Population Pharmacokinetic Modeling of Armodafinil and Its Major Metabolites

Susan Willavize, PhD[1]; Jill Fiedler-Kelly, MS[1]; Elizabeth Ludwig, PharmD[1]; Lingling Guan, PhD[2]

[1]Cognigen Corporation, Buffalo, NY; [2]Teva Pharmaceuticals, Frazer, PA

Address correspondence to:

Susan Willavize, PhD

1780 Wehrle Drive

Buffalo, NY 14221

Tel: 716-633-3463

Email: Susan.Willavize@cognigencorp.com

Fellow of the American College of Clinical Pharmacology: None

Word count: 4486

Tables/Figures: 10, plus 7 supplementary

Number of references: 23

Disclosures

Dr. Susan Willavize reports grants from Teva Pharmaceuticals during the conduct of the modeling.

Jill Fiedler-Kelly reports grants from Teva Pharmaceuticals during the conduct of the modeling.

Dr. Elizabeth Ludwig reports analyses performed as contracted research from Teva Pharmaceuticals during the conduct of the modeling.

Dr. Lingling Guan is an employee of the US Food and Drug Administration (FDA). The research reported in this manuscript was conducted while Dr. Guan was employed at Teva Pharmaceuticals. The views in this manuscript do not necessarily reflect those of the FDA, and no official support or endorsement of this manuscript by the FDA is intended or should be inferred.

Population pharmacokinetic modeling was sponsored by Teva Branded Pharmaceutical Products R&D, Inc. Medical writing assistance was provided by Kathleen Dorries, PhD, and John H. Simmons, MD, of Peloton Advantage and was funded by Teva Branded Pharmaceutical Products R&D, Inc. Teva provided a full review of the manuscript.

ABSTRACT

Population pharmacokinetic models for armodafinil and its major metabolites, *R*-modafinil acid and modafinil sulfone, were developed and selected covariates were investigated. Data from 583 healthy subjects and patients with bipolar I disorder in 11 phase 1-3 studies (8027 concentrations) of armodafinil, given as single or multiple once-daily doses (50-400 mg tablet or capsule), were pooled. A previously developed one-compartment model with first-order absorption, without covariate effects, was initially applied to pooled phase 1 and 2 data. Population modeling was performed with NONMEM, version 7, with the first-order conditional estimation method. Estimated armodafinil apparent oral clearance (CL/F), volume of distribution (Vc/F), and absorption $t_{½}$ were 2.01 L/h, 45 L, and 0.226 h. Armodafinil CL/F and Vc/F increase with weight; predicted steady-state area under the curve is 16.4% higher and 29.1% lower in a patient weighing 50 or 150 kg, relative to a 70-kg patient. Female participants had 10.2% lower armodafinil Vc/F compared with male participants. Age, race (white vs non-white), health status (healthy vs bipolar I disorder), liver function, and renal function were not statistically significant predictors of armodafinil pharmacokinetics. CL/F and Vc/F for *R*-modafinil acid and modafinil sulfone were 16.7 L/h and 8.95 L, and 6.82 L/h and 12.4 L, respectively. Weight did not affect exposure of either metabolite. These population pharmacokinetic models were from the largest population of adults reported to date, and provide a robust characterization of the pharmacokinetics of armodafinil, *R*-modafinil acid, and modafinil sulfone in adults.

Keywords: Armodafinil; Population Pharmacokinetics; Modeling; Modafinil; *R*-modafinil Acid; Modafinil Sulfone

INTRODUCTION

Armodafinil (Nuvigil®; Teva Pharmaceuticals USA, Inc.; North Wales, PA) is an indirect dopamine receptor agonist approved by the US Food and Drug Administration (FDA) to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, shift work disorder, or obstructive sleep apnea treated with continuous positive airway pressure.[1] Following a positive phase 2 proof-of-concept study,[2] the efficacy and safety of armodafinil as an adjunctive treatment for adult patients with depressive episodes associated with bipolar I disorder was assessed in 3 acute, double-blind, placebo-controlled phase 3 studies.[3-5] Significant improvement on the primary efficacy outcome, mean change from baseline to week 8 in the 30-item Inventory of Depressive Symptomatology–Clinician-Rated total score, was observed in only 1 of the 3 studies,[3-5] which prompted the sponsor's decision to terminate the clinical program for this indication.

Armodafinil is the *R*-enantiomer of racemic modafinil (Provigil®; Teva Pharmaceuticals USA, Inc.; North Wales, PA)[6]; modafinil is metabolized mainly by the liver, with approximately 5% to 10% of the parent compound excreted in the urine.[7-9] Two inactive metabolites reach measurable concentrations in plasma, *R*-modafinil acid and modafinil sulfone.[1,8] Amide hydrolysis is the principal metabolic pathway for modafinil; sulfone formation by cytochrome P450 (CYP) 3A4/5 plays a smaller role.[1,8] Metabolites are eliminated mainly via urinary excretion.[1,7,8] The pharmacokinetic profile of armodafinil has been previously characterized in healthy subjects[10,11] and in patients with excessive sleepiness associated with treated obstructive sleep apnea.[12] In healthy subjects, armodafinil pharmacokinetics were dose-proportional at steady state and linear over a 50- to 400-mg dose range. Maximum plasma concentration (C_{max}) occurred approximately 2 hours (T_{max}) after armodafinil administration in fasting subjects.[10] Armodafinil pharmacokinetics were assessed in healthy subjects after administration of tablet and capsule formulations; pharmacokinetic values were similar for the 2 formulations in a post hoc analysis.[13]

A population pharmacokinetic/pharmacodynamic analysis quantitatively compared the predicted efficacy of armodafinil with that of modafinil in patients with excessive sleepiness associated with shift work disorder.[14] Population pharmacokinetic models were developed for modafinil and armodafinil to examine plasma concentrations relative to the wakefulness-promoting effects of the drugs. The pharmacokinetic profiles of modafinil and armodafinil were described by separate models: a two-compartment model with first-order absorption for modafinil, and a one-compartment model with first-order absorption for armodafinil. This analysis extends that work to aid optimization of drug-dosing strategies for armodafinil in patients with bipolar I disorder through development of a population pharmacokinetic model. Separate models were developed for the 2

major circulating metabolites of armodafinil, *R*-modafinil acid and modafinil sulfone. The models were developed to adequately characterize the pharmacokinetic disposition of armodafinil in adult patients with bipolar I disorder and to assess the effect of covariates (including sex, race, body weight, bipolar I disorder status, formulation, liver function, and renal function) to explain sources of intersubject variability in pharmacokinetic parameters. This analysis, which includes a larger subject population compared with previous analyses, characterizes the pharmacokinetics of armodafinil and its 2 major metabolites in adults. The models presented here for the armodafinil metabolites *R*-modafinil acid and modafinil sulfone are the first-ever population pharmacokinetic characterizations of these metabolites.

METHODS

Source Data for the Models

The studies were conducted in accordance with the International Council for Harmonisation Guidelines for Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki. Written informed consent was obtained from all participants before any protocol-required procedures were performed.[2,5,10,11,13,15-18] The plasma concentration data for the population pharmacokinetic models were obtained from 11 studies (**Table S1**), including nine phase 1 studies in healthy adult subjects, and one phase 2 study and one phase 3 study in adult patients experiencing a major depressive episode associated with bipolar I disorder.[2,5,10,11,13,15-18] The protocols for all of the included studies received institutional review board or independent ethics committee approval before initiation.

Of the phase 1 studies that provided data for the models, 7 were open-label studies and 2 were randomized, double-blind, placebo-controlled pharmacokinetic studies. Pharmacokinetic data from healthy subjects who were aged 75 years or older, who received armodafinil in the fed state, or who received armodafinil in combination with a second drug in drug-interaction studies were excluded from the model development. The phase 2 and 3 studies were 8-week, double-blind, placebo-controlled, parallel-group, fixed-dosage studies. Daily dosages of armodafinil used in these studies ranged from 50 to 400 mg. Plasma concentrations obtained in phase 2 and 3 studies were predominantly from patients treated with armodafinil 150 mg/d, titrated at treatment initiation. The phase 3 study also included a 200-mg arm that was terminated early; plasma concentrations from 13 patients in that treatment arm were included in this analysis. Armodafinil formulations used included capsules (two phase 1 studies) and tablets (9 studies).

In phase 1 studies, samples for pharmacokinetic analysis were collected using a rich sampling scheme; samples were collected predose and at specified time points up to 24, 72, or 96 hours post dose, depending on the study (**Table S1**). Phase 2 and 3 studies used sparse sampling; blood samples were collected at screening and at 3 time points over the 8-week treatment period. The date and time of each sample and of the 3 doses immediately preceding sample collection were recorded. Plasma armodafinil, *R*-modafinil acid, and modafinil sulfone concentrations were determined as previously described.[10,11,13,15-18]

Demographic information, clinical laboratory values, treatment assignment, dosing information, pharmacokinetic sampling information, concomitant medication information, and pathophysiologic status indicators from patients and healthy subjects were included with plasma concentrations in the database.

Model Development

Exploratory graphical displays were used to initially assess trends in the data, identify potential outliers, and verify model assumptions. A previously developed one-compartment model with first-order absorption (data on file, Cephalon),[14] without covariate effects, was initially applied to pooled phase 1 and 2 data. Goodness-of-fit was evaluated using graphical and statistical methods, including visual assessment of agreement in scatterplots of measured vs predicted concentrations, size of gradients associated with each parameter at the final iteration of estimation, convergence of the estimation and covariance routines, reasonable parameter estimates based upon the expected relationship, lack of trend or pattern in scatterplots of conditional weighted residuals vs predicted observations and time assessed visually, and other assessments of estimates and plots of predictions and residuals.

Covariates assessed in the population pharmacokinetic model were age, sex, weight, race (white vs non-white), health status (patient vs healthy subject), formulation (tablet vs capsule), baseline liver dysfunction classification[19] and baseline renal dysfunction classification.[20] For categorical variables, categories were combined if any subgroup represented less than 10% of the population. Drug interaction effects could not be explored using the population pharmacokinetic model

because less than 10% of patients were taking concomitant medications classified as CYP3A4 inhibitors, P-glycoprotein inhibitors, or P-glycoprotein inducers (Table 1). The correlation between covariates was examined prior to covariate analysis. Where covariates were found to be highly correlated with other covariates (e.g., $r \geq 0.6$ for two continuous covariates), only one of the highly correlated covariates was selected for evaluation. In fact, the covariates of interest were not correlated in the study data set and, in particular, there was a similar distribution of weights for males and females. Functional forms assessed in covariate analyses included linear, exponential, power, additive or proportional shifts, and piecewise combinations of these forms.

Effects of covariates on the pharmacokinetic parameters Vc/F (apparent central volume of distribution, where F is the relative bioavailability fraction) and CL/F (apparent clearance) were evaluated using forward and backward elimination procedures. Following backward elimination, the reduced multivariable model was evaluated for any remaining biases in the interindividual variability and residual variability (RV) error models. The phase 3 data were then pooled with the phase 1 and 2 data set and the model was refined again using backward elimination. The final model was evaluated using a simulation-based, prediction-corrected visual predictive check method.[21]

Metabolite Model Development

Population pharmacokinetic models were developed for the metabolites *R*-modafinil acid and modafinil sulfone based on the pooled phase 1, 2, and 3 study data set using steps similar to those described for armodafinil model development. Concentrations for each metabolite were fitted separately using the armodafinil dose in µMol.

Statistical Methods

For each analysis, NONMEM computed the value of the objective function (VOF), proportional to minus two times the log likelihood of the data. For forward selection, covariates contributing a change in the minimum VOF of at least 3.84 ($\alpha = 0.05$, 1 *df* for χ^2 distribution) and resulting in a decrease of at least 1% in interindividual variability in the parameter of interest were considered significant. For backward elimination, a covariate was considered significant if its removal resulted in a change in the VOF of at least 10.83 ($\alpha = 0.001$, 1 *df* for χ^2 distribution). Graphical displays were used to assess trends in the data, identify potential outliers, and verify model assumptions. Goodness-of-fit was evaluated using graphical and statistical criteria (as described above).

All exploratory data analyses and presentations of data were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) or KIWI version 1.1 (Cognigen Corporation, Buffalo, NY). Population modeling was performed with NONMEM, version 7, level 1.2 (ICON Development Solutions, Hanover, MD) with the first-order conditional estimation method.

RESULTS

Baseline demographic and clinical characteristics for the 11 studies included in the analysis are shown in **Table 1**. Before data cleaning, 9326 concentration records (696 patients) were available for armodafinil from the phase 1-3 studies. Concentration records were deleted due to missing concentration/sample dates or times, pre-first dose concentrations, duplicate data, trailing concentrations reported as below the lower limit of quantitation (BLQ), no measurable samples, or inadequate washout (11% of records, affecting 14% of subjects). A total of 236 concentration records from healthy volunteers aged 75 years or greater and patients from Study 101 who received armodafinil in a fed state were excluded (representing 3% of records, from 8 patients [representing 1% of patients]). Concentration records were also removed (0.5% of samples, affecting 0.7% of subjects) when drug accountability indicated that less than 85% of the expected doses were taken during the period before the collection of the plasma sample. Finally, 11 concentrations (0.12%) were deleted as graphical outliers. Hence, 8027 concentrations were available from 583 individuals in the phase 1, 2, and 3 studies; this included 264 BLQ concentrations that were initially included in the analysis. The proportions of BLQ records were 3.1%, 7.6%, and 4.6% for the phase 1, 2, and 3 studies, respectively. Armodafinil was administered as the tablet formulation to 80% of individuals in the phase 1 studies and 100% of those in the phase 2 and 3 studies (89% of the analysis population overall; **Table 1**). The dose-normalized plasma armodafinil concentrations (**Figure 1A** and **Figure 1B**)

after administration of the tablet formulation are suggestive of a monoexponential pattern of decline in plasma concentration and are consistent with dose proportionality.

Before data cleaning, there were 8457 and 8436 concentration records (from 602 and 592 subjects) for *R*-modafinil acid and modafinil sulfone, respectively. Concentration records were deleted due to missing concentration/sample dates or times, pre-first dose concentrations, duplicate data, trailing concentrations reported as BLQ, no measurable samples, or inadequate washout (16% of records, affecting 8% of subjects for *R*-modafinil acid; 8% of records, affecting 8% of subjects for modafinil sulfone). Concentration records from healthy volunteers aged 75 years or greater and patients from Study 101 who received armodafinil in a fed state were excluded (2% of records, representing 1% of subjects for each metabolite). Finally, metabolite concentrations that were graphical outliers or associated with high weighted residuals were excluded from model development, representing 1% of records (affecting 1.5% of patients) for *R*-modafinil acid and 5% of records (affecting 3% of patients) for modafinil sulfone. Hence, population pharmacokinetic models for *R*-modafinil acid and modafinil sulfone were developed based on 5863 concentrations from 538 individuals and 6009 concentrations from 520 individuals, respectively. Metabolite concentrations that were BLQ (*R*-modafinil acid, 14.2%; modafinil sulfone, 16.0%) were also excluded, based on the results of the BLQ analysis for armodafinil.

Armodafinil Model Development

A one-compartment model with first-order absorption and first-order elimination parameterized in terms of absorption rate constant (k_a), CL/F, and Vc/F, was suggested by preliminary graphical examination of armodafinil concentration-time data and was found to be an appropriate model. A lag time of absorption was estimated for the tablet formulation but was not required to characterize the absorption of the capsule formulation. The structural base model included interindividual variability estimated for CL/F and Vc/F using exponential error models. Goodness-of-fit plots (not shown) indicated a reasonable model fit for the structural base model.

During the forward-selection process of the covariate analysis, weight was found to be a statistically significant predictor of variability in CL/F, and weight, age, and sex were found to be statistically significant predictors of variability in Vc/F. After backward elimination, effects of weight on CL/F and weight and sex on Vc/F were found to be statistically significant and were retained in the model. For the effect of formulation, a relative bioavailability term was additionally included in the model, significantly reducing the VOF ($P < .001$). The capsule formulation was used only in two phase 1 studies that specifically enrolled male subjects; therefore, the estimate of the relative bioavailability factor is confounded with sex.

Initially, the BLQ values were included in the analysis and the M3 method (Beal 2001[22]) was applied. During the model refinement, BLQ concentrations were examined graphically, overlaid with the probability of being BLQ estimated by NONMEM (as shown for the phase 2 and 3 studies in **Figure S1**). Nearly all BLQ values in the phase 2 and 3 studies occurred at times after dosing associated with a very low predicted probability of being BLQ (probability < 0.01), while BLQ concentrations in the phase 1 studies primarily occurred at times ($\geq$ 23 hours after dosing) associated with a high predicted probability of being BLQ. Because estimated RV was significantly reduced after removal of BLQ concentrations during testing, all BLQ values were excluded from further model development. No remaining biases in the interindividual variability and RV error models were detected; diagnostic plots showed no inadequacies or biases in the covariate models and no remaining trends (not shown).

Final Population Pharmacokinetic Model for Armodafinil

The population mean parameter estimates and associated precisions (standard error of the estimate divided by the estimate, expressed as a percentage [%SEM]) for the final pharmacokinetic model of armodafinil are presented in **Table 2**. Standard errors were estimated using the default method in NONMEM (which combines both the Hessian and the gradient to provide a robust estimate). All fixed and random effect parameters were estimated with good precision (%SEM ≤ 30.0). An exponential model was used to describe the inter-individual variability in apparent clearance (CL/F) and apparent central volume of distribution (Vc/F), and the covariance of CL/F and Vc/F was estimated. Residual variability models were refined to constant coefficient of variation (CCV) error models with separate estimates to describe phase 1, 2, and 3 data in the final model. Residual variability for the phase 2 and 3 data was moderate and for the phase 1 data was relatively small. The goodness-of-fit plots indicated an unbiased model (**Figure S2**).

Armodafinil CL/F and Vc/F were modeled as

$$(CL/F)_j = 2.01 \times \left(\frac{WT_j}{79.5}\right)^{0.452}$$

$$(Vc/F)_j = 45.0 \times \left(\frac{WT_j}{79.5}\right)^{0.828} \times \left(1 \times \left(1 - SEXF_j\right) + 0.898 \times SEXF_j\right)$$

Where *F* is the bioavailability, WT_j is the baseline body weight for the *j*th patient, and $SEXF_j$ is the indicator variable for sex of the *j*th patient (0 for male, 1 for female). **Figure 2** illustrates the model-predicted steady-state concentration vs time profiles after oral administration of armodafinil 150 mg for 14 days for hypothetical male and female patients with median body weights receiving the tablet and capsule formulations. The bioavailability of the capsule formulation was 91.3% relative to the tablet formulation.

The CL/F of armodafinil increases less than proportionally with increasing body weight. For a hypothetical patient with a body weight of 50 or 150 kg, steady-state AUC would be 16.4% higher and 29.1% lower, respectively, relative to a hypothetical patient with a body weight of 70 kg. The Vc/F also increases less than proportionally with increasing body weight. In a hypothetical female patient with a body weight of 60, 70, or 80 kg, armodafinil Vc/F is predicted to be 32.0, 36.4, and 40.6 L, respectively. The distribution volume for a male patient at the same body weights would be 35.6, 40.5, and 45.2 L. Armodafinil Vc/F is 10.2% lower in female patients compared with male patients when weight is included as a covariate for Vc/F in the model. Final model estimates of armodafinil CL/F, Vc/F, and first-order absorption $t_{½}$ for a patient with a median body weight of 79.5 kg were 2.01 L/h, 45.0 L, and 0.226 hours, respectively. The effects of age, race (white vs non-white), health status (healthy subjects vs patients), and liver and renal dysfunction were not statistically significant predictors of armodafinil pharmacokinetics.

Model evaluation plots stratified by health status demonstrated a good fit of the model to the data from both healthy subjects and patients with bipolar I disorder (observed armodafinil concentration vs time in patients with bipolar I disorder is shown with median and 90% prediction interval in **Figure 3**). The final population pharmacokinetic model was used to predict individual steady-state pharmacokinetic exposures of armodafinil for patients in phase 2 and 3 studies by liver and renal function. Exposure, in terms of AUC, appeared similar for patients with mild liver dysfunction compared with patients with normal liver function (**Figure 4A**), although the sample size was quite small. Impaired renal function was associated with generally higher steady-state armodafinil exposure (**Figure 4B**). Similar results were also seen for model-predicted C_{max} (not shown).

R-*modafinil Acid and Modafinil Sulfone Models*

Demographic characteristics for individuals included in the metabolite analysis were similar to those in the armodafinil analysis. Metabolite concentration data were modeled separately for *R*-modafinil acid and modafinil sulfone. As expected, the pattern of BLQ occurrence after dosing for metabolites was similar to that for armodafinil. Because BLQ records were eventually excluded from the analysis of armodafinil concentrations, no BLQ records were included in the population analysis of the metabolite concentrations. The M3 method (Beal 2001[22]) for handling BLQ values was deemed inappropriate for armodafinil and metabolites.

A one-compartment population pharmacokinetic model with first-order absorption and elimination was found to be an appropriate fit for *R*-modafinil acid concentrations, whereas a two-compartment model with first-order absorption and elimination provided an appropriate fit for modafinil sulfone. An absorption lag time (0.219 hour) was included for the tablet formulation but not for the capsule formulation for *R*-modafinil acid, and bioavailability was estimated for the capsule formulation relative to the tablet formulation (0.692 and 0.743, for *R*-modafinil acid and modafinil sulfone, respectively). An exponential model was used to describe the interindividual variability in k_a, CL/F, and Vc/F for *R*-modafinil acid and to describe the interindividual variability in k_a and CL/F for modafinil sulfone. Constant coefficient of variation residual error models were used for both analytes with separate estimates to describe metabolite concentrations from the phase 1, 2, and 3 studies.

Parameter estimates for the two population pharmacokinetic models, including associated precision estimates (%SEM), are listed in **Table 3**. Goodness-of-fit plots for the two metabolite models are provided in **Figures S3** and **S4**. As the true fraction of the administered armodafinil dose that is biotransformed to *R*-modafinil acid and modafinil sulfone is unknown, the administered dose of armodafinil was used for the dose input in the metabolite models, likely resulting in some overestimation of clearances and/or underestimation of volumes. Subjects taking the capsule formulation had exposures approximately 30% to 40% lower for *R*-modafinil acid and modafinil sulfone (and 10% lower for armodafinil) compared with individuals taking the tablet formulation. Model evaluation plots for each metabolite stratified by health status demonstrated a good fit of the model to the data from both healthy subjects and patients with bipolar I disorder (observed metabolite concentration vs time in patients with bipolar I disorder is shown with median and 90% prediction interval in **Figures S5** and **S6**, for *R*-modafinil acid and modafinil sulfone, respectively).

Exploratory graphical analyses of the effect of weight on predicted metabolite exposures (steady-state AUC and C_{max}) showed no apparent trends.

DISCUSSION

This population pharmacokinetic analysis of armodafinil 50 to 400 mg, based on data from more than 500 healthy subjects and patients with bipolar I disorder, extends the findings of the previous population pharmacokinetic analysis[14] to include assessment of the contribution of population characteristics to interindividual variability in plasma armodafinil concentrations as well as characterization of metabolite pharmacokinetics. The model fit to armodafinil concentrations was a one-compartment population pharmacokinetic model with first-order absorption and elimination. Final model estimates of armodafinil CL/F, Vc/F, and first-order absorption $t_{½}$ for a patient with a median body weight of 79.5 kg were 2.01 L/h, 45 L, and 0.226 hours, respectively. The final model included several significant covariates. There was a significant effect of body weight on armodafinil CL/F and Vc/F, and both increased with increasing body weight according to a power function (model estimates of weight exponent [%SEM (95% CI)]: 0.452 [13.9 (0.328, 0.575)] and 0.828 [7.82 (0.701, 0.955)], respectively). These estimated exponents differ from the theoretical allometric values of 0.75 and 1, respectively, but their validity is supported by the sample size, weight range, and 95% confidence intervals. A sex effect on armodafinil Vc/F (beyond the effect of weight) was also observed, and the effect of formulation was described by a relative bioavailability estimate of 0.913 for the capsule formulation. As noted above, however, the estimate of the relative bioavailability is confounded with sex.

Pharmacokinetic analysis of modafinil in patients with cirrhosis of the liver compared with healthy subjects has indicated that the oral clearance of modafinil is decreased by approximately 60% and the steady-state concentration is approximately doubled in patients with chronic hepatic insufficiency.[1,9] The FDA-approved armodafinil dosage is 150 to 250 mg/d; a dose reduction is recommended in patients with severe hepatic impairment.[1] In this analysis, however, liver function did not contribute significantly to the shape of the concentration vs time curve for armodafinil; it should be noted that only 7 patients with liver dysfunction were included, all classified as mild liver dysfunction. Impaired renal function (mild dysfunction, defined as creatinine clearance [CrCL] 60-89 mL/min [n=38], or moderate dysfunction, defined as CrCL 30-59 mL/min [n=1]) was associated with slightly higher, but nonsignificant, steady-state armodafinil exposure compared with normal renal function (CrCL ≥90 mL/min) (**Figure 4B**).

A one-compartment model with first-order absorption was previously developed for armodafinil based on data from healthy subjects and patients with excessive sleepiness associated with shift

work disorder.[14] Final estimates of armodafinil CL/F and Vc/F after oral administration reported for the shift work disorder population model were 0.025 L/h/kg and 0.47 L/kg, respectively, compared with 0.0253 L/h/kg and 0.57 L/kg for the bipolar I disorder population model. Body weight was the only significant covariate in the shift work disorder final population model, with a modest effect on the Vc/F (model estimate [%CV], −0.0003 [10] L/kg).[14] There was no significant effect of sex in the shift work disorder population pharmacokinetic model; however, a sex effect on *R*-modafinil pharmacokinetics was reported in a pharmacokinetic study in healthy subjects aged 19 to 40 years. In that study, C_{max} was significantly higher in women than in men.[7] That finding is consistent with the 10.2% lower Vc/F in women than in men observed in the final model for bipolar I disorder, and suggests higher exposure for women than for men at the same dose. The magnitudes of the effects of weight and sex were relatively small and, while statistically significant, are not expected to be clinically relevant or to warrant dose adjustment.

The model fitted to the metabolite *R*-modafinil acid concentrations was also a one-compartment population pharmacokinetic model with first-order absorption and elimination, whereas a two-compartment model with first-order absorption and elimination was determined to be an appropriate fit for modafinil sulfone concentrations. The model selections for the metabolites were consistent with the shape of representative plasma concentration vs time curves for *R*-modafinil acid and modafinil sulfone[23]: the modafinil sulfone curve shows a substantially slower terminal slope compared with the *R*-modafinil acid curve, indicating a delay in distribution or slower elimination kinetics for modafinil sulfone relative to *R*-modafinil acid. The model estimated CL/F and Vc/F were 16.7 L/h and 8.95 L, respectively, for *R*-modafinil acid, and 6.82 L/h and 12.4 L, respectively, for modafinil sulfone.

Several limitations of the analysis should be noted. Rich concentration data were available from healthy subjects in phase 1 studies, however all data from bipolar I disorder patients were sparsely sampled. As mentioned, the effect of formulation is confounded with sex, as no women were enrolled in studies that utilized the capsule formulation. Liver function and renal function were examined in the model; however, that analysis was limited by the availability of data from patients with mild hepatic or renal impairment only. No patients with severe liver or renal impairment were enrolled in the studies used for the model, and less than 1% of subjects had moderate hepatic or renal impairment. Consequently, no conclusions can be drawn from the results regarding the effects of moderate or severe liver or renal dysfunction on armodafinil pharmacokinetics. Similarly, effects of age on armodafinil population pharmacokinetics may not be fully characterized in the analyses due to the limited age range in the healthy subject population. Although concentrations were available from subjects aged 18 to 74 years, eight of the nine phase 1 studies included in the analysis excluded subjects over 40 or 45 years of age, and the median age for subjects in phase 1 studies was

31 years. All BLQ concentrations were excluded from the data set because it was assumed that the BLQ values in the phase 2 and 3 studies were due to handling errors rather than low analyte concentrations in the sample. This assumption was supported by graphical examination of the data, but it could not be definitively confirmed. Finally, separate models for parent and each metabolite were developed. Although a simultaneous parent-metabolites model would theoretically be advantageous, it would require the assumption of the conversion fraction from parent to each metabolite. This conversion fraction is unknown because the metabolic pathways of armodafinil have not been specifically characterized in clinical studies.

CONCLUSIONS

In this population pharmacokinetic evaluation of armodafinil in healthy subjects and adult patients with bipolar I disorder, plasma armodafinil concentrations were adequately described by a one-compartment model with first-order absorption and first-order elimination, with a small absorption lag time following administration of the tablet formulation. Several covariate effects were significant: CL/F and Vc/F increased less than proportionally with increasing body weight, and Vc/F was 10.2% lower for women than for men (adjusting for weight in the model). The bioavailability of the capsule formulation was 91.3% relative to the tablet formulation. Age, race (white vs non-white), healthy vs bipolar I disorder status, and liver and renal dysfunction were not statistically significant factors in the final armodafinil population pharmacokinetic model. There was no clear trend relating exposure to weight in the *R*-modafinil acid and modafinil sulfone population pharmacokinetic models. Overall, the pharmacokinetic models are based on the largest population of adults reported to date. Thus, they provide a robust characterization of the pharmacokinetics of armodafinil, *R*-modafinil acid, and modafinil sulfone in adults.

REFERENCES

1. Nuvigil [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2015.
2. Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry.* 2010;71(10):1363-1370.
3. Frye MA, Amchin J, Bauer M, Adler C, Yang R, Ketter TA. Randomized, placebo-controlled, adjunctive study of armodafinil for bipolar I depression: implications of novel drug design and heterogeneity of concurrent bipolar maintenance treatments. *Int J Bipolar Disord.* 2015;3(1):34.
4. Calabrese JR, Frye MA, Yang R, Ketter TA; Armodafinil Treatment Trial Study Network. Efficacy and safety of armodafinil for the adjunctive treatment of major depressive episodes associated with bipolar I disorder: a randomized, double-blind, placebo-controlled; multicenter trial. *J Clin Psychiatry.* 2014;75:1054-1061.
5. Ketter TA, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder. *J Affect Disord.* 2015;181:87-91.
6. Provigil [pagkage insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2015.
7. Wong YN, King SP, Simcoe D, et al. Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. *J Clin Pharmacol.* 1999;39(3):281-288.
8. Robertson P, Jr., Hellriegel ET. Clinical pharmacokinetic profile of modafinil. *Clin Pharmacokinet.* 2003;42(2):123-137.
9. Moachon G, Kanmacher I, Clenet M. Pharmacokinetic profile of modafinil. *Drugs Today.* 1996;32:327-337.
10. Darwish M, Kirby M, Hellriegel ET, Yang R, Robertson P, Jr. Pharmacokinetic profile of armodafinil in healthy subjects: pooled analysis of data from three randomized studies. *Clin Drug Investig.* 2009;29(2):87-100.
11. Darwish M, Kirby M, Hellriegel ET, Yang R, Robertson P, Jr. Systemic exposure to armodafinil and its tolerability in healthy elderly versus young men: an open-label, multiple-dose, parallel-group study. *Drugs Aging.* 2011;28(2):139-150.

12. Darwish M, Kirby M, D'Andrea DM, Yang R, Hellriegel ET, Robertson P, Jr. Pharmacokinetics of armodafinil and modafinil after single and multiple doses in patients with excessive sleepiness associated with treated obstructive sleep apnea: a randomized, open-label, crossover study. *Clin Ther.* 2010;32(12):2074-2087.

13. Darwish M, Kirby M, Hellriegel ET, Robertson P, Jr. Armodafinil and modafinil have substantially different pharmacokinetic profiles despite having the same terminal half-lives: analysis of data from three randomized, single-dose, pharmacokinetic studies. *Clin Drug Investig.* 2009;29(9):613-623.

14. Darwish M, Bond M, Ezzet F. Armodafinil and modafinil in patients with excessive sleepiness associated with shift work disorder: a pharmacokinetic/pharmacodynamic model for predicting and comparing their concentration-effect relationships. *J Clin Pharmacol.* 2012;52(9):1328-1342.

15. Darwish M, Bond M, Yang R, Hellriegel ET, Robertson P, Jr. Evaluation of the potential for pharmacokinetic drug-drug interaction between armodafinil and carbamazepine in healthy adults. *Clin Ther.* 2015;37(2):325-337.

16. Darwish M, Bond M, Yang R, Hellriegel ET, Robertson P, Jr. Evaluation of the potential for a pharmacokinetic drug-drug interaction between armodafinil and ziprasidone in healthy adults. *Clin Drug Investig.* 2014;34(10):691-699.

17. Darwish M, Bond M, Yang R, Hellriegel ET, Robertson P, Jr. Evaluation of potential pharmacokinetic drug-drug interaction between armodafinil and aripiprazole in healthy adults. *Pharmacopsychiatry.* 2015;48(04/05):170-175.

18. Darwish M, Bond M, Yang R, Hellriegel ET, Robertson P. Evaluation of potential pharmacokinetic drug-drug interaction between armodafinil and risperidone in healthy adults. *Clin Drug Investig.* 2015;35(11):725-733.

19. Ramanathan RK, Egorin MJ, Takimoto CH, et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. *J Clin Oncol.* 2008;26(4):563-569.

20. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003;139(2):137-147.

21. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J.* 2011;13(2) 143-151.

22. Beal SL. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn.* 2001;28(5):481-504.

23. Gorman SH. Determination of modafinil, modafinil acid and modafinil sulfone in human plasma utilizing liquid-liquid extraction and high-performance liquid chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2002;767(2):269-276.

Figure 1. Dose-Normalized Armodafinil Concentration vs Time Since Last Dose: Tablet Formulation, Phase 1 (Panel A) and Phase 2/3 (Panel B)

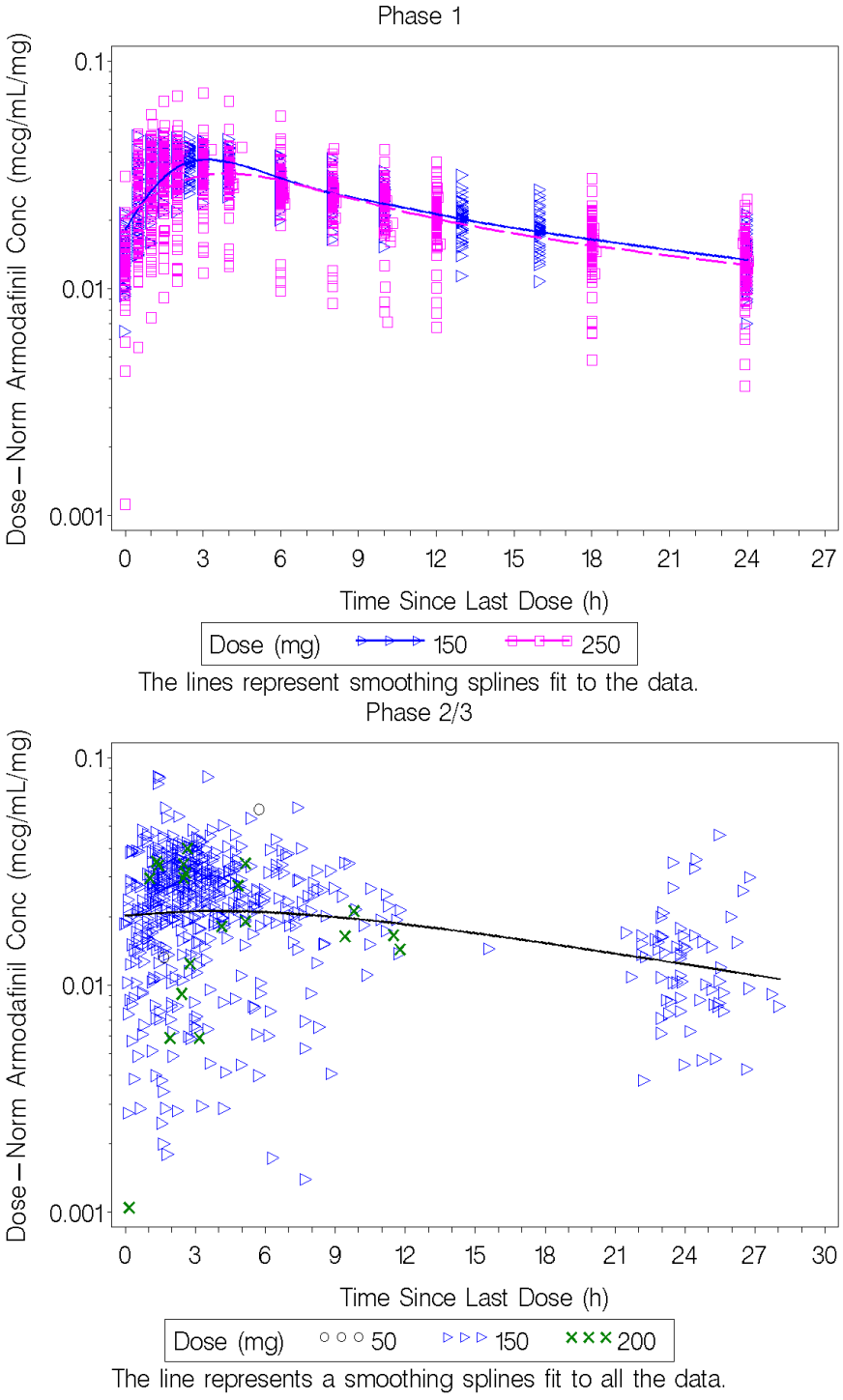


Figure 2. Comparison of Predicted Steady-State Concentration vs Time Profiles of Armodafinil After 150 mg Oral Administration for Hypothetical Patients, by Sex and Formulation. All Individuals Administered the Capsule Formulation Were Male

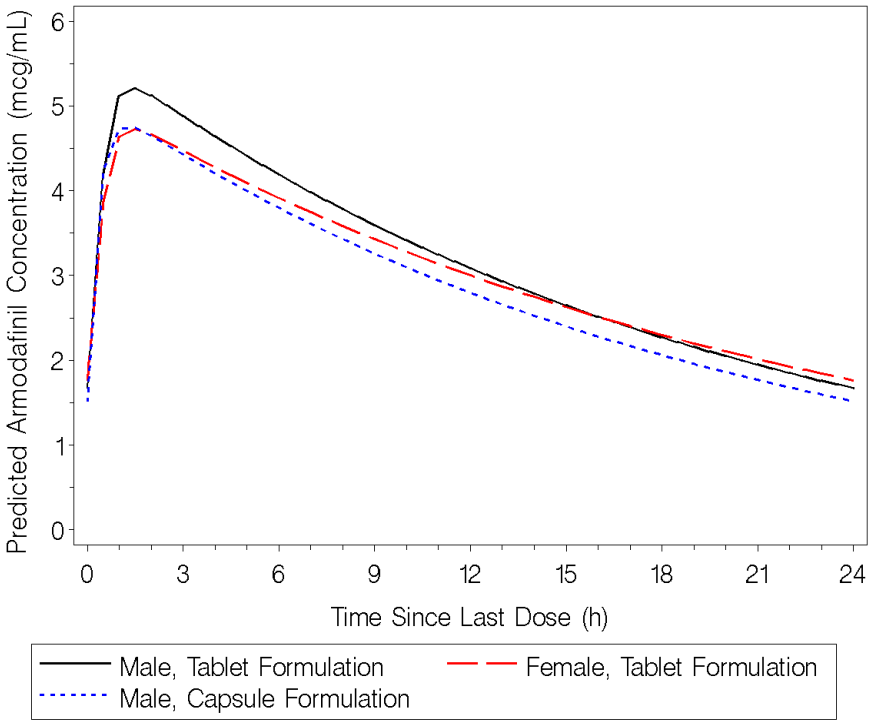


Figure 3. Visual Predictive Check for the Armodafinil Final Population Pharmacokinetic Model With CCV Residual Variability, Patients With Bipolar I Disorder

CCV=constant coefficient of variation.

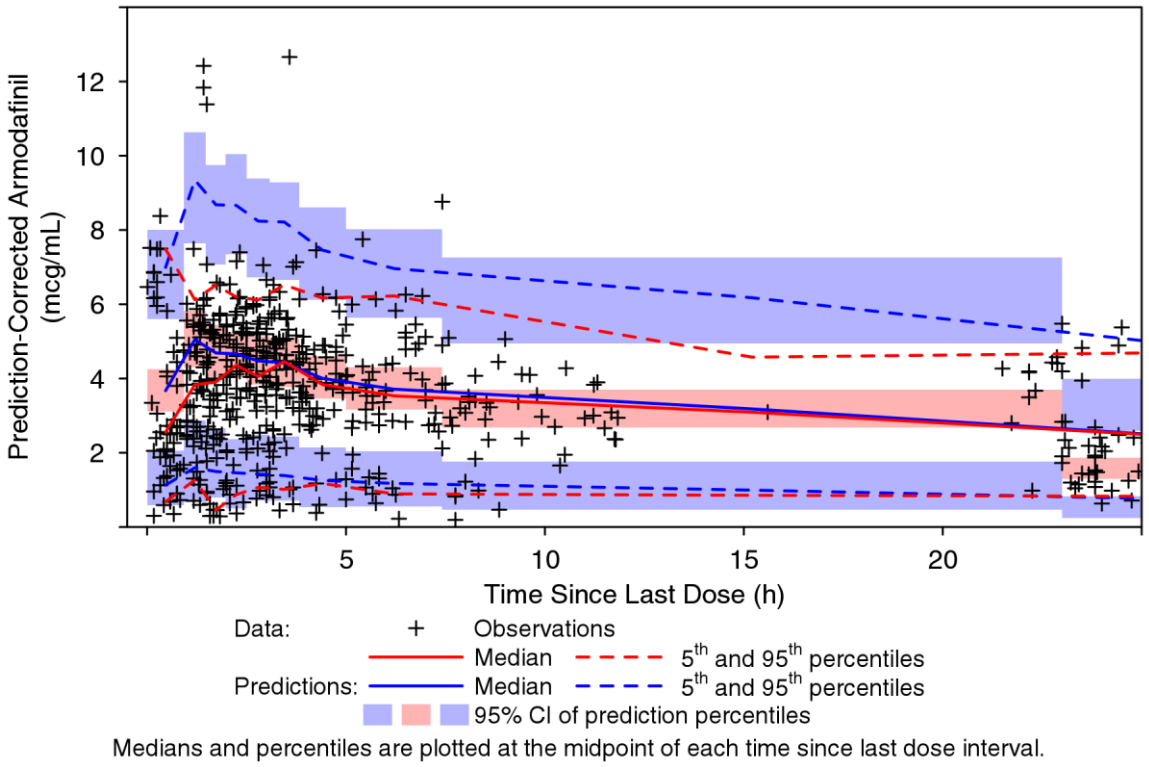


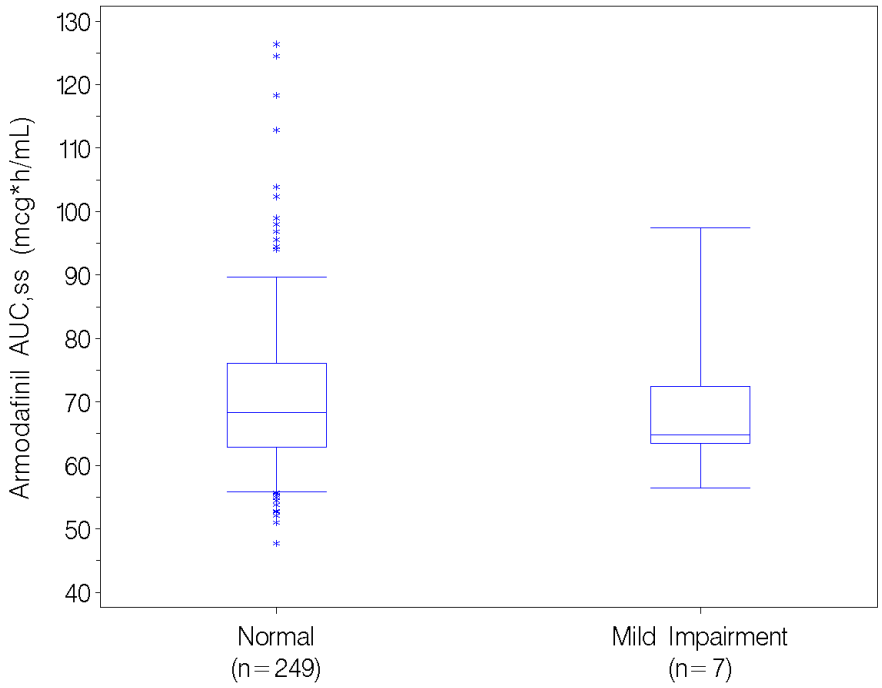
Figure 4. Predicted Armodafinil Steady-State AUC for Patients in Phase 2 and 3 Studies With Normal and Mildly Impaired Liver Function (Panel A) and Renal Function (Panel B)

Boxes represent 25th, 50th, and 75th percentiles; whiskers represent the 5th and 95th percentiles. Asterisks show data points outside this range. The number of subjects is displayed below each box.

AUC_{ss}=area under the concentration-time curve (AUC) at steady state.

Liver function assessed by total bilirubin and aspartate aminotransferase (AST) levels. Normal liver function: total bilirubin and AST ≤ upper limit of normal (ULN); mild liver dysfunction: total bilirubin ≤1.5 ULN, AST >ULN, however AST can be normal or <ULN if total bilirubin in >ULN.

Renal function determined by estimated creatinine clearance (CrCL) based on the Cockcroft and Gault equation. Normal renal function: CrCL ≥90 mL/min; mild renal dysfunction: CrCL 60-89 mL/min; moderate renal dysfunction: CrCL 30-59 mL/min.



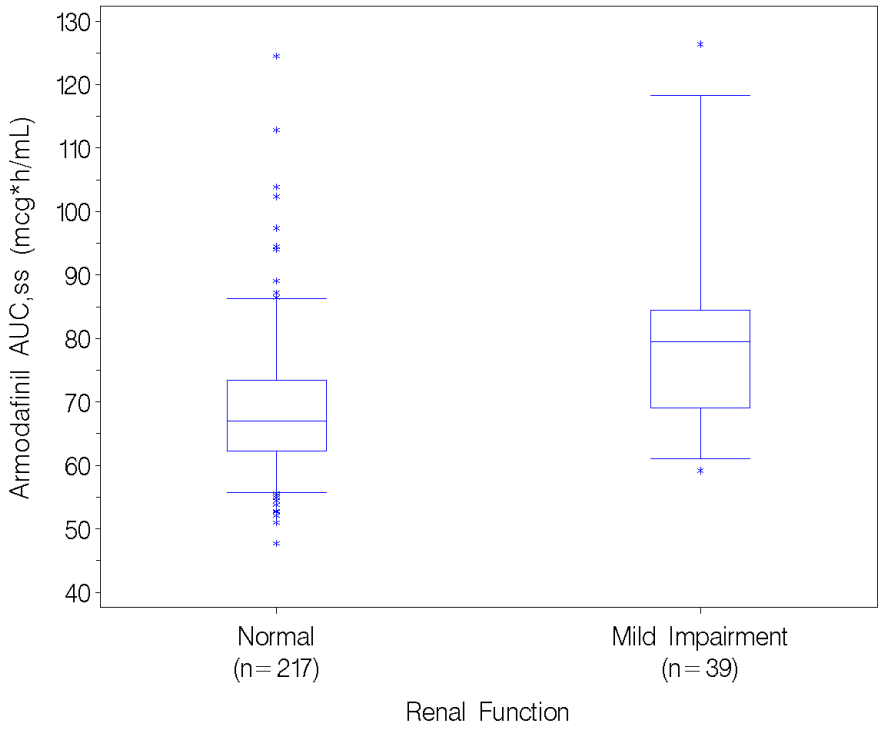


Table 1. Baseline Demographic and Clinical Characteristics of the Data Set Used for Population Pharmacokinetic Modeling

	Phase 1 **n=327**	**Phase 2/3** **n=256**	**Overall** **n=583**
Age, y			
Mean (SD)	32.9 (10.9)	43.0 (11.3)	37.3 (12.1)
Median	31.0	42.5	35.0
Sex, n (%)			
Male	280 (85.6)	116 (45.3)	396 (67.9)
Female	47 (14.4)	140 (54.7)	187 (32.1)
Baseline body weight (kg)			
Mean (SD)	78.70 (11.38)	86.66 (19.90)	82.20 (16.18)
Range	53.2-106.1	49.4-158.1	49.4-158.1
Dose,[a] n (%)			
50 mg	13 (4.0)	1 (0.4)	14 (2.4)
100 mg	12 (3.7)	1 (0.4)	13 (2.2)
150 mg	42 (12.8)	240 (93.8)	282 (48.4)
200 mg	12 (3.7)	13 (5.1)	25 (4.3)
250 mg	224 (68.5)	0 (0.0)	224 (38.4)
300 mg	12 (3.7)	1 (0.4)	13 (2.2)
400 mg	12 (3.7)	0 (0.0)	12 (2.1)
Formulation, n (%)			
Capsule	67 (20.5)	0 (0.0)	67 (11.5)
Tablet	260 (79.5)	256 (100.0)	516 (88.5)

Race, n (%)			
White	199 (60.9)	182 (71.1)	381 (65.4)
Black	102 (31.2)	54 (21.1)	156 (26.8)
Asian	3 (0.9)	4 (1.6)	7 (1.2)
American Indian	1 (0.3)	1 (0.4)	2 (0.3)
Pacific Islander	0 (0.0)	1 (0.4)	1 (0.2)
Other	22 (6.7)	14 (5.5)	36 (6.2)
Liver function,[b] n (%)			
Normal	312 (95.4)	249 (97.3)	561 (96.2)
Mild impairment	14 (4.3)	7 (2.7)	21 (3.6)
Moderate impairment	1 (0.3)	0 (0.0)	1 (0.2)
Renal function,[c] n (%)			
Normal	293 (89.6)	217 (84.8)	510 (87.5)
Mild impairment	33 (10.1)	38 (14.8)	71 (12.2)
Moderate impairment	1 (0.3)	1 (0.4)	2 (0.3)
CYP3A4 Inhibitors, n (%)			
No	327 (100.0)	252 (98.4)	579 (99.3)
Yes	0 (0.0)	4 (1.6)	4 (0.7)
PGP Inducers, n (%)			
No	327 (100.0)	256 (100.0)	583 (100.0)
PGP Inhibitors, n (%)			
No	327 (100.0)	251 (98.0)	578 (99.1)
Yes	0 (0.0)	5 (2.0)	5 (0.9)

[a]Highest dose level administered to each individual was tabulated.

[b]Liver function assessed by total bilirubin and aspartate aminotransferase (AST) levels. Normal liver function: total bilirubin and AST ≤ upper limit of normal (ULN); mild liver dysfunction: total bilirubin ≤1.5 ULN, AST >ULN, however AST can be normal or <ULN if total bilirubin in >ULN; moderate liver dysfunction: total bilirubin >1.5 through 3.0 x ULN and any AST level.

[c]Renal function determined by estimated creatinine clearance (CrCL) based on the Cockcroft and Gault equation. Normal renal function: CrCL ≥90 mL/min; mild renal dysfunction: CrCL 60-89 mL/min; moderate renal dysfunction: CrCL 30-59 mL/min.

Table 2. Parameter Estimates and Standard Errors Obtained From the Final Armodafinil Model

Parameter	**Final Parameter Estimate**		**Interindividual Variability/Residual Variability**	
	Typical value	**%SEM**	**Magnitude**	**%SEM**
k_a (1/h)	3.06	8.65	NE	NA
ALAG1-tab (h)	0.149	20.3	NE	NA
ALAG1-cap (h)	0	FIXED	NE	NA
CL/F (L/h)	2.01	1.38	21.4 %CV	10.1
Weight on CL/F (power)	0.452	13.9		
Vc/F (L)	45.0	1.96	18.9 %CV[a]	30.0
Weight on Vc/F (power)	0.828	7.82		
Female sex on Vc/F (proportional)	0.898	3.99		
F1	0.913	2.38	NE	NA
cov(IIV in Vc/F, IIV in CL/F)[b]	0.0218[a]	24.1	NA	NA
RV phase 1	0.0305[c]	6.78	17.5 %CV	NA
RV phase 2 and 3	0.169[c]	8.93	41.1 %CV	NA

Minimum value of the objective function = 2914.004

[a]The following parameter estimates were found to be highly correlated (r^2 = 0.810): (IIV in Vc/F,cov(IIV in Vc/F, IIV in CL/F)).

[b]The calculated correlation coefficient (r) associated with cov (IIV in Vc/F, IIV in CL/F) was 0.540 with r^2 = 0.292.

[c]Reported estimate is a variance.

ALAG1-cap=absorption lag time following capsule; ALAG1-tab=absorption lag time following tablet; CL/F=apparent clearance; cov=covariance; %CV=coefficient of variation expressed as a percentage; F1=bioavailability of capsule formulation relative to tablet; IIV=interindividual variability; k_a=absorption rate constant; NA=not available; NE=not estimated; RV=residual variability; %SEM=standard error of the mean expressed as a percentage; Vc/F=apparent central volume of distribution.

Table 3. Parameter Estimates and Standard Errors for the Population Pharmacokinetic Models for *R*-Modafinil Acid and for Modafinil Sulfone

	***R*-Modafinil Acid**				**Modafinil Sulfone**			
	Final parameter estimate		**IIV/RV**		**Final parameter estimate**		**IIV/RV**	
Parameter	**Typical value**	**%SEM**	**Magnitude**	**%SEM**	**Typical value**	**%SEM**	**Magnitude**	**%SEM**
k_a (1/h)	0.0431	1.69	23.2 %CV	19.2	0.02379	4.262	35.12 %CV	19.46
ALAG1-tab (h)	0.219	12.0	NE	NE	NE	NE	NE	NE
ALAG1-cap (h)	0	FIXED	NE	NE	NE	NE	NE	NE
CL/F (L/h)	16.7	2.11	40.7 %CV	11.4	6.818	3.266	69.52 %CV	6.022
Vc/F (L)	8.95	7.30	82.7 %CV	12.4	12.35	12.40	NE	NA
Q/F (L/h)	NE	NE	NE	NE	42.63	7.810	NE	NA
Vp/F (L)	NE	NE	NE	NE	94.33	6.213	NE	NA
F1	0.692	5.14	0 %CV	FIXED	0.7426	10.89	NE	NA
RV phase 1	0.0152[3]	8.35	12.3 %CV	NA	0.01164[3]	6.554	10.79 %CV	NA
RV phase 2 and 3	0.109[3]	13.7	33.1 %CV	NA	0.09034[3]	9.602	30.06 %CV	NA
	Minimum value of the objective function = –8224.362				Minimum value of the objective function = –2181.526			

[3]Reported estimate is a variance.
ALAG1-cap=absorption lag time following capsule; ALAG1-tab=absorption lag time following tablet; CL/F=apparent clearance; %CV=coefficient of variation expressed as a percentage; F1=bioavailability of capsule formulation relative to tablet; IIV=interindividual variability; k_a=absorption rate constant; NA=not available; NE=not estimated; Q/F=apparent distributional clearance; RV=residual variability; %SEM=standard error of the mean expressed as a percentage; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution.