six AUC_{ss} (0–24) bins. Exposure was set to 0 for placebo group. Box-and-whisker plots (lower panels) describe distribution of exposure data. Box indicates difference between first and third quartiles of data, showing spread of data. Solid line represents median value; whiskers indicate range of data or 1.5× interquartile distance, whichever is less. Circles plotted outside whiskers exceed these limits and may be considered outliers. AUC_{ss} (0–24), area under the concentration–time curve at steady-state from 0 to 24 hours; b.i.d., twice daily; CAR, continuous abstinence rate; ER, exposure–response; HBW, high body weight (>55 kg); LBW, low body weight (≤55 kg); q.d., once daily

phase 1 studies than the phase 4 study. However, this was expected as measurement error of dosing information and sampling time information can often be larger in sparsely sampled, outpatient studies with non-witnessed dosing, relative to inpatient phase 1 studies. Although compliance issues could have been a potential contributing factor to the higher proportional residual variability in the phase 4 study, based on compliance checks and adherence rates, most participants were shown to be adherent.[18]

In this popPK analysis, there was a small (3%) decrease in inter-individual variance for both CL/F and ka while a larger (16%) decrease was observed for V/F. Hence, similar to previous observations in adolescents,[17] inclusion of covariate effects in the final popPK model described a larger fraction of the total observed inter-individual variance for V/F in comparison to CL/F. Moreover, the covariance terms describing the correlations between the inter-individual variance terms were very small in the final model suggesting that large

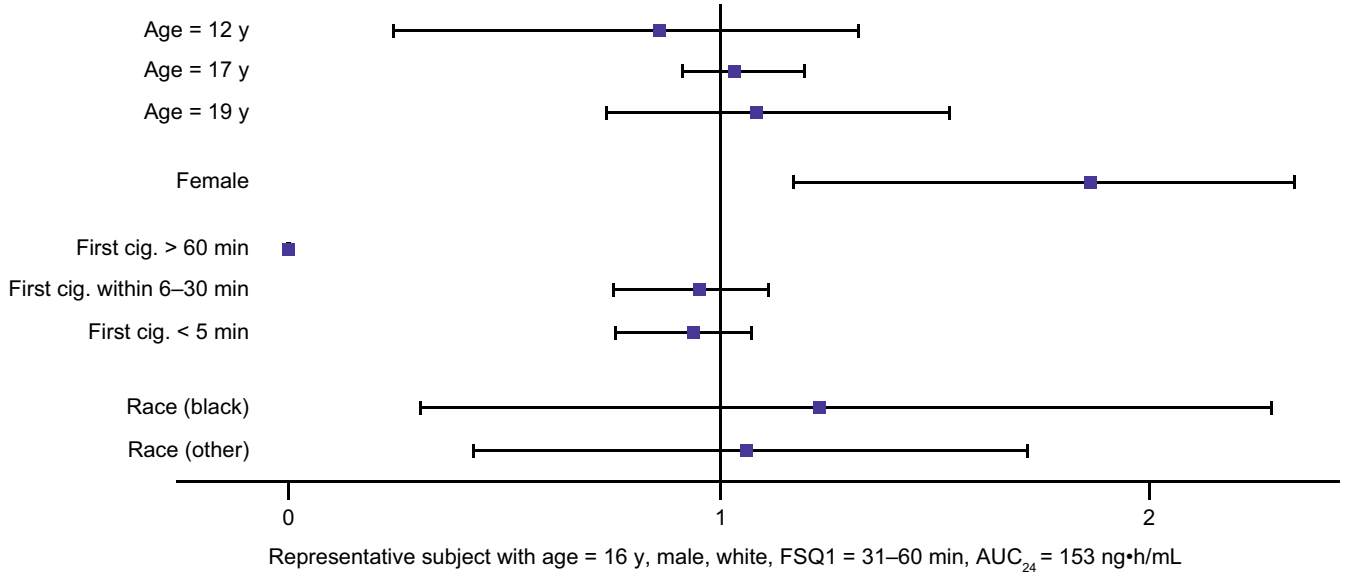

FIGURE 4 Covariate effects on nausea/vomiting incidence (95% CI). 95% CI of ratio generated from 2,800 nonparametric bootstrapped sets of population parameter values using final nausea/vomiting incidence model (754 runs with minimization terminated skipped when calculating bootstrap results). Solid squares represent point estimate for covariate effect relative to representative subject. Error bars represent 95% CI of ratio. AUC_{24}, area under the concentration–time curve from 0 to 24 hours; CI, confidence interval; cig., cigarette; FSQ1, Fagerström Test for Nicotine Dependence score for question 1

fractions of the total observed inter-individual variance were explained with inclusion of the weight, sex, and race covariate effects. Comparison of the plots of subject-specific random effects between base and final models demonstrated that there were no obvious remaining covariate trends. It has been previously reported that varenicline has predictable pharmacokinetic properties and a straightforward dispositional profile that simplifies its use in clinical practice.[14] However, it may be possible that other covariate effects, not included in the varenicline database, could explain some of the remaining variability observed in this adolescent population.

The ER analyses of the phase 4 study for efficacy demonstrated no significant relationship between CAR9–12 and AUC_{24}, which confirms the negative efficacy results reported for the study.[18] This differs from results of ER studies in healthy adults that have shown end-of-treatment abstinence rates to increase linearly with increasing varenicline exposure.[14] The results of the current analyses are, however, consistent with previous findings that smoking cessation therapies are not necessarily efficacious in adults and adolescents alike.[25-27] Notably a recent randomized, placebo-controlled, double-blind clinical trial of varenicline in adolescent smokers aged 14–21 years concluded that varenicline did not improve abstinence measured at the end of treatment, but did show that varenicline-treated smokers reported abstinence more quickly, and had better post-treatment abstinence outcomes.[19] However, few smoking cessation trials have been conducted in adolescents and available results regarding the efficacy of smoking cessation pharmacotherapies are mixed.[28,29] The reasons for a potential differential response to smoking cessation pharmacotherapy in adolescent vs. adult smokers are unclear. However, a role for social and behavioral determinants, including peer pressure, impulsivity, and antisocial behavior, that may be more specific to the adolescent population have been hypothesized.[27,30] In the current analyses at least, varenicline systemic exposure and oral clearance were generally comparable with those of an adult population[31] and therefore do not explain the lack of efficacy in adolescent smokers.

The ER analysis for tolerability found that the probability of a nausea or vomiting event occurring was positively related to varenicline exposure, a finding that is consistent with adult smokers,[31] and that may be attributed to the pharmacological activity of varenicline on nAChRs at central and peripheral levels.[32-34] Further, results demonstrated a significant increase of ~86% in nausea or vomiting incidence for female smokers compared with male smokers, which was consistent with observations in adult smokers where nausea or vomiting incidence was approximately two-fold higher in females compared with males.[31]

CONCLUSIONS

For adolescent smokers, varenicline PK are generally comparable with those of an adult population. The observed range of exposure in the phase 4 study was consistent with that expected for each dose and body-weight group from the results obtained in adolescent PK studies, supporting that varenicline dose and administration were appropriate in the

study. The ER analysis for CAR9–12 demonstrated no significant relationship with AUC_{24}. However, the ER analysis for tolerability showed that the incidence of nausea or vomiting increased with increasing AUC_{24} and is consistent with observations in adult smokers.

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CONFLICT OF INTEREST

DF, KS, VS, TM and WB are employees of Pfizer and may own shares/stock options in Pfizer.

AUTHOR CONTRIBUTIONS

DF, WB, KS, VS, and TM wrote the manuscript. DF and WB designed the research. DF, WB, and KS performed the research. DF, WB, KS, VS, and TM analyzed the data.

DATA AVAILABILITY STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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