Population Pharmacokinetics of Modafinil Film-Coated Tablets in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

Joel S. Owen[1,2]; Ted Grasela[1,3]; Philmore Robertson, Jr.[4]; Mona Darwish[4] — [1]Cognigen Corporation, Buffalo, NY; [2]Auburn University, Auburn, AL; [3]University of Buffalo, Buffalo, NY; [4]Cephalon, Inc., Frazer, PA

ABSTRACT

Purpose: Modafinil is currently being evaluated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. A population pharmacokinetic model was developed describing the pharmacokinetics of modafinil film-coated tablets, including the time course of induction of CL/F, in patients aged 6 to 17 years.

Methods: Data included one Phase 1 (n=24) and four pooled Phase 3 (n=528) studies. Modafinil doses were titrated to a maximum 425 mg/day. Weight-based maximum doses were targeted for patients <30 kg (340 mg) and ≥30 kg (425 mg) in one Phase 3 study. Covariate models were evaluated using forward selection (α=0.05), followed by backward elimination (α=0.01).

Results: A two-compartment model with first-order absorption and elimination best fit the full-profile data from Phase 1. A one-compartment model with induction of CL/F adequately fit the pooled sparse data from Phase 3. Dependence of CL/F on weight was nonlinear, and was greater on Day 1 than after induction. CL/F was induced with a 12-day half-life. V/F was linearly related to weight [V/F (L)=29.2+0.696 (weight-38)]. Elimination half-life for youngest (lighter) patients (age 6) was 6 to 7 hours, and 9 to 10 hours for oldest (heavier) patients (age 17). Effects of BMI, age, dose, gender, and race were not statistically significant predictors of CL/F or V/F. Weight-based dosing consistently provided median exposures of approximately 150 µg·hr/mL at the primary visit of the Phase 3 studies.

Conclusions: The weight-based dosing strategy achieved target exposure of modafinil film-coated tablets in both weight groups. Induction of CL was complete by 7 weeks. After attainment of steady-state, no trend toward changes in pharmacokinetic properties was observed with up to 1 year of dosing.

INTRODUCTION

- Modafinil (SPARLON™ [modafinil] Tablets [C-IV]) is currently under evaluation for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents.
- An overview of the pharmacokinetics of modafinil includes:
  - Rapid rate of absorption, with t_{max} of 2 to 3 hours
  - Serum modafinil concentrations exhibit an apparent mono- or bi-exponential decline from peak, with a $t_{1/2}$ of approximately 8 hours that varies significantly with age ($t_{1/2}$ in adults is approximately 15 hours).
  - A time-dependent reduction in systemic exposure is evident and most likely occurs because of induction of modafinil metabolism.
- An optimal ADHD treatment strategy for modafinil would increase attention during the school day and at home in the evening yet minimize unwanted increased wakefulness in the late evening and night.
- Selection of treatment regimens for the Phase 3 trials was guided by prior pharmacokinetic modeling/simulations of data from Phase 2 studies in children with ADHD. The exposure-response relation with modafinil was assessed following these different dosing regimens.
- The modeling and simulation results suggested that administration of 340 mg and 425 mg in children weighing <30 kg and ≥30 kg, respectively, would achieve a sustained systemic exposure (approximately 150 µg·hr/mL) expected to correlate with a clinically significant effect.
- A population pharmacokinetic analysis was performed with data from one Phase 1 and four Phase 3 studies in children/adolescents with ADHD to characterize the pharmacokinetic profile in children and adolescents and describe the time course of systemic exposure.

OBJECTIVES

- Develop a population pharmacokinetic model for modafinil in order to describe the overall mean population pharmacokinetic profile in children and adolescents (aged 6 to 17 years) with ADHD.
- Identify relevant demographic factors that significantly influence the pharmacokinetic profile of modafinil.
- Estimate individual steady-state systemic exposure measures (AUC) to be used in exploratory pharmacokinetic/pharmacodynamic analyses.

METHODS

Study Design/Data

- Sparse sampling data were pooled from four Phase 3 studies (Studies 2 to 5), and rich sampling data from one Phase 1 study (Study 1) conducted in children/adolescents with ADHD were also included in the analysis (**Figure 1**).

Treatment Regimen

- Initially, 1 oral tablet (85 mg) (Studies 2 to 5) or 2 tablets (170 mg) (Study 1) once daily
- Dose titrated up to 425 mg/day (Study 2, Study 4, and Study 5) or to 340 mg/day (4 tablets) for patients weighing <30 kg or 425 mg/day for patients weighing ≥30 kg (Studies 1 and 3)

Pharmacokinetic Sample Collection

- Study 1 (Phase 1): blood samples collected serially at 0 hour (pre-dose), 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours after dosing
- Studies 2, 3, and 4 (Phase 3): sparse samples collected at the screening visit and at Weeks 1, 2, 3, 5, 7, and 9 (or early termination)
- Study 5 (Phase 3):
  - Samples collected at each monthly visit (or early termination)
  - At the 8-month visit, patients originally participating in Study 1 had blood samples collected in the same manner as for Study 1.

Pharmacostatistical Model

- NONMEM®, Version 5.1.1
- Pharmacokinetic model: various compartmental models
- Interindividual variability determined with the exponential error model
- Residual variability determined with proportional, additive, or additive plus proportional error models

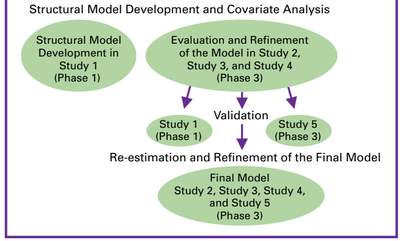
Covariate Analysis

- Diagnostic plots of the change in parameter value (individual Bayesian parameter estimate minus the population mean value) versus each covariate were evaluated to assess the functional form of the relation.
- The potential influence on apparent oral clearance (CL/F) and volume of distribution (V/F) of modafinil of the following covariates was evaluated: age, body mass index (BMI), weight, and gender. The influence of ethnicity, dose/kg, and the mean sulfone metabolite concentration collected on Day 22 was also evaluated as predictors of CL/F.
- Univariate forward selection analyses were performed, followed by stepwise backward elimination.

Statistical Analysis

- Statistical significance: univariate forward-selection analyses: P=.05; backward elimination: P=.001
- Goodness-of-fit of each NONMEM® analysis was assessed by examination of:
  - Scatterplots of measured concentrations, residuals, and weighted residuals versus population predicted concentrations, and weighted residuals versus time since last dose
  - Scatterplots of individual predicted concentrations versus measured concentrations, and individual weighted residuals and absolute individual weighted residuals versus individual predicted concentrations
  - Precision of the parameter estimates as measured by the percent standard error of the mean (%SEM = standard error of the parameter estimate/parameter estimate • 100%)
  - Changes in the estimates of the interindividual and residual variability for the specified model.

Figure 1. Flowchart of Population Pharmacokinetic Model Development Process



Model Validation

- Predictive performance of the Phase 3 model (based on Studies 2 to 4) was assessed using the full-profile data (Study 1) and the sparse data collected following long-term treatment (Study 5).
- Prediction error percent (PE%) [((Observed minus Predicted)/Predicted) • 100] was used as a measure of bias; absolute prediction error |PE|% was used as a measure of precision for individual and population (typical value) predicted modafinil concentrations (Sheiner LB, Beal SL. *J Pharmacokinet Biopharm.* 1981;9:503–512.).
- Distributions of PE% and |PE|% were also evaluated.

RESULTS

Data

- 2453 modafinil concentration values from 528 patients in the Phase 3 studies and 666 concentrations from 24 patients in the Phase 1 study were included in the analysis (**Table 1**).

Table 1. Summary Statistics of Patient Demographics

Characteristic	Phase 1 (n=24)	Pooled Phase 3 Studies[a,b] (n=528)
Age, y, mean (SD)	9.0 (2.3)	10.2 (2.9)
Weight, kg, mean (SD)	32.9 (12.0)	41.7 (16.6)
BMI, kg/m^2, mean (SD)	17.7 (2.8)	19.6 (3.9)
Gender, n (%)		
Male	17 (71)	382 (72)
Female	7 (29)	146 (28)

[a]Note: Study 5 was an open-label continuation of prior studies. 207 of the 330 patients in Study 5 enrolled following participation with active treatment in Studies 2, 3, and 4. The remaining 123 patients were enrolled from the same prior studies but were on placebo. [b]Studies 2, 3, 4, and 5 were pooled.

Pharmacokinetic Model

- A two-compartment model with an absorption lag-time, CL/F described with a power function relation to body weight, and apparent central V/F (V_c/F) modeled as a linear function of body weight provided a reasonable fit to the multiple-dose Phase 1 data.
- A one-compartment model with first-order absorption adequately described the more sparse Phase 3 dataset. The model included a first-order induction process for CL/F with CL/F dependent upon weight. The weight relation was greater at Day 1 versus postinduction. V/F was linearly dependent upon body weight. Parameters of the final model are included in **Table 2**.
- Utilizing a base model, prior to inclusion of induction in CL/F, **Figure 2** shows a systematic underprediction of concentrations in the early weeks.

Figure 2. Distributions of Weighted Residuals From the Base One-Compartment Model With Weight on CL/F and V/F for Studies 2, 3, and 4

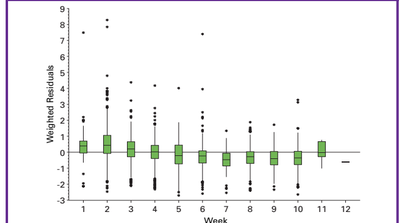
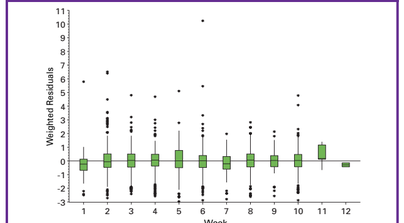


Figure 3. Distributions of Weighted Residuals From the One-Compartment Model With Induction in CL/F for Studies 2, 3, and 4



- The implementation of the induction model largely removed the time dependence observed from the base model, indicating the appropriateness of this model to describe the change in CL/F across time (**Figure 3**).
- A model which included interindividual variability estimated on the induction rate for CL/F (k_{ci}) resulted in no discernible difference in the goodness-of-fit plots, and only a small change in the Minimum Value of the Objective Function (MVOF) (**Figure 4**). Also, median PE% and |PE|% values were slightly greater. Thus, the interindividual variability k_{ci} term was not retained in the model.
- Adequate randomness in the weighted residual values across study day, especially after the long duration of dosing, supports the consistency of the model with Study 5 data, and shows a lack of change in pharmacokinetic properties after extended periods of dosing, even up to 1 year of modafinil once-daily administration (**Figure 5**).

Figure 4. Goodness-of-Fit Plots From the Application of the Prior Phase 3 Model to Study 5

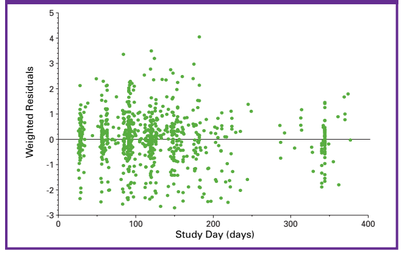
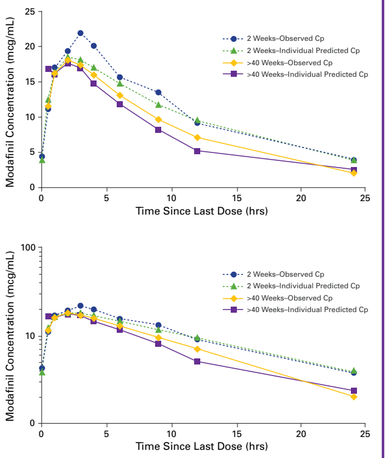


Figure 5. Observed and Individual Predicted Concentration-Time Profiles for a Representative Patient Following 2 Weeks and >40 Weeks of Dosing



- The profiles of a representative patient support the model consistency over 40 weeks.

Table 2. Parameter Estimates and Percent Standard Error of the Mean From the Final One-Compartment Model Estimated in the Pooled Phase 3 Data From Studies 2, 3, 4, and 5

Parameter	Final Parameter Estimate: Population Mean	Final Parameter Estimate: % SEM	Magnitude of Interindividual Variability (%CV): Final Estimate	Magnitude of Interindividual Variability (%CV): % SEM
k_a (1/hr)	1.29	12.5	NE	NA
Induced CL/F (L/hr)	2.75	2.0	15.9	17.5
Exponent of weight on induced CL/F	0.401	410.9		
CL/F intercept (L/hr)	1.31	11.8		
Exponent of weight on CL/F intercept	0.849	25.0		
Rate of induction (1/day)	0.056	15.6	NE	NA
V/F (L)	29.2	4.0	30.5	19.1
Slope of weight on V (L/kg)	0.696	13.7		
Residual variability (%CV)	33.9	5.7	NA	NA
Minimum value of the objective function = 8002.877				

NE = not estimated; NA = not applicable.

The models describing the apparent oral clearance and apparent volume of distribution are provided in Equation 1 through Equation 4 below:

$$CL_{ij} = 2.75 \cdot (Weight_i/38)^{0.401} \quad (1)$$

$$CL_{Pj} = 1.31 \cdot (Weight_i/38)^{0.849} \quad (2)$$

$$TVCL_i\ (L/hr) = CL_{ij} - (CL_{ij} - CL_{Pj}) \cdot e^{0.056t} \quad (3)$$

$$TVV_i\ (L) = 29.2 + 0.696 \cdot (Weight_i - 38) \quad (4)$$

Where:

CL_{ij} = the induced value of CL/F (L/hr) for the j^{th} patient;

CL_{Pj} = the intercept of the induction function (L/hr) for the j^{th} patient;

TVX_i = the typical value of the X parameter (CL or V) for the j^{th} patient;

$Weight_i$ = the weight (kg) of the j^{th} patient (centered about a median weight of 38 kg); and

t = time on therapy (days).

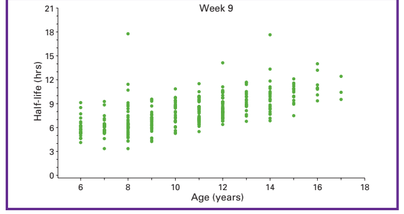
- As with the final parameter estimates, prediction errors and absolute prediction errors for the typical value and individual predictions are essentially unchanged from those of the model development Phase 3 dataset (Studies 2 to 4) (**Table 3**).

Table 3. Prediction Errors for the Final Model in the Pooled Phase 3 Dataset

Prediction error (%) based on typical value predictions	
Median	-0.15
75th percentile	23.50
Absolute prediction error (%) based on typical value predictions	
Median	18.92
75th percentile	35.03
Prediction error (%) based on individual Bayesian value predictions	
Median	0.28
75th percentile	18.86
Absolute prediction error (%) based on individual Bayesian value predictions	
Median	14.80
75th percentile	28.44

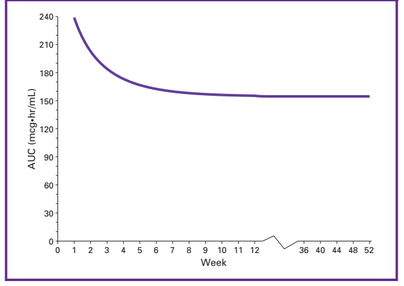
- The use of half-life allowed for the evaluation of the effect of age on the pharmacokinetics independent of weight (**Figure 6**).

Figure 6. Estimated Half-Life of Modafinil Versus Patient Age



- The general trend is that both ends of the age spectrum seem to show little relation with age, and there is a shift which occurs somewhere between 9 and 11 years of age where the half-life increases to the higher level. This finding suggests that, as children age through adolescence and into young adulthood, their predicted pharmacokinetic disposition of modafinil becomes more similar to that of adults (Cephalon, Inc., PROVIGIL® Investigator's Brochure. January 2004).
- The estimated induction half-life is 12.3 days (**Figure 7**).

Figure 7. Model-Predicted AUC for a 38 kg Patient Versus Week of Treatment



CONCLUSIONS

- The empirical model for induction suggests that clearance increases over 6 to 7 weeks with an induction half-life of 12 days. These results suggest that patients are at steady-state at the time of their evaluation.
- Once steady-state CL/F is reached, the pharmacokinetic properties of modafinil do not appear to change after prolonged dosing of up to 1 year.
- The main factors responsible for the difference in pharmacokinetics in children and adolescents are age and weight, with no additional correlation to sex, race, or other demographic factors.
- Body weight was found to be significantly related to both the apparent oral clearance and the apparent volume of distribution of modafinil. Volume was found to increase linearly with weight, while the relation between clearance and weight was a power function which also increased with increasing weight up to around 30 kg, after which clearance was much more constant with increasing weight.
- The estimated half-life for the youngest patients (age 6) studied in this analysis is around 6 to 7 hours and the half-life for the oldest patients (age 7) is around 9 to 10 hours. This shift in half-life appears to occur between 9 and 11 years of age.
- The presented population pharmacokinetic modeling process and Bayesian post hoc analyses provide support for the appropriateness of the dosing decisions for the use of modafinil in children and adolescents with ADHD. In addition, the estimation of systemic exposure in patients with sparse sample collection will allow for the evaluation of exposure-response relations.
- Weight-adjusted doses (340 mg of modafinil in patients weighing <30 kg and 425 mg of modafinil in patients weighing ≥30 kg) consistently achieved exposures within the target range (approximately 150 µg·h/mL).

Presented at the American Association of Pharmaceutical Scientists Annual Meeting and Exposition; November 6–10, 2005; Nashville, TN.

Sponsored by Cephalon, Inc., Frazer, PA.