Published in final edited form as:

J Biopharm Stat. 2016 ; 26(6): 1025–1039. doi:10.1080/10543406.2016.1226326.

A Hierarchical Bayesian Approach for Combining Pharmacokinetic/Pharmacodynamic Modeling and Phase IIa Trial Design in Orphan Drugs: Treating Adrenoleukodystrophy with Lorenzo's Oil

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Abstract

X-linked adrenoleukodystrophy (X-ALD) is a rare, progressive and typically fatal neurodegenerative disease. Lorenzo's Oil (LO) is one of the few X-ALD treatments available, but little has been done to establish its clinical efficacy or indications for its use. In this paper, we analyze data on 116 male asymptomatic pediatric patients who were administered LO. We offer a hierarchical Bayesian statistical approach to understanding LO pharmacokinetics (PK) and pharmacodynamics (PD) resulting from an accumulation of very long chain fatty acids. We experiment with individual- and observational-level errors, various choices of prior distributions, and deal with the limitation of having just one observation per administration of the drug, as opposed to the more usual multiple observations per administration. We link LO dose to the plasma erucic acid concentrations by PK modeling, and then link this concentration to a biomarker (C26, a very long chain fatty acid) by PD modeling. Next, we design a Bayesian Phase IIa study to estimate precisely what improvements in the biomarker can arise from various LO doses, while simultaneously modeling a binary toxicity endpoint. Our Bayesian adaptive algorithm emerges as reasonably robust and efficient while still retaining good classical (frequentist) operating characteristics. Future work looks toward using the results of this trial to design a Phase III study linking LO dose to actual improvements in health status, as measured by the appearance of brain lesions observed via magnetic resonance imaging.

Keywords

Adaptive clinical trial design; Bayesian hierarchical modeling; Lorenzo's Oil; Orphan disease; Pediatric drug development; PK/PD modeling; X-ALD

1 Introduction

X-linked adrenoleukodystrophy (X-ALD) is a rare (incidence of 1:17,000¹⁸), progressive neurodegenerative disease which affects cerebral white matter, peripheral nerves, adrenal cortex and testis¹⁶. It is caused by mutation in the *ABCD1* gene that codes for a peroxisomal transporter²¹. Affected males show a spectrum of phenotypes, including the rapidly progressing childhood cerebral form (CCALD)^{4,10}. Biochemically the disease is characterized by elevated plasma and tissue levels of the saturated very long-chain fatty acids (SVLCFAs) C24:0 and C26:0¹⁷.

To this day, plasma SVLCFA analysis remains the most frequently used diagnostic test for X-ALD in male patients. Interest typically focus on concentration of C26:0, the ratio of C24:0/C22:0, and the ratio C26:0/C22:0¹⁴. It is known that hexacosanoic acid (C26:0) alters physiological properties of membranes²³, and higher levels of C26:0 have been found in normal-appearing white matter of patients with the childhood cerebral phenotype than in those with adrenomyeloneuropathy (AMN)²³. Thus, therapies aiming at lowering SVLCFAs in the central nervous system have been adopted².

Lorenzo's oil (LO), a 4:1 mixture of triacylglycerol forms of oleic acid and erucic acid, is one of the few disease-modifying X-ALD treatments available. It has been shown that administering this oil with moderate reduction of dietary fat normalizes or significantly lowers the levels of SVLCFAs in plasma³. However, little has been done to establish its clinical efficacy or indications for its use². Although several open-label clinical trials (i.e., trials where both the researchers and participants knew which treatment was being administered) were unable to establish the clinical benefit of LO in patients with CCALD^{1,26}, other studies have indicated that LO *can* prevent CCALD when treatment is administered prior to cerebral involvement^{20,19}, and there are also indications of a benefit in the AMN subpopulation¹¹. In toto, however, results are inconclusive. In addition to the problems created by open-label study designs, no pharmacological rationale for LO dosing was available in any of the aforementioned studies.

Bayesian statistical methods easily facilitate adaptive dose-finding and other early-phase studies, permit formal borrowing of strength from other information sources including expert opinion and previous data, and yield probabilistic inference regarding model quantities of interest. In this paper, we develop a hierarchical Bayesian statistical approach for understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of LO and, subsequently, use our findings to design an adaptive Phase IIa dose-finding study of LO that trades off a continuous efficacy and a binary safety endpoint. The difficulty in procuring subjects for clinical trials of rare diseases like X-ALD further motivates Bayesian methods, since they help us efficiently use all pre-existing and accumulating trial data to which we have access.

The remainder of our paper is as follows. In Section 2 we discuss how LO is used in PK and PD analysis. In Section 3 we describe our dataset. We will then describe our statistical PK and PD models in Section 4, and present the results we obtain in from our dataset. Section 5 provides two designs for an adaptive Phase IIa trial seeking to use both efficacy and toxicity data in determining the best treatment regime, and simulates the operating characteristics (power and Type I error) for both. Finally, Section 6 discusses our findings and provides directions for future research.

2 Conceptual Model Framework

Since it is established that LO lowers the level of SVLCFAs, the amount of C26:0 in the plasma can be used as an indicator of the effect of LO on the patient's cerebral white matter. Hence, our aim here is to model the effect of LO administration on the change in C26:0 plasma concentration while adjusting for various covariates specific to individuals and observations, such as the dose of LO administered, the weight of the patient, etc.

LO is a 4:1 mixture of oleic and erucic acid, and therefore administration of LO will increase the levels of erucic acid in plasma. Several papers have shown that erucic acid can normalize C26:0 plasma levels within 4–6 weeks^{22,15}. Hence our broad action plan for modeling can be summarized as:

$$LO \xrightarrow{PK} ErucicAcidConcentration \xrightarrow{PD} changeinC26level \rightarrow BrainMRIabnormalities$$

In this diagram, the first link is captured by the PK modeling, while the second involves PD modeling, both of which we discuss below. Our Section 5 Phase IIa design will permit us to hone in on a rationally-derived LO dose that accounts for both toxicity and efficacy (where in this phase, the latter term refers not to clinical efficacy, but to improvement in biomarker response). The final link in the diagram will require design of a Phase III clinical trial of clinical efficacy, about which we briefly speculate in Section 6.

3 Data Description

We had access to data on 130 subjects screened for this study at the John Hopkins Research Hospital from 2000 to 2014 under an expanded access trial (ClinicalTrials.gov, NCT02233257). Diagnosis of X-ALD was confirmed by plasma SVLFCA assay. Fourteen subjects with incomplete data (i.e., missing either dose, or erucic acid, and/or C26:0 concentrations) were excluded from the study, resulting in $n = 116$ subjects for analysis. These asymptomatic X-ALD children were followed until they developed any brain MRI abnormality. Written informed consent was typically from the parents or guardians, with assent from the subjects as appropriate.

All participants received a daily dose of 2–3mg/kg of LO, a dose calculated to provide roughly 20% of caloric intake. Supplements of essential fatty acids provided another 5% of total caloric need. Fat intake from other sources was limited to 10 to 15% of total calories. When there was a clinically significant reduction of platelet counts, LO was halted and

replaced by glyceryl trioleate at the same dosage. Once the platelet counts returned to normal, LO was restarted at a lower dose and increased gradually.

The study design involved collection of blood samples at baseline as well as every month for the first 6 months, followed by collection at 3- to 6-month intervals after LO administration. Subjects were asked to fast overnight and withhold their morning LO dose until blood collection in the morning. The samples were processed and plasma was analyzed to obtain a fatty acid profile (FAP) for 70 fatty acids including C26:0 and erucic acid. From the 104 subjects, 2384 paired C26:0 and erucic acid concentrations were available to develop the PD model. Hence, we have multiple observations per patient, but only one observation per patient per visit.

Usually in pharmacokinetic studies, we have data from samples collected at various time points after the drug was administered, as shown in Figure 1(a), which helps us derive a detailed picture of how a single dose of the drug behaves after it was administered. This makes tasks such as deriving the half life of the drug, required for rational drug dosing strategies, straightforward. In our case we have only one observation per LO intake, i.e., a situation like that pictured in Figure 1(b). With this less rich type of data, we must make more heroic assumptions in order to estimate the drug's half life.

4 Hierarchical Models for PK/PD Data

4.1 The Pharmacokinetic Model

Let Y denote the erucic acid concentration, and Z be the C26:0 level obtained from the FAP. We also have each patient's weight in kg, denoted here as wt , taken at each reading. For any drug, the average steady state concentration (css) can be written as the dosing rate divided by the *clearance*, which is the volume of the blood cleared totally from the drug (in our case, erucic acid) per unit time⁶. Our erucic acid observations (which we assume are at steady state) are actually comprised of two parts: the *endogenous* part (i.e., erucic acid produced by the body itself) and the *exogenous* part (erucic acid coming from LO administration). Hence for the j th observation on the i th patient, where $i = 1, \dots, 116$ and $j = 1, 2, \dots, n_i$, we model clearance using allometric scaling as

$$clearance_erucic_{ij} = \theta_1 \left(\frac{weight_{ij}}{70} \right)^{\frac{3}{4}}. \quad (1)$$

Since the dose was given in terms of ml, we need to multiply it by the density of erucic acid, which is 0.860 g/ml (and therefore 0.86 * 1000 mg/ml). Thus

$$Rate_erucic_{ij} = \frac{0.86 \times 1000 \times Dose}{24}.$$

Next let $cssex_{ij} = \text{Rate_erucic}_{ij} / \text{clearance_erucic}_{ij}$, where $cssex$ denotes the exogenous css. We assume erucic acid concentration is at steady state. Let $cssav$ denote the average steady state concentration,

$$cssav_{ij} = cssex_{ij} + cssendo_i,$$

where $cssendo_i$ denotes the endogenous css for patient i . We model the observed css Y as this $cssav$ plus some random Gaussian error. Hence in statistical modeling terms, for Y_{ij} , the level of erucic acid observed in the FAP analysis of the j th sample on the i th patient, we have

$$Y_{ij} = cssav_{ij} + (error_{ij} e^{\eta_{3i}}),$$

where $error_{ij} = cssav_{ij} \varepsilon_{1ij}$ and $\varepsilon_{1ij} \sim N(0, \sigma_1^2)$. (2)

Incorporating subject-level variability and utilizing equation (1), we obtain

$$\text{clearance_erucic}_{ij} = \theta_1 \left(\frac{\text{weight}_{ij}}{70} \right)^{\frac{3}{4}} e^{\eta_{1i}}$$

$$\text{and } cssendo_i = \theta_2 e^{\eta_{2i}},$$

where $\eta_{ki} \stackrel{\text{indep}}{\sim} N(0, \omega_k^2)$ for $k = 1, 2, 3$, the number of subject level errors we include in our model, $\theta_l \sim N(\mu_l, \tau_l^2)$ for $l = 1, 2$, and we put a vague Gamma(0.1, 0.1) prior on $\frac{1}{\sigma_1^2}$.

4.2 The Pharmacodynamic Model

The *E_{max}* model is a nonlinear model frequently used in pharmacodynamic dose-response analyses. In this set up, the basic model is

$$Response_{ij} = E_0 - \frac{Emax_i * cssex_{ij}}{EC50_i + cssex_{ij}}, \quad (3)$$

where *E_{max}* denotes the maximum effect attributable to erucic acid concentration, *EC50* denotes the erucic acid concentration which produces half of *E_{max}*, and *E₀* is the basal effect, corresponding to the patient response when the erucic acid concentration is zero¹³. Since in our case the effect is decreasing with increasing concentration of the drug, we will use the minus sign^{25,24} in equation (3). The observed effect is this response plus some error. Converting to a statistical model, for Z_{ij} (the level of C26 observed in the FAP analysis) we have

$$Z_{ij} = (C26endo_i - Effect_{ij})(1 + \varepsilon_{2ij}), \quad (4)$$

where $\varepsilon_{2ij} \stackrel{iid}{\sim} N(0, \sigma_2^2)$. Again, if we wish to add subject-level variability to our model, we can extend (3) by defining $\mathbf{Emax}_i = \theta_3 e^{\eta_{4i}}$, $\mathbf{EC50}_i = \theta_4 e^{\eta_{5i}}$, and in (4) we can also assume $\mathbf{C26endo}_i = \theta_5 e^{\eta_{6i}}$. As in the PK model, $\eta_{ki} \stackrel{indep}{\sim} N(0, \omega_k^2)$ for $k = 4, 5, 6$, the patient-level errors we include, and $\theta_l \sim N(\mu_l, \tau_l^2)$ for $l = 3, 4, 5$. Finally, we again add a vague prior,

$$\frac{1}{\sigma_2^2} \sim \text{Gamma}(0.1, 0.1)$$

Using the data in hand, we seek to fit our Bayesian hierarchical model with some vague and some informative priors in an attempt to estimate all the unknown quantities. We also choose appropriate scales for the error components, both at the individual and observational levels.

Our software platform is WinBUGS¹², which uses Markov chain Monte Carlo (MCMC) methods to sample from the joint posterior distribution of all unknown model parameters. MCMC methods work by successively sampling from a Markov chain that has the desired posterior distribution as its equilibrium distribution. Common examples of MCMC algorithm includes the Gibbs sampler and the Metropolis-Hastings algorithm; see Chapter 3 of Carlin and Louis⁵ for a review.

4.3 Results for the LO PK/PD Data

We fit our model both with and without individual (η_{ki}) and observational (ε_{mij}) level errors, for $k = 1, \dots, 6$ and $m = 1, 2$. The model converged best with no individual level errors, i.e., no η_{ki} terms. Our MCMC approach requires us to assign some starting values for the θ_l , $l = 1, \dots, 5$, and also the σ_m^2 , $m = 1, 2$. We used crude estimates of these parameters derived from

the data in NONMEM; see also Moser et al²⁰. Specifically, we used $\frac{1}{\sigma_1^2} = 3$, $\frac{1}{\sigma_2^2} = 43$, $\theta_1 = 42$, $\theta_2 = 0.5$, $\theta_3 = 0.655$, $\theta_4 = 3.34$, and $\theta_5 = 0.971$.

The resulting parameter estimates are given in Table 1, with corresponding fitted PK and PD curves shown in the left and right panels respectively of Figure 2. The prior and posterior standard deviations as given in the second and fourth columns are very different for θ_1 , θ_3 , θ_4 and θ_5 , indicating that the data were able to inform these posteriors. In particular, the posterior for θ_3 reveals that the average maximal effect of erucic acid is fairly precisely estimated at 0.46 (95% BCI 0.40 to 0.51), and the estimated posterior median erucic level required to produce half of this maximal effect is only 0.84. These values are consistent with the fitted PD curve plotted in the right panel of Figure 2, where we replace all individual level parameters in (4) with their population level estimates. This plot also shows a scatter plot of the calculated $cssex$ versus Z_{ij} for each observation, a solid line showing the fitted model, and a dashed line depicting a loess smooth of the data. The fit in both cases is far from perfect, in particular due to the missing information in the interval $0 < cssex < 7$. For larger $cssex$, the scatter plot has points that are dispersed far away from the fitted lines, perhaps indicating an increasing residual error variance with increasing $cssex$.

In order to see how sensible our PK estimates are, the left panel of Figure 2 offers an exploratory plot. If our estimates of the θ 's are good, then according to (2), if we plot Y_{ij} vs $cssav_{ij}$, the resulting regression line should have slope approximately 1. Here $cssav_{ij}$ is

calculated using our estimated $\hat{\theta}_1$, and $cssendo_i$ is the Y_{ij} value corresponding to $Dose = 0$. For individuals with no $Dose = 0$ measurement, we take $cssav_{ij} = cssex_{ij} + \hat{\theta}_2$, where $\hat{\theta}_2$ is the estimated posterior mean. The left panel of Figure 2 actually shows this plot without a few extremely outlying patients (discarding 69 of the 2558 observations), and also omitting observations with $dose = 0$. We obtain a fitted slope of 1.059, in agreement with our model. Thus, though our PK data are much less informative than our PD data, the Bayesian approach still permits refinement of our prior opinion.

5 Phase IIa Design

5.1 Approximate Linear PD Model

5.1.1 Model Detail—Having investigated the basic PK and PD properties of LO, we now proceed to design a basic Phase IIa trial to determine the toxicity and efficacy (the latter as captured by an improvement in biomarker response) for a few candidate dosing regimes. Consider n patients recruited in a clinical trial having a total duration of J biweekly periods (“bi-weeks”). We first record Z_{i0} , the observed C26 level for patient i at baseline, assuming that all participants have no exogenous erucic acid in their bodies at this time (perhaps after a “washout” period) for $i = 1, \dots, n$. At each bi-week $j = 1, \dots, J$, we administer a daily dose of the drug to patient i that produces an erucic acid steady-state concentration of c_{ij} . We consider five values for c_{ij} : 0, 5, 10, 25 and 35. Hence when we say “a dose level of 5”, we mean a dose large enough and given often enough to produce $cssex = 5$ for that particular patient. These c_{ij} levels were chosen based on the right panel of Figure 2, which indicates a meaningful reduction in Z for $cssex$ as low as 5. As the trial takes place, we observe Z_{ijk} , the C26 level for the i^{th} patient in the j^{th} period on the k^{th} day, $k = 1, \dots, K_{ij}$ (where K_{ij} will typically be 14).

Next we define $X_{ij} = Z_{i0} - \sum_{k=1}^{K_{ij}} \frac{Z_{ijk}}{K_{ij}}$, the average *improvement* in C26 level for patient i in period j . For simplicity, in our initial trial design algorithm we assume $X_{ij} \mid \theta_{ij}$, $\sigma_x^2 \sim N(\gamma_{ij}, \sigma_x^2)$, and further assume

$$\gamma_{ij} = \mu_i^e + \beta_e c_{ij}, \quad (5)$$

where $\mu_i^e \sim N(\mu^e, \sigma_{\mu^e}^2)$ and the “e” superscript denotes “efficacy”. That is, for the moment we assume C26 improvement is *linear* in erucic acid concentration, with every person having their own baseline improvement parameter, μ_i^e . Adding the vague hyperprior distributions $\beta_e \sim \text{Uniform}(-1, 1)$ and $\sigma_{\mu^e}^2 \sim \text{InverseGamma}(0.1, 0.1)$ complete the efficacy model specification. Intuitively, if no dose is given, $E(X_{ij}) = \mu_i^e$ should be zero, since we are assuming Z_{i0} is C26 level at baseline (pre-LO). Hence we assume the true values $\mu^e = 0$ and $\sigma_{\mu^e}^2 = 1$.

Turning to an assessment of the toxicity of LO, we assume toxicity outcomes to be binary variables (e.g., presence or absence of elevated platelet count in the blood, or bone marrow suppression) for each patient every bi-week, i.e.,

$$W_{ij} = \begin{cases} 1 & \text{if toxicity was observed} \\ 0 & \text{if no toxicity was observed} \end{cases}.$$

We assume that π_{ij} , the probability of observing a toxicity for patient i during bi-week j , is such that

$$\text{logit}(\pi_{ij}) = \mu_i^t + \beta_t c_{ij}, \quad (6)$$

where “t” denotes toxicity, and we now assume the linearity of the *logit* of the toxicity probability in c_{ij} . Similar to before, we assume $\mu_i^t \sim N(\mu^t, \sigma_{\mu^t}^2)$ and $\beta_t \sim \text{Uniform}(0,1)$, so again each individual has their own personal propensity for toxicity, and the drug cannot *reduce* toxicity. It is intuitive to believe that at dose zero, π_{ij} will also be essentially zero. A simple calculation shows that $\mu_t = -4$ delivers $\pi_{ij} = 0.01$ at $c_{ij} = 0$. In what follows, we therefore assume the true values $\mu^t = -4$, and $\sigma_{\mu^t}^2 = 0.3$. We also experiment with $\mu^t = -2$ to check robustness of our method to this assumption.

Finally, to introduce correlation between the efficacy and toxicity responses, we can instead assume the following *joint* model for the subject level effects:

$$\begin{pmatrix} \mu_i^e \\ \mu_i^t \end{pmatrix} \sim N_2 \left(\begin{pmatrix} \mu^e \\ \mu^t \end{pmatrix}, \Sigma \right), \quad (7)$$

where Σ takes the form $\begin{pmatrix} \sigma_{\mu^e}^2 & \rho \sigma_{\mu^e} \sigma_{\mu^t} \\ \rho \sigma_{\mu^e} \sigma_{\mu^t} & \sigma_{\mu^t}^2 \end{pmatrix}$. We put a modestly informative **Wishart**(Ω , 20) prior on Σ , and assume $\Omega = \begin{pmatrix} 100 & 0 \\ 0 & 0.02 \end{pmatrix}$ to preserve the imbalance in the scales of $\sigma_{\mu^e}^2$ and $\sigma_{\mu^t}^2$. Setting $\rho = 0.7$ and letting X_j and W_j denote all the efficacy and safety data, respectively, observed up to bi-week j , our dosing algorithm for the i^{th} patient at bi-week j is given in Figure 3. Note that our design is based entirely on posterior exceedance probabilities for toxicity (π_{ij}) and efficacy (γ_{ij}), where we use the thresholds $P_U^{Tox} = 0.8$, $P_L^{Tox} = 0.2$, $P_U^{Eff} = 0.9$, and $P_L^{Eff} = 0.4$. We selected threshold values of $\pi_t = 0.6$ for toxicity and $\theta_e = 0.8$ for efficacy based on clinical and practical considerations; in the next section we check to make sure they deliver a design with acceptable operating characteristics.

To ensure adequate data before the trial's adaptive phase, we assign the starting dose ($c_{ij} = 5$) to all patients i for bi-weeks $j = 1, 2, 3$. Beginning with bi-week $j = 4$, we cycle through the Figure 3 flowchart for each patient i and bi-week j , noting the dose level where each patient stopped due to high efficacy at the current dose level. The next subsection shows the results of a simulation study to evaluate the power and Type I error of this algorithm.

5.1.2 Phase IIa Simulation Results—To put our trial design to the test, we carry out a simulation to estimate the power curves associated with its possible dosing patterns. Our simulation results are based on a trial of $J = 12$ bi-weeks, various values of β_t , Σ as defined in the previous section, and use $L = 1000$ simulated datasets for each combination of n and β_e . For the ℓ^{th} simulated dataset, where $\ell = 1, \dots, L$, we first generate X_{ij} and W_{ij} for all patients in each of the bi-weeks $j = 1, 2, 3$. Next, for bi-week $j = 4, \dots, J$, we first generate X_{ij} and W_{ij} for the current bi-week and calculate the posterior estimates using X_j and W_j (i.e., all X_{im} and W_{im} for $m = 1, \dots, j$). Based on the posterior estimates for bi-week j , we run through the dosing algorithm to determine the dose for each of the patients for bi-week $j+1$. Finally at the end of the J^{th} bi-week, we obtain the posterior 95% equal-tail Bayesian credible interval (BCI)⁵ for β_e . The power of the trial is estimated as the proportion of times among the L simulated datasets that the 95% BCI for β_e does not include 0 (since in our procedure this corresponds to rejecting $H_0: \beta_e = 0$).

The results of our simulation study are given in Table 2, where Monte Carlo standard errors associated with the power estimates are given in parentheses. The power at $\beta_e = 0$ gives us the Type I error, which we would typically want to be around 0.05. The values shown for other levels of β_e give the power of the design at various levels of true efficacy, which we expect to be increasing as either n or β_e increase. Results are shown for three possible toxicity profiles: low ($\beta_t = 0.15$), medium ($\beta_t = 0.3$), and high ($\beta_t = 0.5$).

The power of the design behaves sensibly for $n = 10$, $n = 20$, and $n = 40$, with $n = 40$ delivering very high power at $\beta_e = 0.02$ unless toxicity of LO is high. The estimated Type I errors are mostly within 2 standard errors of 0.05 and constantly less than 0.10; they could of course be reduced further by changing some of our many design parameters, such as the threshold values θ_e and π_t in the dosing algorithm. Figure 3 depicts the increasing nature of the power function for each n . Obviously our plot is not particularly detailed, but could be easily augmented simply by rerunning our simulations for more values of β_e . In our trial, $n = 40$ corresponds to a “stretch” enrollment size, but $n = 20$ also produces good performance provided toxicity is low.

Table 3 gives the proportion of simulated patients assigned to each dose for each n , β_e , and β_t in our simulation. We note that when toxicity is low, most patients are assigned to higher, more efficacious doses, as expected. However, for higher toxicity ($\beta_t = 0.5$), higher doses are rarely if ever assigned, and many patients actually revert to dose 0, especially for small n (i.e., lower information trials). Thus our design appears to have sensible and acceptable frequentist operating characteristics.

Before moving on, we consider robustness of our results to an increase in the true μ_t to -2 (i.e., higher baseline toxicity of LO). The effect seems to be a slight inflation of Type I error

when $\beta_t = 0.15$, but similar power overall (Table 4). We also now see more patients dropping back to lower doses, including even dose 0 for the higher information trial (n=40; Table 5).

5.2 Emax PD Model

5.2.1 Model Detail—In this section we incorporate the Emax model we used in Subsection 4.2 into our Phase IIa design. In the design utilized in Section 5.1, we assumed an approximating linear PD model for the improvement in biomarker response due to Lorenzo's Oil. While this was computationally convenient for our design calculations, the right panel of Figure 2 suggests the relationship may be nonlinear. As such, in this section we return to model (3), estimated from the FAP data in Section 4.3. Since in our design we are estimating the difference of C26:0 from baseline, we replace (5) with

$$\gamma_{ij} = \frac{\theta_3 c_{ij}}{\theta_{4i} + c_{ij}},$$

where as before θ_3 and θ_{4i} correspond to the *Emax* and *EC50* parameters, respectively, and c_{ij} again denotes the steady state erucic acid concentration for subject i during bi-week j . By analogy with μ_i^e , each subject is allowed to have his or her own *EC50* parameter. We adopt the priors $\theta_3 \sim \text{Normal}(\mu_3, \sigma_{\mu_3}^2)$ and $\theta_{4i} \sim \text{Normal}(\mu_4, \sigma_{\mu_4}^2)$, and also select the vague hyperprior distributions $\mu_3 \sim \text{Uniform}(-10, 10)$ and $\mu_4 \sim \text{Uniform}(-10, 10)$. We assign $\sigma_{\mu_3}^2 = 1$ and $\sigma_{\mu_4}^2 = 1$. Clearly θ_3 now drives the efficacy of LO, just as β_e did in our earlier design (5).

To begin with, we set $\beta_t = 0.15$ and assume no correlation between the efficacy and toxicity parameters, θ_{4i} and μ_i^t , although one could model such correlation using a bivariate normal prior as in (7). In what follows, toxicity is simply defined as in the previous subsection according to (6), where we assume $\mu_i^t \sim \text{Normal}(\mu^t, \sigma_{\mu^t}^2)$ independently of the θ_{4i} , and where $\mu^t = -4$ and $\sigma_{\mu^t}^2 = 0.3$. Our dosing algorithm remains the same as given in Figure 3, but where now $P_U^{\text{Tox}} = 0.9$ and $P_L^{\text{Tox}} = 0.5$. In our Emax model, the efficacy and toxicity models are assumed independent of each other, though the cut-offs have not changed (i.e., $\pi_t = 0.6$ and $\theta_e = 0.8$).

5.2.2 Phase IIa Simulation Results—We carried out some simulation studies to study the behavior of our Emax model in the same manner as in Subsection 5.1.2. To make the results of this design comparable with that of the previous design, we have kept the same toxicity properties for our simulated datasets. For all subjects i , we assume $\theta_{4i} = 0.8931$, the estimate of θ_4 obtained in Section 4.3. We study the Type I error and power for varying values of n and θ_3 , again to give us an idea as to the operating characteristics of our design.

In spite of the nonlinearity introduced by the Emax model, trial operating characteristics remain reasonable. Table 6 provides some results under various choices of efficacy and toxicity parameters. The Type I errors (corresponding to $\theta_3 = 0$) are consistently around 0.05, and the power seems to escalate fairly quickly to desirable levels with increasing θ_3 ;

see Figure 5 for power curves in the case where $\beta_t = 0.15$ (low drug toxicity). The θ_3 estimated in Section 4.3 is approximately 0.5, for which the power here is almost 1 even for n as small as 10. Although the Emax model does perform well, it runs much more slowly than the linear model. Hence to the extent that the linear model can be thought of a good approximation to the true efficacy curve, opting for the linear model will lead to much faster computations. Certainly the right panel of Figure 2 offers little justification for *either* model, offering possibly more support for the simpler alternative.

The doses assigned to patients at the end of the trial (also shown in Table 6) are slightly different under the Emax model. Previously, with a small increase in efficacy, the number of subjects assigned to higher doses saw a slight increase. In this case we had to inflate the efficacy parameter θ_3 all the way to 1 in order to see a substantial probability of stopping at the lowest nonzero dose, 5. As can be seen in Table 6, for $\theta_3 = 1$ cases shown when $\beta_t = 0.15$, the high assured efficacy of LO means more patients are responding very well and hence don't need to take a high dose (25 or 35). Also, on increasing the toxicity to $\beta_t = 0.3$ or $= 0.5$, we see fewer or even no patients being assigned to the higher doses, no doubt due in part to the flatness of the fitted Emax curve for larger LO doses.

6 Conclusions and Future Work

In this paper we have presented a fully Bayesian method for evaluating the PK and PD of LO, as well as a Bayesian adaptive design for a Phase IIa trial to determine a dose that is both safe and effective (i.e., leads to improvement in biomarker response). Advantages of our method include the ability to get sensible estimates for a PK/PD model using what little data we have, possibly augmented by expert opinion. Our design is adaptive to interim individual toxicity and efficacy results, a desirable trait when dealing with a rare pediatric disease like X-ALD. The design also has a very reasonable Type I error (to guard against the chance that LO is not effective), as well as reasonably high power to detect the benefit of LO when it is effective, for all values of n that are feasible for our proposed Phase IIa study.

Limitations of our method include failure of our preliminary PK/PD data to adequately inform the posterior estimate of θ_2 , the parameter corresponding to the endogenous erucic concentration level. We have also not been able to incorporate individual-level errors in our model due to its already-high level of complexity. As has been discussed in many recent Bayesian modeling contexts, the power and flexibility of MCMC computational methods tempts the practitioner to fit models too large and complex for the data to reliably support. In our setting, sparse data compounds the problem, forcing us to work harder to combat overparametrization that inevitably leads to unstable algorithm convergence and parameter estimates. As for the Phase IIa design, our dose-finding algorithm can be rather sensitive to the precise level of toxicity assumed for LO (Tables 3, 5), and these toxicities are somewhat vaguely defined at present. As such, our model may require modification if our assumptions are not consistent with real Phase IIa data.

Future work aims to further develop our suite of adaptive clinical trial techniques. As discussed previously, this design is amenable to various possible models of improvement in biomarker response. The Emax model will often be preferred based on pharmacological

justification for the drug's effect on the biomarker. An advantage of using the Emax model in Phase IIa is we can update our model with the new data coming in; i.e., we can update our estimates of θ_4 and θ_3 in Phase IIa to make them more reliable. The subject pool for PK studies is often demographically or medically different from the subject pool in Phase IIa or Phase III, and hence being able to update the PK/PD parameters at a later stage may give us an estimate based on a more representative subject sample. However, if for some reason the proposed Emax model is debatable, such as in our case where the data are not rich enough to accommodate individual-level errors or justify the Emax shape, or in cases where the subject population for the PK/PD and the Phase IIa are distinct, we may sensibly opt for the linear model (5). The linear model's computational advantages with respect to the MCMC algorithm also offer a trade-off worth considering.

Our ultimate goal is to design a Phase III study using CT/MR-detected brain abnormalities (instead of C26 biomarker response) as the primary endpoint. Such a study would likely be an open-label study with many key characteristics (starting dose, blood sample collection times, etc.) determined by the outcome of our Phase IIa study, and feature Bayesian adaptive adjustments (say, for making dosing adjustments, or permitting early stopping for efficacy or futility) as needed. We also look ahead toward the use of hierarchical commensurate prior methods^{7,8,9} to incorporate relevant historical information in this rare pediatric disease setting, especially important here due to the small sample sizes inherent in any trial in this disease. Such methods allow adaptive borrowing of information when justified, but at the same time are robust to prior information that emerges as inconsistent with the accumulating trial data.

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Appendix

Below we provide the WinBUGS code that produces the PK/PD data analysis results in Table 1. It is hoped that practitioners will be able to modify this code, and thus apply our approach in their own challenging PK/PD settings.

Since the simulation results in Section 5 require more complex code (calling BUGS or JAGS repeatedly from R, once for each of L simulated datasets), this code (as well as the full dataset for the PK/PD example below) is relegated to the last author's software page, <http://www.biostat.umn.edu/brad/software.html>.

```
## PK/PD WinBUGS code for the X-ALD (Lorenzo's Oil) model
## NOTE: In what follows, DV2 = Y in the paper, and DV3 = Z in the paper
model{
  for(i in 1:116){
    endoeruc[i] <- theta[2]
    emax[i] <- theta[3]
    ec50[i] <- theta[4]
    c26endo[i] <- theta[5]
    eta1[i]~dnorm(0,w[1])
    eta2[i]~dnorm(0,w[2])
    eta3[i]~dnorm(0,w[3])
    eta4[i]~dnorm(0,w[4])
    eta5[i]~dnorm(0,w[5])
    eta6[i]~dnorm(0,w[6])
    for(k in offset[i]:(offset[i+1]-1)){
      tvcleruc[k] <- theta[1]*pow((WT[k]/70),0.75)
      cleruc[k] <- tvcleruc[k]
      rateeruc[k] <- DOSE[k] * (35.83)
      cssex[k] <- rateeruc[k]/cleruc[k]
      cssav[k] <- cssex[k]+endoeruc[i]
      precDV2[k] <- sigma[1]/cssav[k]*cssav[k]
      DV2[k]~dnorm(cssav[k], precDV2[k])
      e[k] <- emax[i]*cssex[k]
      d[k] <- ec50[i]+cssex[k]
      effect[k] <- e[k]/d[k]
      diff[k] <- c26endo[i]-effect[k]
      precDV3[k] <- sigma[2]/(diff[k]*diff[k])
      DV3[k]~dnorm(diff[k],precDV3[k])
    }
  }
  theta[1]~dnorm(42.3,t1)
  theta[2]~dnorm(0.582,t2)
  theta[3]~dnorm(0.655,t3)
  theta[4]~dnorm(3.34,t4)
  theta[5]~dnorm(0.971,t5)
  for(j in 1:6){w[j] ~ dgamma(1,1)}
```

```

for (j in 1:2) {sigma[j] ~ dgamma(0.1,0.1)}
} # end of BUGS code
## INITS:
list(theta = c(42, 0.5, 0.655, 3.34, 0.971),
w = c(1.228, 0.6849, 11.037, 20.61, 0.432, 33.44),
sigma=c(3,43))
## DATA: (NOTE: there are TWO loads, the list here, and the primary data matrix
below)
list(t1=0.04,t2=100,t3=100,t4=0.01,t5=100,
offset=c(
1, 17, 62, 103, 132, 153, 175, 184, 225, 259, 286, 306, 322, 357, 391, 431, 465, 508, 523,
535, 589, 619, 627, 631, 670, 707, 748, 766, 802, 847, 890, 925, 957, 965, 971, 1007, 1032,
1053, 1093, 1119, 1138, 1165, 1203, 1248, 1256, 1277, 1283, 1315, 1356, 1390, 1408, 1436,
1467, 1505, 1543, 1556, 1559, 1604, 1611, 1635, 1650, 1654, 1660, 1689, 1716, 1741, 1766,
1799, 1822, 1847, 1864, 1875, 1893, 1909, 1930, 1951, 1975, 1999, 2002, 2023, 2027, 2053,
2084, 2111, 2124, 2147, 2166, 2182, 2194, 2219, 2248, 2257, 2270, 2285, 2306, 2321, 2330,
2347, 2358, 2371, 2387, 2402, 2409, 2415, 2422, 2433, 2444, 2453, 2468, 2483, 2497, 2514,
2523, 2530, 2541, 2542, 2550))

## Here is the primary data matrix:

WT[] DOSE[] DV2[] DV3[]
19.5 0.0 0.59 0.46
19.5 9.0 85.19 0.41
19.5 9.0 10.85 0.35
19.5 9.0 5.45 0.45
19.5 9.0 18.47 0.29
19.5 9.0 14.90 0.24
19.5 9.0 16.50 0.40
19.5 9.0 35.75 0.28
22.8 9.4 50.72 0.36
22.8 9.4 11.76 0.30
22.8 9.4 9.17 0.43
22.8 9.4 71.82 0.51
25.4 9.8 2.05 0.58
..... [snip] .....
35.2 10.8 24.77 0.45
END

```

Figure 1. Two types of PK data where the circles denote the values of the observations that were recorded. Fig (a) multiple observations per dose; (b) single observation per dose.

Figure 2.

Left panel: plot of the PK data (Y_{ij} vs. estimated $cssav_{ij}$) along with the fitted regression line, which has slope 1.059; right panel: plot of the PD data (Z_{ij} vs. estimated $cssex_{ij}$) along with the fitted Emax curve.

Figure 3.
Dosing algorithm for Phase IIa trial design, patient i , bi-week $j = 4$.

Figure 4. Plot depicting the power curve at each value of n with increasing β_e for $\beta_t = 0.15$ (low toxicity).

Figure 5. Plot depicting the power curve for the Emax model at each value of n with increasing θ_3 for $\theta_{4i} = 0.8931$ and $\mu_t = -4$ (low overall toxicity) and $\beta_t = 0.15$ (low drug toxicity).

Table 1

Table depicting parameter estimates obtained from the model described

node	prior sd	mean	posterior sd	MC error	2.5%	median	97.5%
σ_1		0.002215	6.269E-5	8.32E-7	0.002093	0.002215	0.002341
σ_2		4.438	0.1509	0.003391	4.145	4.435	4.742
θ_1 (clearance)	5	31.0	0.6158	0.01766	29.82	30.99	32.22
θ_2 (essendo)	0.1	0.6083	0.1003	0.003036	0.4162	0.6139	0.8022
θ_3 (Emax)	0.1	0.4573	0.02572	0.002346	0.3968	0.4591	0.5105
θ_4 (EC50)	10	0.8931	0.6321	0.04938	-0.1921	0.8446	2.207
θ_5 (C26endo)	0.1	0.8822	0.02605	0.002383	0.8256	0.8848	0.9313

Table 2

Estimated power (standard error) of the Phase IIa design for various choices of β_e , β_t and n at $\mu^t = -4$.

β_t (toxicity)	0.15		
β_e (efficacy)	0	0.01	0.02
n			
	0.059(0.007)	0.325(0.015)	0.749(0.014)
	0.068(0.008)	0.559(0.016)	0.969(0.005)
	0.057(0.007)	0.795(0.013)	0.999(0.001)
β_t (toxicity)	0.3		
β_e (efficacy)	0	0.01	0.02
n			
	0.062(0.008)	0.173(0.012)	0.362(0.015)
	0.072(0.008)	0.29(0.014)	0.677(0.015)
	0.052(0.007)	0.52(0.016)	0.966(0.006)
β_t (toxicity)	0.5		
β_e (efficacy)	0	0.01	0.02
n			
	0.064(0.008)	0.101(0.01)	0.212(0.013)
	0.038(0.006)	0.152(0.011)	0.462(0.016)
	0.056(0.007)	0.359(0.015)	0.808(0.012)

Table 3

Proportion of patients being assigned to each dose for all 1000 datasets for choices of β_e, β_t and n at $\mu' = -4$.

	β_t	β_e	dose=0	dose=5	dose=15	dose=25	dose=35
n=10	0.15	0	0	0.178	0.062	0.366	0.394
		0.01	0	0.192	0.078	0.342	0.388
		0.02	0	0.205	0.096	0.294	0.406
n=20		0	0	0.173	0.053	0.331	0.442
		0.01	0	0.19	0.06	0.28	0.47
		0.02	0	0.201	0.083	0.241	0.475
n=40		0	0.002	0.172	0.032	0.327	0.467
		0.01	0.002	0.188	0.054	0.263	0.494
		0.02	0	0.203	0.077	0.2	0.52
n=10	0.3	0	0	0.667	0.102	0.231	0
		0.01	0	0.647	0.126	0.226	0
		0.02	0	0.611	0.159	0.23	0
n=20		0	0.022	0.675	0.122	0.181	0
		0.01	0.024	0.641	0.154	0.181	0
		0.02	0.019	0.607	0.181	0.194	0
n=40		0	0.15	0.502	0.257	0.091	0
		0.01	0.198	0.453	0.261	0.088	0
		0.02	0.216	0.443	0.246	0.095	0
n=10	0.5	0	0.19	0.584	0.226	0.001	0
		0.01	0.158	0.637	0.205	0.001	0
		0.02	0.146	0.67	0.182	0.002	0
n=20		0	0.172	0.361	0.467	0	0
		0.01	0.16	0.409	0.431	0	0
		0.02	0.15	0.457	0.393	0	0
n=40		0	0.069	0.263	0.668	0	0
		0.01	0.073	0.285	0.642	0	0

0	0	0.604	0.324	0.073	0.02		
$S_1=35$	$S_1=35$	$S_1=35$	$S_1=35$	$S_1=35$	$S_1=35$	$S_1=35$	$S_1=35$

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Table 4

Estimated power (standard error) of the Phase IIa design for $\beta_t = 0.15$ and various choices of β_e and n at $\mu^t = -2$.

β_t (toxicity)	0.15		
β_e (efficacy)	0	0.01	0.02
n			
	0.075(0.008)	0.16(0.012)	0.394(0.015)
	0.077(0.008)	0.275(0.014)	0.716(0.014)
	0.051(0.007)	0.529(0.016)	0.959(0.006)

Proportion of patients being assigned to each dose for all 1000 datasets for $\beta_f = 0.15$ and various choices of β_e and n at $t = -2$.

Table 5

	β_f	β_e	dose=0	dose=5	dose=15	dose=25	dose=35
n=10	0.15	0	0.001	0.567	0.099	0.333	0
		0.01	0	0.574	0.124	0.301	0.001
		0.02	0	0.528	0.157	0.314	0.001
n=20		0	0.009	0.575	0.132	0.284	0
		0.01	0.006	0.546	0.153	0.294	0
		0.02	0.005	0.518	0.199	0.279	0
n=40		0	0.123	0.468	0.234	0.175	0
		0.01	0.122	0.449	0.26	0.169	0
		0.02	0.117	0.422	0.292	0.169	0

Table 6

Estimated power (standard error) of the Phase IIa design (column 4) and proportion of patients being assigned to each dose (columns 5–9) using the Emax model for various choices of θ_3 , β_t , and n at $\mu^* = -4$ and $\theta_4^* = 0.8931$ for all i .

n	β_t	θ_3	power	dose=0	dose=5	dose=15	dose=25	dose=35
	0.15	0	0.049(0.007)	0.1	0.06	0.21	0.34	0.29
		0.2	0.503(0.016)	0.1	0.07	0.21	0.35	0.27
		0.5	0.998(0.001)	0.1	0.07	0.2	0.36	0.27
		1	1(0)	0.01	0.55	0.29	0.13	0.03
		0	0.049(0.007)	0.1	0.07	0.23	0.32	0.28
		0.2		0.1	0.07	0.23	0.32	0.29
			0.0792(0.009)					
		0.5	1(0)	0.1	0.07	0.22	0.32	0.29
		1	1(0)	0	0.6	0.28	0.1	0.02
		0	0.047(0.007)	0.09	0.06	0.25	0.32	0.28
		0.2	0.966(0.006)	0.09	0.07	0.24	0.32	0.28
		0.5	1(0)	0.09	0.06	0.25	0.31	0.28
		1	1(0)	0	0.71	0.23	0.05	0
	0.3	0	0.072(0.008)	0.25	0.36	0.28	0.11	0
		0.5	0.998(0.001)	0.25	0.35	0.28	0.12	0
		0	0.048(0.007)	0.27	0.34	0.27	0.12	0
		0.5	0.5(0.016)	0.28	0.34	0.25	0.12	0
		0	0.055(0.007)	0.31	0.32	0.26	0.11	0
		0.5	1(0)	0.31	0.32	0.26	0.11	0
	0.5	0	0.05(0.007)	0.48	0.16	0.35	0	0
		0.5	0.991(0.003)	0.47	0.17	0.36	0	0
		0	0.054(0.007)	0.51	0.19	0.3	0	0
		0.5	1(0)	0.5	0.19	0.3	0	0
		0	0.046(0.007)	0.5	0.19	0.31	0	0
		0.5	1(0)	0.5	0.2	0.3	0	0