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Modeling and Simulation of Orlistat to Predict Weight Loss and Weight Maintenance in Obesity Patients

Kiyohiko Nakai1,*, Russell Wada2, Satofumi Iida1, Takehiko Kawanishi1 and Yoshiaki Matsumoto3

1Clinical Research Planning Department, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan
2Quantitative Solutions, Inc., CA, USA
3School of Pharmacy, Nihon University, Chiba, Japan

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Summary: Orlistat is used clinically worldwide as an anti-obesity drug. It is a chemically synthesized hydrogenated derivative of lipstatin and is an inhibitor of gastric and pancreatic lipases. It has been found to reduce the absorption of dietary fat in the gastrointestinal tract. Modeling and simulation based on pharmacokinetic/pharmacodynamic analysis is becoming increasingly used in the design of clinical trials to assure that the trials are of high quality and are conducted efficiently. We developed a clinical trial simulation model for orlistat based on Phase III clinical study data. This innovative weight loss model includes the relationships between orlistat dose, changes in fecal fat excretion, and weight loss, and also incorporates a dropout function. The model guided the dose-finding strategy and allowed simulation of long-term clinical outcomes of orlistat.

Keywords: orlistat; Xenical; modeling and simulation; weight loss model; population pharmacodynamics; obesity

Introduction

The rising prevalence of obesity is evident worldwide. Obesity is associated with numerous health problems, including diabetes mellitus, hyperlipidemia, atherosclerotic disease, sleep apnea, gall bladder disease, and some types of cancer.1) Obesity is also clearly established as a major risk factor for cardiovascular disease.2) A contributing factor to obesity is an excessive intake of dietary fat.

Orlistat is clinically used worldwide as an anti-obesity drug. It is a chemically synthesized hydrogenated derivative of lipstatin and is an inhibitor of gastric and pancreatic lipases. It has been found to reduce the absorption of dietary fat in the gastrointestinal tract. When administered with fat-containing foods, orlistat partially inhibits the hydrolysis of triglycerides and free fatty acids. This effect can be measured using 24-h fecal fat excretion as a representative pharmacodynamic parameter.3)

Venables and Ripley reported a simple weight loss function8) and the U.S. Food and Drug Administration (FDA) released an obesity model in their Disease-Specific Model Library.9) However, no examples of these models applied to any anti-obesity drug have been reported yet. We applied Venables and Ripley’s simple weight loss function to orlistat’s clinical trial data to create an innovative weight loss model for use in clinical trial simulations. This model used 24-h fecal fat excretion as a pharmacodynamic parameter and incorporated a dropout function constructed by a Bayesian approach. A trial simulation based on this model was able to select a statistically optimal clinical dose that would ensure both the efficacy and safety of orlistat.

Materials and Methods

Data: The body weight data were extracted from the publication of Rössner et al.10) by using Engauge Digitizer 4.1 (open-source digitizing software developed by Mark Mitchell) and used to create a trial simulation model. In the clinical study by Rössner et al., subjects had a 4-week diet run-in and then received 0, 60, or 120 mg orlistat three times a day over a period of 2 years. During the 4-week diet run-in and over the first year, patients were given a...
nutrionally balanced diet that was designed to cause a 600-kcal daily energy deficit and to supply about 30% of energy as fat. During the second year of the trial, all subjects continued on the same treatment, with the diet adjusted as follows: for those subjects who had lost ≥3 kg between Week 40 and Week 52, the daily caloric intake was prescribed at a level equivalent to the estimated total daily energy expenditure minus 10% kcal/day, whereas those subjects who lost <3 kg during this period were considered relatively weight stable and the first year diet was continued.

Model: The scheme of the weight loss model which we developed is shown in Figure 1. Both the weight loss and regain are described as first-order functions because the energy expenditure decreases if the body weight decreases. The FDA suggests first-order functions to describe both the weight loss and regain model. Net weight loss for patients on the placebo was modeled as the sum of two opposing forces of equal magnitude but with different onset times due to the differences in the dietary condition between the first and the second year in the clinical study of Rössner et al. The equations are summarized below.

**Weight Loss functions for placebo patients**

\[
\text{Weight Loss} (t) = E_{\text{on}} \times [1 - \exp(-k_{\text{on}} \times (t - T_{\text{start}}))] \quad (1)
\]

\[
\text{Weight Regain} (t) = E_{\text{off}} \times [1 - \exp(-k_{\text{off}} \times (t - T_{\text{start}}))] \quad (2)
\]

\[
\text{Net Weight Loss} (t) = \text{Weight Loss} (t) - \text{Weight Regain} (t) \quad (3)
\]

where Weight Loss, Weight Regain, and Net Weight Loss are defined respectively as the weight loss, weight regain, and net weight change from the baseline at time \( t \). \( E_{\text{on}} \) and \( E_{\text{off}} \) are the steady-state magnitudes of weight loss and weight regain. The rate constants to achieve steady state are \( k_{\text{on}} \) and \( k_{\text{off}} \). The time at which diet therapy started following the run-in phase is \( T_{\text{start}} \).

In differential equation form, the weight loss equations [Eqs. (1) and (2)] can be written as follows:

\[
\frac{d(\text{WL})}{dt} = -k_{\text{on}} \times \text{WL} + k_{\text{on}} \times E_{\text{on}} \quad (4)
\]

\[
\frac{d(\text{WR})}{dt} = -k_{\text{off}} \times \text{WR} + k_{\text{off}} \times E_{\text{off}} \quad (5)
\]

**Weight Loss function for orlistat-treated patients**

Equation (3) was modified as follows [Eq. (6)] to incorporate a linear effect of fat excretion:

\[
\text{Net Weight Loss} = \text{Weight Loss} - \text{Weight Regain} + \text{Orlistat Effect} \quad (6)
\]

\[
\text{Orlistat Effect} = \text{WtCh} \times [1 - \exp(-k_{\text{onset}} \times (t - T_{\text{start}}))] \quad (7)
\]

**Fecal Fat Excretion function**

\[
\text{WtCh} = \text{Slope} \times \text{Fat Excretion} \quad (8)
\]

\[
\text{Fat Excretion} = E_{0} + E_{\text{max}} \times D/(E_{\text{max}} + D) \quad (9)
\]

In the equations above, WtCh is the maximum treatment effect by orlistat. The rate of onset of orlistat is \( k_{\text{onset}} \). The slope of the linear relationship between fat excretion and weight change is Slope. Finally, the value of Fat Excretion for subjects on placebo is \( E_{0} \), and the value of Fat Excretion for subjects on orlistat is calculated according to the \( E_{\text{max}} \) model using the parameters of Zhi et al., which were \( E_{0} (\%) = 5.29 \pm 1.05 \) (mean ± SE), \( E_{\text{max}} (\%) = 27.9 \pm 2.9 \), and \( ED_{50} \) (mg) = 98.1 ± 34.4. In Eq. (9), \( D \) represents the dose of orlistat (mg).

In addition, a dropout model was incorporated into the analysis in order to account for the dropouts in the clinical study of Rössner et al. This allows us to simulate dropouts and Last Observation Carried Forward (LOCF) analysis in order to calibrate our model against the data of Rössner et al., which included LOCF analysis. In the Rössner’s study, the reported dropout data was 35% at Week 52 and 44% at Week 104. Thus, a piecewise-constant dropout model was assumed, where patients drop out at one fixed hazard rate during the first year, and at another rate during the second year. The hazard model equations are described below.

**Dropout function**

\[
h(t) = h_{1} \text{ if Wk 0 < t ≤ Wk 52} \quad (10)
\]

\[
h(t) = h_{2} \text{ if Wk 52 < t ≤ Wk 104} \quad (10)
\]

\[
\text{Prob (in study at time } t_{1} \text{ | in study at time } t_{1}) = 1 - \exp(-h \times (t_{2} - t_{1})) \quad (11)
\]

\[
\text{Prob (in study at Wk 104 | in study at Wk 52) = 1} - \exp(-h_{2} \times 52) \quad (12)
\]

\[
\text{Prob (in study at Wk 52 in study at Wk 52)} = 1 - \exp(-h_{1} \times 52) \quad (13)
\]

Using Eqs. (12) and (13), the hazard rates \( h_{1} \) and \( h_{2} \) were set to 0.00825 wk\(^{-1}\) and 0.00278 wk\(^{-1}\) respectively to account for the observed dropouts of 35% and 44%. For this model, an assumption was made that dropouts were not correlated to efficacy or adverse events because the main reason for premature withdrawal was treatment refusal.2)

**Software:** S-PLUS 6.0 Release 2 (Insightful Co., Seattle, WA, USA) was used to fit the model through a least-squares optimization algorithm. Pharsight Trial Simulator Version 2.1.1 (Pharsight Co., Cary, NC, USA) was used to allow for testing of analytical questions for future clinical trial designs.

**Results**

**Modeling:** First, the placebo data were extracted from the publication by Rössner et al.\(^2\) The data were in the form of time in weeks and response (percentage change in weight from baseline). The placebo response was biphasic. Weight loss was immediate, with a response due to diet after the run-in period. The weight loss effect occurred primarily in the first year, and maximum weight loss occurred at Week 36. Weight then began to be regained and continued to increase through the end of the second year. About half of the maximum lost weight was regained by Week 104. These observations match data from another large orlistat study.\(^1\)

In nonlinear regression analysis to determine the parameters \( k_{\text{on}}, k_{\text{off}}, E_{\text{on}}, \) and \( E_{\text{off}} \) the magnitudes of response could not be reliably estimated, because the offset of weight loss occurred before the maximum onset could be observed. We attempted to fix the parameter values of both \( E_{\text{on}} \) and \( E_{\text{off}} \) with the fixed \( h_{1} \) (0.00825/week) and \( h_{2} \) (0.00278/week). Sensitivity analysis was performed to estimate the fixed values for \( E_{\text{on}} \) and \( E_{\text{off}} \). Ten, 15, 20, 25, 30, 35...
and 40% were tested in this sensitivity analysis as $E_{on}$ and $E_{off}$. The best fit was observed at 25% (data not shown) and the fitting was not improved by increasing the fixed value over 25%; therefore, we decided to fix both $E_{on}$ and $E_{off}$ at 25%. Parameter values of the placebo weight loss model are summarized in Table 1. A comparison of the model prediction and the observed data is depicted in Figure 2. The model without the dropout function predicted a response at Week 36 that was greater than the observed value. In comparison, the prediction of the model with the dropout function showed good agreement with the observed weight loss at all time points. This result showed that the dropout function was necessary for this placebo weight loss model.

Next, to estimate the effect of treatment by orlistat, the relationship between the change in fecal fat excretion (percentage relative to ingested fat) that was induced by orlistat dose (fat excretion) and weight loss was incorporated into the placebo weight loss model described above. Fat excretion was not reported in the clinical study of Rössner et al.; therefore, the data for this analysis originated from two different studies, one study was reported by Zhi et al.11 for fat excretion. Fat excretion after orlistat administration was used as a marker for the primary endpoint for a human bioequivalent study;13 this shows that fat excretion is a robust marker that seems to be valid for comparison between different studies. Fat excretion was calculated according to the method of Zhi et al.11 when orlistat was administered at doses of 0, 60, or 120 mg three times a day. The magnitude of weight loss at Week 36 from Rössner et al.2) was approximated. Fat excretion against weight loss was plotted, and it was noticed that the relationship was linear (Fig. 3). The value of Slope was estimated by running the S-PLUS script and the results were visually compared with the response data from Rössner et al.2) The parameter values are summarized in Table 1, and the comparison of the model predictions with the data are summarized in Figure 4. At doses of 0, 60, and 120 mg three times a day, the predicted values based on our weight loss model were very similar to the observed values. Therefore, this weight loss model was considered to be able to predict weight loss by orlistat treatment with high accuracy.

Finally, the inter-subject variability was incorporated into the model by adding correlated variability to both $E_{on}$ and $E_{off}$. Regarding the inter-subject variability, only $E_{on}$ and $E_{off}$ were assessed because the magnitude of inter-subject variability of weight loss seemed to be similar between the placebo and orlistat treatment groups in the clinical study of Rössner et al.2) and $E_{on}$

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### Table 1. Estimated parameters for the weight loss model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Estimate</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2} k_{on}$</td>
<td>weeks</td>
<td>18.2</td>
<td>[14.3, 23.2]</td>
</tr>
<tr>
<td>$t_{1/2} k_{off}$</td>
<td>weeks</td>
<td>42.2</td>
<td>[33.0, 53.3]</td>
</tr>
<tr>
<td>$E_{on}$</td>
<td>%</td>
<td>25$^b$</td>
<td>—</td>
</tr>
<tr>
<td>$E_{off}$</td>
<td>%</td>
<td>25$^b$</td>
<td>—</td>
</tr>
<tr>
<td>$h_1$</td>
<td>1/week</td>
<td>0.00825$^a$</td>
<td>—</td>
</tr>
<tr>
<td>$h_2$</td>
<td>1/week</td>
<td>0.00278$^a$</td>
<td>—</td>
</tr>
<tr>
<td>$t_{1/2} k_{onset}$</td>
<td>weeks</td>
<td>18.2$^c$</td>
<td>—</td>
</tr>
<tr>
<td>Slope</td>
<td>—</td>
<td>—0.2</td>
<td>—</td>
</tr>
<tr>
<td>$E_{on}/E_{off}$ SD</td>
<td>%</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>$E_{on}/E_{off}$ Corr.</td>
<td>—</td>
<td>0.85</td>
<td>—</td>
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</tbody>
</table>

$^a$2SE in both directions, $^b$Fixed, $^c$Set to equal $k_{on}$.
and $E_{\text{off}}$ are independent from drug effect. We tried to match the magnitude of inter-subject variability observed at Week 36 and the observation that variability stayed relatively constant thereafter. When uncorrelated variability was added to both $E_{\text{on}}$ and $E_{\text{off}}$ the total variability increased up to Week 104. On the other hand, when completely correlated variability was added, the total variability reached a maximum at about Week 36 to Week 52, then decreased towards zero at Week 104. SE values are approximated as 0.6% at all time points after Week 36, and increasing linearly to 0.6% over the first 36 weeks. The variability parameter values are summarized in Table 1.

**Simulation:** The obtained model was implemented in the Pharsight Trial Simulator (TS2). First, the weight loss model functions, which were developed as described above, were translated faithfully in TS2, and the parameter values (Table 1) were input into TS2. Then, the weight loss data at doses of 0 (placebo), 60, 120, and 240 mg orlistat three times a day were simulated from time 0 to 2 years. This simulation was done by extrapolating beyond the dose range used to develop the model (up to 120 mg). The simulations were run with 100 patients per arm, and the number of replications was 10 simulated trials.

Mean percent change from baseline per arm at 1-year was compared with other arms via a t-test. The LOCF method of analysis was used to handle dropouts. Table 2 shows the p-values for the 10 trial replications.

**Discussion**

The prevalence of obesity is rising and it is associated with numerous health problems. Orlistat inhibits gastric and pancreatic lipases and reduces the absorption of dietary fat in the gastrointestinal tract. Robust prediction of weight loss makes it possible to determine the most appropriate orlistat regimen.

In this study, we developed a trial simulation model based on data from a large Phase III trial with orlistat. In order to adequately incorporate the effect of orlistat into the simple weight loss function, the dose–response relationship to fat excretion—which is a sensitive pharmacodynamic marker of orlistat—was incorporated into this function. This model includes several assumptions and limitations: (i) Energy expenditure is reported to be decreased by a decrease in body weight, thus, both the weight loss and regain were assumed to be first-order functions. (ii) In the clinical study of orlistat from which the weight loss data was taken for this modeling, the study period was 2 years; however, the dietary conditions in the first and the second year were different. To describe this difference, net weight loss was modeled as the sum of two opposing forces of equal magnitude but with different onset times. (iii) Because the data for fat excretion were not reported in that clinical study, those from a different study were used for this modeling. Di Marco et al. used the fat excretion after orlistat administration as the marker for the primary endpoint for a human bioequivalence study, so fat excretion appears to be a robust marker that is valid for comparison between different studies. (iv) From the figure of the time–weight-loss profile reported by Rössner et al., the inter-subject variability of body weight seemed to be similar between the placebo group and the orlistat treatment group. Hence, with respect to the variability of model parameters, only $E_{\text{on}}$ and $E_{\text{off}}$, which were independent of the effect of orlistat, were assessed. Eventually, this model was able to capture the onset and offset of orlistat’s effect on weight loss, as well as the variability profile over time.

Venables and Ripley reported a simple weight loss function that considered only weight change with respect to time, and did not incorporate the function of drug amount. The FDA released an obesity model in its Disease-Specific Model Library. That model was a placebo model and also did not include the treatment effect of drugs. Neither the function nor the model above had yet been applied to any obesity drugs. As described above, we applied the simple weight loss function to orlistat to create an innovative weight loss model for use in a clinical trial simulation by using 24-h fecal fat excretion as a pharmacodynamic parameter and incorporating a dropout function constructed by a Bayesian approach.

Danhof et al. reported that the ultimate goal of PK/PD modeling was the prediction of long-term clinical outcomes. To approach this goal, our PD model included not only pharmacodynamic aspects (i.e., the relationships between orlistat dose, change in fecal fat excretion, and weight loss) but also a dropout function, which needs to be incorporated into PD models of drugs that show a large dropout rate such as orlistat. To the best of our knowledge, this is the first such PD model for weight loss with anti-obesity drugs. By running the model in the TS2 trial simulator, we were able to predict the weight loss profile for several doses of orlistat. We concluded that it should be possible to detect a statistical difference from placebo at 60, 120, and 240 mg orlistat three times a day with adequate statistical power.

To enhance the reliability of this trial simulation model, it should be applied to other clinical trials of orlistat or other anti-obesity drugs. Moreover, an actual clinical study based on results of the trial simulation should be conducted, and the model confirmed by comparing the simulated values prospectively with the observed values.

Overall, we developed a clinical trial simulation model for orlistat with an innovative weight loss model. Our model accounted for the relationships between orlistat dose, change in fecal fat excretion, and weight loss, and also included a dropout function. It provided a dose-finding strategy and allowed the simulation of the long-term clinical outcomes of orlistat.

**References**


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Table 2. Comparison of treatment groups with 100 patients per arm using a t-test

<table>
<thead>
<tr>
<th>Replicate number</th>
<th>120 mg vs. 240 mg</th>
<th>120 mg vs. 60 mg</th>
<th>120 mg vs. Placebo</th>
<th>240 mg vs. 60 mg</th>
<th>240 mg vs. Placebo</th>
<th>60 mg vs. Placebo</th>
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<tr>
<td>1</td>
<td>0.373</td>
<td>0.259</td>
<td>0.020</td>
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<td>0.003</td>
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<tr>
<td>2</td>
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<td>0.069</td>
<td>0.011</td>
<td>0.398</td>
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<tr>
<td>3</td>
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<td>0.004</td>
<td>0.351</td>
<td>0.000</td>
<td>0.012</td>
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<tr>
<td>4</td>
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<td>0.642</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>5</td>
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<td>0.530</td>
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Statistical power (%): 10% 10% 90% 20% 100% 70%

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