Molecular Genetics and Metabolism Reports 22 (2020) 100552

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Effects of paroxetine, ketoconazole, and rifampin on the metabolism of eliglustat, an oral substrate reduction therapy for Gaucher disease type 1

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ARTICLE INFO

Keywords:
Eliglustat
Pharmacokinetics
Drug interactions
Paroxetine
Ketoconazole
Rifampin
CYP2D6 metabolism
OATP inhibitor

ABSTRACT

Eliglustat is an oral glucosylceramide synthase inhibitor indicated for the long-term treatment of adults with Gaucher disease type 1 and CYP2D6 extensive, intermediate, or poor metabolizer phenotypes. Eliglustat is metabolized primarily by CYP2D6 and to a lesser extent by CYP3A4 and is a substrate of P-glycoprotein (P-gp). Three studies evaluated the effects of paroxetine (strong CYP2D6 inhibitor), ketoconazole (strong CYP3A4 and P-gp inhibitor), and rifampin (strong CYP3A4/P-gp inducer; OATP inhibitor) on the pharmacokinetics of orally administered eliglustat in healthy adults. An 8.9-fold increase in eliglustat exposure following co-administration of multiple-dose eliglustat and paroxetine is attributed to inhibition of CYP2D6-mediated metabolism of eliglustat by paroxetine. A 4.3-fold increase in eliglustat exposure following co-administration of multiple-dose eliglustat and ketoconazole is attributed to inhibition of CYP3A4-mediated metabolism and/or P-gp-mediated transport of eliglustat by ketoconazole. Co-administration of eliglustat with oral doses of rifampin reduced eliglustat exposure by > 85% due to induction of CYP3A4/P-gp by rifampin, while a single intravenous dose of rifampin had no effect on eliglustat, confirming that eliglustat is not an OATP substrate. Depending on CYP2D6 metabolizer phenotype, co-administration of eliglustat with CYP2D6 and/or CYP3A inhibitors or CYP3A inducers may alter eliglustat exposure, warrant dosage adjustment or use with caution, or be contraindicated.

1. Introduction

Gaucher disease (GD) is one of the most prevalent lysosomal storage disorders, affecting approximately 1 in 40,000 people in the general population and 1 in 850 people of Ashkenazi Jewish ancestry [1]. GD type 1 (GD1) accounts for > 90% of all GD cases in Western countries [2,3]. GD1 is caused by a deficiency of acid β-glucosidase activity due to mutations in the acid β-glucosidase (*GBA*) gene. This reduced acid β-glucosidase activity leads to lysosomal accumulation of glucosylceramide and other substrates primarily in macrophages, which function to clear the blood of old and damaged cells [3]. These enlarged lipid-laden macrophages progressively infiltrate the reticuloendothelial organs (liver, spleen, and bone marrow) and lungs [3], leading to hepatosplenomegaly, anemia, thrombocytopenia, and skeletal complications.

Eliglustat (Cerdelga®, Sanofi Genzyme, Cambridge, MA, USA) is a first-line oral substrate reduction therapy indicated for the long-term treatment of adults with GD1 who are cytochrome P450 2D6 (CYP2D6) extensive (EM), intermediate (IM), or poor (PM) metabolizers (> 90% of GD1 patients [4,5]) [6,7]. The term "extensive metabolizer" is equivalent to the preferred term "normal metabolizer" in the new Clinical Pharmacogenetics Implementation Consortium guidelines [8]. The dosage of eliglustat varies depending on the CYP2D6 phenotype: 84 mg twice daily (BID) for CYP2D6 EMs and IMs and 84 mg once daily (QD) for CYP2D6 PMs [6,7]. Each 100-mg capsule of eliglustat tartrate contains 84 mg of eliglustat active moiety. Eliglustat is a ceramide analogue that is a specific and potent (in vitro IC_{50} = 24 nM) inhibitor of glucosylceramide synthase [9,10]. By partially blocking glucosylceramide synthesis, eliglustat helps to restore the balance between glucosylceramide synthesis and degradation, thereby reducing glucosylceramide accumulation in lysosomes and ameliorating symptoms [11]. Phase 2 and 3 trials in adult GD1 patients (NCT00358150; ENGAGE, NCT00891202; ENCORE, NCT00943111) have shown that eliglustat is effective and has a favorable safety and tolerability profile in both treatment-naïve patients [12,13] and patients previously stabilized on enzyme replacement therapy (ERT) [14,15]. Eliglustat is

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https://doi.org/10.1016/j.ymgmr.2019.100552
Received 17 December 2019; Accepted 17 December 2019

approved in > 50 countries, including the United States (US) [6], the European Union (EU) [7], Australia and Japan, as a first line therapy for the long-term treatment of adults with GD1 who are CYP2D6 EMs, IMs, or PMs.

Eliglustat is metabolized primarily by CYP2D6 and to a lesser extent by a second cytochrome P450 enzyme, CYP3A4 [16,17]. In previous studies of eliglustat in healthy volunteers, subjects with slower CYP2D6 metabolism experienced higher drug exposure following multiple doses [16]. Eliglustat is also a substrate of the efflux transporter P-glycoprotein (P-gp) [11]. Eliglustat could potentially be co-administered with other medications in GD patients, some of which may affect the CYP oxidative enzymes and/or transport systems. It is important to determine whether drugs that induce or inhibit these metabolic pathways and transport systems might result in clinically significant alterations of systemic eliglustat exposure. These three studies assessed the potential for a clinically relevant drug interaction by determining the pharmacokinetics (PK) and safety of eliglustat when administered alone and concurrently with paroxetine (a strong CYP2D6 inhibitor), ketoconazole (a strong inhibitor of CYP3A and P-gp), or rifampin (a strong inducer of CYP3A4 and intestinal P-gp, as well as an inhibitor of OATPs) in healthy adult subjects.

2. Materials and methods

2.1. Objective

Three separate studies were conducted to evaluate the effects of paroxetine, ketoconazole, and rifampin on the single- and multiple-dose PK, safety, and tolerability of eliglustat in healthy men and women.

2.2. Ethics

All studies were conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines established by the International Conference on Harmonization (ICH). The protocols and informed consent form were reviewed and approved by an institutional review board (IRB; PRACS Institute, Ltd., Fargo, ND, USA for the paroxetine and ketoconazole studies; IntegReview, Ltd., Austin, TX, USA for the rifampin study) complying with the requirements of United States Title 21 of Code of Federal Regulations Part 50 and the ICH E6(R1) before enrollment of subjects. All participants signed informed consent prior to enrollment.

2.3. Key inclusion and exclusion criteria

The studies enrolled men and non-pregnant women in good general health between 18 and 45 years old who weighed between 50 and 100 kg with a body mass index < 30 kg/m^2 (< 32 kg/m^2 in the rifampin study). Subjects were required to abstain from caffeine 2 h prior to and 4 h after dosing in each treatment period in the paroxetine and ketoconazole studies and 12 h before dosing until after the last 24-h PK sample was collected in the rifampin study; from alcohol throughout the paroxetine and ketoconazole studies and 48 h before dosing until completion of the safety follow-up visit in the rifampin study; from smoking during all three studies and for at least 6 months prior to providing informed consent in the rifampin study; from tobacco-containing products during the rifampin study; and from ingestion of products containing grapefruit or Seville oranges for 72 h in the paroxetine and ketoconazole studies and 2 weeks before and during the rifampin study. Subjects were excluded if they had a clinically significant laboratory or cardiac assessment (e.g., prolonged QT/QTc interval or history of risk factors for Torsades de Pointes) or used unapproved medications within 7 days prior to the first dose of study drug and throughout the remainder of the study in the paroxetine and ketoconazole studies or within 30 days (or 5 half-lives) before the first dose of study drug until completion of the safety follow-up visit in the rifampin study. Additionally, CYP2D6 PMs were excluded from the paroxetine and ketoconazole studies.

2.4. CYP2D6 genotyping

Molecular analysis of the CYP2D6 gene was performed at screening using the xTAG® CYP2D6 Kit from Luminex Corporation. The CYP2D6 assay incorporated multiplex polymerase chain reaction (PCR) and multiplex allele-specific primer extension with Luminex's proprietary Universal Tag sorting system on the Luminex® l00 / 200 Instrument. Raw data (mean fluorescence intensity signals) were analyzed by the xTAG® Data Analysis Software, and results were provided as qualitative calls. The alleles detectable using this platform were: *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *29, *35, *41 and duplicates. CYP2D6 phenotype was predicted based on genotype. Subjects were categorized as CYP2D6 ultra-rapid metabolizer (URM), EM, IM, or PM. The four predicted phenotypes follow the CYP2D6 activity score proposed by Gaedigk et al. [18] CYP2D6 phenotyping was part of subject selection for the paroxetine and ketoconazole studies, which were to include only CYP2D6 non-PMs, but not for the rifampin study, which allowed all phenotypes.

2.5. Study designs

Fig. 1 shows the study designs for each study.

2.5.1. Paroxetine study

This was an open-label, fixed-sequence study conducted at PRACS Institute, Ltd. (Fargo, ND, USA). The dose of eliglustat (84 mg BID) was selected from a previous Phase 1 clinical study that determined eliglustat 84 mg BID to be safe and well tolerated and represents the therapeutic dose for CYP2D6 EMs and IMs [16]. The dose of paroxetine (30 mg once daily QD) is within the approved therapeutic dose range and was selected for maximum CYP2D6 enzyme inhibition based on clinical drug-drug interaction studies that used paroxetine as a CYP2D6 enzyme inhibitor [19]. The three treatment periods were as follows: Screening (Day −21 to Day −2), Period 1 (Day −1 through morning of Day 2; single oral dose of eliglustat on Day 1), Period 2 (Day 2 starting with evening dose through Day 8 evening dose; repeated oral doses of eliglustat BID), Period 3 (Day 9 morning dose through the morning of Day 18; repeated oral doses of eliglustat BID and paroxetine 30 mg QD), and a Safety Follow-up visit (Day 25). Eliglustat doses were administered under fasted conditions (8 h before morning dose and 2 h before evening dose). Blood samples were collected for up to 36 h on Day 1, up to 12 h on Day 8, and up to 72 h on Day 18. Additional pre-dose samples were collected on Days 3 to 7 and 9 to 17. Plasma was obtained and analyzed for eliglustat concentrations.

2.5.2. Ketoconazole study

This was an open-label, fixed-sequence study conducted at PRACS Institute, Ltd. (Fargo, ND, USA). The dose of eliglustat (84 mg BID) was selected based on the same rationale as for the paroxetine study. The dose of ketoconazole (400 mg QD) is the highest approved therapeutic dose and was selected to maximize the potential for interaction based on clinical drug-drug interaction studies that used ketoconazole as a CYP3A enzyme inhibitor [19]. The three treatment periods were as follows: Screening (Day −28 to Day −2), Period 1 (Day −1 through evening of Day 2; single oral dose of eliglustat on Day 1), Period 2 (Day 2 starting with evening dose through Day 8 evening dose; repeated oral doses of eliglustat BID), Period 3 (Day 9 morning dose through the morning of Day 15; repeated oral doses of eliglustat BID and ketoconazole 400 mg QD), and Safety Follow-up (Day 22). Eliglustat doses were administered under fasted conditions (8 h before morning dose and 2 h before evening dose). Blood samples were collected for up to 36 h on Day 1, up to 12 h on Day 8, and up to 72 h on Day 15. Additional pre-dose samples were collected on Days 3 to 7, and 9 to 14. Plasma was obtained and analyzed for eliglustat concentrations.

Paroxetine Study

	Screening	Active Doses			Safety Follow-up
	Days -21 to -2	Day -1 to 2	Days 2 to 8	Days 9 to 18	Day 25
Dosage		Eli 84 mg PO x 1	Eli 84 mg PO BID	Eli 84 mg PO BID + paroxetine 30 mg PO QD	
PK sampling		Day 1	Day 8	Day 18	

Ketoconazole Study

	Days -28 to -2	Day -1 to 2	Day 2 to 8	Day 9 to 15	Day 22
Dosage		Eli 84 mg PO x 1	Eli 84 mg PO BID	Eli 84 mg PO BID + ketoconazole 400 mg PO QD	
PK sampling		Day 1	Day 8	Day 15	

Rifampin Study

	Days -60 to -2	Day 1	Days 2-6		Day 12	Days 13 to 17*	Day 24
Dosage (CYP2D6 PMs)		Eli 84 mg PO x 1	Eli 84 mg PO BID	Washout x 5 days	Eli 84 mg PO x 1 + rifampin 600 mg IV x 1	Eli 84 mg PO BID + rifampin 600 mg PO QD	
Dosage (CYP2D6 non-PMs)		Eli 127 mg PO x 1	Eli 127 mg PO BID		Eli 127 mg PO x 1 + rifampin 600 mg IV x 1	Eli 127 mg PO BID + rifampin 600 mg PO QD	
PK sampling		Day 1	Day 6		Day 1	Day 6	

* Six subjects received rifampin + eliglustat from Day 14 to 18 and additional doses of eliglustat on Day 13. Their blood samples for PK were drawn on Day 18.

BID: twice daily; Eli: eliglustat; PK: pharmacokinetic; PO: orally; QD: once daily.

Fig. 1. Summary of study designs.

2.5.3. Rifampin study

This was a single-site, unblinded, open-label, fixed-sequence, crossover, two-treatment period study conducted at PPD Development, LP (Austin, TX, USA). The dose of eliglustat was determined for each subject based on their CYP2D6 phenotype: CYP2D6 PMs received 84 mg doses and CYP2D6 non-PMs (EMs, IMs, and URMs) received 127 mg doses. The dose of rifampin (600 mg QD) is within the approved therapeutic dose range and was selected to ensure maximal induction of CYP and P-gp systems. The two treatment periods were as follows: Screening (Days −60 through −2), Period 1 (single oral dose of eliglustat on Day 1, followed by repeated doses of eliglustat BID for 5 days), Period 2 (single intravenous [IV] dose of rifampin 600 mg and a single oral dose of eliglustat on Day 12, followed by oral doses of rifampin 600 mg QD and eliglustat BID for 5 days), and a Safety Follow-up visit (Day 24). There was a washout period of at least 5 days between administrations of eliglustat in each treatment period. All morning doses (eliglustat and/or rifampin) were administered under fasted conditions (8 h prior to morning dose and, on Days 1 and 6, 4 h after morning eliglustat dose). Fasting was not required for evening doses. Blood samples were collected up to 24 h post-dose on Days 1 and 6 and at pre-dose on Days 3 to 5. Plasma was obtained and analyzed for eliglustat concentrations in Periods 1 and 2 and for rifampin concentrations in Period 2. It should be noted that the 127 mg dose of eliglustat administered during this study is higher than the approved dose of 84 mg.

2.6. Bioanalysis

Plasma concentrations of eliglustat were measured at Charles River Laboratories, Quebec, Canada, using a validated liquid-tandem mass spectrometry method with lower limits of quantification of 0.5 ng/mL (paroxetine study) or 0.2 ng/mL (rifampin and ketoconazole studies). For quantification of eliglustat, human plasma samples were protein-precipitated with acetonitrile (ACN) containing the internal standard (^{13}C stable isotope of eliglustat). The mixture was vortexed and then diluted with sodium phosphate buffer (25 mM; pH 7.4). The resulting sample was centrifuged, and an aliquot of the supernatant was extracted by solid phase extraction (SPE) using Waters (Milford, MA, USA) Oasis HLB SPE 96-well plate. The final SPE eluent was dried under a stream of nitrogen, and the residues were reconstituted in 0.2% formic acid in water:ACN, 75:25 (v/v). The reconstituted samples were then injected into a liquid chromatographic system equipped with Merck Chromolith SpeedROD RP-18e (50 × 4.6 mm id) column using formic acid in water (0.1:99.9, v/v) and formic acid in acetonitrile (0.1:99.9, v/v) as eluants (60:40, v/v). A triple quadrupole tandem mass spectrometer detector operated with atmospheric-pressure chemical ionization was used. The mass spectrometer was operated in the positive multiple reaction monitoring mode monitoring transitions: m/z 405.31 → 84.02 for eliglustat and m/z 409.31 → 84.08 for 13C stable isotope of eliglustat. The method was validated for two calibration ranges: 0.500 to 1000 ng/mL (high range) and 0.200 to 200 ng/mL (low range). For both calibration ranges, the intra-run and inter-run

accuracies (M%D) were within 15% of nominal values and the intra-run and inter-run precisions (CV%) were < 15%. Assay reproducibility was further confirmed by incurred sample reanalysis (ISR), and assay specificity was demonstrated in the presence of selected concomitant medication.

2.7. Pharmacokinetic analysis

Eliglustat PK parameters were calculated using non-compartmental analysis (WinNonLin, Pharsight, St. Louis, MO, USA) and included maximum concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration (AUC) versus time curve extrapolated to infinity ($AUC_{0-\infty}$), terminal half-life ($t_{1/2z}$) after single dose, and C_{max}, t_{max}, and AUC versus time curve over dosing interval ($AUC_{0-\tau}$) after repeated doses.

2.8. Statistical analysis

The effects of paroxetine, ketoconazole, and rifampin on eliglustat pharmacokinetics were assessed for the log-transformed PK parameters using a linear mixed-effects model with a fixed term for treatment and a random term for subject. The estimate and 90% confidence interval (CI) for the ratio of parameters was calculated by first computing the estimate with CI of the difference between treatments (eliglustat + concomitant drug versus eliglustat alone) in the linear mixed model framework, and then converting to ratios of adjusted geometric means using the anti-log transformation.

2.9. Safety assessments

Safety measurements included treatment-emergent adverse events (AEs), clinical laboratory testing, vital signs, physical exams, alcohol and drug testing, serum or urine pregnancy testing for women of childbearing potential, 12-lead electrocardiogram (ECG), and 12 h of continuous telemetry. Treatment-related AEs were defined as any AE that was assessed as possibly, probably, or definitely related to study drug.

3. Results

3.1. Subject disposition and baseline characteristics

Subject demographics for all three studies are presented in Table 1. Of 36 subjects enrolled in the paroxetine study, 33 (91.7%) completed the study according to the protocol and three subjects (8.3%) discontinued prematurely due to AEs. Of the 36 subjects enrolled in the ketoconazole study, 33 subjects (91.7%) completed the study according to the protocol and three subjects (8.3%) discontinued prematurely due to family emergencies. The majority of participants in the paroxetine and ketoconazole studies (91.7% and 94.4%, respectively) were categorized as CYP2D6 EMs; no CYP2D6 PMs were enrolled in those studies. Of the 25 subjects enrolled in the rifampin study, 23 (92.0%) subjects completed the study, one subject discontinued prematurely due to a dosing error because of scheduling, and one subject discontinued due to a serious AE that was unrelated to study drug (traffic accident death). An additional subject with the same CYP2D6 genotype (EM) was enrolled to replace the subject who was lost because of a dosing error.

3.2. Pharmacokinetics

Fig. 2 displays the mean eliglustat plasma concentrations after administration of eliglustat alone or with paroxetine, ketoconazole, or rifampin.

3.2.1. Single and multiple-dose administration of eliglustat alone and in combination with paroxetine

In CYP2D6 non-PMs, following co-administration of eliglustat 84 mg BID with paroxetine 30 mg QD, eliglustat C_{max} and $AUC_{0-\tau}$ increased by 7.3- and 8.9-fold, respectively (7.0- and 8.4-fold in CYP2D6 EMs only) compared to eliglustat alone (Table 2). Median t_{max} was consistent at 2.0 h for single-dose and multiple-dose eliglustat treatment and was slightly increased to 3.0 h during co-administration.

After co-administration with eliglustat, paroxetine concentrations appeared to be about 1.5- to 2-fold higher than expected. Paroxetine concentrations increased to near steady-state by the last day of dosing with plasma trough concentrations on Day 18 ranging from 17.6 to 128 ng/mL. Since there was no paroxetine monotherapy arm in this study, no formal statistical analysis of the paroxetine PK was done.

3.2.2. Single and multiple-dose administration of eliglustat alone and in combination with ketoconazole

In CYP2D6 non-PMs, following co-administration of eliglustat 84 mg BID with ketoconazole 400 mg QD, eliglustat C_{max} and $AUC_{0-\tau}$ increased by 3.8- and 4.3-fold, respectively (4.0- and 4.4-fold in CYP2D6 EMs only) compared to eliglustat alone (Table 2). Median t_{max} was consistent, ranging from 1.6 h and 2.0 h following a single dose and multiple-doses of eliglustat, respectively, to 2.3 h during co-administration.

Table 1
Subject demographics and baseline characteristics.

	Paroxetine study (N = 36)	Ketoconazole study (N = 36)	Rifampin study (N = 25)
Sex			
Female	19 (52.8%)	18 (50.0%)	5 (20.0%)
Male	17 (47.2%)	18 (50.0%)	20 (80.0%)
Age, years, mean (min, max)	24.6 (18, 39)	25.8 (18, 45)	27.3 (19, 41)
Weight, kg, mean (min, max)	69.5 (51.3, 91.7)	72.2 (50.8, 98.1)	74.5 (54.9, 99.1)
Body mass index kg/m^2, mean (min, max)	24.2 (18.6, 29.0)	25.5 (20.6, 29.4)	25.1 (20.5, 30.7)
Race			
American Indian/Alaskan Native	3 (8.3%)	4 (11.1%)	0 (0.0%)
Asian	1 (2.8%)	2 (5.6%)	0 (0.0%)
Black/African American	1 (2.8%)	1 (2.8%)	5 (20.0%)
Native Hawaiian/Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	31 (86.1%)	29 (80.6%)	20 (80.0%)
CYP2D6 phenotype			
Poor metabolizer	0 (0.0%)	0 (0.0%)	6 (24.0%)
Intermediate metabolizer	1 (2.8%)	0 (0.0%)	2 (8.0%)
Extensive metabolizer	33 (91.7%)	34 (94.4%)	12 (48.0%)
Ultra-rapid metabolizer	2 (5.6%)	2 (5.6%)	5 (20.0%)

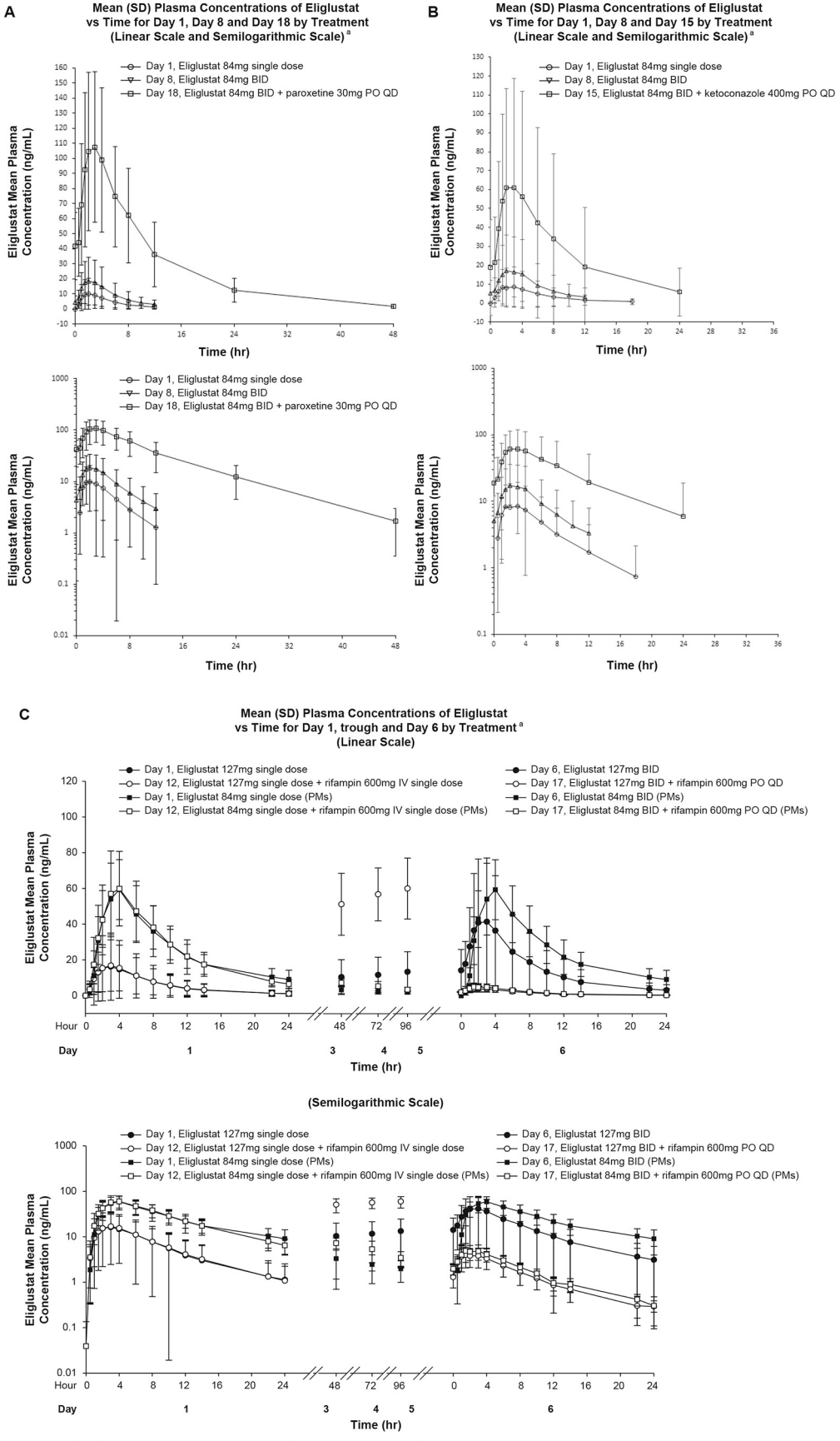

Fig. 2. Mean (SD) eliglustat plasma concentrations after administration of eliglustat alone or with (A) paroxetine, (B) ketoconazole, and (C) rifampin in CYP2D6 non-PMs and CYP2D6 PMs. All subjects, linear and semilogarithmic scales. PM: CYP2D6 poor metabolizer; BID: twice daily; QD: once daily; PO: orally administered.

Table 2
Mean (SD) PK parameters of single and multiple-dose administration of eliglustat in the presence and absence of paroxetine and ketoconazole in healthy men and women.

Parameters	Eliglustat 84 mg single dose		Eliglustat 84 mg BID		Eliglustat 84 mg BID + paroxetine 30 mg QD		Eliglustat 84 mg single dose		Eliglustat 84 mg BID		Eliglustat 84 mg BID + ketoconazole 400 mg QD	
	Day 1		Days 2 to 8		Days 9 to 18		Day 1		Days 2 to 8		Days 9 to 15	
	All (N = 36)	CYP2D6 EMs only (N = 33)	All (N = 36)	CYP2D6 EMs only (N = 33)	All (N = 33)	CYP2D6 EMs only (N = 30)	All (N = 36)	CYP2D6 EMs only (N = 34)	All (N = 33)	CYP2D6 EMs only (N = 31)	All (N = 33)	CYP2D6 EMs only (N = 31)
C_{max} (ng/mL)	10.7 (10.7)	10.9 (10.9)	19.3 (15.5)	19.4 (15.1)	110 (51.9)	110 (54.2)	9.87 (11.3)	10.3 (11.4)	18.6 (19.5)	19.5 (19.7)	67.2 (59.7)	71.0 (59.6)
$AUC_{0-\infty}$ (ng·h/mL)	78.1 (68.6)[a]	77.4 (68.4)[b]	–	–	–	–	73.2 (93.7)[c]	77.2 (95.2)[d]	–	–	–	–
$AUC_{0-\tau}$ (ng·h/mL)	–	–	120 (96.7)[c]	120 (92.3)	848 (415)[c]	847 (430)	–	–	113 (131)	119 (133)	474 (522)	501 (527)
t_{max} (h)	2.0 (1.0–4.0)	–	2.0 (0.5–3.0)	–	3.0 (1.5–4.0)	–	1.6 (0.5–3.05)	–	2.0 (1.0–4.0)	–	2.3 (1.0–4.0)	–
$t_{1/2z}$ (h)	4.2 (1.62)	–	–	–	–	–	5.1 (1.4)	–	–	–	–	–

a: N = 30; b: N = 28; c: N = 34; d: N = 32; e: median and range reported; $AUC_{0-\infty}$: area under the plasma concentration versus time curve extrapolated to infinity; $AUC_{0-\tau}$: area under the plasma concentration curve from time 0 to 12 h; BID: twice daily; C_{max}: maximum observed concentration; CYP: cytochrome P450; EM: extensive metabolizer; QD: daily; PK: pharmacokinetic; SD: standard deviation; t_{max}: time to achieve C_{max}, reported as median (minimum, maximum); $t_{1/2z}$: terminal elimination half-life.

3.2.3. Single-dose of eliglustat alone and in combination with IV rifampin

A single 30-min infusion of rifampin 600 mg administered with a single oral dose of eliglustat 84 mg (CYP2D6 PMs) or 127 mg (CYP2D6 non-PMs) had no effect on mean eliglustat exposure in CYP2D6 PMs and resulted in a minimal increase in eliglustat AUC (24% and 11%) in CYP2D6 EMs and in URMs, respectively (Table 3). Median t_{max} was similar (4 h) under both conditions in PMs, while t_{max} increased from 2.0 h to 3.0 h in CYP2D6 non-PMs. Mean $t_{1/2z}$ was slightly decreased when eliglustat was administered with IV rifampin compared with a single dose of eliglustat alone in CYP2D6 PMs and remained consistent in CYP2D6 non-PMs (Table 3).

3.2.4. Multiple-dose administration of eliglustat alone and in combination with oral rifampin

Following multiple administration of eliglustat 84 mg BID with oral rifampin 600 mg QD in CYP2D6 PMs, eliglustat C_{max} and $AUC_{0-\tau}$ were reduced by > 95% compared with eliglustat administered alone (Table 3). Median t_{max} was similar (2.5 and 3.0 h) in the presence and absence of rifampin, respectively. Following multiple administration of eliglustat 127 mg BID with oral rifampin 600 mg QD, eliglustat C_{max} and $AUC_{0-\tau}$ were reduced by > 85% in CYP2D6 non-PMs when compared with eliglustat administered alone (Table 3). Median t_{max} was similar (1.5 and 2.0 h) in the presence and absence of rifampin, respectively. Table 4 shows the treatment ratio estimates for eliglustat PK parameters in CYP2D6 PMs and non-PMs.

3.2.5. Eliglustat alone

In all three studies, after a single dose of eliglustat, the mean $t_{1/2z}$ ranged from 4.2 to 5.11 h. Following repeated doses of eliglustat, steady-state for eliglustat was achieved by approximately 4 days based on graphical examination of eliglustat plasma concentration before treatment administration during repeated dosing (C_{trough}) values.

3.3. Safety

Table 5 displays a summary of AEs in each study.

3.3.1. Paroxetine co-administration with eliglustat

Safety was assessed following a single dose of eliglustat (Day 1; N = 36), during multiple doses of eliglustat alone (Days 2 to 8; N = 36), and during concomitant dosing of eliglustat with paroxetine (Days 9 to 18; N = 35). The frequency of AEs was greater during concomitant dosing (194 events in 32 [91.4%] subjects) compared with multiple-dose eliglustat (31 events in 15 [41.7%] subjects). Two (5.6%) subjects reported treatment-related AEs following a single dose of eliglustat, and 10 (27.8%) subjects reported treatment-related AEs during multiple-dose eliglustat. Following concomitant dosing, 23 (65.7%) subjects reported AEs related to eliglustat, 25 (71.4%) subjects reported AEs related to paroxetine, and 23 (65.7%) subjects reported AEs possibly related to both eliglustat and paroxetine. Most of the treatment-related AEs reported throughout the study were mild in intensity. Moderate treatment-related AEs reported by more than two subjects included clinically significant increases in blood pressure in six (17.1%) subjects during concomitant dosing that was deemed probably related to paroxetine, headache in one (2.8%) and four (11.4%) subjects during multiple-dose eliglustat and concomitant dosing, respectively, moderate gastritis in two (5.6%) subjects following multiple-dose eliglustat, and application site dermatitis in 11 (31.4%) subjects during concomitant dosing. No deaths or serious AEs occurred, and no events were deemed severe in intensity. Three (8.3%) subjects discontinued treatment due to gastritis (eliglustat alone; possibly related), dizziness and nausea (concomitant dosing; dizziness possibly related to eliglustat and possibly related to paroxetine; nausea possibly related to eliglustat and probably related to paroxetine), and nausea and panic attack (concomitant dosing; nausea and panic attack both possibly related to eliglustat and probably related to paroxetine).

Table 3
Mean (SD) PK parameters of single- and multiple-dose administration of eliglustat in the presence and absence of rifampin in healthy men and women.

	Monotherapy period				Concomitant dosing period			
	Day 1		Days 2 to 6		Day 1		Days 2 to 6	
CYP2D6 PMs	Eliglustat 84 mg single dose		Eliglustat 84 mg BID		Eliglustat 84 mg single dose + rifampin 600 mg IV single dose		Eliglustat 84 mg BID + rifampin 600 mg oral QD	
C_{max} (ng/mL)	61.4 (17.8)		113 (36.1)		60.5 (22.0)		5.70 (2.50)	
$AUC_{0-\infty}$ (ng·h/mL)	627[a] (150)		–		676 (240)		–	
$AUC_{0-\tau}$ (ng·h/mL)	–		922 (304)		–		38.0 (11.8)	
t_{max} (h)*	4.0 (3.0, 4.0)		3.0 (3.0, 4.0)		4.0 (3.0, 4.0)		2.5 (1.5, 3.0)	
$t_{1/2z}$ (h)	8.9 (0.77)		–		6.9 (0.53)		–	
CYP2D6 Non-PMs	Eliglustat 127 mg single dose		Eliglustat 127 mg BID		Eliglustat 127 mg single dose + rifampin 600 mg IV single dose		Eliglustat 127 mg BID + rifampin 600 mg oral QD	
	Non-PMs (N = 19)	IMs/EMs only (N = 14)	Non-PMs (N = 19)	IMs/EMs only (N = 14)	Non-PMs (N = 19)	IMs/EMs only (N = 14)	Non-PMs (N = 18)	IMs/EMs only (N = 13)
C_{max} (ng/mL)	17.7 (19.8)	22.6 (21.2)	42.8 (36.4)	54.7 (35.4)	17.9 (14.6)	22.6 (14.2)	4.67 (3.02)	4.89 (3.30)
AUC (ng·h/mL)	154 (168)	198 (176)	–	–	165[b] (137)	220[c] (127)	–	–
$AUC_{0-\tau}$ (ng·h/mL)	–	–	295 (246)	378 (236)	–	–	29.3 (14.5)	31.0 (14.5)
t_{max} (h)*	2.0 (0.5, 4.0)	–	2.07 (1.0, 4.0)	–	3.0 (0.51, 6.0)	–	1.5 (0.68, 3.0)	–
$t_{1/2z}$ (h)	6.55 (27.1)	–	–	–	6.60 (27.8)[b]	–	–	–

* t_{max} reported as median (minimum, maximum); a: N = 5; b: N = 17; c: N = 12. $AUC_{0-\infty}$: area under the plasma concentration versus time curve extrapolated to infinity; AUC_{0-t}: area under the plasma concentration curve from time 0 to 12 h; BID: twice daily; C_{max}: maximum observed concentration; t_{max}: time to achieve C_{max}, reported as median (minimum, maximum); CYP: cytochrome P450; EM: extensive metabolizer; IM: intermediate metabolizer; IV: intravenous; Non-PMs: EMs, IMs, and ultra-rapid metabolizers; PM: poor metabolizer; QD: daily; t_{max}: time to achieve C_{max}, reported as median (minimum, maximum); $t_{1/2z}$: terminal elimination half-life.

3.3.2. Ketoconazole co-administration with eliglustat

Safety was assessed following a single dose of eliglustat (Day 1; N = 36), during multiple doses of eliglustat alone (Days 2 to 8; N = 34), and during concomitant dosing of eliglustat with ketoconazole (Days 9 to 15; N = 33). The frequency of AEs was slightly higher during the concomitant-dosing period (33 AEs in 16 [48.5%] subjects) compared with the multiple-dose eliglustat period (21 AEs in 11 [32.4%] subjects). Two (5.6%) subjects reported treatment-related AEs following a single dose of eliglustat, and 8 (23.5%) subjects reported treatment related AEs during multiple-dose eliglustat. Following concomitant dosing, 12 (36.4%) subjects reported AEs related to eliglustat, 11 (33.3%) subjects reported AEs related to ketoconazole, and 11 (33.3%) subjects reported AEs possibly related to both eliglustat and ketoconazole. AEs of moderate intensity included headache reported by one (2.9%) subject during multiple-dose eliglustat and dysmenorrhea reported by one (2.9%) subject during multiple-dose eliglustat and by one (3.0%) subject during concomitant dosing. Most treatment-related AEs were mild, except for a moderately severe event of headache reported by one (2.9%) subject, which was deemed possibly related to eliglustat and unlikely related to ketoconazole. There were no clinically significant prolongations of QTcF interval. All other AEs reported during the study were mild in intensity. There were no deaths, serious AEs, events deemed severe in intensity, or treatment discontinuations due to AEs.

3.3.3. Rifampin co-administration with eliglustat

Safety was assessed following a single dose of eliglustat (Day 1; N = 25), during multiple-dose eliglustat (Days 2 to 6; N = 8), and during concomitant dosing of eliglustat with IV (Day 12; N = 25) and oral rifampin (Days 13 to 17; N = 24). Five (20.0%) subjects reported treatment-related AEs following treatment with eliglustat alone. During concomitant dosing with IV rifampin, one (4.0%) subject reported an AE related to eliglustat and eight (32%) subjects reported AEs related to rifampin. During concomitant dosing with oral rifampin, 2 (8.3%) subjects reported AEs related to eliglustat and 3 (12.5%) subjects reported AEs related to rifampin. One subject discontinued the study after completing all study doses and assessments, except for a repeat laboratory assessment from the follow-up visit, because of a road traffic accident resulting in death that was unrelated to study drug. Overall, AEs were mild in severity except for three (12.0%) subjects who reported moderate AEs that were treatment-related. Nausea, vomiting, and retching was reported by one (4.0%) subject during the multiple doses of eliglustat alone, and dizziness was reported by one (4.0%) subject after completing multiple doses of eliglustat alone. One (4.0%) subject reported presyncope related to IV catheter insertion in preparation for IV rifampin. Apart from the accidental death, no other AEs were assessed as serious or severe, and all AEs resolved by the end of the study.

4. Discussion

Eliglustat is approved at a dosage of 84 mg twice daily for patients who are CYP2D6 EMs and IMs, as well as a reduced dose of 84 mg once daily for CYP2D6 PMs, and IM or EM patients who are taking certain concomitant medications also metabolized by the CYP2D6 and CYP3A pathways [6,7]. Treatment guidelines for eliglustat based on the US Prescribing Information and the European Union Summary of Product Characteristics (SmPC) include dosing recommendations based on CYP2D6 phenotype and concomitant use of CYP2D6 inhibitors with or without CYP3A inhibitors and CYP3A inducers [20,21]. CYP2D6 URMs, CYP2D6 indeterminate metabolizers, and patients in whom CYP2D6 genotype testing has not been performed are not eligible for eliglustat therapy. These treatment guidelines are a valuable resource in the treatment of GD1 patients for physicians who aim to offer their patients a daily oral therapy as a first-line alternative to ERT.

Co-administration of eliglustat with paroxetine, a strong CYP2D6 inhibitor, and ketoconazole, a strong CYP3A inhibitor, both of which were expected to reduce eliglustat metabolism, increased eliglustat concentrations. Co-administration of eliglustat with rifampin, a strong CYP3A inducer that was expected to increase eliglustat metabolism, significantly decreased eliglustat concentrations. Eliglustat concentrations did not significantly change following inhibition of the OATP1B1 and OATP1B3 transporters by a single dose of IV rifampin, which is a potent inhibitor of OATP under these conditions. The implications for concomitant medication use and rationale behind recommendations for dose adjustment or contraindication for concomitant use are discussed below. It should be noted that as a substrate of CYP2D6 and CYP3A, the metabolism of eliglustat in CYP2D6 EMs would be predominantly via the CYP2D6 pathway, with a lesser contribution of CYP3A. On the other hand, since CYP2D6 PMs have little or no CYP2D6 function, eliglustat

Table 4
Treatment ratio estimates (90% CI) for eliglustat PK parameters in the presence of paroxetine, ketoconazole, or rifampin (in CYP2D6 PMs and non-PMs).

	Treatment	Ratio (%) of geometric least squares mean	90% CI of ratio
Paroxetine (all subjects)			
Multiple Dose, Day 9			
C_{max}	Test: 30 mg paroxetine oral QD + 84 mg eliglustat oral BID (N = 33) Reference: 84 mg eliglustat oral BID alone (N = 36)	7.31	(5.85, 9.13)
$AUC_{0\text{-}t}$	Test: 30 mg paroxetine oral QD + 84 mg eliglustat oral BID (N = 33) Reference: 84 mg eliglustat oral BID alone (N = 34)	8.93	(7.15, 11.1)
Ketoconazole (all subjects)			
Multiple Dose, Day 9			
C_{max}	Test: 400 mg ketoconazole oral QD + 84 mg eliglustat oral BID (N = 33) Reference: 84 mg eliglustat oral BID alone (N = 33)	3.84	(3.40, 4.32)
$AUC_{0\text{-}t}$	Test: 400 mg ketoconazole oral QD + 84 mg eliglustat oral BID (N = 33) Reference: 84 mg eliglustat oral BID alone (N = 33)	4.27	(3.87, 4.71)
Rifampin			
CYP2D6 PMs			
Single Dose, Day 1			
C_{max}	Test: 600 mg rifampin IV + 84 mg eliglustat oral (N = 6) Reference: 84 mg eliglustat oral (N = 6)	0.97	(0.86, 1.10)
$AUC_{0\text{-}\infty}$	Test: 600 mg rifampin IV + 84 mg eliglustat oral (N = 6) Reference: 84 mg eliglustat oral (N = 5[a])	0.95	(0.88, 1.03)
Multiple Dose, Day 6			
C_{max}	Test: 600 mg rifampin oral QD + 84 mg eliglustat oral BID (N = 6) Reference: 84 mg eliglustat oral BID alone (N = 6)	0.05	(0.04, 0.06)
$AUC_{0\text{-}t}$	Test: 600 mg rifampin oral QD + 84 mg eliglustat oral BID (N = 6) Reference: 84 mg eliglustat oral BID alone (N = 6)	0.04	(0.03, 0.05)
CYP2D6 non-PMs			
Single Dose, Day 1			
C_{max}	Test: 600 mg rifampin IV + 127 mg eliglustat oral (N = 19) Reference: 127 mg eliglustat oral alone (N = 19)	1.19	(0.98, 1.44)
$AUC_{0\text{-}\infty}$	Test: 600 mg rifampin IV + 127 mg eliglustat oral (N = 17[b]) Reference: 127 mg eliglustat oral alone (N = 19)	1.19	(0.98, 1.45)
Multiple Dose, Day 6			
C_{max}	Test: 600 mg rifampin oral QD + 127 mg eliglustat oral BID (N = 18[b]) Reference: 127 mg eliglustat oral BID alone (N = 19)	0.16	(0.11, 0.22)
$AUC_{0\text{-}t}$	Test: 600 mg rifampin oral QD + 127 mg eliglustat oral BID (N = 18[b]) Reference: 127 mg eliglustat oral BID alone (N = 19)	0.15	(0.11, 0.21)

$AUC_{0\text{-}\infty}$: area under the plasma concentration versus time curve extrapolated to infinity; $AUC_{0\text{-}t}$: area under the plasma concentration curve from time 0 to 12 h; BID: twice daily; CI: confidence interval; C_{max}: maximum observed concentration; CYP: cytochrome P450; IV: intravenous; Non-PMs: extensive, intermediate, and ultra-rapid metabolizers; PM: poor metabolizer; QD: daily.

[a] One subject was not evaluable for PK parameters estimation.

[b] Three subjects were not evaluable for PK parameter estimation.

metabolism would almost exclusively be via the CYP3A pathway in this population, thus rendering the potential for interaction with CYP2D6 inhibitors of any potency negligible. Overall, the magnitude of drug interaction would depend on CYP2D6 phenotype and if the pathway inhibited is the CYP2D6 pathway (CYP2D6 EMs > IMs > PMs) or CYP3A pathway (CYP2D6 PMs > CYP2D6 IMs > CYP2D6 EMs).

The distribution of CYP2D6 phenotypes in the studies is similar to what is seen in the general population [22] and also reflects what was seen among the 393 patients with Gaucher disease treated with eliglustat in a phase 2 or 3 clinical trial [5,23]. In both the general population and among patients with GD1, approximately 80% of individuals have a CYP2D6 EM phenotype. The results of these studies, along with other clinical and preclinical data, have been used to develop a physiologically-based pharmacokinetic (PBPK) model for predicting pharmacokinetics of eliglustat administered in combination with moderate or weak CYP2D6 and/or CYP3A inhibitors in subjects with various CYP2D6 phenotypes [24]. This PBPK model was further used to predict pharmacokinetics of eliglustat in these drug interaction scenarios in patients with hepatic impairment.

4.1. Effect of paroxetine and concomitant use of CYP2D6 inhibitors with eliglustat

Paroxetine is an orally administered psychotropic drug that is metabolized primarily by CYP2D6 and is known to be a strong inhibitor of CYP2D6 [17]. It is therefore used as a probe CYP2D6 inhibitor to assess

Table 5
Summary of adverse events in studies of eliglustat co-administration with paroxetine, ketoconazole, or rifampin.

	Paroxetine study (N = 36)		Ketoconazole study (N = 36)		Rifampin study (N = 25)	
	Number of subjects N (%)	Number of events N	Number of subjects N (%)	Number of events N	Number of subjects N (%)	Number of events N
Any adverse event (AE)	33 (91.7%)	233	20 (55.6%)	58	17 (68.0%)	65
Any treatment-related AE	26 (72.2%)	155	15 (41.7%)	45	11 (44.0%)	39
Severe AEs	0 (0.0%)	0	0 (0.0%)	0	1 (4%)	1[a]
Serious AEs	0 (0.0%)	0	0 (0.0%)	0	1 (4%)	1[a]
Discontinuations due to AE	3 (8.3%)	5	0 (0.0%)	0	1 (4%)	1[a]

[a] One subject experienced a serious AE of road traffic accident that resulted in death that the investigator assessed as severe and unrelated to eliglustat or rifampin.

the effect on substrates of CYP2D6 such as eliglustat. The 7- to 9-fold increase in eliglustat mean PK parameters in CYP2D6 non-PMs following concomitant dosing with paroxetine when compared to multiple-dose eliglustat alone is consistent with *in vitro* data for eliglustat.

Eliglustat was well tolerated when administered alone and with paroxetine. Most AEs were mild to moderate in intensity and transient. However, there was an increased frequency of AEs when eliglustat was administered concomitantly with paroxetine. Several AEs (hypertension, tachycardia, nausea, diarrhea, headache, feeling cold, cold sweat, tremor, and mood changes) that occurred during concomitant dosing are known AEs for paroxetine and likely due to increased paroxetine exposure during concomitant dosing since paroxetine is also metabolized by CYP2D6 and eliglustat is a direct and time-dependent inhibitor of CYP2D6. This interaction was explored in a separate study that evaluated the effect of eliglustat on the PK of metoprolol, a sensitive CYP2D6 substrate, in healthy adult CYP2D6 non-PMs [25].

Overall, co-administration of eliglustat with a potent metabolic inhibitor such as paroxetine can significantly increase eliglustat exposure in CYP2D6 non-PMs. Therefore, concomitant use of eliglustat with strong CYP2D6 inhibitors in GD1 patients with CYP2D6 EM or IM phenotype warrants a reduction in eliglustat dose, requires additional monitoring, and/or is contraindicated depending on the local prescribing information. Taking into account the substantial effect observed with a strong CYP2D6 inhibitor, dose adjustment of eliglustat may also be needed for coadministration with moderate CYP2D6 inhibitors. For medications that exhibit dose-dependent inhibition of CYP2D6, physicians should reassess the dose of eliglustat in the case that the dose of the concomitant medication changes.

Concomitant administration of a CYP2D6 inhibitor would not be expected to alter eliglustat metabolism in CYP2D6 PMs since the CYP2D6 pathway is minimally functional in these patients, and therefore alteration in eliglustat dose for co-administration with CYP2D6 inhibitors is not warranted in this population.

4.2. Effect of ketoconazole and concomitant use of CYP3A inhibitors with eliglustat

Oral ketoconazole is a systemic broad-spectrum antifungal agent and a strong inhibitor of CYP3A and P-gp [17]. It is used as a probe CYP3A4 inhibitor to assess the effect on substrates of CYP3A4 such as eliglustat. To ensure the safety of patients administered eliglustat, it is important to define the impact of drugs that inhibit CYP3A and/or P-gp, such as ketoconazole, on eliglustat exposure.

The 4-fold increase in eliglustat exposure when co-administered with ketoconazole shows an interaction consistent with ketoconazole's inhibition of CYP3A-mediated metabolism, inhibition of P-gp efflux in the gut, or both. Co-administration of eliglustat with a strong metabolic inhibitor, such as ketoconazole, is expected to result in significant increases in eliglustat exposure, which may require a temporary dose reduction or the exclusion of CYP3A and/or P-gp inhibitors as concomitant medications. Overall, eliglustat administered alone and with ketoconazole was well tolerated. However, the use of eliglustat with strong CYP3A inhibitors may warrant a reduction in eliglustat dose, require additional caution, or be contraindicated in GD1 patients of CYP2D6 EM and IM phenotype, depending on the local prescribing information [6,7]. In CYP2D6 PMs, the elimination of eliglustat is almost entirely via the CYP3A pathway since the CYP2D6 pathway is minimally functional. Therefore, in GD1 patients of CYP2D6 PM phenotype, the use of eliglustat with CYP3A inhibitors may be contraindicated, not recommended, or allowed with caution, depending on the potency of the inhibitor.

4.3. Effect of rifampin and concomitant use of CYP3A inducers with eliglustat

Rifampin, a semisynthetic antibiotic indicated for the treatment of tuberculosis, is a potent inducer of intestinal and hepatic CYP3A enzymes and intestinal P-gp transporters, as well as an inhibitor of OATPs [17,26].

After a single IV infusion, rifampin is used as a probe OATP potent inhibitor in clinical drug interaction studies [27,28]. In vitro data showed that eliglustat is not a substrate of OATPs. These data are consistent with the negligible changes in eliglustat exposure (< 19%) observed in the presence of a single IV infusion of rifampin.

After repeated oral administration, rifampin is used as a probe CYP3A/P-gp potent inducer in clinical drug interactions studies. After repeated co-administration of eliglustat with oral rifampin, substantial decreases in eliglustat exposure were observed, consistent with rifampin's induction of intestinal and hepatic CYP3A that leads to enhanced first-pass metabolism. The slightly greater effect of rifampin on eliglustat exposure observed in CYP2D6 PMs is consistent with the greater relative contribution of CYP3A to eliglustat metabolism in CYP2D6 PMs.

Overall, eliglustat administered alone and with rifampin was well tolerated. Co-administration of eliglustat with a potent metabolic inducer, such as rifampin, is expected to result in significant reductions in eliglustat exposure and may require the exclusion of inducers as concomitant medications. This significant drug-drug interaction has implications for patient therapy as strong CYP3A inducers will likely reduce efficacy of eliglustat. As such, the use of eliglustat with strong CYP3A inducers is not recommended in GD1 patients who are CYP2D6 EMs, IMs, or PMs [6,7].

4.4. Concomitant use of CYP2D6 and CYP3A inhibitors with eliglustat in adults with GD1

Eliglustat is contraindicated for CYP2D6 EMs or IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor. These scenarios would impair the two main pathways of eliglustat metabolism and result in substantially elevated eliglustat exposure. The US and EU drug labels for eliglustat include recommendations for dose adjustments of eliglustat when taking other concomitant medications beyond those discussed in the studies reported herein [6,7]. Physicians should refer to local labeling recommendations.

4.5. Conclusions

Depending on a GD1 patient's CYP2D6 phenotype, co-administration of eliglustat with CYP2D6 and/or CYP3A4 inhibitors may increase eliglustat exposure, and thus, warrants dosage adjustment, requires additional caution, and/or is contraindicated. Additionally, co-administration of eliglustat with strong CYP3A inducers will likely reduce efficacy of eliglustat and is not recommended.

Funding

This research was sponsored by Sanofi Genzyme. Jennifer Ibrahim, M. Judith Peterschmitt, Leorah Ross, Nathan Thibault, and Sandrine Turpault are currently employed by Sanofi Genzyme. Gerald F. Cox is a former employee of Sanofi Genzyme. Lucie Vu is a former postdoctoral fellow of Sanofi Genzyme/MCPHS University.

Author contributions

M. Judith Peterschmitt was involved in study design. All authors analyzed and interpreted the data. Lucie Vu drafted the manuscript. All authors reviewed early and final drafts of the manuscript and were fully responsible for the content and editorial decisions related to this manuscript.

Acknowledgements

The authors gratefully acknowledge the contributions of Yiding Hu, PhD, Kenneth Liu, PharmD, Stacy Ho, PhD, and Vanaja Kanamaluru, PhD, of Sanofi Genzyme, and Laurie LaRusso of Chestnut Medical Communications (funded by Sanofi Genzyme) in preparation of this manuscript.

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