Physiologically-Based Pharmacokinetic Model Development, Validation, and Application for Prediction of Eliglustat Drug–Drug Interactions

Siddhee A. Sahasrabudhe[1,2], Shen Cheng[2,4], Mahmoud Al-Kofahi[2], Jeanine R. Jarnes[2], Neal J. Weinreb[3] and Reena V. Kartha[1,2,*]

Eliglustat is a glucosylceramide synthase inhibitor indicated as a long-term substrate reduction therapy for adults with type 1 Gaucher disease, a lysosomal rare disease. It is primarily metabolized by cytochrome P450 2D6 (CYP2D6), and variants in the gene encoding this enzyme are important determinants of eliglustat pharmacokinetics (PK) and drug–drug interactions (DDIs). The existing drug label addresses the DDIs to some extent but has omitted scenarios where both metabolizing CYPs (2D6 and 3A4) are mildly or moderately inhibited. The objectives of this study were (i) to develop and validate an eliglustat physiologically-based pharmacokinetic (PBPK) model with and without drug interactions, (ii) to simulate untested DDI scenarios, and (iii) to explore potential dosing flexibility using lower dose strength of eliglustat (commercially not available). PK data from healthy adults receiving eliglustat with or without interacting drugs were obtained from literature and used for the PBPK model development and validation. The model-predicted single-dose and steady-state maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of eliglustat were within 50–150% of the observed values when eliglustat was administered alone or coadministered with ketoconazole or paroxetine. Then as model-based simulations, we illustrated eliglustat exposure as a victim of interaction when coadministered with fluvoxamine following the US Food and Drug Administration (FDA) dosing recommendations. Second, we showed that with lower eliglustat doses (21 mg, 42 mg once daily) the exposure in participants of intermediate and poor metabolizer phenotypes was within the outlined safety margin (C_{max} <250 ng/mL) when eliglustat was administered with ketoconazole, where the current recommendation is a contraindication of coadministration (84 mg). The present study demonstrated that patients with CYP2D6 deficiency may benefit from lower doses of eliglustat.

Study highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Eliglustat is an oral substrate reduction therapy for the treatment of adults with type-1 Gaucher disease. Eliglustat can interact with many other drugs, complicating and potentially limiting its use in polypharmacy situations.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Prediction of eliglustat drug–drug interactions using a validated physiologically-based pharmacokinetic model and exploration of lower doses in drug interaction situations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The physiologically-based pharmacokinetic (PBPK) model of eliglustat is described. Untested clinical scenarios are simulated, and lower eliglustat doses were explored for their utility in dosing flexibility and safety.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The PBPK model can be used to provide some indication for dose adjustment in polypharmacy situations. Lower doses can be explored as an alternative to the full and currently marketed eliglustat dose when drug interactions are likely and interruption or nonuse of eliglustat could be disadvantageous for patients with Gaucher disease.

[1]Center for Orphan Drug Research, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, USA; [2]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, USA; [3]Department of Human Genetics, University of Miami Miller School of Medicine, Miami, Florida, USA; [4]Present address: Metrum Research Group, Tariffville, Connecticut, USA. *Correspondence: Reena V. Kartha (rvkartha@umn.edu)

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Gaucher disease (GD) is a lysosomal storage disorder where the deficient activity of the lysosomal enzyme, acid β-glucosidase, leads to the accumulation of glucosylceramides and related substrates in the liver, bone marrow, spleen, lung, and brain.[1] There are three main GD phenotypes: type 1 (GD1), type 2 (GD2), and type 3 (GD3). Unlike GD2 and GD3, GD1 is considered a non-neuronopathic form of the disease although the risk for peripheral neuropathy, Parkinson's disease, and Lewy body dementia increase with age in patients usually after 50 years of age.[2] Although still a rare disease, GD1 is the most common form of GD in the United States and Europe, with an incidence of ~ 1 in 40,000 to 1 in 60,000 live births.[1] GD1 is especially prevalent among those of Ashkenazi Jewish ancestry.[1] There are two governmentally authorized approaches to treat GD1: intravenous enzyme replacement therapy (ERT) and oral substrate reduction therapy (SRT).[3,4] Eliglustat is a first-line oral SRT for adults with GD1, who are cytochrome P450 (CYP) 2D6 poor metabolizers (PMs), intermediate metabolizers (IMs), or extensive metabolizers (EMs).[1] The relatively small number of patients who are ultrarapid metabolizers (URMs) are currently ineligible for the eliglustat prescription.[1] According to the standard definitions of CYP2D6 metabolizer phenotypes based on the consensus activity scores, the EM phenotype is considered "normal metabolizers."[5]

Eliglustat is extensively metabolized by CYP2D6 and to a lesser extent by CYP3A (fraction of drug metabolized; fm CYP 0.86, 0.14 respectively).[6] Eliglustat also produces time-dependent inhibition of CYP2D6.[7] *In vitro*, eliglustat exhibited inhibitory potential on CYP2D6 in a competitive and time-dependent manner, due to which a subsequent clinical study evaluated its potential of interacting with metoprolol, a sensitive CYP2D6 substrate.[8] In the drug label, the eliglustat dose is based on the individual's CYP2D6 metabolizer phenotype, and concomitant usage of CYP2D6 and/or CYP3A inhibitors or inducers.[9] Some of the drug-interaction management mentioned in the drug label warrants dose adjustment and at the extreme, suggests contraindication. The label omits complex scenarios such as multiple CYP inhibitions that may result from multiple concomitant medications.[9] The eliglustat dosing guidelines (**Figure 1**), based on CYP2D6 genotype-derived metabolizer status, may appear simple and straightforward to some prescribing physicians who may not be aware that the laboratory-reported phenotypes (PM, IM, EM, URM) are subject to wide interindividual differences and variable, drug-specific, phenotypic manifestations.[10] Prescribing eliglustat with other medications can be quite complicated because categorization of drugs as strong, intermediate, or weak inhibitors is not always precise, and physicians may not have the resources to ascertain such information, especially in the case of newer drugs.[11]

Inhibition of eliglustat metabolism resulting from drug–drug interaction (DDI) can potentially have severe consequences. For instance, based on the concentration-QT relationship, there is a risk of QT prolongation when eliglustat concentrations reach >250 ng/mL.[6,12] Eliglustat is currently marketed at only a single dose level, 84-mg capsules. Thus, the current labeling requires eliglustat to be stopped in certain situations where interaction is inevitable. However, it is unknown how the frequency and the duration of such interruptions affect the loss of disease control and it is likely to be highly variable. Many patients with GD1 use one or more prescription or over-the-counter concomitant medications and naturopathic (herbal) supplements.[13,14] Polypharmacy may constrain the ability to start or maintain eliglustat therapy. Indeed, this issue has been of concern during the still ongoing coronavirus disease 2019 (COVID-19) pandemic.[15]

<table>
<tr><th rowspan="2">Concomitant drugs</th><th colspan="3">CYP2D6 metabolizer status</th></tr>
<tr><th>EMs</th><th>IMs</th><th>PMs</th></tr>
<tr><td colspan="4">CYP2D6 inhibitor</td></tr>
<tr><td>Strong</td><td colspan="2" rowspan="2">Reduce frequency of CERDELGA 84 mg to once daily</td><td rowspan="2">Continue CERDELGA 84 mg once daily[a]</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Weak</td><td colspan="2">Continue CERDELGA 84 mg twice daily</td></tr>
<tr><td colspan="4">CYP3A inhibitor</td></tr>
<tr><td>Strong</td><td rowspan="2">Reduce frequency of CERDELGA 84 mg to once daily</td><td colspan="2">Contraindicated</td></tr>
<tr><td>Moderate</td><td colspan="2">Avoid coadministration</td></tr>
<tr><td>Weak</td><td colspan="2">Continue CERDELGA 84 mg twice daily</td><td>Avoid coadministration</td></tr>
<tr><td colspan="4">CYP2D6 inhibitor concomitantly with a strong CYP3A inhibitor</td></tr>
<tr><td>Strong</td><td colspan="3" rowspan="2">Contraindicated</td></tr>
<tr><td>Moderate</td></tr>
<tr><td colspan="4">CYP2D6 inhibitor concomitantly with a moderate CYP3A inhibitor</td></tr>
<tr><td>Strong</td><td colspan="2" rowspan="2">Contraindicated</td><td rowspan="2">Avoid coadministration[a]</td></tr>
<tr><td>Moderate</td></tr>
<tr><td colspan="4">CYP3A Inducer</td></tr>
<tr><td>Strong</td><td colspan="3">Avoid coadministration</td></tr>
</table>

[a]No effect of CYP2D6 inhibitor due to little or no CYP2D6 activity in CYP2D6 PMs.

Figure 1 Prevention and management strategies of drug interactions affecting Eliglustat (Cerdelga®) based on CYP2D6 metabolizer status and concomitant interacting drug. Red markings denote the scenarios simulated in this study coupled with lower eliglustat doses. CYP2D6, cytochrome P450 2D6; CYP3A, cytochrome P450 3A; EMs, extensive metabolizers; IMs, intermediate metabolizers; PMs, poor metabolizers. The figure is adapted from the full prescribing information of eliglustat (Cerdelga®), accessed on April 30, 2022 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205494s003lbl.pdf.

Physiologically-based pharmacokinetic (PBPK) modeling and simulation is an *in silico* approach that incorporates blood flow and tissue composition of organs of a human body to define the pharmacokinetics (PK) of drugs.[16,17] PBPK modeling was used to guide dose selection and labeling for eliglustat.[6,17] However, it is important to note that the explicit details of the model are not publicly available. The US Food and Drug Administration's (FDA's) NDA review of Cerdelga® (brand name for eliglustat; henceforth called the review document) notes some of the model parameters that can be used as a starting point for PBPK model development.[6]

The objectives of this study were (i) to develop and validate the eliglustat PBPK model with and without drug interactions, (ii) to simulate untested DDI scenarios, and (iii) to explore potential dosing flexibility using lower doses of eliglustat (commercially not available, compounding of eliglustat capsules is not recommended).

METHODS

Study design and setup

The present study consisted of three parts. Model development and optimization, and model validation, followed by the model simulation to extrapolate other DDI scenarios (**Figure 2**). Model development, validation, and simulations were performed using Simcyp (2019, version 19 release 1; Certara, Sheffield, UK). Data assembly and plotting were performed using RStudio (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). For all the simulations performed in Simcyp, Mersenne Twister (MT19937) was used as the random number generator, with 1 as the seed number. All simulations were conducted with the "Healthy volunteer" population that was built into Simcyp, with certain modifications, as mentioned in **Table S1**, consistent with the FDA's review document. Data available through published literature were utilized and ranged from single ascending dose, multiple ascending doses, food effect, bioavailability, steady-state PK, and drug interactions studies, in healthy volunteers within phase I or phase II trials (Table 1). WebPlotDigitizer (version 4.5)[18–21] was used to extract raw data from the figures in the reference literature. C_{max} and AUC values presented in the corresponding reference studies were also extracted where applicable. The details of each simulation performed are provided in **Table S2**. Virtual populations were edited to match the demographic information noted in each of the reference studies used for model development and validation. The virtual trials were designed based on the dosing regimens and sampling schedules used in the corresponding reference studies. Eliglustat (free base) doses equivalent to the amounts of conjugated salts were used in the simulations when applicable.

Eliglustat PBPK model development

A summary of eliglustat PBPK model parameters with the sources for the information is detailed in **Table S1**. The development of the eliglustat PBPK model comprised of three stages. First, model parameters were extracted from the FDA's review document and used as an input to construct the eliglustat compound file within Simcyp. Second, the constructed eliglustat compound file was used to simulate eliglustat single-dose and steady-state PK as presented in a reference DDI study.[22] Third, drug exposures were compared between the simulated and reference studies for evaluation of model performance. The acceptance criteria of 50–150% of the reference values were used during the model

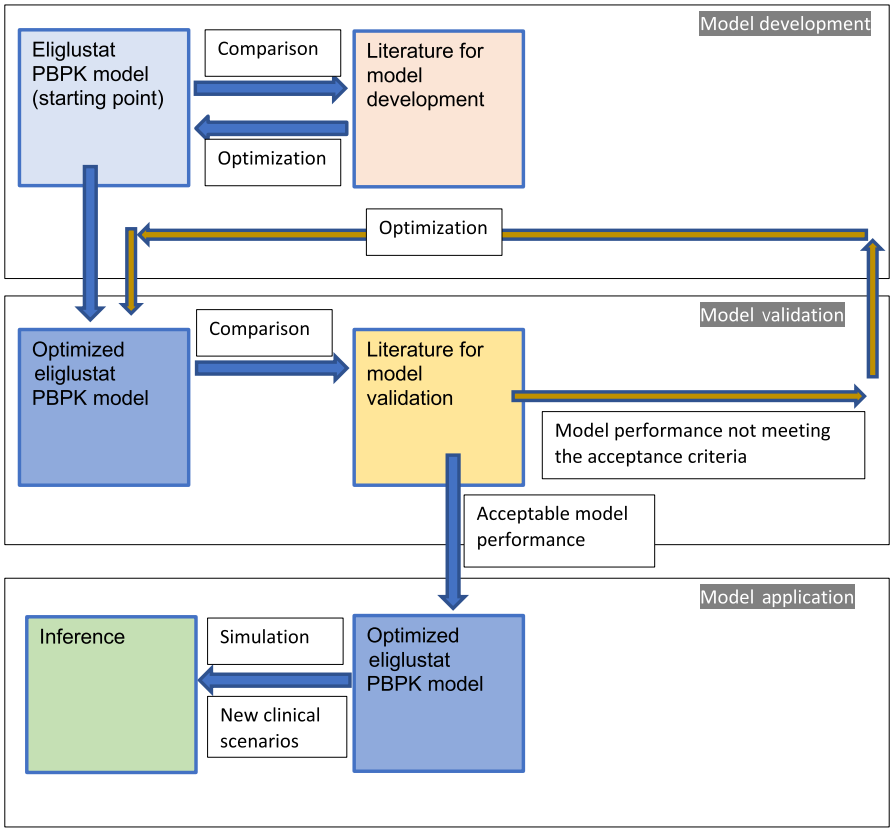

Figure 2 Overall study workflow showing stepwise model development, validation, and its application. Model development and optimization are shown as an iterative process. Following an acceptable model performance in the validation step, the model was used to simulate new interaction scenarios. The literature pieces used for model development and validation were mutually exclusive. PBPK, physiologically-based pharmacokinetic.

Table 1 Summary of the literature used in eliglustat model development and validation

Data	Dose / dosage form used in the reference	Use in eliglustat PBPK model	References
FDA's PBPK review of Cerdelga	N/A (information on *in vitro*, physicochemical and metabolic parameters of eliglustat is used for the PBPK model development)	Development	US FDA, Clinical Pharmacology Biopharmaceutics Review
Eliglustat single-dose PK, multiple-dose PK, and DDI with paroxetine	Eliglustat 84 mg b.i.d., oral capsule. Paroxetine, 30 mg q.d., oral	Development	Vu *et al*.[22]
Eliglustat single-dose PK, multiple-dose PK DDI with ketoconazole	Eliglustat 84-mg b.i.d., oral capsule, Ketoconazole, 400-mg q.d., oral	Development	Vu *et al*.[22]
Eliglustat single-dose PK	0.3, 1, 2, 5 mg/kg, oral, eliglustat tartrate formulated as a liquid containing 1% masking agent	Validation	Peterschmitt *et al*.[7]
Eliglustat single-dose PK (results not shown)	Eliglustat 84-mg oral capsule	Validation	Thibault *et al*.[8]
Eliglustat multiple-dose PK	50 mg, 200 mg in males and females (oral, gelatin capsules of eliglustat tartrate 50 mg and 100 mg)	Validation	Peterschmitt *et al*.[7]

b.i.d., twice daily; DDI, drug–drug interaction; N/A, not applicable; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; q.d., once daily.

development and validation.[6,17] If the model predictions were beyond the acceptable range, model optimization within biological plausibility was considered. All simulations executed during the model development stage were performed in 10 trials with each study design element set according to the reference study.

PBPK models of other compounds used in the study

The initial PBPK models and compound files for metabolic inhibitors ketoconazole and paroxetine were used from the Simcyp built-in repository. These compound files were modified according to the FDA's review document (**Table S1**). The constructed metabolic inhibitor compound files were used together with the constructed eliglustat compound file to simulate eliglustat drug exposures in various DDI settings presented in the literature.[22] Model predictions were evaluated using the statistical approach presented in the respective section below.

If the simulated AUC and C_{max} departed beyond 50–150% of the reference parameters, model optimization was considered necessary. Local sensitivity analyses were first performed to identify the most influential parameter in model predictions in the inhibitor interaction panel. Parameter values were adjusted across 100-fold of the original values, and the impact of the parameter changes on model predictions was visually inspected. Once identified, the influential parameter was then estimated using the parameter estimation toolbox in Simcyp using a Nelder-Mead method with weighted least squares as the objective function. The default termination criteria were used during the parameter estimation processes.

For fluvoxamine, the default compound file in Simcyp was used for simulating the eliglustat PK profile in the eliglustat and fluvoxamine coadministration scenario.

Eliglustat model validation

Model validation was performed using a fresh set of reference data that was not used in the model development. Eliglustat model validation was performed by simulating various dose levels at single dose and at steady state, and by comparing plasma concentration-time profiles of eliglustat against the corresponding reference profiles.[7] Exposure parameters such as AUC and C_{max} were also compared.

Statistical procedure for calculating PK parameter ratios

For the AUC calculations, the linear up and log down method was used within Simcyp. Throughout the present analysis, the magnitude of the predicted DDI was quantified as AUC and C_{max} ratios in the presence or absence of a perpetrator drug. The effects of paroxetine, ketoconazole, and fluvoxamine on eliglustat exposures (C_{max} and AUC) were assessed using geometric mean ratios (GMRs). GMR was computed using a linear mixed-effects model with a fixed-effect term for treatment and a random effect term for the patient.[22] Point estimates for the GMR and 90% confidence intervals (CIs) were calculated.

Eliglustat model applications

Simulations were conducted to explore new clinical scenarios. Each of the simulations was performed with 100 virtual participants. The metabolic capability i.e., CYP2D6 metabolizer phenotype of the virtual population, was controlled with the "Fixed Trial Design" option in Simcyp.[23] Median, 5th, and 95th percentiles for the simulated PK profiles were computed. The upper limit of safe concentration used was 250 ng/mL. Steady-state C_{max} and AUC of eliglustat were simulated with and without modulators.

Application 1: Assessing the appropriateness of the eliglustat doses used in participants with different CYP2D6 metabolic statuses. The FDA-recommended eliglustat dosage regimen is 84 mg twice daily (b.i.d.) in CYP2D6 EMs and IMs, and 84 mg once daily (q.d.) in CYP2D6 PMs.[9] These dosing regimens were simulated for 10 days. The percentage of virtual participants with at least one steady-state concentration exceeding 250 ng/mL was calculated. In the subsequent application (*Application 2*), the aim was to identify the eliglustat dose at which that percentage would plummet to null, indicating improved safety from the cardiac safety perspective.

Application 2: Evaluating the potential usefulness of lower doses of eliglustat in a ketoconazole coadministration setting. Simulations were performed over 10 days with eliglustat 84 mg b.i.d. in CYP2D6 EM and IM participants or 84 mg q.d. in CYP2D6 PM participants. To simulate coadministration with a DDI perpetrator, we administered a 400-mg q.d. dose of ketoconazole on Day 11 with a reduction of the

eliglustat dose to 84 mg q.d. in CYP2D6 EM or IM participants. The coadministration of these drugs was investigated on Day 19 either with a simultaneous administration or with a staggered administration, 12 hours apart, where eliglustat was given at 9:00 a.m. and ketoconazole at 9:00 p.m. The percentage of virtual participants with at least one steady-state concentration exceeding 250 ng/mL was calculated.

To explore the potential usefulness of lower doses in participants with CYP2D6 IM and PM phenotype, 42 and 21 mg doses of eliglustat were simulated with the same dosing interval adjustments as mentioned above. The percentage of virtual participants with at least one steady-state concentration exceeding 250 ng/mL was then calculated.

Application 3: Evaluation of changes in eliglustat exposure following coadministration of fluvoxamine. Simulations were performed over 10 days with eliglustat 84 mg b.i.d. in CYP2D6 EMs and IMs or 84 mg q.d. in CYP2D6 PMs. Consistent with the study design described by Lenze *et al*., 100 mg thrice daily dose of fluvoxamine was administered starting on Day 11 (ref. [24]). The magnitude of change in eliglustat steady-state exposure was assessed following coadministration of fluvoxamine.

RESULTS

Model development

A minimal PBPK model of eliglustat was developed. **Figure 3** shows the satisfactory performance of the eliglustat PBPK model by comparing the model-predicted drug exposure metrics, i.e., C_{max} and AUC, against the reference ones. Plasma concentration-time profiles following an eliglustat single dose, multiple dose, and coadministration with ketoconazole or paroxetine also suggested the model adequately characterized the observations. In the interaction settings, it was noted that compound files for ketoconazole and paroxetine could be optimized for better alignment between observed[22] and simulated results. The Simcyp parameter estimation toolbox improved model prediction for paroxetine, but not ketoconazole, wherein additional sensitivity analyses were performed to further optimize the model predictions. The optimized parameters were the competitive inhibitory constant (K_i) of ketoconazole on CYP2D6 and the maximum rate of inactivation (K_{inact}) for mechanism-based inhibition of paroxetine on CYP3A4, with the optimized values of 1.7 μM and 4.07/hour respectively.

Following optimization, the model adequately predicted the observed plasma concentration-time profiles of eliglustat (**Figure 3a,b**). Moreover, the predicted C_{max} and AUC following an eliglustat single dose, multiple-dose steady state, and steady state when coadministered with interacting drugs were in agreement with reference values (**Figure 3c,d**). We also compared the simulated and literature-reported GMR of C_{max} and AUC for eliglustat coadministered with ketoconazole and paroxetine (**Figure 4**). It should be noted that the GMRs of AUC and C_{max} calculated from the 10 simulated trials were randomly scattered around the observed values and were consistent with reference GMRs, suggesting little evidence of bias in model-simulated C_{max} and AUC.

Model validation

The reference plasma concentration-time profiles[7] were adequately characterized by the simulated data at various dose levels (**Figures 5** and **S1**). Additionally, the median C_{max} and AUC values were predicted within 50–150% of the reference values (**Figure 5**). Steady-state validation was also performed. The

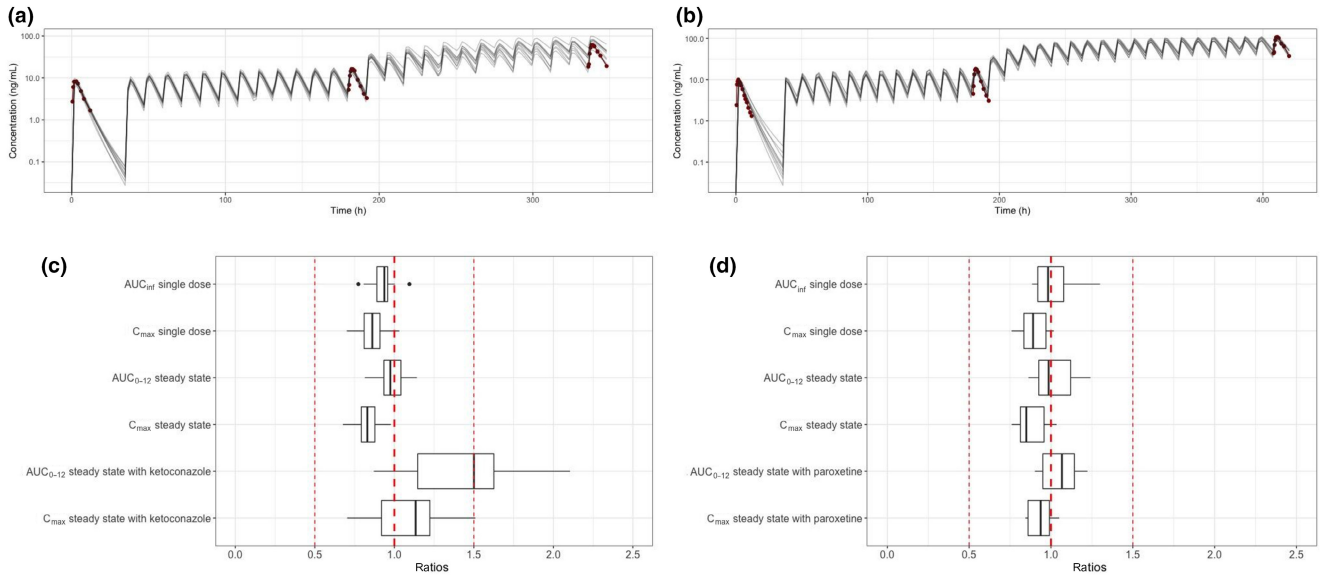

Figure 3 Predictive checks of developed eliglustat PBPK model. Predicted mean PK profiles when eliglustat was administered as an 84-mg single dose, at steady state following 84 mg b.i.d. and at steady state with (**a**) 400-mg q.d. ketoconazole and (**b**) 30-mg q.d. paroxetine. Gray lines are each trial's predicted mean PK profiles (10 trials in total). Red dots are the literature-reported mean PK profiles. Plots **a** and **b** are on a log scale. The ratio between predicted and observed C_{max} and AUC in (**c**) eliglustat and ketoconazole coadministration arm and (**d**) eliglustat and paroxetine coadministration arm. Thick dashed lines indicate the ratio of 1. Thin dashed lines represent ratios of 0.5 and 1.5. AUC, the area under the concentration-time curve; $AUC_{0\text{-}12}$, partial AUC; AUC_{inf}, area under the plasma concentration-time profile from time 0 extrapolated to infinite time; b.i.d., twice daily; C_{max}, maximum concentration; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic; q.d., once daily.

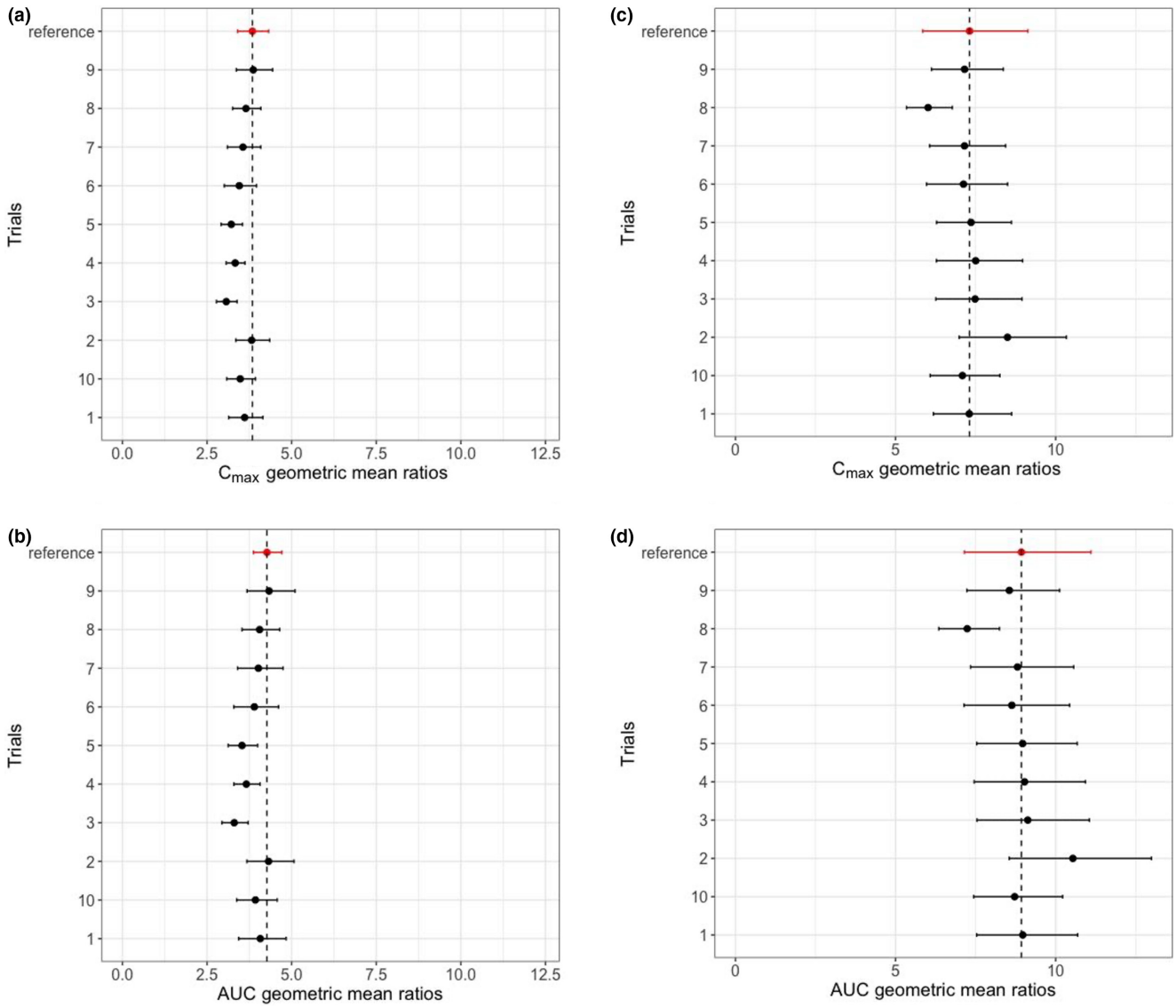

Figure 4 Predictive check for ketoconazole and paroxetine coadministration. Predicted vs. observed geometric mean ratios of (**a**) C_{max} and (**b**) AUC in eliglustat and ketoconazole coadministration arm. Predicted vs. observed geometric mean ratios of (**c**) C_{max} and (**d**) AUC in eliglustat and paroxetine coadministration arm. Dots represent geometric mean ratio, and error bars are the 95% confidence intervals. Red and black colors represent literature-reported (reference) and predicted ratios, respectively. AUC, the area under the concentration-time curve; C_{max}, maximum concentration.

side-by-side comparison of predicted and observed C_{max} and AUC (reported as mean (SD)) at varying doses is provided in Table 2. The model-predicted concentrations after repeated 50-mg dose (42-mg eliglustat free base) in male volunteers appeared to trend higher in comparison with the literature-reported profiles (Table 2; **Figure S1**). However, it is important to note that the observed plasma profiles are from a small number of volunteers ($N = 4$), and the reference study did not report individual CYP2D6 phenotypes. Thus, for these simulations, the trial design allowed random sampling for the individual CYP2D6 phenotype. Given that eliglustat PK heavily depends on the CYP2D6 phenotype of an individual, as it affects oral absorption, first-pass metabolism, and rate of clearance of eliglustat from the body,[6] in the context of not knowing the CYP2D6 phenotype explicitly, our predicted steady-state PK profiles were generally acceptable.

Model application

Applications 1 and 2. Model-simulated PK profiles in individuals with CYP2D6 EM, IM, and PM phenotypes following the administration of the FDA-recommended eliglustat doses are shown in **Figure S2**. Although eliglustat steady-state concentrations in IMs were higher than those in EMs, these concentrations were within the safety margin (<250 ng/mL) in all CYP2D6 phenotypes.

In contrast, the simulated eliglustat plasma concentration-time profiles when it was coadministered with ketoconazole either together or 12 hours apart (staggered), were observed to introduce safety concerns in CYP2D6 IMs and PMs (**Figure S3**). As summarized in **Table S3**, 41% and 25% of the simulated participants displayed at least one plasma concentration of

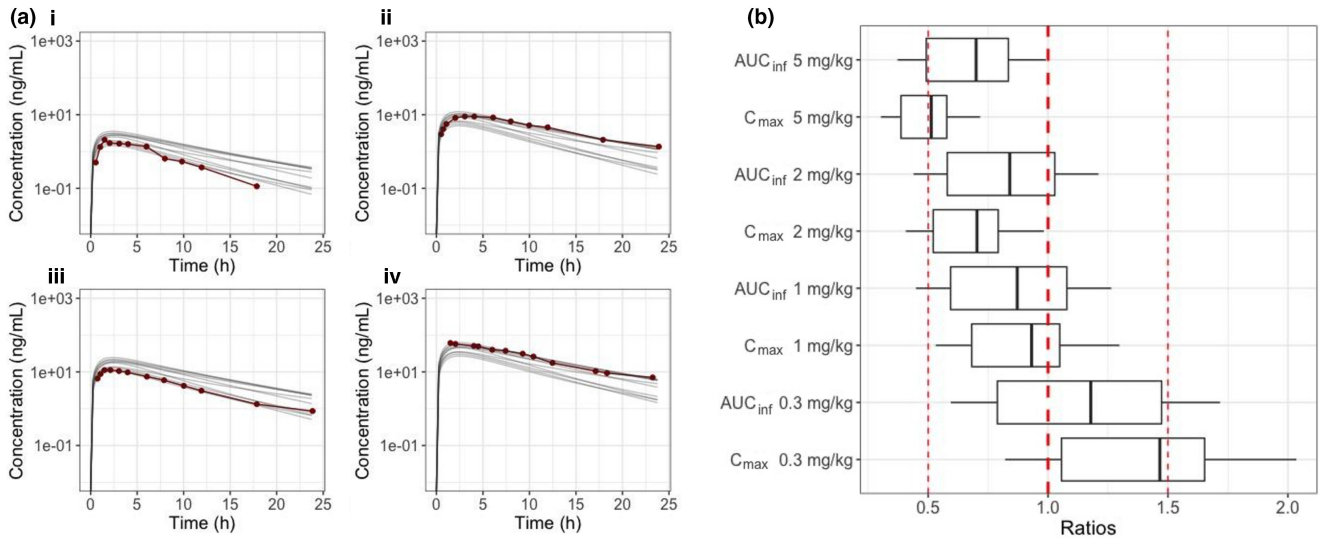

Figure 5 Model validation following single dose of eliglustat administration. (**a**) Predicted vs. observed concentration-time profiles when eliglustat was administered as a single dose of either (**i**) 0.3 mg/kg, (**ii**) 1 mg/kg, (**iii**) 2 mg/kg or (**iv**) 5 mg/kg. Gray lines are each trial's predicted mean PK profiles (10 trials in total). Red dots are the literature-reported mean PK profiles. Plots are on a log scale. (**b**) The ratio between predicted and observed C_{max} and AUC. Thick dashed lines indicate the ratio of 1. Thin dash lines represent ratios of 0.5 and 1.5. AUC, the area under the concentration-time curve; C_{max}, maximum concentration; PK, pharmacokinetic.

eliglustat ≥250 ng/mL in CYP2D6 IM and PM, respectively. As expected, with the FDA-recommended dose adjustments, i.e., switch from b.i.d. to q.d. dosing in EM, only 1% of the CYP2D6 EMs displayed at least one plasma concentration of eliglustat ≥250 ng/mL.

Given that safety concerns persisted after switching from 84 mg b.i.d. to q.d. in CYP2D6 IM patients, alternative eliglustat dose adjustments were explored. Adjusting the eliglustat dose from 84 mg b.i.d. to 42 mg q.d. or 21 mg q.d. when coadministered with ketoconazole in CYP2D6 IM and PM patients relieved the supratherapeutic concentrations and hence the safety concerns (**Figure S4a,b**). The proportion of patients with one or more plasma concentrations of eliglustat ≥250 ng/mL in CYP2D6 IM and PM patients reduced to 3% and 0%, respectively, when 42-mg and 21-mg doses were implemented.

Application 3. Prospective simulations of the interactions between eliglustat and fluvoxamine showed that the GMR of C_{max} was 2.9 in EMs and IMs, whereas it was only 1.63 in PMs. Similarly, the GMR of AUC was 3.36 in EMs and IMs, whereas it was only 1.79 in PMs. It was observed that no simulated participant had any steady-state concentration beyond the safety threshold of 250 ng/mL (**Figure S4c**).

DISCUSSION

While SRT is rarely offered to children and teenagers, ERT is frequently started before age 16–18 and must be continued throughout life for a sustained benefit.[25] The option for long-term maintenance therapy using an oral agent vs. an intravenous infusion offers several advantages, e.g., freedom from catheter-related infection risks, and acute and delayed infusion reactions.[26] Most notable is its impact on the quality of life in terms of the convenience of taking an oral therapy vs. a chronic biweekly infusion. Miglustat, the first introduced oral treatment for GD, is associated with gastrointestinal side effects due to inhibition of disaccharidase activity in the gut. The consequent risk of frequent osmotic diarrhea and abdominal bloating greatly limits the use of this second-line agent in clinical practice.[27,28] Eliglustat, on the other hand, a first-line agent, is not associated with disaccharidase inhibition, is generally very well tolerated in many patients, and has scored well on surveys of patient satisfaction, highlighting the clinical usefulness of improving eliglustat dosing and safety.[4,29,30]

Table 2 Eliglustat steady-state validation results

Dose/demographics	Observed C_{max} (ng/mL)	Simulated C_{max} (ng/mL)	Observed $AUC_{0\text{-}12}$ (h·ng/mL)	Simulated $AUC_{0\text{-}12}$ (h·ng/mL)
50 mg/male (*N* = 4)	3.72 (2.22)	14.1 (13.0)	21.4 (14.7)	114 (109)
50 mg/female (*N* = 4)	11.0 (2.74)	15.8 (14.0)	57.1 (13.8)	112 (111)
200 mg/male (*N* = 4)	111 (75.4)	68.3 (50.9)	496 (382)	557 (421)
200 mg/female (*N* = 4)	131 (105)	81.0 (62.2)	966 (797)	631 (485)

Table shows the predicted vs. observed C_{max} and AUC. Numbers are expressed as mean (SD). Observed parameter values are as reported for Day 10 of dosing by Pitterschmitt *et al*. (2011).
AUC, area under the concentration-time curve; AUC_{0-12}, partial AUC; C_{max}, maximum concentration.

Furthermore, after transitioning from ERT to eliglustat, some patients have had incremental improvement in splenomegaly and plasma biomarkers.[29,31,32]

An increasing number of patients, particularly as they age, can expect to acquire polypharmacy as they develop symptomatic comorbidities, either related or unrelated to GD1. A recent publication reports an analysis of US national databases of real-world prescription practices in patients (N = 374) with GD1. On average, a patient with GD1 uses seven comedications.[33] There are no literature reports of prescription trends in patients receiving eliglustat; nevertheless, it is reasonable to assume that it would be similar. Moreover, patients with a sizeable medication burden may never be offered the option of eliglustat because of added complexity in clinical management due to potential DDIs. Some such individuals conceivably could be candidates for eliglustat where, in conjunction with therapeutic drug monitoring, encapsulated doses of eliglustat lower than 84 mg are clinically available.

This study is the first to report the development and validation of a PBPK model for eliglustat that might improve its use in select patient populations, allowing more patients to safely take advantage of oral therapy for effective management of their GD1. We depended exclusively on publicly available information, such as FDA review documents and literature on eliglustat. Nevertheless, we presented robust results. The CYP2D6 phenotype has a prominent impact on the PK of eliglustat; with an 84-mg b.i.d. dose, the eliglustat systemic exposure (AUC) for CYP2D6 PM:IM:EM is roughly 7:3:1.[6] Since the dosing varies based on the CYP2D6 phenotypes, we studied the DDI impact in individuals of EM + IM and PM phenotypes in two separate simulations, when applicable. We chose to simulate the DDI between fluvoxamine and eliglustat because the original drug label does not address the scenario where the interacting drug (e.g., fluvoxamine) causes mild or moderate suppression of multiple CYPs.[34] Our simulations showed that the effect of fluvoxamine coadministration on eliglustat PK is lower than that observed with coadministration of ketoconazole or paroxetine, suggesting a dose adjustment or stoppage of eliglustat is not warranted from a cardiac safety point of view.

In this study, we showed the applicability of a PBPK model for assessing the applicability of lower eliglustat doses, despite not being clinically available. Testing lower doses was also suggested by the FDA as a postmarketing commitment for Cerdelga®.[35] The results of those postmarketing commitment studies are not published, causing a major knowledge gap. The only commercially marketed dose by the original sponsor is 84 mg; however, with the expiration of exclusivity and patent rights,[36] generic competitors[37] might invest in the development of lower doses. Besides, the lower doses (21 mg, 42 mg) were recently used in a pediatric clinical study[38] highlighting the need for lower doses, and perhaps indicating development efforts in that direction. Our simulation study could serve as a proof of concept that the 42 mg and 21 mg doses that seem to improve safety in the studied interaction scenarios would benefit patients by offering greater flexibility with eliglustat dosing. This is particularly important as innovative drugs enter the market and as emerging drug combinations get tested as a part of prevention and treatment searches for a range of morbid conditions (e.g., new infections like COVID-19).

Interestingly, the present model showed no difference in the simulated percentage of participants having at least one concentration above 250 ng/mL between the simultaneous and the staggered coadministration of eliglustat and ketoconazole (**Table S3**), although the simulated concentration-time profiles appeared to be different (in shape and appearance of the bands of 5th and 95th percentiles of the model-predicted PK profiles) between simultaneous and staggered administration (**Figures S3 and S4**). This may result from the relatively small number (N = 100) of participants simulated (**Table S2**) and the small difference in the simulated concentration ranges between the two coadministration scenarios. Nevertheless, the size of the simulation was adequate for addressing the objectives of the simulation scenarios. Additionally, the magnitudes of DDI between eliglustat and fluvoxamine across CYP2D6 phenotypes were somehow unexpected (GMR of AUC: 3.36 (EMs and IMs); 1.79 (PMs)). Fluvoxamine is a moderate CYP3A4 inhibitor and a weak CYP2D6 inhibitor.[34] Intuitively, the magnitudes of DDI between fluvoxamine and eliglustat should be higher in CYP2D6 PM individuals as compared with the CYP2D6 EM + IM individuals. However, it is noted that eliglustat itself is also a competitive and mechanism-based inhibitor of CYP2D6 as well as a competitive inhibitor of CYP3A4 (**Table S1**).[6] The self-inhibition of eliglustat was anticipated to increase the complexity of DDI between eliglustat and fluvoxamine to another dimension which may have led to the unintuitive DDI magnitudes simulated across CYP2D6 phenotypes.

There are several limitations to this study. Firstly, we digitized the plots from the published literature and although digitization makes up for the unavailability of raw data, it is not without some compromise on accuracy. It is widely accepted that sensitivity analyses and parameter estimation allow the renewed opportunity to optimize the model performance.[39] In this study, the sensitivity analyses and the parameter estimation were calculated from the extracted digitized data, making room for potential error. Secondly, owing to the lack of observed interaction data for DDI between eliglustat and fluvoxamine, it was not possible to optimize the fluvoxamine model file, and this study had to utilize the existing fluvoxamine model file as such from the model repository within Simcyp. Thirdly, the present model appeared to inadequately characterize the PK nonlinearity of eliglustat. As the dose of eliglustat increased, the model appeared to gradually underpredict the AUC and C_{max} (**Figure 5**). However, the model-predicted exposure metrics were still well captured within the prespecified threshold (50–150%) across the dose range studied when eliglustat is administered as a single dose. The mechanism behind the PK nonlinearity of eliglustat[6] may warrant further investigations, and a better PK model could be developed with a more mechanistic understanding to better characterize the dose nonlinearity of eliglustat PK. Lastly, in this study, we only studied eliglustat as a victim drug. As stated in the earlier sections of the manuscript, eliglustat can be a perpetrator in a coadministration setting owing to the time-dependent inhibition of CYP2D6.[6,7] Previously, eliglustat's effect as a perpetrator was studied using metoprolol as a marker substrate, as reported by Thibault *et al.*[8] Exploring eliglustat's potential as a perpetrator, perhaps checking if the lower doses have a different

or any clinical advantage to that effect, though out of scope for the current report, represents a promising future direction for extension of this work.

CONCLUSION

We report a validated PBPK model of eliglustat. The model provided valuable insights in clinically untested eliglustat DDI scenarios. Lower doses of eliglustat could be a useful alternative to the regular dose in DDI situations which currently lead to the contraindication of eliglustat. In the case of eliglustat, where the dosing is CYP2D6 genotype-guided, the developed PBPK model and its applications in evaluating DDIs can serve as a useful tool for guiding clinicians who care for patients with GD1.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

N.J.W. is a consultant, speaker for Sanofi, and a member of the Scientific Advisory Committee for the Sanofi-Genzyme Gaucher Registry. N.J.W. is also a consultant for Takeda Pharmaceutical Company Limited, Pfizer Inc, and Avrobio Inc. R.V.K. has received Investigator-Initiated Awards from the NIH, Ligand Pharmaceuticals, Pfizer Inc., and Sanofi for studies not related to the presented work. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

S.A.S. and S.C. wrote the manuscript. S.A.S., R.V.K., N.J.W., and M.A.K. designed the research. S.A.S. and S.C. performed the research. S.A.S., S.C., J.R.J., and N.J.W. analyzed the data.

1. Balwani, M. *et al*.Recommendations for the use of eliglustat in the treatment of adults with Gaucher disease type 1 in the United States. *Mol. Genet. Metab.* **117**, 95–103 (2016).
2. Rosenbloom, B. *et al*. The incidence of Parkinsonism in patients with type 1 Gaucher disease: data from the ICGG Gaucher Registry. *Blood Cells Mol. Dis.* **46**, 95–102 (2015).
3. Bennett, L.L. & Fellner, C. Pharmacotherapy of gaucher disease: current and future options. *P T.* **43**, 274–281 (2018).
4. Belmatoug, N. *et al*. Management and monitoring recommendations for the use of eliglustat in adults with type 1 Gaucher disease in Europe. *Eur. J. Intern. Med.* **37**, 25–32 (2017).
5. Caudle, K.E. *et al*. Standardizing CYP2D6 genotype to phenotype translation: consensus recommendations from the clinical pharmacogenetics implementation consortium and Dutch pharmacogenetics working group. *Clin. Transl. Sci.* **13**, 116–124 (2020).
6. Center for Drug Evaluation and Research. US Food and Drug Administration. Clinical Pharmacology and Biopharmaceutics Review(s). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf> (2009).
7. Peterschmitt, M.J. *et al*. Safety, tolerability, and pharmacokinetics of eliglustat tartrate (Genz-112638) after single doses, multiple doses, and food in healthy volunteers. *J. Clin. Pharmacol.* **51**, 695–705 (2011).
8. Thibault, N. *et al*. Effect of eliglustat on the pharmacokinetics of digoxin, metoprolol, and oral contraceptives and absorption of eliglustat when coadministered with acid-reducing agents. *Mol. Genet. Metab.* **129**, 278–285 (2020).
9. Full prescribing information [Cerdelga] (Eliglustat). <https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205494s003lbl.pdf> (2018).
10. Pey, A.L. Towards accurate genotype–phenotype correlations in the CYP2D6 gene. *J. Pers. Med.* **10**, 1–4 (2020).
11. Gaedigk, A., Dinh, J.C., Jeong, H., Prasad, B. & Leeder, J.S. Ten years' experience with the CYP2D6 activity score: a perspective on future investigations to improve clinical predictions for precision therapeutics. *J. Pers. Med.* **8**, 15 (2018). https://doi.org/10.3390/jpm8020015.
12. Ruskin, J.N. *et al*. How a concentration-effect analysis of data from the eliglustat thorough electrocardiographic study was used to support dosing recommendations. *Mol. Genet. Metab.* **131**, 211–218 (2020).
13. Almeida, A., de Frutos, L.L., Medrano-Engay, B., Ribate, P. & Giraldo, P. Metabolizing profile of the cytochrome pathway *CYP2D6*, *CYP3A4* and *ACBC1* transporter in Spanish Gaucher disease patients. *Mol. Genet. Metab.* **132**, S14 (2021).
14. Gaucher Community Alliance. <https://mailchi.mp/b096f14398cc/the-gca-spring-newsletter-is-here>.
15. Mistry, P. *et al*. Gaucher disease and SARS-CoV-2 infection: emerging management challenges. *Mol Genet Metab.* **130**, 164–169 (2020).
16. Storelli, F., Matthey, A., Lenglet, S., Thomas, A., Desmeules, J. & Daali, Y. Impact of CYP2D6 functional allelic variations on phenoconversion and drug–drug interactions. *Clin. Pharmacol. Ther.* **104**, 148–157 (2018).
17. Shebley, M. *et al*. Physiologically based pharmacokinetic model qualification and reporting procedures for regulatory submissions: a consortium perspective. *Clin. Pharmacol. Ther.* **104**, 88–110 (2018).
18. Moeyaert, M., Maggin, D. & Verkuilen, J. Reliability, validity, and usability of data extraction programs for single-case research designs. *Behav. Modif.* **40**, 874–900 (2016).
19. Aydin, O. & Yassikaya, M.Y. Validity and reliability analysis of the PlotDigitizer software program for data extraction from single-case graphs. *Perspect. Behav. Sci.* **45**, 239–257 (2021).
20. Drevon, D., Fursa, S.R. & Malcolm, A.L. Intercoder reliability and validity of WebPlotDigitizer in extracting graphed data. *Behav. Modif.* **41**, 323–339 (2017).
21. Ankit, R. WebPlotDigitizer Version: 4.5 <https://automeris.io/WebPlotDigitizer/> (2021).
22. Vu, L. *et al*. Effects of paroxetine, ketoconazole, and rifampin on the metabolism of eliglustat, an oral substrate reduction therapy for Gaucher disease type 1. *Mol. Genet. Metab. Rep.* **22**, 100552 (2020).
23. Certara UK Limited Help File. In *Simcyp Population Based Simulator (version 18/1) [Computer Software]* (2019).
24. Lenze, E.J. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA* **324**, 2292–2300 (2020).

25. Weinreb, N.J. *et al*. The diagnosis and management of Gaucher disease in pediatric patients: where do we go from here? *Mol. Genet. Metab.* **136**, 4–21 (2022).
26. Karimian, Z., Whitley, C.B., Rudser, K.D. & Utz, J.R.J. Delayed infusion reactions to enzyme replacement therapies. *JIMD Rep.* **34**, 63–70 (2017).
27. Belmatoug, N. *et al*. Gastrointestinal disturbances and their management in miglustat-treated patients. *J. Inherit. Metab. Dis.* **34**, 991–1001 (2011).
28. Full prescribing information [Zavesca] (Miglustat). <https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021348s010lbl.pdf> (2017).
29. Cox, T.M. *et al*. Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. *Blood* **129**, 2375–2383 (2017).
30. Cox, T.M. *et al*. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. *Lancet* **385**, 2355–2362 (2015).
31. Mistry, P.K. *et al*. Real-world effectiveness of eliglustat in treatment-naïve and switch patients enrolled in the international collaborative Gaucher group Gaucher registry. *Am. J. Hematol.* **95**, 1038–1046 (2020).
32. Kleytman, N. *et al*. Incremental biomarker and clinical outcomes after switch from enzyme therapy to eliglustat substrate reduction therapy in Gaucher disease. *Mol. Genet. Metab. Rep.* **29**, 100798 (2021).
33. Utz, J., Whitley, C.B., van Giersbergen, P.L.M. & Kolb, S.A. Comorbidities and pharmacotherapies in patients with Gaucher disease type 1: the potential for drug-drug interactions. *Mol. Genet. Metab.* **117**, 172–178 (2016).
34. US Food and Drug Administration. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers> (2022).
35. Center for Drug Evaluation and Research. Other review(s) <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000OtherR.pdf>.
36. PubChem. Eliglustat Depositor-Supplied Patent Identifiers <https://pubchem.ncbi.nlm.nih.gov/compound/Eliglustat#section=Depositor-Supplied-Patent-Identifiers&fullscreen=true> Accessed August 11, 2022.
37. FDA Orange Book cumulative supplement 8, August 2022: Eliglustat tartrate <https://www.fda.gov/media/72973/download>. Accessed July 31, 2022.
38. Lee, N.C. *et al*. Safety and efficacy of eliglustat combined to enzyme replacement therapy for lymphadenopathy in patients with Gaucher disease type 3. *Mol. Genet. Metab. Rep.* **31**, 100867 (2022).
39. Hsieh, N.H., Reisfeld, B., Bois, F.Y. & Chiu, W.A. Applying a global sensitivity analysis workflow to improve the computational efficiencies in physiologically-based pharmacokinetic modeling. *Front. Pharmacol.* **9**, 1–17 (2018).