CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205494Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA	205494/SDN33
Submission Date:	6/25/2014
Brand Name	Cerdelga®
Generic Name	Eliglustat Tartrate
OCP review team	Elizabeth Shang [Primary Reviewer] Ping Zhao [PBPK Lead] Sarah Dorff [GTT Reviewer] Sue-Chih Lee [DCP3 Team Leader]
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Genzyme
Formulation; Strength(s)	Oral Capsule; 84 mg (free base)
Proposed Indication:	Long-term treatment of adult patients with Gaucher disease type 1

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1. Executive Summary

This review addendum contains: 1) the review of the sponsor's proposed reclassification of CYP2D6 phenotypes in healthy subjects, 2) the assessment of the impact of the reclassification on characterizing eliglustat pharmacokinetics (PK) in CYP2D6 extensive metabolizers (EMs) and intermediate metabolizers (IMs), and subsequently dose adjustment of eliglustat in various drug-drug interaction (DDI) scenarios, and 3) (b) (4) which was still under discussion when the original Clinical Pharmacology Review was filed in DARRTS on June 16, 2014. During the Late Cycle Meeting on June 18, 2014, Genzyme informed the Agency that CYP2D6 phenotypes in subjects genotyped by the (b) (4) were reclassified after the original NDA submission to harmonize the data with phenotypes obtained from studies genotyped by (b) (4) As a result, the PK parameters of eliglustat as stratified by the CYP2D6 phenotype and the dose adjustment for several DDI scenarios were affected. With the acceptance of the CYP2D6 phenotype reclassification by the GTT reviewers, the PK and DDI information for the affected studies was re-evaluated, which is captured in Section 2 of this addendum. It was determined by pharmacometric reviewers that the reclassification did not impact the pharmacometric analysis.

(b) (4)

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP3) has reviewed the information in SDN33 as submitted on June 25, 2014. The rationale and algorithm for the reclassification of CYP2D6 phenotypes have been found to be acceptable. Accordingly, the PK parameters of eliglustat as stratified by CYP2D6 phenotype as well as the dosing recommendations for DDI scenarios are revised.

The following tables provide the revised DDI information, including the fold change in systemic exposures to eliglustat at 100 mg twice daily (BID) for EMs and IMs with different types of CYP inhibitors and relevant dosing recommendations. These replace the previous tables presented in Section 1.3.3 of the original Clinical Pharmacology Review.

Table 1. Effect of various CYP inhibitors on systemic exposure to Eliglustat and dose adjustment recommendations in CYP2D6 EMs

Perpetrator Drug(s)	Study	Cmax Ratios	AUC_{0-12h} Ratios	Cmax	AUC_{0-12h}	Dosing Recommendation
Paroxetine and ketoconazole (Strong CYP2D6 and CYP3A4 inhibitors)	PBPK Simulation	16.7	24.2	412	4470	Contraindicate
Terbinafine and fluconazole (Moderate CYP2D6 and CYP3A4 inhibitors)	PBPK Simulation	10.2	13.6	251	2512	Contraindicate
Paroxetine (30 mg QD) (Strong CYP2D6 inhibitors)	Dedicated* DDI Study	6.99	8.41	210	1429	100 mg once daily (QD)**
Terbinafine (Moderate CYP2D6 inhibitors)	PBPK Simulation	3.80	4.49	93.9	831	100 mg QD
Ketoconazole (400 mg QD) (Strong CYP3A4 inhibitors)	Dedicated* DDI Study	3.98	4.39	120	747	(b) (4)
Fluconazole (Moderate CYP3A4 inhibitors)	PBPK Simulation	2.77	3.21	68.5	593	

*Mean PK parameters (Cmax and AUC) presented here were scaled from healthy subjects to patients.
** This recommendation is based upon the results from dedicated DDI study (eliglustat BID) and PBPK simulation on interaction between eliglustat 100 mg QD and paroxetine 30 mg QD (Appendix 1).

Table 2. Effect of various CYP inhibitors on systemic exposure to Eliglustat and dose adjustment recommendations in CYP2D6 IMs

CYP Inhibitors	Study	Cmax Ratios	AUC_{0-12h} Ratios	Cmax	AUC_{0-12h}	Dosing Recommendation
Paroxetine and ketoconazole (Strong CYP2D6 and CYP3A4 inhibitors)	PBPK Simulation	7.48	9.81	470	5170	Contraindicate
Terbinafine and fluconazole (Moderate CYP2D6 and CYP3A4 inhibitors)	PBPK Simulation	4.16	4.99	261	2630	Contraindicate
Paroxetine (Strong CYP2D6 inhibitors)	PBPK Simulation	2.12	2.31	133	1220	100 mg QD*
Terbinafine (Moderate CYP2D6 inhibitors)	PBPK Simulation	1.55	1.64	97.2	866	100 mg QD
Ketoconazole (Strong CYP3A4 inhibitors)	PBPK Simulation	4.36	5.41	274	2850	Contraindicated
Fluconazole (Moderate CYP3A4 inhibitors)	PBPK Simulation	2.53	2.85	159	1500	Not recommended

* This recommendation is based upon the PBPK simulation results on interaction between eliglustat 100 mg QD and paroxetine 30 mg QD (Appendix 1).

Table 3. Effect of various CYP inhibitors on systemic exposure to Eliglustat and dose adjustment recommendation in CYP2D6 PMs

CYP Inhibitors	Study	Cmax Ratios	AUC_{0-24h} Ratios	Cmax	AUC_{0-24h}	Dosing Recommendation
Ketoconazole (Strong CYP3A4 inhibitors)	PBPK Simulation	4.27	6.22	321	5950	Contraindicate
Fluconazole (Moderate CYP3A4 inhibitors	PBPK Simulation	2.38	2.95	179	2820	Not recommended
Ranitidine (Weak CYP3A4 inhibitors)	See Appendix 1 for Justification					Not recommended

In the original review, (b) (4) This was based upon the fact that the sponsor had included paroxetine CYP3A inhibition in their PBPK modeling and simulation and the in vitro finding on the

inhibition of CYP3A by paroxetine in the published literature.[1] However, the Agency also acknowledges that no in vivo study on this matter has been found in the published literature. Additional PBPK simulation supported 100 mg QD dosing when eliglustat is co-administered with paroxetine in EMs and IMs, same for co-administration of a pure strong CYP2D6 inhibitor (Appendix 1). Therefore, the Agency decided not to differentiate paroxetine from other known CYP2D6 inhibitors in this label.

2 Summary of the Changes in Clinical Pharmacology Information

2.1 Reclassification of CYP2D6 Phenotype

Following the Late Cycle Meeting, the applicant provided subject level genotype data and reclassified phenotype data based on CYP2D6 activity score.[2] Reclassification resulted in phenotypes that are consistent with the phenotype interpretation of currently available FDA 510(k) cleared devices (xTAG® CYP2D6 Kit v3 and AmpliChip® Cytochrome P450 Genotyping test) and is acceptable. Four Phase 1 studies (GZGD00204, GZGD01807, GZGD02007, and GZGD02707) in healthy subjects genotyped by the (b) (4) were impacted as these studies were conducted before the FDA cleared devices were available. Since the two cleared tests result in the same phenotype results, the reclassification is acceptable. The main impact was that the majority of the IMs based upon (b) (4) genotype became EMs (**Table 4**). Consequently, there was only one IM subject who received 100 mg BID out of all the phase 1 studies in the eliglustat clinical program. No phenotype status change in PMs occurred.

Table 4. Number of subjects whose CYP2D6 phenotype was reclassified by Study ID.

Study ID	(b) (4) algorithm	(b) (4) algorithm	Change from (b) (4)
	IM	IM	
204	13	0	All → EM
1807	9	0	All → EM
2007	8	1	7 → EM
2707	3	0	All → EM
Total	**33**	**1**	**32/33 →EM**
	EM	EM	
204	5	5	No change
1807	7	6	1 → URM
2007	7	7	No change
2707	7	6	1 → URM
Total	26	24	2/26 → **URM**
	URM	URM	
204	2	1	1 → EM
1807	1	1	No Change
2007	1	1	No Change
2707	1	1	No change
Total	5	4	1/5 →**EM**

[1] von Moltke LL, Greenblatt DJ, Court MH, et al., Inhibition of alprazolam and desipramine hydroxylation in vitro by paroxetine and fluvoxamine: comparison with other selective serotonin reuptake inhibitor antidepressants. J Clin Psychopharmacol. 1995 Apr;15(2):125-31.
[2] Gaedigk A1, Simon SD, Pearce RE, et al., The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. Clin Pharmacol Ther. 2008 Feb;83(2):234-42.

Note: the number of subjects presented is the number of subjects screened, not the number of subjects available for PK analysis.

2.2 Revisions in Eliglustat PK in Healthy Subjects

The following subsections of the original Question-Based Review are revised.

2.2.1 Single dose PK of 100 mg Eliglustat

Following single dose of 100 mg eliglustat, the systemic exposures were the highest in PMs with the longest T1/2 of 9 hours, followed by IMs and EMs (**Table 5**). The systemic exposures in two URMs were the lowest. These are consistent qualitatively with the findings presented in the original Clinical Pharmacology Review but the numerical values have changed. **Table 5** should replace Table 18 and relevant information in Table 19.

Table 5. Mean (CV%) of eliglustat plasma PK parameters after single oral dose of 100 mg in healthy subjects who are EMs, IMs or URMs

CP2D6 Phenotype	Parameters (units)	STUDYID	N	Mean	CV%
EM	AUC (ng×hr/mL)	GZGD01807	32	77.2	123
		GZGD01907	22	45.8	53.0
		GZGD02007	28	77.4	88.3
EM	CMAX (ng/mL)	GZGD01807	34	10.3	110
		GZGD01907	22	5.94	49.8
		GZGD02007	33	10.9	99.7
EM	TMAX* (hr)	GZGD01807	34	1.50	[0.50, 3.05]
		GZGD01907	22	2.00	[1.50, 4.00]
		GZGD02007	33	2.02	[1.03, 4.02]
EM	THALF (hr)	GZGD01807	34	5.23	25.4
		GZGD01907	22	6.10	24.0
		GZGD02007	28	4.20	37.9
IM	AUC (ng×hr/mL)	GZGD01907	2	253	39.4
		GZGD02007	1	158	
IM	CMAX (ng/mL)	GZGD01907	2	25.4	42.3
		GZGD02007	1	19.7	
IM	TMAX* (hr)	GZGD01907	2	3.50	[3.00, 4.00]
		GZGD02007	1	3.02	
IM	THALF (hr)	GZGD01907	2	6.99	8.91
		GZGD02007	1	6.12	
URM	AUC (ng×hr/mL)	GZGD01807	2	9.61	0.29
		GZGD02007	1	17.6	
URM	CMAX (ng/mL)	GZGD01807	2	1.82	35.5
		GZGD02007	2	2.81	27.5
URM	TMAX* (hr)	GZGD01807	2	1.26	[1.02, 1.50]
		GZGD02007	2	1.03	[1.02, 1.03]
URM	THALF (hr)	GZGD01807	2	3.07	32.1
		GZGD02007	1	2.29	
*Median [Min, Max]					

2.2.2 Single dose PK of 50, 200, and 350 mg Eliglustat

In all subjects (EMs), systemic exposure increased with increase of dose. The terminal t1/2 appeared to increase with dose increase from 50 to 200 mg. These are consistent qualitatively with previous finding presented in the original Clinical Pharmacology Review. The median Tmax was slightly prolonged with increase of doses. The following table should replace Table 20 in the original Clinical Pharmacology Review.

Table 6. Descriptive statistics of PK parameters following single dose (Day 1) ranging from 50 mg to 350 mg BID in EMs (Study GZGD00204)

DOSE (mg)	Parameters (units)	N	Mean	CV%
50	AUCinf (ng×hr/mL)	6	19.1	41.1
	CMAX (ng/mL)	8	2.48	33.7
	TMAX* (hr)	8	1.5	[0.5,3]
	THALF (hr)	6	3.69	33.3
200	AUCinf (ng×hr/mL)	7	294	110
	CMAX (ng/mL)	8	33.0	91.1
	TMAX* (hr)	8	1.75	[1, 4]
	THALF (hr)	7	5.36	25.0
350	AUCinf (ng×hr/mL)	8	678	62.7
	CMAX (ng/mL)	8	107	55.3
	TMAX* (hr)	8	2.5	[1, 3.1]
	THALF (hr)	8	5.65	7.09
*Median [Min, Max]				

2.2.3 Multiple doses PK of 50, 200, and 350 mg Eliglustat

In all subjects (EMs), systemic exposure increased with increase of dose. These are consistent with previous finding presented in the original Clinical Pharmacology Review. The following table should replace Table 22 in the original Clinical Pharmacology Review.

Table 7. Descriptive statistics of eliglustat PK parameters in healthy subjects on Day 10 (Study GZGD00204)

DOSE (mg)	Parameters (unit)	N	Mean	CV%
50	AUCtau (ng×hr/mL)	8	39.3	59.1
	CMAX (ng/mL)	8	7.35	61.5
	TMAX* (hr)	8	1.5	[1.5, 2.02]
200	AUCtau (ng×hr/mL)	7	697	84.6
	CMAX (ng/mL)	7	119	68.0
	TMAX* (hr)	7	1.5	[1, 3]
350	AUCtau (ng×hr/mL)	6	1447	47.1
	CMAX (ng/mL)	6	231	38.4
	TMAX* (hr)	6	1.5	[2, 4]
*Median [Min, Max]				

2.2.4 Time to steady-state

The original analysis based upon the study results from GZGD02007 and GZGD01807 showed that steady-state following 100 mg PO BID was reached within four days of dosing in both EMs and IMs. Following the reclassification, only one IM subject remained an IM in the two studies. The rest were all EMs. The time to reach steady-state remains the same for EMs when the majority of IMs become EMs since the original analysis indicated that time to steady state between the two phenotypes were the same.

2.2.5 Multiple doses of eliglustat 100 mg BID

The systemic exposures were the highest in PMs followed by IM (N=1) and EMs. The URMs systemic exposures were the lowest. These findings were consistent qualitatively with those in the original Clinical Pharmacology Review. The t1/2 in EMs is 6.5 hours, which is derived from the study that was not affected by the CYP2D6 phenotype reclassification. The following table (**Table 8**) should replace Table 21 in the original Clinical Pharmacology Review.

Table 8. Mean (CV%) of eliglustat plasma PK parameters after multiple oral doses of 100 mg BID in healthy subjects

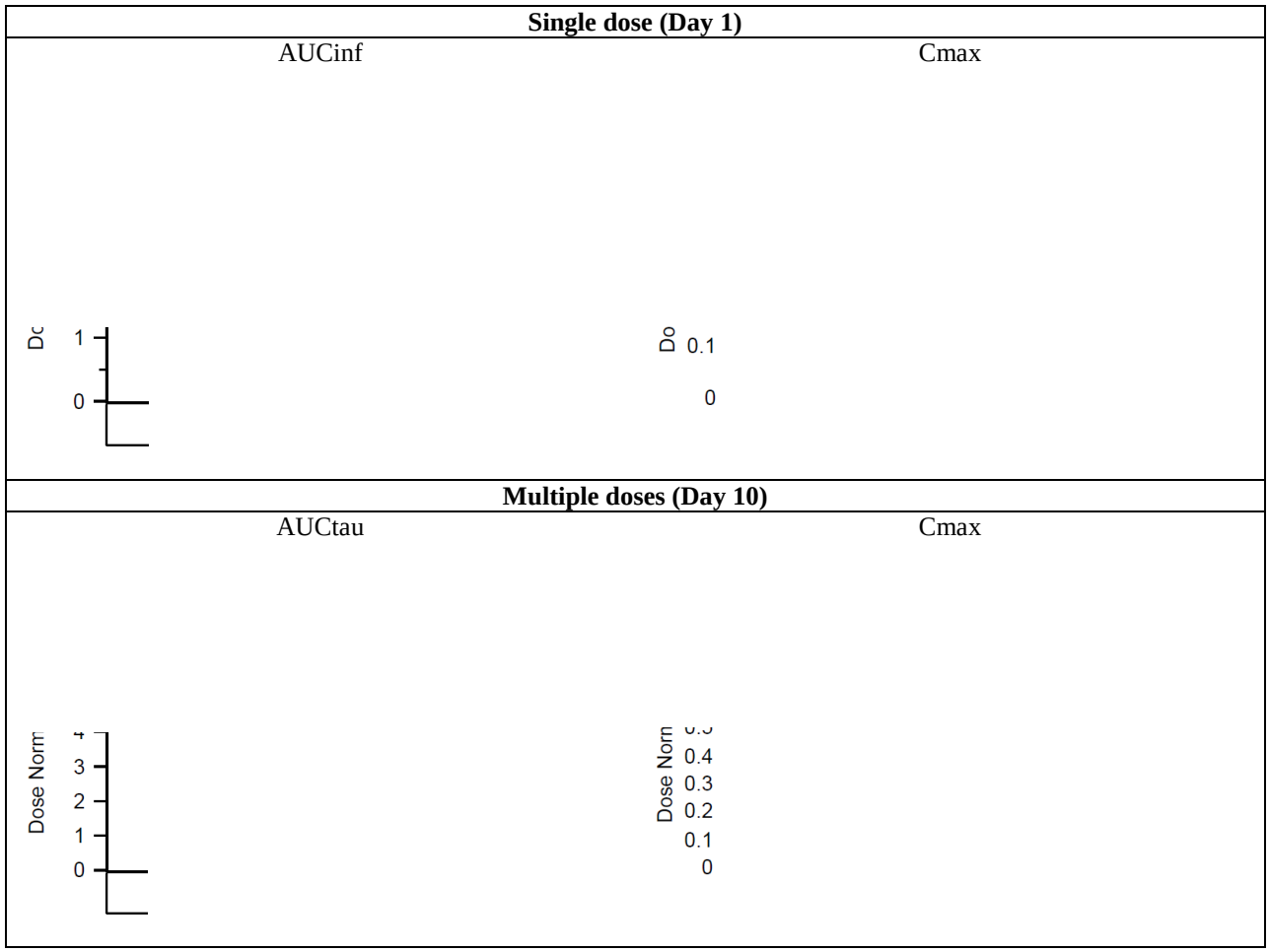
Parameters	Dosing Duration	CYP2D6	STUDY ID	N	Mean	CV%
AUC0-12h (ng×hr/mL)	6	EM	GZGD01807	31	119	112
			GZGD02007	31	120	77.0
	7		GZGD02107	8	76.3	36.8
	10		GZGD02707	24	143	160
Cmax (ng/mL)	6	EM	GZGD01807	31	19.5	101
			GZGD02007	33	19.4	77.8
	7		GZGD02107	8	12.1	42.3
	10		GZGD02707	24	25.0	141
Tmax (hr)*	6	EM	GZGD01807	31	2.02	[1.02, 4.02]
			GZGD02007	33	2.02	[0.50, 3.02]
	7		GZGD02107	8	2.00	[1.50, 2.07]
	10		GZGD02707	23	1.50	[0.50, 3.00]
CLss/F (L/hr)	6	EM	GZGD01807	31	1573	67.1
			GZGD02007	31	1165	73.5
T1/2 (hr)	7	EM	GZGD02107	8	6.48	10.7
AUC_{0-12h} (ng×hr/mL)	6	IM	GZGD02007	1	306	
Cmax (ng/mL)	6	IM	GZGD02007	1	44.6	
Tmax (hr)*	6	IM	GZGD02007	1	2.02	
CLss/F (L/hr)	6	IM	GZGD02007	1	275	
AUC0-12h (ng×hr/mL)	5	PM	GZGD02407	6	922	33.0
	10		GZGD02707	3	1057	38.3
Cmax (ng/mL)	5	PM	GZGD02407	6	113	32.1
	10		GZGD02707	3	137	39.5
Tmax (hr)*	5	PM	GZGD02407	6	3.00	[3.00, 4.00]
	10		GZGD02707	3	3.00	[2.00, 3.00]
T1/2 (hr)	5	PM	GZGD02407	6	8.86	7.74
CL/F (L/hr)	5	PM	GZGD02407	6	62.2	32.3
AUC_{0-12h} (ng×hr/mL)	8	URM	GZGD01807	2	17.1	33.6
			GZGD02007	2	23.8	6.25
	10		GZGD02707	1	12.4	
Cmax (ng/mL)	8	URM	GZGD01807	2	3.96	48.9
			GZGD02007	2	4.49	17.64
	10		GZGD02707	2	3.03	26.4
Tmax (hr)	8	URM	GZGD01807	2	1.27	[1.02, 1.52]
			GZGD02007	2	1.26	[1.02, 1.50]
	10		GZGD02707	2	0.5	[0.5, 0.5]
CLss/F (L/hr)	8	URM	GZGD01807	2	5245	33.6
			GZGD02007	2	3555	6.17
	10		GZGD02707	2	7060	5.41

*Median [Min, Max]; Oral solution used in Study GZGD02107.

2.2.6 What is the degree of PK linearity or non-linearity based on the dose-concentration relationship?

Following single- and multiple-dose of 50, 200, and 350 mg eliglustat, systemic exposure (AUC and Cmax) increased in a more than dose-proportional manner (**Figure 1**). Eliglustat exhibits non-linear PK in subjects who are CYP2D6 EMs. Linearity in IMs was no longer evaluable because of the reclassification. **Figure 1** in this addendum replaces Figures 22 and 23 in the original Clinical Pharmacology Review. Note that these were parallel dose groups.

Figure 1. Dose normalized AUC and Cmax following single- and multiple-dose of eliglustat 50, 200, and 350 mg in EMs (Study GZGD00204)



2.2.7 How do the PK parameters change with time following chronic dosing?

The sponsor reported a 2-fold increase in exposure (AUC) following multiple dosing in EMs after 100 mg BID of eliglustat (**Table 9**).

Table 9. Ratios of AUC in healthy subjects who are CYP2D6 EMs.

Eliglustat dose	AUC ratios Mean ± SD (Geometric Mean) [CV%]
50 mg BID *	2.39 ± 0.781 (2.29) [32.7]
100 mg BID **	1.83 ± 0.712 (1.66) [38.8]
200 mg BID *	3.50 ± 2.15 (3.08) [61.6]
350 mg BID *	3.19 ± 1.12 (3.02) [35.0]
* Data from GZGD00204 study (AUC0-12 Day 10 vs AUC Day 1) [N=6] ** Data from combined study GZGD02007 and GZGD01807 (AUC0-12 Day 8 vs AUC Day 1) [N=58]	

Source Data: Sponsor's response to labeling edits on August 6, 2014.

2.2.8 How does the PK of the drug in healthy subjects compare to that in patients?

As noted in the original review, a direct comparison between the PK of eliglustat in healthy subjects and patients is not feasible because the patients in the Phase 2 and Phase 3 studies received titration doses guided by the trough concentrations of eliglustat while healthy subjects did not receive the drug in this manner. However, it appeared previously that systemic exposure (AUC) in patients who are CYP2D6 EM and IM was about 2-fold higher. The magnitude of the exposure difference was about 25% after reclassification of CYP2D6 phenotypes because the majority of the healthy subjects who were IMs were reclassified as EMs.

2.2.9 What is the inter-subject variability of PK parameters in healthy subjects?

The inter-subject variability is no longer estimatable in IMs since there is only one subject in this category. The inter-subject variability of AUCtau and Cmax in EMs following 100 mg BID ranged from 37 to 160% and 42 to 141%, respectively (**Table 8**). The variability found in EMs is still higher than that in PMs (36%), which is consistent with the findings presented in the original Clinical Pharmacology Review. Relevant values in Table 27 of the original review should be replaced with the updated values in **Table 8** provided in this addendum.

2.2.10 Effect of paroxetine, a strong CYP2D6 inhibitor

Statistical comparison of plasma eliglustat with and without paroxetine is presented in the table below. The expected Cmax and AUC in EMs and relevant dose adjustment recommendation for concomitant use of a strong CYP2D6 inhibitor are provided in **Table 1**. Based upon PBPK simulation (Appendix 1), eliglustat dose should be reduced to 100 mg QD in EMs and IMs when paroxetine or other CYP2D6 inhibitors are co-administered. Table 40 in the original review should be replaced by **Table 10**. Table 41 in the original review should be deleted.

Table 10. Statistical comparison of plasma eliglustat exposure following 100 mg BID with and without paroxetine in CYP2D6 EMs

CYP2D6 Phenotype	Parameter	Treatment	Geometric LS Mean	Ratios (%) (Test/Ref)‡	90% CI
EM	AUCtau (ng×hr/mL)	Eliglustat alone	92.5	840	653, 1082
		Paroxetine+Eliglustat	778		
	Cmax (ng/mL)	Eliglustat alone	14.5	699	533, 919
		Paroxetine+Eliglustat	101		
‡Test = Paroxetine+Eliglustat, Ref = Eliglustat alone					

2.2.11 Effect of ketoconazole, a strong CYP3A inhibitor

Statistical comparison of plasma eliglustat with and without ketoconazole is presented in the table below. The expected Cmax and AUC in EMs and relevant dose adjustment recommendation for concomitant use of a strong CYP3A inhibitor are provided in **Table 1**. Based upon PBPK simulation (Appendix 1), eliglustat dose should be reduced to 100 mg QD in EMs when a strong CYP3A inhibitor is co-administered. However, eliglustat should be contraindicated to co-administration with a strong CYP3A inhibitor in IMs. Table 43 in the original review should be replaced by **Table 11**. Table 44 in the original review should be deleted.

Table 11. Statistical comparison of plasma eliglustat exposure following 100 mg BID with and without ketoconazole in EMs

CYP2D6 Phenotype	Parameter	Treatment	Geometric LS Mean	Ratios (%) (Test/Ref)‡	90% CI
EM	AUCtau (ng×hr/mL)	Eliglustat alone	74.4	440	399, 485
		Ketoconazole+Eliglustat	327		
	Cmax (ng/mL)	Eliglustat alone	12.8	399	355, 449
		Ketoconazole+Eliglustat	51.0		
‡Test = Ketoconazole+Eliglustat, Ref = Eliglustat alone					

3 Appendix 1. PBPK Review Addendum

Physiological-based Pharmacokinetic Modeling Review - Addendum

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 205494
Drug Name	Eliglustat Tartrate (Genz-112638)
Proposed Indication	Long-term treatment of adults patients with Gaucher Disease type 1
Clinical Division	CDER/ODEIII/DGIEP
PBPK Reviewer	Ping Zhao, Ph.D
Sponsor	Genzyme Corporation

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Objectives

The objectives of this addendum are three-fold. First, the addendum updates changes of the original PBPK review (original review) as a result of reclassification of certain study subjects with regard to their CYP2D6 phenotypes. The original review has been included in clinical pharmacology question based review, which was finalized on June 16, 2014. Second, the FDA reviewer conducted additional PBPK simulations using sponsor's models to evaluate the effect of a strong CYP2D6 inhibitor paroxetine on the PK of eliglustat in subjects taking 100 mg oral dose of eliglustat once daily (q.d.). Third, a rationale was provided for co-administration of eliglustat and a CYP3A inhibitor in CYP2D6 poor metabolizers, with additional simulations conducted to update the effect of a moderate CYP3A inhibitor fluconazole on eliglustat PK (100 mg twice daily) in CYP2D6 poor metabolizers.

Summary of the addendum

1. Comments on the changes due to reclassification of study subjects on CYP2D6 phenotyping

During late cycle meeting, the sponsor indicated that several study subjects originally classified as CYP2D6 intermediate metabolizers (IMs) have been reclassified as extensive metabolizers (EMs) (see Dr. Shang's clinical pharmacology review addendum for details on reclassification and studies being affected by this reclassification). Because the reclassification does not affect datasets used for model development, simulation results remain unchanged. However, observed PK values used for comparison with simulated values in several figures and tables should be updated with new information. Given the short review timeline, these figures and tables are not updated and comments are provided in **Table 1** below.

1. Table 1. Addendum of original PBPK review as a result of reclassification of CYP2D6 phenotyping of several study subjects

Original figures/tables	Comments
Figure 1 "Comparison of the predicted and observed pharmacokinetic parameters (Sim/Obs) for eliglustat in the absence of perpetrators in EMs".	Sim/Obs values for study 1807 and study 2007 need to be recalculated
Table 4 "PBPK predicted and observed effects of CYP2D6 inhibitor paroxetine and CYP3A inhibitor ketoconazole on eliglustat in subjects with different CYP2D6 phenotype".	Observed results for EMs and IMs need to be updated. In-text description of Table 4 should reflect that IM data were based on n=1 IM subject
Table 5 "Observed and predicted pharmacokinetic parameters for eliglustat in CYP2D6 IM population (Values are mean [minimum, maximum])"	Observed results for IMs need to be updated. In-text description of Table 5 should reflect that for study 1807 and study 2007, data were based on n=1 IM subject. Throughout the review, discussions on (b) (4)

2. Simulation of the effect of paroxetine on eliglustat exposure in EMs or IMs taking 100 mg oral dose of eliglustat once daily

SimCYP® software (V11.1, Sheffield, UK) was used by the FDA reviewer to conduct additional PBPK simulations. The workspace files "genz100mgqd-paroxetine-ketoconazole-em-day18.wks", and "genz100mgqd-paroxetine-ketoconazole-im-day18.wks", submitted by the sponsor as part of the response to FDA's information request on March 19, 2014 were used for the simulation of the effect of paroxetine (30 mg q.d.) on eliglustat PK in EMs or IMs taking 100 mg oral q.d. dose. Briefly, ketoconazole model was not selected so that drug interactions only occur between eliglustat and paroxetine. Simulations used 36 subjects (EM or IM healthy subjects, 18-39 years old, proportion of female = 0.528) per trial and a total of 10 trials (n=360 subjects). Eliglustat was given to virtual EMs or IMs orally at 100 mg q.d. for 18 days. On day 9, subjects were co-administered with paroxetine orally at 30 mg q.d. for 10 days. Steady-date PK of eliglustat on day 18 (0-24 hr) in the absence and in the presence of paroxetine are summarized in **Table 2**.

2. Table 2. PBPK simulated steady-state eliglustat exposure (day 18) in EM or IM subjects taking 100 mg q.d. with or without paroxetine (population mean [min, max])

	Without paroxetine co-administration		With paroxetine co-administration	
	$AUC_{0\text{-}24hr}$ (ng/mL.h)	Cmax (ng/mL)	$AUC_{0\text{-}24hr}$ (ng/mL.h)	Cmax (ng/mL)
EMs	146 (11, 1569)	17 (1, 158)	1121 (56, 5061)	89 (6, 291)
IMs	434 (37, 2203)	41 (4, 180)	1212 (56, 5705)	94 (6, 300)

3. Rationale for co-administration of eliglustat and a CYP3A inhibitor in CYP2D6 poor metabolizers

Although CYP3A plays less important role in eliglustat hepatic metabolism than CYP2D6 in EMs, it is expected to be the predominant pathway in poor metabolizers (PMs). In EMs co-administered with a strong CYP3A inhibitor ketoconazole, eliglustat AUC increased by approximately 4 fold. After intravenous administration, eliglustat has a systemic clearance approaching the value of hepatic blood flow. These findings suggest that eliglustat has high hepatic extraction ratio and intestinal CYP3A may significantly contribute to the first pass metabolism of eliglustat. These hypotheses are supported by PBPK simulations. Simulations show that in CYP2D6 PMs, eliglustat behaves as a sensitive CYP3A substrate with AUC increased by >5 fold in the presence of strong CYP3A inhibitor ketoconazole, and by nearly 3-fold in the presence of a moderate CYP3A inhibitor fluconazole (**Table 3**). Co-adminisatration of any drug that inhibits CYP3A may result in increased eliglustat exposure in PMs. Therefore, co-administration of eliglustat with CYP3A inhibitors (weak, moderate (b) (4) in PMs, is not recommended.

SimCYP® software (V11.1, Sheffield, UK) was used by the FDA reviewer to conduct additional PBPK simulations. The workspace files "genz-100mgqd-flucon-pm.wks" submitted by the sponsor as part of the response to FDA's information request on Jan 10, 2014 were used for the simulation of the effect of fluconazole on eliglustat PK in PMs taking 100 mg oral dose twice daily (b.i.d.). Simulation used 10 healthy CYP2D6 PMs (20-50 years old, proportion of female of 0.5) per trial and a total of 10 trials (n=100 subjects). **Table 3** includes changes of Table 10 of the original review.

3. **Table 3. Predicted eliglustat exposure in PMs in the absence and presence of enzyme inhibitors (Mean [minimum, maximum], changes (underscored) were made to Table 10 of original PBPK review)**

Eliglustat Dose	**CYP Inhibitors**	**Cmax (ng/mL)**	**AUC_{tau} (ng/mL h) 0-12h for b.i.d. 0-24h for q.d.**	**C_{trough} (ng/mL)**	**Tables, [reference]**
100 mg b.i.d	NA[a]	105 [6.95, 489]	957 [49.1, 5270]	51.3 [1.46, 371]	Table 20, [5]
100 mg q.d	NA[a]	75.2 [6.04, 287]	956 [49.1, 5290]	15.0 [0.117, 152]	Table 21, [5]
100 mg b.i.d	Strong CYP3A4 inhibitors ketoconazole[a]	**478**[$] [119, 1260]	5300 [1100, 14300]	392 [52.3, 1110]	Table 20, [5]
100 mg q.d	Ketoconazole[b]	**321**[$] [114, 709]	5950 [1310, 14700]	147 [6.74, 519]	Table 21, [5]
100 mg b.i.d	Moderate CYP3A4 inhibitor fluconazole[c]	~~**395**[$] **[29.3, 1939]**~~ **272**[$] [29, 931]	~~7214 [346, 40979]~~ **2754**[$] [239, 10357]	~~300 [11, 1775]~~ Not reported	FDA in house analysis
100 mg q.d.	Fluconazole[c]	179 [23.1, 530]	2820 [248, 10500]	63.5 [1.27, 333]	Table 6, [4]

Values are population mean [minimum, maximum]. Ten trials for each simulation experiment. [a] *36 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 15 with ketoconazole coadministered from Day 9 to Day 15 [5];* [b] *36 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 15 with ketoconazole coadministered from Day 9 to Day 15. [5];* [c] *10 subjects/trial receiving repeated doses of eliglustat (100 mg b.i.d. or q.d.) from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with fluconazole coadministered from Day 8 to Day 18 (Period 2) [4].*

FDA analysis included results of eliglustat PK from 9 am to 9 pm on day 18 (12 hours interval)

[$]*Value exceeding 250 ng/mL threshold*

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/s/

ELIZABETH Y SHANG
08/18/2014

SARAH E DORFF
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Signed on behalf of Ping Zhao - reviewer from DPM - PBPK reviewer/analysis.

SUE CHIH H LEE
08/19/2014

Clinical Pharmacology Review

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Submission Dates:	9/20/2013, 11/27/2013, 12/6/2013, 12/9/2013, 12/12/2013, 12/16/2013, 1/17/2014, 2/19/2014, 2/21/2014, 2/24/2014, 2/25/2014, 3/28/2014, 4/28/2014, 4/29/2014, 5/16/2014
Brand Name:	Cerdelga®
Generic Name:	Eliglustat tartrate
Formulation:	Oral capsule
OCP Reviewers:	Elizabeth Shang, Ph.D., R.Ph. (Primary) Sandhya Apparaju, Ph.D. (In vitro study review)
Pharmacometrics Reviewers:	Anshu Marathe, Ph.D. & Justin Earp, Ph.D.
GTT Reviewer:	Sarah Dorff, Ph.D.
PBPK Reviewer:	Yuzhuo Pan, Ph.D.
OCP Team Leader:	Sue-Chih Lee, Ph.D.
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PBPK Lead:	Ping Zhao, Ph.D.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Gastroenterology and Inborn Errors Products
Sponsor:	Genzyme
Submission Type:	Original NDA; NME; Priority Review with Major Amendment
Sponsor's Proposed Dosing regimen:	84 mg (free base) BID for CYP2D6 Extensive metabolizers and Intermediate metabolizers
Indication:	Long-term treatment of adult patients with Gaucher disease type 1

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1 EXECUTIVE SUMMARY

The current submission is the original NDA for eliglustat for the following indication:

Long-term treatment of adult patients with Gaucher disease type 1 (GD1).

Gaucher disease is a rare, autosomal recessive lysosomal storage disorder caused by a deficiency in the lysosomal enzyme glucocerebrosidase (or acid-β glucosidase), which catalyzes the hydrolysis of glucosylceramide (or GL-1) to glucose and ceramide. This enzyme deficiency results in the accumulation of GL-1, especially in the liver, spleen, and bone marrow. Eliglustat is a selective glucosylceramide synthase inhibitor for substrate reduction therapy (SRT) to reduce the synthesis and hence the accumulation of GL-1.

Currently available therapies for GD1 include intravenously administered enzyme replacement therapies (Cerezyme, Vpriv and Elelyso) and a second-line oral SRT (Zavesca). This NDA qualifies for a priority review because of the potentially favorable risk/benefit ratio of the product and its convenience in oral administration.

The sponsor is proposing a fixed oral dosing regimen of 84 mg (free base; equivalent to 100 mg tartrate salt) twice daily (BID) in patients who are CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs). The sponsor intends to exclude use of eliglustat in CYP2D6 (b) (4) ultra-rapid metabolizers (URMs). The to-be-marketed product is eliglustat capsules 84 mg, each containing eliglustat tartrate 100 mg. Hereafter, the eliglustat dose refers to the salt form unless otherwise specified since that was the designation used by the sponsor during their drug development.

To support the approval of this NDA, the sponsor conducted an array of clinical pharmacology-related studies. A total of twenty-four in vitro studies were performed to facilitate the mechanistic understanding in the absorption, distribution and metabolism characteristics and CYP enzyme- and transporter-mediated drug-drug interaction (DDI) potentials of eliglustat. The phase 1 studies evaluated in healthy subjects the eliglustat pharmacokinetics (PK) and short term safety, mass balance, pharmacodynamics (PD), clinical DDIs, QT prolongation potential (thorough QT study), relative and absolute bioavailability, and food-effect on eliglustat PK. In addition, population PK, exposure-response for efficacy and safety, and physiologically-based pharmacokinetics (PBPK) modeling and simulations were performed. Validated analytical methods were employed for assay of eliglustat concentrations in plasma and urine samples across studies.

The clinical studies conducted in GD1 patients consist of one phase 2 and two phase 3 (ENGAGE and ENCORE) studies. Status of CYP2D6 phenotype of each patient was determined before the administration of eliglustat using FDA cleared tests. In all three studies, patients were started with eliglustat tartrate 50 mg PO BID and a dose titration strategy was employed in an attempt to ascertain that the individual trough concentration of eliglustat at steady-state (SS) would not be below 5 ng/mL. The titration involved one step increase to 100 mg BID for the Phase 2 and ENGAGE studies while the ENCORE trial allowed one further dose increase to 150 mg BID. All the CYP2D6 PMs (N=5) were dosed at 50 mg BID without the need for dose increase based upon their trough concentrations. For efficacy, the ENGAGE study demonstrated that eliglustat treatment was superior to placebo and the ENCORE study showed that eliglustat treatment was non-inferior to Cerezyme.

Eliglustat is primarily metabolized by CYP2D6 and, therefore, CYP2D6 genotype/phenotype greatly impacts the PK of eliglustat. Four key questions were raised during the review of this NDA, which are given below along with the current positions on these issues:

1. *Is the sponsor's proposed one fixed oral dosing regimen (100 mg BID) for both CYP2D6 EMs and IMs acceptable? Is therapeutic drug monitoring (i.e., assessment of eliglustat trough concentrations) necessary?*

   In terms of efficacy, one fixed dosing regimen of 100 mg BID for both EMs and IMs is considered acceptable and there is no need to measure and maintain trough eliglustat concentrations at or above 5 ng/mL. Although pharmacometrics analyses revealed an exposure-response (E-R) relationship for efficacy, patients who had trough concentrations below 5 ng/mL appeared to demonstrate clinical benefit notwithstanding the small sample size available for analysis. (Sections 1.3.1, 1.3.2, and 2.3.4). The patients in ENGAGE and Phase 2 study were treated successfully at doses of 100 mg BID or lower. Regarding safety considerations, please refer to Question #3 below.

2. *Can we recommend a dose for patients who are CYP2D6 PMs?*

   OCP recommends a dosing regimen of 100 mg once daily (QD) for PMs. The sponsor is prepared to market only one strength (i.e., eliglustat tartrate 100 mg), limiting the dosing regimens that can be considered. At the dose of 100 mg BID proposed for EMs and IMs, PMs would have approximately 6- to 7-fold higher AUC and Cmax compared to EMs, and 2- to 3-fold higher AUC and Cmax compared to IMs. A dosing regimen of 100 mg every other day can bring the eliglustat AUC to a level between EMs and IMs given 100 mg BID. This dosing regimen, however, is considered impractical in terms of patient compliance and no further assessment was made. Based on the observed data and PBPK predictions, a 100 mg QD regimen will likely result in a Cmax of approximately 80 ng/mL, which is lower than 250 ng/mL and is likely not to result in any QT related safety concerns. For a Cmax of 250 ng/ml, the mean (upper 90% CI) of ΔΔQTcF are predicted to be 6.4 (9.4) ms, which is below the regulatory threshold set as the upper limit based on the thorough QT study. For other aspects of safety considerations, refer to Question #3 below.

3. *To guide dosing in CYP2D6 IMs and PMs and dose adjustment in DDI scenarios, what is the maximum systemic exposure that is considered safe based on the clinical safety database?*

   Because of the dose titration design and restrictions in concomitant medications in the Phase 2 and Phase 3 studies, the systemic exposures in these studies were relatively low and few patients experienced the higher systemic exposures expected for IMs given 100 mg BID or PMs given 100 mg QD as compared to EMs given 100 mg BID (Section 2.3.5.1.2, Figure 17 and Figure 18). On the other hand, eliglustat does not appear to have a narrow therapeutic index in view of the current safety database.

   Based on discussions with the clinical team, no major safety concerns have been identified for eliglustat in Phase 2 and Phase 3 studies. No meaningful E-R relationship for adverse reactions was observed except for nervous system disorders, which was primarily driven by headaches. Overall the incidence rates for adverse events were low (see Section 2.3.4.4). Thus exposures achieved in the Phase 2 and Phase 3 studies are considered safe. Including the available exposure data from the ongoing phase 3b (EDGE) study, the highest individual

exposure ($AUC_{0\text{-}24h}$) achieved is 1984 ng×hr/mL, with 20 patients with $AUC_{0\text{-}24h}$> 800 ng×hr/mL and 7 patients with $AUC_{0\text{-}24h}$ > 1100 ng×hr/mL. The mean $AUC_{0\text{-}24h}$ for IMs at 100 mg BID and PMs at 100 mg QD are expected to lie within 800-1100 ng×hr/mL.

The Clinical Pharmacology Review Team met with the Clinical Review Team on May 7, 2014 to discuss the maximum systemic exposure that will be safe in patients. The clinical team considered that the exposures expected at 100 mg BID for IMs and 100 mg QD for PMs are acceptable in view of the clinical experience with eliglustat in terms of systemic exposure and safety data gathered from the Phase 2 and Phase 3 studies. The mean $AUC_{0\text{-}24h}$ of 1100 ng×hr/mL also serves as the threshold mean exposure to guide dosage adjustment in DDI scenarios as the safety at higher exposures is uncertain, taking into consideration the intersubject variabilities in PK parameters.

4. *CYP2D6 genotyping of patients is essential for dosing of eliglustat. Is this feasible without concurrent approval of a test kit by the Center for Devices and Radiological Health (CDRH)?*

   In clinical studies of eliglustat, CYP2D6 genotype and phenotype were determined using FDA-cleared assays. As the FDA proposed use of eliglustat is limited to patients who are CYP2D6 EMs, IMs and PMs (e.g., not indicated in indeterminate metabolizers), CYP2D6 genotype testing is essential for the safe and effective use of eliglustat. FDA-cleared tests are available for genotyping CYP2D6. CDRH was consulted regarding use of available tests as a companion diagnostic for eliglustat; CDRH has provisionally recommended that the available tests are suitable to identify candidates for eliglustat therapy and that labeling should reference use of an FDA-cleared test to identify the indicated populations (CDRH review pending at the time the current review was filed).

1.1 RECOMMENDATIONS

The acceptability of specific drug information is provided below:

Decision	Acceptable to OCP?	Comment
Overall	☒ Yes ☐ No ☐ N/A	
Evidence of effectiveness	☒ Yes ☐ No ☐ N/A	
Proposed dose for general population	☐ Yes ☒ No ☐ N/A	The proposed dose (84 mg BID, free base) for patients who are CYP2D6 extensive or intermediate metabolizers is acceptable. (b) (4) [redacted] In patients who are CYP2D6 poor metabolizers, the dose of eliglustat should be 84 mg (free base) PO once daily.

1.2 PHASE IV REQUIRMENTS/COMMITMENTS

- Conduct a study to assess the impact of hepatic impairment on the eliglustat PK. Use the Child-Pugh classification to define the degree of hepatic impairment. Eliglustat is almost exclusively eliminated through metabolism via CYP2D6 and CYP3A4 in the liver. A hepatic impairment study can inform appropriate dosing in these patients.
- Conduct a dedicated study to assess the effect of renal impairment on eliglustat PK. A reduced design may be used. Renal function may be estimated by either Cockcroft-Gault equation or estimated glomerular filtration rate (eGFR) from the Modification of Diet in Renal Disease (MDRD) Study. PK study in subjects with moderate renal impairment may be needed if significant changes in systemic exposure of eliglustat in subjects with severe renal impairment are observed compared to those with normal renal function. Eliglustat is intended for chronic use. Although eliglustat is minimally eliminated through renal excretion, a renal impairment study is necessary because renal impairment can indirectly impact drug metabolism.
- (b) (4) [redacted]
- (b) (4) [redacted]

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1.3 CLINICAL PHARMACOLOGY SUMMARY

1.3.1 Dose Recommendations

- *CYP2D6 EMs and IMs: 100 mg BID*
- *CYP2D6 PMs: 100 mg QD*
- *CYP2D6 URMs: A safe and effective dose has not been determined.*

The sponsor's proposed eliglustat dose of 100 mg PO BID in patients who are CYP2D6 EMs or IMs is acceptable as described above (see Section 1). The proposed exclusion of CYP2D6 URMs is also acceptable because even at a high dose of 200 mg BID, the exposure in URMs are ~57% and ~82% lower than the exposures for EMs and IMs at 100 mg BID, respectively. The local safety, e.g. gastrointestinal tolerability, and potential toxicity due to high metabolite concentrations at a higher dose (in order to match systemic exposure in URMs to EMs or IMs) is unknown.

(b) (4)

Eliglustat 100 mg PO QD may be used in patients who are CYP2D6 PMs. Limited data are available; five PMs (one in Phase 2 study and four in ENCORE) received eliglustat 50 mg BID for at least one year with acceptable adverse event (AE) profiles. At 100 mg QD, the predicted Cmax is less than 250 ng/mL. Thus, the likelihood for QT-related safety concerns is low. At 100 mg QD, the AUC in PMs will be within the exposures achieved in the study (Section 2.3.4.5). Based on the clinical database, the safety at the expected exposure is deemed acceptable by the clinical team. Additionally, no clinically meaningful E-R relationship was observed for AEs except for nervous system disorders.

1.3.2 Exposure-Response (E-R) Findings

Efficacy

Effects on spleen and liver volume, hemoglobin, and platelets tended to be greater with increasing steady state average trough concentrations of eliglustat in treatment naïve subjects based on Phase 2 and Phase 3 study data. Although E-R relationship was observed, patients with drug concentration lower than 5 ng/mLshowed clinically meaningful response. For treatment experienced patients in ENCORE, i.e., previously treated with a drug in ERT category, no clinically relevant E-R relationship was observed.

Safety

Eliglustat increased the QTc and PR intervals in a concentration- dependent manner. However, at the supratherapeutic dose of 800 mg the largest upper bounds of the 2-sided 90% CI for the mean difference between 800 mg eliglustat and placebo is 9.1 ms, which are below, the regulatory threshold. Based on concentration-QT relationship, it is predicted that for a Cmax of 250 ng/mL, the mean (upper 90% CI) of ΔΔQTcF are predicted to be 6.4 (9.4) ms. Thus, based on the concentration-QT relationship, there appears to be no QT related safety concerns for drug concentrations below 250 ng/mL.

No meaningful E-R relationship was observed except for nervous system disorders where a relationship was observed and this was primarily driven by headaches. Overall the incidence rates for AEs were low. No major safety concerns have been identified for eliglustat by the medical reviewers in DGIEP.

1.3.3 Pharmacokinetics

Eliglustat PK is highly dependent on CYP2D6 phenotype. At 100 mg BID, the eliglustat systemic exposure (AUC) ratio for PM/IM/EM is roughly 7:3:1. In CYP2D6 EMs and IMs, the eliglustat PK is time-dependent and the systemic exposure increases are more than proportional to dose. The PK of eliglustat in CYP2D6 PMs appears to be linear and time-independent.

Absorption

Eliglustat is a highly permeable drug based on *in vitro* studies in Caco-2 cell monolayers. Eliglustat exhibited high bidirectional permeability which was higher at all tested concentrations (12.5, 125, and 1250μM) than the internal high permeability standard labetalol. It is formally classified as a Biopharmaceutics Classification System (BCS) Class I drug. In CYP2D6 EMs, median time to reach maximum plasma concentration (Tmax) occurs between 1.5 to 2 hours following multiple doses of eliglustat tartrate 100 mg BID. In IMs and PMs, median Tmax occurs at 2 and 3 hours, respectively. Eliglustat systemic exposure increased up to 3-fold at steady state compared to after the first dose. Significant first-pass metabolism occurs following oral administration.

Food does not have a clinically relevant effect on eliglustat PK.

Distribution

Eliglustat is moderately bound to human plasma proteins (76 to 83%). Eliglustat exhibited low in vitro red blood cell partitioning. After intravenous (IV) administration in EMs, the volume of distribution of eliglustat was 835 L, suggesting wide distribution to tissues.

Metabolism and Elimination

Eliglustat is a substrate for CYP2D6, CYP3A4 and P-glycoprotein transporter. Metabolism of eliglustat was predominantly mediated by CYP2D6 and to a lesser extent CYP3A4. Overall, more than ten metabolites of eliglustat have been identified, seven of which were formed via CYP2D6 in *in vitro* studies.

The primary metabolic pathways of eliglustat involve sequential oxidation of the octanoyl moiety followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety, or a combination of the two pathways, resulting in multiple oxidative metabolites. None of the identified metabolites are active against glucosylceramide synthase activity.

After oral administration of 100 mg [^{14}C]-eliglustat, the majority of the administered dose is excreted in urine (41.8%) and feces (51.4%), mainly as metabolites. After 50 mg IV administration, mean eliglustat total body clearance was 88 L/hr in CYP2D6 EMs. Following multiple oral doses of 84 mg eliglustat BID, terminal elimination half-life (T1/2) was approximately 6.5 hours in EMs and 9 hours in PMs.

Specific Populations

Based on the population PK analysis, subject status (healthy versus GD1 patients) was identified as a covariate for clearance (CL) and volume of distribution (V). CL and Vc were 1.95 and 1.71 times higher in healthy subjects than in patients.

Sex, body weight, age, race, and serum creatinine clearance (> 47 mL/min) had limited or no

impact on the PK of eliglustat.

Drug-Drug Interactions

The proposed dose, systemic exposures and drug interaction potential differ among CYP2D6 phenotypes, genetic or drug-induced.

In vitro drug-drug interaction potential

Substrate for CYP isozymes: Eliglustat is a substrate for CYP2D6 and CYP3A4 (see above).

CYP inhibition: In vitro, eliglustat exhibited competitive inhibitory effect toward CYP2D6 and CYP3A4, with apparent Ki values of 5.82 μM for CYP2D6 and 27.0 μM for CYP3A4 (using midazolam as the probe substrate). Eliglustat also exhibited time-dependent inhibition (TDI) of CYP2D6. Clinically relevant inhibition of CYP3A4 at the systemic level by eliglustat is not anticipated; however inhibition at the gut level cannot be ruled out based on in vitro information. CYP2D6 inhibition is expected in vivo.

CYP induction: Eliglustat does not appear to cause *in vitro* enzyme induction.

Substrate for transporters: In vitro studies showed that eliglustat is a substrate for P-gp; it does not appear to be a substrate for other transporters (BCRP, OAT1B1, OAT1B3, MRPs and OAT1).

Transporter inhibition: In vitro eliglustat inhibited P-gp transporter with an IC_{50} of 22 μM.

It does not inhibit BCRP, OAT1B1, OAT1B3, MRP class of efflux transporters and OAT1.

In vivo Drug-drug interactions

(A) Eliglustat as a victim drug

Effect of various CYP inhibitors on eliglustat PK

The following tables show the magnitude of eliglustat systemic exposure change at 100 mg BID with different types of CYP inhibitors and relevant dosing recommendations.

CYP2D6 EMs

Perpetrator Drug(s)	Study	Cmax Ratios	AUC_{0-12h} Ratios	Cmax	AUC_{0-12h}	Dosing Recommendation
Paroxetine (30 mg QD) and ketoconazole (400 mg QD) (Strong CYP2D6 and CYP3A4 inhibitors)	PBPK Simulation	16.7	24.2	470	5170	Contraindicate
Terbinafine and fluconazole (Moderate CYP2D6 and CYP3A4 inhibitors)	PBPK Simulation	10.2	13.6	251	2512	Contraindicate
[redacted]						(b) (4)
Strong CYP2D6 inhibitors	Infer from exposure in CYP2D6 PMs					100 mg QD
Terbinafine Moderate CYP2D6 inhibitor	PBPK Simulation	3.80	4.49	93.9	831	100 mg QD
Ketoconazole Strong CYP3A4 inhibitors	Dedicated* DDI Study	4.25	4.40	127	747	(b) (4)
Fluconazole Moderate CYP3A4 inhibitor	PBPK Simulation	2.77	3.21	68.5	593	(b) (4)

*Mean PK parameters (Cmax and AUC) presented here were scaled from healthy subjects to patients.

CYP2D6 IMs

CYP Inhibitors	Study	Cmax Ratios	AUC_{0-12h} Ratios	Cmax	AUC_{0-12h}	Dosing Recommendation
Paroxetine and ketoconazole	PBPK Simulation	7.48	9.81	449	3924	Contraindicate
Terbinafine and fluconazole	PBPK Simulation	4.16	4.99	261	2630	Contraindicate
[redacted] (b) (4)						
Strong CYP2D6 inhibitors	Infer from exposure in CYP2D6 PMs					100 mg QD
Terbinafine Moderate CYP2D6 inhibitors	PBPK Simulation	1.55	1.64	97.2	866	100 mg QD
Ketoconazole Strong CYP3A4 inhibitors	Dedicated* DDI Study	3.04	4.09	183	1637	[redacted] (b) (4)
Fluconazole Moderate CYP3A4 inhibitors	PBPK Simulation	2.53	2.85	159	1500	Not recommended
*Mean PK parameters (Cmax and AUC) presented here were scaled from healthy subjects to patients.						

CYP2D6 PMs

CYP Inhibitors	Study	Cmax Ratios	AUC_{0-24h} Ratios	Cmax	AUC_{0-24h}	Dosing Recommendation
Ketoconazole Strong CYP3A4 inhibitors	PBPK Simulation	4.27	6.22	321	5950	Contraindicate
Fluconazole Moderate CYP3A4 inhibitors	PBPK Simulation	2.38	2.95	179	2820	Not recommended
Weak CYP3A4 inhibitors	Infer from results of paroxetine (strong CYP2D6 inhibitors **and** weak CYP3A4 inhibitors) DDI study in EMs					Not recommended

Effect of CYP3A inducers on Eliglustat PK

Concomitant use of eliglustat with multiple doses of strong CYP3A4/5 inducers is not

recommended.

Systemic exposure (Cmax and AUCtau) of eliglustat decreased by approximately 90-95% following co-administration of 126 mg eliglustat BID with rifampin (a strong CYP3A4 inducer) 600 mg PO once daily.

Effect of OATP (organic anion transporting polypeptide) inhibitors on eliglustat PK

Systemic exposure of eliglustat was similar with or without co-administration of single 600 mg IV dose of rifampin regardless of subjects' CYP2D6 phenotype.

Effect of P-gp inhibitors on eliglustat PK

The effect of P-gp inhibitors on the systemic exposure of eliglustat, a P-gp substrate, has not been studied clinically. Eliglustat is a BCS class 1 drug and is primarily eliminated through metabolism. Therefore, P-gp inhibitors are not expected to have a clinically significant effect on eliglustat PK.

Effect of gastric pH-modifying agents on eliglustat PK

Gastric pH-modifying agents (Maalox®, Tums®) and proton-pump inhibitors (Protonix®) did not have a clinically relevant effect on eliglustat exposure. This is consistent with the expectation for a BCS Class 1 drug.

(B) Eliglustat as a perpetrator drug

Effect on an oral contraceptive, a CYP3A substrate

Eliglustat is an inhibitor of CYP3A in the *in vitro* study. However, repeat dosing of eliglustat 100 mg BID did not decrease the exposures to ethinylestradiol and norethindrone from Ortho-Novum 1/35, and therefore eliglustat is not expected to impact the efficacy or safety of Ortho-Novum 1/35.

Effect on metoprolol, a CYP2D6 substrate

Co-administration with eliglustat 150 mg BID in EMs resulted in 2.3- and 1.7-fold increases in AUC and Cmax of metoprolol (50 mg), respectively. In IMs, metoprolol AUC and Cmax increased by 63% and 18%, respectively. For patients already on eliglustat and start metoprolol, start metoprolol from the lower end of the dose; 2) for patients who are on metoprolol and now need eliglustat, reduce the metoprolol dose by half (due to > 100% increase in exposure) and then re-adjust metoprolol dose for response. Lower doses of CYP2D6 substrate drugs may be required.

Effect on digoxin, a P-gp substrate

Co-administration of eliglustat with digoxin 0.25 mg resulted in the increase in digoxin AUC and Cmax by 49% and 70%, respectively. Serum digoxin concentrations should be measured before initiating eliglustat. Reduce digoxin concentrations by decreasing digoxin dose approximately 30% or by modifying the digoxin dosing frequency and continue monitoring.

1.3.4 Efficacy and Safety

The clinical efficacy results from the phase 3 studies are shown in Table 1 and Table 2. The primary efficacy endpoints were achieved in both studies while the safety profiles based on the clinical experiences in GD1 patients so far did not point to particular safety concerns associated

with the systemic exposures to eliglustat. For details, refer to the clinical review by Dr. Karyn Berry, Medical Officer of DGIEP.

Table 1. Summary of clinical efficacy results in patients treated with eliglustat (ENGAGE study)

Primary and Secondary Endpoints		**Eliglustat (N = 20)**	**Placebo (N = 20)**	**Treatment Difference**
Percentage change in spleen volume (MN) from Baseline to Week 39 (Primary endpoint)	LS Mean (SEM)	-27.77 (2.37)	2.26 (2.37)	-30.03 § (3.35)
	95% CI	-32.57, -22.97	-2.54, 7.06	-36.82, -23.24
Percentage change in liver volume (MN) from Baseline to Week 39	LS Mean (SEM)	-5.20 (1.64)	1.44 (1.64)	-6.64 § (2.33)
	95% CI	-8.53, -1.87	-1.89, 4.78	-11.37, -1.91
Percentage change in hemoglobin (g/dL) from Baseline to Week 39	LS Mean (SEM)	0.69 (0.23)	-0.54 (0.23)	1.22 § (0.32)
	95% CI	0.23, 1.14	-1.00, -0.08	0.57, 1.88
Percentage change in platelet count ($x10^9$/L) from Baseline to Week 39	LS Mean (SEM)	32.00 (5.95)	-9.06 (5.95)	41.06 § (8.44)
	95% CI	19.94, 44.06	-21.12, 3.00	23.95, 58.17
§ p-value < 0.01				

Source Data: Section 2.7.3, page 29.

Table 2. Summary of clinical efficacy results in patients treated with eliglustat (ENCORE study)

Primary Endpoint		**Eliglustat (N = 99)**	**Cerezyme (N = 47)**
Patients Stable for 52 Weeks	N (%)	83 (83.8)	44 (93.6)
	95% CI	75.1, 90.5	82.5, 98.7
	Treatment Difference	-9.8% (-18.6, 3.3)*	
Patients meeting spleen volume criterion	N (%)	67 (94.4)	39 (100.0)
	95% CI	86.2, 98.4	--
Patients meeting liver volume criterion	N (%)	95 (96.0)	44 (93.6)
	95% CI	90.0, 98.9	82.5, 98.7
Patients meeting hemoglobin criterion	N (%)	94 (94.9)	47 (100.0)
	95% CI	88.6, 98.3	--
Patients meeting platelets criterion	N (%)	92 (92.9)	47 (100.0)
	95% CI	86.0, 97.1	--
* Agresti and Caffo Adjusted 95% CI			

Source Data: GZGD02607 CSR, Table 10-1 and Table 10-2.

Among 393 patients with GD1 were exposed to eliglustat, five deaths were reported but none was treatment emergent death. Eighty-five percent of patients had treatment emergent AEs (TEAEs). Forty-five patients (11%) had severe TEAEs and with 35 (9%) of them had serious AEs (SAEs). Five patients had SAEs considered related to drug: syncopal episode (3), 2° AV block (1), ventricular tachycardia (1). Based on discussions with the clinical team, no major safety concerns have been identified for eliglustat in Phase 2 and Phase 3 studies. For details on safety, refer to the clinical review by Dr. Karyn Berry, Medical Officer of DGIEP.

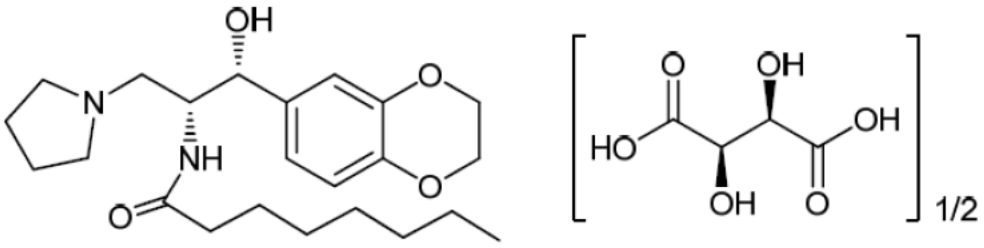
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Physico-chemical properties

1. Structural formula: $C_{23}H_{36}N_2O_4 + ½ (C_4H_6O_6)$. Eliglustat tartrate is the (b) (4) tartaric acid salt of the free base Genz-99067. The salt comprises (b) (4) of Genz-99067 to (b) (4) of (b) (4) tartaric acid. For simplicity it is defined as (b) (4) of Genz-99067 and (b) (4) of (b) (4) tartaric acid.



2. Established name: Eliglustat tartrate
3. Molecular Weight: 479.59 Da (free base: 404.54 Da)

Eliglustat is a Biopharmaceutics Classification System (BCS) Class I drug. The BCS Classification Committee accepted this classification in 2011 based upon the data provided by the sponsor. See 2.6.1 for the review on permeability data.

2.1.2 What are the sponsor's proposed mechanism of action and therapeutic indications?

Gaucher disease is caused by a deficiency of the lysosomal enzyme, glucocerebrosidase that results in the accumulation of its major natural substrate, glucosylceramide, especially in the liver, spleen, and bone marrow.

Eliglustat is a selective inhibitor of glucosylceramide synthase and is intended to reduce the rate of synthesis of GL-1 to match its impaired rate of catabolism in patients with GD1, thereby preventing GL-1 accumulation and alleviating clinical manifestations. Eliglustat is thus a substrate reduction therapy (SRT) for GD1.

Eliglustat is proposed to be indicated for the long-term treatment of adult patients with GD1.

2.1.3 What is the sponsor's proposed dosage and route of administration?

The sponsor's proposed dose is 100 mg (salt form, equivalent to 84 mg free base) administered orally twice a day in patients who are CYP2D6 IMs or EMs.

Note that in the subsequent sections of this review, eliglustat dose refers to that for the salt form.

2.2 What is the regulatory history of this product?

Eliglustat is considered a new molecular entity (NME) for purposes of FDA review.

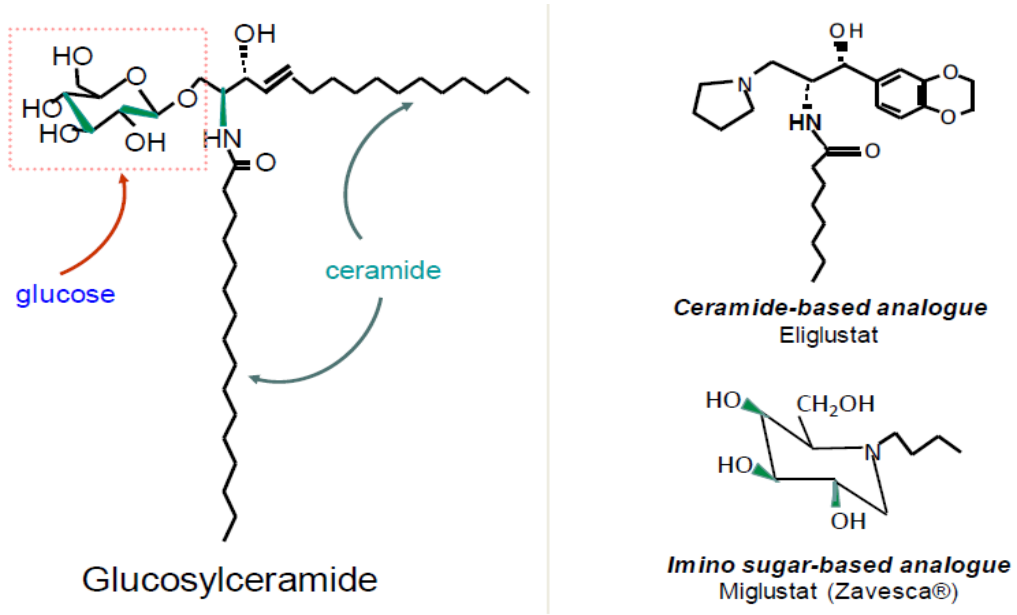
The initial IND was filed under IND 67,589 on December 31, 2003. The End-of-Phase 2 PreNDA meeting was held on May 21, 2013. The Agency agreed that hepatic and renal impairment studies could be conducted as Post-Marketing Requirements (PMRs). According to Dr. Lara Dimick, Medical Team Leader of DGIEP, most patients with GD1 do not have hepatic or renal impairment.

2.2.1 What is unique about eliglustat and are there are any other substrate reduction therapy (SRT) products marketed?

The only currently approved SRT product for Gaucher Disease is miglustat (Zavesca®). Miglustat was approved by the FDA in 2003 under NDA 021348. It is a second-line drug indicated for the treatment of adult patients with mild to moderate GD1 for whom enzyme replacement therapy is not a therapeutic option (e.g. due to constraints such as allergy, hypersensitivity, or poor venous access).

Eliglustat is similar in structure to the ceramide moiety that inhibits glucosylceramide synthase by resembling the ceramide substrate for the enzyme. Miglustat, on the other hand, resembles the glucose moiety of GL-1 and competitively and reversibly inhibits the enzyme (Figure 1).

Figure 1. Chemical structure of glucosylceramide (GL-1; left), eliglustat (top right) and miglustat (bottom right)



Source data: Section 2.5, Figure 2

Besides SRT, there are three approved products for GD1 as the first line therapy in the enzyme replacement therapy (ERT) category: imiglucerase, velaglucerace α, and taliglucerase α. All these drugs are administered by IV route.

2.3 GENERAL CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical development program for eliglustat consists of seventeen clinical studies, including thirteen Phase 1 studies in healthy subjects and four in patients with Gaucher disease (one Phase 2 study, two pivotal Phase 3 studies and one Phase 3b study[1]) in addition to twenty-four clinical pharmacology related in vitro studies. The clinical studies supporting the NDA are listed in Table 3.

Clinical Pharmacology Studies

Refer to Table 3 for a brief description of study design for Phase 1 studies. Pharmacokinetic (PK) evaluations were conducted in all the clinical studies. In this review, summary of the PK parameters stratified by CYP2D6 phenotype (PM, IM, EM, and URM) was performed by the FDA primary reviewer based upon individual PK parameters submitted by the Sponsor. Statistical analysis stratified by CYP2D6 phenotype in DDI studies was also performed by the FDA primary reviewer. The sponsor's summary and statistical analysis in DDI studies was stratified by CYP2D6 PMs and non-PMs (IM/EM/URM) only.

PBPK analysis was performed based upon PK data from relevant Phase 1 studies. Review of PBPK analysis can be found in Appendix 4.3.

Clinical Efficacy/Safety Studies

Refer to Table 3 for a brief description of the Phase 2 and Phase 3 (ENGAGE and ENCORE) studies. Both the Phase 2 and ENGAGE studies enrolled treatment-naive patients while the ENCORE study enrolled treatment-experienced patients being switched-over from ERT (Cerezyme) to eliglustat. In these studies, the starting dose of eliglustat was 50 mg PO BID. In the Phase 2 and ENGAGE studies, the doses were increased to 100 mg PO BID in Week 4 if Week 2 eliglustat trough concentration was < 5 ng/mL. In ENCORE study, the doses were further increased from 100 mg BID to 150 mg PO BID in Week 6 if Week 4 eliglustat trough concentration was < 5 ng/mL.

The value of 5 ng/mL was chosen because the *in vitro* IC_{50} for GL-1 inhibition is approximately 10 ng/mL. The dose-titration method was used during the clinical development to ensure the desired exposure level for efficacy was achieved, while the starting dose of 50 mg BID was intended to minimize the risk of excessive exposure in patients who were CYP2D6 PMs.

Population PK analysis was performed using all the PK data from Phase 1, 2, and 3 studies.

CYP2D6 Genotyping/Phenotyping in the Clinical Studies

Genotyping for CYP2D6 allelic variants was performed to infer CYP2D6 phenotype in all clinical studies except the single ascending dose study (GZGD00103) and food effect study (GZGD00404). Refer to Section 2.7.1 for the review on methodology.

[1] The complete clinical study report of the Phase 3b study was not included in the original submission.

Table 3. Summary of individual clinical studies

Study Type	Study No.	Eliglustat Dosing Regimen and Duration	No. of Subjects Treated
Phase 1 Studies in Healthy Subjects			
Relative bioavailability of Phase 3 and common blend capsules	GZGD03811	150 mg single dose (4 periods)	22
Food effect	GZGD00404	300 mg single dose (2 periods)	24
Single ascending dose	GZGD00103	0.01, 0.03, 0.1, 0.3, 1.0, 2.0, 3.0, 5.0, 7.0, 10.0, 15.0, 20.0, or 30.0 mg/kg oral solution single dose (Day 1)	74
Multiple ascending dose	GZGD00204	50, 200, or 350 mg (Day 1) 50, 200, or 350 mg BID x 11 days (Day 2 to Day 12)	24
Absolute bioavailability, PK, mass balance, excretion, and metabolism	GZGD02107	50 mg IV single dose (Day 1) 100 mg (Day 8) 100 mg BID x 6 days (Day 9 to Day 14) 100 mg radiolabeled oral solution (Day 15)	10
Thorough QT/QTc	GZGD01707	200 mg and 800 mg single dose	45
Ketoconazole (strong CYP3A and P-gp inhibitor)	GZGD01807	100 mg BID x 7 days (2 periods)	36
Paroxetine (strong CYP2D6 inhibitor)	GZGD02007	100 mg BID x 7 days followed by 100 mg BID x 10 days	36
Rifampin (strong CYP and P-gp inducer)	GZGD02407	100 or 150 mg g single dose (Day 1 of 2 periods) 100 mg or 150 mg BID x 5 days (Day 2 to Day 6 of 2 periods)	25
Antacids and pantoprazole	GZGD01907	100 mg single dose (4 periods)	24
Digoxin (P-gp substrate)	GZGD03610	100 or 150 mg BID x 7 days (Day 11 to Day 17)	28
Metoprolol (CYP2D6 substrate)	GZGD04112	150 mg BID x 6 days (Day 3 to Day 8)	14
Norethindrone / ethinyl estradiol (oral contraceptive, Ortho- Novum 1/35)	GZGD02707	100 mg BID x 11 days (Day 39 to Day 49)	29
Phase 2 and Phase 3 Studies in Patients			

Phase 2 open label study in treatment-naïve patients	GZGD00304 (4 years)	Through Year 4: 50 mg BID x 20 days (Day 1 to Day 20) followed by 50 or 100 mg BID x 49 weeks (Day 20 to Week 52) followed by 50, 100, or 150 mg BID x 3 years (Week 54 to Year 4)	26
	GZGD03310 (biomarker sub-study)	Through Year 3: See above	21
Phase 3 randomized, double-blinded and placebo controlled efficacy/safety study in treatment-naïve patients	ENGAGE / GZGD02507 (Primary Analysis Period)	Primary Analysis Period: 50 mg BID x 4 weeks followed by 50 or 100 mg BID x 35 weeks	20
Phase 3 randomized, open-label, with active comparator (cerezyme) efficacy/safety study in patients switching from enzyme replacement therapy	ENCORE / GZGD02607 (Primary Analysis Period)	Primary Analysis Period: 50 mg BID x 4 weeks (Day 1 to Week 4) followed by 50 or 100 mg BID x 4 weeks (Week 4 to Week 8) 50, 100, or 150 mg BID x 44 weeks (Week 8 to Week 52)	106
Phase 3b efficacy/safety study in patients who were treatment-naïve, off prior treatment, or receiving enzyme replacement therapy	EDGE / GZGD03109 (Lead-in Period)	Lead-in Period: 50 mg BID x 4 weeks (Day 1 to Week 4). 50 or 100 mg BID (Week 4 to Week 8) 50, 100, or 150 mg BID (Week 8 up to Week 78)	170

Source Data: Section 2.7.2, Table 2.

2.3.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Clinical Endpoints

The primary efficacy endpoint in the phase 3 double-blind and placebo-controlled study (ENGAGE) was percent change in spleen volume at Week 39. This measure has been used as one of the components in the primary efficacy endpoint for previous approval of ERTs and an SRT. It is deemed sensitive and clinically meaningful to serve as the primary efficacy endpoint. The secondary endpoints included absolute changes in hemoglobin level, percent change in liver volume and platelet count. The primary efficacy endpoint in phase 3 open-label with active comparator study (ENCORE) was percent of patients who remain stable in hematological parameters (hemoglobin level and platelet count), spleen and liver volumes for 52 weeks. The secondary endpoints included Total T- and Z-scores for bone mineral density of femur and lumbar spine, hemoglobin level, platelet count, and spleen and liver volumes assess by MRI.

The clinical efficacy of eliglustat in patients was demonstrated in ENGAGE and ENCORE. In the ENGAGE study, eliglustat demonstrated superior efficacy over placebo (Section 1.3.4, Table 1). In ENCORE, eliglustat was non-inferior to Cerezyme (Section 1.3.4, Table 2).

Biomarkers

Several biomarkers, including plasma GL-1, were explored during the clinical development of this drug. Results for some biomarkers were inconsistent among patients or studies. However, the result for plasma GL-1 was consistent among the Phase 2 and Phase 3 studies. As this biomarker is related to the mechanism of action, the findings on plasma GL-1 were reviewed and summarized below.

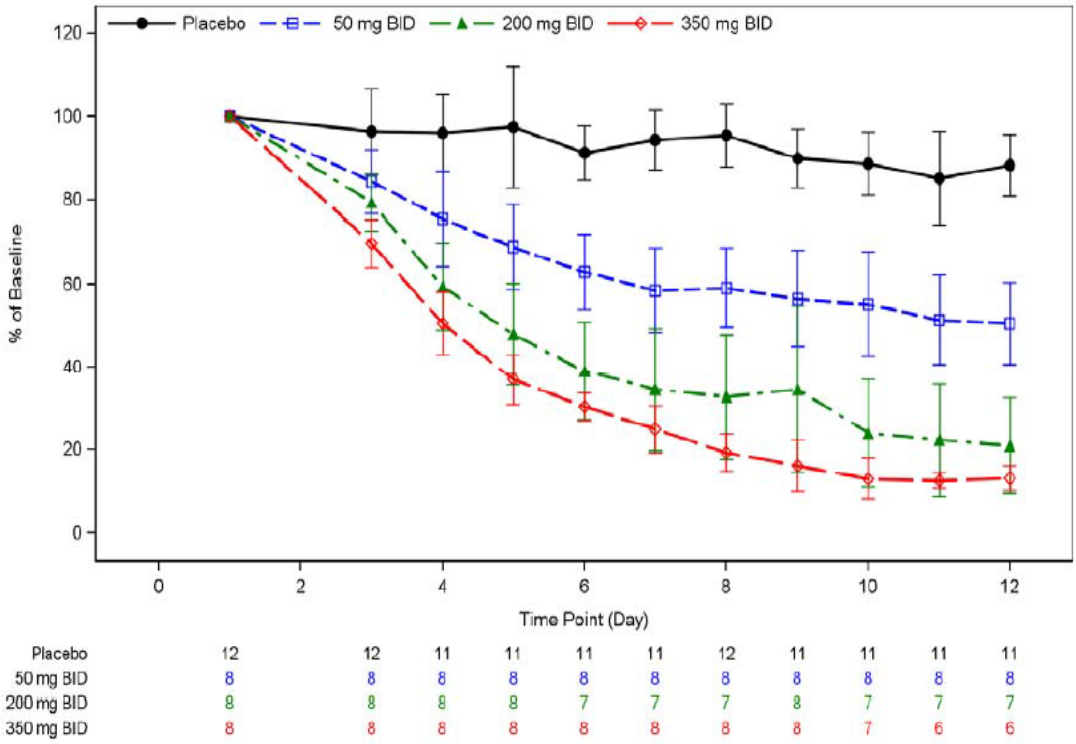
Patients with GD1 have deficient glucocerebrosidase activity which results in the accumulation of glucosylceramide (GL-1) in a variety of tissues and organs. Circulating GL-1 levels are also known to be elevated in GD1 patients. However, circulating GL-1 is traditionally not used as a clinical biomarker of efficacy for GD1 because of its relatively minor elevation in GD1 patients as well as the unclear relationship between GL-1 levels stored in cells and GL-1 levels in circulation.[2,3]

As part of the clinical development program for eliglustat, plasma GL-1 concentrations were measured as a marker of eliglustat pharmacological activity (substrate reduction by inhibition of GL-1 synthesis). Plasma GL-1 concentrations were obtained from healthy subjects in study GZGD00204 and in GD1 patients in the Phase 2, ENGAGE, and ENCORE studies.

After multiple doses of eliglustat in healthy subjects (GZGD00204), a dose-dependent decrease in plasma GL-1 was observed. GL-1 decreased across all eliglustat doses explored, with a mean change from baseline ranging from 50 to 90%.

[2] Dekker N, van Dussen L, Hollak CE et al., Elevated plasma glucosylsphingosine in Gaucher disease: relation to phenotype, storage cell markers, and therapeutic response. Blood. 2011 Oct 20;118(16).
[3] Aerts JM, Kallemeijn WW, Wegdam W et al., Biomarkers in the diagnosis of lysosomal storage disorders: proteins, lipids, and inhibodies. J Inherit Metab Dis. 2011 Jun;34(3):605-19.

Figure 2. Mean (95% CI) percent change from baseline in plasma GL-1 in healthy subjects (Study GZGD00204)



Source Data: Sponsor's submission Section 2.7.2 Summary of Clinical Pharmacology, Figure 1.

In studies of treatment naive GD1 patients (Phase 2 and ENGAGE), GL-1 was measured at screening, on day 30 (Phase 2 only), and at Weeks 4 (ENGAGE only), 13, 26, 39, and 52 (Phase 2 only). Baseline plasma GL-1 levels were above normal (> 6.6 µg/mL) in the majority of patients (21 of 24 in Phase 2, 19 of 20 receiving eliglustat in ENGAGE) and normalized in most patients by the end of each study's primary analysis period. The mean percentage reduction from baseline was 80% at week 52 in the Phase 2 study and 75% at week 39 in patients receiving eliglustat in ENGAGE (Table 4).

In treatment experienced patients (ENCORE), GL-1 was measured at screening and Weeks 13, 26, 39, and 52. As patients had previously received ERT, fewer patients had baseline GL-1 levels above normal compared to treatment naïve patients (22 of 96 patients had plasma GL-1 of > 6.6 µg/mL). Patients who switched to receive eliglustat had a reduction in GL-1 levels at Week 13 and maintained this decrease through Week 52, with a 61% decrease from baseline in plasma GL-1 levels.

Table 4. Median (Range) of plasma GL-1 in GD1 patients.

	Untreated Patients			Previously Treated Patients	
	ENGAGE (GZGD02507)		Phase 2 (GZGD00304)	ENCORE (GZGD02607)	
	Eliglustat (N=20)	Placebo (N=20)	Eliglustat (N=26)	Eliglustat (N=99)	Cerezyme (N=46)
Plasma GL-1, µg/mL					
N 20		20	25	96	47
Normal range	<2.0 to 6.6				
Baseline	11.70 (6.3, 27.9)	8.35 (5.6, 18.4)	12.00 (5.9, 21.7)	5.20 (2.7, 10.5)	5.50 (2.9, 11.5)
End of Primary Analysis Period (Week 39 or 52) [a]	2.40 (2.0, 9.7)	7.55 (4.8, 16.2)	2.10 (2.0, 4.4) [b]	2.00 (2.0, 4.9)	5.0 (2.2, 12.0)
Percentage Change from Baseline to End of Primary Analysis Period [a]	-74.77 (-88.76, -43.44)	-3.19 (-64.71, 29.27)	-79.8 (-89.2, -64.2) [b]	-60.78 (-80.8, -11.8)	-12.70 (-54.9, 58.1)

[a] The end of the primary analysis period was Week 39 of ENGAGE and Week 52 of Phase 2 and ENCORE.
[b] n=21
Source Data: Sponsor's submission Section 2.7.2 Summary of Clinical Pharmacology, Table 51.

Overall, the reduction in plasma GL-1 concentration observed in patients receiving eliglustat is consistent with the mechanism of action of eliglustat as a substrate reduction therapy that inhibits glucosylceramide synthase.

2.3.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess PK parameters and exposure response relationships?

Yes. Refer to Section 2.3.5.7.

2.3.4 Exposure-response (E-R)

2.3.4.1 What are the characteristics of the exposure-response (E-R) relationships (dose-response, concentration-response) for efficacy?

There is a trend for increase in response (decline in spleen and liver volume from baseline, increase in hemoglobin levels and platelet count from baseline) with increasing steady state average trough concentrations of the drug as evidenced in treatment naïve subjects in both Phase 2 (GZGD00304) and ENGAGE study. However, for treatment experienced patients (who were switched from ERT to eliglustat), there was no clinically relevant E-R relationship observed (Appendix 4.1).

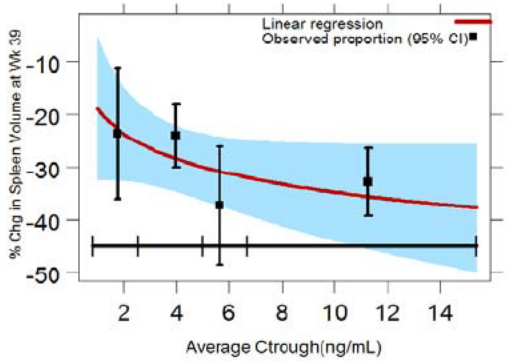
ENGAGE: There is a trend for increase in response with increasing steady state trough concentrations of the drug in treatment naïve subjects with GD1 in the Phase 3 study after 39 weeks of administration of eliglustat (Figure 3). There is a trend for decrease in percentage change in spleen and liver volume with increasing steady state trough concentrations (Figure 3). There is a trend for increase in percentage change in platelet count and change in hemoglobin

from baseline with increasing steady state trough concentrations (Figure 3). The primary endpoint for the study was percentage change in spleen volume from baseline at week 39. The secondary endpoints included percentage change in liver volume and platelet count and absolute change in hemoglobin levels from baseline. The analysis was conducted using data from 19 subjects out of the 20 subjects enrolled in the eliglustat arm. One patient withdrew prior to week 39 assessment.

Phase 2 (GZGD00304): Similar to the ENGAGE study, there is a trend for increase in response with increasing steady state trough concentrations of the drug in treatment naïve subjects with GD1 in the Phase 2 study after 4 years of administration of eliglustat (Figure 4). There is a trend for decrease in percentage change in spleen volume and liver volume, increase in percentage change in platelet count and change in hemoglobin level from baseline with increasing steady state trough concentrations of the drug (Figure 4). The analysis was conducted using data from 18 subjects who had spleen and liver volume measurements both at baseline and at 48 months of treatment. Similarly, the analysis was conducted using data from 19 subjects who had hemoglobin and platelet count measurements both at baseline and at 48 month of treatment. A total of twenty six subjects receiving at least 1 dose of eliglustat were enrolled in the study. Seven subjects discontinued prior to 48 month assessment.

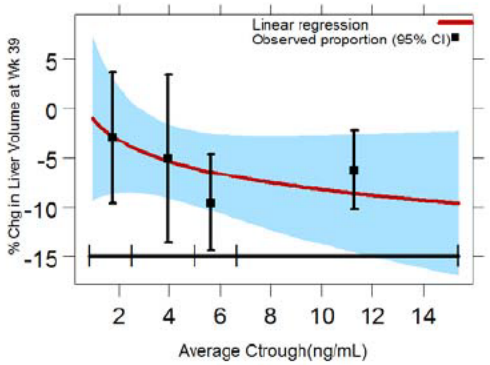
ENCORE: There is no E-R relationship for the primary composite endpoint of proportion of patients who remained stable with respect to organ volumes (spleen and liver) and hematological parameters after 52 weeks of treatment with eliglustat in GD1 patients who had reached therapeutic goals with enzyme replacement therapy and were switched to eliglustat (Figure 5). There is a trend for decrease in percentage change in spleen volume (co-primary endpoint) at week 52 with increasing steady state trough concentrations (Figure 5). The percentage change in spleen volume is 4.4% in the lowest concentration quartile while it is -12.1% in the highest concentration quartile (Table 5). This trend should however be interpreted with caution because as shown in Table 5, although a difference in percentage change in spleen volume is observed between the lowest and highest quartile, the absolute values of spleen volume at week 52 range between 3.0-3.1 multiples of normal (MN) among various quartiles. Thus the differences observed in percentage change in spleen volume is likely not to have any clinical impact in these subjects who were stabilized and met their therapeutic goals at the beginning of the study.

A Percentage Change in Spleen Volume



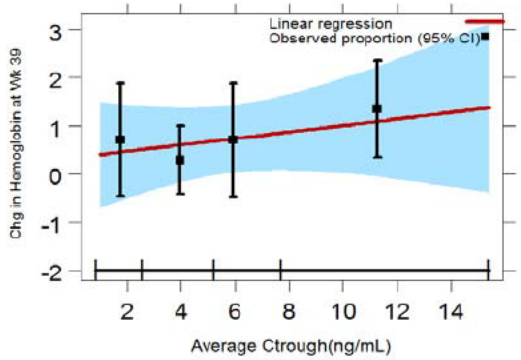
Placebo=2.26%

B Percentage Change in Liver Volume



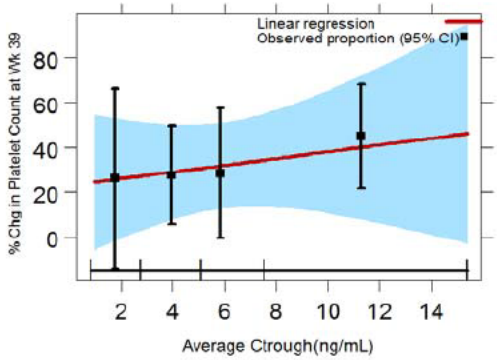
Placebo=1.44%

C Change in Hemoglobin



Placebo = -.054

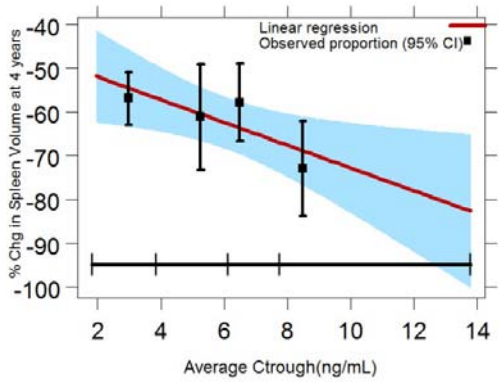
D Percentage Change in Platelet Count



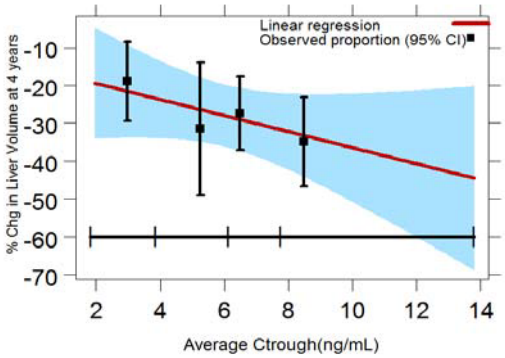
Placebo = -9.06%

Figure 3. The relationship for A) percentage change in spleen volume, B) percentage change in liver volume, C) change in hemoglobin and D) percentage change in platelet count from baseline after 39 weeks of treatment with steady state average trough concentration of the drug in ENGAGE (Phase 3) study. Solid black symbols represent the observed mean value in each C_{trough} quartile. The black bars represent the 95% confidence interval of the mean. The solid red line represents the mean linear regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Average C_{trough} represents the average of weeks 13, 26 and 39. The response in the placebo arm of the study is also shown.

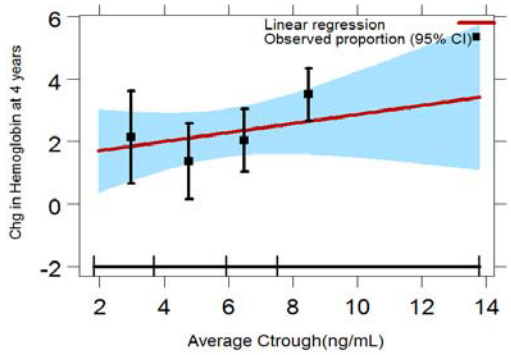
A Percentage Change in Spleen Volume



B Percentage Change in Liver Volume



C Change in Hemoglobin



D Percentage Change in Platelet Count

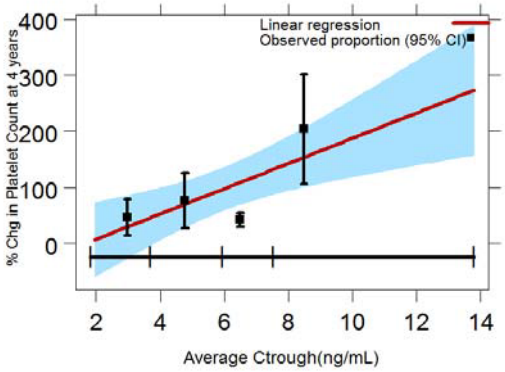
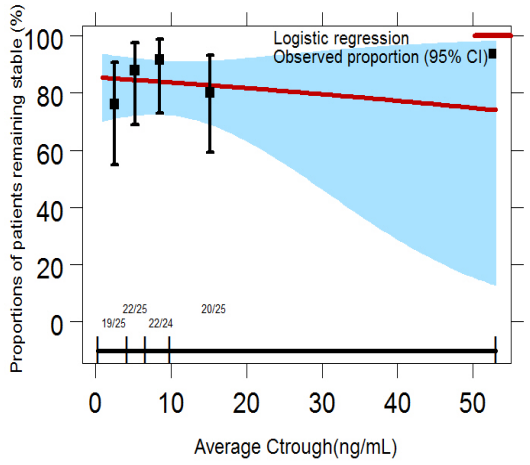


Figure 4. The relationship for A) percentage change in spleen volume, B) percentage change in liver volume, C) change in hemoglobin and D) percentage change in platelet count from baseline after 4 years of treatment with steady state average trough concentration of the drug in GZGD00304 study. Solid black symbols represent the observed mean value in each C_{trough} quartile. The black bars represent the 95% confidence interval of the mean. The solid red line represents the mean linear regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Average C_{trough} represents average of multiple trough measurements from day 30 to month 48.

A Primary Composite Endpoint- Proportion of patients remaining stable after 52 weeks of treatment



B Percentage Change in Spleen Volume

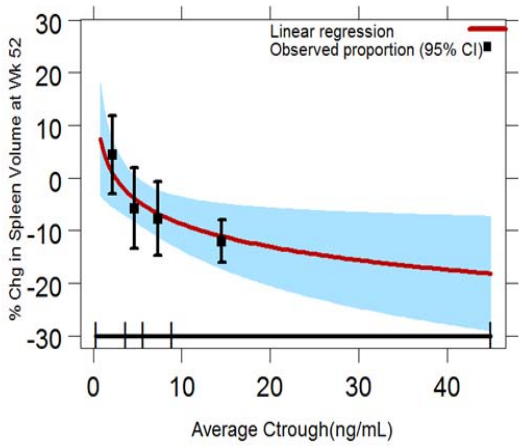


Figure 5. The relationship for A) proportion of patients remaining stable and B) percentage change in spleen volume from baseline after 52 weeks of treatment with steady state average trough concentration of the drug in ENCORE study. Solid black symbols represent the observed mean value in each C_{trough} quartile. The black bars represent the 95% confidence interval of the mean. The solid red line represents the mean logistic (A) and linear (B) regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Average C_{trough} represents the average of weeks 13, 26, 39 and 52.

Table 5. Percentage change in spleen volume from baseline, spleen volume at baseline and at Week 52 by mean steady state trough concentration quartiles

Concentration quartile	Median Ctrough (ng/ml)	N	Baseline spleen volume (MN)	Spleen volume at week 52 (MN)	Percentage change in spleen volume at week 52 (%)
0.31+ thru 3.6	2.1	18	2.9	3.1	4.4
3.6 + thru 5.6	4.6	17	3.3	3.1	-5.8
5.6 + thru 8.8	7.3	17	3.2	3.1	-7.8
8.8 + thru 44.9	14.5	18	3.3	3.0	-12.1

2.3.4.2 Is measuring drug concentrations and maintaining patients above 5 ng/mL critical for treatment?

No, a 5 ng/ml concentration threshold may not be necessary for successful treatment. While sample sizes are limited, treatment naïve patients in study GZGD00304 with drug concentrations lower than 5 ng/ml showed clinically meaningful effects with respect to changes in spleen volume, liver volume and hemoglobin level (for details see Pharmacometrics review).

For subjects with drug concentrations lower than 5 ng/ml, the spleen volume decreased from 12.3 MN at baseline to 5.3 MN after 4 years of treatment (Table 6). For subjects with drug

concentrations greater than 5 ng/ml, the spleen volume decreased from 20.5 MN at baseline to 6.6 MN., The spleen volumes were comparable after 4 years. Figure 6 shows the average steady state concentration achieved by individual patients in the study. As shown, 7 out of 18 subjects had concentrations lower than 5 ng/ml with lowest concentration lower than 2 ng/ml.

For subjects with drug concentrations lower and greater than 5 ng/ml, the liver volume was 1.1 MN and 1.2 MN respectively after 4 years of treatment. The hemoglobin levels in the two groups were 13.5 and 13.6 g/dL. Based on discussions with the clinical reviewer, the changes in spleen volume, liver volume and hemoglobin levels in the lower concentration group were considered meaningful and comparable to the values observed with long term treatment with enzyme replacement therapy. [4] According to Pastores et. al. a long term (3-4 years) therapeutic goal for treatment of GD1 should be to reduce and maintain spleen volume to ≤ 2 to 8 times normal. While the platelet count did not achieve normal levels and were lower in the <5 ng/ml group ($106x10^9$/L) compared to >=5 ng/mL group ($139x10^9$/L), the value in the lower concentration group were above the threshold of clinical concern. Based on Pastores et. al. 2004, spontaneous bleeding is rarely observed in patients with Gaucher disease when the platelet count exceeds $30x10^9$/L.

The sponsor conducted similar analysis in extensive metabolizers who were treated at the 100 mg BID dose in GZGD00304 study. The analysis showed that patients with drug concentration lower that 5 ng/ showed clinically meaningful response and spleen volume, liver volume, hemoglobin level and platelet count achieved similar levels in both low (<5 ng/ml) and high (>=5 ng/ml) concentration groups after 4 years of treatment (Figure 7).

Table 6. Mean changes from baseline in the GZGD00304 Study, by average plasma steady state trough concentrations.

Concentration Group	N	Baseline Value	Value at 4 years	Percentage change /change * at 4 years
Spleen volume (MN)				
<5 ng/mL	7	12.3	5.3	-57 %
>=5 ng/mL	11	20.5	6.6	-66 %
Liver volume (MN)				
<5 ng/ml	7	1.4	1.1	-22 %
>=5 ng/ml	11	1.9	1.2	-32 %
Platelet count (10^9/L)				
<5 ng/ml	8	70	106	53%
>=5 ng/ml	11	68	140	126%
Hemoglobin (g/dL)				
<5 ng/ml	8	11.6	13.5	1.9
>=5 ng/ml	11	11.1	13.6	2.5

[4] Pastores GM, Weinreb NJ, Aerts H et al., Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004 Oct;41(4 Suppl 5):4-14.

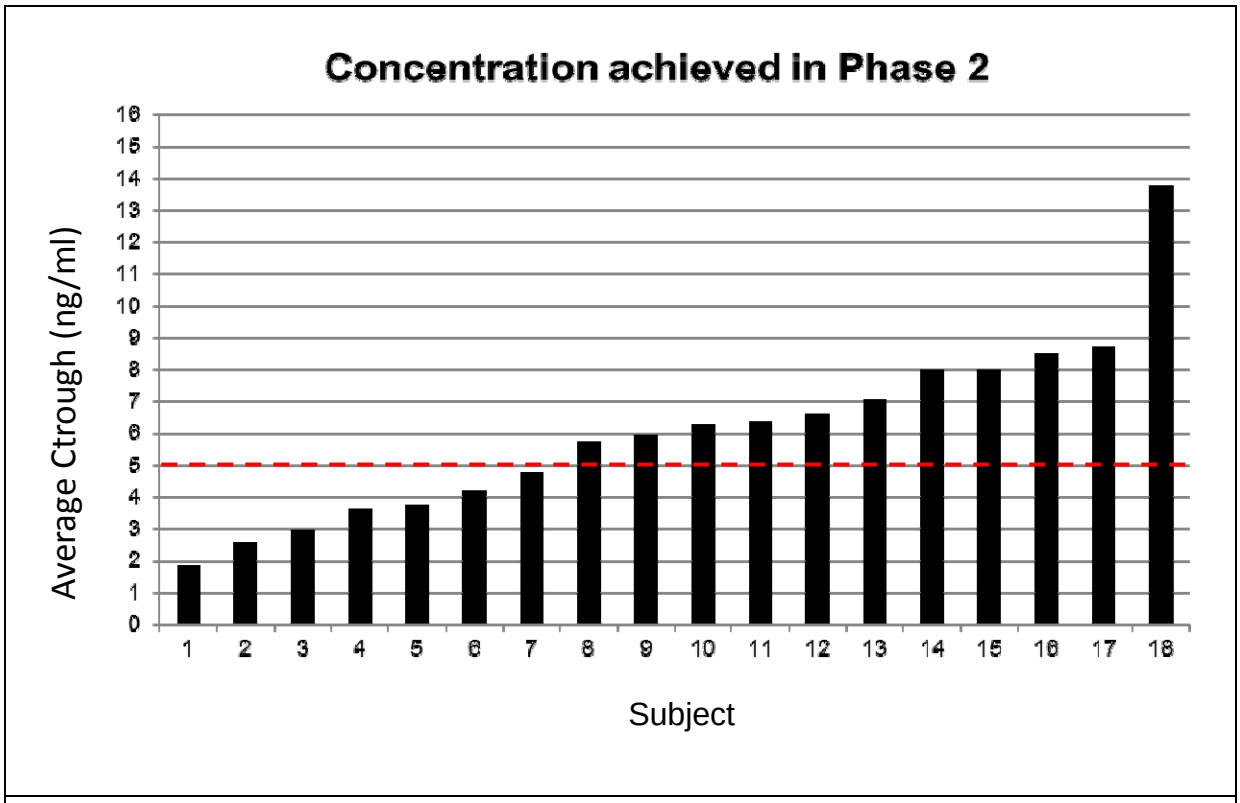


Figure 6. Average steady state concentration achieved by individual subjects in GZGD00304 study

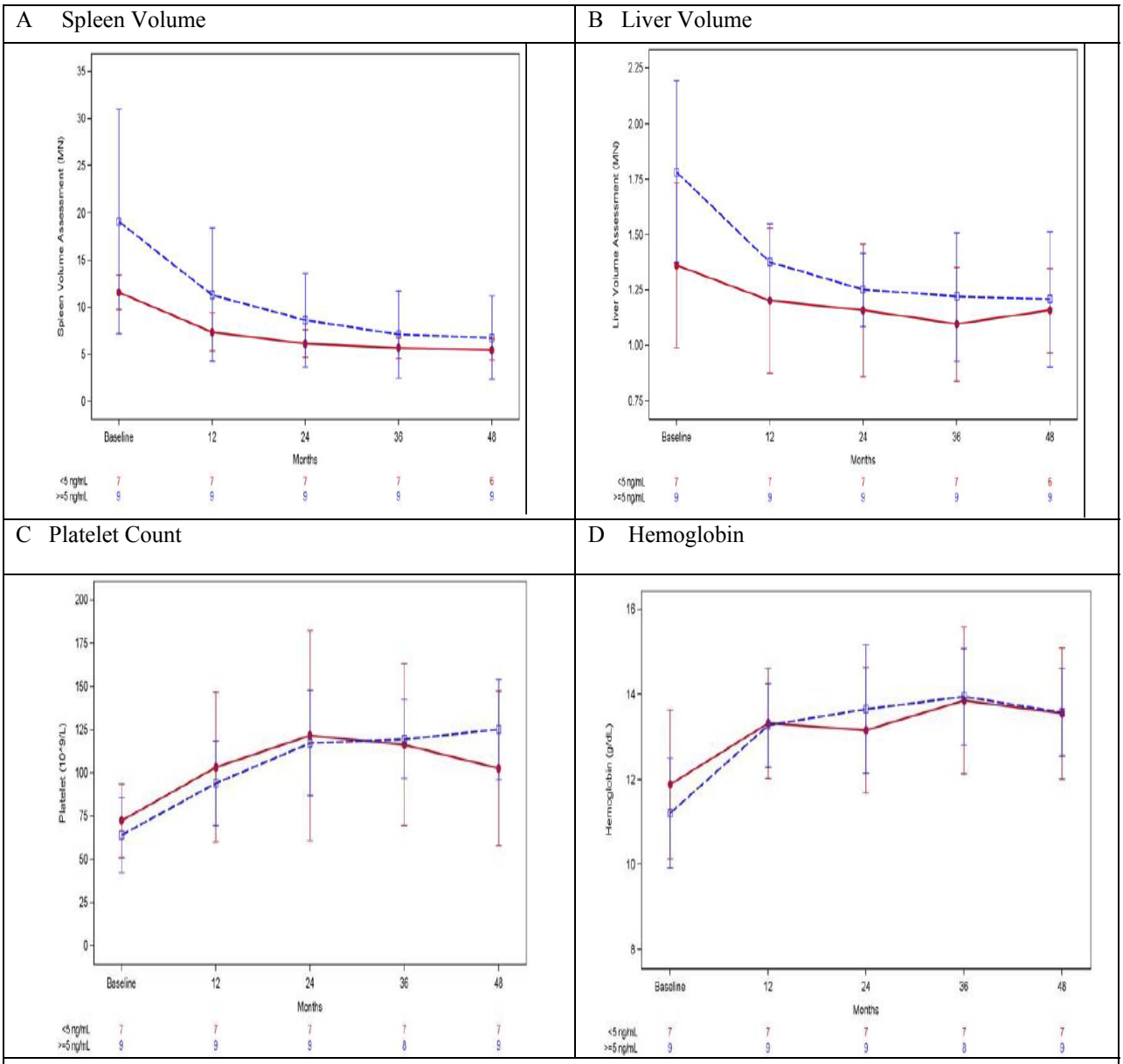


Figure 7. Time-profiles for A) spleen volume, B) liver volume, C) platelet count and D) hemoglobin after 4 years of treatment with eliglustat in Phase 2 study by average plasma steady state trough concentration levels for extensive metabolizers receiving 100 mg BID. Red and blue lines represents patients with concentrations < 5 ng/ml and ≥ 5 ng/ml respectively.

Source Data: Figure 1 of sponsor's eliglustat background meeting package (SDN21)

2.3.4.3 Does this drug prolong the QT or QTc interval?

Eliglustat increased the QTc and PR intervals in a dose-dependent manner. For QTcF, the largest upper bounds of the 2-sided 90% CI for the mean difference between 200 mg eliglustat and placebo, and between 800 mg eliglustat and placebo are 3.3 ms and 9.1 ms, respectively. However, these increases are below the 10 ms regulatory threshold as described in the ICH E14 Guidance (Table 7). Two subjects whose baseline PR was under 200 ms experienced a maximum change of 18 ms (Appendix 4.2).

Table 7. Point estimates and the 90% CIs corresponding to the largest upper bounds for eliglustat (200 mg and 800 mg)

	200 mg Eliglustat	**800 mg Eliglustat**
ΔΔQTcF mean (90% CI)	0.9 (-1.4, 3.3)	6.6 (4.1, 9.9)
ΔΔPR mean (90% CI)	3.5 (1.2, 5.8)	14.1 (11.8, 16.4)
ΔΔQRS mean (90% CI)	0.6 (-0.3, 1.6)	4.2 (3.2, 5.2)

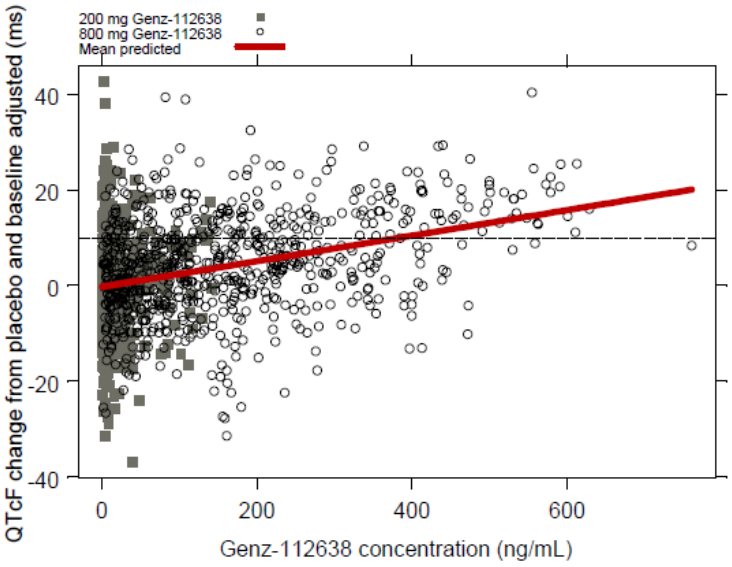
Source: QT-IRT review in Appendix 4.2

2.3.4.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

QT Prolongation:

There was a concentration dependent increase in QTc. The relationship between eliglustat concentrations and ΔΔ QTcF is visualized in Figure 8. An increase in ΔΔ QTcF is observed with increasing drug concentration. The mean (upper 90% CI) predicted ΔΔQTcF at the mean Cmax of 16.7 ng/ml and 237 ng/ml for the 200 mg and 800 mg doses achieved in the QT study are 0.18 (1.7) ms and 6.06 (8.9) ms as shown in

Table 8 (Appendix 4.2). For a Cmax of 250 ng/mL, the mean (upper 90% CI) of ΔΔQTcF are predicted to be 6.4 (9.4) ms, which is below the regulatory threshold (Table 9). Thus based on the concentration-QT relationship, there appears to be no QT related safety concerns for drug concentrations below 250 ng/mL.



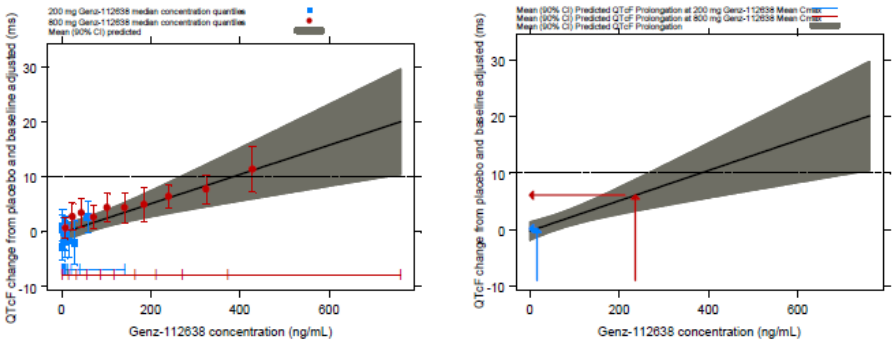


Figure 8. ΔΔ QTcF vs. eliglustat concentration. Top panel -The circles represent the raw data and the red line represents the population prediction mean ΔΔ QTcF. Bottom Left-Concentration Quantile plot. The concentration range in each quantile is denoted by the horizontal blue and red lines for the 200 mg and 800 mg dose levels. The blue and red symbols represent the mean (90 % CI) of ΔΔ QTcF in each quantile. The population predicted ΔΔ QTcF (mean and 90% CI) is shown with the black line and shaded grey area. Bottom Right - Predicted ΔΔ QTcF at geometric mean Cmax of the two dose levels.

Source: QT-IRT review in Appendix 4.2

Table 8. Predicted change of ΔΔQTcF interval at geometric mean Cmax of eliglustat observed in

the thorough QT study

Dose Group	Predicted change in ΔΔ QTcF interval (ms)	
	Mean	90% Confidence Interval
200 mg Genz-112638		
Geometric Mean C_{max} (16.7 ng/mL)	0.176	(-1.35; 1.7)
800 mg Genz-112638		
Geometric Mean C_{max} (237 ng/mL)	6.06	(3.24; 8.88)

Table 9. Predicted QT prolongation at the steady state mean Cmax of 250 ng/mL

Predicted mean (90%CI, ms) change in	At mean Cmax of 250 ng/mL
QTcF	**6.4 (3.4, 9.4)**
PR	**11.2 (8.9, 13.4)**
QRS	**3.5 (1.9, 5.1)**

Other adverse events:

E-R analysis was performed on all adverse events listed in the ISS dataset. An E-R relationship was identified for moderate and severe nervous system disorders in pooled data from Phase 3 studies (ENGAGE and ENCORE). The proportion of patients experiencing moderate and severe nervous system disorders increased with increasing $AUC_{0\text{-}tau}$ and Cmax (Figure 9). This relationship was primarily driven by patients experiencing headaches. There was an increase in the proportion of patients experiencing moderate and severe headaches with increasing exposure (Figure 10). The exposure range for each quartile of eliglustat $AUC_{0\text{-}tau}$ and Cmax values are shown in

Table 10. Similar results were obtained when steady state C_{trough} was used as the exposure metric.

Other adverse events may have had a significant slope, but did not appear to exhibit a clinically meaningful relationship within the observed eliglustat exposures, or consistent relationship across severity of the event, or consistent relationship across PK parameters, or had too few occurrences to consider the relationship meaningful (For details see Pharmacometrics review).

E-R relationships were also evaluated for GI related adverse events (Figure 11). There appears to be a slight increase in the proportion of patients with moderate and severe GI related AEs in the fourth quartile (11/30) compared to the rest (6/30, 7/29, 4/29 in 1st, 2nd and 3rd quartile). Based on discussions with the clinical team, these GI related AEs were considered to be clinically not significant.

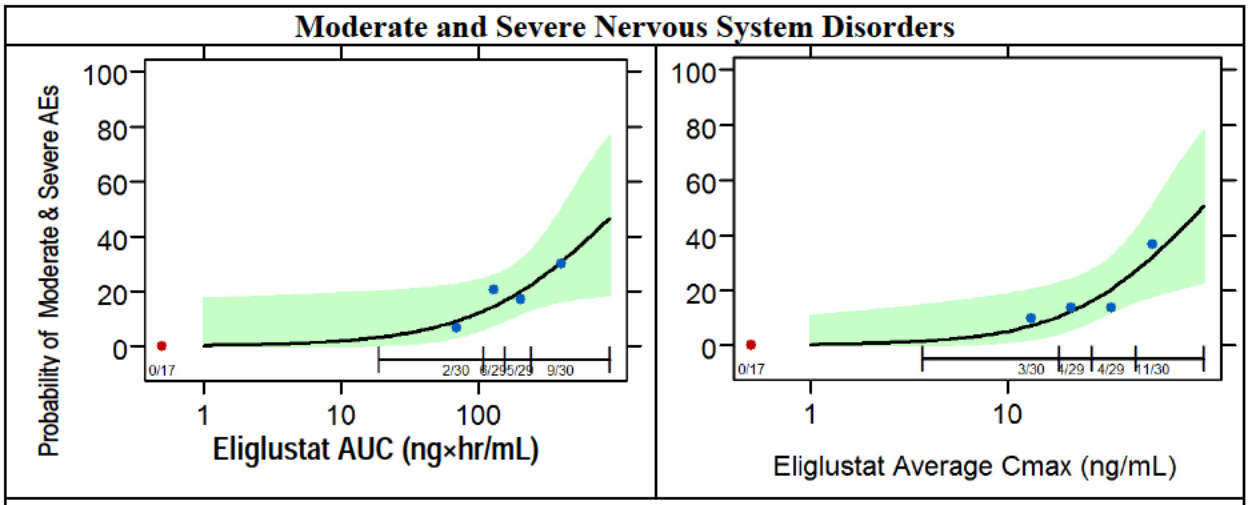


Figure 9. E-R relationship for moderate and severe nervous system disorders by AUC (left panel) and Cmax (right panel). The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and eliglustat data simultaneously, assuming placebo concentrations of eliglustat were zero. Data points are the probability for the placebo (red) and eliglustat (blue). Exposure bins are denoted by the bars at the bottom of the plot.

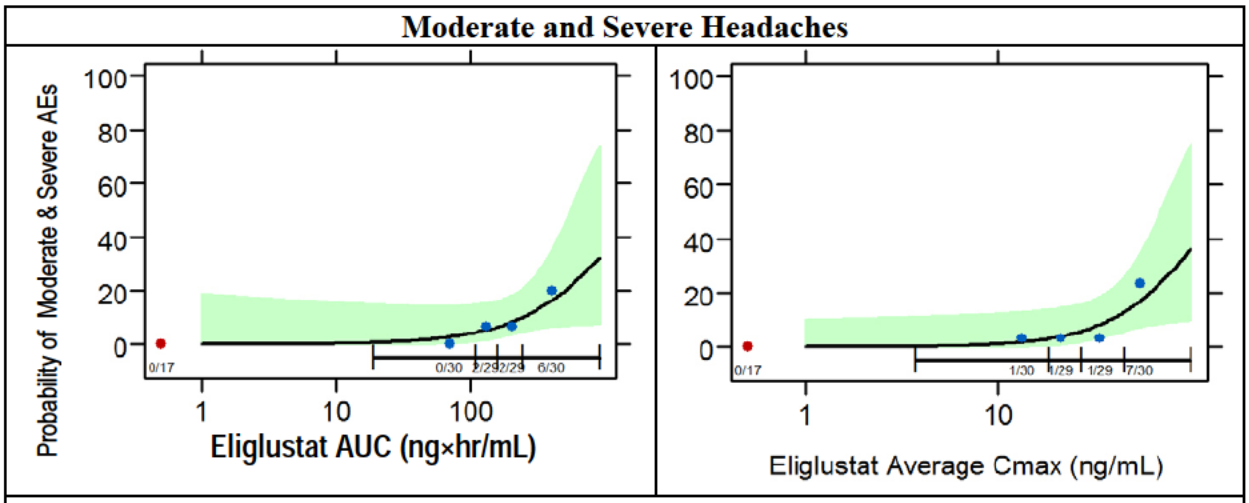


Figure 10. E-R relationship for moderate and severe headaches by AUC (left panel) and Cmax (right panel). The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and eliglustat data simultaneously, assuming placebo concentrations of eliglustat were zero. Data points are the probability for the placebo (red) and eliglustat (blue). Exposure bins are denoted by the bars at the bottom of the plot.

Table 10. Average steady state PK parameter range for each exposure quartile in the E-R

analysis for safety events.

(b) (4)

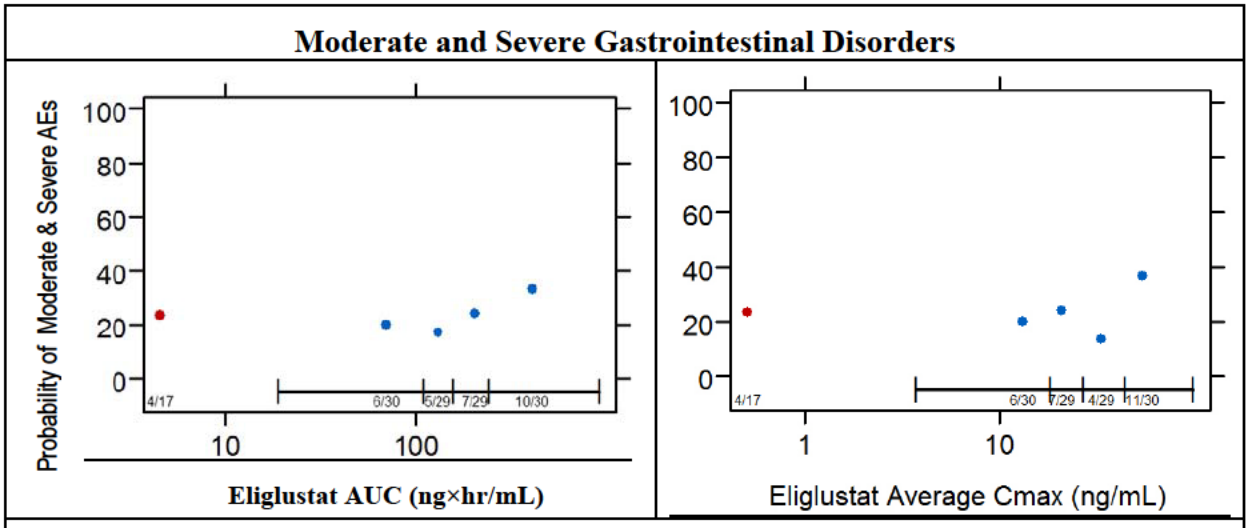


Figure 11. E-R relationship for moderate and severe gastrointestinal disorders by AUC (left panel) and Cmax (right panel). Data points are the probability for the placebo (red) and eliglustat (blue). Exposure bins are denoted by the bars at the bottom of the plot.

2.3.4.5 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The sponsor proposed fixed dosing regimen of 100 mg BID for EMs or IMs without measuring drug concentrations is acceptable. Reviewers also agree to sponsor's proposal of not recommending dosing for URMs. (b) (4) based on the PBPK simulations, observed PK data, exposure-response for efficacy and safety, the reviewer proposes a 100 mg QD dose for PMs.

A titration based dosing scheme was employed by the sponsor in Phase 2 and Phase 3 studies (Section 2.3.1). This algorithm was employed in order to maintain plasma concentrations of 6 to 14 ng/mL (Section 8.4.4 of sponsor's Phase 2 study CSR). This was considered a reasonable exposure for achieving efficacy. However, because of genetic polymorphisms in the elimination pathway of eliglustat, variability in plasma concentrations was expected. By initially dosing all patients with 50 mg BID, patients who are poor metabolizers of eliglustat were not expected to have plasma concentrations above 150 ng/mL, the concentration that was associated with gastrointestinal AEs. In all cases where subjects experienced Grade 2 gastrointestinal AEs, the maximum observed plasma concentration (Cmax) of eliglustat on Day 1 was greater than 100 ng/mL, and exceeded 150 ng/mL by Day 12 (Section 8.4.4 of sponsor's Phase 2 study CSR). The distribution of patients by various dose and CYP2D6 phenotype status in Phase 2, ENGAGE and ENCORE studies are shown in Table 11, Table 12 and Table 13, respectively. Among the

extensive metabolizers in the treatment naïve population, the majority were at a stable dose of 100 mg BID (18/25 in Phase 2; 16/18 in ENGAGE); remaining at lower dose of 50 mg BID or 50 md QD. There was only one intermediate metabolizer in the ENGAGE and was treated at 50mg BID. In the switched study (ENCORE), the number of extensive metabolizers at the 50 mg BID, 100 mg BID and 150 mg BID doses were 10, 31 and 42. The number of intermediate metabolizers at the 50 mg BID, 100 mg BID and 150 mg BID doses were 7, 4 and 1. While a titration based dosing scheme was implemented in Phase 2 and Phase 3 studies, the sponsor's proposed dose is a fixed dose of 100 mg BID in intermediate and extensive metabolizers. Thus greater than 50% of IMs and EMs in ENCORE were at dose levels lower and higher compared to sponsor's proposed dose. No dosing recommendation is provided for (b) (4) ultra-rapid metabolizers in the current label.

Table 11. Distribution of patients by CYP2D6 phenotype status and dose in Phase 2 study

CYP2D6 phenotype	50 mg QD (N=2)	50 mg BID (N=6)	100 mg BID (N=18)
PM		1	
EM	2	5	18

Table 12. Distribution of patients by CYP2D6 phenotype status and dose in ENGAGE

CYP2D6 phenotype	50 mg BID (N=3)	100 mg BID (N=17)
IM	1	
EM	2	16
URM		1

Table 13. Distribution of patients by CYP2D6 phenotype status and dose in ENCORE

CYP2D6 phenotype	50 mg BID (N=21)	100 mg BID (N=35)	150 mg BID (N=49)
PM	4	0	0
IM	7	4	1
EM	10	31	42
URM	0	0	4
Indeterminate	0	0	2

Extensive and Intermediate Metabolizers:

Based on the efficacy, safety and PK findings and E-R relationship for efficacy and safety from Phase 2, ENGAGE and ENCORE studies, the 100 mg BID dose appears reasonable for IMs and EMs.

There is a trend for increase in efficacy parameters with increasing drug concentrations in Phase2 and ENGAGE study (Section 2.3.4.1). While an E-R relationship was identified, a subgroup analysis suggested that treatment naïve patients in the Phase 2 study with drug concentrations lower than 5 ng/ml showed clinically meaningful effects with respect to efficacy parameters and 5 ng/ml concentration threshold may not be necessary for successful treatment (see section 2.3.4.2). The Phase 2 and ENGAGE study comprised of treatment naïve subjects that had a higher disease burden compared to subjects in ENCORE who were stabilized on enzyme replacement therapy as evidenced by higher spleen volumes at baseline (Table 14). The patients in ENGAGE and Phase 2 study were treated successfully at doses of 100 mg BID or lower. Thus from an efficacy perspective, 100 mg BID appears to be reasonable for extensive and

intermediate metabolizers.

Based on discussion with the clinical team, no major safety concerns have been identified for eliglustat. Exposure-response relationships were evaluated for adverse events based on system organ class and MEDRA preferred term. No meaningful ER relationship was observed except for nervous system disorders and this was primarily driven by headaches. Overall the incidence rates of AEs were low. An increase in QT prolongation was observed with increasing drug concentration. For a Cmax of 250 ng/ml, the mean (upper 90% CI) of ΔΔQTcF are predicted to be 6.4 (9.4) ms, which is below the regulatory threshold. Thus based on the concentration-QT relationship, there appears to be no QT related safety concerns for drug concentrations below 250 ng/ml (Section 2.3.4.3).

The mean Cmax predicted by PBPK simulations in intermediate and extensive metabolizers at the 100 mg BID dose are 63 ng/ml and 25ng/ml; which are below the threshold for QT concerns. For details regarding the PBPK simulations, see Dr. Ping Zhao's PBPK review. The mean predicted AUC 0-12 values for intermediate and extensive metabolizers at the 100 mg BID dose are 527 ng×hr/mL and 185 ng×hr/mL respectively. The observed AUC 0-12h values for intermediate and extensive metabolizers at the 100 mg BID dose in ENCORE study are 400 and 201 ng×hr/mL (Table 16). The AUC values for EMs in ENGAGE and Phase 2 were lower than the observed value in ENCORE (see Section 2.3.5.1.1.2). The PBPK model appears to over-predict the exposure for IMs and EMs. Thus, the exposure in IMs and EMs upon administration of a fixed dose of 100 mg BID are likely to fall within the predicted (527 ng×hr/mL for IMs, 185ng×hr/mL for EMs) and observed values (400 ng×hr/mL for IMs, 201 ng×hr/mL for EMs). Using a conservative approach, a higher exposure as predicted by the model is used to draw inferences on the likely impact on safety. Figure 12 shows the observed $AUC_{0\text{-}12h}$ in all patients in Phase 2, ENGAGE and ENCORE studies by CYP2D6 status dose. The graph also includes subject with $AUC_{0\text{-}12h}$>400 ng×hr/mL from the phase 3b (EDGE) study. Overall the predicted exposures in IMs and EMs at the 100 mg BID dose falls within the exposures observed in the studies; although data is limited at high exposures. There are 8 and 24 patients (Figure 12) who had $AUC_{0\text{-}12h}$ > 527 ng×hr/mL and $AUC_{0\text{-}12h}$ > 400 ng×hr/mL respectively. This limited clinical experience at high exposures ($AUC_{0\text{-}12h}$ > 400 ng×hr/mL) needs to be put in context of GD1 being a rare disease with an incidence of 1 in 100,000 live births in general population. Based on National Organization of Rare Disease, there are likely to be ~5700 GD1 patients in USA. There are likely to be ~490 IM patients based on 8.6% IM patients of the whole patient population as observed in the trials which is consistent with the known distribution as reported in literature (Hick et. al. 2013).

In summary, given the lack of safety concerns with eliglustat, no meaningful exposure response relationship for safety, and that exposures in IMs and EMs at 100 mg BID are expected to fall within the exposures achieved in Phase 2 and Phase 3 studies, the 100 mg BID dose appears reasonable.

Table 14. Baseline spleen volume in treatment arm in Phase2, ENGAGE and ENCORE

Study	N	Baseline Spleen Volume (MN) Mean (SD)
Phase 2	26	20.0 (12.8)
ENGAGE	20	13.9 (5.9)
ENCORE	99	3.23 (1.37)

Table 15. Predicted eliglustat exposure (Mean (90% CI)) in intermediate and extensive metabolizers at 100 mg BID dose by PBPK

CYP2D6 status	Cmax (ng/mL)	AUC_{tau} (ng×hr/mL) 0-12h for b i.d.
Extensive Metabolizer	25 (22.5, 27)	185 (166, 203)
Intermediate Metabolizer	63 (58, 67)	527 (484, 570)

Values are mean from simulation of ten trials with 36 subjects/trial. For details see PBPK review in Appendix 4.3

Table 16. Observed eliglustat exposure (Mean (90%CI) for EMs and Mean (range) for IMs) in ENCORE study at Week 52

Dose	CYP2D6 status	N	Cmax (ng/mL)	AUC_{tau} (ng×hr/mL) 0-12h for b.i.d.
100 mg BID	**Extensive Metabolizer**	30	35 (29, 41)	201 (166, 236)
100 mg BID	**Intermediate Metabolizer**	4	58.7 (40, 108)	400 (248, 830)

Source: Table 12-1, 12-4 and 12-5 of clinical study report.
For details and observed eliglustat concentrations in ENGAGE and Phase 2 study, see Section 2.3.5.1.2 of this review.

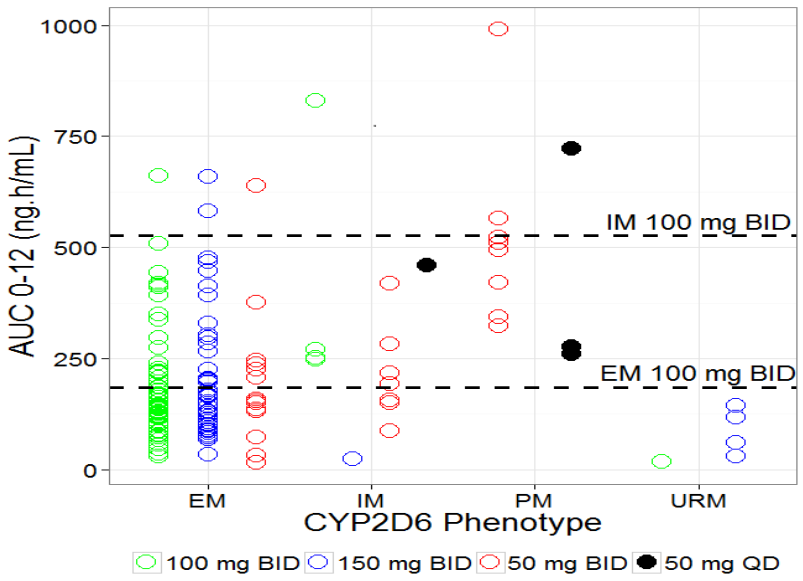


Figure 12. Observed exposure (AUC_{0-12}) in individual patients by CYP2D6 phenotype. The horizontal lines represent the mean predicted exposure by PBPK simulation for intermediate and extensive metabolizers at 100 mg BID dose. For patients at 50 mg QD, the AUC_{0-12h} is approximately calculated at $AUC_{0-24h}/2$.

Poor and Ultra-rapid Metabolizers:

Based on the efficacy, safety, and PK findings and E-R relationship for efficacy and safety, a 100 mg QD dose is recommended for poor metabolizers. A safe and effective dose has not been determined for patients who are CYP2D6 URMs.

Based on PBPK simulations, the predicted Cmax in poor metabolizers at 100 mg QD dose is 75 ng/ml which is significantly below 250 ng/ml and is likely not to result in any QT related safety concerns (Table 17). For details regarding the PBPK simulations, see Dr. Ping Zhao's PBPK review. The predicted AUC_{0-24h} is 956 ng×hr/mL (Table 17) which is similar to the predicted AUC_{0-24h} of 1054 ng×hr/mL (AUC_{0-24h}= AUC_{0-24h}x2=527x2; Table 15) for intermediate metabolizers at the 100 mg BID dose. As stated above, these exposures are within the exposures that were achieved in Phase 2 and Phase 3 studies. Additionally, 5 PM patients in ENCORE and Phase 2 received the 50 mg BID dose and similar exposures (AUC_{0-24h}) are likely to be achieved under the 100 mg QD regimen based on linear PK. Dosing recommendation is not being provided for ultra-rapid metabolizers (URMs) because even with a high dose of 200 mg BID, the AUC values are ~50% and ~82% lower than the values for extensive and intermediate metabolizers at the 100 mg BID dose respectively. While with doses higher than 200 mg BID, it may be possible to match the exposure of the parent drug in URMs to the exposure in EMs at 100 mg BID, the effect of increased concentration of metabolites at the higher dose on safety is unknown.

Table 17. Predicted eliglustat exposure (Mean (90% CI)) in PMs and URMs by PBPK

Eliglustat	**CYP2D6 status**	**Cmax (ng/mL)**	**AUC_{tau} (ng×hr/mL) 0-12h for b i.d. 0-24h for q.d.**
100 mg q.d.	**Poor Metabolizer**	75 [71, 79]	956 [884, 1028]
200 mg b.i.d.	**Ultra Rapid metabolizer**	14 (11,17)	97 (77,117)

PMs Values are from simulation of ten trials with 36 subjects/trial. URMS Values are from simulation of ten trials with 10 subjects/trial. For details see PBPK review in Appendix 4.3

2.3.5 PK characteristics of the drug and its major metabolites

Eliglustat PK is highly dependent of CYP2D6 phenotype. At 100 mg BID, the steady state eliglustat plasma AUC ratio for PM/IM/EM is approximately 7:3:1. In CYP2D6 EMs and IMs, the eliglustat PK is time-dependent and the systemic exposure increases in a more than dose proportional manner. The PK of eliglustat in CYP2D6 PMs appears to be linear and time-independent.

2.3.5.1 What are the single dose and multiple dose PK parameters?

2.3.5.1.1 Healthy subjects

2.3.5.1.1.1 Single Dose

Single dose PK of 100 mg eliglustat

The single dose PK of the proposed dose of 100 mg from four Phase 1 clinical studies was summarized in Table 18 and Table 19. Comparison of the systemic exposure to eliglustat across the four CYP2D6 phenotypes was presented in Figure 13. Following single dose of 100 mg eliglustat, the systemic exposures were the highest in PMs with the longest T1/2 of 9 hours, followed by IMs and EMs. The systemic exposures in two URMs were the lowest.

The mean concentration-time profile following single oral dose administration of 100 mg eliglustat is presented in Figure 14. Single-dose dose escalation study results (GZGD00103) in healthy subjects were not reviewed because the sponsor did not perform CYP2D6 genotype on these subjects and the study was a parallel design with each subject assigned to one of the dose levels.

Table 18. Mean (CV%) of eliglustat plasma PK parameters after single oral dose of 100 mg in healthy subjects who are EMs or IMs.

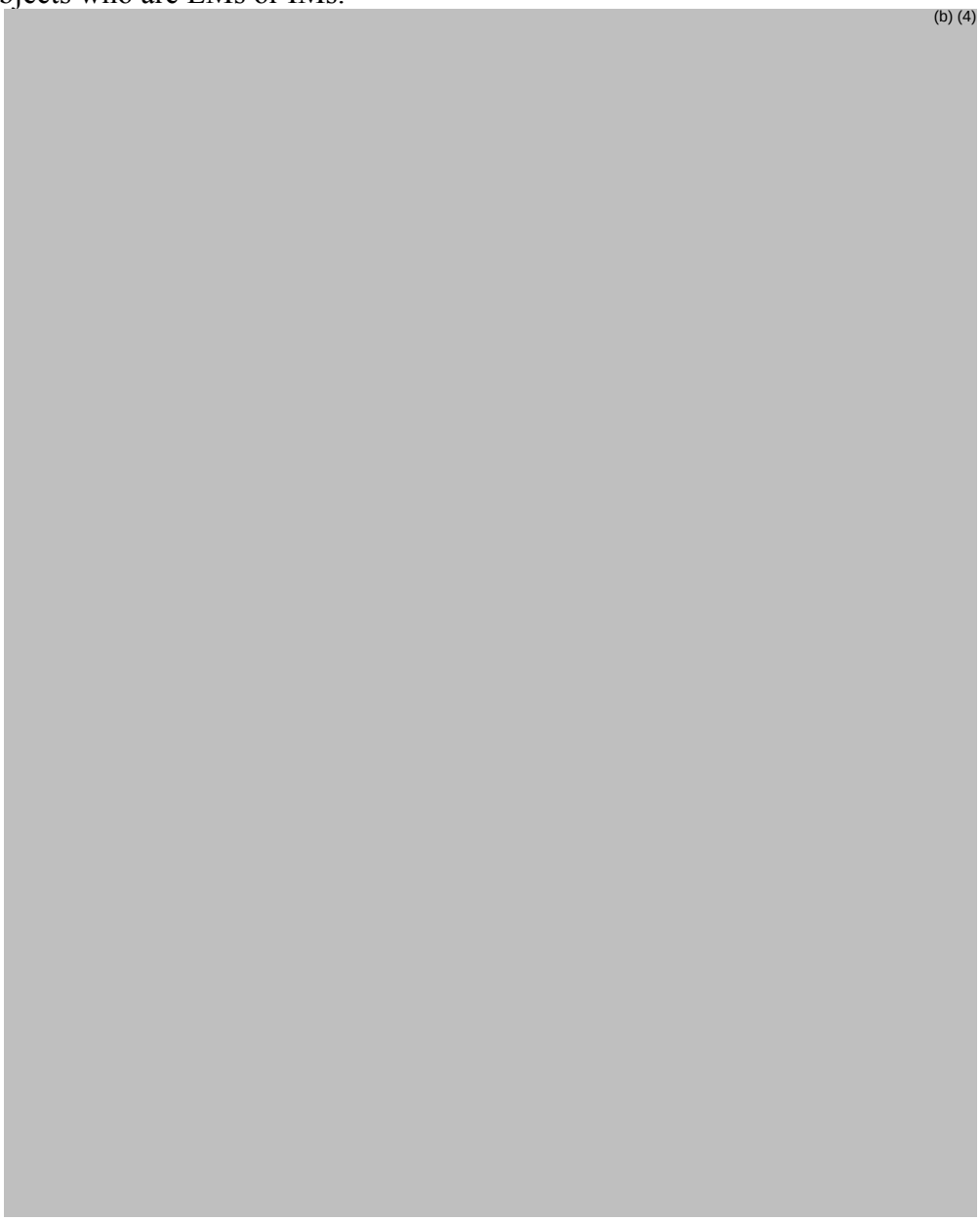
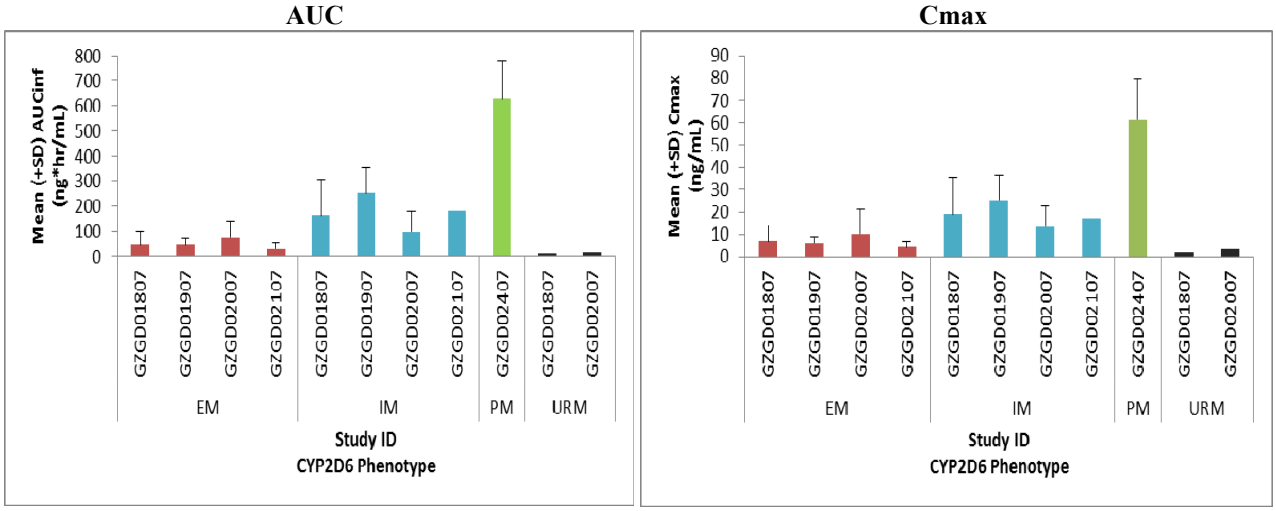


Table 19. Mean (CV%) of eliglustat plasma PK parameters after single oral dose of 100 mg in healthy subjects who are PMs or URMs

(b) (4)

Figure 13. Mean(+SD) of systemic exposure (AUC and Cmax) to eliglustat 100 mg single dose in EMs, IMs, PMs, and URMs across the studies in healthy subjects.

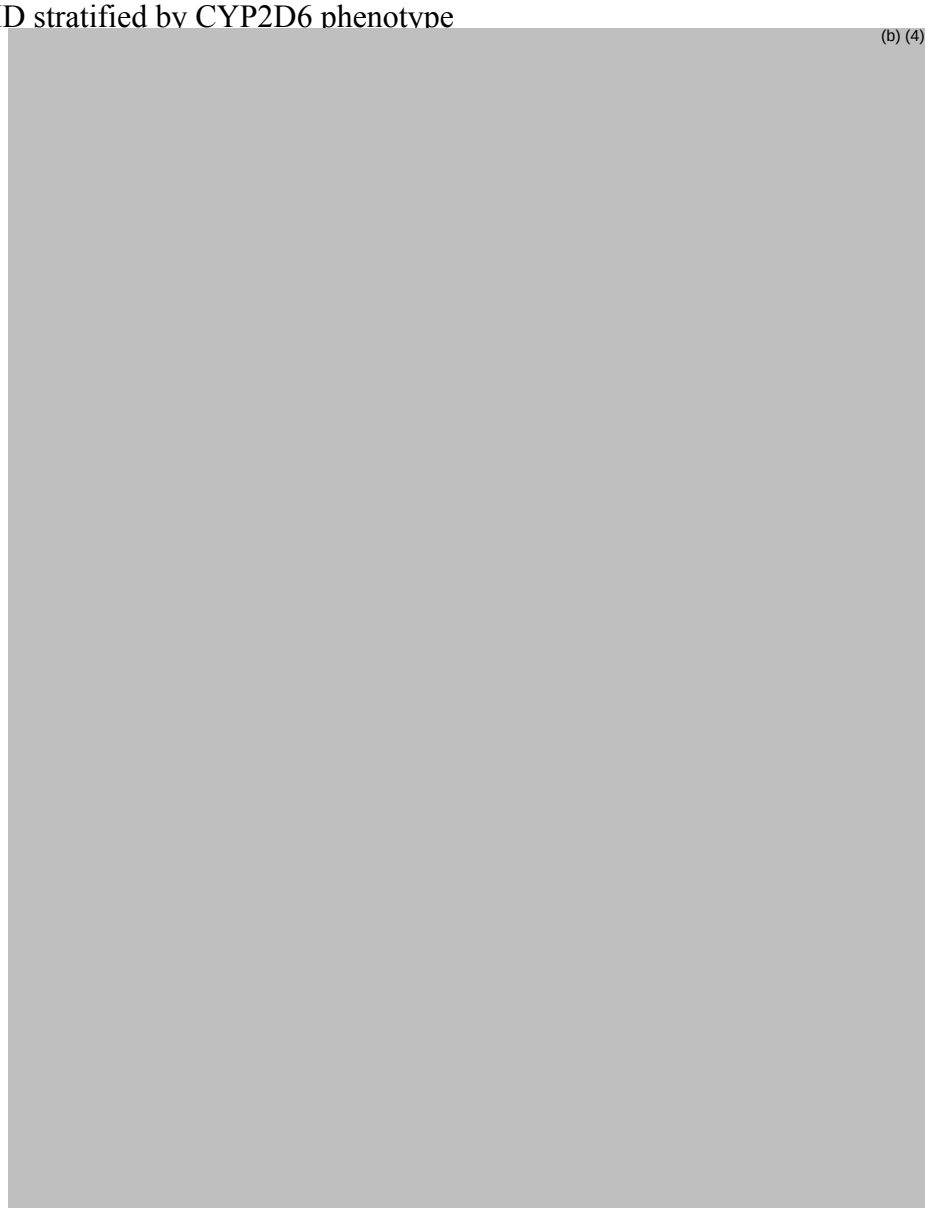


Source Data: Reviewer's Analysis

Single dose PK of 50, 200, and 350 mg Eliglustat

Single dose PK from doses ranging from 50 to 350 mg was also evaluated on Day 1 of the multiple-dose dose escalation study (GZGD00204, Table 20). The number of subjects in each dose group was small when they were stratified by CYP2D6 phenotypes therefore the estimation of PK parameters is less robust. In all of the subjects, systemic exposure increased with increase of dose. For dose linearity assessment, see Section 2.3.5.9. Median Tmax was similar across the doses in EMs and IMs. The terminal t1/2 appeared to increase with increase of doses in EMs.

Table 20. Descriptive statistics of PK parameters following single doses (Day 1) ranging from 50 to 350 mg BID stratified by CYP2D6 phenotype



2.3.5.1.1.2 Multiple-dose

100 mg BID

The multiple doses PK of the proposed dose of 100 mg BID from three clinical studies in the healthy volunteers are summarized below (Table 21).

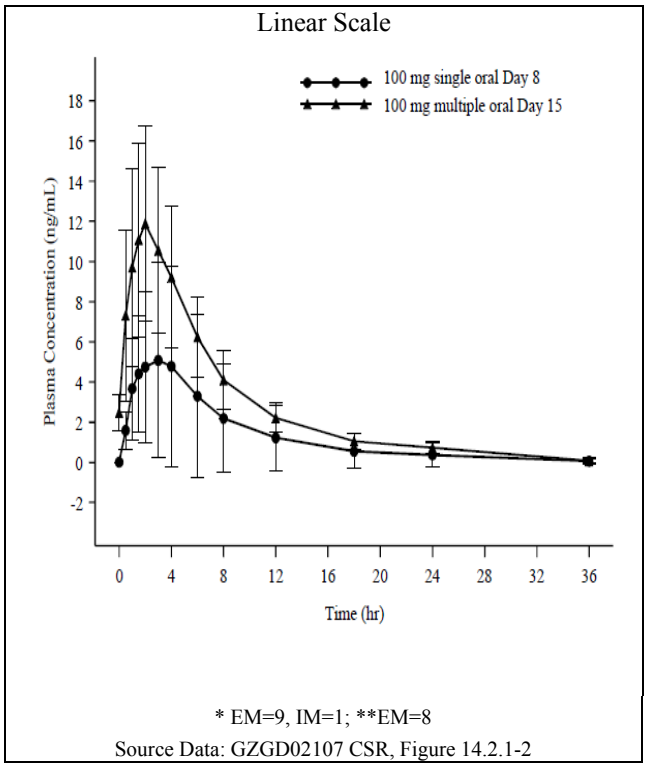
Among the three clinical studies, Only Study GZGD2107 has the PK sampling time (up to 36 hours) scheme supporting the estimation of terminal T1/2. The other two studies had PK sampling time up to 12 hours. The T1/2 was not reported by the sponsor in these studies.

Comparison of the systemic exposure to multiple doses of 100 mg eliglustat across the four CYP2D6 phenotypes was presented in Figure 15. The systemic exposures were the highest in PMs with the longest T1/2 of ~9 hours, followed by IMs and EMs (T1/2 of 6.5 hour). The

systemic exposures in two URMs were the lowest.

The mean concentration-time profiles of eliglustat 100 mg single dose and 100 mg BID was presented in Figure 14.

Figure 14. Mean (SD) Concentration-Time Profiles for Eliglustat in Plasma following Single Oral Administration of 100 mg (N=10*) and after Multiple Oral Dose Administration of 100 mg BID Eliglustat (N=8**)



* EM=9, IM=1; **EM=8

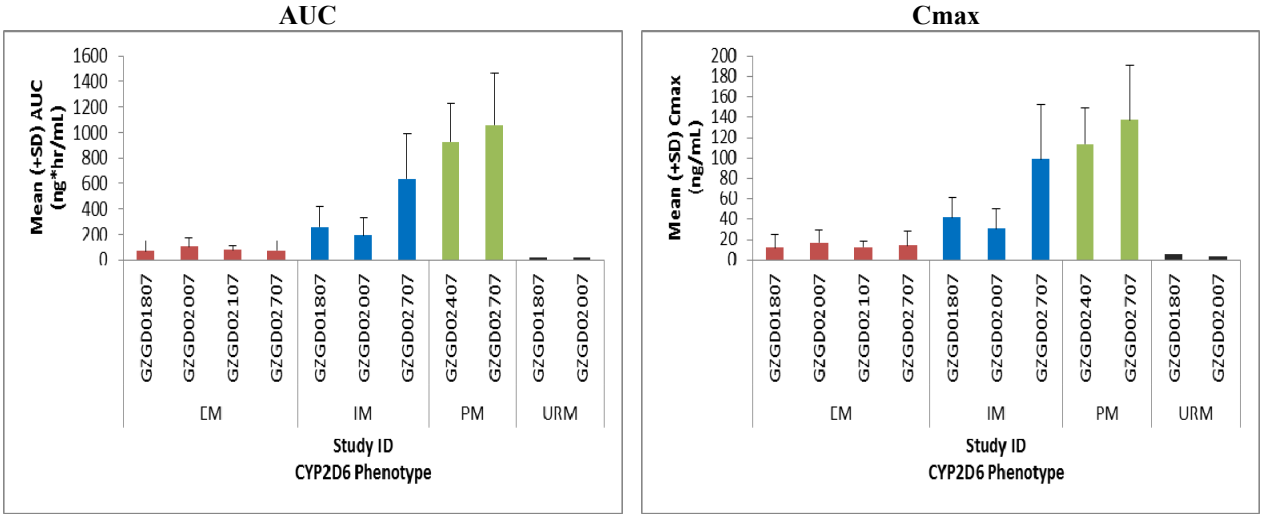
Source Data: GZGD02107 CSR, Figure 14.2.1-2

Table 21. Mean (CV%) of eliglustat plasma PK parameters after multiple oral doses of 100 mg BID in healthy subjects

(b) (4)

Source Data: Reviewer's analysis

Figure 15. Mean (+SD) of systemic exposures (AUC_{0-12h} and Cmax) to multiple doses of eliglustat 100 mg in EMs, IMs, PMs, and URMs across the studies in healthy subjects.



Source Data: Reviewer's Analysis

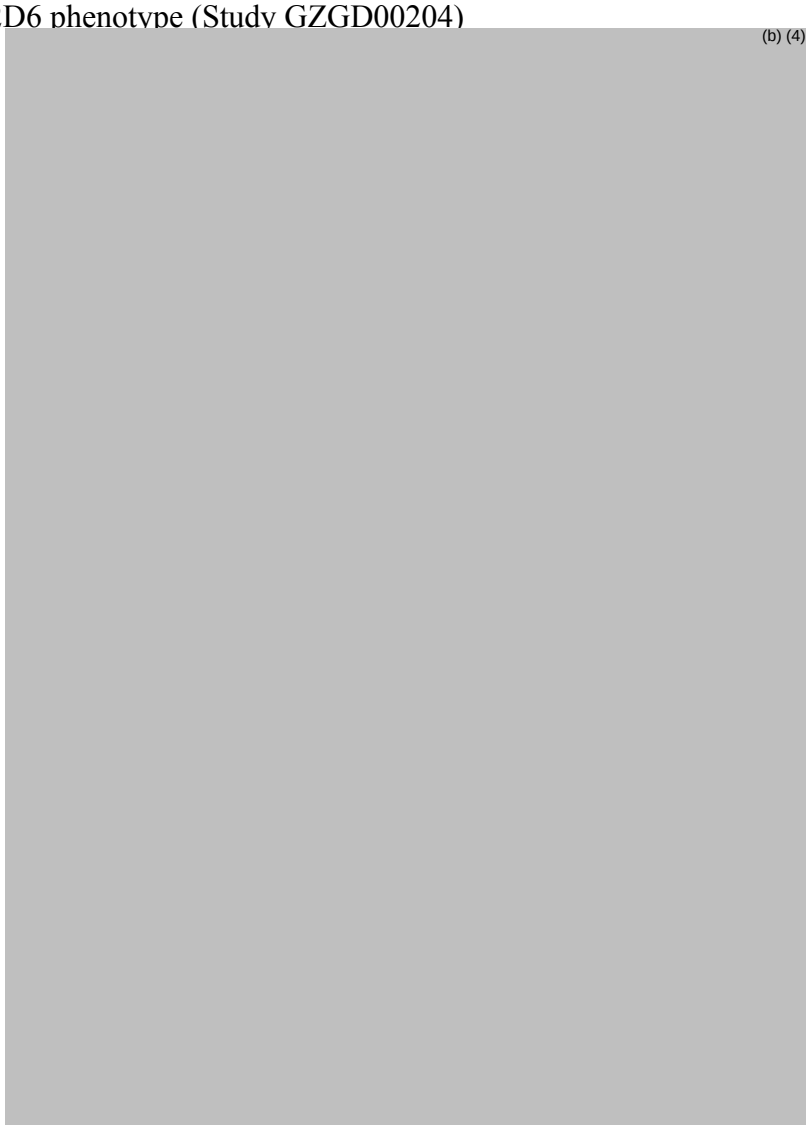
Oral dosing of eliglustat 100 mg once daily in PMs has not been studied. However, based upon the principle of linear PK of eliglustat in PMs, the AUC_{0-24h} at 100 mg QD is expected to be same as that at 50 mg BID (922 to 1057 ng×hr/mL) and Cmax is estimated to be 89 ng/mL based on all the data for PMs. Simulations using PBPK models showed that mean values of Cmax and AUC_{0-24h} in PMs following 100 mg QD will reach 75.2 ng/mL and 956 ng×hr/mL, respectively (Appendix 4.3).

50, 200, and 350 mg BID

Multiple-dose PK from doses ranging from 50 to 350 mg were evaluated in study GZGD00204 (Table 28). The number of subjects in each dose group was small when they were stratified by CYP2D6 phenotypes therefore the estimation of PK parameters is less robust. In all of the subjects, systemic exposure increased with increase of dose. For dose linearity, see Section 2.3.5.9. Median Tmax ranged from 1.5 hours to 3 hours and 1.5 hour to 2 hours in EMs and IMs, respectively. The terminal t1/2 appeared to be similar across three doses in EMs. In IMs, the terminal T1/2 increased with dose increase from 50 mg to 200 mg but decreased slightly in the 350 mg cohort compared to 200 mg cohort.

Table 22. Descriptive statistics of eliglustat PK parameters in healthy adult subjects on Day 10 stratified by CYP2D6 phenotype (Study GZGD00204)

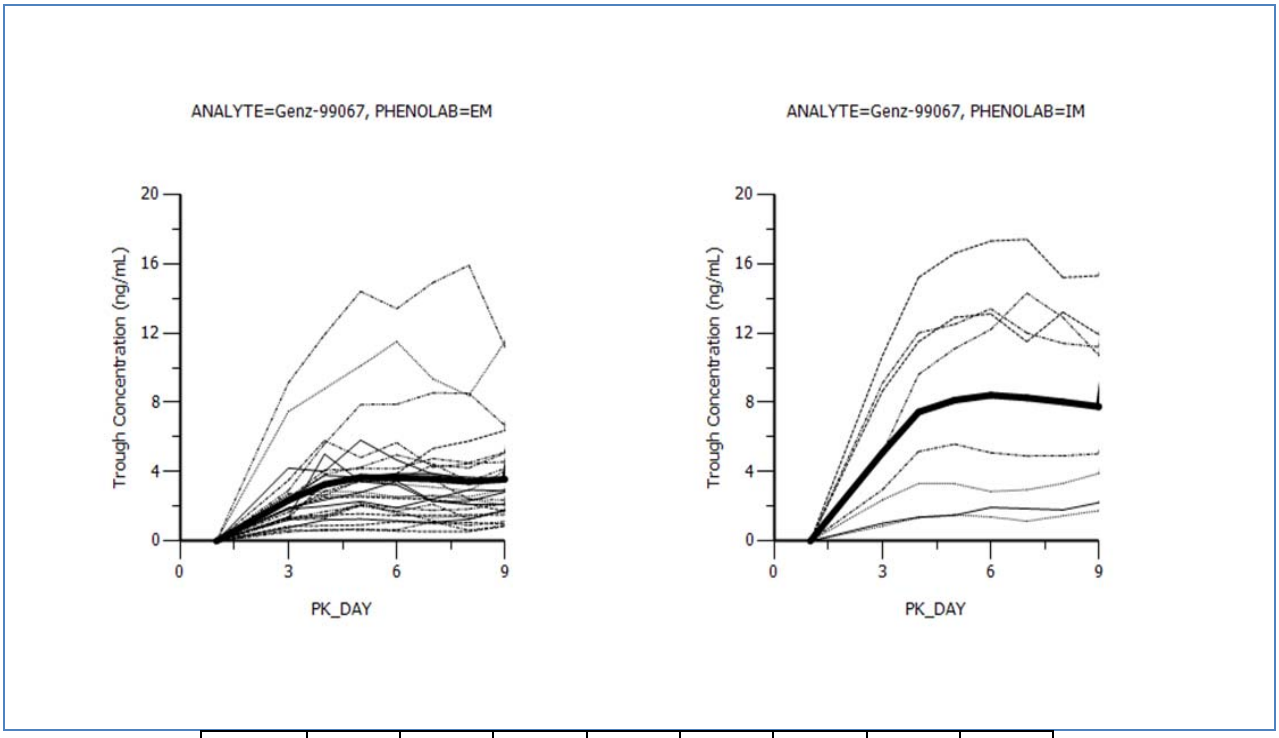
(b) (4)



Time to steady-state

Eliglustat trough concentration (pre-dose before AM dose) was measured from Day 3 to Day 9 following 100 mg single oral dose on Day 1 and 100 mg BID starting at PM on Day 2 (GZGD02007). The steady-state was reached (Figure 16) within four days of dosing in both EMs and IMs. Same time to steady-state was found in EMs in another study (GZGD01807).

Figure 16. Individual (dotted line) and mean (solid line) trough concentrations of eliglustat versus time profile stratified CYP2D6 phenotype (Study GZGD02007) following multiple doses of 100 mg eliglustat (Reviewer's Analysis)



Dosing	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
AM	×		×	×	×	×	×	×
PM		×	×	×	×	×	×	×

Source Data: Reviewer's Analysis

2.3.5.1.2 Patients with GD1

Eliglustat PK in patients with GD1 were evaluated in one Phase 2 study (Study GZGD00304) and two Phase 3 studies (ENGAGE and ENCORE) at the time of the submission. Refer to Section 2.3.1 for study design. The plasma PK sampling schemes used in ENGAGE and ENCORE were same at the end of primary analysis period (PAP): Predose, Hour 1, 1.5, 2, 3, 4, and 8. In the Phase 2 study, the plasma PK sampling scheme at the end of PAP was: Predose, Hour 1, 2, 3, and 6. The AUCtau calculations used trough concentration (Predose) as the 12 hour concentration.

The systemic exposure (Cmax and AUC) in patients enrolled in the phase 2 and Phase 3 studies are shown in Table 23 and Table 24 summarized below. Because of the dose titration design in these studies, Cmax and AUC values listed in these tables for a particular dose and specific CYP2D6 phenotype may not represent accurately the values for that phenotype. Therefore, estimation of PK parameters for patients with a specific CYP2D6 phenotype needs to take that into consideration. The parameters for 50 mg BID in PMs do not have this issue since all the PMs received this dosing regimen. Estimation of PK parameters in patients who are IMs or PMs is challenging due to the limited number of patients with these phenotypes in the Phase 2 and 3 studies.

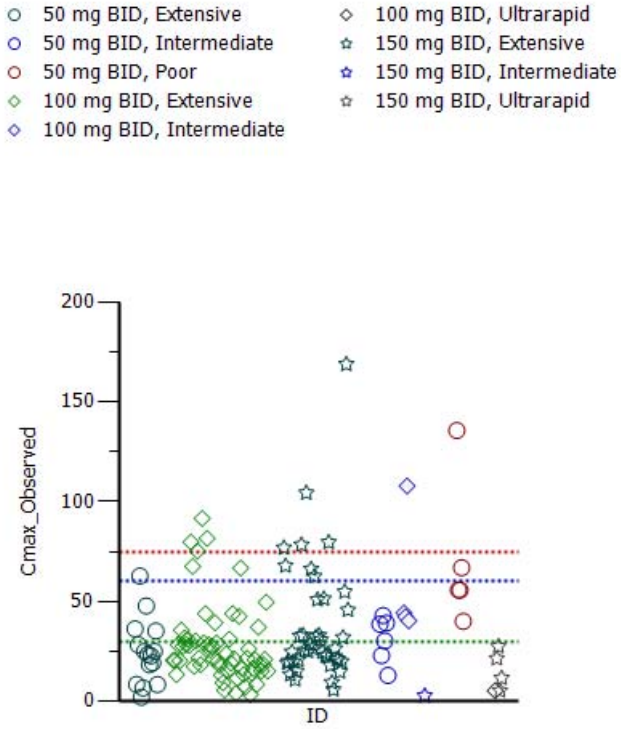
For patients given 50 mg eliglustat BID (Table 23), the AUCtau and Cmax ranged from 143 to 214 ng×hr/mL and 20.6 to 26.8 ng/mL, respectively, in EMs. In IMs (Table 24), the AUCtau and Cmax ranged from 87.1 to 200 ng×hr/mL and 13.1 to 34.9 ng/mL, respectively. In PMs (Table 25), the AUCtau and Cmax ranged from 322.84 to 648 ng×hr/mL and 40.13 to 78.5 ng/mL, respectively. The median Tmax ranging from 2 to 3 hours, appeared to be similar across the four phenotype groups.

For patients given 100 mg eliglustat BID, the AUCtau and Cmax ranged from 128 to 201 ng×hr/mL and 19.1 to 35.1 ng/mL, respectively, in EMs. In IMs, the AUCtau and Cmax were 400 ng×hr/mL and 58.7 ng/mL, respectively. The median Tmax was 1.5 hours.

For patients given 150 mg eliglustat BID, the AUCtau and Cmax were 195 ng×hr/mL and 38.1 ng/mL, respectively, in EMs. The median Tmax was 2.0 hours. In URMs, the AUCtau and Cmax were 88.5 ng×hr/mL and 16.6 ng/mL, respectively. The median Tmax was 2 hours. No IMs or PMs received the 150 mg dose.

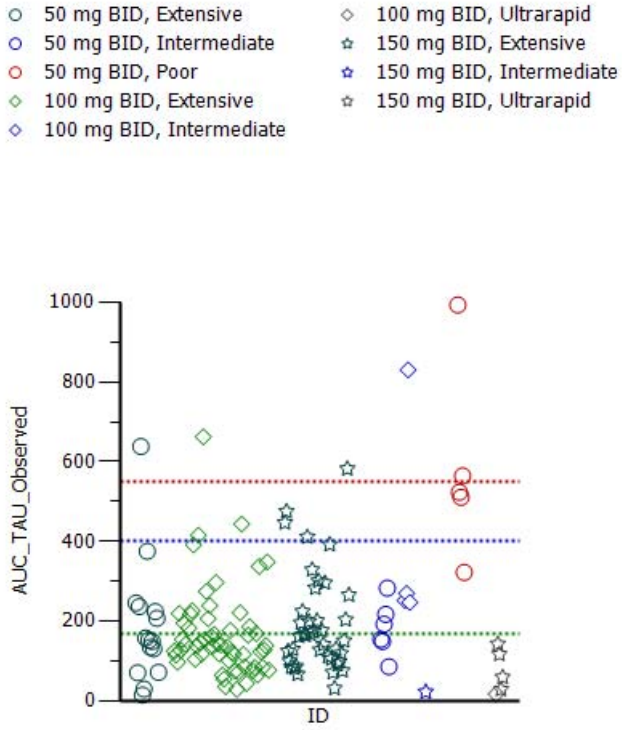
The distributions of AUC and Cmax in all the patients in the Phase 2, ENGAGE, and ENCORE studies are shown in Figure 17 and Figure 18. These plots provide a picture of the systemic exposure that is associated with the Phase 2/3 study safety database. For EMs and IMs, the reference lines represent the mean systemic exposures receiving 100 mg BID following dose titration because of their trough concentrations following 50 mg BID lower than 5 ng/mL. Taking consideration of the exposure in EMs and IMs receiving either 50 mg BID (no dose titration) or 150 mg BID (further dose increase because of trough concentration < 5 ng/mL with 100 mg BID), the expected systemic exposures of 100 mg BID in patients are estimated to be 150 ng×hr/mL in EMs and 450 ng×hr/mL in IMs if there had been no dose titration.

Figure 17. Individual Cmax by dose and CYP2D6 phenotype at the end of primary analysis period of each study.



Green dotted line represents the mean Cmax of EMs receiving eliglustat 100 mg BID
Blue dotted line represents the mean Cmax of IMs receiving eliglustat 100 mg BID
Red dotted line represents the mean Cmax of PMs receiving eliglustat 100 mg BID
Source Data: Reviewer's Analysis

Figure 18. Individual AUCtau by dose and CYP2D6 phenotype at the end of primary analysis period of each study.



Green dotted line represents the mean AUC of EMs receiving eliglustat 100 mg BID
Blue dotted line represents the mean AUC of IMs receiving eliglustat 100 mg BID
Red dotted line represents the mean AUC of PMs receiving eliglustat 100 mg BID
Source Data: Reviewer's Analysis

Table 23. Mean (CV%) of plasma PK parameters on Day 1 and at Week 52 (Phase 2, ENCORE) or Week 39 (ENGAGE) in patients who are CYP2D6 EMs.

Study ID	**Dose**	**50 mg**	**50 mg BID**	**100 mg BID**	**150 mg BID**
Phase 2	**Visit**	**Day 1**	**Week 52**	**Week 52**	
	N	25	4	17	
	Cmax (ng/mL)	8.372 (71.17)	22.06 (50.61)	19.07 (57.52)	
	Median Tmax (hr) (Min - Max)	1.5 (1 – 4)	2.05 (1 – 3)	2.9 (1 - 3.1)	
	AUCtau (ng×hr/mL)	N/A	159.7 (44.05)	140.5 (63.17)*	
ENGAGE	Visit	Day 1	Week 39	Week 39	
	N	18	2	13	
	Cmax (ng/mL)	6.40 (96.2)	20.6 (15.1)	23.7 (76.3)	
	Median Tmax (hr) (Min - Max)	1.74 (0.92 - 4.00)	2.09 (2.00 - 2.17)	2.00 (1.00 - 4.00)	
	AUCtau (ng×hr/mL)	N/A	143 (6.92)	128 (85.7)	
ENCORE	Visit	Day 1	Week 52	Week 52	Week 52
	N	84	9	30	41
	Cmax (ng/mL)	6.03 (105)	26.8 (74.4)	35.1 (60.7)	38.1 (80.7)
	Median Tmax (hr) (Min – Max)	1.99 (0.70 - 4.58)	2.50 (1.00 - 4.07)	2.02 (1.00 - 4.08)	1.98 (0.98 - 4.00)
	AUCtau (ng×hr/mL)	N/A	214 (91.3)	201 (58.7)**	195 (64.3)***

*N=16; **N=29; ***N=40

Table 24. Mean (CV%) of plasma PK parameters on Day 1 and at Week 52 (ENCORE) or Week 39 (ENGAGE) in patients who are CYP2D6 IMs.

Study ID	Dose	50 mg	50 mg BID	100 mg BID	150 mg BID
ENGAGE	Visit	Day 1	Week 39	Week 39	
	N	1	1		
	Cmax (ng/mL)	11.7	13.1		
	Tmax (hr)	2.00	2.08		
	AUCtau (ng×hr/mL)	N/A	87.1		
ENCORE	Visit	Day 1	Week 52	Week 52	Week 52
	N	12	5	4	1
	Cmax (ng/mL)	13.7 (69.9)	34.9 (23.2)	58.7 (55.7)	2.94
	Median Tmax (hr) (Min - Max)	2.00 (1.00 – 4.48)	2.00 (1.00 - 4.05)	1.51 (1.02 - 2.02)	3.00
	AUCtau (ng×hr/mL)	N/A	200 (27.1)	400 (71.6)	24.24

Table 25. Mean (CV%) of plasma PK parameters on Day 1 and at Week 52 (Phase 2, ENCORE) in patients who are CYP2D6 PMs.

Study ID	Dose	50 mg	50 mg BID
	Visit	Day 1	Week 52
Phase 2	N	1	1
	Cmax (ng/mL)	22.4	40.2
	Tmax (hr)	1.5	2
	AUCtau (ng×hr/mL)	N/A	322.84
	AUCinf (ng×hr/mL)	272	--
	T1/2 (hr)	9.32	—
ENCORE	N	4	4
	C_{max} (ng/mL)	40.1 (33.3)	78.5 (48.9)
	Median Tmax (hr) (Min - Max)	3.51 (2.00 – 4.00)	3.00 (1.83 - 4.18)
	AUCtau (ng×hr/mL)	N/A	648 (35.6)

Table 26. Mean (CV%) of plasma PK parameters on Day 1 and at Week 52 (ENCORE) or Week 39 (ENGAGE) in patients who are CYP2D6 URMs.

Study ID	Dose	50 mg BID	100 mg BID	150 mg BID
ENGAGE	Visit	Day 1	Week 39	Week 39
	N	1	1	
	Cmax (ng/mL)	2.00	5.39	
	Tmax (hr)	1.98	1.00	
	AUCtau (ng×hr/mL)	N/A	18.8	
	T1/2 (hr)	N/A	3.49	
ENCORE	Visit	Day 1		Week 52
	N	4		4
	Cmax (ng/mL)	3.31 (108)		16.6 (59.7)
	Median Tmax (hr) (Min - Max)	1.12 (1.00 - 2.00)		2.02 (1.00 - 2.12)
	AUCtau (ng×hr/mL)	N/A		88.5 (58.8)

2.3.5.2 How does the PK of the drug in healthy subjects compare to that in patients?

A direct comparison between the PK of eliglustat in healthy volunteers and patients are not feasible because the clinical studies for the two populations are different. Patients received eliglustat in a titration manner with dose adjustments made based upon steady-state trough concentrations measured at the protocol specific time points. Healthy subjects did not receive the dose in a dose titration manner. With this caveat in mind, it appeared that systemic exposure (AUC) in CYP2D6 EM and IM patients was approximately 2-fold higher compared to healthy subjects. A population PK analysis suggests that the higher systemic exposure observed in patients was mostly due to a lower volume of distribution (Section 2.4.1).

2.3.5.3 What is the inter-subject and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-subject variability

Table 27 shows that the inter-subject variability of systemic exposure (AUCtau) following multiple doses administration was high in healthy subjects who are EMs ranging from 36.8% to 117%. The inter-subject variability was lower in IMs ranging from 62% to 68%. The inter-subject variability was 33%, the lowest in PMs. Similarly (

Table 28), the inter-subject variability of systemic exposure (AUCtau) was high in patients who are EMs ranging from 59% to 86%. The inter-subject variability was lower in IMs ranging from

62% to 68%. The inter-subject variability was 36%, the lowest in PMs.

Table 27. Inter-subject varaiblity (CV%) of eliglustat systemic exposures (Cmax and AUCtau) after multiple oral doses of 100 mg BID in healthy subjects stratified by CYP2D6 phenotype

(b) (4)

Table 28. Inter-subject variability (CV%) of eliglustat systemic exposures (Cmax and AUCtau) after multiple oral doses of 100 mg BID in EMs and IMs or 50 mg BID in PMs

Parameters	Time (Week)	CYP 2D6	STUDYID	N	CV%
AUCtau (ng×hr/mL)	52	EM	Phase 2	16	63.2
	39		ENGAGE	13	85.7
	52		ENCORE	30	58.7
Cmax (ng/mL)	52	EM	Phase 2	17	57.5
	39		ENGAGE	13	76.3
	52		ENCORE	17	60.7
AUCtau (ng×hr/mL)	52	IM	ENCORE	4	71.6
Cmax (ng/mL				4	55.7
AUCtau (ng×hr/mL)	52	PM	ENCORE	4	35.6
Cmax (ng/mL)				4	48.9

The larger inter-subject variability in EMs relative to IMs and PMs is likely because of the fact that eliglustat is a sensitive CYP2D6 substrate with low oral bioavailability and an auto-inhibitor of CYP2D6. Subjects who are EMs have abundant CYP2D6 compared to subjects who are IMs. Subject who are PMs have minimal intrinsic CYP2D6 activities.

Single Dose Intra-Subject Variability

Intra-subject variability (within subject) of eliglustat 150 mg single dose was measured in the healthy subjects in a single dose, two-treatment, two-sequence, four-period replicated crossover study (Study GZGD08311). The largest within-subject CV was 25% for AUClast and AUC0-inf and 23% for Cmax (Table 29). Eliglustat does not exhibit high intra-subject variability.

Table 29. Statistical analysis of plasma PK parameters for eliglustat for variability estimation

Parameter (Unit)	Treatment	n	Within-Subject SD		
			Estimate	95% CI[a]	*P* Value[b]
AUC_{last} (ng•h/mL)	R	22	0.25	0.19, 0.36	0.538
	T	22	0.14	0.10, 0.20	
$AUC_{0\text{-}inf}$ (ng•h/mL)	R	22	0.24	0.18, 0.34	0.533
	T	22	0.14	0.10, 0.20	
C_{max} (ng/mL)	R	22	0.23	0.18, 0.33	0.517
	T	22	0.19	0.14, 0.27	

Abbreviations: CI, confidence interval; SD, standard deviation.

Treatment T = Test treatment: One 150-mg common blend capsule of eliglustat.

Treatment R = Reference treatment: Three 50-mg Phase 3 capsules of eliglustat.

Note: A linear mixed-effects model on the natural logarithms of the parameters was performed using period as a fixed term and subject as a random term for SD estimation.

[a] The 95% CIs were obtained by the exact chi-square method for within-subject SD.

[b] Differences between treatment within-subject SD were tested by the classical *F* test.

Source Data: GZGD03811 Clinical Study Report Synopsis, Table 1.

2.3.5.4 What are the characteristics of drug absorption?

The mean value of absolute bioavailability (F) for eliglustat in EMs was 3.42% when the 50mg IV eliglustat was used as the reference product (Table 30). The F in one IM subject was 14.11%. Eliglustat has limited bioavailability in EMs because of extensive first pass metabolism following oral administration. It is noteworthy that F depends on the IV dose given due to auto-inhibition of CYP2D6 by eliglustat. If the IV dose is higher than 50 mg, the F will be smaller and vice versa.

Table 30. Descriptive statistics of PK parameters for single IV dose (one hour infusion) (Day 1, 50 mg) or single oral dose (Day 8) of eliglustat stratified by CYP2D6 phenotype

CYP2D6	VISIT	Parameters	N	Mean	CV%
EM	DAY 1	AUCinf (ng×hr/mL)	9	482	8.20
		Cmax (ng/mL)	9	108	24.12
		Tmax (hr)*	9	1.00	[0.50, 1.50]
		T1/2 (hr)	9	6.56	6.86
		CL (L/hr)	9	88.2	8.81
		Vz (L)	9	835	12.7
IM	DAY 1	AUCinf (ng×hr/mL)	1	653	
		Cmax (ng/mL)	1	93.2	
		Tmax (hr)	1	1.08	
		T1/2 (hr)	1	6.87	
		CL (L/hr)	1	64.6	
		Vz	1	641	
EM	DAY 8	AUCinf (ng×hr/mL)	9	32.0	69.7
		Cmax	9	4.17	71.4
		Tmax*	9	1.52	[1.00, 4.00]
		T1/2	9	5.30	25.7
		CLF	9	3831	58.4
		F (%)	9	3.42	73.8
IM	DAY 8	AUCinf (ng×hr/mL)	1	184	
		Cmax (ng/mL)	1	17.3	
		Tmax (hr)	1	4.00	
		T1/2 (hr)	1	6.99	
		CL/F (L/hr)	1	457.92	
		F (%)	1	14.11	
*Median [Min, Max]					

Source Data: Reviewer's Analysis

2.3.5.5 What are the characteristics of drug distribution?

The estimated volume of distribution following single IV dose of 50 mg eliglustat was 835 L in EMs and 641 L in one IM (Table 36), indicating eliglustat is widely distributed into tissues.

Eliglustat is moderately bound to human plasma proteins. The mean percent bound of eliglustat to human plasma proteins was 82.9%, 79.5% and 76.4% at 0.01, 0.1 and 1.0 μM, respectively. The extent of binding of eliglustat tartrate, the free base of eliglustat to plasma proteins was determined at 0.01, 0.1 and 1.0 μM in human plasma using rapid equilibrium dialysis and quantitated by liquid chromatography with tandem mass spectrometry (LC-MS/MS). The results are listed below.

Species	Compound	Concentration (μM)	Percent Bound (%) Mean ± SD (n=4)	Percent f_u (%) Mean ± SD (n=4)
Human	Genz-99067	0.0100	82.9 ± 1.59	17.1 ± 1.59
		0.100	79.5 ± 1.10	20.5 ± 1.10
		1.00	76.4 ± 2.49	23.6 ± 2.49
	Ketamine (control)	1.00	50.0 ± 2.17	50.0 ± 2.17
	Quinidine (control)	1.00	74.8 ± 0.589	25.2 ± 0.589
	Warfarin (control)	1.00	99.5 ± 0.193	0.539 ± 0.193

Red blood cell (RBC) partitioning of eliglustat: [^{14}C]-eliglustat exhibited low RBC partitioning with KRBC/Plasma of less than 2. In whole blood from men, the mean KRBC/Plasma was 1.68 ± 0.254 and 1.83 ± 0.200 at 0.1 and 1.0 μM of [^{14}C]-eliglustat, respectively. In whole blood from women, the mean KRBC/Plasma was 1.83 ± 0.0767 and 1.86 ± 0.178 at 0.1 and 1.0 μM of [^{14}C]-eliglustat, respectively. Metoprolol and chloroquine were used as the low and high RBC partition controls.

Gender	Compound	Conc. in Whole Blood (μM)	$K_{RBC/Plasma}$ ± SD	$K_{b/p}$ ± SD
Male	[^{14}C]-Genz-112638	0.1	1.68 ± 0.254	1.31 ± 0.114
		1.0	1.83 ± 0.200	1.37 ± 0.0898
	Metoprolol (low RBC partition control)	1.0	0.972 ± 0.369	0.988 ± 0.166
	Chloroquine (high RBC partition control)	1.0	10.0 ± 1.82	5.06 ± 0.818
Female	[^{14}C]-Genz-112638	0.1	1.83 ± 0.0767	1.32 ± 0.0299
		1.0	1.86 ± 0.178	1.34 ± 0.0695
	Metoprolol (low RBC partition control)	1.0	1.18 ± 0.0956	1.07 ± 0.0373
	Chloroquine (high RBC partition control)	1.0	11.3 ± 1.78	5.03 ± 0.693

2.3.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Results from the mass balance study showed that hepatic metabolism is the major route of elimination for this BCS Class 1 drug. Total combined recovery of unchanged eliglustat in urine and feces combined was less than 1%.

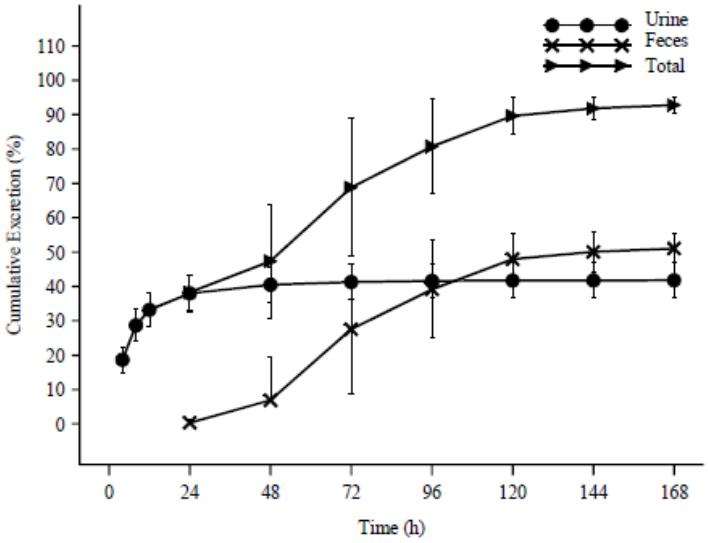
A Mass Balance study was conducted as a subpart (Period 4) of the Study GZGD02107 (See Section 2.3.5.4). Following multiple doses of 100 mg unlabeled eliglustat PO BID for five days, eight healthy subjects who are CYP2D6 EMs received single oral dose of 100 mg [^{14}C]-eliglustat solution (~100 μCi). Blood samples for metabolic profiling were collected predose and 1, 4, and 8 hours after [^{14}C]-eliglustat dosing. Urine and feces samples were also collected.

The cumulative excretion of total radioactivity over time following 100-mg [^{14}C]-eliglustat is shown in Figure 19 and Table 31. At Hour 168, >90% of the radioactivity dose was excreted in

feces and urine. Urinary excretion of drug was rapid, with most of the ^{14}C radioactivity of the doses recovered in the first 24 hours, while fecal recovery was essentially complete by 120 hours.

Mean recovery at steady state of unchanged eliglustat in urine over the dosing interval of 12 hours was 0.466%. In feces over a 24-hour period, it was 0.128% of the dose. Total combined recovery of unchanged eliglustat in urine and feces combined was less than 1%. This indicates that the predominant route of excretion of eliglustat is through metabolism, with minimal excretion of unchanged drug. Mean renal clearance for unchanged eliglustat was 5.27 L/hr.

Figure 19. Mean (SD) of cumulative excretion of total radioactivity in urine, feces, and combined over time following administration of 100-mg ^{14}C oral solution



Source Data: GZGD02107 CSR Figure 11-2

Table 31. Summary of the mean (SD) PK parameters for Genz-99067 (eliglustat) and total radioactivity in urine and feces following administration of 100-mg ^{14}C oral solution

Matrix	Analyte	Total Ae (mg)	Total % Excreted (%)	CL_R (L/hr)
		(N=8)	(N=8)	(N=8)
Urine	Genz-99067	0.400 (0.150)	0.466 (0.177)	5.27 (0.727)
	Total Radioactivity	42.5 (5.24)	41.8 (5.12)	7.91 (0.570)
Feces	Genz-99067	0.110 (0.0950)	0.128 (0.111)	NA
	Total Radioactivity	NC	51.4 (3.96)	NA
Urine and Feces	Total Radioactivity	NA	93.2 (2.08)	NA

Source Data: GZGD02107 CSR Table 11-4

A summary of the mean (SD) PK parameters for total radioactivity in plasma and whole blood and eliglustat following administration of 100 mg ^{14}C oral solution is presented in Table 32. The mean Cmax for total radioactivity in plasma was approximately 53-fold higher than the mean

Cmax for unchanged eliglustat in plasma. The mean AUC0-inf for total radioactivity in plasma was approximately 71-fold higher than the mean AUC0-tau value observed for unchanged eliglustat in plasma. These results indicate that the majority of the exposure to total radioactivity is due to circulating metabolites.

Mean Cmax and AUCinf for total radioactivity in plasma were 36% and 30% higher than those in whole blood, indicating that eliglustat and its circulating metabolites are not retained in the red blood cells.

Table 32. Mean (SD) of PK parameters for total radioactivity in plasma and whole blood following administration of [^{14}C] eliglustat oral solution

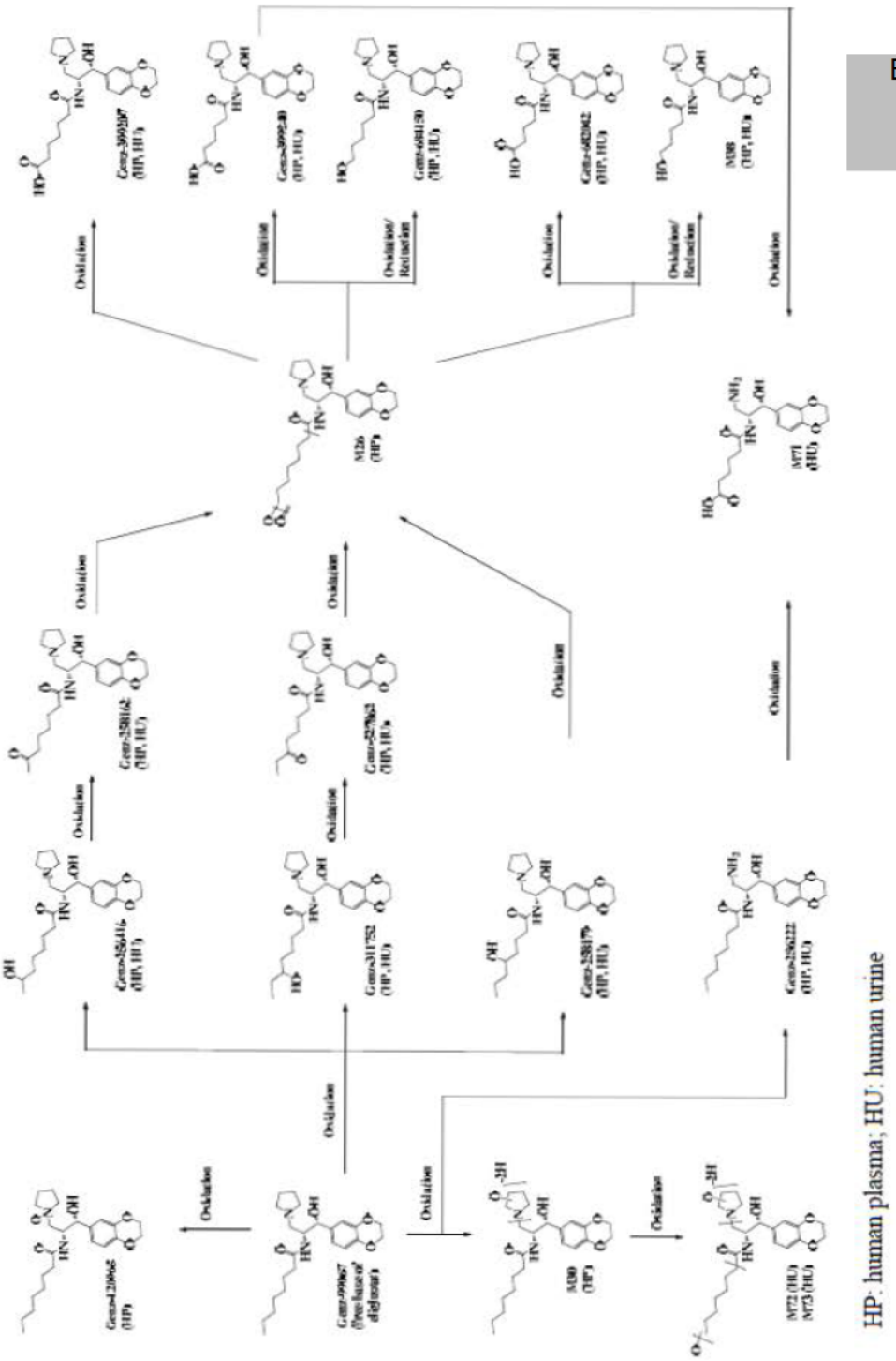
	Total Radioactivity		**[^{14}C] Eliglustat (Multiple Doses)**
PK parameter (units)	**Plasma**	**Whole Blood**	**Plasma**
Cmax (ng eq./mL)	643 (175)	411 (99.1)	12.1 (5.11)
Median Tmax (hr) (Min, Max)	1.50 (1.00, 1.58)	1.50 (1.00, 1.58)	2.00 (1.50, 2.07)
AUC0-last (ng eq.×hr/mL)	4681 (741)	2903 (604)	N/A
AUC0-inf (ng eq. ×hr/mL)	5396 (804)	3825 (778)	76.3 (28.1)*
T1/2 (hr)	9.73 (0.792)	10.4 (3.16)	6.48 (0.692)
CL/F (L/hr)	18.9 (2.76)	27.1 (5.27)	1293 (545)
Vz/F (L)	265 (38.3)	388 (84.5)	11935 (4648)
*$AUC_{0\text{-}12h}$			

Source Data: GZGD02107 CSR, Table 11-5 and Table 11-3

2.3.5.7 What are the characteristics of drug metabolism?

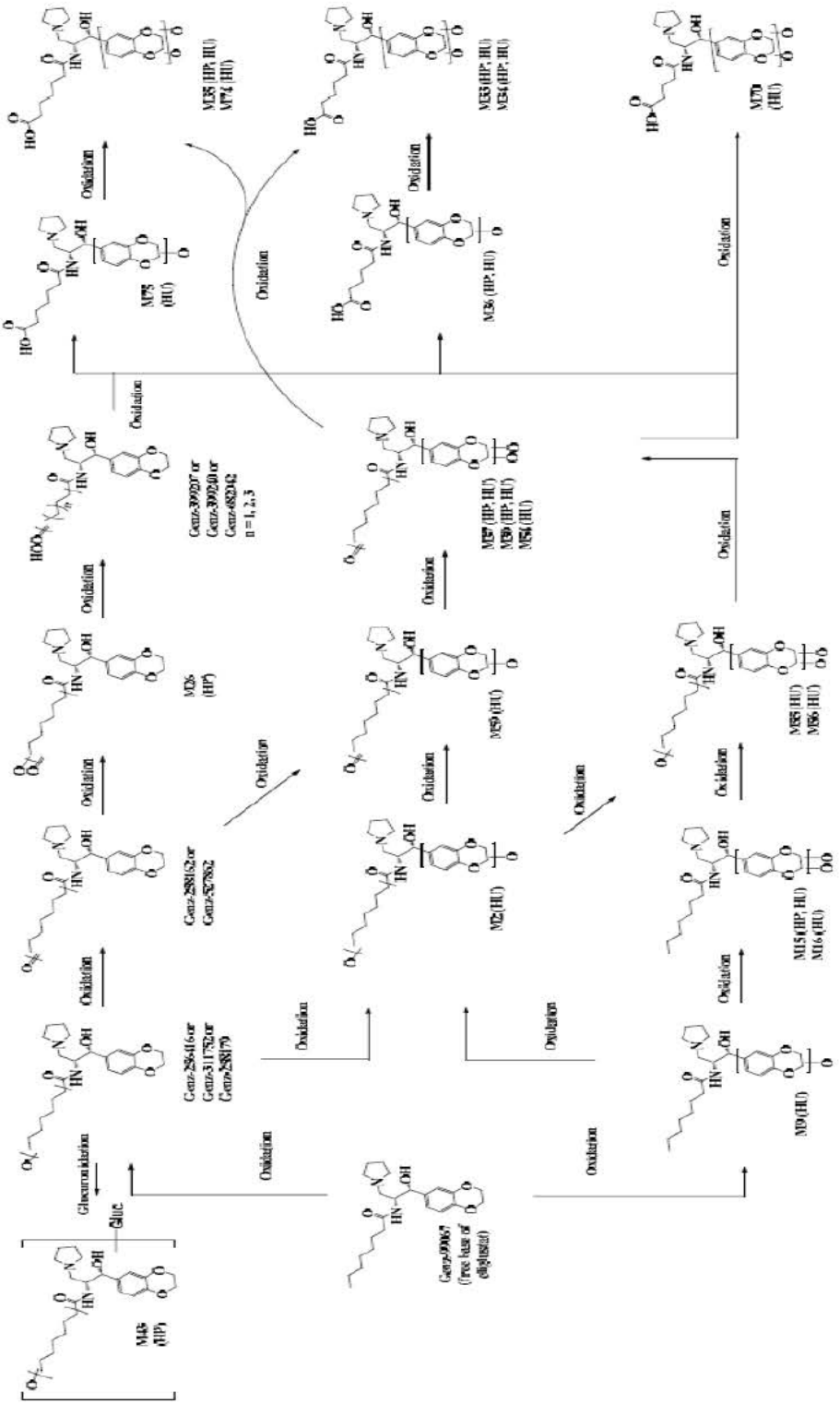
Oxidative metabolism is the major pathway. Eliglustat is mainly metabolized through CYP2D6 with minor metabolism by CYP3A4/5 (Also see 2.5.2.2). The metabolism involves sequential oxidation of the octanoyl moiety followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety, or a combination of the two pathways. The proposed human metabolic pathways are shown in Figure 20 and Figure 21.

Figure 20. Sponsor's proposed metabolic pathway of eliglustat in human plasma (in the octanoyl and pyrrolidine moieties).



Source Data: Section 2.7.2 Summary of Clinical Pharmacology Studies, Figure 11.

Figure 21. Sponsor's proposed metabolic pathway of eliglustat in human plasma (in the octanoyl and 2,3 dihydrobenzodioxane moieties).



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2.3.5.7.1.1 Metabolites

Metabolites in Plasma

Twenty-one metabolites were observed in the human plasma following oral administration of [^{14}C]-eliglustat 100 mg in Study GZGD02107. The structures of the metabolites were determined for ten metabolites by comparing mass spectral fragmentation patterns and liquid chromatographic retention times with those of authentic reference standards. Structures for another eleven metabolites that lacked reference standards were proposed based on MS^n spectra interpretation and supportive high resolution mass spectra data.

The ten metabolites with confirmed structures are: Genz-399240, Genz-399207, Genz-256416, Genz-311752, Genz-258179, Genz-527862, Genz-258162, Genz-120965, Genz-256222, Genz-682042. Genz-399240 is the only metabolite with exposure exceeding 10% of total drug-related exposure measured by radioactivity in plasma (16%) (Table 33). Steady-state metabolite:parent (M:P) AUC ratio for Genz-399240 was the highest (8.78 fold) among the ten metabolites with structures identified following repeated dosing of eliglustat 100 mg BID. Except Genz-256222 and Genz-120965, all the rest of the metabolites can be considered as major metabolites because their M:P ratios exceed 0.1. Drug-drug interaction potential of Genz-399240, Genz-399207, Genz-256416, Genz-311752, Genz-258179, Genz-527862, Genz-258162, and Genz-682042 was evaluated *in vitro* as their M:P ratios exceeded 0.25 (Section 2.5.2.3.1.1).

Nine metabolites in plasma were also measured in patients (Phase 2 study). Genz-682042 was not measured at the time due to its structure being undetermined at the time of the study. Genz-120965, Genz-256222, and Genz-258179 were negligible metabolites having M:P ratios < 10%.

Comparison of metabolites between PMs (N=6) receiving 100 mg BID and URMs receiving 150 mg BID (N=5) were also conducted (Study GZGD02407) (Table 34). Systemic exposure (AUClast) of the following metabolites was higher in PMs relative to URMs on both Day 1 (single dose) and Day 6 (multiple doses): Genz-256222, Genz-258179 and Genz-311752. Systemic exposure was higher in URMs relative to PMs on both Day 1 (single dose) and Day 6 (multiple doses) for the following metabolites: Genz-256416, Genz-258162, Genz-399207 and Genz-399240. Mean Genz-682042 AUClast values were similar on Day 1 between poor and ultra-rapid 2D6 metabolizers, but were higher in poor 2D6 metabolizers on Day 6. Exposure to Genz-120965 was similar on Day 6 and for Genz-527862 tended to be similar on Day 1 and Day 6 between PMs and URMs.

Table 33. Mean (SD) plasma metabolite:parent ratios of radioactivity and AUC for eliglustat metabolites (Study GZGD02107).

Dose (SD/MD)	PK Parameter	Metabolites										Genz-99067 (parent)
		Genz-399240	Genz-399207	Genz-256416	Genz-311752	Genz-258179	Genz-527862	Genz-258162	Genz-120965	Genz-256222	Genz-682042	
MD	Metabolite: Total Radioactivity Ratio [g]	0.16 (0.05)	0.06 (0.02)	0.07 (0.03)	0.03 (0.01)	0.00 (0.00)	0.03 (0.01)	0.06 (0.02)	0.00 (NA[d])	0.00 (0.00)	0.02 (0.01)	NA
MD	Metabolite: Parent Drug Ratio [g]	8.78 (6.42)	3.63 (2.67)	3.30 (1.42)	1.28 (0.50)	0.24 (0.08)	1.43 (0.44)	3.08 (1.12)	ND	0.09 (0.04)	1.05 (0.81)	NA

Source Data: Section 2.7.2 Summary of Clinical Pharmacology, Table 56

Table 34. Mean (SD) of systemic plasma exposure of metabolites in PMs and URMs (Study GZGD02407)

Dose (SD/MD)	PK Parameter	Metabolites										Genz-99067 (parent)
		Genz-399240	Genz-399207	Genz-256416	Genz-311752	Genz-258179	Genz-527862	Genz-258162	Genz-120965	Genz-256222	Genz-682042	
SD	$AUC_{0\text{-last}}$ (h ng/mL) [a]	PM: 195 (84.1) / URM: 661 (134)	PM: 72.6 (32.6)/ URM: 282 (69.5)	PM: 44.5 (11.6)/ URM: 215 (41.2)	PM: 114 (33.0)/ URM: 82.3 (21.4)	PM: 24.4 (7.91) / URM: 9.54 (3.21)	PM: 60.1 (18.8)/ URM: 74.3 (20.1)	PM: 54.9 (12.4)/ URM: 270 (68.8)	PM: 0.372 (0.411)/ URM: 0.649 (0.43)	PM: 19.1 (8.41) / URM: 10.3 (8.28)	PM: 48.8 (29.1)/ URM: 50.4 (14.7)	PM: 610 (217)/ IEUM: 142 (155)
Dose (SD/MD)	PK Parameter	Metabolites										Genz-99067 (parent)
		Genz-399240	Genz-399207	Genz-256416	Genz-311752	Genz-258179	Genz-527862	Genz-258162	Genz-120965	Genz-256222	Genz-682042	
MD	$AUC_{0\text{-last}}$ (h ng/mL) [a]	PM: 504 (194)/ URM: 1090 (255)	PM: 186 (76.7)/ URM: 471 (145)	PM: 106 (28.4)/ URM: 381 (102)	PM: 297 (94.0)/ URM: 149 (47.2)	PM: 65.9 (21.5)/ URM: 19.8 (8.73)	PM: 168 (58.5)/ URM: 137 (46.9)	PM: 131 (37.6)/ URM: 452 (130)	PM: 0.853 (0.628)/ URM: 0.612 (0.34)	PM: 54.5 (15.7)/ URM: 20.9 (17.5)	PM: 190 (106)/ URM: 104 (40.6)	PM: 1262 (449)/ IEUM: 365 (308)

[a] Metabolite data are reported separately for poor metabolizers (PMs) and ultra-rapid metabolizers (URMs). For Genz-99067, data are reported for PMs and for intermediate, extensive and ultra-rapid metabolizers (IEUMs).

Source Data: Section 2.7.2 Summary of Clinical Pharmacology, Table 56

Metabolites in Urine

Thirty-one metabolites were detected in human urine after repeated dosing of 150 mg BID in healthy subjects who are CYP2D6 non-PM or 100 mg BID in subjects who are CYP2D6 PM (Study GZGD03610). The structures of nine metabolites were determined: Genz-256416 (M5), Genz-311752 (M6), Genz-258179 (M7), Genz-256222 (M11), Genz-258162 (M17), Genz-527862 (M18), Genz-399240 (M24), Genz-399207 (M25), and Genz-682042 (M31). These metabolites were also found in the plasma. The major metabolites in human urine were 7- and 6-hydroxyl metabolites M5 and M6, 7- and 6- ketone metabolites M17 and M18, and acid metabolites M24 and M25. Compared with CYP2D6 extensive and ultra-rapid metabolizers, mean relative amounts of the major metabolites, M5, M6, M17, M18, M24 and M25 in human urine were notably lower in the group of CYP2D6 poor metabolizers.

Pharmacological activity of the metabolites

Ten metabolites with confirmed structures showed no significant inhibition of glucosylceramide synthase activity with their IC_{50} values being > 1 µM (Table 35). Their ability to inhibit GL-1 synthase was 1/55 to 1/1,500 fold of eliglustat. It can be concluded that these metabolites are inactive.

Table 35. Mean IC_{50} values for eliglustat and metabolites in microsomes and intact cells.

Eliglustat

Cell type	Assay	IC50 (nM)	IC50 (ng/ml)
Human A375, melanoma	Microsomes; NBD-labeled GL-1	20	8
Murine B16, melanoma	Intact cells, cell surface GM3	57	23

Source Data: Section 2.6.2 Pharmacology Written Summary, Table 2

Metabolites

Metabolite	Metabolite Structure	IC_{50}, GL-1 A375 microsomes		IC_{50}, GM3 intact B16 cells	
		µM	µg/ml[a]	µM	µg/ml[a]
Genz-399240	5-carboxy	> 30	> 12	> 10	> 4.1
Genz-399207	6-carboxy	> 30	> 12	> 10	> 4.2
Genz-256416	7-hydroxyl	1.4	0.59	3.8	1.5
Genz-258162	7-keto	1.1	0.46	1.9	0.79
Genz-527862	6-keto	1.8	0.75	3.2	1.3
Genz-311752	6-hydroxyl	2.9	1.2	1.5	0.63
Genz-682042	4-carboxy	> 30	> 12	> 10	> 3.9
Genz-258179	5-hydroxyl	2.1	0.89	2.5	1.1
Genz-256222	amino	6.9	2.4	4.9	1.7
Genz-120965	N-oxide	9.4	3.9	2.2	0.93

[a] Genz-99067

Source Data: Section 2.4 Nonclinical Overview, Table 10.

2.3.5.8 What are the characteristics of drug excretion?

Mass balance study (GZGD02107) indicated that about 42% of the radioactive dose was recovered in urine and 51% in feces from healthy subjects who are EMs. Less than 1% total radioactivity of unchanged eliglustat was found in urine and feces, suggesting that metabolism is the primary elimination pathway for eliglustat. The estimated renal clearance is low (5.27 L/hr) in EMs compared to total clearance of 88 L/hr following IV dosing. The total clearance following IV dosing was 64.5 L/hr in the subject who is IM (N=1).

2.3.5.9 Based on PK parameters, what is the degree of linearity or non-linearity based on the dose-concentration relationship?

Single doses

Following single dose of 50 mg, 200 mg, and 350 mg eliglustat, systemic exposures (Cmax and AUC) increased in a more than dose-proportional manner (Figure 22). Because of the small sample size, more detailed comparisons within particular phenotypes are not made.

Figure 22. Dose normalized AUC and Cmax following single dose of eliglustat 50 mg, 200 mg, and 350 mg in EMs and IMs (Study GZGD00204).

(b) (4)

Multiple doses

Eliglustat exhibits non-linear PK in subjects who are CYP2D6 EMs, IMs. Following multiple doses of 50 mg, 200 mg, and 350 mg BID for 10 days, steady-state Cmax and AUCtau increased in a more than dose proportional manner in EMs (Figure 23). In IMs, the steady-state Cmax and AUC increased in a more than dose proportional manner following multiple doses of 50 mg and 200 mg BID. There was only one IM that received multiple doses of 350 mg BID, precluding dose linearity assessment.

Since there was no PM enrolled in this study, linearity in PMs was not evaluated. However, linear PK is expected in PMs. The only one URM enrolled in the study received 50 mg BID dose. There are insufficient data to evaluate the linearity in URMs.

Figure 23. Dose normalized systemic exposures (AUCtau and Cmax) on Day 10 in EMs and IMs (Study GZGD00204).

2.3.5.10 How do the PK parameters change with time following chronic dosing?

Following multiple doses of 50 mg, 200 mg, and 350 mg eliglustat for 10 days, the systemic exposures (Cmax and AUC) are greater than that of single doses across all dose levels and in EMs and IMs (Table 36). There is only one URM receiving 50 mg with the steady-state Cmax being 82% of that from single dose.

Table 36. Ratios of AUC (RAUC) and Cmax (RCmax) between Day 10 and Day 1 for various doses of eliglustat stratified by CYP2D6 phenotype (Study GZGD00204)

Parameters	CYP2D6	DOSE	N	Mean	SD	CV%
RAUC	EM	50	4	1.94	0.30	15.20
RAUC	EM	200	3	4.20	2.93	69.80
RAUC	EM	350	5	3.42	1.07	31.17
RAUC	IM	50	2	3.28	0.64	19.39
RAUC	IM	200	3	2.79	1.22	43.66
RAUC	IM	350	1	2.00		
RAUC	URM*	50	0			
RCMAX	EM	50	4	2.60	1.12	43.22
RCMAX	EM	200	4	6.43	7.07	109.94
RCMAX	EM	350	5	3.21	1.62	50.38
RCMAX	IM	50	3	3.61	0.65	18.06
RCMAX	IM	200	3	3.32	1.42	42.89
RCMAX	IM	350	1	2.65		
RCMAX	URM	50	1	0.82		

*AUCinf is not estimable in this subject;
RAUC=AUCtau,ss/AUCinf,Day1
Note: AUCtau on Day 1 was not reported by the sponsor

Source Data: Reviewer's Analysis based upon the listing of parameters submitted

Similarly, systemic exposures (AUC and Cmax) increased in EMs and IMs following multiple doses of 100 mg BID compared to that of 100 mg single dose (Table 37).

Table 37. Ratios of AUC and Cmax between steady state and Day 1 of 100 mg eliglustat stratified by CYP2D6 phenotype

Parameters	CYP2D6	Study	N	Mean	SD	CV%
RAUC	EM	GZGD02007	25	2.40	1.60	66.95
RCmax	EM	GZGD02007	27	2.30	1.61	70.09
RAUC	IM	GZGD02007	8	2.52	0.65	25.84
RCmax	IM	GZGD02007	8	2.36	0.52	21.87
RAUC	URM	GZGD02007	1	1.34		
RCmax	URM	GZGD02007	1	1.17		
RAUC	EM	GZGD02107	8	3.19	0.964	30.21
RAUC2	EM	GZGD02107	8	2.56	0.742	28.95

RAUC=AUCtau,ss/AUC0-12hr,Day1
RAUC2= AUCtau,ss/AUCinf,Day1

Source Data: Reviewer's Analysis based upon the listing of parameters submitted

Table 38 showed that systemic exposures (AUC and Cmax) increased in EM, IMs, URM following multiple doses of 150 mg BID comparing to that of 150 mg single dose. Systemic exposure increased in PM as well following multiple doses of 100 mg BID comparing to that of 100 mg single dose.

Table 38. Ratios of AUC and Cmax between Day 6 and Day 1 of eliglustat stratified by CYP2D6 phenotype (Study GZGD02407).

Dose	Parameter	CYP2D6	N	Mean	SD	CV%
150	RAUC	EM	12	3.44	1.19	34.74
150	RCmax	EM	12	3.27	1.21	37.09
150	RAUC	IM	2	2.62	1.27	48.45
150	RCmax	IM	2	2.64	1.44	54.39
150	RAUC	URM	5	2.68	0.85	31.77
150	RCmax	URM	5	2.44	0.69	28.23
100	RAUC	PM	6	2.13	0.26	12.18
100	RCmax	PM	6	1.86	0.32	16.98

Source Data: Reviewer's Analysis based upon the listing of parameters submitted

2.4 INTRINSIC FACTORS

2.4.1 What intrinsic factors (age, sex, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Age: Based on population PK analysis, there is no effect on age on the PK of eliglustat. Age was not identified as a covariate in population PK analysis. Thus no dose adjustment based on age is required.

Sex: There is no effect of sex on eliglustat PK. Population PK analysis comprising of 59% males and 41% females did not identify sex as a significant covariate affecting eliglustat PK. Thus no dose adjustment based on sex is required.

Race: There is no effect of race on eligustat PK. The PopPK analysis, which included 65% Caucasians, 9% African-Americans, 9% Jewish, 7% Hispanics, 7% Asians, and 3% others, did not identify race/ethnicity as a significant covariate influencing eliglustat PK. Thus no dose adjustment based on race is required.

Weight: Population PK included body weights ranging from 41 to 136 kg. There was no effect of body weight on eliglustat clearance and body weight was not identified as a covariate on clearance. The central compartment (Vc) increased with body weight. In subsequent simulations of 3 typical EM patients receiving a 100 mg BID dose, over the range of body weight (40.7 [minimum], 71.1 [median] and 136 [maximum] kg), there was no impact on steady state AUC0-12 (i.e., values were the same for each of the 3 patients) and Cmax ranged from 26.2 to 20.0 ng/mL. Thus no dose adjustment based on body weight is required.

Disease: Subject status (healthy versus GD1 patients) was identified as a covariate on clearance and volume. CL and Vc were 1.95 and 1.71 times higher in healthy subjects than in patients. Figure 24 shows the box plots for CL and Vc by subject status from the final model.

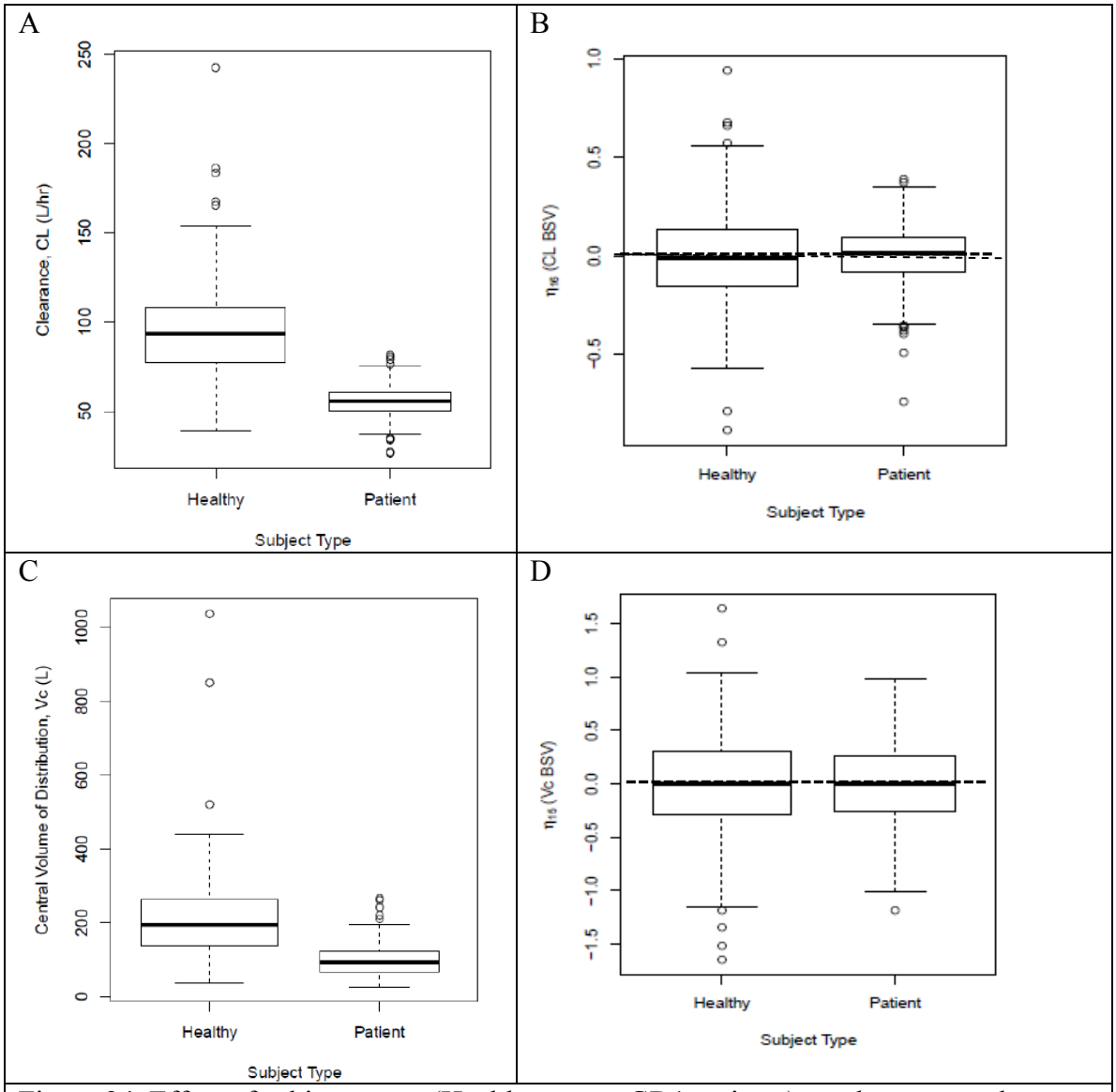


Figure 24. Effect of subject status (Healthy versus GD1 patients) on clearance and volume. A) Clearance, B) Inter-individual variability on CL C) Volume of distribution and D) Inter-individual variability on Vc versus subject status.

Source Data: Sponsor's Population PK report

CYP2D6 Phenotype

Observed data: CYP2D6 phenotype was a main source of intrinsic variability affecting the systemic exposure to eliglustat. Table 21 shows data obtained in healthy subjects. Following multiple doses of 100 mg BID, mean systemic exposures (AUCtau and Cmax) in PMs are 11.3- and 8.4-fold those in EMs. The T1/2 is longer in PMs (8.86 hours) than that in EMs (6.48 hours). Mean systemic exposures (AUCtau and Cmax) in IMs are 2.8- and 2.7-fold those in

EMs. No data on T1/2 in IMs were available for comparison. The median Tmax is similar between EMs and IMs (1.5 to 2 hours). The median Tmax of 3 hours is slightly longer in PMs. Based on data obtained from patients in the Phase 2, ENGAGE, and ENCORE studies, the AUC ratio in PM/IM/EM was estimated to be approximately 7:3:1.

Mean systemic exposures (AUCtau and Cmax) following multiple doses of 100 mg BID in URMs (N=2) are 26.9% and 34.6% of those in EMs.

Population PK analysis: CYP2D6 phenotype was identified as a covariate on bioavailability (F). CYP2D6 PMs were also found to have an estimate of CL that was fractionally less (0.703) than that of other subjects. Sponsor's population PK model did not characterize the PK of PMs adequately as evidenced by a significant deviation from zero in eta plot of bioavailability (Appendix 4.1). Due to these limitations, the population PK model was not used for simulations for dosing recommendations in poor metabolizers. The dosing recommendation in poor metabolizers was based on observed data and PBPK modeling. The model predicted that at the 100 mg BID dose, there is a 2.8 fold and 2.7 fold increase in steady state $AUC_{0\text{-}12h}$ and Cmax in IMs compared to EMs which is consistent with observed data.

GBA Genotype

The majority of patients (91%) enrolled in the Phase 2 study, ENGAGE, and ENCORE had GBA genotypes that included the common N370S and/or L444P mutations. The pooled distribution of genotypes in these studies was as follows: N370S/L444P 32%, N370S/N370S 21%, N370S/Other 33%, L444P/Other 4.2%, Other/Other 9.4%. Mutations that result in GD1 have residual GBA activity (<10% of normal)[5], however, the genotype-phenotype correlation is unclear. Based on the mechanism of action of eliglustat (reduction of substrates for GBA), treatment response is not likely to differ by GBA genotype.

2.4.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.4.2.1 Pediatric patients

The PK of eliglustat has not been studied in pediatric subjects. The sponsor requested a waiver of pediatric studies since eliglustat was grated orphan drug designation on September 17, 2008.

2.4.2.2 Renal impairment

A dedicated renal impairment study was not conducted. Based on population PK analysis, there was no effect of creatinine clearance on eliglustat PK. The lowest value of creatinine clearance included in the analysis was 47 mL/min. There were no subjects in the severe renal impairment category that were included in the analysis. Renal impairment study will be required in PMR/PMC. Meanwhile, eliglustat is not indicated in patients with moderate to severe renal impairment or ESRD.

[5] Desnick RJ, Schuchman EH, Enzyme replacement therapy for lysosomal diseases: lessons from 20 years of experience and remaining challenges. Annu Rev Genomics Hum Genet. 2012;13:307-35.

2.4.2.3 Hepatic impairment

A dedicated hepatic impairment study was not conducted. Hepatic impairment study will be required in PMR/PMC. Meanwhile, eliglustat is not indicated in patients with hepatic impairment.

2.4.2.4 What pregnancy and lactation use information is there in the application?

The PK of eliglustat has not been studied in pregnant women. In addition, no clinical studies were performed to determine if eliglustat is excreted into human milk.

2.5 EXTRINSIC FACTORS

2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet (other than high-fat meal), smoking or alcohol use on the PK or PD of eliglustat. The effect of a high fat meal is discussed in Section 2.6.4. Based on the information on the enzymes that metabolize eliglustat, smoking is unlikely to alter the PK of this drug. Grapefruit juice and herbal products that are known to modulate CYP3A4 will have similar effect as drugs that are CYP3A4 inhibitors/inducers. Drug-drug interactions are discussed below.

2.5.2 Drug-drug interactions

2.5.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes, based on in vitro studies, eliglustat is a substrate for CYP2D6, CYP3A4 enzymes and P-glycoprotein transporter (P-gp). In vitro, it is also an inhibitor of CYP2D6, CYP3A4 and P-gp. Therefore, there is good likelihood of in vivo drug-drug interactions with eliglustat as a victim as well as a perpetrator drug. Since CYP2C19 may contribute to <20% of eliglustat metabolism at lower eliglustat concentrations such as those seen in EMs (≤ 0.05 μM), and because at higher concentrations such as those seen in CYP2D6 poor metabolizers (0.25 μM), the role of CYP2C19 becomes insignificant. A clinically significant drug interaction in the presence of CYP2C19 modulators is considered unlikely.

2.5.2.2 Is the drug a substrate of CYP enzymes?

Yes. Studies of eliglustat (0.01 and 0.05 μM) in recombinant human CYP450 enzymes and in human liver microsomes (HLM) suggest that this drug is metabolized by CYP2D6 (major in EMs and IMs), CYP3A4, and CYP2C19. However, at the mean eliglustat concentration (>0.075 μM) as observed in EM patients receiving 100 mg BID, the contribution of CYP2C19 becomes insignificant.

The relative contributions of CYP1A2, CYP2D6, CYP2C19 and CYP3A4 to the metabolism of eliglustat in HLM were approximately 12 %, 54%, 19% and 15% at 0.01 μM, and 0%, 54%, 16% and 30% at 0.05 μM, respectively. Using higher concentrations of eliglustat (0.1, 1 and 10 μM), CYP2D6 and CYP3A4 were determined to be major contributors to the metabolic clearance of the drug in HLM. The relative contributions of CYP2D6 and CYP3A4 to the NADPH-dependent clearance of eliglustat were ~ 60% and 38% at 0.1 μM, 48% and 52% at 1.0 μM, and 35% and 50% at 10.0 μM respectively, suggesting that the contributions of CYP

isozymes to eliglustat metabolism was concentration-dependent.

In pooled HLMs from a CYP2D6 poor metabolizer (*4/*4 genotype), eliglustat was exclusively metabolized (100 % relative contribution) by CYP3A4 at concentrations of 0.01 and 0.05 μM (4.05 and 20.2 ng/mL) but the CYP2C19 polymorphic status of this individual is unknown. At both concentrations, metabolism of eliglustat was completely inhibited in the presence of a CYP3A inhibitor (azamulin) but no inhibition of eliglustat metabolism was observed with isozyme-selective inhibitors of CYP1A2, CYP2C9, CYP2C19, or CYP2D6.

Since CYP2D6 appears to be the predominant enzyme involved in the metabolism of eliglustat, an influence of (b) (4) of CYP2D6 isozyme on the PK of eliglustat is likely to be significant.

2.5.2.2.1 Eliglustat as a victim drug: Effect of In vivo CYP inhibitors

The effect of CYP inhibitors on the exposure of eliglustat was evaluated by two dedicated DDI studies in healthy subjects using paroxetine as a strong CYP2D6 inhibitor and ketoconazole as a strong CYP3A inhibitor. No PMs were enrolled in these DDI studies. Because patients with GD1 have higher systemic exposure compared to healthy subjects, the FDA reviewers calculated the expected Cmax and AUCtau in these two DDI scenarios by applying the observed fold changes to the mean exposure estimated in patients who are EMs or IMs receiving the proposed dose of 100 mg BID.

The effect of moderate CYP2D6 inhibitors, moderate CYP3A inhibitors, combination of strong CYP2D6 **and** strong CYP3A inhibitors, and combination of moderate CYP2D6 **and** moderate CYP3A inhibitors was evaluated using PBPK modeling and simulation (Appendix 4.3).

The effect of strong or moderate CYP3A inhibitor on the exposure of eliglustat in PMs was evaluated using PBPK modeling and simulation (Appendix 4.3).

The threshold for AUCtau increase due to DDI was set to be no more than the mean AUCtau in PM receiving 100 mg QD, a dose proposed by the Agency. In PMs, the mean AUCtau following 50 mg BID was 550 ng×hr/mL (Figure 18). PBPK simulation showed that 100 mg PO QD in PMs resulted in AUC0-24hr of 956 ng×hr/mL, comparable to the observed AUC0-24h (2 × AUCtau) in PMs with 50 mg PO BID. The threshold for Cmax increase was set to be no more than 250 ng/mL because of concerns of QT prolongation.

2.5.2.2.1.1 Effect of paroxetine, a strong CYP2D6 inhibitor and a weak CYP3A inhibitor

Effect of paroxetine on the PK of eliglustat was evaluated in an open-label fixed-sequence, 3-period study in 36 healthy subjects (EM=27, IM=8, URM=1) (Table 39).

Table 39. Summary of the study design

	Period 1	Period 2	Period 3
Activities	Day 1	Days 2-8	Days 9-18
Dose	Eliglustat 100 mg ×1	Eliglustat 100 mg BID*	Paroxetine 30 mg PO QD +100 mg Eliglustat BID
PK sampling for Eliglustat	Day 1	Day 8	Day 18
Trough PK sampling		Days 3-8	Days 9 to 18
*Elglustat dose started in the evening of Day 2 Sampling Time on Day 1: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours Sampling Time on Day 8: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours Sampling time on Day 18: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours Days 9 to 18: Trough samples of eliglustat and paroxetine			

Graphical examination indicates near steady state concentrations were achieved as the ranges of concentrations being consistent in the subject population from Day 15 through Day 18.[6]

The mean systemic exposures (AUC and Cmax) to eliglustat increased significantly in EMs, IMs and URM following the co-administration of eliglustat and paroxetine relative to multiple dosing of eliglustat alone (Table 40). For EMs, the mean systemic exposures (AUC and Cmax) were 10-fold and 8.2-fold those without paroxetine treatment. For IMs, the mean systemic exposures (AUC and Cmax) were 5.2-fold and 4.1-fold those without paroxetine treatment. For the only one URM, the mean systemic exposures (AUC and Cmax) were 28.4- fold and 22-fold of those without paroxetine treatment, respectively. Note that paroxetine inhibited the elimination of eliglustat via CYP2D6 metabolism pathway and to some extent CYP3A metabolism pathway.

[6] Liston HS, DeVane CL, Boulton DW, et al. Differential time course of cytochrome P450 2D6 enzyme inhibition by fluoxetine, sertraline, and paroxetine in healthy volunteers. J Clin Psychopharmacol. 2002 Apr;22(2):169-173.

Table 40. [redacted]

2.5.2.2.1.2 Effect of Strong CYP2D6 Inhibitors (without an inhibition of CYP3A pathway)

The effect of a strong CYP2D6 inhibitor in EMs and IMs has not been evaluated in the clinical study. However, the dose adjustment can be inferred by the exposure data in poor metabolizers. It is expected that the exposure resulted from concomitant use of a strong CYP2D6 inhibitor in EMs and IMs will be comparable to that in poor metabolizers. Therefore, *reduce eliglustat dose to 100 mg QD is recommended in both EMs and IMs in this DDI scenario*.

2.5.2.2.1.3 Effect of moderate CYP2D6 inhibitors

CYP2D6 EMs and IMs

Effect of a moderate CYP2D6 inhibitor on the systemic exposure of eliglustat was evaluated by PBPK simulation (See Appendix 4.3). In EMs, co-administration of eliglustat 100 mg BID with the moderate CYP2D6 inhibitor (terbinafine) will result in 3.8- and 4.5-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUCtau were 93.9 ng/mL and 831 ng×hr/mL. Similar exposure was predicted for IMs (Cmax: 97.2 ng/mL: AUC: 866 ng×hr/mL).

Reduce eliglustat dose to 100 mg QD for both EMs and IMs.

2.5.2.2.1.4 Effect of ketoconazole, a strong CYP3A inhibitor and P-gp inhibitor

Effect of ketoconazole on the PK of eliglustat was evaluated in an open-label fixed-sequence, 3-period study in 36 healthy subjects (EM=24, IM=8, URM=1) (Table 42).

Table 42. Summary of the study design

	Period 1	Period 2	Period 3
Activities	Day 1	Days 2-8	Days 9-15
Dose	Eliglustat 100 mg ×1	Eliglustat 100 mg BID*	Ketoconazole 400 mg PO QD +100 mg Eliglustat BID
PK sampling	Day 1	Day 8	Day 15
*Elglustat dose started in the evening of Day 2			

The mean systemic exposures (AUC and Cmax) to eliglustat increased in EMs, IMs and the URM following the co-administration of eliglustat and ketoconazole relative to multiple dosing of eliglustat alone (Table 43). For EMs and IMs, the mean systemic exposures (AUC and Cmax) were ~4-fold those without ketoconazole treatment. For the only subject who is an URM, the systemic exposures (AUC and Cmax) were 3-fold and 2.2- fold those without ketoconazole treatment, respectively. Although the fold increases following co-administration of ketoconazole were similar between EMs and IMs, the AUCtau (1068 ng×hr/mL) and Cmax (131 ng/mL) values to eliglustat in IMs were significantly higher than those in EMs (AUCtau: 473.5 ng×hr/mL; Cmax 67.2 ng/mL).

Table 43. Statistical comparison of plasma eliglustat exposure following 100 mg BID and with or without ketoconazole (healthy subjects)

CYP2D6 Phenotype	Parameter	Treatment	Geometric LS Mean	Ratios (%) (Test/Ref)‡	90% CI
IM	AUCtau (ng×hr/mL)	Eliglustat alone	214	409	224, 747
		Ketoconazole+Eliglustat	877		
	Cmax (ng/mL)	Eliglustat alone	37.0	304	184, 501
		Ketoconazole+Eliglustat	113		
EM	AUCtau (ng×hr/mL)	Eliglustat alone	48.6	440	302, 639
		Ketoconazole +Eliglustat	214		
	Cmax (ng/mL)	Eliglustat alone	8.38	425	293, 618
		Ketoconazole +Eliglustat	35.6		
‡ Test = Paraxetine+Eliglustat, Ref = Eliglustat alone					

Source Data: Reviewer's analysis

The expected Cmax and AUC in EMs and IMs and relevant dose adjustment recommendation following concomitant use of a strong CYP3A inhibitor is provided in Table 44.

Table 44. Dose adjustment recommendation on concomitant use of eliglustat with a strong CYP2D6 CYP3A inhibitor.

CYP2D6 Phenotype	Perpetrator Drug(s)	Cmax Ratios	AUC0-12 Ratios	Expected Cmax in Patients	Expected AUC0-12h in Patients	Dosing Recommendation
EM	**Ketoconazole Strong CYP3A inhibitors**	4.25	4.40	127	747	100 mg QD
IM		3.04	4.09	183	1637	(b) (4)

Source Data: Reviewer's Analysis

CYP2D6 PM

Effect of a strong CYP3A inhibitor on eliglustat systemic exposure in PM was not evaluated in clinical study. PBPK simulation (Appendix 4.3) showed that concomitant use of eliglustat 100 mg BID with ketoconazole would resulted in 4.5- and 5.5-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUC were 478 ng/mL and 5300 ng×hr/mL, respectively. Simulation results also showed that the Cmax and AUC would reach 321 ng/mL and 5950 ng×hr/mL if eliglustat 100 mg QD was co-administered with ketoconazole.

Co-administration of eliglustat with strong CYP3A inhibitors in PMs is contraindicated.

2.5.2.2.1.5 Effect of moderate or weak CYP3A4 inhibitors

Effect of a moderate CYP3A4 inhibitor on the systemic exposure of eliglustat was evaluated by

PBPK simulation (See Appendix 4.3).

EMs and IMs

In EMs, co-administration of eliglustat 100 mg BID with the moderate CYP3A4 inhibitor (fluconazole) will result in 2.8- and 3.2-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUCtau were 68.5 ng/mL and 593 ng×hr/mL.

Reduce eliglustat dose to 100 mg QD when co-administers with moderate CYP3A4 inhibitors in patients who are CYP2D6 EMs.

In IMs, co-administration of eliglustat 100 mg BID with the moderate CYP3A4 inhibitor (fluconazole) will result in 2.5- and 2.9-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUCtau were 159 ng/mL and 1500 ng×hr/mL.

Concomitant use of eliglustat with moderate CYP3A4 inhibitors in IMs is not recommended.

PMs

Co-administration of eliglustat 100 mg BID with the moderate CYP3A4 inhibitor (fluconazole) will result in 3.8- and 7.5-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUCtau were 395 ng/mL and 7214 ng×hr/mL. Simulation results also showed that the Cmax and AUC would reach 179 ng/mL and 2820 ng×hr/mL if eliglustat 100 mg QD was co-administered with fluconazole.

Based upon the conclusion made from dedicated paroxetine DDI study in EMs and IMs, it can be inferred that concomitant use with a weak CYP3A inhibitor in PM is not recommended.

Co-administration of eliglustat with moderate or weak CYP3A4 inhibitors in PMs is not recommended.

2.5.2.2.1.6 Effect of a strong CYP2D6 inhibitor *and* a strong CYP3A inhibitor

Effect of a strong CYP2D6 inhibitor *and* a strong CYP3A inhibitor on the systemic exposure of eliglustat was evaluated by PBPK simulation (See Appendix 4.3). (b) (4)

In EMs, co-administration of eliglustat 100 mg BID with paroxetine *and* ketoconzole will result in 17- and 24-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUCtau were 470 ng/mL and 5170 ng×hr/mL.

In IMs, co-administration of eliglustat 100 mg BID with paroxetine *and* ketoconzole will result in 7.5- and 9.8-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUCtau were 449 ng/mL and 3924 ng×hr/mL.

*Co-administration of eliglustat with a strong CYP2D6 inhibitor **and** a strong CYP3A inhibitor is contraindicated in both EMs and IMs.*

2.5.2.2.1.7 Effect of a moderate CYP2D6 inhibitor *and* a moderate CYP3A inhibitor

Effect of a moderate CYP2D6 inhibitor *and* a moderate CYP3A inhibitor on the systemic exposure of eliglustat was evaluated by PBPK simulation (See Appendix 4.3).

In EMs, co-administration of eliglustat 100 mg BID with terbinafine *and* fluconazole will result in 11- and 14-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUCtau were 251 ng/mL and 2512 ng×hr/mL.

In IMs, co-administration of eliglustat 100 mg BID with terbinafine and fluconazole will result in 4.2- and 5.0-fold increase in Cmax and AUCtau. The predicted mean Cmax and AUCtau were 261 ng/mL and 2630 ng×hr/mL.

*Co-administration of eliglustat with a moderate CYP2D6 inhibitor **and** a moderate CYP3A4 inhibitor is contraindicated in both EMs and IMs.*

2.5.2.2.1.8 Effect of rifampin, a CYP3A4/5 and P-gp inducer

Effect of rifampin on the PK of eliglustat was evaluated in an open-label fixed-sequence, 2-period study in 25 healthy subjects (PM=6, IM=2, EM=12, URM=5) (Table 45).

Table 45. Summary of the study design

		Period 1		Washout period	Period 2	
CYP2D6 Phenotype	Activities	Day 1	Days 2 – 6	5 days	Day 1	Days 2-6*
Non-PMs	Dose	Eliglustat 150 mg ×1	150 mg BID		Rifampin 600 mg IV × 1+150 mg Eliglustat ×1	Rifampin 600 mg PO QD + 150 mg Eliglustat BID
	PK sampling	Day 1	Day 6		Day 1	Day 6
PMs	Dose	100 mg ×1	100 mg BID		Rifampin 600 mg IV × 1+100 mg Eliglustat ×1	Rifampin 600 mg PO QD+100 mg Eliglustat PO BID
	PK sampling	Day 1	Day 6		Day 1	Day 6
* Six subjects received Rifampin+Eliglustat from Day 3 to 7 and additional doses of eliglustat on Day 2. Their blood samples for PK were drawn on Day 7.						

The mean systemic exposures (AUCinf and Cmax) to 100 mg eliglustat single dose was similar with or without rifampin single IV dose (Table 46 and Table 47) indicating that OATP inhibitors have minimal effect on eliglustat PK.

Table 46. Statistical comparison of plasma eliglustat exposure after *single* dose of eliglustat 100 mg alone or in combination with rifampin in CYP2D6 in EMs, IMs, and URMs

	CYP2D6 Phenotype	Geometric LS Mean (Ref)	Geometric LS Mean (Test)	**Ratios (%) (Test/Ref)**[ǂ]	90% CI (Lower Bound)	90% CI (Upper Bound)
AUCinf (ng×hr/mL)	EM	102	124	122	88.6	168
	IM	248	311	125	27.8	564
	URM	28.4	32.4	114	84.7	154
Cmax (ng/mL)	EM	12.4	14.7	119	89.0	159
	IM	22.4	32.1	143	14.7	1387
	URM	3.93	4.35	111	82.9	148
[ǂ] Test = Rifampin+Eliglustat, Ref = Eliglustat alone						

Source Data: Reviewer's Analysis

Table 47. Statistical comparison of plasma eliglustat exposure after *single* dose of eliglustat 100 mg alone or in combination with rifampin in CYP2D6 PMs

Dose Regimens	Parameter	Treatment	Geometric LS Mean	Ratios (%) (Test/Ref)‡	90% CI
Single Dose	AUCinf (ng×hr/mL)	Eliglustat+Rifampin (N=6)	644	95.2	88.1%, 103%
		Eliglustat (N=5)	677		
	Cmax (ng/mL)	Eliglustat+Rifampin (N=6)	57.3	97.3	86.0%, 110%
		Eliglustat (N=6)	58.9		

‡ Test = Rifampin+Eliglustat, Ref = Eliglustat alone

Source Data: Reviewer's Analysis

The mean systemic exposures (AUCtau and Cmax) to eliglustat reduced significantly in PMs, EMs, IMs and URM following multiple doses co-administration of eliglustat and rifampin relative to multiple dosing of eliglustat alone (Table 48 and Table 49). For EMs, the mean systemic exposures (AUC and Cmax) were ~89% lower. For IMs, the mean systemic exposures (AUC and Cmax) were reduced by ~90%. For EMs, the mean systemic exposures (AUC and Cmax) were ~89% lower. For PMs, the mean systemic exposures (AUC and Cmax) were ~95% lower. For URM, the mean systemic exposures (AUC and Cmax) were reduced by ~60%.

Concomitant use of eliglustat with multiple doses of strong CYP3A4 inducers is not recommended.

Table 48. Statistical comparison of plasma eliglustat exposure after *multiple* doses of eliglustat 150 mg alone or in combination with rifampin in CYP2D6 EMs, IMs, and URMs.

	CYP2D6 Phenotype	Geometric LS Mean (Ref)	Geometric LS Mean (Test)	Ratios (%) (Test/Ref)‡	90% CI Lower Bound	90% CI Upper Bound
Cmax (ng/mL)	EM	37.3	4.07	10.9	5.80	20.6
	IM	54.7	4.97	9.10	4.08	20.3
	URM	9.24	3.70	40.1	24.8	64.9
AUCtau (ng×hr/mL)	EM	254	26.4	10.4	5.55	19.5
	IM	412	35.2	8.54	3.61	20.2
	URM	58.5	22.2	38.0	21.3	67.7

‡ Test = Rifampin+Eliglustat, Ref = Eliglustat alone

Source Data: Reviewer's Analysis

Table 49. Statistical comparison of plasma eliglustat exposure after *multiple* doses of eliglustat 100 mg BID or in combination with rifampin in CYP2D6 PMs

Dose Regimens	Parameter	Treatment	Geometric LS Mean	Ratios (%) (Test/Ref)[‡]	90% CI
Multiple Doses	AUCtau (ng×hr/mL)	Eliglustat+Rifampin (N=6)	36.56	4.13	3.48%, 4.90%
		Eliglustat (N=6)	885		
	Cmax (ng/mL)	Eliglustat+Rifampin (N=6)	5.28	4.89	3.94%, 6.06%
		Eliglustat (N=6)	108		
[‡] Test = Rifampin+Eliglustat, Ref = Eliglustat alone					

Source Data: Reviewer's Analysis

2.5.2.2.1.9 Effect of P-gp inhibitors on Eliglustat PK

The effect of P-gp inhibitors on the systemic exposure of eliglustat has not been studied clinically. Eliglustat is a BCS class 1 drug. Therefore, P-gp inhibitors are not expected to have a clinically significant effect on eliglustat PK.

2.5.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.5.2.3.1 *In vitro* studies

2.5.2.3.1.1 Inhibition potential

Competitive inhibition potential of eliglustat

In human liver microsomes, eliglustat (tested up to 10 μM concentrations) showed a competitive inhibitory effect toward CYP2D6 and CYP3A4, with apparent Ki values of 5.82 μM for CYP2D6 and 27.0 μM for CYP3A4 (using midazolam as the probe substrate). The potential for eliglustat to inhibit the metabolism of CYP3A4 substrates systemically is low as I/ki is <0.1. However, since I2/ki is >10 there is potential for eliglustat to inhibit CYP3A4 at the gut level.

No significant inhibitory effect of eliglustat was noted on human CYP450 isozymes CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (using testosterone as the probe substrate) at the concentrations tested (i.e. apparent Ki values > 50.0 μM).

Time-dependent inhibition (TDI)

At the therapeutic concentrations, eliglustat also exhibited TDI of CYP2D6 activity in vitro, using human liver microsomes, recombinant CYP2D6 and cryopreserved human hepatocytes. This also results in time-dependent PK of eliglustat as observed earlier.

Inhibition kinetic parameters were determined with the inactivation constant k_{inact} and inhibition constant K_I of 0.0151, 0.0610 and 0.00754 min^{-1} and 1.05, 2.83 and 0.488 μM (425, 1140, and 197 ng/mL of eliglustat) in human liver microsomes, *rh*CYP2D6, and cryopreserved human hepatocytes, respectively. The TDI effect of CYP2D6 gradually dissipated as the concentration of eliglustat was increased and no inhibition was observed at concentrations greater than 5.56 μM, up to 50.0 μM, which are much higher than the therapeutic concentrations.

In the IC50 shift experiment, Genz-99067 within the concentration range of 0.0686 to 1.85 μM in the secondary incubation exhibited lower CYP2D6 residual activities in the presence of

NADPH regenerating system compared to those in the pre-incubation set at the same concentration range of Genz-99067 but in the absence of NADPH regenerating system. This time-dependent decrease of CYP2D6 activity was not observed at the higher Genz-99067 concentration range of 5.56 to 50.0 µM in the secondary incubation.

There was no significant inhibitory effect of eliglustat toward other human CYP450 isozymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP2J2, and CYP3A4

Inhibition potential of metabolites

The direct or time-dependent inhibition potential of the ten metabolites of eliglustat towards major CYP450 enzymes was evaluated. Genz-256222 exhibited competitive inhibition of CYP2D6 and CYP3A4/5 (midazolam 1´-hydroxylase) with Ki of 0.399 µM and 8.51 µM, respectively. Genz-256222 also exhibited competitive inhibition of CYP3A4/5 (testosterone 6β-hydroxylase) with Ki of 10.2 µM, using competitive inhibition model. The calculated R values (1 + [I]/ki) of < 1.1, the potential for clinically relevant inhibition appears to be low. Genz-120965 exhibited time-dependent inhibition of CYP2D6 within the concentration range of 0.250 to 20.0 µM with KI of 8.44 µM and kinact of 0.0206 min-1. The remaining metabolites did not exhibit direct or time-dependent inhibition of major drug metabolizing enzymes.

Genz-256222 and Genz-120965 are not major metabolites in humans as their M:P Ratios being < 0.1 (Section 2.3.5.7.1.1).

2.5.2.3.1.2 Induction potential

Induction potential of eliglustat

There appears to be low potential for induction of CYP1A2, CYP2B6, and CYP3A4 enzymes by eliglustat at the concentrations examined in primary cultures of human hepatocytes (0.01- 1 µM eliglustat), and cryopreserved human hepatocytes (up to 10 µM eliglustat).

Human hepatocyte cultures were treated daily for three consecutive days with fresh dosing solutions of Genz-112638 (0.01, 0.1 and 1 µM) and positive controls, 3-Methylcholanthrene, 3-MC (2 µM), Phenobarbital, PB (1000 µM) and Rifampicin, RIF (10 µM). Negative control cultures were treated with vehicle (0.1% DMSO). After completion of the treatment period, CYP450 enzyme activities were determined by adding appropriate CYP450 marker substrates for CYP1A2 (Phenacetin 100 uM), CYP2B6 (Bupropion 500 uM) and CYP3A4 (testosterone 200 uM) directly to the monolayers. The marker metabolites acetaminophen, hydroxybupropion and 6b-hydroxytestosterone were measured in the incubation samples using appropriate LC-MS/MS analyses. Increases in enzyme activity that were ≥40% of the respective positive control(s) were considered an indication of demonstrable induction.

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu727	Hu728	Hu730	Hu727	Hu728	Hu730	Hu727	Hu728	Hu730
3-MC (2 µM)	100	100	100	2.8	2.1	4.1	-1.8	-0.86	-1.7
Phenobarbital (1000 µM)	0.63	3.6	3.3	100	100	100	57.8	75.0	81.0
Rifampicin (10 µM)	0.43	0.94	1.5	36.2	23.5	44.8	100	100	100
Genz-112638 (0.01 µM)	0.04	0.32	0.01	-0.07	0.09	-0.46	-1.5	1.2	11.6
Genz-112638 (0.1 µM)	0.04	0.04	-0.16	0.01	-0.09	-0.63	-2.1	-0.42	2.9
Genz-112638 (1 µM)	0.09	0.08	-0.02	0.03	0.37	-0.51	-1.5	-0.63	1.5

Induction potential of metabolites

Eliglustat metabolite pool did not induce CYP1A2, CYP2B6 and CYP3A4/5 activity and corresponding mRNA expression. Cultured human hepatocytes were treated with a pool of ten eliglustat metabolites at concentrations 10-fold higher than their clinically relevant Cmax following a 150 mg dose [Genz-256416 (2.38 μM), Genz-311752 (2.38 μM), Genz-399207 (2.38 μM), Genz-258179 (0.238 μM), Genz-120965 (0.238 μM), Genz-527862 (2.39 μM), Genz-399240 (12.3 μM), Genz-682042 (2.55 μM), Genz-258162 (2.39 μM), and Genz-256222 (0.286 μM)].

2.5.2.3.2 *In vivo* studies: eliglustat as a perpetrator drug

2.5.2.3.2.1 Effect of eliglustat on metoprolol, a CYP2D6 substrate

Effect of eliglustat on CYP2D6 substrate metoprolol was evaluated in an open-label fixed-sequence, 2-period study in 14 healthy subjects (EMs=8, IMs=5). Single oral dose of 50 mg metoprolol was given on Day 1 of Period 1 and Day 7 of Period 2. The washout period was 6 days. Eliglustat 150 mg PO BID was given starting on Day 3 of Period 2 for 5 days.

Following multiple doses of eliglustat 150 mg BID, systemic exposures (AUC and Cmax) to metoprolol increased compared to metoprolol administration alone. In EMs, AUC and Cmax increased by 132% and 72% (Table 50). In IMs, AUC and Cmax increased by 63% and 18%, respectively.

Concomitant use of eliglustat with a sensitive CYP2D6 substrate should be cautious. If warranted, the dose of the victim drug can be decreased by 50%.

The therapeutic concentration of metoprolol to achieve beta-blocking activity is 35 to 212 ng/mL.[7] Antihypertensive activity of metoprolol is not correlated to plasma concentrations, and there is considerable variability in plasma concentrations following a given dose. In this drug interaction study, the Cmax values of metoprolol following co-administration of eliglustat and metoprolol in all subjects were below 212 ng/mL. Factoring in the 132% increase in AUC in EMs, the following dosing strategy for metoprolol is recommended: *1) for patients already on eliglustat and start metoprolol, start metoprolol from the lower end of the dose; 2) for patients who are on metoprolol and now need eliglustat, reduce the metoprolol dose by half (due to > 100% increase in exposure) and then readjust metoprolol dose for response.*

Table 50. Statistical Analysis of Plasma PK Parameters for Metoprolol in EMs and IMs.

PP	CYP2D6 Phenotype	Geometric LS Mean Ref	Geometric LS Mean Test	Ratios (%) (Test/Ref)[‡]	90% CI Lower Bound	90% CI Upper Bound
AUCinf (ng×hr/mL)	EM	290	675	232	197	274
	IM	871	1421	163	138	193
Cmax (ng/mL)	EM	62.1	107	172	139	211
	IM	121	144	118	97.1	145
[‡] Test = Metoprolol+Eliglustat, Ref = Eliglustat alone						

Source Data: Reviewer's Analysis

[7] Micromedex Drug Consult: Metoprolol. Database assessed May 2014.

2.5.2.3.2.2 Eliglustat on oral contraceptives, a substrate of CYP3A4/5

Effect of multiple-dose eliglustat on the PK of norethindrone (NE) and ethinyl estradiol (EE) was evaluated in an open-label fixed-sequence, two-period study in 29 healthy female subjects with childbearing potential (EM=22, IM=3, PM=3, URM=1). In Period 1, all subjects received Ortho-Novum 1/35 daily for 28 days (21 days of active drug and 7 days of placebo drug). In Period 2, all subjects received another 21 days of Ortho-Novum 1/35 and 7 days of placebo pills. All subjects received eliglustat 100 mg BID for 11 days (from Day 11 to Day 21 in Period 2).

No differences in plasma exposure of EE and NE with the presence of eliglustat compared with those without the presence of eliglustat in EMs (Table 51). For IMs the systemic exposures (Cmax and AUCtau) to EE were increased by 16%. However, the degree of increase in EE should not affect the contraceptive effect of OC. The changes in systemic exposures to NE were less than 10% in IMs. Similarly, the changes in systemic exposures to EE and NE were less than 10% in PMs with or without eliglustat. It is concluded that eliglustat may be given with Ortho-Novum 1/35 without dose adjustment in patients who are CYP2D6 PM, IM or EM.

Table 51. Statistical comparison of plasma EE and NE exposure by treatment stratified by CYP2D6 phenotype.

Parameter	ANALYTE	CYP2D6 Phenotype	Geometric LS Mean Ref	Geometric LS Mean Test	Ratios (%) (Test/Ref)[‡]	90% CI Lower Bound	90% CI Upper Bound
AUCtau	EE (pg×hr/mL)	EM	1054	1057	100	96.2	104
Cmax	EE (pg/mL)	EM	124	127	102	97.8	107
AUCtau	NE (ng×hr/mL)	EM	140	139	98.9	95.5	103
Cmax	NE (ng/mL)	EM	21.3	22.0	103	94.4	112
AUCtau	EE (pg×hr/mL)	IM	1040	1203	116	106	127
Cmax	EE (pg/mL)	IM	119	137	116	97.4	137
AUCtau	NE (ng×hr/mL)	IM	142	152	107	70.9	161
Cmax	NE (ng/mL)	IM	21.7	22.8	105	83.6	132
AUCtau	EE (pg×hr/mL)	PM	1053	1104	105	84.7	130
Cmax	EE (pg/mL)	PM	131	131	100	75.3	134
AUCtau	NE (ng×hr/mL)	PM	128	121	94.4	79.5	112
Cmax	NE (ng/mL)	PM	16.7	19.6	117	95.4	144
[‡] Test = EE/NE+Eliglustat, Ref = EE/NE alone							

Source Data: Reviewer's analysis

2.5.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

2.5.2.4.1 *In vitro* studies

Eliglustat is both a substrate and an inhibitor of MDR1 transporter (P-gp).

Eliglustat was transported by P-gp active transporter across the MDCKII-MDRI monolayers, as noted by decrease in efflux ratios of eliglustat in presence of known P-gp inhibitor drugs, PSC833 and verapamil. Eliglustat is also an inhibitor of P-gp, as noted by the decrease in the efflux ratio of P-gp substrate drug digoxin in presence of 50 μM eliglustat. The IC_{50} for eliglustat against P-gp is determined to be 22 ± 12 μM.

The substrate and the inhibition potential of Genz-112638 for P-glycoprotein (P-gp, MDR1) were evaluated in the MDCKII-MDR1 cell model. MDCKII was used as the control cell model. In the first part, the bidirectional permeability assay of Genz-112638 was conducted at three concentrations (1, 10 and 100μM). In the second part, Genz-112638 (1 μM) was incubated in the presence of MDR1 inhibitors PSC833 (10 μM) and verapamil (60 μM), respectively. Third part of this study evaluated MDR1 inhibition potential of Genz-112638 in the MDCKII-MDR1 cell model. Digoxin (10μM) was used as a positive control substrate. In the final phase of this study the IC50 of Genz-112638 in the MDCKII-MDR1 cell model was determined. Digoxin (5 μM) was used as a probe substrate. Genz-112638 was tested at five different test concentrations, 3.1, 9.3, 28, 83 and 250 μM.

The net efflux ratio of Genz-112638 showed higher B-A permeability than A-B permeability at tested concentrations, indicating active transport of this compound in MDCKIIMDR1 cells. The observed efflux ratios (ER) were 5.7 (1μM), 4.6 (10μM) and 1.5 (100μM) on MDCKII-MDR1 cells, while ER values of approximately 1 were observed in case of the parental MDCKII cells. The highest observed efflux ratio was 5.7 (net efflux ratio was 6.9) at 1 μM.

Genz-112638 efflux ratio decreased from 4.8 to 1.4 in the presence of PSC833 (10μM) and decreased to 1.2 in the presence of verapamil (60μM). The results were consistent with a repeat experiment. The net efflux ratio of Genz-112638 decreased from 5.6 to 1.0 in the presence of PSC833 (10μM) and decreased to 1.1 in the presence of verapamil (60 μM).

The efflux ratio for digoxin (10μM) on MDCKII-MDR1 cells in the absence of Genz-112638 was 18. Genz-112638 at 50μM moderately inhibited digoxin transport on MDCKII-MDR1 cells (ER = 7.7). The IC50 for Genz-112638 was determined to be 22 ± 12 μM.

The pool of ten eliglustat metabolites at 10-fold higher concentrations than clinically anticipated, also did not inhibit the transport of typical substrate mediated by MDR1, BCRP, BSEP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 transporters.

2.5.2.4.2 In vivo study – Effect of eliglustat on digoxin, a P-gp substrate

Effect of multiple-dose eliglustat on the PK of digoxin was evaluated in an open-label fixed-sequence, two-period study in 28 healthy subjects (Table 52). Subjects who are CYP2D6 poor metabolizers (N=4) received eliglustat 100 mg BID while others received 150 mg BID (EM: N=19; IM: N=1; URM: N=4).

Table 52. Study Design of digoxin DDI study.

		Period 1	Washout period	Period 2
CYP2D6 Phenotypes	Activities	Day 1	10 days	Days 1-17
non PMs	Dose	Digoxin 0.25 mg ×1		150 mg Eliglustat BID Digoxin 0.25 mg ×1 on Day 15
	PK sampling for plasma Eliglustat	n/a		Trough samples on Days 15, 16, 17, and 18
	PK sampling for Digoxin in plasma and urine	Days 1 to 3*		Days 1 to 3*
PMs	Dose	Digoxin 0.25 mg ×1		100 mg Eliglustat PO BID Digoxin 0.25 mg ×1 on Day 15
	PK sampling for plasma Eliglustat	n/a		Trough samples on Days 15, 16, 17, and 18
	PK sampling for Digoxin in plasma and urine	Days 1 to 3*		Days 1 to 3*
* Plasma sampling time: Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours Urine sampling interval: 0 to 6 hours, 6 to 12 hours, 12 to 24 hours, 24 to 48 hours, and 48 to 72 hours				

The PK parameters of digoxin with or without eliglustat is listed in Table 53. Following co-administration of 150 mg BID of eliglustat and digoxin in EMs/IMs/URMs, the systemic exposures (AUClast and Cmax) increased by 41% and 64%, respectively. Co-administration of 100 mg BID of eliglustat in PMs resulted in 37% increase in AUClast and 68% increase in Cmax. Tmax and T1/2 of digoxin was similar with or without eliglustat treatment, which is consistent with the expectation that the interaction happens at the gut level. Pooling data from all the subjects (Table 54), the systemic exposure (AUClast and Cmax) of digoxin increased by 49% and 70%, respectively.

Table 53. Mean (CV%) of Serum PK Parameters of Digoxin

Parameters	Digoxin Alone (N=28)	Eliglustat + Digoxin	
		Eliglustat 100 mg (N=4)	Eliglustat 150 mg (N=23: URM =4 EM=19, IM=1)
$AUC_{0\text{-}72h}$ (ng×hr/mL)	14.9[a] (19.3)	NA*	16.3 [b] (17.2)
AUClast (ng×hr/mL)	9.66 (42.8)	13.2 (24.8)	13.6 (26.4)
Cmax (ng/mL)	1.03 (36.7)	1.73 (16.8)	1.69 (28.2)
Tmax (hr)**	1 [0.5, 3]	0.875 [0.5, 1.5]	0.75 [0.5, 2]
T1/2 (hr)	30.6 [c] (19.9)	NA	31.8 [d] (26.2)
[a] N=9; [b] N=12; [c] N=6; [d] N=7; * AUC0-72 was not calculated due to Digoxin concentration at Hour 72 was below LLOQ; ** Median [Min, Max]			
AUC0-inf was not estimable due to percent extrapolation (%AUC0-inf, ex) ≤ 20%, predefined by the sponsor.			

Source Data: Study GZAD03610, Clinical Study Report, Table 11-2.

Table 54. Statistical Comparison of Serum Digoxin Exposure by Treatment (N=28)

Parameter	Treatment	Geometric LS Mean	Ratios (%) (Test/Ref)[‡]	90% CI
AUClast (ng×hr/mL)	Digoxin alone (N=28)	8.73	148.60	132.99, 166.05
	Digoxin+Eliglustat (N=27)	12.97		
Cmax (ng/mL)	Digoxin alone (N=28)	0.96	169.76	156.47, 184.19
	Digoxin+Eliglustat (N=27)	1.64		
[‡] Test = Digoxin+Eliglustat, Ref = Digoxin alone Note: Genotype-by-treatment interaction was evaluated, and the interaction was not significant for any parameter.				

Source Data: Study GZAD03610, Clinical Study Report, Table 11-3.

Digoxin has a narrow therapeutic index. Serum digoxin concentrations less than 0.5 ng/mL have been associated with diminished efficacy, while concentrations above 2 ng/mL have been associated with increased toxicity without increased benefit.[8] Even as digoxin serum levels increase above 1.2 ng/mL, there is a potential for increase in adverse reactions. The digoxin concentrations (Cmax) increased greater than 50% in EMs and PMs. Based upon the dose adjustment recommendation in the current digoxin label (Section 7.2), *serum digoxin concentrations should be measured before initiating concomitant drugs. Reduce digoxin concentrations by decreasing dose by approximately 30% or by modifying the dosing frequency*

[8] Digoxin Product Label.

and continue monitoring.

Digoxin PK in Urine

The amount (Ae) of digoxin excreted in urine over 72 hours after dosing was increased by 15%, 6%, 24% and 26% in PMs, IM, EM, and URM, respectively when digoxin 0.25 mg was co-administered with eliglustat compared with digoxin administered alone), which is consistent with the increase in serum systemic exposure. The renal clearance (CLr) appeared to be similar between the treatments with the limited subjects available for this assessment.

Table 55. Digoxin PK in Urine

	Treatment[a]			
	Digoxin Alone	Eliglustat + Digoxin		
	n = 28	Eliglustat 100 mg n = 4	Eliglustat 150 mg n = 23	Pooled Eliglustat 100 and 150 mg n = 27
Ae (ng)				
Mean	88104	105170	106980	106712
CV (%)	22.0	23.8	17.1	17.7
CL_r (L/h)				
Mean	6.36[e]	NA	6.71[e]	6.71[e]
CV (%)	22.7	NA	16.4	16.4

[a].Single oral dose of digoxin 0.25 mg on Day 1. Repeat oral doses of eliglustat 150 mg twice daily, or 100 mg twice daily for CYP2D6 poor metabolizers, on Days 11 through 17 with coadministration of a single oral dose of digoxin 0.25 mg on Day 15. [e] N=12

Source Data: Study GZAD03610, Clinical Study Report, Table 11-2.

2.5.2.5 Are there other metabolic/transporter pathways that may be important?

No. Eliglustat is not a substrate of BCRP, OAT1B1, OAT1B3, MRPs and OAT1. It did not inhibit BCRP, OAT1B1, OAT1B3, MRPs and OAT1 at clinical relevant concentrations.

Eliglustat is not a substrate of the BCRP transporter. It inhibited BCRP-mediated transport of prazosin in a concentration dependent manner with a high IC_{50} average of 126 µM.

Eliglustat does not appear to be a substrate for OATP1B1. It showed low levels of substrate potential for OATP1B3 at the concentrations tested (15 and 50 µM). Eliglustat did not interact with the MRP efflux transporters, MRP1, MRP2, MRP3, MRP4 and MRP5 in the concentration range tested (up to 300 µM). It did not interact with the OAT1 uptake transporter in the concentration range tested (up to 300 µM).

Eliglustat inhibited the OAT3 mediated E3S transport with a maximal inhibition of 67% and an IC_{50} value of 198µM. Drug did not inhibit the OATP2B1 mediated E3S transport; however, E3S uptake increased with a maximal effect of 225% compared to control.

Eliglustat inhibited the OATP1B1 mediated E3S transport with a maximal inhibition of 70% and an IC50 value of 150µM. It inhibited the OATP1B3 mediated Fluo-3 transport with a maximal inhibition of 85% and an IC_{50} value of 100 µM.

Eliglustat inhibited the accumulation of taurocholic acid in bile-salt export pump, BSEP expressing vesicles with an IC_{50} of 325 ± 25 µM.

Based on the in vivo concentrations noted for eliglustat, the IC_{50} values noted above for various transporter inhibitions do not appear to be clinically relevant.

2.5.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Not applicable.

2.6 GENERAL BIOPHARMACEUTICS

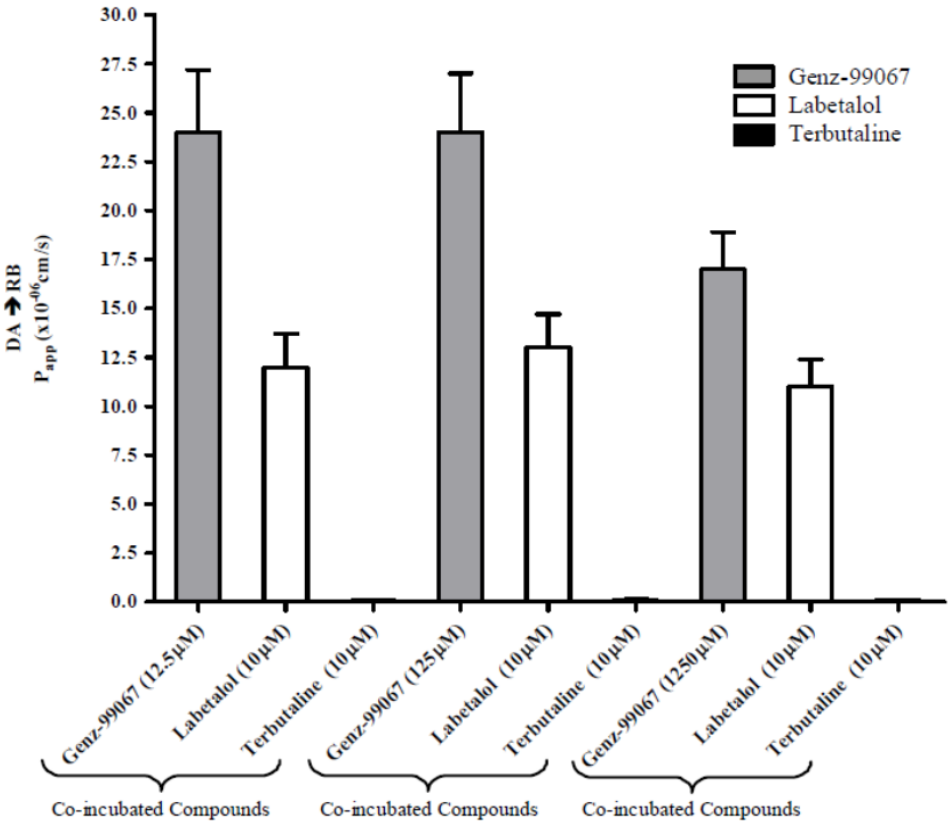
2.6.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Eliglustat is a BCS Class I drug (DS/DP). The BCS committee reviewed the solubility, permeability and dissolution data and made this conclusion. The determination was conveyed to the Sponsor on February 17, 2012.

In vitro permeability: The bidirectional permeability of Genz-99067 (eliglustat) in Caco-2 cell system was assessed at 12.5, 125 and 1250µM. The test concentrations for Genz-99067 were selected based upon 0.01, 0.1 and 1 times the clinical dose strength of 150mg Genz-112638 dissolved in 250mL. Labetalol and terbutaline were included at 10 µM test concentrations in all experiments as the internal high permeability standard and the internal low permeability standard, respectively. All tested concentrations of Genz-99067 exhibited higher permeability than the internal high permeability standard labetalol. The ratios of permeability of Genz-99067 to that of labetalol were 2.0, 1.9 and 1.6 at concentrations of 12.5, 125 and 1250µM Genz-99067, respectively. These data support classification of Genz-99067 as a high permeability drug substance.

Summary of Caco-2 permeability of Genz-99067 in the absence and presence of co-incubated compounds is in the table and figure below.

Analyte	Test Conc. (µM)	Co-Incubated Compounds	DA→RB				DB→RA				Efflux Ratio
			P_{app} ($x10^{-6}$ cm/s)		Mass Balance (%)		P_{app} ($x10^{-6}$ cm/s)		Mass Balance (%)		
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Genz-99067	12.5	None	23	2.3	92	3.5	24	3.0	96	1.5	1.0
Genz-99067	125	None	22	1.8	95	2.3	22	2.8	100	7.8	1.0
Genz-99067	1250	None	22	2.0	95	2.5	13	1.1	97	1.2	0.61
Genz-99067	12.5	10µM Labetalol 10µM Terbutaline	24	3.2	85	5.6	23	1.5	96	4.0	0.93
Genz-99067	125	10µM Labetalol 10µM Terbutaline	24	3.0	94	7.2	20	1.8	95	2.1	0.85
Genz-99067	1250	10µM Labetalol 10µM Terbutaline	17	1.9	96	4.0	14	1.2	99	2.3	0.79



2.6.2 What is the composition of the to-be-marketed formulation?

Eliglustat drug product is formulated as a hard gelatin capsule. Each capsule contains 84 mg eliglustat free base (equivalent to 100 mg of eliglustat tartrate) and microcrystalline cellulose, lactose monohydrate, hypromellose and glyceryl behenate / (b) (4) The components of the drug product, as well as the quantity, function and quality standard of each component, is summarized in Table 56.

Table 56. Composition of eliglustat hard capsules

Component	Reference to Quality Standard	Function	Amount (mg/capsule) [a]
Capsule Blend Composition			
Eliglustat[b]	In-house	drug substance	(b) (4)
Microcrystalline cellulose	NF / Ph.Eur.		(b) (4)
Lactose monohydrate	NF / Ph.Eur.		
Hypromellose	USP / Ph.Eur.		
Glyceryl behenate / (b) (4)	NF / Ph.Eur.		
Capsule			
Size 2 hard gelatin capsules (printed with black ink)[c]	In-house	encapsulation	1 capsule

[a] Target amounts provided. Refer to 3.2.P.3.2 for the ranges for each excipient.
[b] Each capsule contains 84 mg of eliglustat (which is equivalent to 100 mg of eliglustat tartrate)
Source data: Section 3.2.P.1, Table 1.

2.6.3 How is the proposed to-be-marketed formulation linked to other formulations used in the clinical studies?

Eliglustat is a BCS Class I drug. The in vitro dissolution study showed that the dissolution is > (b) (4)% in (b) (4) minutes. Refer to Dr. Tien Mein Chen's review from ONDQA in DARRTS. Therefore, bioequivalence study is not required to link the to-be-marketed formation to other formations in the clinical study.

However, the sponsor conducted a single dose, two-treatment, two-sequence, four-period replicated crossover study (Study GZGD08311) to evaluate the relative bioavailability of the common blend proposed commercial formulation (to-be-marketed formulation, one (b) (4) mg capsule) relative to the Phase 3 formulation ((b) (4) Phase 3 capsules) in healthy subjects. The results (Table 57) indicated that there was no difference between the test formulation (to-be-marketed formation) compared with the reference formulation (Phase 3 formulation).

Table 57. Statistical Analysis of Relative Bioavailability of Eliglustat

Parameter (Unit)	Treatment	n	Geometric Means	95% CI of the Geometric Means	Ratio (%) of Geometric Means (T/R)	90% CI of the Ratio	Intra-Subject CV (%)
AUC_{last} (ng•h/mL)	R	22	97.91	66.90, 143.29	100.58	94.13, 107.47	21.3
	T	22	98.48	65.72, 147.57			12.9
AUC_{0-inf} (ng•h/mL)	R	22	102.35	70.51, 148.56	100.33	94.02, 107.07	20.5
	T	22	102.69	69.01, 152.81			12.9
C_{max} (ng/mL)	R	22	14.93	10.64, 20.96	102.10	94.58, 110.21	21.8
	T	22	15.24	10.51, 22.10			18.0

Abbreviations: CI, confidence interval; CV, coefficient of variation.
Treatment T = Test treatment: One (b) (4) common blend capsule of eliglustat.
Treatment R = Reference treatment: (b) (4) Phase 3 capsules of eliglustat.
Note: An analysis of variance was performed on the natural logarithms of the parameters with sequence, period, and treatment as fixed terms and treatment for each subject within sequence as a random effect. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

Source Data: GZGD03811 Clinical Study Report Synopsis, Table 2.

2.6.4 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of high-fat meal on PK of eliglustat was evaluated in the single-dose of 300 mg (6 of 50-mg capsule), two-period, cross-over study in 24 healthy male adult subjects (19 – 43 years of age). All the subjects were non-smokers. CYP2D6 phenotyping was not conducted in this study. The high fat breakfast meal served during the fed state consisted of 2 whole chicken eggs fried in real butter, 2 strips of fried bacon, 2 slices of white toast with 2 teaspoons of butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. The amount of calories from fat was approximately 50 percent of total caloric content of the meal.

Eliglustat is a BCS Class 1 drug. Therefore, type of formulation used in the food effect study does not affect the results. On the other hand, eliglustat has high first-pass effect and food can influence its bioavailability. Administration of eliglustat with a high fat breakfast resulted in a 15% decrease in Cmax but no change in AUC (Table 58). The median Tmax was increased from 2 to 3 hours under fed condition. This is consistent with the fact that eliglustat is a BCS Class 1 drug with rapid dissolution. However, the 15% reduction in Cmax under fed condition was unlikely to affect clinical efficacy of eliglustat. Therefore, *eliglustat can be taken without regard to meals.*

Table 58. Summary of PK Parameters (mean ± SD) of 300 mg Eliglustat and Statistical comparison of Cmax and AUC of eliglustat

Parameter	Fed (N=24)	Fasted (N=24)	Geometric Mean Ratio (Fed/Fasted) x 100%	90% Confidence Interval
Cmax (ng/mL)	79.1 ± 65.9	88.3 ± 76.2	85.20	67.93, 106.87
Median Tmax (hr) [min – max]	3.00 [1.00 – 6.00]	2.00 [0.95 – 4.00]	--	--
AUC (0-t) (ng×hr/mL)	678 ± 638	606 ± 585	104.69	88.83, 123.37
AUC (0-∞) (ng×hr/mL)	696 ± 656	623 ± 601	104.44	89.04, 122.51
T½ (hr)	6.11 ± 1.37	6.68 ± 1.09	--	--

Source Data: GZGD00404 CSR, Panel 11.2 and Panel 11.3

2.6.5 What is the effect of gastric acid reducing agents on the bioavailability of eliglustat from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product?

The effect of gastric pH-altering agents (antacids or proton pump inhibitors) on the absorption of eliglustat was evaluated in the single-dose (100 mg), three-period cross-over study with a fixed – sequence fourth period (Table 59) in 24 healthy adult subjects. There was a 7-day washout between each treatment period (Periods 1 to 3). Period 4 started 24 hours after the end of Period 3.

Table 59. Treatment sequences

Sequence	Period 1 (Days -1 to 2)	Period 2 (Days 8 to 10)	Period 3 (Days 16 to 18)	Period 4 (Days 18 to 25)	Subject Numbers
1	A	B	C	D	EM: 4
2	A	C	B	D	EM: 3; IM: 1
3	B	A	C	D	EM: 3; IM: 1
4	C	A	B	D	EM: 4
5	C	B	A	D	EM: 4
6	B	C	A	D	EM: 4

- Treatment A = single oral dose (1 capsule) of 100 mg Genz-112638 (reference treatment)
- Treatment B = single oral dose of Maalox Advanced Maximum Strength Liquid (4 teaspoons equivalent to approximately 1600 mg aluminum hydroxide, 1600 mg magnesium hydroxide, and 160 mg simethicone) within 3 minutes before a single oral dose of 100 mg Genz-112638 (test treatment)
- Treatment C = single oral dose (2 tablets) of Tums 500 mg Chewable Tablets within 3 minutes before a single oral dose of 100 mg Genz-112638 (test treatment)
- Treatment D = 40 mg (1 tablet) of Protonix QD on the mornings of Days 18 through 24. On Day 25, subjects received 40 mg Protonix within 3 minutes before a single dose of 100 mg Genz-112638 (test treatment)

Administration of eliglustat with Maalox, Tums, or pantoprazole resulted in 15%, 12%, and 8% increase in Cmax, respectively. Similar increases (6 to 14%) in AUC were also observed (Table 60). No changes in median Tmax were found. However, up to15% increase in Cmax and up to 14% increase in AUC are unlikely to affect clinical safety of eliglustat. Therefore, *eliglustat can be co-administered with antacids, proton pump inhibitors and other gastric pH-reducing agents.*

Table 60. Summary of PK parameters (mean ± SD) of 100 mg eliglustat and statistical comparison of Cmax and AUC of eliglustat

Parameter	A Eliglustat (N=24)	B Eliglustat +Maalox (N=23)	C Eliglustat +Tum (N=21)	D Eliglustat +Protonix (N=21)	Geometric Mean Ratio (B/A, C/A, D/A) x 100%	90% Confidence Interval
Cmax (ng/mL)	7.56 (6.57)	9.06 (7.92)	8.10 (6.58)	8.98 (9.32)	114.6 111.6 107.7	99.29, 132.36 96.12, 129.66 91.39, 126.97
AUC (0-t) (hr•ng/mL)	58.1 (60.2)	68.7 (69.8)	61.8 (62.9)	66.5 (75.7)	113.9 109.7 105.7	98.79, 131.27 94.55, 127.15 89.45, 124.85
AUC (0-∞) (hr•ng/mL)	63.1 (66.3)	74.7 (77.8)	67.5 (71.5)	75.4 (85.8)**	113.6 109.1 108.6	98.91, 130.48 94.44, 126.04 92.44, 127.62
Median Tmax (hr)* [min – max]	2.00 [1.50 – 4.00]	2.00 [1.00 – 4.00]	2.00 [1.00 – 4.00]	2.00 [1.00 – 4.02]	N/A	N/A
t½ (h)	6.18 (1.43)	5.99 (1.37)	6.25 (1.53)	6.05 (1.71)	N/A	N/A
** N=20						

Source Data: Table 11.2 and Table 11.3, GZGD01907 CSR

2.7 ANALYTICAL SECTION

2.7.1 Are the methods used to determine CYP2D6 genotype in eliglustat clinical studies acceptable?

Yes. Analyses were performed using FDA 510(k) cleared tests, with the (b) (4) using the xTAG® CYP2D6 Kit v3 (Luminex Corporation) and (b) (4) using the AmpliChip® Cytochrome P450 Genotyping test (Roche) and GeneChip Microarray Instrumentation (Affymetrix). The (b) (4) classified study participants according to seven CYP2D6 phenotypes: poor (PM), poor to intermediate (PM-IM), intermediate (IM), intermediate to extensive (IM-EM), extensive (EM), extensive to ultra-rapid (EM-URM), or ultra-rapid (URM) (Table 61). In the analyses performed by (b) (4), study participants were classified into one of 4 CYP2D6 phenotypes: PM, IM, EM, or URM. The laboratory responsible for genotyping each clinical study and the genotypic criteria used to assign phenotypic categories are presented in Table 61. All participant samples analyzed by the (b) (4) classified as IM-EM or EM-URM would have been classified as EMs by (b) (4) (Table 61). No study participants enrolled in eliglustat clinical studies were classified as PM-IM by the (b) (4)

Table 61. Predicted CYP2D6 phenotype by genotype as determined by the [(b) (4)] and [(b) (4)]

Laboratory	Study No.	Predicted CYP2D6 Phenotype						
		PM	PM-IM	IM	IM-EM‡	EM‡	EM-URM‡	URM
[(b) (4)]	GZGD00204 GZGD01707 GZGD01807 GZGD02007 GZGD02707 Phase 2	*4/*4 *4/*5 *4/*6	*2/*4 dup *4/*17	*1/*3 *1/*4 *1/*5 *1/*6 *2/*4 *2/*5 *9/*10 *10/*17	*1/*2 *1/*9 *2/*2 *2A/*3 *2A/*4 *2A/*5 *2A/*6 *2A/*9 *2A/*17	*1/*1 *2/*2A	*1/*2A *2A/*2A	*1/*2A dup
[(b) (4)]	GZGD02107 GZGD03811 GZGD01907 GZGD02407 GZGD03610 GZGD04112 Phase 2 ENGAGE ENCORE EDGE	*3/*3 *3/*4 *4/*4 *4/*5 *4/*6	NA	*3/*10, *3/*41 *4/*9 *4/*10 or *4/*10 dup *4/*17 *4/*29 *4/*41 *5/*9 *5/*10 *6/*41 *10/*10 *10/*41 *17/*41 *41/*41 or *41/*41 dup	NA	*1/*1, *1/*2, *1/*3 or *1/*3 dup *1/*4 or *1/*4 dup *1/*5, *1/*9 *1/*10 or *1/*10 dup *1/*17 *1/*41 or *1/*41 dup *2/*2 *2/*4 or *2/*4 dup *2/*5, *2/*6 *2/*9 or *2/*9 dup *2/*10 *2/*41 or *2/*41 dup	NA	*1/*1 dup *1/*2 dup *2/*2 dup

‡ EMs by [(b) (4)]

Source Data: Section 2.7.2, Table 54.

In clinical practice, alternative approaches may be used to determine CYP2D6 phenotype. Compared with results from [(b) (4)] phenotype as determined using the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for activity score (PharmGKB) resulted in concordant phenotypes in 94% of subjects in Phase 2, ENGAGE and ENCORE studies. Discordant results were either EMs [(b) (4)] who became indeterminate (CPIC, due to missing duplication attribution) or IMs [(b) (4)] being classified as EMs (CPIC). Therefore, phenotypic classification based on alternative approaches (such as activity score) are not expected to result in meaningful differences in the prescribed dose.

2.7.2 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Metabolite concentrations were measured in mass balance study, DDI studies (GZGD02407 and GZGD03610). None of the metabolites are active metabolites.

2.7.3 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Table 62 showed the summary of bioanalytical validation for eliglustat. Two validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods were developed for the determination of eliglustat in human plasma. The first one [(b) (4)] 140045) was developed and validated by [(b) (4)] [(b) (4)]. The second one [(b) (4)]-141364) was developed and validated by [(b) (4)] [(b) (4)]

In Study [(b) (4)]-140045, the LC-MS/MS analytical method was validated over the concentration

range 0.500 to 1000 ng/mL in human plasma. In Study (b) (4)-141364, the LC-MS/MS analytical method was re-validated over a lower concentration range which was more suitable for sample analysis and for changes in instrumentation.

Metabolites of eliglustat were assayed using qualified LC-MS/MS methods with an LLOQ of 0.5 ng/mL for studies GZGD02107 and GZGD02407 and with LLOQs ranging from 0.339 to 0.501 ng/mL for the Phase 2 study.

Table 62. Summary of bioanalytical validation for eliglustat in plasma and urine

Study Reference	Matrix	Assay	Assay Volume (µL)	LLOQ (ng/mL)	ULOQ (ng/mL)	QC Levels (ng/mL)	Intra-Run		Inter-Run		LTS (days)
							RE range (%)	CV range (%)	RE range (%)	CV range (%)	
(b) (4) 140045	plasma	LC-MS/MS	50	0.5	1000	1.5, 300, 700	-10.1 to 2.3	0.9 to 11.4	-6.4 to -2.1	1.5 to 9.2	199 (-80°C)
(b) (4) 141364, (b) (4) 141505	plasma	LC-MS/MS	50	0.2	200	0.6, 100, 150	-11.1 to 15.0	0.7 to 5.1	-2.2 to 3.4	10.1 to 11.5	190 (-20°C)[a] 1169 (-80°C)[a]
(b) (4) 140046	urine	LC-MS/MS	50	0.5	1000	1.5, 300, 700	-4.8 to 0.9	1.6 to 4.7	NA	NA	180 (-80°C)
DMPK12-R063[b]	plasma	LC-MS/MS	50	0.2	200	0.2, 0.6, 40, 100, 150	-11.3 to 10.8	0.9 to 7.4	-7.3 to 6.5	3.7 to 5.7	NA
DMPK13-R002[b]	plasma	LC-MS/MS	50	0.2	200	0.2, 0.6, 10, 100, 150	-2.5 to 14.7	0.7 to 11	2.0 to 7.8	2.3 to 9.0	NA

CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; LTS, long term stability; NA, not applicable; QC, quality control; RE, relative error; ULOQ, upper limit of quantification

[a] Results for -20°C and -80°C LTS in human plasma are presented in (b) (4) 141505.

[b] DMPK12-R063 and DMPK13-R002 are cross-validations of (b) (4) 141364.

Source Data: Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 3.

The standard curve and QC data indicated that the plasma and urine assay methods for eliglustat were precise and accurate. Details of the analytical methods for each study were reviewed in the individual study reviews. Details of the analytical validation method for eliglustat in feces were reviewed in the individual study review for GZGD02107. The standard curve and QC data indicated that the feces assay method for eliglustat was precise and accurate.

3 LABELING RECOMMENDATIONS

Labeling revisions are ongoing. Please refer to the final approved labeling when available. Detailed recommendations will be sent to the sponsor regarding the correct formatting and organization as well as the content related to Highlights, Dosage and Administration, Drug Interactions, Specific Populations as well as Clinical Pharmacology sections of the PLR labeling. The following dosing proposals or labeling language different from sponsor's original proposals are recommended by OCP:

- Dose recommendation in CYP2D6 PMs;
- DDI dose adjustment recommendations in PMs;
- Contraindicate concomitant use of eliglustat with a strong CYP2D6 **and** a weak CYP3A inhibitor (paroxetine);
- Reduce eliglustat to 100 mg QD when it is co-administered with strong CYP2D6 inhibitors or moderate CYP2D6 inhibitors in EMs and IMs;
- Reduce eliglustat to 100 mg QD when it is co-administered with strong or moderate CYP3A inhibitors, including grapefruit product or its juice, in EMs
- Concomitant use of eliglustat with strong or moderate CYP3A inhibitor, including grapefruit product or its juice, in IMs is not recommended;
- Dose adjustment of digoxin when co-administered with eliglustat;
- Dose adjustment of metoprolol when co-administered with eliglustat.
- Renal impairment: eliglustat is not indicated in patients with moderate to severe renal impairment or ESRD
- Hepatic impairment: eliglustat is not indicated.

4 APPENDIX

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 205494
Submission Number (Date)	September 20, 2013
Compound	Eliglustat
Indication	Long term treatment of adult patients with Gaucher Disease type 1 (GD1)
Dosing Regimen	100 mg BID orally for CYP2D6 intermediate (IM) and extensive (EM) metabolizers
Dosage strength	100 mg oral capsule
Clinical Division	DGIEP
Primary PM Reviewer	Anshu Marathe, Ph.D., Justin Earp, Ph.D.
Secondary PM Reviewer	Nitin Mehrotra, Ph.D.

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there exposure-response (E-R) relationship for effectiveness in Phase 2 (GZGD00304) and Phase 3 (ENGAGE and ENCORE) studies?

There is a trend for increase in response (decline in spleen and liver volume from baseline, increase in hemoglobin levels and platelet count from baseline) with increasing steady state average trough concentrations of the drug as evidenced in treatment naïve subjects in both Phase 2 (GZGD00304) and Phase 3 (ENGAGE) study. However, for treatment experienced patients (who were switched from ERT to eliglustat), there was no clinically relevant E-R relationship observed.

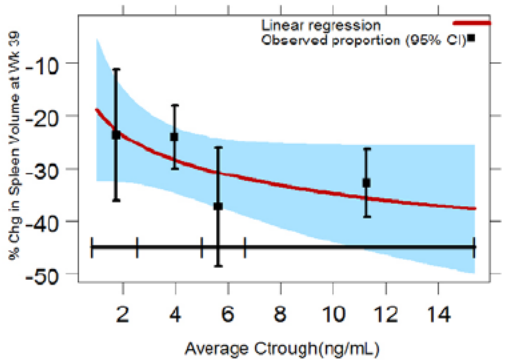
Phase 3 (ENGAGE): There is a trend for increase in response with increasing steady state trough concentrations of the drug in treatment naïve subjects with GD1 in the Phase 3 study after 39 weeks of administration of eliglustat (Figure 1). There is a trend for decrease in percentage change in spleen and liver volume with increasing steady state trough concentrations (Figure 1). In addition, there is a trend for increase in percentage change in platelet count and change in hemoglobin from baseline with increasing steady state trough concentrations (Figure 1). The primary endpoint for the study was percentage change in spleen volume from baseline at week 39. The secondary endpoints included percentage change in liver volume and platelet count and absolute change in hemoglobin levels from baseline. The analysis was conducted using data from 19 subjects out of the 20 subjects enrolled in the eliglustat arm. One patient withdrew prior to week 39 assessment.

Phase 2 (GZGD00304): Similar to the ENGAGE study, there is a trend for increase in response with increasing steady state trough concentrations of the drug in treatment naïve subjects with GD1 in the Phase 2 study after 4 years of administration of eliglustat (Figure 2). In addition, there is a trend for decrease in percentage change in spleen volume and liver volume, increase in percentage change in platelet count and change in hemoglobin level from baseline with increasing steady state trough concentrations of the drug (Figure 2). The analysis was conducted using data from 18 subjects who had spleen and liver volume measurements both at baseline and at 48 months of treatment. Similarly, the analysis was conducted using data from 19 subjects who had hemoglobin and platelet count measurements both at baseline and at 48 month of treatment. A total of twenty six subjects receiving at least 1 dose of eliglustat were enrolled in the study. Seven subjects discontinued prior to 48 month assessment.

Phase 3 (ENCORE): There is no E-R relationship for the primary composite endpoint of proportion of patients who remained stable with respect to organ volumes (spleen and liver) and hematological parameters after 52 weeks of treatment with eliglustat in GD1 patients who had reached therapeutic goals with enzyme replacement therapy and were switched to eliglustat (Figure 3). There is a trend for decrease in percentage change in spleen volume (co-primary endpoint) at week 52 with increasing steady state trough concentrations (Figure 3). The percentage change in spleen volume is 4.4% in the lowest concentration quartile while it is -12.1% in the highest concentration quartile (Table 1). This trend should however be interpreted with caution because as shown in Table 1, although a difference in percentage change in spleen volume is observed between the lowest and highest quartile, the absolute values of spleen volume at week 52 range between 3.0-3.1 multiples of normal (MN) among various quartiles. Thus the differences observed in percentage change in spleen volume is likely not to have any clinical impact in these subjects who were stabilized and met their therapeutic goals at the beginning of the study. The analysis for the primary composite endpoint was conducted using data from all 99 subjects in the per-protocol set for efficacy evaluation. The analysis for the change in spleen was conducted using data from all 70 subjects who had spleen measurements both at baseline and week 52.

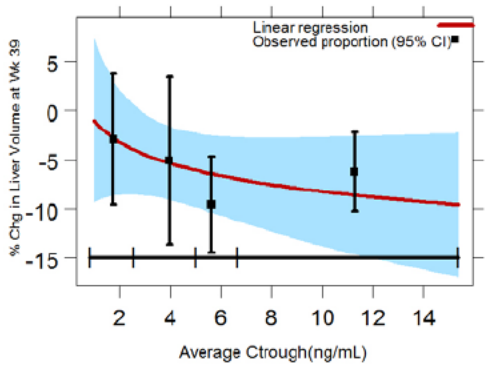
There is no exposure response relationship for secondary endpoints of percentage change in liver volume and change in hemoglobin from baseline (Figure 4). An increase in percentage change in platelet count from baseline (secondary endpoint) is observed with increasing steady state trough concentration. However as stated for percentage change in spleen volume, this relationship should be interpreted with caution as no exposure response relationship was observed for proportion of patients who remained stable with respect to platelet count and greater than 90% of subjects remained stable even in the lowest concentration quartile.

A Percentage Change in Spleen Volume



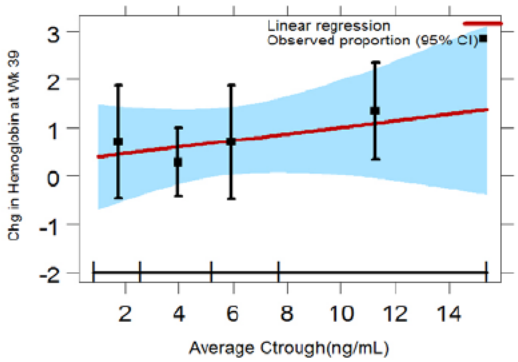
Placebo=2.26%

B Percentage Change in Liver Volume



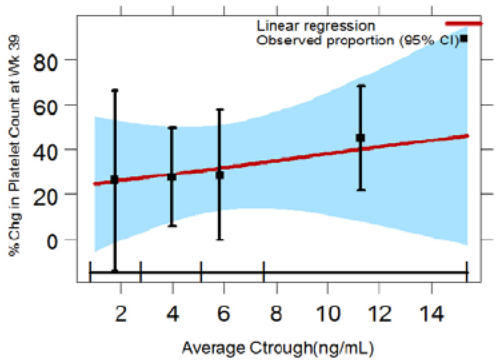
Placebo=1.44%

C Change in Hemoglobin



Placebo = -.054

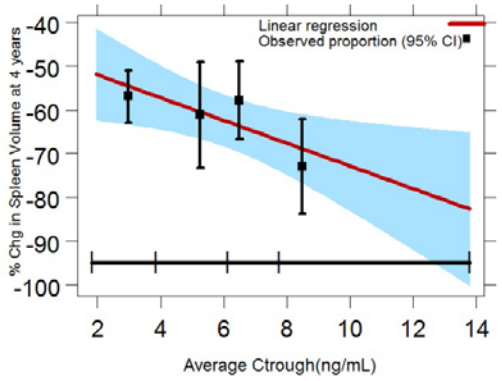
D Percentage Change in Platelet Count



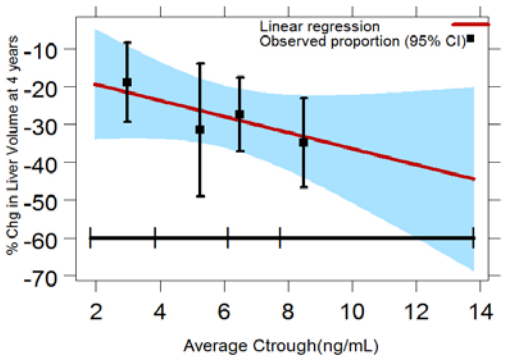
Placebo = -9.06%

Figure 1: The relationship for A) percentage change in spleen volume, B) percentage change in liver volume, C) change in hemoglobin and D) percentage change in platelet count from baseline after 39 weeks of treatment with steady state average trough concentration of the drug in ENGAGE (Phase 3) study. Solid black symbols represent the observed mean value in each C_{trough} quartile. The black bars represent the 95% confidence interval of the mean. The solid red line represents the mean linear regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Average C_{trough} represents the average of weeks 13, 26 and 39. The response in the placebo arm of the study is also shown.

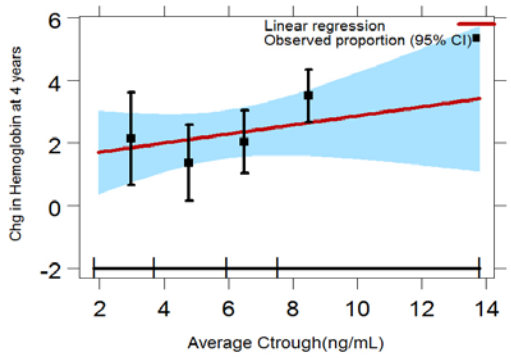
A Percentage Change in Spleen Volume



B Percentage Change in Liver Volume



C Change in Hemoglobin



D Percentage Change in Platelet Count

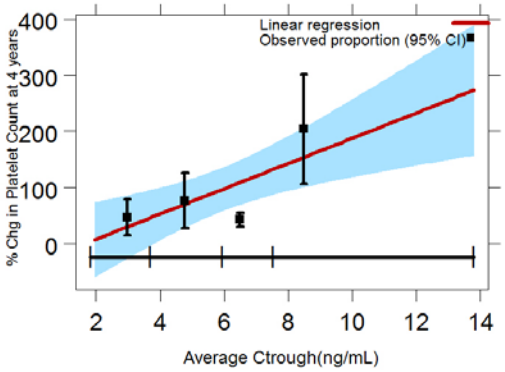
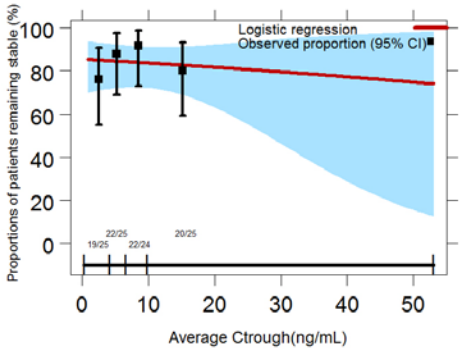
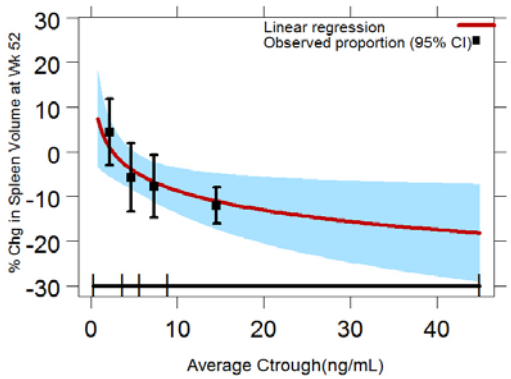


Figure 2: The relationship for A) percentage change in spleen volume, B) percentage change in liver volume, C) change in hemoglobin and D) percentage change in platelet count from baseline after 4 years of treatment with steady state average trough concentration of the drug in GZGD00304 study. Solid black symbols represent the observed mean value in each C_{trough} quartile. The black bars represent the 95% confidence interval of the mean. The solid red line represents the mean linear regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Average C_{trough} represents average of multiple trough measurements from day 30 to month 48.

A Primary Composite Endpoint- Proportion of patients remaining stable at week 52



B Percentage Change in Spleen Volume



C Stability – Spleen volume

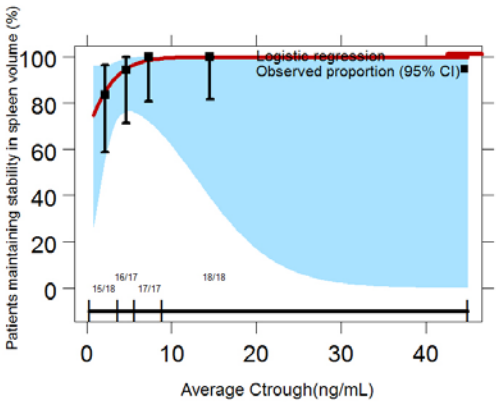
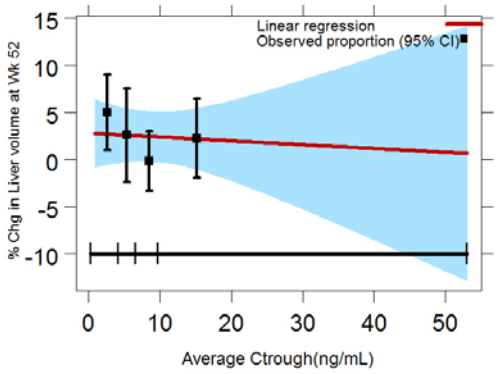


Figure 3: The relationship for A) proportion of patients remaining stable, B) percentage change in spleen volume from baseline and C) proportion of patients remaining stable with respect to spleen volume after 52 weeks of treatment with steady state average trough concentration of the drug in ENCORE (Phase 3) study. Solid black symbols represent the observed mean value in each C_{trough} quartile. The black bars represent the 95% confidence interval of the mean. The solid red line represents the mean logistic (A and C) and linear (B) regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Average C_{trough} represents the average of weeks 13, 26, 39 and 52.

Table 1: Percentage change in spleen volume from baseline, spleen volume at baseline and at week 52 by mean steady state trough concentration quartiles

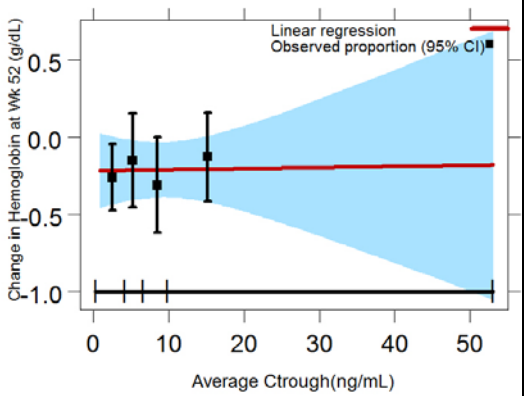
Concentration quartile	Median Ctrough (ng/ml)	N	Baseline spleen volume (MN)	Spleen volume at week 52 (MN)	Percentage change in spleen volume at week 52 (%)
0.31 to 3.6	2.1	18	2.9	3.1	4.4
3.6 to 5.6	4.6	17	3.3	3.1	-5.8
5.6 to 8.8	7.3	17	3.2	3.1	-7.8
8.8 to 44.9	14.5	18	3.3	3.0	-12.1

A Percentage Change in Liver Volume



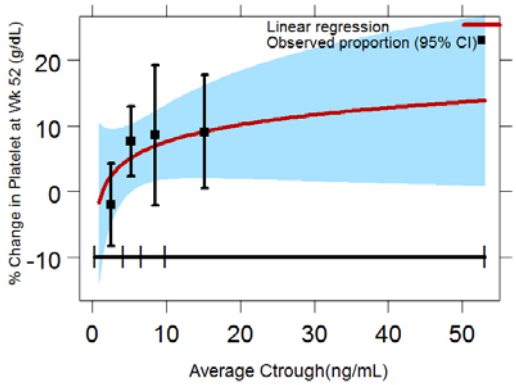
N=97

B Change in Hemoglobin



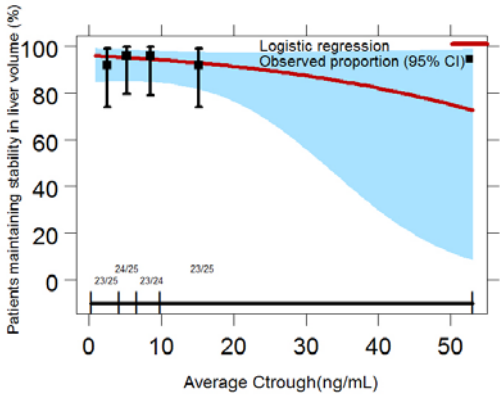
N=99

C Percentage Change in Platelet Count



N=99

D Stability – Platelet Count



N=99

Figure 4: The relationship for A) percentage change in liver volume, B) change in hemoglobin, C) percentage change in platelet count from baseline and D) proportion of patients remaining stable with respect to liver volume after 52 weeks of treatment with steady state average trough concentration of the drug in ENCORE (Phase 3) study. Solid black symbols represent the observed mean value in each C_{trough} quartile. The black bars represent the 95% confidence interval of the mean. The solid red line represents the mean linear (A, B, C) and logistic (D) regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Average C_{trough} represents the average of weeks 13, 26, 39 and 52.

Table 2: Percentage change in platelet count from baseline, platelet count at baseline and at week 52 by mean steady state trough concentration quartiles

Concentration quartile	Median Ctrough (ng/ml)	N	Baseline platelet count (10^9/L)	Platelet count at week 52 (10^9/L)	Percentage change in platelet count at week 52 (%)
0.31 to 4.1	2.5	25	187	181	-2.0
4.1 to 6.5	5.2	25	205	219	7.6
6.5 to 9.8	8.5	24	217	231	8.6
9.8 to 53	15.2	25	214	231	9.1

1.1.2 Is measuring drug concentrations and maintaining patients above 5 ng/ml critical for treatment?

No, a 5 ng/ml concentration threshold may not be necessary for successful treatment. While sample sizes are limited, treatment naïve patients in study GZGD00304 with drug concentrations lower than 5 ng/ml showed clinically meaningful effects with respect to changes in spleen volume, liver volume and hemoglobin level.

For subjects with drug concentrations lower than 5 ng/ml, the spleen volume decreased from 12.3 MN at baseline to 5.3 MN after 4 years of treatment (Table 3). For subjects with drug concentrations greater than 5 ng/ml, the spleen volume decreased from 20.5 MN at baseline to 6.6 MN. The spleen volumes were comparable after 4 years. Figure 5 shows the average steady state concentration achieved by individual patients in the study. As shown, 7 out of 18 subjects had concentrations lower than 5 ng/ml with lowest concentration lower than 2 ng/ml.

For subjects with drug concentrations lower and greater than 5 ng/ml, the liver volume was 1.1 MN and 1.2 MN respectively after 4 years of treatment. The hemoglobin levels in the two groups were 13.5 and 13.6 g/dL. Based on discussions with the clinical reviewer, the changes in spleen volume, liver volume and hemoglobin levels in the lower concentration group were considered meaningful and comparable to the values observed

with long term treatment with enzyme replacement therapy. [1] According to Pastores et. al. a long term (3-4 years) therapeutic goal for treatment of GD1 should be to reduce and maintain spleen volume to ≤ 2 to 8 times normal. While the platelet count did not achieve normal levels and were lower in the <5 ng/ml group ($106x10^9$/L) compared to >=5 ng/mL group ($139x10^9$/L), the value in the lower concentration group were above the threshold of clinical concern. Based on Pastores et. al. 2004, spontaneous bleeding is rarely observed in patients with Gaucher disease when the platelet count exceeds $30x10^9$/L.

The sponsor conducted similar analysis in extensive metabolizers who were treated at the 100 mg BID dose in GZGD00304 study. The analysis showed that patients with drug concentration lower that 5 ng/ showed clinically meaningful response and spleen volume, liver volume, hemoglobin level and platelet count achieved similar levels in both low (<5 ng/ml) and high (>=5 ng/ml) concentration groups after 4 years of treatment (Figure 6).

[1] Pastores GM, Weinreb NJ, Aerts H et al., Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004 Oct;41(4 Suppl 5):4-14.

Table 3: Mean Changes from Baseline in the GZGD00304 Study, by Average Plasma Steady State Trough Concentration Levels.

Concentration Group	N	Baseline Value	Value at 4 years	Percentage change /change at 4 years
Spleen volume (MN)				
<5 ng/mL	7	12.3	5.3	-57 %
>=5 ng/mL	11	20.5	6.6	-66 %
Liver volume (MN)				
<5 ng/ml	7	1.4	1.1	-22 %
>=5 ng/ml	11	1.9	1.2	-32 %
Platelet count (10^9/L)				
<5 ng/ml	8	70	106	53%
>=5 ng/ml	11	68	140	126%
Hemoglobin (g/dL)				
<5 ng/ml	8	11.6	13.5	1.9
>=5 ng/ml	11	11.1	13.6	2.5

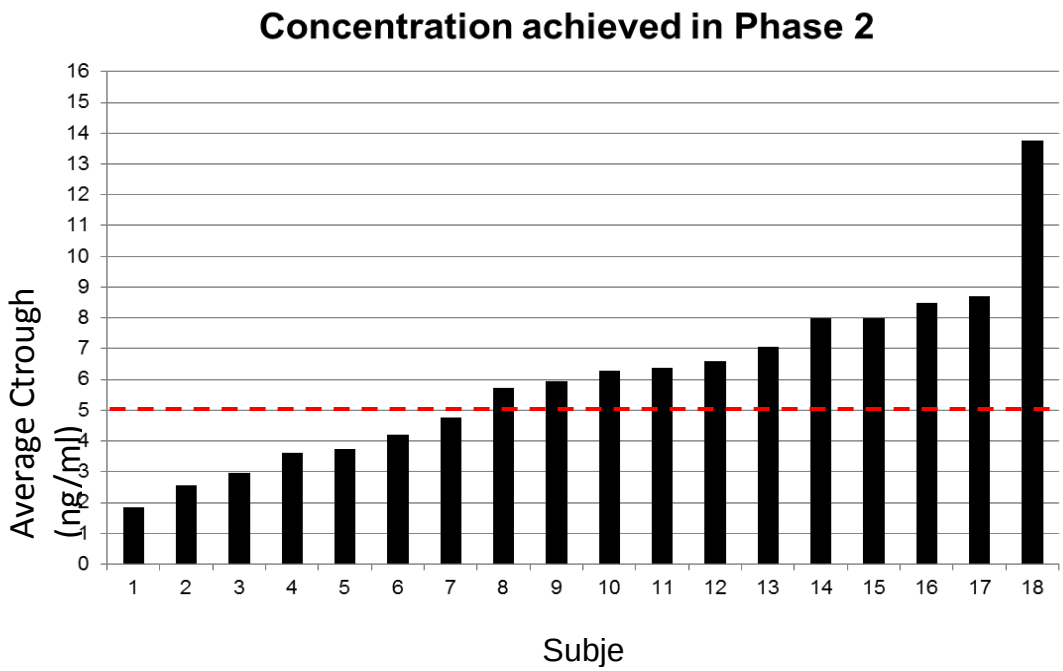
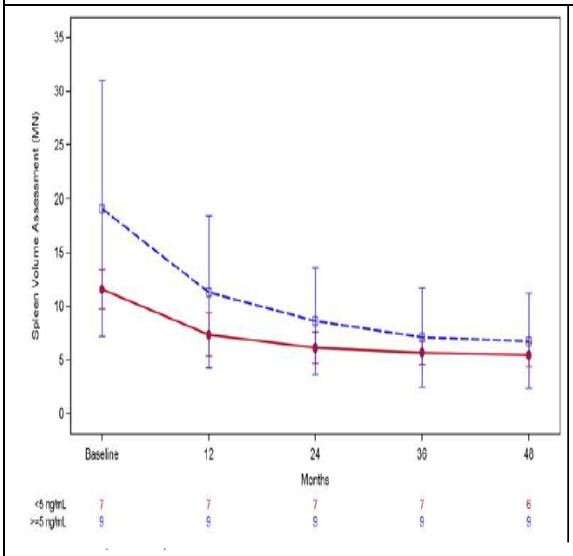
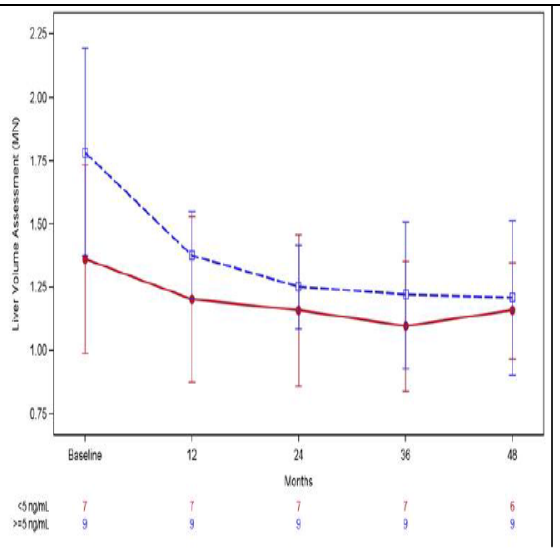


Figure 5: Average steady state concentration achieved by individual subjects in GZGD00304 study

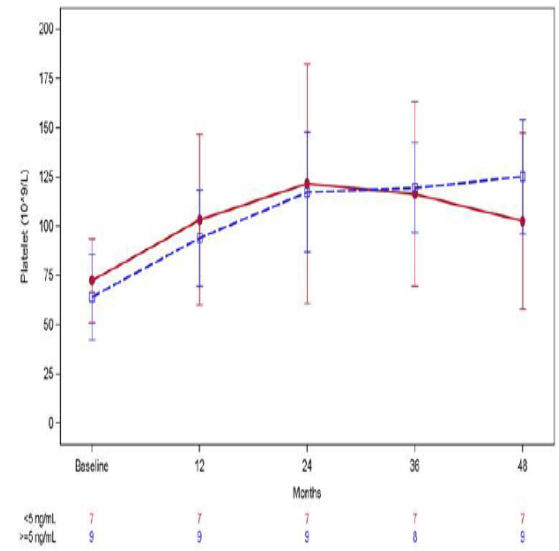
A Spleen Volume



B Liver Volume



C Platelet Count



D Hemoglobin

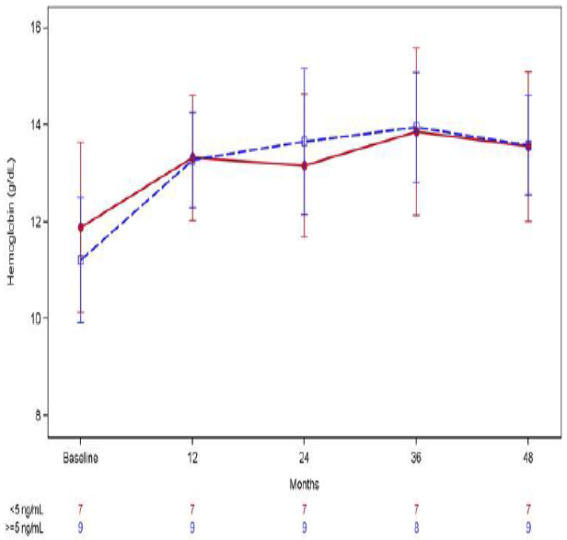


Figure 6: Time-profiles for A) spleen volume, B) liver volume, C) platelet count and D) hemoglobin after 4 years of treatment with eliglustat in Phase 2 study by average plasma steady state trough concentration levels for extensive metabolizers receiving 100 mg BID. Red and blue lines represents patients with concentrations < 5 ng/ml and ≥ 5 ng/ml respectively. Source Data: Figure 1 of sponsor's eliglustat background meeting package (SDN21)

1.1.3 Is there exposure-response relationship for safety?

QT Prolongation: There was a concentration dependent increase in QTc. The relationship between eliglustat concentrations and ΔΔ QTcF is visualized in Figure 6. An increase in ΔΔ QTcF is observed with increasing drug concentration (QT-IRT Review). The mean (upper 90% CI) predicted ΔΔQTcF at the mean Cmax of 16.7 ng/ml and 237 ng/ml for the 200 mg and 800 mg doses achieved in the QT study are 0.18 (1.7) ms and 6.06 (8.9) ms (Table 4). For a Cmax of 250 ng/ml, the mean (upper 90% CI) of ΔΔQTcF are predicted to be 6.4 (9.4) ms (Table 5). Thus based on the concentration-QT relationship, there appears to be no QT related safety concerns for drug concentrations below 250 ng/ml.

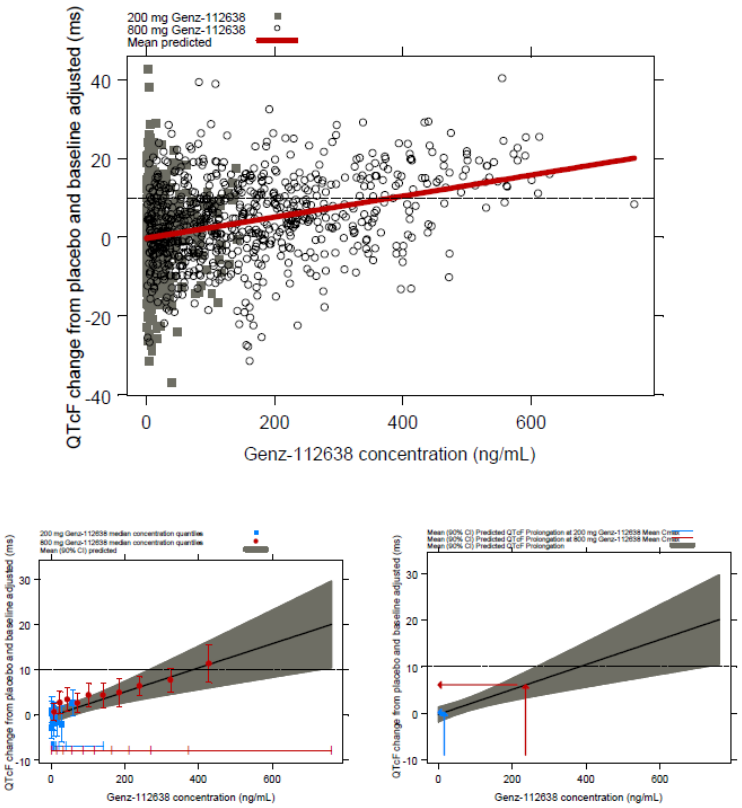


Figure 7: ΔΔ QTcF vs. Eliglustat concentration. Top panel -The circles represent the raw data and the red line represents the population prediction mean ΔΔ QTcF. Bottom Left-Concentration Quantile plot. The concentration range in each quantile is denoted by the horizontal blue and red lines for the 200 mg and 800 mg dose levels. The blue and red symbols represent the mean (90 % CI) of ΔΔ QTcF in each quantile. The population predicted ΔΔ QTcF (mean and 90% CI) is shown with the black line and shaded grey area. Bottom Left - Predicted ΔΔ QTcF at geometric mean Cmax of the two dose levels. Source: QT-IRT review

Table 4: Predicted Change of ΔΔQTcF Interval at Geometric Mean Cmax of Eliglustat observed in the QT study

Dose Group	Predicted change in ΔΔ QTcF interval (ms)	
	Mean	90% Confidence Interval
200 mg Genz-112638		
Geometric Mean C_{max} (16.7 ng/mL)	0.176	(-1.35; 1.7)
800 mg Genz-112638		
Geometric Mean C_{max} (237 ng/mL)	6.06	(3.24; 8.88)

Source: QT-IRT Review

Table 5: Predicted QT prolongation at the steady state Mean Cmax of 250 ng/ml

Predicted mean (90%CI, ms) change in	At mean Cmax of 250 ng/mL
QTcF	**6.4 (3.4, 9.4)**
PR	**11.2 (8.9, 13.4)**
QRS	**3.5 (1.9, 5.1)**

Source: QT-IRT Review

Other adverse events:

E-R analysis was performed on all adverse events listed in the ISS dataset. An E-R relationship was identified for moderate and severe nervous system disorders in pooled data from Phase 3 studies (ENGAGE and ENCORE). The proportion of patients experiencing moderate and severe nervous system disorders increased with increasing $AUC_{0\text{-}tau}$ and Cmax (Figure 8). This relationship was primarily driven by patients experiencing headaches. There was an increase in the proportion of patients experiencing moderate and severe headaches with increasing exposure (Figure 9). The exposure range for each quartile of eliglustat $AUC_{0\text{-}tau}$ and Cmax values are shown in Table 6. Similar results were obtained when steady state C_{trough} was used as the exposure metric.

Other adverse events may have had a significant slope, but did not appear to exhibit a clinically meaningful relationship within the observed eliglustat exposures, or consistent relationship across severity of the event, or consistent relationship across PK parameters, or had too few occurrences to consider the relationship meaningful.

E-R relationships were also evaluated for GI related adverse events (Figure 10). There appears to be a slight increase in the proportion of patients with moderate and severe GI related AEs in the fourth quartile (11/30) compared to the rest (6/30, 7/29, 4/29 in 1st, 2nd

and 3rd quartile). Based on discussions with the clinical team, these GI related AEs were not considered to be clinically significant.

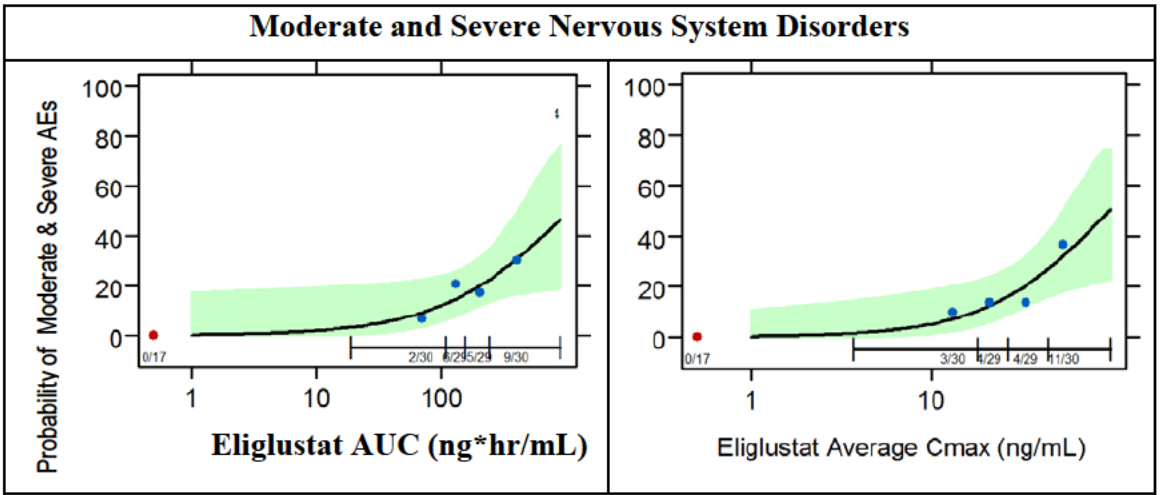


Figure 8. ResponseE-R relationship for moderate and severe nervous system disorders by AUC (left panel) and Cmax (right panel). The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and eliglustat data simultaneously, assuming placebo concentrations of eliglustat were zero. Data points are the probability for the placebo (red) and eliglustat (blue). Exposure bins are denoted by the bars at the bottom of the plot.

Table 6: Average Steady-State PK Parameter Range for each Exposure Quartile in the Exposure-Response Analysis for Safety Events.

PK Parameter	Q1	Q2	Q3	Q4
Average SS AUC (ng*hr/mL)	19 - 113	113 - 176	176 - 297	297 - 906
Average SS Cmax (ng/mL)	3.71 - 18.4	18.4 - 31.2	31.2 - 48.9	48.9 - 99.8

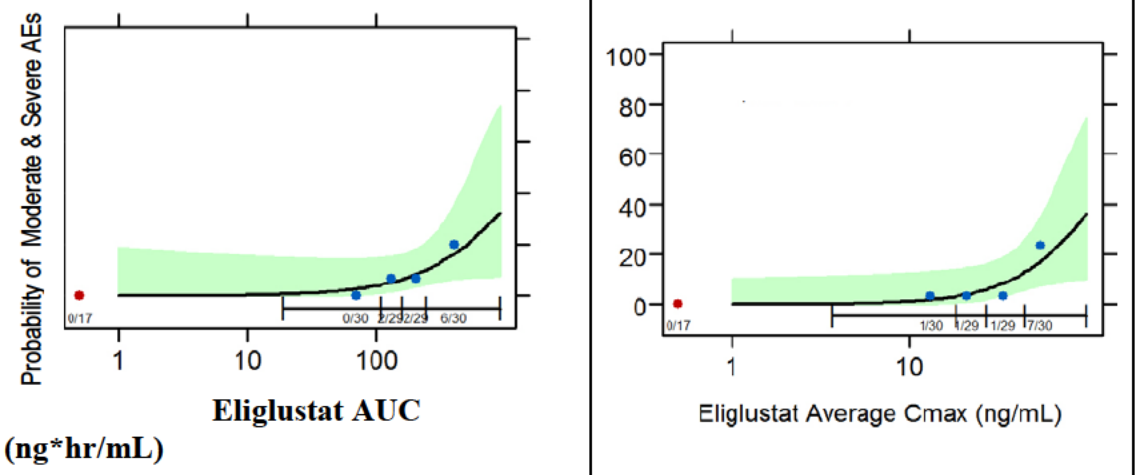


Figure 9. E-R relationship for moderate and severe headaches by AUC (left panel) and Cmax (right panel). The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and eliglustat data simultaneously, assuming placebo concentrations of eliglustat were zero. Data points are the probability for the placebo (red) and eliglustat (blue). Exposure bins are denoted by the bars at the bottom of the plot.

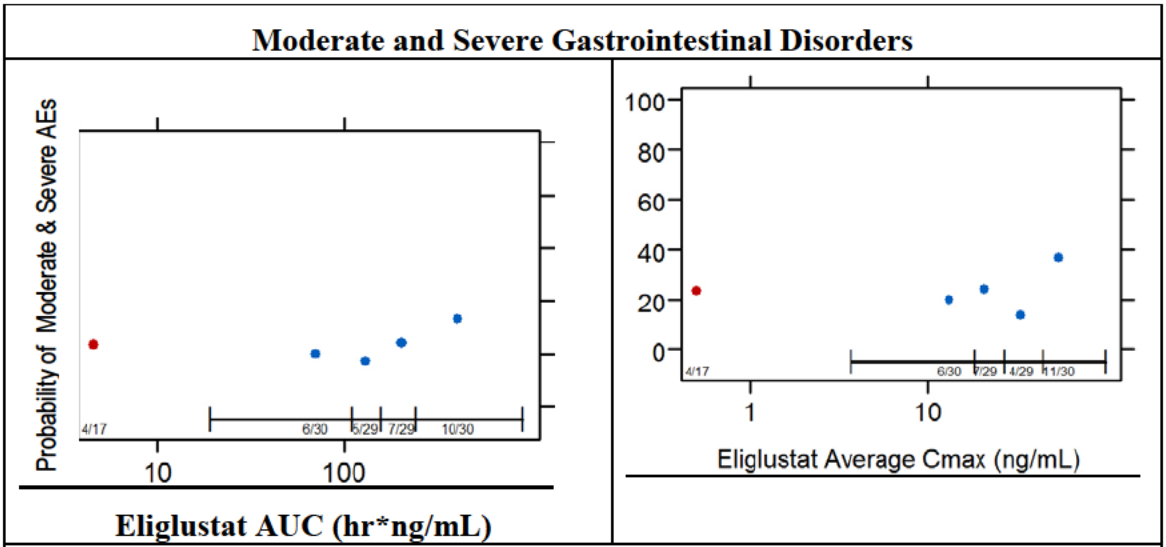


Figure 10 E-R relationship for moderate and severe gastrointestinal disorders by AUC (left panel) and Cmax (right panel). Data points are the probability for the placebo (red) and eliglustat (blue). Exposure bins are denoted by the bars at the bottom of the plot.

1.1.4 Is the proposed dose of 100 mg BID in intermediate and extensive metabolizers appropriate? What would be an appropriate dosing recommendation/ labeling for CYP2D6 poor and ultra-rapid metabolizers?

The sponsor proposed fixed dosing regimen of 100 mg BID for EMs or IMs without measuring drug concentrations is acceptable. For the purpose of labeling in the current review cycle,reviewers agree to sponsor's proposal of not indicating eliglustat for URMs. (b) (4) based on the PBPK simulations, observed PK data, exposure-response for efficacy and safety, the reviewer proposes a 100 mg QD dose for PMs.

A titration based dosing scheme was employed by the sponsor in Phase 2 and Phase 3 studies (See section 2.3.1 of the Clinical Pharmacology Review). This algorithm was employed in order to maintain plasma concentrations of 6 to 14 ng/mL (section 8.4.4 of sponsor's Phase 2 (gzgd00304) CSR). This was considered a reasonable exposure for achieving efficacy. However, because of genetic polymorphisms in the elimination pathway of eliglustat, variability in plasma levels was expected. By initially dosing all patients with 50 mg BID, patients who are poor metabolizers of eliglustat were not expected to have plasma levels above 150 ng/mL, the concentration that was associated with gastrointestinal AEs in the Phase 1b study according to the sponsor. In Phase 1b study, in all cases where subjects experienced Grade 2 gastrointestinal AEs, the maximum observed plasma concentration (Cmax). of eliglustat on Day 1 was greater than 100 ng/mL, and exceeded 150 ng/mL by Day 12. (section 8.4.4 of sponsor's Phase 2 (gzgd00304) CSR) The distribution of patients by various dose and CYP2D6 phenotype status in Phase 2, ENGAGE and ENCORE studies are shown in Table 7, Table 8, and Table 9 respectively. Among the extensive metabolizers in the treatment naïve population, the majority were at a stable dose of 100 mg BID (18/25 in Phase 2; 16/18 in ENGAGE); remaining at lower dose of 50 mg BID or 50 md QD. There was only one intermediate metabolizer in the ENGAGE and was treated at 50mg BID. In the switched study (ENCORE), the number of extensive metabolizers at the 50 mg BID, 100 mg BID and 150 mg BID doses were 10, 31 and 42. The number of intermediate metabolizers at the 50 mg BID, 100 mg BID and 150 mg BID doses were 7, 4 and 1. While a titration based dosing scheme was implemented in Phase 2 and Phase 3 studies, the sponsor's proposed dose is a fixed dose of 100 mg BID in intermediate and extensive metabolizers. Thus greater than 50% of IMs and EMs in ENCORE were at dose levels lower and higher compared to sponsor's proposed dose. No dosing recommendation is provided for (b) (4) ultra-rapid metabolizers in the current label.

Table 7: Distribution of patients by CYP2D6 phenotype status and dose in Phase 2 study

CYP2D6 phenotype	**50 mg QD (N=2)**	**50 mg BID (N=6)**	**100 mg BID (N=18)**
PM		1	
EM	2	5	18

Table 8: Distribution of patients by CYP2D6 phenotype status and dose in ENGAGE

CYP2D6 phenotype	**50 mg BID (N=3)**	**100 mg BID (N=17)**
IM	1	
EM	2	16
URM		1

Table 9: Distribution of patients by CYP2D6 phenotype status and dose in ENCORE

CYP2D6 phenotype	**50 mg BID (N=21)**	**100 mg BID (N=35)**	**150 mg BID (N=49)**
PM	4	0	0
IM	7	4	1
EM	10	31	42
URM	0	0	4
Indeterminate	0	0	2

Extensive and Intermediate Metabolizers:

Based on the efficacy, safety and pharmacokinetic findings and E-R relationship for efficacy and safety from Phase 2, ENGAGE and ENCORE studies, the 100 mg BID dose appears reasonable for IMs and EMs.

There is a trend for increase in efficacy parameters with increasing drug concentrations in Phase2 and ENGAGE study (section 1.1.1). While an E-R relationship was identified, a subgroup analysis suggested that treatment naïve patients in the Phase 2 study with drug concentrations lower than 5 ng/ml showed clinically meaningful effects with respect to efficacy parameters and 5 ng/ml concentration threshold may not be necessary for successful treatment (section 1.1.2). The Phase 2 and ENGAGE study comprised of treatment naïve subjects that had a higher disease burden compared to subjects in ENCORE who were stabilized on enzyme replacement therapy as evidenced by higher spleen volumes at baseline (Table 10). The patients in ENGAGE and Phase 2 study were treated successfully at doses of 100 mg BID or lower. Thus from an efficacy perspective, 100 mg BID appears to be reasonable for extensive and intermediate metabolizers.

Based on discussion with the clinical team, no major safety concerns have been identified for eliglustat. Exposure-response relationships were evaluated for adverse events based on system organ class and MEDRA preferred term. No meaningful ER relationship was observed except for nervous system disorders and this was primarily driven by

headaches. Overall the incidence rates of AEs were low. An increase in QT prolongation was observed with increasing drug concentration. For a Cmax of 250 ng/ml, the mean (upper 90% CI) of ΔΔQTcF are predicted to be 6.4 (9.4) ms, which is below the regulatory threshold. Thus based on the concentration-QT relationship, there appears to be no QT related safety concerns for drug concentrations below 250 ng/ml (section 1.1.3).

The mean Cmax predicted by PBPK simulations in intermediate and extensive metabolizers at the 100 mg BID dose are 63 ng/ml and 25 ng/ml; which are below the threshold for QT concerns (Table 11). For details regarding the PBPK simulations, see Dr. Ping Zhao's PBPK review. The mean predicted AUC 0-12 values for intermediate and extensive metabolizers at the 100 mg BID dose are 527 ng/mL*h and 185 ng/mL*h respectively. The observed AUC 0-12h values for intermediate and extensive metabolizers at the 100 mg BID dose in ENCORE study are 400 and 201 ng*/ml*hr (Table 12). The AUC values for EMs in ENGAGE and Phase 2 were lower than the observed value in ENCORE (see Section 2.3.5.1.1.2 of the Clinical Pharmacology Review). The PBPK model appears to over-predict the exposure for IMs and EMs. Thus, the exposure in IMs and EMs upon administration of a fixed dose of 100 mg BID are likely to fall within the predicted (527 ng/mL*h for IMs, 185ng/mL*h for EMs) and observed values (400 ng/mL*h for IMs, 201 ng/mL*h for EMs). Using a conservative approach, a higher exposure as predicted by the model is used to draw inferences on the likely impact on safety. Figure 11 shows the observed $AUC_{0\text{-}12h}$ in all patients in Phase 2, ENGAGE and ENCORE studies by CYP2D6 status dose. The graph also includes subject with $AUC_{0\text{-}12}$>400 ng/mL*h from the EDGE study. Overall the predicted exposures in IMs and EMs at the 100 mg BID dose falls within the exposures observed in the studies; although data is limited at high exposures. There are 8 and 24 patients (Figure 12) who had AUC0-12 > 527 ng/mL*h and AUC0-12 > 400 ng/mL*h respectively. This limited clinical experience at high exposures ($AUC_{0\text{-}12h}$> 400 ng/ml*hr) needs to be put in context of GD1 being a rare disease with an incidence of 1 in 100,000 live births in general population. Based on National Organization of Rare Disease, there are likely to be ~5700 GD1 patients in USA. There are likely to be ~490 IM patients based on 8.6% IM patients of the whole patient population as observed in the trials which is consistent with the known distribution as reported in literature (Hicks et. al. 2013, Clinical Pharmacology and Therapeutics 93(5):402-8).

In summary, given the lack of safety concerns with eliglustat, no meaningful exposure response relationship for safety, and that exposures in IMs and EMs at 100 mg BID are expected to fall within the exposures achieved in Phase 2 and Phase 3 studies, the 100 mg BID dose appears reasonable.

Table 10: Baseline spleen volume in treatment arm in Phase2, ENGAGE and ENCORE

Study	**N**	**Baseline Spleen Volume (MN) Mean (SD)**
Phase 2	26	20.0 (12.8)
ENGAGE	20	13.9 (5.9)
ENCORE	99	3.23 (1.37)

Table 11: Predicted eliglustat exposure (Mean (90% CI)) in intermediate and extensive metabolizers at 100 mg BID dose by PBPK

CYP2D6 status	**Cmax (ng/mL)**	**AUC_{tau} (ng/mL h) 0-12h for b.i.d.**
Extensive Metabolizer	25 (22.5, 27)	185 (166, 203)
Intermediate Metabolizer	63 (58, 67)	527 (484, 570)

Values are mean from simulation of ten trials with 36 subjects/trial. For details see PBPK review

Table 12: Observed eliglustat exposure (Mean (90%CI) for EMs and Mean (range) for IMs) in ENCORE study at Week 52

Dose	**CYP2D6 status**	**N**	**Cmax (ng/mL)**	**AUC_{tau} (ng/mL h) 0-12h for b.i.d.**
100 mg BID	Extensive Metabolizer	30	35 (29, 41)	201 (166, 236)
100 mg BID	Intermediate Metabolizer	4	58.7 (40, 108)	400 (248, 830)
Source: Table 12-1, 12-4 and 12-5 of clinical study report. For details see section 2.3.5.1.12 of the Clinical Pharmacology Review				

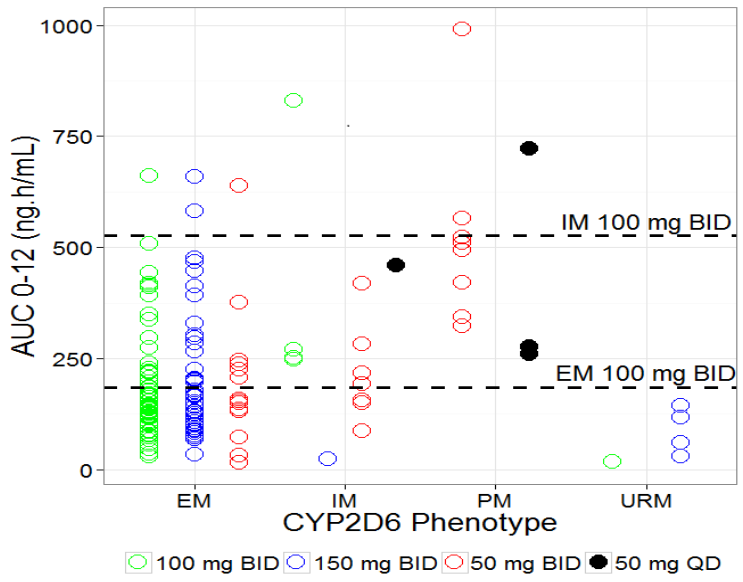


Figure 11. Observed exposure (AUC_{0-12}) in individual patients by CYP2D6 phenotype status. The horizontal lines represent the mean predicted exposure by PBPK simulation for intermediate and extensive metabolizers at 100 mg BID dose. For patients at 50 mg QD, the AUC_{0-12} is approximately calculated at $AUC_{0-24}/2$.

Poor and Ultra-rapid Metabolizers:

Based on the efficacy, safety, and pharmacokinetic findings and E-R relationship for efficacy and safety, a 100 mg QD dose is recommended for poor metabolizers. For the purpose of labeling in the current review cycle, use of eliglustat in URMs is not indicated.

Based on PBPK simulations, the predicted Cmax in poor metabolizers at 100 mg QD dose is 75ng/ml which is significantly below 250 ng/ml and is likely not to result in any QT related safety concerns (Table 13). For details regarding the PBPK simulations, see Dr. Ping Zhao's PBPK review. The predicted AUC0-24 is 956 ng/ml*h (Table 13) which is similar to the predicted AUC0-24 of 1054 ng/ml*h (AUC_{0-24}= AUC_{0-24}x2=527x2; Table 11) for intermediate metabolizers at the 100 mg BID dose. As stated above, these exposures are within the exposures that were achieved in Phase 2 and Phase 3 studies. Additionally, 4 PM patients in ENCORE at the 50 mg BID dose and similar exposures (AUC0-24) are likely to be achieved under the 100 mg QD regimen based on linear PK (Table 14). Dosing recommendation is not being provided for ultra-rapid metabolizers (URMs) because even with a high dose of 200 mg BID, the AUC values are ~50% and ~82% lower than the values for extensive and intermediate metabolizers at the 100 mg BID dose respectively. While with doses higher than 200 mg BID, it may be possible to match the exposure of the parent drug in URMs to the exposure in EMs at 100 mg BID, the effect of increased level of metabolites at the higher dose on safety is unknown.

Table 13: Predicted eliglustat exposure (Mean (90% CI)) in PMs and URMs by PBPK

Eliglustat	**CYP2D6 status**	**Cmax (ng/mL)**	**AUC_{tau} (ng/mL h) 0-12h for b.i.d. 0-24h for q.d.**
100 mg q.d.	**Poor Metabolizer**	75 [71, 79]	956 [884, 1028]
200 mg b.i.d.	**Ultra Rapid metabolizer**	14 (11,17)	97 (77,117)

PMs: Values are from simulation of ten trials with 36 subjects/trial. URMS: Values are from simulation of ten trials with 10 subjects/trial. For details see PBPK review.

Table 14: Observed eliglustat exposure (Mean(range)) in poor metabolizers in ENCORE

Eliglustat	**CYP2D6 status**	**Visit**	**N**	**Cmax (ng/mL)**	**AUC_{tau} (ng/mL h) 0-12h for b.i.d.**
50 mg b.i.d.	**Poor Metabolizer**	Week 52	4	78.5 (67, 136)	648 (565, 992)

1.2 Recommendations

Division of Pharmacometrics has reviewed NDA 205494 and finds the NDA acceptable provided an agreement regarding the label language and dosing regimen can be reached between the sponsor and the Agency.

- Division of Pharmacometrics recommends a daily dose of 100 mg for CYP2D6 poor metabolizers with Gaucher disease (GD1).
- The Division agrees with sponsor's proposed dose of 100 mg twice daily for intermediate and extensive metabolizers.
- The Division agrees to sponsor's proposal of not indicating eliglustat for ultra-rapid metabolizers in the current review cycle.

1.3 Label Statements

See section 3 of Clinical Pharmacology Review.

2 PERTINENT REGULATORY BACKGROUND

Eliglustat is considered a new molecular entity (NME). The proposed indication is long-term treatment of adult patients with Gaucher disease type 1 (GD1). Gaucher disease is a rare, autosomal recessive lysosomal storage disorder. The proposed dosing regimen is 100 mg BID for intermediate and extensive metabolizers. The End-of-Phase 2 PreNDA meeting was held on May 21, 2013.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK Analysis

Primary objective of sponsor's population PK analysis were:

1. To develop a population PK model for eliglustat to describe concentration-time data arising from Phase 1, Phase 2 and Phase 3 data.
2. To identify and quantify covariate which describe variability in the PK of eliglustat.
3. To evaluate the final population PK model using simulation techniques.

3.1.1 Methods

The data used for the population PK analysis is summarized in Table 15 which includes 10 phase 1 studies, 1 phase 2 study (GZGD00304) and 2 phase 3 (ENCORE and EDGE) studies. The proportion of EMs and IMs the dataset were 42.8% and 14.7% respectively (Table 16). 20 PMs were included in the analysis that constituted 3.88% of the dataset (Table 16). The model included data for all 26 patients in the Phase 2 study, 98 of 106 patients receiving eliglustat in the primary analysis period of ENCORE, and 80 of 170 patients (77 in the final model) in the Lead-in Period of EDGE. After excluding subjects without a known CYP2D6 phenotype, a total of 405 subjects with 12,234 concentrations were used to develop the final model.

Table 15: Data used for Sponsor's Population PK analysis

Study	Phase	N (Subjects)	N (Observations)	Dosing
GZGD00103	1	74	1258	0.01 to 30.0 mg/kg single oral dose
GZGD00204	1	24	1122	50, 200 or 350 mg multiple oral dose
GZGD00404	1	24	671	300 mg single oral dose on 2 occasions
GZGD01707	1	45	1868	200 and 800 mg single oral dose on 2 occasions
GZGD01807	1	36	1619	100 mg multiple oral dose
GZGD01907	1	24	1157	100 mg single oral dose on 4 occasions
GZGD02007	1	36	1737	100 mg multiple oral dose
GZGD02107	1	10	424	50 mg single IV dose and 100 mg multiple oral dose
GZGD02407	1	25	1541	100 or 150 mg multiple oral dose
GZGD02707	1	29	377	100 mg multiple oral dose
GZGD00304	2	26	1670	50 or 100 mg multiple oral dose
All Studies	1 and 2	353	13444	0.01 mg/kg to 800 mg

Study	Phase	N (Subjects)	N (Observations)	Dosing
GZGD00304*	2	26	1697	50, 100 or 150mg multiple oral dose
GZGD02607	3	98	1385	50, 100 or 150 mg multiple oral dose
GZGD03109	3	80	932	50, 100 or 150 mg multiple oral dose
All Studies	2 and 3	204	4014	50, 100 or 150 mg multiple oral dose

Source: Table1 and Table 26 from sponsor's population PK report

Table 16: Summary demographics for all studies in population PK model

Statistic	AGE (yr)	HT (cm)	WT (kg)	CRCL (mL/min)	BILI (µmol/L)	ALB (g/L)	ALT (U/L)	AST (U/L)	ALP (U/L)	Metabolizer Status	RACE	SEX
N 516		516	516	516	516	516	516	516	516	89 (17.2%) NR	337 (65.3%) Cauc.	305 (59.1%) M
Mean 30.6		170	72.4	121	12.5	43.9	21.9	23.8	66.5	20 (3.88%) PM	9 (1.74%) Am.Ind.	211 (40.9%) F
SD 11.8		9.97	13.8	25.7	6.08	3.52	11.5	7.63	21.7	76 (14.7%) IM	34 (6.59%) Asian	-
CV 38.6		5.85	19	21.3	48.4	8.02	52.6	32	32.6	46 (8.91%) IM-EM[a]	48 (9.3%) Af.Am.	-
Median 26		170	71.1	119	12	44	19	22	63	221 (42.8%) EM	7 (1.36%) Other	-
Min 18		128	40.7	47	0 33		7 12		17	50 (9.69%) EM-URM[a]	44 (8.53%) Jewish	-
Max 71		200	136	271	51	54	104	77	204	14 (2.71%) URM	37 (7.17%) Hisp.	-

Source: POH0373 Table 29

ALB=albumin; ALP=alkaline phosphatase; ALT=alanine aminotransferase; Af Am=African American; Am Ind=American Indian; AST=aspartate aminotransferase; BILI=bilirubin; Cauc=Caucasian; CRCL=creatinine clearance; CV=coefficient of variation; EM=extensive; EM-URM=extensive ultra-rapid; Hisp=Hispanic; HT=height; IM=intermediate; IM-EM=intermediate to extensive; F=female; M=Male; Max=maximum; Min=minimum; NR=not reported; P=poor; SD=standard deviation; URM=ultra-rapid; WT=weight

[a]: A small number of IM-EM and EM-URM patients were treated in the Phase 2 study (N=10 IM-EM and N=5 EM-URM) compared to the number of EM patients in the Phase 2 study and ENCORE

Source: Table 29 from sponsor's population PK report

3.1.2 Results

The best model to fit the dataset was a 2-compartment disposition model with an oral bioavailability fraction (F) followed by a sequential zero and first-order absorption process. The parameter estimates are shown in Table 17.

Table 17: Parameter Estimates from Sponsor's Population PK Model

Parameter (units)	Theta	Parameter Estimate (SE%)	BSV Estimate CV% (SE%)	BOV Estimate CV% (SE%)
F (CYP2D6 EM)	θ_1	0.0417 (9.7)	84.7 (11.4)	44.2 (7.8)
CYP2D6 PM on F	θ_2	18.8 (10.8)		
CYP2D6 IM on F	θ_3	3.3 (13.0)		
CYP2D6 IM to EM on F	θ_4	1.26 (15.9)		
CYP2D6 EM to UR	θ_5	1.15 (18.5)		
CYP2D6 UR on F	θ_6	0.434 (42.2)		
Chronic dosing on F (CYP2D6 PM)	θ_7	1.16 (4.1)		
Chronic dosing on F (not CYP2D6 PM)	θ_8	1.99 (3.4)		
800 mg dose on F (not CYP2D6 PM)	θ_9	4.07 (6.6)		
E_{max} for Paroxetine on F (CYP2D6 IM)	θ_{10}	3.1 (10.0)		
E_{max} for Paroxetine on F (not CYP2D6 PM or IM)	θ_{11}	7.17 (9.7)		
E_{t50} for Paroxetine on F (number of once-daily doses)	θ_{12}	0.567 (43.4)		
E_{max} for Ketoconazole on F	θ_{13}	3.49 (8.2)		
E_{t50} for Ketoconazole on F (number of once-daily doses)	θ_{14}	0.661 (13.8)		
Rifampin effect on F	θ_{15}	0.709 (4.0)		
D1 (hr)	θ_{16}	0.603 (5.0)	67.7 (9.5)	
800 mg dose on D1 (not CYP2D6 PM)	θ_{17}	2.35 (12.3)		
KA (/hr)	θ_{18}	0.438 (5.5)	23.2 (26.1)	
V_c (L)	θ_{19}	96.1 (11.6)	59.6 (16.4)	
Weight effect exponent on V_c	θ_{20}	0.91 (17.6)		
CL_{p1} (L/hr)	θ_{21}	52.5 (6.8)		
V_{p1} (L)	θ_{22}	272 (6.1)		
CL (L/hr)	θ_{23}	55.6 (7.6)	27.3 (14.2)	
E_{max} for Paroxetine on CL	θ_{24}	0.511 (5.7)		
E_{t50} for Paroxetine on CL (number of once-daily doses)	θ_{25}	1.67 (16.3)		
CYP2D6 Effect on D1	θ_{26}	-0.96 (9.2)		
Shape for distribution on RUV	θ_{27}	3.07 (22.4)		
Effect of CYP2D6 PM on CL	θ_{28}	0.703 (9.8)		
Effect of Healthy Volunteer Status on CL	θ_{29}	1.71 (5.0)		
Effect of Healthy Volunteer Status on V_c	θ_{30}	1.95 (8.9)		
RUV Healthy Subjects (CV%)		19.8 (5.8)	26.0 (17.5)	
RUV Patients (CV%)		29.7 (7.4)	26.0 (17.5)	

Source: Table 36 from the population PK report

Effect of Age, Gender, Race and Body Weight on PK

Based on population PK analysis there is no clinically relevant effect on age, gender, race and body weight on the PK of eliglustat. Thus no dose adjustment based on these factors is required. Population PK analysis comprised of 59% males and 41% females. The PopPK analysis included 65% Caucasians, 9% African-Americans, 9% Jewish, 7% Hispanics, 7% Asians, and 3% others. Population PK included body weights ranging from 41 to 136 kg.

Age, gender, body weight, and race were not identified as a covariate on clearance. Figure 12 shows that the inter-individual variability in clearance cannot be explained by these factors.

The central compartment (Vc) increased with body weight (Figure 14). In subsequent simulations of 3 typical EM patients receiving a 100 mg BID dose, over the range of body weight (40.7 [minimum], 71.1 [median] and 136 [maximum] kg), there was no impact on steady state AUC0-12 (i.e., values were the same for each of the 3 patients) and Cmax ranged from 26.2 to 20.0 ng/mL. Thus no dose adjustment based on body weight is required.

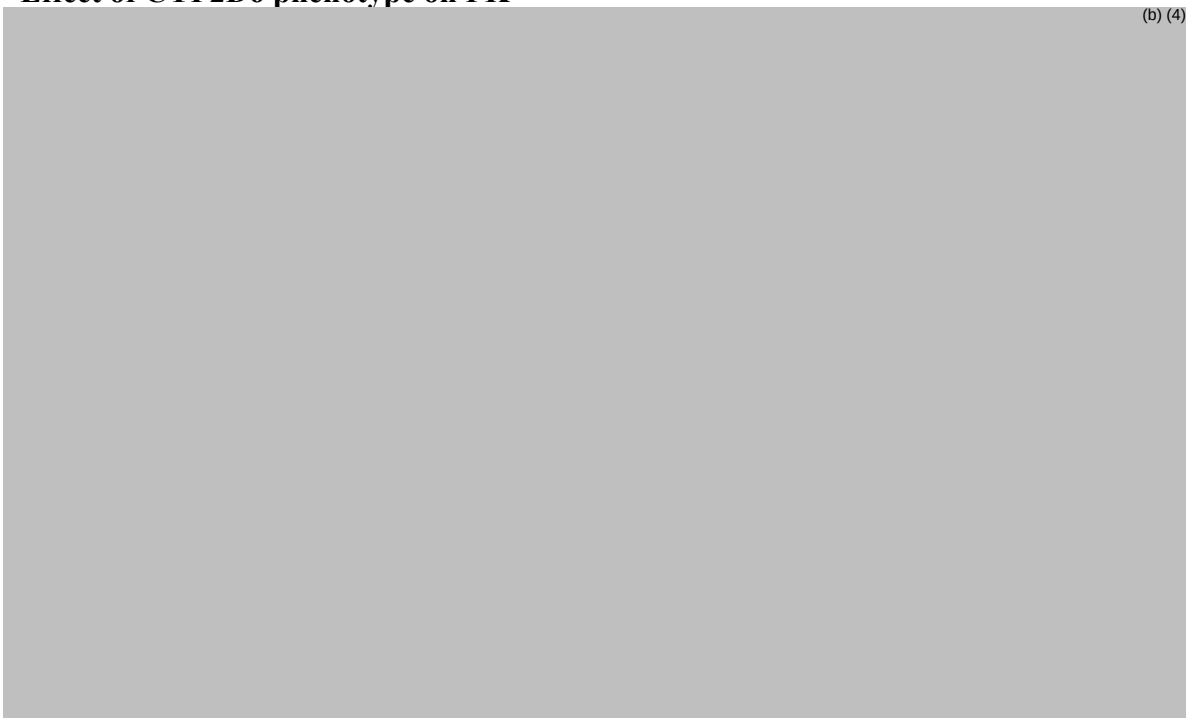
Effect of Creatinine Clearance on PK

Creatinine clearance was not identified as a covariate on clearance. Figure 12 shows that the inter-individual variability in clearance cannot be explained creatinine clearance. The lowest value of creatinine clearance included in the analysis was 47 mL/min. There were no subjects in the severe renal impairment category.

Effect of subject status (healthy versus GD1 patients) on PK

Subject status (healthy versus GD1 patients) was identified as a covariate on clearance and volume. CL and Vc were 1.95 and 1.71 times higher in healthy subjects than in patients (Table 17). Figure 10 shows the box plots for CL and Vc by subject status from the final model.

Effect of CYP2D6 phenotype on PK



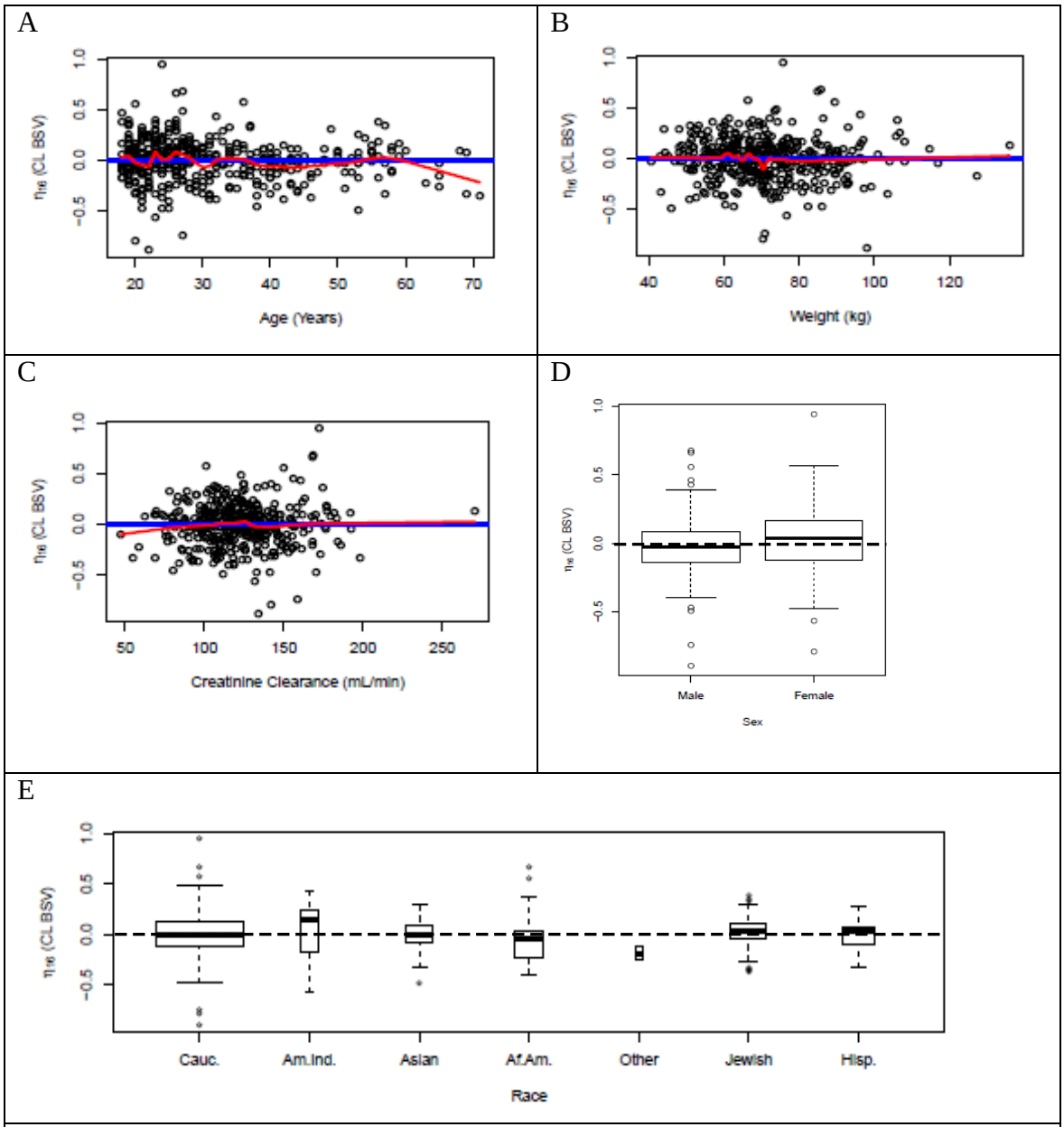


Figure 12: Inter-individual variability on clearance versus A) age, B) weight, C) creatinine clearance, D) gender and E) race on clearance. Source: Sponsor's Population PK report

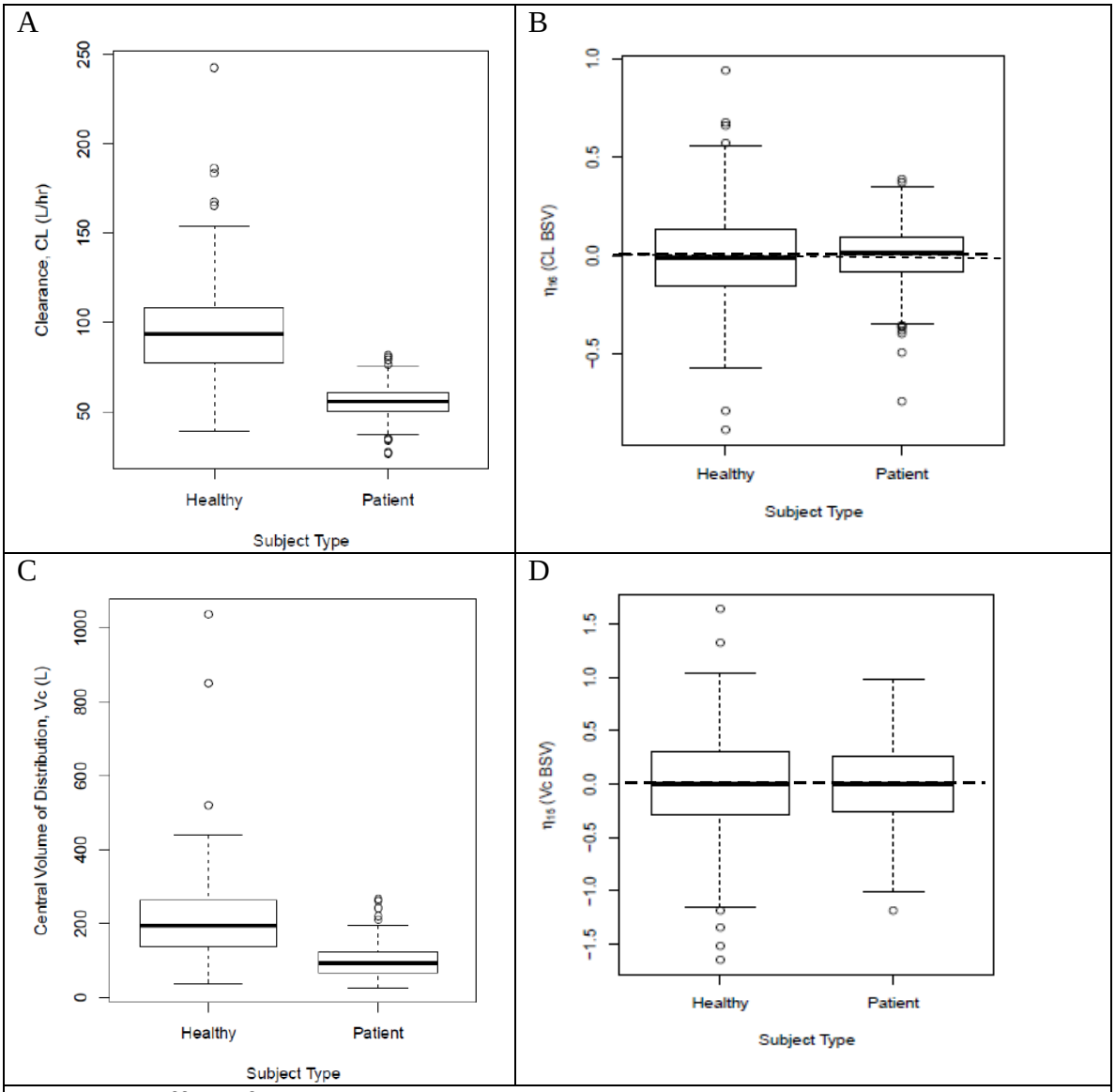


Figure 13: Effect of subject status (Healthy versus GD1 patients) on clearance and volume. A) Clearance, B) Inter-individual variability on CL C) Volume of distribution and D) Inter-individual variability on Vc versus subject status. Source: Sponsor's Population PK report

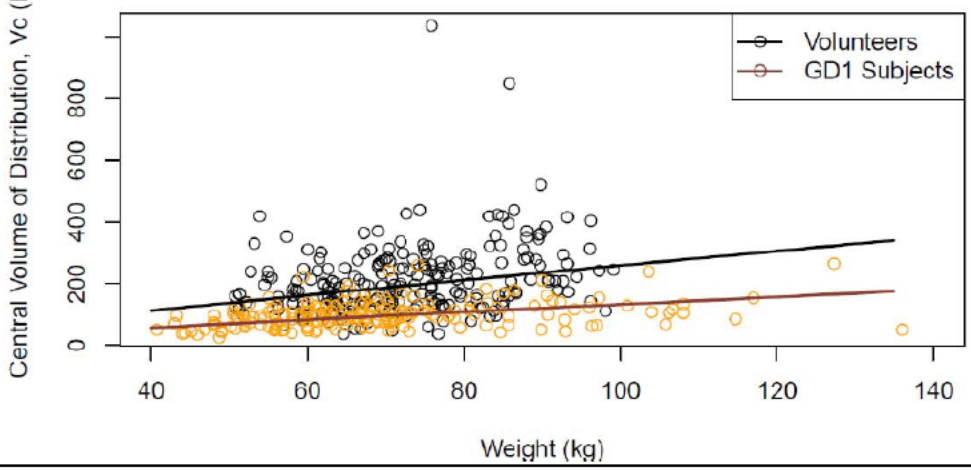


Figure 14: Effect of body weight on Vc. Source: Sponsor's Population PK report

Reviewer's comments on sponsor's population PK analysis:

- (b) (4) *The dosing recommendations in PMs were based on observed data and PBPK modeling. FDA reviewer did not attempt to refine the model that could adequately describe PK of PMs since observed data and PBPK model was deemed sufficient to make a regulatory decision regarding dosing in PMs. The population PK model predicted that at the 100 mg BID dose, there is a 2.8 fold and 2.7 fold increase in steady state $AUC_{0\text{-}12h}$ and C_{max} in IMs compared to EMs which is consistent with observed data.*

- *The reviewer agrees with sponsor's assessment that gender, body weight, age, and race had limited or no impact on the pharmacokinetics of eliglustat as these were not identified as covariates on drug clearance.*

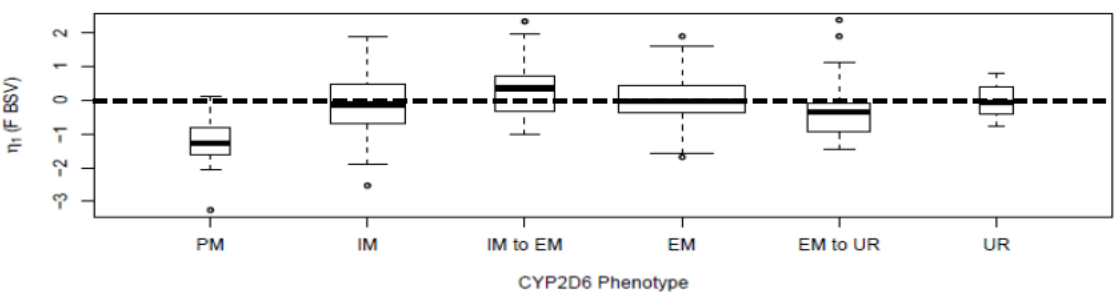


Figure 15: Inter-individual variability on F versus CYP2D6 Phenotype. Source: Figure 125 Sponsor's Population PK report

3.2 Exposure-Response Analysis for Effectiveness

The sponsor conducted exposure-response analysis for Phase 2 and Phase 3 studies.

3.2.1 Data

Data from ENGAGE, ENCORE and Phase 2 trials were utilized for sponsor's analysis.

3.2.2 Results

ENGAGE

"No statistically significant correlations were observed between Genz-99067 steady-state PK parameters (average Ctrough, Week 39 Cmax, and Week 39 AUC0-tau) and efficacy parameters, although visual examination suggested some trends with efficacy parameters showing improvement from Baseline to Week 39 (Figure 16). Evaluation of a larger dataset in a pooled analysis across clinical studies may elucidate these trends. While analyses stratified by average steadystate trough concentration (<5 ng/mL, ≥5 ng/mL) suggested that patients with higher average Ctrough may have better responses, these analyses are to be interpreted with caution given the considerable within- and between-patient variability in trough concentrations. On average, patients in both Ctrough strata improved relative to placebo group, and pronounced treatment responses were observed for "low Ctrough" individuals as well as "high Ctrough" individuals."
Source: Sponsor's CSR for 2507, section 13.1.4, page 215.

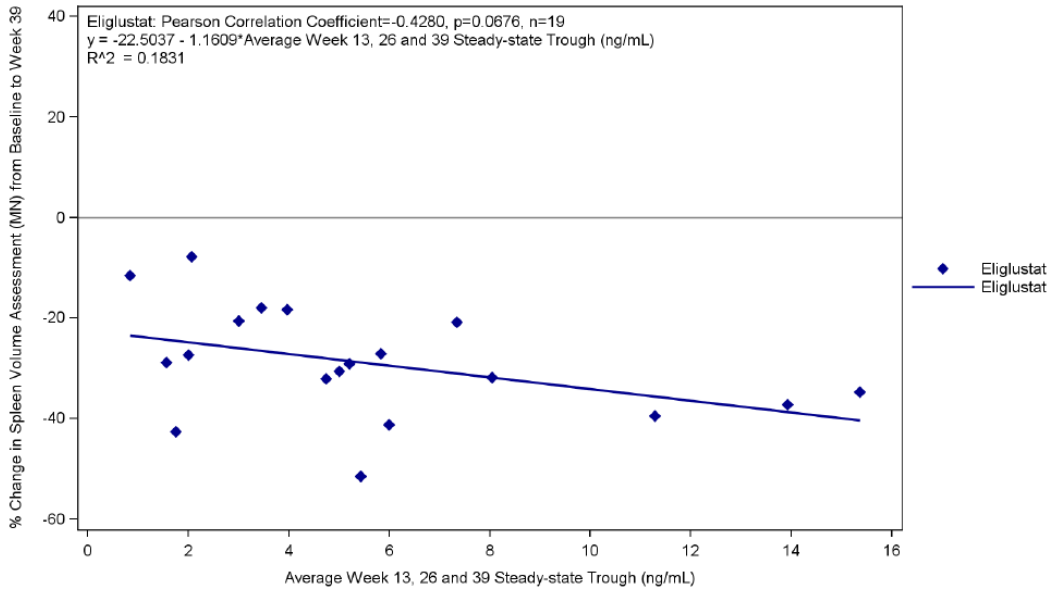
PHASE 2

Trends for increase in efficacy parameters with average steady state trough concentrations were observed (Figure 17). The relationship between Genz-99067 PK parameters at steady-state (Ctrough, Cmax, and AUC0-tau) and changes in hemoglobin, platelet count, spleen volume (MN and percent change) and liver volume (MN and percent change) was evaluated. Both percent and absolute changes in spleen were significantly correlated with all 3 PKparameters (i.e., eliglustat exposure). For details see sponsor's CSR for GZGD00304, section 12.1.6, page 203.

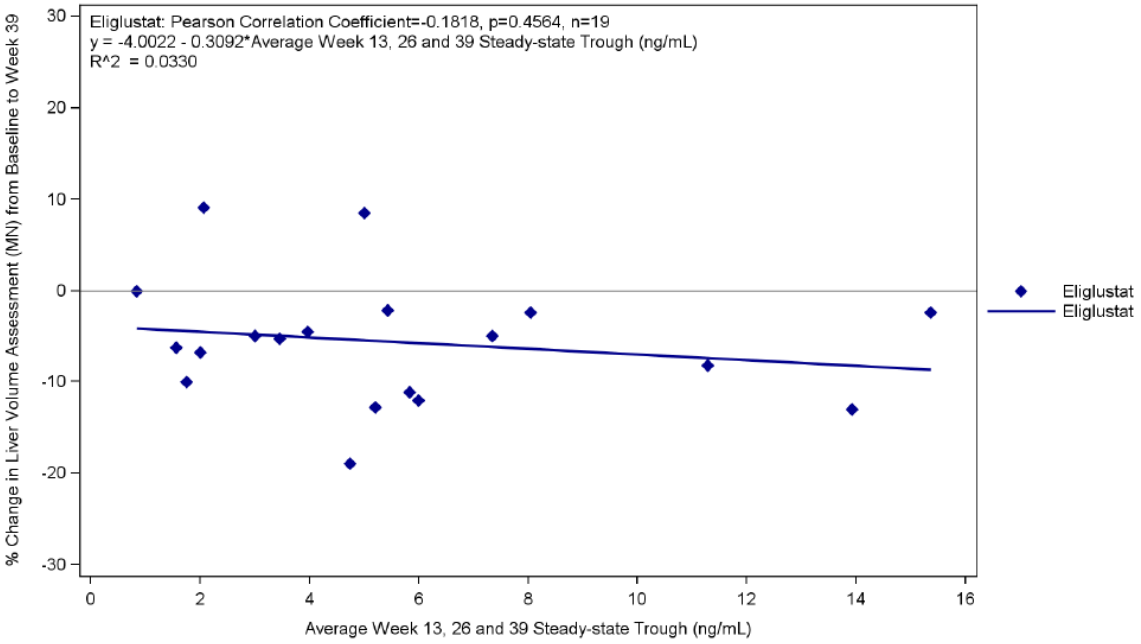
Reviewer's comments:

- *The sponsor's conclusion that there is trend for increase in efficacy variables with exposure in Phase 2 and ENGAGE study is consistent with reviewer's assessment (section 1.1.1).*

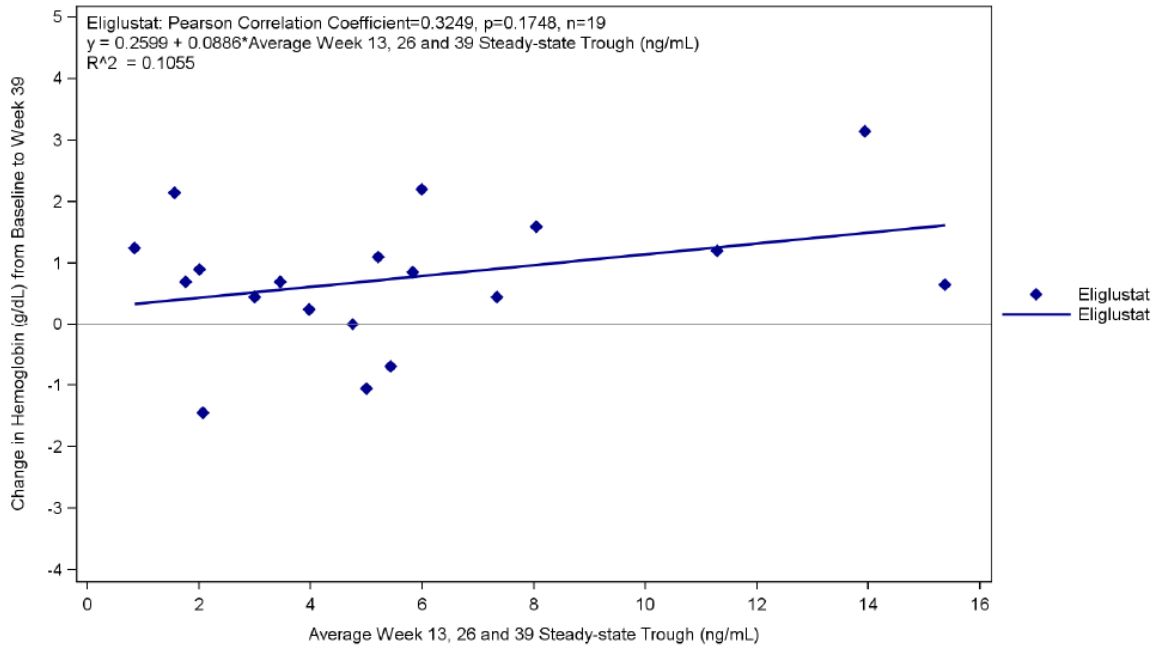
Percentage Change in Spleen Volume



Percentage Change in Liver Volume



Change in Hemoglobin



Percentage Change in Platelet Count

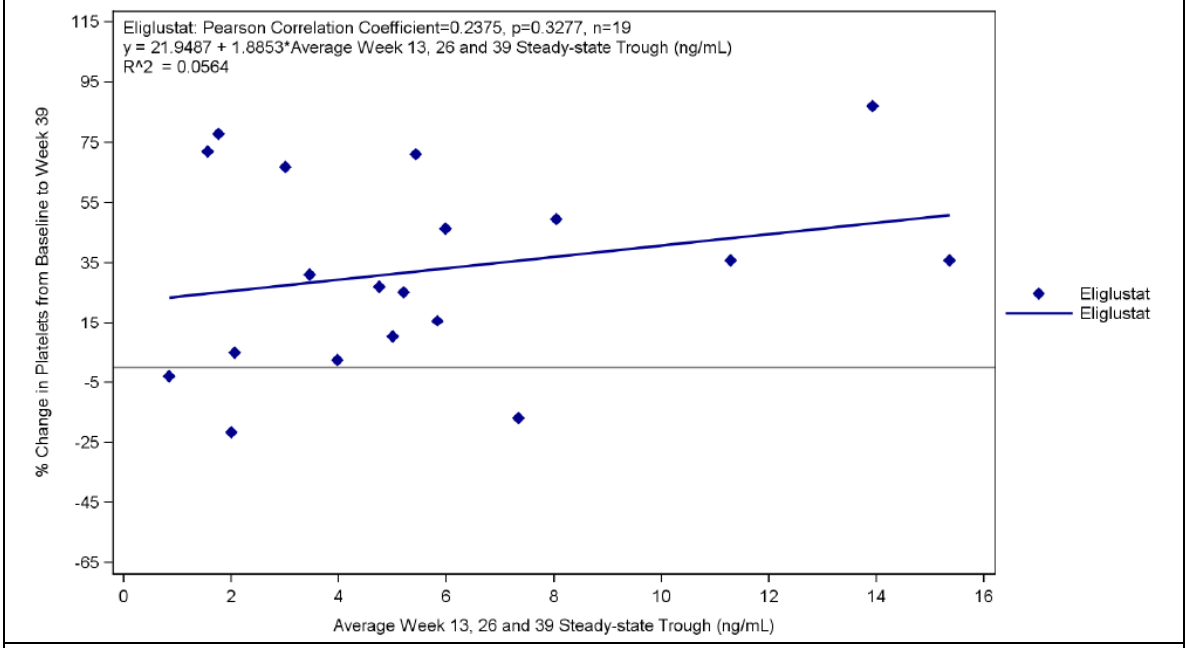
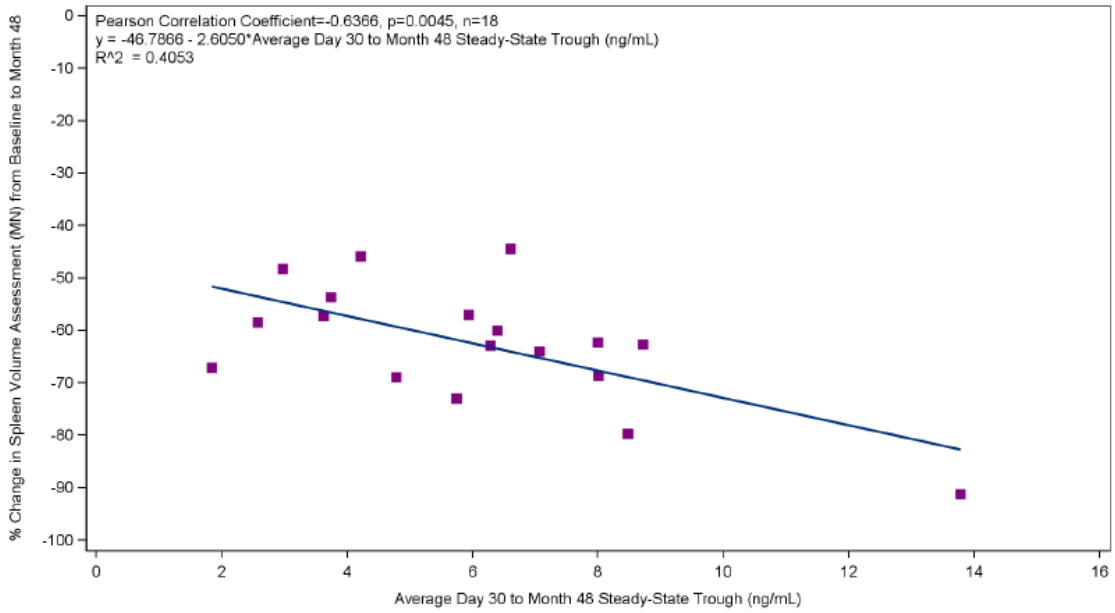
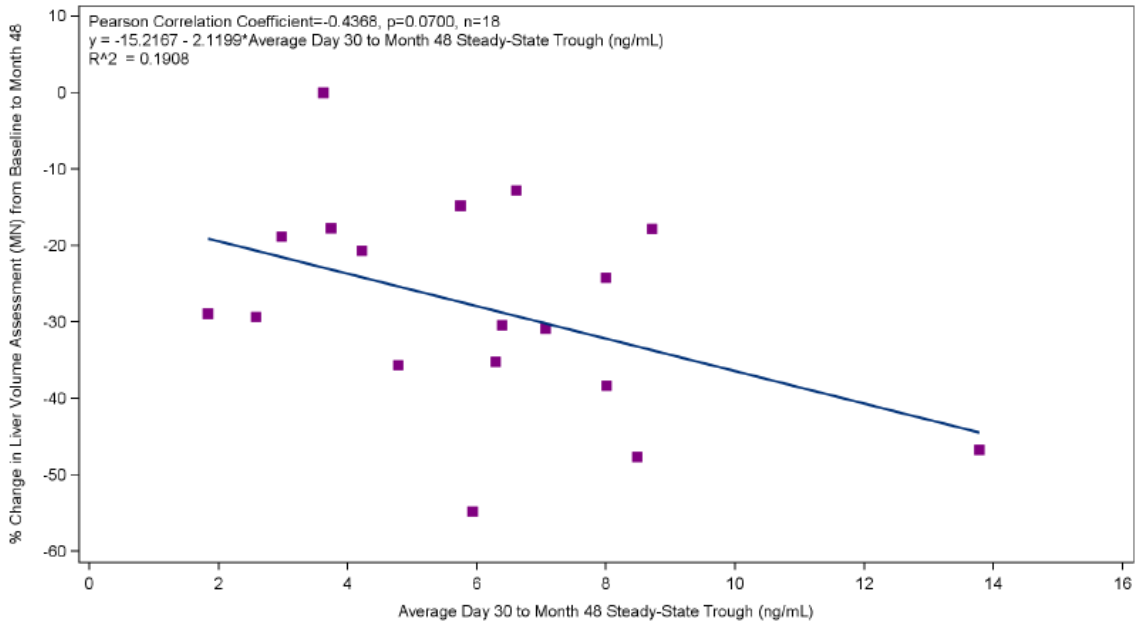


Figure 16: Scatter Plot of Percentage Change in Spleen Volume , Percentage Change in Liver Volume, Change in Hemoglobin, Percentage change in Platelet Count from Baseline to Week 39 by Average Steady-State Trough in ENGAGE study
Source: Figure 14.2.1.6.3, 14.2.2.17.3, 14.2.2.5.3 and14.2.2.11.3 from clinical study report.

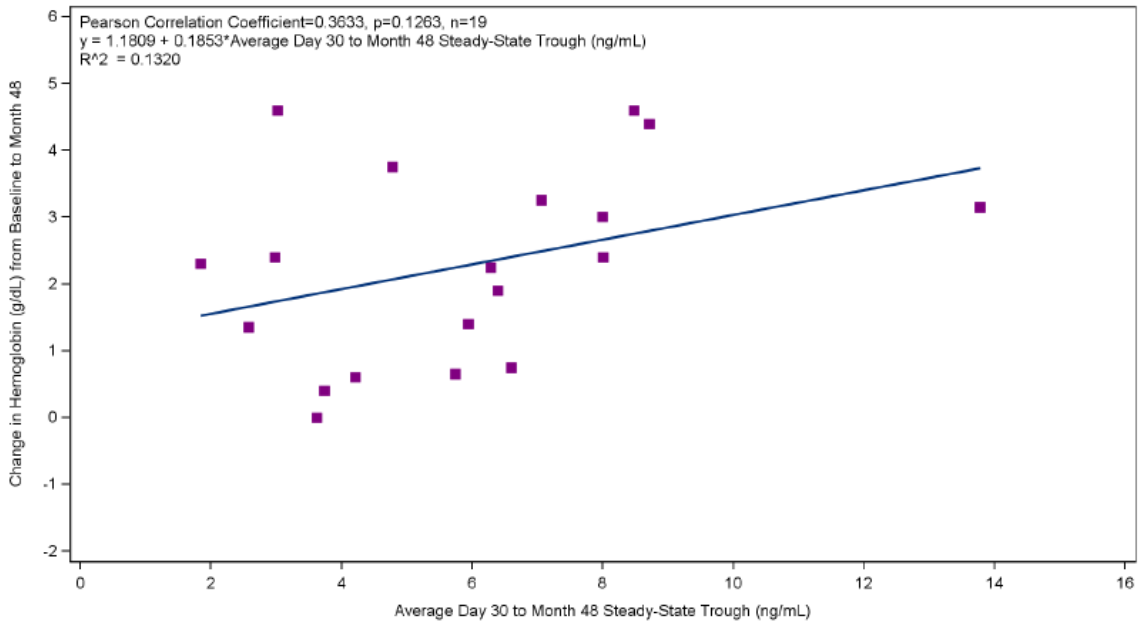
Percentage Change in Spleen Volume



Percentage Change in Liver Volume



Change in Hemoglobin



Percentage Change in Platelet Count

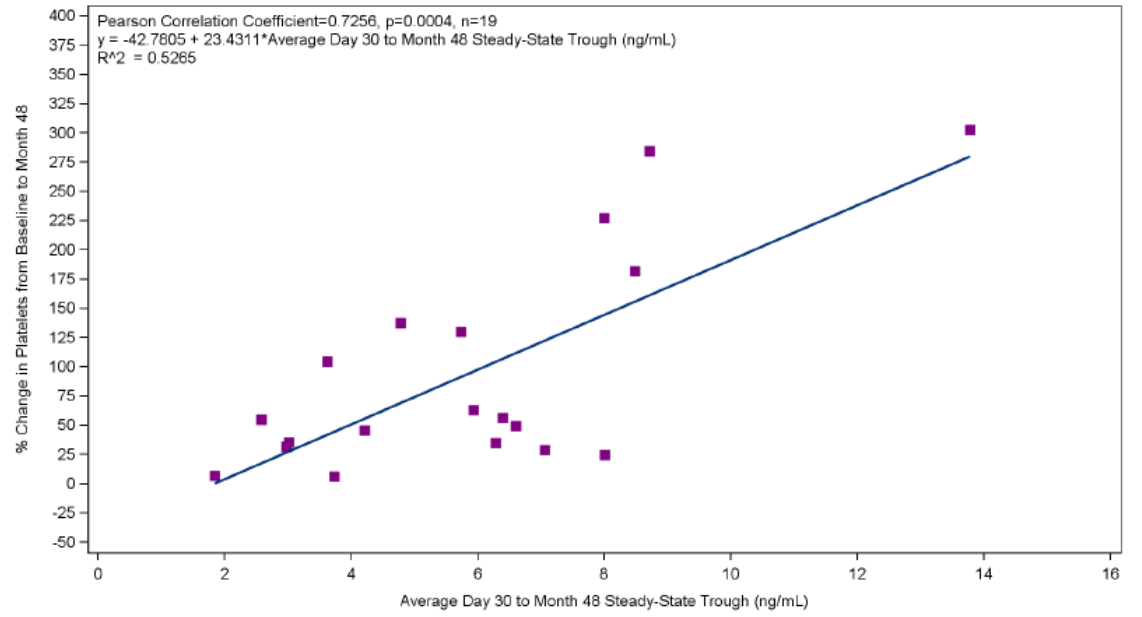


Figure 17: Scatter Plot of Percentage Change in Spleen Volume , Percentage Change in Liver Volume, Change in Hemoglobin, Percentage change in Platelet Count from Baseline to 4 years by Average Steady-State Trough in Phase2 study
Source: Figure 14.2.22.1, 14.2.23.1, 14.2.20.1 and14.2.21.1 from clinical study report.

4 RESULTS OF REVIEWER'S ANALYSIS

4.1 Objectives

The reviewer's analysis objectives are:

1. To determine if there is exposure-response relationship for efficacy variables.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 18. A linear regression analysis was conducted. The exposure metric used in the analysis was either average steady state Ctrough or the log of average steady state Ctrough. The effect of baseline value of each endpoint, age and weight was also assessed. The analysis is limited due to small sample size in ENGAGE and Phase 2. S-PLUS was used for the reviewer's analyses.

Table 18: Analysis Data Sets.

Study Number	Name	Link to EDR
ENGAGE	adeff.xpt	**\\cdsesub1\evsprod\nda205494\0000\m5\datasets\gzgd02507\analysis\adam\datasets\adeff.xpt**
	adsl.xpt	**\\cdsesub1\evsprod\nda205494\0000\m5\datasets\gzgd02507\analysis\adam\datasets\adsl.xpt**
	adpc.xpt	**\\cdsesub1\evsprod\nda205494\0000\m5\datasets\gzgd02507\analysis\adam\datasets\adpc.xpt**
Phase 2	adeff.xpt	**\\cdsesub1\evsprod\nda205494\0000\m5\datasets\gzgd00304\analysis\adam\datasets\adeff.xpt**
	adsl.xpt	**\\cdsesub1\evsprod\nda205494\0000\m5\datasets\gzgd00304\analysis\adam\datasets\adsl.xpt**
	adpc.xpt	**\\cdsesub1\evsprod\nda205494\0000\m5\datasets\gzgd00304\analysis\adam\datasets\adpc.xpt**
ENCORE	adeff.xpt	**\\cdsesub1\evsprod\nda205494\0026\m5\datasets\gzgd02607\analysis\adam\datasets\adeff.xpt**
	adpc.xpt	**\\cdsesub1\evsprod\nda205494\0000\m5\datasets\gzgd02607\analysis\adam\datasets\adpc.xpt**

4.3 Results

See section 1.1.1

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND	67,589
Generic Name	Genz-112638
Sponsor	Genzyme Corporation
Indication	Type 1 (b) (4) Gaucher disease
Dosage Form	Tablets
Drug Class	Glucosylceramide Synthase Inhibitor
Therapeutic Dose	The current Phase 2 dose is (b) (4) 100 mg bid
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	(b) (4)
Application Submission Date	11 December 2008
Review Classification	Standard
Date Consult Received	17 December 2008
Clinical Division	DGP / HFD 180

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Genz-112638 increased the QTc and PR intervals in a dose- and concentration-dependent manner. For QTcF, the largest upper bounds of the 2-sided 90% CI for the mean difference between GENZ-112638 (200 mg and 800 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance (Table 4). For PR, the largest upper limits of the 2-sided 90% CI for the mean difference between Genz-112638 (200 mg and 800 mg) and placebo were 5.8 ms and 16.4 ms, respectively (Table 9). Two subjects whose baseline PR was under 200 ms experienced a maximum change of 18 ms.

Even though the supratherapeutic dose (800 mg) produced a geometric mean C_{max} value 14-fold higher than the geometric mean C_{max} for the therapeutic dose (200 mg), these concentrations may not be sufficient to cover the high clinical exposure scenario (e.g., drug interaction with CYP2D6 inhibitor, elderly, and hepatic impairment). Data are not available to determine the impact of CYP2D6 phenotype status, metabolic inhibition with CYP3A4 inhibitor, PgP inhibition, hepatic impairment, and renal impairment on the exposure to Genz-112838.

In this randomized, double-blinded, four-way crossover study, 47subjects received Genz-112638 200 mg, Genz-112638 800 mg, placebo, and moxifloxacin 400 mg. Forty-two (42) subjects completed the study and were used in the analysis. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that the assay sensitivity of the study was established.

1.2 RESPONSE TO QUESTIONS FROM SPONSOR

1.2.1 Does FDA agree that the cardiac data collected from the current single dose thorough QT/QTc (TQT) study in combination with all other information available from Phase 1 and Phase 2 studies, provide sufficient safety data to permit initiation of the proposed Phase 3 Studies of Genz-112638?

QT-IRT Comment: Yes, with ECG monitoring in subsequent studies (see our response to question 2).

1.2.2 Genzyme considers the Thorough QT/QTc (TQT) study a negative study as defined by ICH E14 and seeks FDA concurrence on the study conclusions. In addition, does the Agency have any specific comments and/or guidance with regard to the QTc gender differences noted?

QT-IRT Comment: Even though the study can be claimed to be a negative study as defined by ICH E14, Genz-112638 is prolonging the QTc and PR intervals in a dose- and concentration-dependent manner. Additional ECG monitoring after multiple dose administration at T_{max} should be performed in phase 3 clinical studies to capture any clinical meaningful changes in ECG parameters in the patient population. Your proposed ECG monitoring plan in Studies GZGD02507 and GZGD02607 is acceptable to collect these data.

Based on our analysis, female subjects were found to be more sensitive to the QTc prolonging effects of Genz-112638; however, the clinical significance of this finding is unknown. To determine if this finding is reproducible, we recommend that you evaluate potential sex-related effects of Genz-112638 using the ECGs collected in the phase 3 studies.

2 QT-IRT COMMENTS

1. Although there were no subjects who had an absolute QRS interval greater than 120 ms, a trend for QRS interval prolongation (Figure 8). The largest upper limits of 90% CI for the QRS mean differences between 200 mg Genz-112638 and placebo, and between 800 mg Genz-112638 and placebo are 1.6 ms and 5.2 ms, respectively.

3 BACKGROUND

Genzyme Corporation is developing Genz-112638 as a potential oral drug that could impact the pathogenic process in Gaucher disease. Gaucher disease is characterized by lysosomal accumulation of glucosylceramide due to mutations in the enzyme acid-ß glucosidase resulting in impaired glucosylceramide hydrolysis, leading to severe systemic manifestations including organomegaly, anemia, thrombocytopenia and bone disease. The sponsor believes that Genz-112638 may regulate the pathogenic process in Gaucher

disease by decreasing the synthesis of glucosy1ceramide to a level where the residual enzyme activity of the mutant glucocerebrosidase, the enzyme deficient in Gaucher disease, can degrade glucosylceramide.

The QT-IRT had reviewed the TQT protocol but the sponsor preceded with this single dose TQT study prior to receiving feedback from the FDA. They were advised to continue with phase 3 clinical trials incorporating intensive ECG monitoring. The need for a repeat TQT using the recommended multiple-dose design was to be determined based on the results of this single dose study.

3.1 MARKET APPROVAL STATUS

GENZ-112638 is not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

Source: IB- dated 9 Feb 2007 and QT-IRT Protocol Review

> "Genz-112638 demonstrated significant inhibition of the HERG tail current in HEK293 cells with an IC50 of 0.35µg/mL in 0.1 % DMSO, suggesting a potential for QT interval prolongation.

Table 1: In Vitro Assays for Genz-112638 and Its Metabolites

Metabolites of Genz-112638, identified (not quantitated) in plasma from Phase 1a Data Summary (non-GLP assays)

27-Jun-07

		In Vitro Assays for Glucosylceramide Synthase Inhibition				
		cell surface GM1	**GlcCer Synthase**		**Cytochrome P450**	
		intact human K562 cells	A375 human melanoma cells	**hERG**	(fluorogenic substrates in rP450)	
Genz #	**Metabolite Structure**	FACS assay **IC50 (uM)**	microsome preparations **IC50 (uM)**	(RapidICE assay) **IC50 (uM)**	**3A4 IC50 (uM)**	**2D6 IC50 (uM)**
Genz-399240	5-carboxy	not active (to 10 uM)	to be done	none (to 30 uM)	to be done	to be done
Genz-399207	6-carboxy	not active (to 0.5 uM)	to be done	none (to 30 uM)	to be done	to be done
Genz-256416	7-hydroxyl	0.345 uM	to be done	IC50 > 30 uM	>5 uM	>5 uM
Genz-311752	6-hydroxyl	0.995 uM	to be done	IC50 > 30 uM	>5 uM	>5 uM
Genz-256179	5-hydroxyl	0.273 uM	to be done	IC50 > 30 uM	>5 uM	>5 uM
Genz-120965	N-oxide	0.916 uM	to be done	IC50 > 30 uM	>5 uM	>5 uM
Genz-256222	amino	IC50 > 10 uM	to be done	IC50 = 5.1 uM	3.7 uM	>5 uM
Genz-527862	6-keto	to be done	1.4 uM	< 50% at 30 uM	to be done	to be done
Genz-256162	7-keto	1.8 uM	1.1 uM	IC50 > 30 uM	>5 uM	>5 uM
Genz-112638	**C8 parent**	**0.014- 0.03 uM**	**.015 - .027 uM**	**0.7 uM**	**>5 uM**	**1.9 uM**

> "This was followed up with an ex vivo electrophysiology study in dog Purkinje fibers. While there was no evidence of potassium channel block in that study, there was a dose-related decrease in the upstroke amplitude of the action potential and a decrease in the action potential duration (APD) at concentrations of 0.3 to 100 µg/ml, suggesting a predominant effect on sodium channel currents in this model system. Although only 2 of 4 preparations showed a very small change in APD (only evident at 3 Hz) at 0.3 µg/ml, the NOEL was defined as 0.1 µg/ml.

"Further studies to evaluate the potential effects of Genz-11263 8 on cardiovascular function were conducted in vivo in the dog. The cardiac telemetry study showed no effects on QT interval at single oral doses as high as 80 mg/kg, although there was a dose-related increase in the QRS duration ranging from 3 ms at 10 mg/kg to 8.9 ms at 80 mg/kg. QRS prolongation was initiated 30 to 60 minutes post-dose, corresponding to the T max measured in PK studies. Increased QRS duration in the telemetry study was correlated to peak plasma levels and was evident at concentrations similar to those where ex vivo effects were observed in Purkinje fibers. For example, in a PK study in the dog, an oral dose of 10mg/kg was shown to produce a C_{max} of approximately 1 μg/ml, similar to the concentration of Genz-99067 in the Purkinje fiber study where small but significant effects on APD were measured. QRS prolongation was completely reversed at all doses studied with recovery corresponding in time to clearance of the compound from plasma.

"In the cardiac telemetry study in the dog, there was also an increased PR interval (19 to 22 ms) at doses of 50 and 80 mg/kg. These effects are consistent with a predominant action of Genz-112638 on sodium channels and depolarization. The overall NOEL for this study was determined to be 3 mg/kg.

"To further understand the effects of Genz-112638 on cardiac conduction, an additional study was performed with dogs where the compound was administered as a 2 minute IV infusion to anesthetized, instrumented dogs. Stimulating and recording electrodes were placed directly on the heart, and ECG limb electrodes were positioned in the standard configuration. Plasma levels of Genz-99067 at the end of each infusion were 2, 4.5 and 7.7 μg/ml at 1, 2.5 and 5 mg/kg respectively. The 3 doses studied caused some changes in heart rate and blood pressure parameters. The low dose of 1 mg/kg caused only a slight increase in RR interval in the ECG. However, significant increases in a number of ECG parameters, including a prolongation of the corrected QT interval, were measured at doses of 2.5 and 5 mg/kg. In addition, there were dose-related increases in atrioventricular and intra-ventricular, but not intra-atrial, conduction time measured at all 3 doses. Thus, it was possible to define a NOAEL in this study for ECG effects (1 mg/kg) but not for hemodynamic parameters or decrease of cardiac conduction time."

Reviewer's Comment: In vitro studies demonstrate a dose- and concentration-related inhibition of hERG current, decrease of APD and upstroke amplitude of the action potential. In vivo studies demonstrate a dose-related prolongation of the QT interval, AV/intra-ventricular conduction times, and, increase in PR interval and QRS prolongation (consistent with a predominant effect on sodium and possibly calcium channels).

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: QT-IRT Review for Type C Meeting Package (SDN 054) dated 17 July 2008

"Cardiac Safety Summary:

Source: Dr. Joel Morganroth's Cardiovascular Safety Report dated 6/9/2008

"In the reviewer's opinion, whether these (non-clinical) data suggest that Genz-112638 affects potassium, sodium and/or calcium channels in man is unclear since the limitations in measuring ECG intervals in the dog and the lack of good predictions from APD in in vitro data to man will be best determined in the intense ECG evaluation in man being done in the E14 Thorough ECG Trial.

"The Genz-112638 Phase 1 program has consisted of 3 clinical trials (GZGDOOI03, GZGD00404, and GZGD00204) with a total of 159 healthy volunteers (122 Genz-112638 patients and 37 placebo patients). The objective of the Phase 1 program was to assess the safety, maximal tolerabi1ty, PK, and food effect of Genz-112638.

"In the Phase la single-dose escalation study (GZGDOOI03) in healthy normal volunteers, Genz-112638 was administered in doses ranging from 0.01 mg/kg to 30 mg/kg. In this study, plasma Genz-99067 concentrations correlated with dose and observed maximal concentrations reached 1852 ng/ml on-average with 2613 ng/ml being the highest observed concentration.

- At > 10 mg/kg, the ECG data showed a short-term prolongation in QRS duration that persisted through the 4-hour post-treatment ECG, substantial placebo-adjusted mean changes in QT/QTc from baseline, and increases from 30 to 60 ms in some individual QTc measurements. These ECG findings were not apparent for Genz-112638 doses ≤ 5 mg/kg where the Genz-99067 mean Cmax concentration was 91 ng/ml.
- No subject in any treatment group showed an increase in QRS duration of 50% from baseline, although a dose-dependent prolongation in QRS duration was observed. At 1.5 hours after treatment, the placebo-adjusted changes from baseline in QRS duration were 7.5 ±1.8 ms, 9.9 ± 2.7 ms, 12.9 ± 4.1 ms, and 28.7 ± 6.5 ms for the 10, 15, 20 and 30 mg/kg treatment groups, respectively. The prolongation of QRS duration persisted through the 4-hour post-treatment ECG. The increases in QRS duration were reflected in simultaneous changes in QT/QTc interval for the treatment groups at higher doses of Genz-112638.
- Four cardiac-related AEs in 4 unique subjects who received Genz-112638 were reported, including accelerated idioventricular rhythm (Cohort 2, 0.03 mg/kg), atrioventricular block second degree (Cohort 3, 0.1 mg/kg), atrial fibrillation (Cohort 3, 0.1 mg/kg) and bradycardia (Cohort 13, 30 mg/kg). None of these events met DLT criteria. All of these AEs, with the exception of the accelerated idioventricular rhythm, were considered by the investigator to be possibly related to study drug. All subjects recovered without sequelae.
- Genz-112638 also showed a positive concentration-electrocardiogram (ECG) relationship with all the parameters studied: QTcB interval, QTcF interval, QTcgc interval, QRS interval, and heart rate. Based upon extrapolation of the correlation of PK and ECG, it was determined that a 5 ms increase in QTcF intervals on average could be expected to occur when the Genz-99067 plasma concentration is approximately 240 ng/ml, which

was observed when the single daily Genz-112638 dose was 10 mg/kg or higher.

"In the Phase Ib multi-dose study (GZGD00204) Genz-112638 was administered twice daily (BID) for 9 days. Subjects were assigned to 1 of 3 ascending treatment cohorts (8 on drug and 4 on placebo): 50 mg BID, 200 mg BID or 350 mg BID. A total of 3 cardiac rhythm-related AEs in unique subjects were reported: accelerated idioventricular rhythm (Cohort 1, 50 mg BID), tachyarrhythma (Cohort 2, 200 mg BID) and ventricular tachycardia (Cohort 2, placebo). All 3 events were asymptomatic, transient and noted on telemetry only.

"No clinically significant cardiac rhythm abnormalities by ECG were observed in any subject. While some small changes were observed in QTc, QRS and other ECG parameters in the study, these changes were not clinically significant and showed no clear pattern relative to Genz-112638 drug administration or dose. The observed concentration range was much larger in Study GZGDOO103, with plasma concentrations up to 2613 ng/ml observed, as compared to 355 ng/ml in Study GZGD00204. Hence, the single-dose study had more patients treated at higher doses, higher power, and therefore a much larger potential signal-to-noise ratio with which to detect a concentration-effect relationship as compared to the multidose study.

"Study GZGD00304 is an on-going Phase 2, open-label, multi-center study of the efficacy, safety and PK profile of Genz- 112638 at doses of 50 or 100 mg BID administered over 52 weeks in Gaucher Type 1 patients, the first study of Genz-11263 8 in the proposed patient population. As of May 2008, 26 patients have been enrolled. There has been no evidence of ventricular tachycardia by Holter monitoring and no subject has had an absolute QTcF interval exceeding 500 ms. No central tendency data are available. No clinically concerning cardiac adverse events were noted as of January 2008.

"Based on the available data, this author, in concert with the FDA, believes that since there is accumulation of parent after multiple dosing vs. single dose and that there are extensive metabolites without current kinetic characterization (in some part involving P450 3A4), a parallel study dosing to steady state (5 days) is necessary to fully understand the ECG effects of this new agent. The sponsor will review the steady state data in Phase 2 to understand the metabolite profile and its contribution to the total exposure of the drug and also to review the maximum tolerated multi-dose from Phase 1 program to determine the path forward to evaluate QT prolongation."

"Cardiac AE Review

Source: Dr. Joseph Alpert's Cardiac AE Review dated 6/29/2007

Three cardiac AE's are reported in the phase 2 study:-

- Monomorphic asymptomatic ventricular tachycardia (3 couplets) 12 hrs post study drug administration (Patient 0302). The external reviewer suggested that there was a possible relationship to study drug in this case as widening of the complexes was noted and recommended repeating the

Holter off-drug and re-challenging the patient if no arrhythmias were noted

- Mobitz Type 1 second degree heart block (Patient 0105) both prior and post- Genz112638 wash-out period at study week 52. The external reviewer felt this was of no significance
- Non-sustained 4-beat run of asymptomatic VT 6 hours post-dose. Plasma level of the drug was below LLOQ (Patient 0202). Patient experienced a second episode of asymptomatic, 7-beat slow ventricular tachycardia with a different morphology from the first dose 13 hours post-dose. Patient experienced runs of ventricular and supraventricular ectopy in a Holter done 2 months after study drug discontinuation and had a history of mitral valve prolapse. The external reviewer felt this was unrelated to study drug

Reviewer's Comment: There does not appear to be a signal for QT prolongation-related adverse events i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, based on information currently available from the phase 2 study.

3.4 CLINICAL PHARMACOLOGY

Appendix 5.1 summarizes the key features of Genz-112638's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT had reviewed the protocol but the sponsor preceded with this single dose TQT study prior to receiving feedback from the FDA.

The sponsor submitted the study report for Genz-112638 including electronic dataset and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Determine if Genz-112638 Delays Cardiac Repolarization as Determined by the Measurement of QT/QTc Interval in Healthy Subjects

4.2.2 Protocol Number

GZGD01707

4.2.3 Study Dates

11 April 2008 – 17 May 2008

4.2.4 Objectives

The primary objective of this study was to evaluate the effect of Genz-112638 administered as a single therapeutic (200 mg) and a single, supra-therapeutic dose

(800 mg) on cardiac repolarization as determined by measuring the QT/QTc interval in healthy, normal male and female subjects.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, double-blind, placebo-controlled, crossover study in healthy, normal male and female subjects to determine if Genz-112638 administered as a single therapeutic (200 mg) and a single, supra-therapeutic dose (800 mg) delays cardiac repolarization as determined by the measurement of QT/the corrected QT (QT/QTc) interval.

A total of 47 subjects (22 males and 25 females) were enrolled to achieve at least 40 evaluable subjects. Forty-two subjects completed the study. The study consisted of four treatment periods and at least 5 to 7 days between periods. Each subject's duration of participation was approximately 72 days.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatments will be administered double-blinded using a double dummy approach. In each treatment period, the set of 9 capsules (1 large and 8 small) that subjects received appeared to be the same. The composition of the set of 7 capsules for each treatment is as follows:

- Placebo: One moxifloxacin placebo capsule and eight Genz-112638 placebo capsules
- Genz-112638 200 mg: One moxifloxacin placebo capsule, two 100-mg Genz-112638 capsules, and six Genz-112638 placebo capsules
- Genz-112638 800 mg: One moxifloxacin placebo capsule and eight 100-mg Genz-112638 capsules
- Moxifloxacin 400 mg: One 400-mg moxifloxacin capsule and eight Genz-112638 placebo capsules

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The following four treatments were used in the study.

- Genz-112638 200 mg
- Genz-112638 600 mg
- Placebo
- Moxifoxacin 400 mg (over encapsulated)

Subjects were randomized to four different sequences (William square design) of these treatments.

4.2.6.2 Sponsor's Justification for Doses

"The choice of the single, therapeutic dose of Genz-112638 (200 mg) was made based upon review of the safety and PK profiles from the Phase 1 a single-dose study (GZGDOO103) and Phase 1b multiple-dose study (GZGD00204). The highest therapeutic dose in a current, on-going Phase 2 clinical trial (GZGD00304) is 100 mg of Genz-112638 twice daily (BID). Interpolated results of the multiple-dose Phase 1 b study (GZGD00204) indicated that 10 days of BID administration of 100 mg Genz-112638 would result in an average maximal plasma concentration of approximately 20 ng/mL. Analysis of the PK data from the Phase 1a study (GZGDOO103) indicated that to achieve a maximal plasma concentration of 20 ng/mL after single dose administration of Genz-112638, approximately 200 mg ofGenz-112638 is required. Hence, 200 mg of Genz-112638 was selected as the therapeutic dose equivalent in this study.

"The choice of the single, supra-therapeutic dose (800 mg) was based on the outcome of a multiple dose drug interaction study with paroxetine, a strong cytochrome P-450 2D6 (CYP 2D6) inhibitor (GZGD02007) such that the majority of subjects will likely have Genz-99067 (the free base of the (b) (4) tartaric acid salt Genz-112638 as it exists in plasma) at observed concentrations similar to or higher than concentrations observed at the therapeutic dose in the presence of paroxetine. The sponsor's choice of a single dose administration strategy was based on prior evidence supporting that the effect of Genz-112638 on QT/QTc interval was concentration dependent. In healthy volunteers (Phase 1a), a 5 ms increase in QTc interval was observed on average when the plasma concentration of Genz-99067 was >= 240 ng/mL. This concentration was achieved at single doses >= 10 mg/kg. Further, Genz-112638 was not tolerated when healthy subjects were dosed at 350 mg BID in the phase 1b study (GZGD00204) where 5 of the 8 subjects in this cohort discontinued dosing due to AEs predominantly associated with recurrent gastrointestinal symptoms, such as nausea and vomiting, and nervous system symptomatology, such as dizziness and headache. Single dosing was utilized by the sponsor to achieve higher plasma concentrations while ensuring subject tolerability and study completion."

Reviewer's Comments: Even though the supratherapeutic single dose is sufficient to address the scenario of a strong CYP2D6 inhibitor (7- to 9- fold increase in exposure), the worst clinical scenario may not be covered, such as an elder patient with hepatic impairment taking a strong CYP2D6 inhibitor, since the impact of age and hepatic impairment on PK is unknown while both of these two factors may further increase the drug exposure.

4.2.6.3 Instructions with Regard to Meals

Subjects will be fasted prior to dosing. A subject was permitted to drink water 1 hour post-dose and eat approximately 4 hours post-dose.

Reviewer's Comments: Acceptable. Coadministration with a high fat meal decreases C_{max} (Appendix 5.1). Also meals can affect QT interval.

4.2.6.4 ECG and PK Assessments

ECG interval values in triplicate were extracted from the Holter monitoring device and averaged for each of the following observation time points: Prior to dosing at 1 hour, 40 minutes, and 20 minutes which served as the baseline for the baseline adjustment in the analysis of the data.

Following dosing, ECG interval values in triplicate were extracted from the Holter monitoring device and averaged for each of the following observation time points: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, and 22.5 hours. The observation window during which ECGs were expected to be extracted from the Holter monitoring device was from the start of the time point until approximately 5 minutes after the time point.

Blood samples were collected for PK analysis at the following times in each treatment period:

- Day 1 (Treatment): Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, and 22.5 hours post-dose.
- Day 2 (Follow-up): At 30 and 36 hours post-dose.

4.2.6.5 Baseline

The pre-dose baseline, which was calculated by taking the average of the pre-dose assessments done in triplicate at -60, -40, and -20 minutes prior to dosing on Day 1, was used.

4.2.7 ECG Collection

On Day 1 (Treatment) of each treatment period, subjects were connected to a continuous 12-Lead Holter monitoring device (Mortara H12+, Milwaukee, WI. USA) and ECG interval values in triplicate were extracted from the Holter monitoring device and averaged for each of the following observation time points specified above. Immediately prior to the start of each ECG time point, site staff reminded the subject to remain in a supine position.

The ECG signal for each 24-hour session in each subject was recorded on 40-MB compact flash memory cards provided to the site.

ECGs were sent to a central laboratory, (b) (4) for a treatment-blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment. To ensure consistency in the blinded reads the following were included as part of the reading and analysis process:

a) All ECGs on a subject were read by a single reader

b) Inter-reader variability was assessed by having a sub-set of reading interpreted by a second reader

c) Lead used for all measurements when appropriate was lead II (V5 when lead II was not interpretable and ifV5 was not interpretable the next best lead was used)

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 47 healthy subjects (22 males and 25 females), 18-45 yrs of age, and weight of 50-100 kg were enrolled to achieve at least 40 evaluable subjects.

Forty-two subjects (18 males and 24 females) completed the study. Subjects 102 and 109 (both male) were withdrawn after completing Treatment Period 1 (placebo) due to receiving antibiotics prescribed to treat infections unrelated to study drug. Subject 116 (male) was withdrawn during the check-in process for Treatment Period 3 due to a positive urine cotinine test. Subject 118 (male) was withdrawn during the check-in process for Treatment Period 4 due to a positive urine drug screen. Subject 208 (female) completed Treatment Period 1 (800 mg of Genz-112638) before she was withdrawn prior to dosing in Treatment Period 2 due to the inability to draw blood.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint to assess cardiac repolarization safety was based on QTcF interval. Linear mixed-effects models were used to characterize the relationship between treatment and various ECG parameters. Each dependent variable was doubly-corrected for the pre-dose baseline on Day 1 and time-matched placebo treatment, i.e., the so-called (b) (4) correction. Time, sequence, treatment, treatment period, and treatment by time interaction were treated as categorical variables. No covariates were included in the model other than sex. Numerator degrees of freedom were estimated using (b) (4) Subjects were nested within sequence and will be modeled using a random intercept, thereby allowing each subject to have their own baseline within each treatment period.

Reviewer's Comments: Upon the inspection of the sponsor's program named "CALCI-ECG-CORRECTED.SAS", it appears that the analyses were carried out differently from what was stated above. The sponsor used the raw QTcF as the dependent variable in the model as compared to (b) (4) as stated above. Also, the sponsor seemed to use Kenwardroger method to calculate the degrees of freedom instead of the stated (b) (4) Although the outcome and conclusions were not affected by this operation, the sponsor should clarify any deviations.

Sponsor's results are presented in Table 1. The QTcF mean change from baseline showed no signal for any QTc effect since the upper 1-sided 95% confidence intervals for both the single clinical and supra-therapeutic dose were less than 10 ms. The time matched analysis for the QTcF endpoint revealed that the moxifloxacin group met the assay sensitivity criteria outlined in the statistical plan with most time points having a mean difference >5 ms and the upper confidence interval around the mid-teens.

Table 1: Placebo-Corrected Change from Baseline – Estimates from Mixed Model: QTcF

(Source: Sponsor's Table 14.2.3.16)

	Genz-112638 200 mg		Genz-112638 800 mg		Moxifloxacin 400 mg	
Time	Estimate [1]	Upper Bound [2]	Estimate [1]	Upper Bound [2]	Estimate [1]	Upper Bound [2]
0.5 Hr	0.3	3.0	0.4	3.2	4.2	8.2
1 Hr	-1.0	1.8	2.0	4.8	7.9	11.9
1.5 Hr	-2.2	0.5	4.2	7.0	9.1	13.1
2 Hr	-0.7	2.1	4.4	7.2	9.0	12.9
2.5 Hr	-0.7	2.1	5.9	8.7	10.7	14.7
3 Hr	-0.3	2.4	5.7	8.5	11.1	15.1
3.5 Hr	-1.1	1.7	3.9	6.7	8.6	12.5
4 Hr	-0.0	2.7	5.3	8.1	12.1	16.1
4.5 Hr	-0.3	2.4	5.6	8.4	10.8	14.8
5 Hr	-0.5	2.3	5.4	8.2	11.5	15.4
5.5 Hr	-0.7	2.1	5.3	8.1	10.4	14.4
6 Hr	-1.1	1.7	4.4	7.2	12.0	15.9
7 Hr	-0.3	2.4	6.5	9.3	7.9	11.8
8 Hr	-1.2	1 6	4.1	7.0	8.0	12.0
10 Hr	0.7	3.5	4.0	6.9	8.1	12.0
12 Hr	-0.6	2.2	2.6	5.5	6.0	10.0
14 Hr	0.4	3.1	4.0	6.8	5.4	9.3
22.5 Hr	-1.4	1.3	0.5	3.3	2.9	6.9
Mean	-0.5	4.0	3.2	7.7	9.8	14.5

[1] Mixed Model ANOVA is fit for qtcf and includes terms for - baseline, period, sequence : treatment, gender, time, and time by treatment, gender by treatment, and gender by treatment by time interactions.
[2] Upper Bound = upper one-sided 95% ANOVA model based confidence limit.
p-value for gender main effect is 0.1911 and Tx*gender IA = <.0001.

Reviewer's Comments: We confirmed the sponsor's conclusions of lack of QTc effect for the study drug and establishment of assay sensitivity in our independent analyses presented in Section 5.2.

4.2.8.2.2 Categorical Analysis

The outlier analysis is exploratory only since there is little power to detect genetically sensitive individuals to potential QT prolonging drugs in a small sample size in healthy volunteers. Nevertheless, the specific outlier criteria are a new abnormal U wave, new >500 ms absolute QTc duration and > 60 ms change from baseline. For QTcF there were no specific outliers for Genz-112638. The nonspecific outlier criterion is a 30-60 ms change from baseline which showed 2 subjects in the 800-mg Genz-112638 dose group meeting this criterion and no subject for any other treatment group.

4.2.8.3 Safety Analysis

No SAEs or deaths were reported during this study.

The number of subjects reporting at least 1 TEAE was highest in the 800-mg Genz-112638 (8 subjects; 17.8%) and moxifloxacin (7 subjects; 16.7%) groups and was lowest in the 200-mg Genz-I12638 (4 subjects; 9.1%) and placebo (5 subjects; 11.1%) groups.

The most frequently reported TEAEs were dizziness (4 subjects in the 800-mg Genz-112638 group, 2 subjects in the moxifloxacin group, and 1 subject in the 200-mg Genz-112638 group) and nausea (3 subjects in the 800-mg Genz-112638 group, 2 subjects in the moxifloxacin group, and 1 subject in the 200-mg Genz-112638 group). The majority of TEAEs were mild in intensity and all AEs resolved by the end of the study.

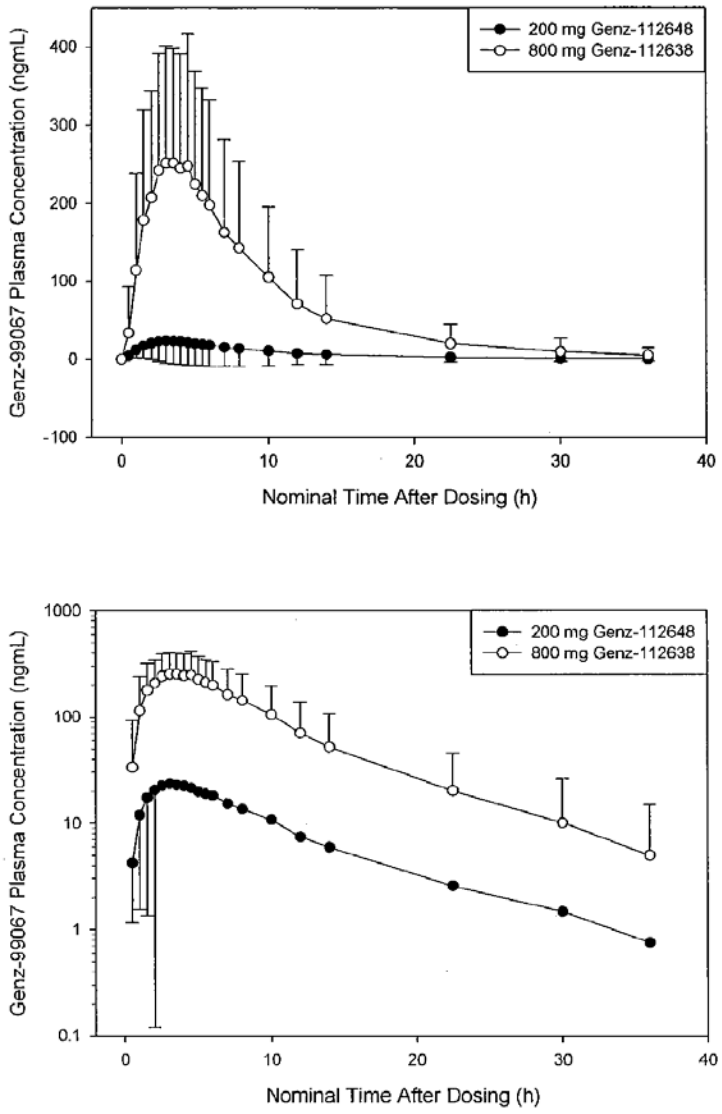
No clinically significant abnormalities were noted for clinical laboratory, or safety 12-1ead ECG assessments.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The concentration time profiles of Genz-99067 plasma concentrations for the 200-mg and 800-mg dose regimens are shown in Figure 1.

Figure 1: Concentration Time Profiles of Genz-99067 Plasma Concentrations (Top: Normal Scale; Bottom: Semi-log Scale)



Total exposures of Genz-99067 as assessed by $AUC_{0\text{-last}}$ were 247.04 ng*h/mL and 2463.81 ng*h/mL after a single therapeutic dose (200 mg) and supratherapeutic dose (800 mg) of Genz-112638, respectively. Mean peak exposures of Genz-99067 as assessed by C_{max} were 26.54 ng/mL and 299.21 ng/mL in the 200-mg and 800-mg Genz-1 12638 treatment groups, respectively.

Median time to reach C_{max} (T_{max}) was longer in the 800-mg Genz-11638 treatment group (3.6 hours) than in the 200-mg Genz-112638 treatment group (2.6 hours). The mean t1/2 values were similar for both the 200-mg and 800-mg Genz-112638 treatment groups (5.73 and 6.02 hours, respectively). Apparent clearance values in the 200-mg and 800-mg Genz-112638 treatment groups were 1919.5 L/h and 501.5 L/h, respectively.

4.2.8.4.2 Exposure-Response Analysis

The PK-PD analysis explored the relationship between the placebo-corrected (placebo-adjusted) change from baseline in QTc intervals (QTcI, QTcF, QTcG and QTcB) and

plasma concentrations of Genz-99067 (the free base of the (b)(4) tartaric acid salt Genz-112638 as it exists in plasma).

Linear mixed effects models were used to characterize the concentration-effect relationship. In a typical linear mixed model, both intercept and slope are allowed to vary between individuals. Further, it is assumed that the subject-specific intercept and subject-specific slope can be correlated. Lastly, it is assumed that observations within a subject are correlated over time using a power spatial matrix.

The following table details the pharmacokinetic-pharmacodynamic model results showing that the slopes of the relationships for plasma concentration of parent and the predicted QTc change at Cmax.

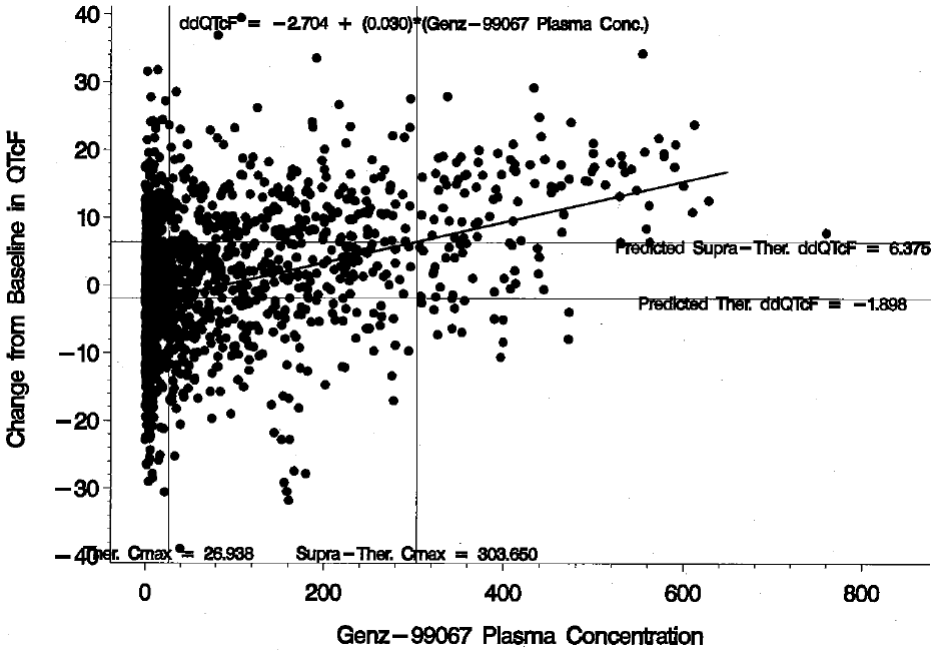
Table 2: Placebo-Corrected Change from Baseline versus the Genz-99067 Plasma Concentration - Estimates from Linear Mixed Model
(Source: Sponsor's Table 14.2.3.21)

				Therapeutic Dose		Supra-Therapeutic Dose		
QT Parameter	Slope of Plasma Conc.	Standard Error of Plasma Conc.	p-value	Predicted QTc at Mean Therapeutic Cmax 26.938	One-sided Upper 95% Confidence Bound of Predicted QTc	Predicted QTc at Mean Therapeutic Cmax 303.650	One-sided Upper 95% Confidence Bound of Predicted QTc	Overall Model Fit
QTcF	0.0254	0.0019	0.0000	0.1334	1.5116	7.1723	8.6925	<.0001
QTcI	0.0243	0.0018	0.0000	-0.1852	1.2279	6.5256	8.0658	<.0001
QTcG	0.0229	0.0018	0.0000	0.0235	1.4912	6.3700	7.9609	<.0001
QTcB	0.0307	0.0026	0.0000	0.3196	1.7923	8.8068	10.5160	<.0001

[1] Linear Mixed Model if fit for change from baseline (placebo-correct) versus the plasma concentration as a fixed effect with subject included in the model as a random effect. Delta delta is individual calculated, not model based.
[2] Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

The following figure show the relationship between QTcF duration and plasma concentration from paired samples taken in both dose groups for Genz-112638.

Figure 2: QTcF Change from Baseline versus Genz-99067 Plasma Concentration
(Source: Sponsor's Figure 14.2.3.1)



A positive relationship was observed between Genz-99067 plasma concentrations and placebo-corrected QTcF intervals. After administration of a single 200-mg dose of Genz-112638, having a mean C_{max} of 26.938 ng/mL, the expected increase in placebo-corrected QTcF interval was 0.13 ms with an upper 1-sided 95% CI limit of 1.5 ms. At the supra-therapeutic 800-mg dose, having a mean C_{max} of 303.650 ng/mL, the expected increase in placebo-corrected QTcF interval was 7.2 ms with an upper 95% CI limit of 8.7 ms.

The sponsor also applied the similar method to double-delta PR interval (ddPR). A positive relationship was observed between Genz-99067 plasma concentrations and ddPR($p < 0.0001$). At the mean C_{max} of 24 ng/mL in the 200 mg dose group and 255 ng/mL in the 800 mg dose group, the expected increase in ddPR intervals was 1.42 ms (95% CI: 0.0914 to 2.74 ms) and 11.1 ms (95% CI: 8.44 to 13.76 ms), respectively.

Reviewer's Comments: Minor discrepancies were noticed in the numerical reports for C_{max}, ddQTcF prediction and model parameters in different parts of the sponsor's report. The overall conclusions were not affected.

REVIEWERS' ASSESSMENT

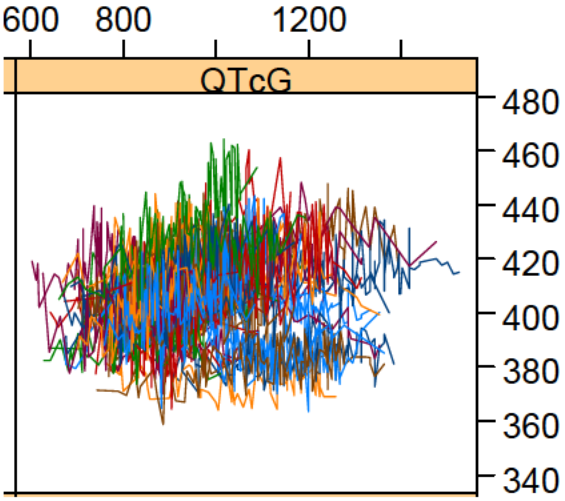
4.3 Evaluation of the QT/RR Correction Method

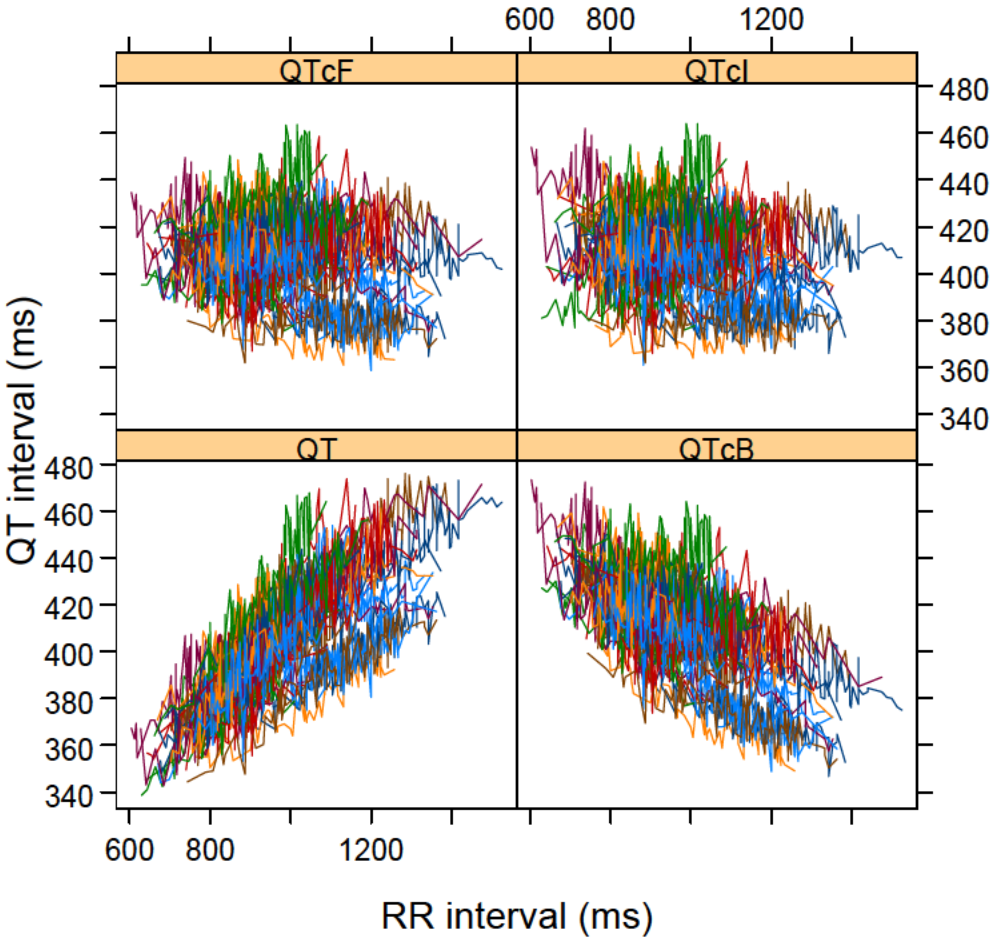
We evaluated the linear relationships between different correction methods (QTcB, QTcF, QTcG (population correction), QTcI) and RR. We used the mean sum of squared slopes (MSSS) as the criterion based on the post dose data. Baseline values were excluded in the validation. The smaller this value is, the better the correction. Based on the results listed in Table 3 and Figure 3, it appears that QTcF and QTcI are equally better than QTcB and QTcG. To be consistent with the sponsor's proposed primary endpoint, we also used QTcF as the primary correction method for our analysis.

Table 3: Mean Sum of Squared Slopes for Different QT Correction Methods (Post Dose Only)

Treatment Group	Correction Method							
	QTcB		QTcF		QTcG		QTcI	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
200 mg Genz-11263	44	0.0054	44	0.0008	44	0.0019	44	0.0008
800 mg Genz-11263	45	0.0064	45	0.0011	45	0.0020	45	0.0011
Moxifloxacin	42	0.0052	42	0.0014	42	0.0031	42	0.0016
All	45	0.0054	45	0.0014	45	0.0028	45	0.0013

Figure 3: QT, QTcB, QTcF, QTcG and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)





4.4 Statistical Assessments

4.4.1 QTc Analysis

4.4.1.1 Analysis of Study Drug Effect and Assay Sensitivity

We used mixed model to analyze the ΔQTcF effect for each time point. The model includes TREATMENT, SEQUENCE, and PERIOD, and baseline values as fixed effects; and SUBJECT as a random effect. We also included sex as a covariate in the model to account for variations due to gender. We used Satterthwaite's method to calculate the degrees of freedom. The analysis results are listed in the following table.

Table 4: Analysis Results of ΔQTcF and ΔΔQTcF at Each Time Point by Treatment

		Treatment Group								
		200 mg Genz-11263			800 mg Genz-11263			Moxifloxacin		
	Placebo	ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF	
Time (hrs)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0.5	-1.9	-1.6	0.3	(-1.8, 2.4)	-1.2	0.7	(-1.4, 2.8)	2.3	4.2	(2.1, 6.3)
1	-1.0	-2.2	-1.1	(-3.5, 1.2)	1.0	2.0	(-0.3, 4.4)	6.7	7.7	(5.3, 10.1)
1.5	0.2	-2.1	-2.3	(-5.0, 0.4)	4.5	4.3	(1.6, 7.0)	9.3	9.1	(6.4, 11.9)
2	-0.1	-0.7	-0.6	(-2.9, 1.6)	4.5	4.6	(2.3, 6.8)	8.8	8.9	(6.6, 11.2)
2.5	0.9	0.3	-0.6	(-3.1, 1.9)	7.0	6.1	(3.6, 8.6)	11.6	10.7	(8.2, 13.2)
3	-0.2	-0.5	-0.3	(-2.8, 2.3)	5.7	5.9	(3.3, 8.4)	10.8	11.0	(8.4, 13.6)
3.5	1.9	0.7	-1.1	(-3.7, 1.4)	6.0	4.1	(1.6, 6.6)	10.4	8.5	(5.9, 11.1)
4	-1.0	-0.8	0.2	(-2.3, 2.6)	4.6	5.6	(3.1, 8.0)	11.2	12.2	(9.7, 14.6)
4.5	0.6	0.2	-0.4	(-3.0, 2.2)	6.4	5.7	(3.1, 8.3)	11.3	10.7	(8.0, 13.3)
5	-0.8	-1.3	-0.5	(-2.9, 2.0)	4.6	5.5	(3.0, 7.9)	10.7	11.5	(9.0, 14.0)
5.5	0.6	0.1	-0.5	(-3.0, 2.0)	6.1	5.5	(3.0, 8.0)	11.2	10.6	(8.1, 13.2)
6	0.9	-0.1	-1.0	(-3.6, 1.6)	5.5	4.6	(2.0, 7.1)	12.9	12.0*	(9.3, 14.6)
7	0.8	0.7	-0.1	(-2.6, 2.4)	7.3	6.6	(4.1, 9.1)	9.8	9.0	(6.4, 11.5)
8	-4.1	-5.1	-1.0	(-2.9, 1.0)	0.1	4.2	(2.2, 6.1)	4.9	8.9	(7.0, 10.9)
10	-5.8	-4.8	0.9	(-1.4, 3.3)	-1.7	4.1	(1.8, 6.5)	3.0	8.8	(6.4, 11.1)
12	-3.1	-3.3	-0.2	(-2.5, 2.1)	-0.1	3.0	(0.7, 5.3)	3.7	6.8	(4.5, 9.1)
14	-3.3	-2.8	0.5	(-1.8, 2.8)	0.9	4.2	(1.9, 6.5)	2.7	5.9	(3.6, 8.3)
22.5	0.4	-1.0	-1.4	(-4.1, 1.3)	1.1	0.7	(-2.0, 3.4)	3.6	3.2	(0.4, 5.9)

*The lower bound of the 90% CI is 7.5 ms after Bonferroni adjustment for 18 time points.

The largest upper bounds of the 2-sided 90% CI for the mean difference between 200 mg Genz-112638 and placebo, and between 800 mg Genz-112638 and placebo are 3.3 ms and 9.1 ms, respectively, which are below 10 ms, the regulatory threshold.

For the moxifloxacin group, the largest lower bound of the unadjusted 90% confidence interval is 9.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower bound is 7.5 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

The similar analyses results for each gender subgroup are provided in Table 5 and Table 6. The comparisons of ΔΔQTcF by gender for each treatment group are shown in Figure 4. It appears that the females had longer QTcF intervals (ΔΔQTcF means reached 8-10 ms at multiple time points) than the males after treatment of 800 mg Genz-112638. The differences were not as obvious after the 200-mg or moxifloxacin treatments. Due to the small sample size (N about 20), QTc prolongation among females can not be concluded at this time.

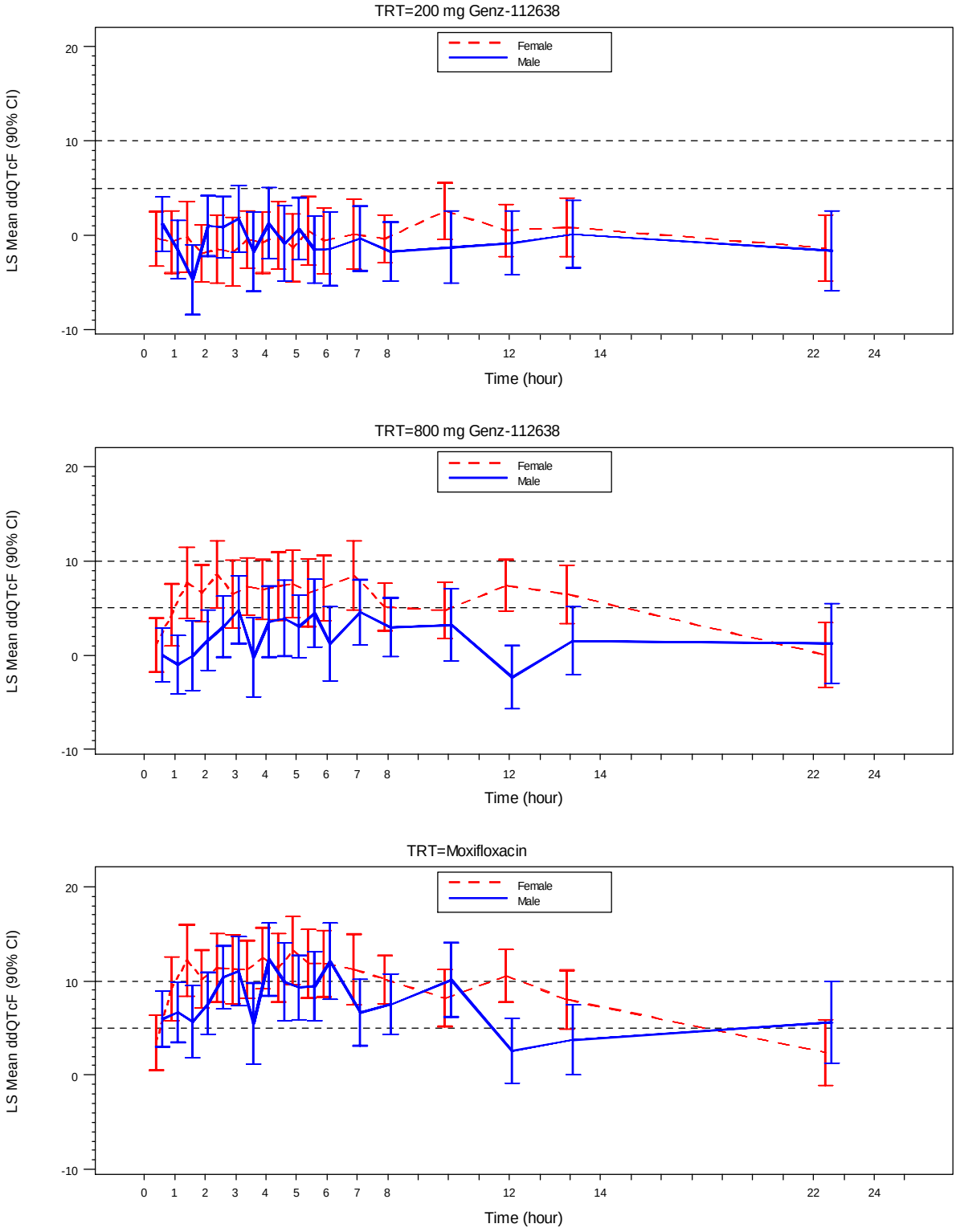
Table 5: Analysis Results of ΔQTcF and ΔΔQTcF at Each Time Point by Treatment: Females

		Treatment Group								
		200 mg Genz-112638			800 mg Genz-112638			Moxifloxacin		
	Placebo	ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.5	-1.1	-1.5	-0.4	(-3.3, 2.5)	-0.1	1.1	(-1.8, 3.9)	2.3	3.4	(0.5, 6.3)
1	-0.2	-0.9	-0.7	(-4.0, 2.6)	4.1	4.3	(0.9, 7.6)	9.0	9.1	(5.8, 12.5)
1.5	-0.7	-0.9	-0.2	(-4.0, 3.6)	6.9	7.7	(3.9, 11.4)	11.4	12.2	(8.3, 16.0)
2	1.6	-0.4	-1.9	(-5.0, 1.1)	8.1	6.6	(3.5, 9.6)	11.7	10.2	(7.1, 13.3)
2.5	2.1	0.6	-1.5	(-5.1, 2.1)	10.7	8.6	(5.0, 12.1)	13.5	11.3	(7.7, 15.0)
3	2.0	0.2	-1.8	(-5.4, 1.9)	8.5	6.5	(2.8, 10.1)	13.2	11.2	(7.6, 14.9)
3.5	2.2	1.7	-0.5	(-3.5, 2.6)	9.4	7.3	(4.2, 10.3)	13.3	11.2	(8.1, 14.3)
4	1.2	0.4	-0.8	(-4.0, 2.4)	8.1	6.9	(3.7, 10.2)	13.5	12.4	(9.1, 15.6)
4.5	2.0	2.0	0.0	(-3.6, 3.6)	9.3	7.3	(3.7, 10.9)	13.3	11.4	(7.7, 15.0)
5	0.3	-1.0	-1.4	(-4.9, 2.2)	7.9	7.5	(4.0, 11.1)	13.5	13.2	(9.6, 16.8)
5.5	1.7	2.2	0.5	(-3.2, 4.1)	8.4	6.6	(3.0, 10.2)	13.6	11.8	(8.2, 15.5)
6	2.2	1.6	-0.6	(-4.1, 2.9)	9.3	7.1	(3.7, 10.6)	14.0	11.8	(8.3, 15.4)
7	-1.8	-1.7	0.1	(-3.6, 3.8)	6.6	8.5	(4.8, 12.1)	9.4	11.2	(7.5, 14.9)
8	-5.9	-6.3	-0.4	(-2.9, 2.1)	-0.8	5.1	(2.6, 7.6)	4.2	10.1	(7.6, 12.7)
10	-7.4	-4.8	2.6	(-0.4, 5.6)	-2.6	4.7	(1.8, 7.7)	0.8	8.1	(5.1, 11.1)
12	-6.9	-6.4	0.5	(-2.3, 3.2)	0.5	7.4	(4.7, 10.1)	3.6	10.5	(7.7, 13.3)
14	-4.7	-3.8	0.8	(-2.2, 3.9)	1.8	6.4	(3.4, 9.5)	3.3	8.0	(4.9, 11.1)
22.5	-0.7	-2.0	-1.4	(-4.8, 2.1)	-0.7	0.0	(-3.4, 3.5)	1.7	2.4	(-1.1, 5.9)

Table 6: Analysis Results of ΔQTcF and ΔΔQTcF at Each Time Point by Treatment: Males

		Treatment Group								
		200 mg Genz-112638			800 mg Genz-112638			Moxifloxacin		
	Placebo	ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.5	-2.6	-1.4	1.2	(-1.7, 4.1)	-2.6	-0.0	(-2.9, 2.9)	3.4	6.0	(3.0, 8.9)
1	-1.5	-3.1	-1.5	(-4.6, 1.6)	-2.5	-1.0	(-4.1, 2.1)	5.1	6.7	(3.5, 9.8)
1.5	1.5	-3.2	-4.7	(-8.4, -1.0)	1.5	-0.1	(-3.8, 3.7)	7.2	5.6	(1.8, 9.5)
2	-1.4	-0.4	1.0	(-2.2, 4.2)	0.2	1.6	(-1.6, 4.8)	6.2	7.6	(4.3, 10.9)
2.5	-0.2	0.7	0.9	(-2.4, 4.1)	2.9	3.0	(-0.2, 6.3)	10.2	10.4	(7.0, 13.7)
3	-2.2	-0.4	1.8	(-1.8, 5.3)	2.6	4.8	(1.3, 8.4)	8.8	11.0	(7.4, 14.7)
3.5	2.1	0.4	-1.7	(-5.9, 2.5)	1.9	-0.2	(-4.4, 4.0)	7.6	5.5	(1.2, 9.8)
4	-2.9	-1.6	1.3	(-2.5, 5.0)	0.7	3.5	(-0.2, 7.3)	9.4	12.3	(8.4, 16.1)
4.5	-0.4	-1.3	-0.9	(-4.9, 3.1)	3.5	3.9	(-0.1, 8.0)	9.5	9.9	(5.8, 14.0)
5	-1.7	-1.0	0.7	(-2.6, 4.0)	1.4	3.1	(-0.2, 6.4)	7.6	9.3	(5.9, 12.7)
5.5	-0.3	-1.8	-1.5	(-5.1, 2.0)	4.2	4.5	(0.9, 8.0)	9.1	9.4	(5.8, 13.1)
6	0.1	-1.4	-1.4	(-5.4, 2.5)	1.3	1.2	(-2.8, 5.2)	12.2	12.1	(8.0, 16.1)
7	4.2	3.8	-0.3	(-3.8, 3.1)	8.7	4.6	(1.1, 8.0)	10.8	6.7	(3.1, 10.2)
8	-1.4	-3.1	-1.7	(-4.8, 1.4)	1.5	3.0	(-0.2, 6.1)	6.1	7.5	(4.3, 10.7)
10	-3.8	-5.1	-1.3	(-5.1, 2.6)	-0.6	3.2	(-0.6, 7.0)	6.3	10.1	(6.2, 14.0)
12	1.6	0.7	-0.8	(-4.2, 2.5)	-0.8	-2.3	(-5.7, 1.0)	4.1	2.6	(-0.9, 6.0)
14	-1.1	-1.0	0.1	(-3.5, 3.7)	0.4	1.5	(-2.1, 5.1)	2.6	3.7	(0.0, 7.4)
22.5	1.7	0.0	-1.6	(-5.8, 2.6)	2.9	1.2	(-3.0, 5.5)	7.3	5.6	(1.3, 10.0)

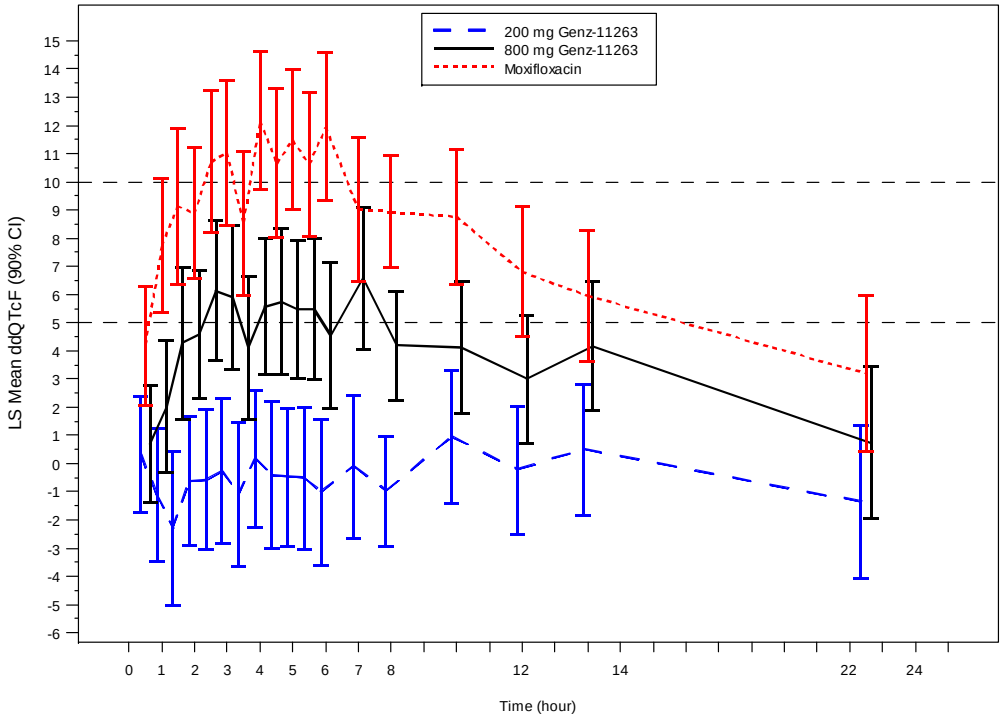
Figure 4: ΔΔQTcF Time Course by Gender and Treatment Group



4.4.1.2 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 5: ΔΔQTcF Time Course



4.4.1.3 Categorical Analysis

Table 7 lists the number of subjects whose absolute QTcF values are ≤ 450 ms, and between 450 ms and 480 ms. None of the subjects had a QTcF of above 480 ms. Table 8 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 7: Categorical Analysis for QTcF

Treatment Group	Total N	QTcF <=450 ms	450 ms < QTcF <=480 ms
Baseline	47	46 (97.9%)	1 (2.1%)
200 mg Genz-11263	44	44 (100%)	0 (0.0%)
800 mg Genz-11263	45	44 (97.8%)	1 (2.2%)
Moxifloxacin	42	40 (95.2%)	2 (4.8%)
Placebo	45	45 (100%)	0 (0.0%)

Table 8: Categorical Analysis of ΔQTcF

Treatment Group	N	ΔQTcF <=30 ms	30 ms< ΔQTcF <=60 ms
200 mg Genz-11263	44	44 (100%)	0 (0.0%)
800 mg Genz-11263	45	44 (97.8%)	1 (2.2%)
Moxifloxacin	42	42 (100%)	0 (0.0%)
Placebo	45	45 (100%)	0 (0.0%)

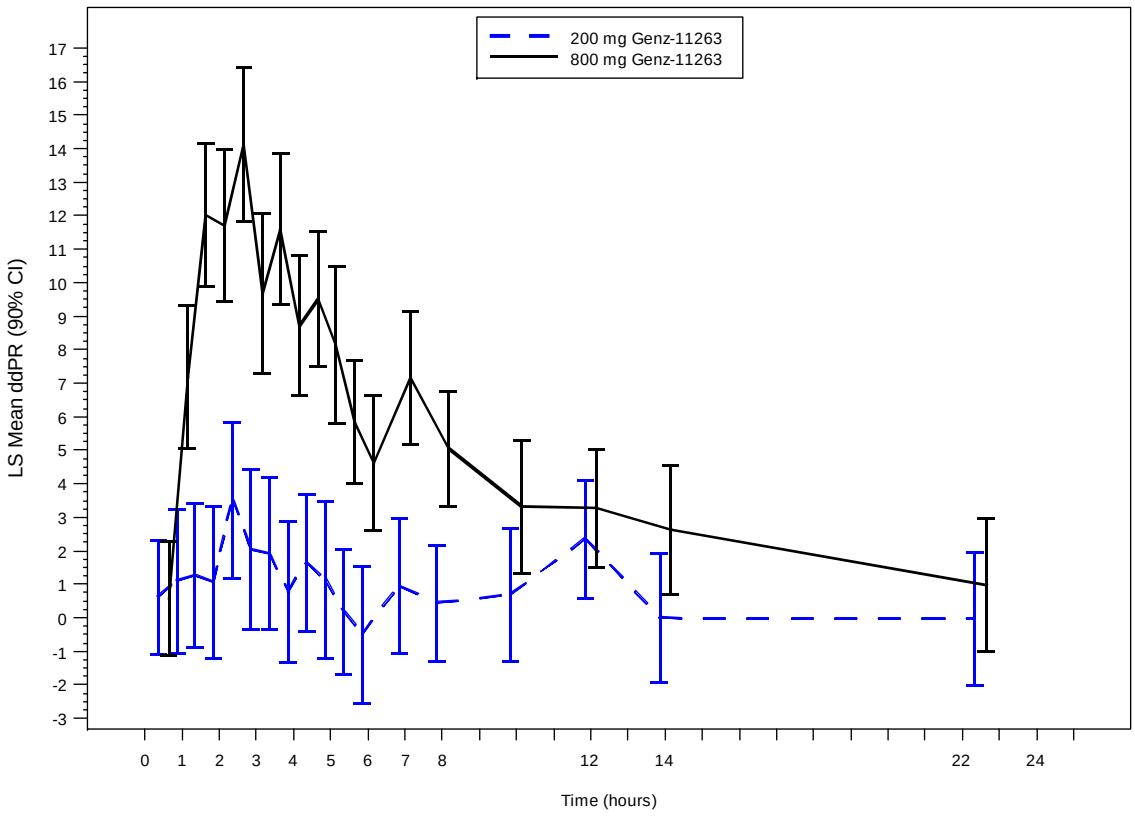
4.4.2 PR Analysis

The same statistical analysis used for QTcF was performed for PR intervals. The point estimates and the 90% confidence intervals are presented in Table 9 and also shown in Figure 6. The largest upper limits of 90% CI for the PR mean differences between 200 mg Genz-112638 and placebo, and between 800 mg Genz-112638 and placebo are 5.8 ms and 16.4 ms, respectively.

Table 9: Analysis Results of ΔPR and ΔΔPR for Study Drug

		Treatment Group					
		200 mg Genz-11263			800 mg Genz-11263		
	Placebo	ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0.5	-1.4	-0.8	0.6	(-1.1, 2.3)	-0.8	0.6	(-1.1, 2.3)
1	-0.2	0.9	1.1	(-1.0, 3.2)	7.0	7.2	(5.0, 9.3)
1.5	-1.5	-0.2	1.3	(-0.9, 3.4)	10.5	12.0	(9.9, 14.2)
2	-0.4	0.6	1.1	(-1.2, 3.3)	11.3	11.7	(9.4, 14.0)
2.5	-3.5	0.0	3.5	(1.2, 5.8)	10.6	14.1	(11.8, 16.4)
3	-1.5	0.5	2.0	(-0.4, 4.4)	8.2	9.7	(7.3, 12.1)
3.5	-4.0	-2.1	1.9	(-0.4, 4.1)	7.6	11.6	(9.3, 13.8)
4	-3.0	-2.2	0.8	(-1.3, 2.9)	5.7	8.7	(6.6, 10.8)
4.5	-4.1	-2.4	1.6	(-0.4, 3.7)	5.5	9.5	(7.5, 11.5)
5	-3.3	-2.2	1.1	(-1.2, 3.5)	4.8	8.1	(5.8, 10.5)
5.5	-3.4	-3.3	0.2	(-1.7, 2.0)	2.4	5.8	(4.0, 7.7)
6	-2.5	-3.0	-0.5	(-2.5, 1.5)	2.1	4.6	(2.6, 6.7)
7	-5.7	-4.7	0.9	(-1.1, 3.0)	1.5	7.2	(5.2, 9.2)
8	-6.8	-6.4	0.4	(-1.3, 2.1)	-1.8	5.0	(3.3, 6.8)
10	-7.8	-7.1	0.7	(-1.3, 2.7)	-4.5	3.3	(1.3, 5.3)
12	-9.3	-6.9	2.3	(0.6, 4.1)	-6.0	3.3	(1.5, 5.0)
14	-6.5	-6.5	-0.0	(-2.0, 1.9)	-3.9	2.6	(0.7, 4.5)
22.5	-3.1	-3.1	-0.1	(-2.0, 1.9)	-2.1	1.0	(-1.0, 3.0)

Figure 6: ΔΔPR Time Course



The PR analyses are also repeated for each gender group. The results are presented in Table 10, Table 11 and Figure 7 below.

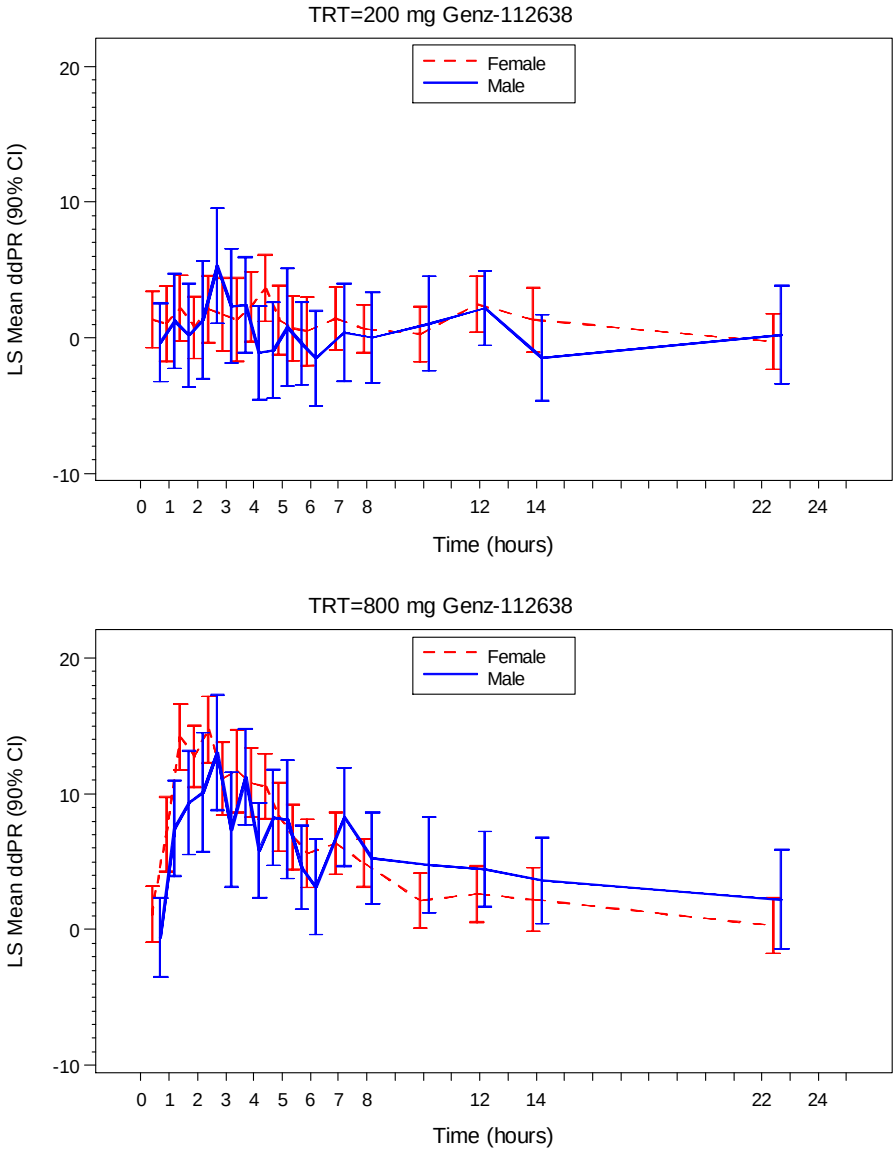
Table 10: Analysis Results of ΔPR and ΔΔPR for Study Drug: Females

		Treatment Group					
		200 mg Genz-112638			800 mg Genz-112638		
	Placebo	ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0.5	-1.1	0.2	1.3	(-0.8, 3.4)	0.0	1.1	(-0.9, 3.2)
1	-0.3	0.7	1.0	(-1.7, 3.8)	6.7	7.0	(4.3, 9.7)
1.5	-2.7	-0.5	2.2	(-0.3, 4.6)	11.5	14.2	(11.8, 16.6)
2	-0.1	0.6	0.7	(-1.6, 3.0)	12.6	12.7	(10.5, 15.0)
2.5	-3.2	-1.1	2.1	(-0.4, 4.6)	11.6	14.7	(12.3, 17.2)
3	-1.7	-0.0	1.7	(-1.0, 4.4)	9.4	11.1	(8.4, 13.8)
3.5	-3.9	-2.6	1.3	(-1.8, 4.4)	7.8	11.7	(8.6, 14.7)
4	-4.0	-1.8	2.3	(-0.3, 4.8)	6.7	10.8	(8.2, 13.3)
4.5	-5.3	-1.7	3.6	(1.2, 6.1)	5.2	10.5	(8.1, 12.9)
5	-3.6	-2.3	1.3	(-1.3, 3.8)	4.7	8.3	(5.8, 10.8)
5.5	-3.3	-2.7	0.7	(-1.7, 3.1)	3.5	6.8	(4.4, 9.2)
6	-3.1	-2.6	0.5	(-2.1, 3.0)	2.5	5.6	(3.1, 8.1)
7	-5.7	-4.3	1.4	(-0.9, 3.7)	0.6	6.3	(4.0, 8.6)
8	-6.7	-6.1	0.6	(-1.1, 2.4)	-1.9	4.9	(3.1, 6.6)
10	-7.4	-7.2	0.2	(-1.8, 2.3)	-5.3	2.1	(0.1, 4.1)
12	-9.2	-6.7	2.4	(0.4, 4.5)	-6.6	2.6	(0.6, 4.7)
14	-7.0	-5.7	1.3	(-1.1, 3.7)	-4.8	2.2	(-0.2, 4.6)
22.5	-3.2	-3.5	-0.3	(-2.4, 1.8)	-3.0	0.3	(-1.8, 2.3)

Table 11: Analysis Results of ΔPR and ΔΔPR for Study Drug: Males

		Treatment Group					
		200 mg Genz-112638			800 mg Genz-112638		
	Placebo	ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0.5	-1.6	-2.0	-0.4	(-3.3, 2.5)	-2.2	-0.6	(-3.5, 2.3)
1	-0.1	1.1	1.2	(-2.3, 4.7)	7.4	7.4	(3.9, 11.0)
1.5	-0.1	0.1	0.2	(-3.6, 4.0)	9.2	9.3	(5.5, 13.2)
2	-0.8	0.5	1.3	(-3.1, 5.6)	9.3	10.1	(5.7, 14.5)
2.5	-3.9	1.4	5.3	(1.0, 9.5)	9.1	13.0	(8.8, 17.3)
3	-1.2	1.1	2.3	(-1.9, 6.5)	6.1	7.4	(3.1, 11.6)
3.5	-4.3	-1.8	2.4	(-1.1, 5.9)	7.0	11.2	(7.7, 14.8)
4	-1.7	-2.8	-1.1	(-4.6, 2.3)	4.1	5.8	(2.3, 9.3)
4.5	-2.8	-3.7	-0.9	(-4.4, 2.6)	5.5	8.2	(4.7, 11.8)
5	-3.1	-2.4	0.8	(-3.6, 5.1)	5.0	8.1	(3.7, 12.5)
5.5	-3.5	-3.9	-0.4	(-3.5, 2.6)	1.1	4.6	(1.5, 7.6)
6	-1.7	-3.3	-1.5	(-5.0, 2.0)	1.4	3.1	(-0.4, 6.6)
7	-5.8	-5.5	0.4	(-3.2, 4.0)	2.4	8.3	(4.7, 11.9)
8	-7.1	-7.1	-0.0	(-3.3, 3.3)	-1.9	5.3	(1.9, 8.6)
10	-8.3	-7.3	1.0	(-2.5, 4.5)	-3.6	4.7	(1.2, 8.2)
12	-9.6	-7.4	2.2	(-0.6, 4.9)	-5.1	4.4	(1.7, 7.2)
14	-6.1	-7.6	-1.5	(-4.7, 1.7)	-2.5	3.6	(0.4, 6.8)
22.5	-3.0	-2.8	0.2	(-3.4, 3.8)	-0.8	2.2	(-1.4, 5.9)

Figure 7: PR Time Course by Gender and Treatment



The categorical analysis results for PR are presented in Table 12. There was one subject in the 200-mg Genz-112638 group and two subjects in the 800-mg Genz-112638 group who had PRs of above 200 ms. A detailed pre and post dose results for these subjects are presented in Table 13.

Table 12: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR >=200 ms
Baseline	47	46 (97.9%)	1 (2.1%)
200 mg Genz-11263	44	43 (97.7%)	1 (2.3%)
800 mg Genz-11263	45	42 (93.3%)	3 (6.7%)

Table 13: Detailed Results for the Subjects Whose PR were 200 ms or above at Post Dose

Subject ID	Treatment	Period	Time (hrs.)	PR at Baseline	PR at Post-Dose	PR Change
113	200 mg Genz-112638	1	0.5	206.8	210.0	3.2
	200 mg Genz-112638	1	1	206.8	214.7	7.9
	200 mg Genz-112638	1	1.5	206.8	213.7	6.9
	200 mg Genz-112638	1	2	206.8	211.0	4.2
	200 mg Genz-112638	1	2.5	206.8	210.3	3.6
	200 mg Genz-112638	1	3	206.8	210.3	3.6
	200 mg Genz-112638	1	3.5	206.8	205.0	-1.8
	200 mg Genz-112638	1	4	206.8	203.7	-3.1
	200 mg Genz-112638	1	4.5	206.8	202.0	-4.8
	200 mg Genz-112638	1	6	206.8	204.3	-2.4
	200 mg Genz-112638	1	22.5	206.8	205.0	-1.8
	800 mg Genz-112638	3	0.5	212.1	211.0	-1.1
	800 mg Genz-112638	3	1	212.1	225.0	12.9
	800 mg Genz-112638	3	1.5	212.1	228.0	15.9
	800 mg Genz-112638	3	2	212.1	219.7	7.6
	800 mg Genz-112638	3	2.5	212.1	212.3	0.2
	800 mg Genz-112638	3	3	212.1	212.3	0.2
	800 mg Genz-112638	3	3.5	212.1	217.0	4.9
	800 mg Genz-112638	3	4	212.1	213.3	1.2
	800 mg Genz-112638	3	4.5	212.1	210.7	-1.4
	800 mg Genz-112638	3	5	212.1	209.7	-2.4
	800 mg Genz-112638	3	5.5	212.1	205.0	-7.1
	800 mg Genz-112638	3	6	212.1	204.3	-7.8
	800 mg Genz-112638	3	7	212.1	209.0	-3.1
	800 mg Genz-112638	3	14	212.1	204.0	-8.1
	800 mg Genz-112638	3	22.5	212.1	201.0	-11.1
210	800 mg Genz-112638	3	1.5	187.3	201.0	13.7
	800 mg Genz-112638	3	2	187.3	202.0	14.7
	800 mg Genz-112638	3	2.5	187.3	203.0	15.7
	800 mg Genz-112638	3	3	187.3	200.7	13.3
	800 mg Genz-112638	3	3.5	187.3	205.0	17.7
	800 mg Genz-112638	3	4	187.3	200.7	13.3
	800 mg Genz-112638	3	4.5	187.3	202.0	14.7
216	800 mg Genz-112638	1	3	185.0	203.3	18.3
	800 mg Genz-112638	1	3.5	185.0	200.3	15.3
	800 mg Genz-112638	1	4	185.0	201.0	16.0

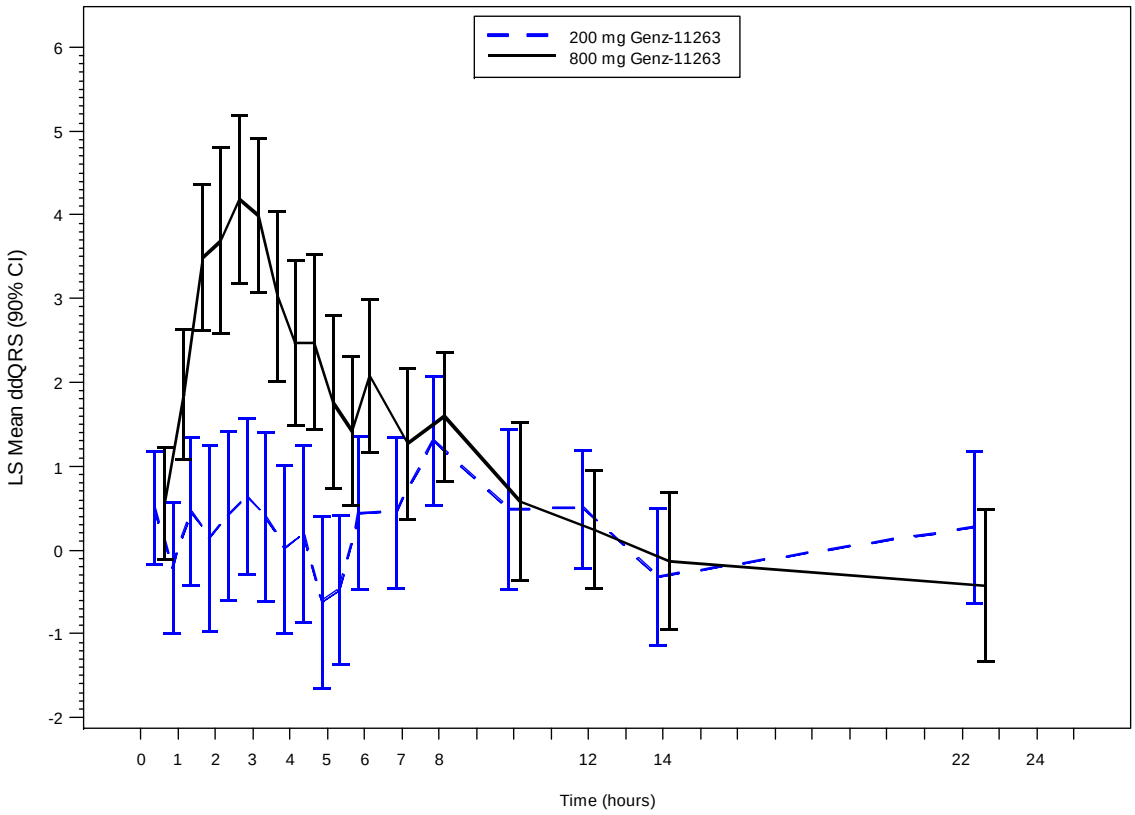
4.4.3 QRS Analysis

The same statistical analysis used for QTcF was performed for QRS intervals. The point estimates and the 90% confidence intervals are presented in Table 14 and also shown in Figure 8. The largest upper limits of 90% CI for the QRS mean differences between 200 mg Genz-112638 and placebo, and between 800 mg Genz-112638 and placebo are 1.6 ms and 5.2 ms, respectively. There were no subjects who had an absolute QRS interval greater than 120 ms.

Table 14: Analysis Results of ΔQRS and ΔΔQRS for Study Drug

		Treatment Group					
		200 mg Genz-11263			800 mg Genz-11263		
	Placebo	ΔQRS	ΔΔQRS		ΔQRS	ΔΔQRS	
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0.5	-0.1	0.4	0.5	(-0.2, 1.2)	0.5	0.6	(-0.1, 1.2)
1	0.3	0.0	-0.2	(-1.0, 0.6)	2.1	1.9	(1.1, 2.6)
1.5	-0.4	0.1	0.5	(-0.4, 1.3)	3.1	3.5	(2.6, 4.4)
2	-0.3	-0.2	0.1	(-1.0, 1.2)	3.4	3.7	(2.6, 4.8)
2.5	-0.8	-0.4	0.4	(-0.6, 1.4)	3.4	4.2	(3.2, 5.2)
3	-1.0	-0.4	0.6	(-0.3, 1.6)	3.0	4.0	(3.1, 4.9)
3.5	-0.3	0.1	0.4	(-0.6, 1.4)	2.7	3.0	(2.0, 4.0)
4	-0.4	-0.4	0.0	(-1.0, 1.0)	2.1	2.5	(1.5, 3.5)
4.5	-0.5	-0.3	0.2	(-0.9, 1.2)	1.9	2.5	(1.4, 3.5)
5	-0.1	-0.7	-0.6	(-1.7, 0.4)	1.7	1.8	(0.7, 2.8)
5.5	0.0	-0.4	-0.5	(-1.4, 0.4)	1.5	1.4	(0.5, 2.3)
6	-0.9	-0.4	0.4	(-0.5, 1.4)	1.2	2.1	(1.2, 3.0)
7	0.7	1.2	0.4	(-0.5, 1.3)	2.0	1.3	(0.4, 2.2)
8	-0.5	0.8	1.3	(0.5, 2.1)	1.1	1.6	(0.8, 2.4)
10	-0.6	-0.2	0.5	(-0.5, 1.4)	-0.1	0.6	(-0.4, 1.5)
12	-0.7	-0.2	0.5	(-0.2, 1.2)	-0.5	0.2	(-0.5, 0.9)
14	0.0	-0.3	-0.3	(-1.1, 0.5)	-0.1	-0.1	(-0.9, 0.7)
22.5	0.2	0.5	0.3	(-0.6, 1.2)	-0.2	-0.4	(-1.3, 0.5)

Figure 8: ΔΔQRS Time Course



4.5 CLINICAL PHARMACOLOGY ASSESSMENTS

4.5.1 Genz-112638 Concentration-QTcF Analysis

The relationship between ΔΔ QTcF and Genz-112638 concentrations was investigated by linear mixed-effects modeling.
The following three linear models were considered:

- Model 1 is a linear model with an intercept;
- Model 2 is a linear/ model with mean intercept fixed to 0 (with variability);
- Model 3 is a linear model with no intercept.

Table 15 summarizes the results of the Genz-112638 concentration - QTcF analyses. Model 1 was used for further analysis since the model with intercept was found to fit the data best. The predicted ΔΔ QTcF at mean peak Genz-112638 concentration can be found in Table 16.

Table 15: Exposure-Response Analysis of Genz-112638 associated ΔΔQTcF Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ddQTcF = Intercept + slope * Genz-112638 Concentration		
Intercept (ms)	-0.27 (-1.89; 1.35) 0.7802	6.07
Slope (ms per ng/mL)	0.0267 (0.0132; 0.0403) 0.0023	0.05
Residual Variability (ms)	7.9	--
Model 2: ddQTcF = Intercept + slope * Genz-112638 Concentration (Fixed Intercept)		
Intercept (ms)	0	6.08
Slope (ms per ng/mL)	0.0257 (0.0135; 0.0379) 0.0013	0.05
Residual Variability (ms)	7.9	--
Model 3: ddQTcF = slope * Genz-112638 Concentration (No Intercept)		
Slope (ms per ng/mL)	0.0217 (0.0104; 0.0329) 0.0029	0.04
Residual Variability (ms)	9.22	--

Table 16: Predicted Change of ΔΔQTcF Interval at Geometric Mean Peak Genz-112638 Concentration using Model 1

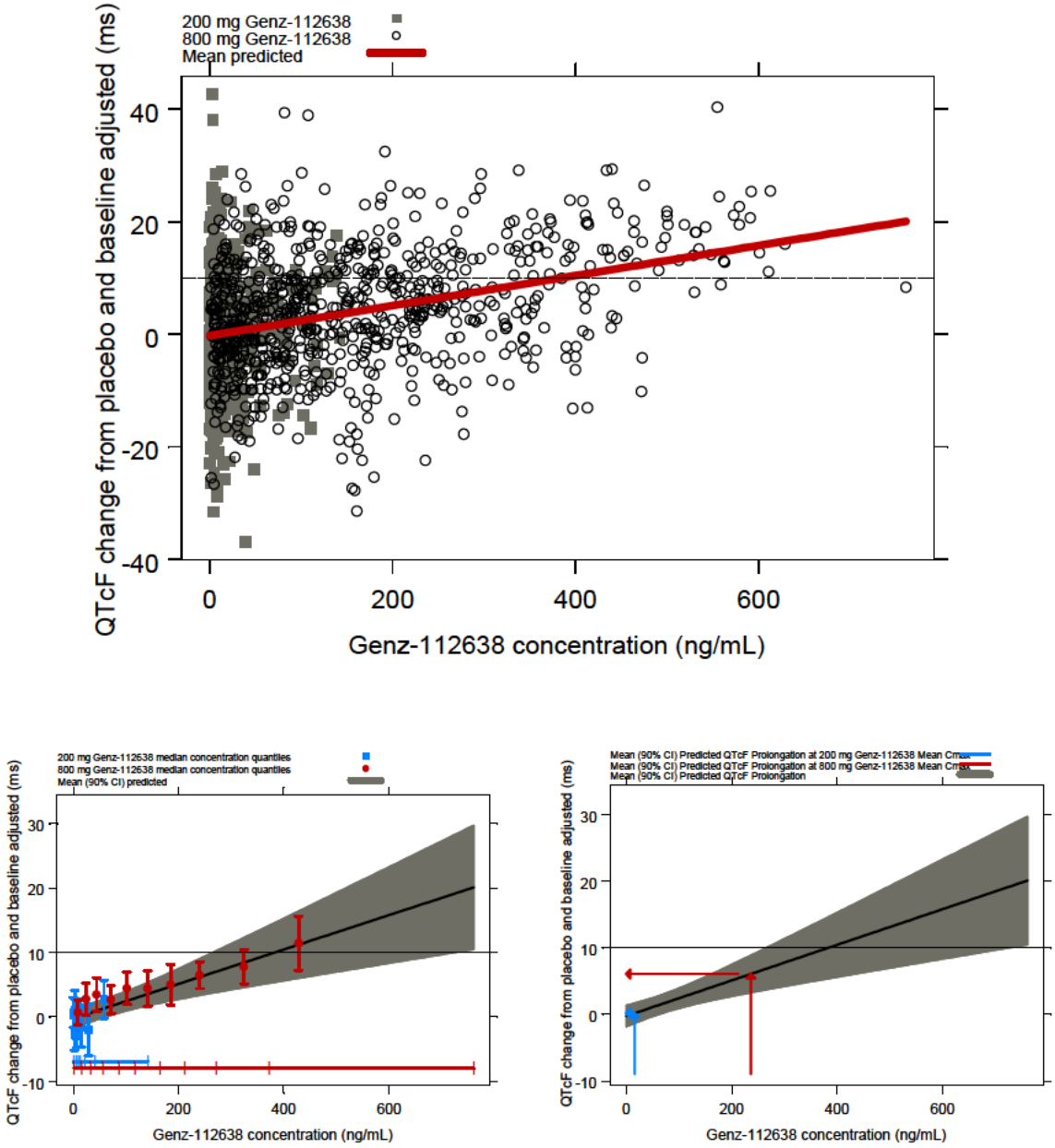
Dose Group	Predicted change in ΔΔ QTcF interval (ms)	
	Mean	90% Confidence Interval
200 mg Genz-112638		
Geometric Mean C_{max} (16.7 ng/mL)	0.176	(-1.35; 1.7)
800 mg Genz-112638		
Geometric Mean C_{max} (237 ng/mL)	6.06	(3.24; 8.88)

The relationship between Genz-112638 concentrations and ΔΔ QTcF is visualized in Figure 9 where the raw data is shown on top together with the population predictions.

The goodness-of-fit is illustrated in the bottom left graph of Figure 9 showing the observed median-quantile concentrations and associated mean ΔΔ QTcF (90% CI) together with the mean (90% CI) predicted ΔΔ QTcF (black line with shaded grey area).

The mean (90% CI) predicted ΔΔ QTcF at mean C_{max} is shown in the bottom right graph of Figure 9.

Figure 9: ΔΔQTcF vs. Genz-112638 concentration. Observed data (Top), Concentration Quantile plot (Bottom Left), and Predicted ΔΔ QTcF at geometric mean C_{max} (Bottom Right).



Similar analysis was conducted for male and female subjects, respectively, to evaluate the sponsor's finding on different QT prolongation for male and female subjects. The results show that female subjects have higher sensitivity to QTc prolongation as indicated by the steeper slope for the concentration-QTcF relationship (Table 17). Similar exposure of

Genz-112638 (Table 18) was achieved in both male and female subjects, suggesting the observed larger QTc prolongation in female subjects is not due to a difference in pharmacokinetics. For female subjects, the predicted ΔΔQTcF at the geometric mean peak Genz-112638 concentration at the supra-therapeutic dose is 10.2 ms with 90% CI of (6.71, 13.6), which should be considered a positive finding.

Table 17: Exposure-Response Analysis of Genz-112638 Associated ΔΔQTcF Prolongation Stratified by Gender

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ddPR = Intercept + slope * Genz-112638 Concentration		
Male		
Intercept (ms)	-0.89 (-2.8; 1.02) 0.4305	4.49
Slope (ms per ng/mL)	0.0109 (-0.00921; 0.0311) 0.3566	0.04
Residual Variability (ms)	7.77	--
Female		
Intercept (ms)	0.25 (-2.28; 2.77) 0.8675	7.01
Slope (ms per ng/mL)	0.0387 (0.0211; 0.0563) 0.0018	0.04
Residual Variability (ms)	8.02	

Table 18: Predicted Change of ΔΔQTcF Interval at Geometric Mean Peak Genz-112638 Concentration using Model 1 Stratified by Gender

Dose Group	Predicted change in ΔΔQTcF interval (ms)	
	Mean	90% Confidence Interval
Male		
200 mg Genz-112638		
Geometric Mean C_{max} (16.8 ng/mL)	-0.707	(-2.54; 1.13)
800 mg Genz-112638		
Geometric Mean C_{max} (214 ng/mL)	1.45	(-2.69; 5.6)
Female		
200 mg Genz-112638		
Geometric Mean C_{max} (16.6 ng/mL)	0.891	(-1.46; 3.24)
800 mg Genz-112638		
Geometric Mean C_{max} (256 ng/mL)	10.2	(6.71; 13.6)

There is a clear linear relationship between Genz-112638 concentrations and QTc prolongation even though the study is negative as defined by ICH E14. Since the exposure of Genz-112638 in clinical practice could be higher than what was achieved under the supratherapeutic dose, QTc prolongation beyond the regulatory concern is possible. More importantly, female subjects were found to be more sensitive to the QT prolonging effect of Genz-112638. The clinical relevance of this finding in not known.

4.5.2 Genz-112638 Concentration-PR Interval Analysis

The relationship between ΔΔPR and Genz-112638 concentrations was also investigated by linear mixed-effects modeling.

Table 19 summarizes the results of the Genz-112638 concentration - ΔΔPR analyses based on Model 1. Model 1 was used for further analysis since the model with intercept was found to fit the data best. The predicted ΔΔPR at mean peak Genz-112638 concentration can be found in Table 20.

Table 19: Exposure-Response Analysis of Genz-112638 associated ΔΔPR Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ddPR = Intercept + slope * Genz-112638 Concentration		
Intercept (ms)	0.49 (-0.67; 1.65) 0.4803	4.3
Slope (ms per ng/mL)	0.0427 (0.0341; 0.0513) <0.0001	0.028
Residual Variability (ms)	6.7	--

Table 20: Predicted Change of ΔΔPR Interval at Geometric Mean Peak Genz-112638 Concentration using Model 1

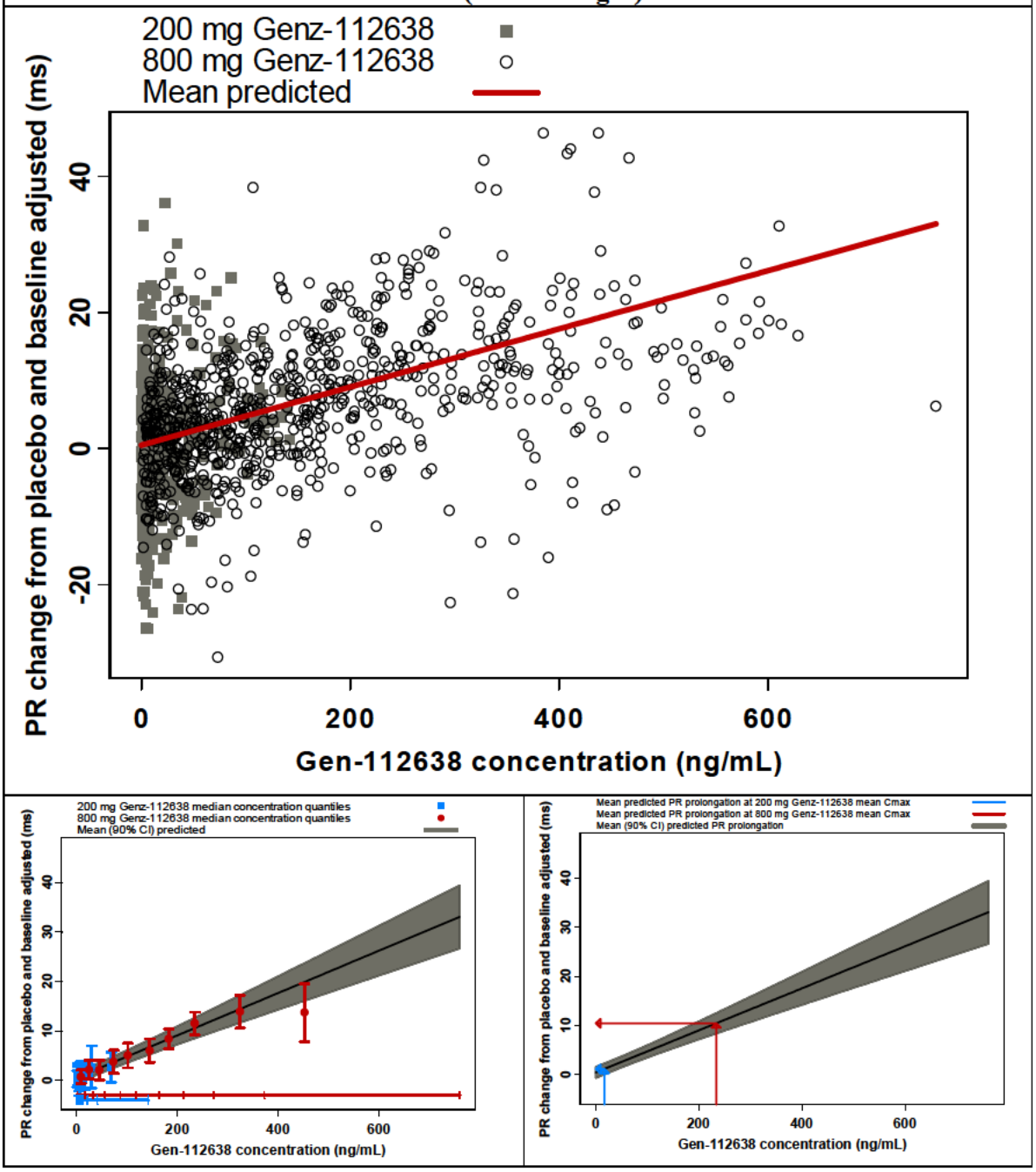
Dose Group	Predicted change in ΔΔ PR interval (ms)	
	Mean	90% Confidence Interval
200 mg Genz-112638		
Geometric Mean C_{max} (16.5 ng/mL)	1.19	(0.057; 2.33)
800 mg Genz-112638		
Geometric Mean C_{max} (233 ng/mL)	10.5	(8.36; 12.6)

The relationship between Genz-112638 concentrations and ΔΔPR is visualized in **Figure 10** where the raw data is shown on top together with the population predictions.

The goodness-of-fit is illustrated in the bottom left graph of **Figure 10** showing the observed median-quantile concentrations and associated mean ΔΔ PR (90% CI) together with the mean (90% CI) predicted ΔΔPR (black line with shaded grey area).

The mean (90% CI) predicted ΔΔPR at mean C_{max} is shown in the bottom right graph of **Error! Reference source not found.**.

Figure 10: ΔΔPR vs. Genz-112638 concentration. Observed data (Top), Concentration Quantile plot (Bottom Left), and Predicted ΔΔ PR at geometric mean Cmax (Bottom Right).



The quantile plot indicates that the linear model can only describe the relationship between ΔΔPR and Genz-99067 plasma concentration up to approximately 350 ng/ml, beyond which a non-linear relationship is suggested by the data. Nevertheless, a clear positive relationship is identified between ΔΔPR and Genz-99067 plasma concentration.

4.6 CLINICAL ASSESSMENTS

4.6.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines i.e. sudden cardiac death, syncope, seizure or significant ventricular arrhythmias occurred in this study.

4.6.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 99% of the ECGs were annotated in the primary lead II, with less than 0.2% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

4.6.3 PR and QRS intervals

Genz-112638 did appear to increase the PR interval in a dose- and concentration-dependent manner (Table 9, Figure 6,Figure 10). The largest upper limits of the 90% CI for the PR mean differences between 200 mg Genz-112638 and placebo, and between 800 mg Genz-112638 and placebo are 5.8 ms and 16.4 ms, respectively. Two subjects whose baseline PR was under 200 ms experienced a maximum change of 18 ms.

Although there were no subjects who had an absolute QRS interval greater than 120 ms, a trend was also observed with the QRS interval (Figure 8). The largest upper limits of 90% CI for the QRS mean differences between 200 mg Genz-112638 and placebo, and between 800 mg Genz-112638 and placebo are 1.6 ms and 5.2 ms, respectively.

4.7 PROPOSED ECG MONITORING PLAN IN PHASE 3 CLINICAL STUDIES

4.7.1 Protocol Number GZG02507

- Design: Randomized, double-blind, placebo-controlled, multi-center study followed by an open-label period.
- Duration: 2 years (0.75 y double-blind, 1.25 y open-label)
- Dose: 50 mg bid; increased to 100 mg (if Week 2 trough < 5 ng/ml)
- Pertinent exclusion criteria:
    - The patient is known to have any of the following criteria: clinically significant coronary artery disease including history of myocardial infarction or ongoing signs or symptoms consistent with cardiac ischemia or heart failure; or clinically significant arrhythmias or conduction defect such as 2nd or 3rd degree AV block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia.
    - The patient has received any medication within 30 days prior to dosing that may induce or inhibit CYP2D6 or any medication that may cause QTc interval prolongation..
    - ECG Assessments Study

Timepoint	Screening Period Day -28 to Day -1		Double-Blind Primary Analysis Period (Day 1 to Week 39)						Open-Label Period (Post-Week 39 [Day 1 of the Open-Label Period] to Study Completion)										Assessments Repeated (± 14 days)	Study Completion or Patient Discontinuation /Withdrawal [A]
			Treatment Period						Treatment Period											
			4-week Dose-Adjustment (± 3 days)			(± 14 days)			4-week Dose-Adjustment (± 3 days)			(± 14 days)							
			Day 1	Wk 2	Wk 4	Wk 13	Wk 26	Wk 39	Wk 39 +1 Day [B]	Wk 41	Wk 43	Wk 52	Wk 65	Wk 78	Wk 91	Wk 104	Wk 117	Wk 130	Every 3 Months	
a.m.	X																			
Pre-dose (a.m. at 0 hours)			X [C]						X [C]											X
Post-dose																				
1 hour			X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	
2 hours			X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	
3 hours			X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	
4 hours			X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Total Timepoints	1	0	5	0	4	4	4	4	5	0	4	4	4	4	4	4	4	4	4	1

[A] A single, 12-Lead ECG will be performed at study completion.
[B] Week 39 +1 Day refers to the first dosing day in the Open-Label Period after all Week 39 study assessments have been completed.
[C] Three 12-lead ECGs will be performed 5 to 10 minutes apart prior to the morning pre-dose on Day 1 (a.m. at 0 hours). If ECGs and blood samples are scheduled at the same time, ECGs will be performed first.

ECGs will be collected in a digital format to allow accurate assessments of any potential cardiac effects. All ECGs will be read centrally by independent reviewer.

24-hour Holter monitoring will be performed at Screening (prior to Day -7) and at Weeks 13 and 52 (at Week 13, patients who initially received Genz-112638 wil be at steady state; at Week 52, patients who initially received placebo then transitioned to Genz-112638 at Week 39 will be at steady state). Note: If a patient discontinues/withdraws from the study prior to Week 52, Holter monitoring will be performed at discontinuation/withdrawal. Holter monitoring data will be reviewed by the ECG core laboratory, and the results will be reported to the Investigator and Sponsor.

4.7.2 Protocol Number GZG02607

- Design: A Phase 3, Multi-Center, Multi-National, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety
- Duration: 1 year
- Dose: 50 mg bid; increased to 100 mg (if Week 2 trough < 5 ng/ml)
- Pertinent exclusion criteria:
    - The patient is known to have any of the following criteria: clinically significant coronary artery disease including history of myocardial infarction or ongoing signs or symptoms consistent with cardiac ischemia or heart failure; or clinically significant arrhythmias or conduction defect such as 2nd or 3rd degree AV block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia.
    - The patient has received any medication within 30 days prior to dosing that may induce or inhibit CYP2D6 or any medication that may cause QTc interval prolongation.

- ECG Assessments Study

after Week 104)

Timepoint	Screening Periods Day -28 to Day -1		Dose-Adjustment Period (± 3 days)			Treatment Period (± 14 days)								Assessments Repeated Every 3 Months (± 14 days)	Study Completion or Patient Discontinuation/ Withdrawal [A]
	1	2	Day 1	Wk 2	Wk 4	Wk 13	Wk 26	Wk 39	Wk 52	Wk 65	Wk 78	Wk 91	Wk 104		
a.m.	X														
Pre-dose (a.m. at 0 hours)			X[B]												
1 hour post-dose			X		X	X	X	X	X	X	X	X	X	X	X
2 hours post-dose			X		X	X	X	X	X	X	X	X	X	X	
3 hours post-dose			X		X	X	X	X	X	X	X	X	X	X	
4 hours post-dose			X		X	X	X	X	X	X	X	X	X	X	
Total Timepoints	**1**	**0**	**5**	**0**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**1**

[A] A single, 12-Lead ECG will be performed at study completion.
[B] Three 12-lead ECGs will be performed 5 to 10 minutes apart prior to the morning pre-dose on Day 1 (a.m. at 0 hours). If ECGs and blood samples are scheduled at the same time, ECGs will be performed first.

ECGs will be collected in a digital format to allow accurate assessments of any potential cardiac effects.

24-hour Holter monitoring will be performed at Screening (prior to Day -7) and at Weeks 13, 52, 104, and at study completion.

5 APPENDICES

5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Structural Properties	404.5 D; solubility 1.88 mg/mL in USP pH 7.4 buffer; mLogP 3.6; Rule of 5 violations: 0	
Therapeutic dose	The current Phase 2 dose is (b) (4) 100 mg bid	
Maximum tolerated dose	(b) (4)	
Principal adverse events	Phase 1 Single dose (related treatment emergent Grade 2 or higher): headache, dizziness, throat irritation, hypotension, bradycardia, nausea Phase 1 Multiple dose (related treatment emergent Grade 2 or higher): nausea, vomiting, headache, dizziness Phase 2 (related treatment emergent Grade 2 or higher): None	
Maximum dose tested	Single Dose	30 mg/kg
	Multiple Dose	350 mg bid for 11 days
Exposures Achieved at Maximum Tested Dose	Single Dose	Cmax @ 30 mg/kg: 1852 ± 1076 ng/mL AUC(0-∞) @ 30 mg/kg: 10528 ± 5471 ng*h/mL
	Multiple Dose	350 mg bid at steady-state: AUC(0-τ)ss: 1287 ± 428 ng*h/mL; Cmax,ss: 278 ± 62 ng/mL; 100 mg bid at steady-state in the presence of a strong CYP 2D6 inhibitor: AUC(0-τ)ss: 785 ng*h/mL; Cmax,ss: 102 ng/mL
Range of linear PK	0.01 to 30 mg/kg single dose; 50 to 350 mg bid multiple dose *this range represents the range of tested doses and not the linear range, which was not determined because of the occurrence of adverse events	
Accumulation at steady state	Accumulation at steady-state was greater than predicted based on single dose kinetics; ~3- to 5-fold accumulation ratio based on Cmax and AUC	
Metabolites	Putative metabolites have been synthesized and 9 found present in plasma samples from Phase 2. *See attached table below.* In hERG testing (Rapid ICE assay) Genz-256222 is 5-fold less potent than 112638; the remainder have IC_{50}s >30 μM. Genz-256222 has an IC_{50} of 3.7 μM against CYP 3A4;; the remaining metabolite have an IC_{50} against CYP3A4 & 2D6 IC50s of > 5 μM. However, Genz-256222 is not detected in plasma at clinical doses. Further, the metabolites are ≥ 10-fold less potent than Genz-99067.	
Metabolism	Appears to be catalyzed primarily by CYP 2D6 with contribution by CYP 3A4 (b) (4) Appears to inhibit the metabolism of CYP 2D6 (IC50 1.92 ∝M)	
Absorption	Absolute/Relative Bioavailability	Not determined
	Tmax	1-2 hours for parent and metabolites
	BCS Class	I (Maximum absorbable dose based on dose to solubility ratio of < 250 estimated to be ~7 g)
Distribution	Vz/F	5322 ± 5864 L at 200 mg bid
	% bound	62% bound in human plasma
	Transporters	p-glycoprotein substrate; no others examined

Elimination	Route	• <1.5% excreted unchanged in urine after single dose administration • No other routes of elimination examined			
	Terminal t½	• 6.0 ± 1.0 hours at 200 mg bid • 6.4 to 14.7 hours for metabolites			
	CL/F	Time-dependent: 38.5 ± 45.6 L/min at 200 mg bid on Day 1 12.1 ± 16.3 L/min at 200 mg bid on Day 12			
Intrinsic Factors	Age	Not examined			
	Genetics	CYP 2D6 metabolizer status: Although a formal genotype analysis has not been conducted, results across studies suggest a rank order correlation between Genz-99067 exposure and CYP 2D6 enzyme activity with extensive metabolizers having lower exposure than poor metabolizers			
	Sex	Results are inconsistent across studies: • In Study GZGD00204, females had consistently higher concentrations than males; Cmax,ss: 158 ± 131 ng/mL females at 200 mg bid on Day 12 vs. 130 ± 88.5 ng/mL for males; AUC(0-τ)ss: 1000 ± 818 ng*h/mL females at 200 mg bid on Day 12 vs. 556 ± 424 ng*h/mL for males. • In Study GZGD01707, males appeared to have higher exposure than females but the results were not statistically significant.			
	Race	Not examined			
	Hepatic & Renal Impairment	Not examined			
Extrinsic Factors	Drug interactions	Paroxetine (strong CYP 2D6 inhibitor): 7- to 9-fold increase in AUC(0-τ)ss and Cmax,ss Ketoconazole (strong CYP 3A4 and P-glycoprotein inhibitor): results pending			
	Food Effects	300 mg single dose fast vs high fat meal			
		Fasting	Fasting	Fed	Estimate (90% CI)
		Cmax (ng/mL)	88.3 ± 76.2	79.1 ± 65.9	85 (68-107)
		AUC(0-∞) (ng*h/mL)	623 ± 601	696 ± 656	105 (89-123)
		Tmax (h)	2.00	3.00	
Expected High Clinical Exposure Scenario	Co-administration with strong CYP 2D6 inhibitors may lead to a 7- to 9-fold increase in exposure				
Note: All means are reported as ± standard deviation.					

5.2 TABLE OF STUDY ASSESSMENTS FOR STUDY GZGD01707

Table 9-1 Schedule of Study Assessments

	TREATMENT PERIOD 1						TREATMENT PERIODS 2, 3, and 4				FINAL STUDY FOLLOW-UP/ WITHDRAWAL*
	Screening		Admission	Placebo Lead-in	Treatment	Follow-up	Admission	Placebo Lead-in	Treatment	Follow-up	
	Screening 1	Screening 2									
	Days -32 to -22	Days -21 to -3[f]	Day -2	Day -1	Day 1	Day 2	Day -2	Day -1	Day 1	Day 2	5 to 7 Days after Treatment Period 4
Obtain Written Informed Consent	X										
Assign Screening Number	X										
Medical History	X										
Demographics and Baseline Characteristics	X										
Inclusion/Exclusion Criteria	X										
Physical Examination (including height & weight)[A]	X		X				X				X
Vital Signs	X		X	X	X[B]	X[B]	X	X	X[B]	X[B]	X
Plasma Hematology	X										X
Serum Chemistry[C]	X										X
Electrolyte Testing[D]	X		X		X	X	X		X	X	X
CPK/Troponin Assessment	X				X[E]	X			X[E]	X	
Urine Tests	X		X				X				X
Urine Pregnancy Test (female subjects of childbearing potential)	X		X				X				X
Controlled Substance Analysis	X		X				X				
HIV, Hepatitis B & C	X										
Screening ECG	X[F]										
Blood Sample for *CYP 2D6* Genotyping	X[G]										
24 Hour Holter Monitoring		X[H]									
Assign Enrollment No.			X								
Clinic Admission			X				X				
12-Lead Holter ECG				X[I]	X[I]	X[I]		X[I]	X[I]	X[I]	
Study Drug Administration				X[J]	X[K]			X[J]	X[K]		

	TREATMENT PERIOD 1						TREATMENT PERIODS 2, 3, and 4				FINAL STUDY FOLLOW-UP/ WITHDRAWAL*
	Screening		Admission	Placebo Lead-in	Treatment	Follow-up	Admission	Placebo Lead-in	Treatment	Follow-up	
	Screening 1	Screening 2									
	Days -32 to -22	Days -21 to -3[f]	Day -2	Day -1	Day 1	Day 2	Day -2	Day -1	Day 1	Day 2	5 to 7 Days after Treatment Period 4
Blood Sample for PK Analysis				X[L]	X[L]	X[L]		X[L]	X[L]	X[L]	X
Safety ECG[M]				X	X			X	X		X
Clinic Discharge						X				X	
AE Assessment	◄ Continuous Monitoring ►										
Concomitant Medications/Therapies	◄ Continuous Monitoring ►										

* Subjects who are withdrawn or discontinued from the study for any reason should return to the study unit 5 to 7 days after their withdrawal/discontinuation for a Final Study Follow-up visit.

[f] The last day to complete the 24-hour Holter monitoring at Screening 2 will be Day -14 in order to ensure that the Holter monitoring and *CYP 2D6* genetic testing results are obtained prior to Admission (Day -2).

[A] Physical examinations include weight (without shoes and wearing the lightest possible clothing) and height (at Screening 1 only)

[B] Measure vital signs after the subject has been sitting for approximately 5 minutes pre-dose (at 0 hours) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose. Vital signs should not be measured until approximately 5 minutes after the ECG timepoint.

[C] All subjects must have fasted at least 8 to 12 hours prior to the collection of the blood sample for serum chemistry testing.

[D] Electrolyte testing includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, and phosphorous.

[E] Collect blood samples for CPK/Troponin assessment pre-dose (at 0 hours).

[F] A subject's Screening ECG will be conducted while the subject remains in a supine position for at least 10 minutes prior to conducting the ECG.

[G] Blood samples for *CYP 2D6* genotyping will be collected during Screening 1, but will not be tested until after the subject's Holter monitor review has indicated that the subject can be enrolled in the study.

[H] All screening assessments must be considered by the Investigator to be either within normal limits or not clinically significant before the dosing of a subject occurs. Once subjects have acceptable Screening 1 assessments, the subject will have a 24-hour Holter monitor assessment during Screening 2. Subjects will not be enrolled until the 24-hour Holter monitor results have been reviewed by a board certified cardiologist to determine whether there are findings that would preclude treatment.

[I] After an overnight fast of at least 8 to 12 hours, subjects will be connected to a 12-Lead ECG Holter monitoring device. ECG interval values in triplicate will be extracted from the Holter monitoring device and averaged for each of the following observation timepoints: On Day -1 (Placebo Lead-in) at pre-dose (at 0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, and 24 hours (Day 1) post-dose; on Day 1 (Treatment: Placebo, Genz-112638 [200 or 600 mg], or moxifloxacin) pre-dose (at 0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, and 24 hours (Day 2) post-dose. Immediately prior to the start of each ECG timepoint, site staff should remind the subject to remain in a supine position as motionless as possible and to refrain from speaking. Staff should check lead attachments and proper functioning of the Holter device. From 30 minutes pre-dose until approximately 6 hours post-dose, subjects should remain on bed rest (with exceptions of bathroom visits). Meals and environmental stimulation including television, conversation, and disruptions caused by other subjects or site staff activities, should be restricted. After approximately 4 hours post-dose, meals, blood collections, vital sign measurements, or study activities and disruptions should not occur during ECG timepoints.

[J] Subjects will receive a set of 7 placebo capsules orally with approximately 8 oz of water. A subject will be permitted to drink water 1 hour post-dose and eat approximately 4 hours post-dose.

[K] Subjects will receive a set of 7 capsules orally of either placebo, Genz-112638 [200 or 600 mg], or moxifloxacin with approximately 8 oz of water in the morning of Day 1 of each treatment period between 6:00 am and 9:00 am. All subjects must have fasted at least 8 to 12 hours prior to dosing. A subject will be permitted to drink water 1 hour post-dose and eat approximately 4 hours post-dose.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 67589	GENZYME CORP	GENZ-112638 CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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02/05/2009

YANING WANG
02/05/2009

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02/05/2009

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02/05/2009

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 16, 2014

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Jessica Benjamin, RPM
DGIEP

Subject: QT-IRT Consult to DGIEP (NDA 205494)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated November 13, 2013 regarding labeling. The QT-IRT received and reviewed the following materials:

- Your consult
- Draft Label
- ISS section 9.5.2 (ECGs phase 2 and 3 studies)
- TQT study review (Feb 5th 2009)

QT-IRT Comments for DGIEP

QT-IRT conducted further analysis with datasets of the TQT study submitted for eliglustat. Results show no proarrhythmia risk at the predicted steady-state Cmax achieved (b) (4) ng/ml) for the GD1 patients with CYP2D6 phenotype (Table 1).

Table 1

Predicted mean (90%CI, ms) change in	At therapeutic mean Cmax of (b) (4) ng/mL proposed in the draft label	At mean Cmax of 250 ng/mL interested by the review team	At supra-therapeutic mean Cmax of 500 ng/mL used in the draft label (b) (4)
QTcF	(b) (4)	**6.4 (3.4, 9.4)**	
PR		**11.2 (8.9, 13.4)**	
QRS		**3.5 (1.9, 5.1)**	

However, QTc, PR and QRS prolongation are expected at steady-state supratheraputic scenario Cmax (e.g., more than 10 ms mean change in QTcF may be expected when mean Cmax is higher than 250 ng/mL) (Table 1). The PR effect size is unlikely to be clinically meaningful in healthy subjects. In patients with pre-existing AV nodal disease and/or being co-administered agents that block the AV node, the PR prolongation may become clinically important.
QRS effect size is not clinically meaningful in healthy subjects and probably not in patients.

Overall the pooled Eliglustat Safety Set was small (a total of 393 patients). No sudden cardiac deaths, Torsade de pointes or clinically meaningful AV-block cases were reported.
One subject (GZGD00304/0302) was withdrawn from study GZGD0034 after the first dose of Eliglustat due to a ventricular tachycardia episode that required hospitalization and was considered by the investigator to be possibly related to Eliglustat.

Data reported from electrocardiogram monitoring during phase 2 and 3 studies showed no clinically relevant changes in QTcF. Seven subjects had PR intervals > 200 ms and increase from baseline ≥ 25%. One had a clinically meaningful PR prolongation.
Eighteen subjects had a post-baseline QRS ≥ 120 ms, two of them had postbaseline increases of 30 and 50%, which are clinically meaningful.

BACKGROUND

QT-IRT reviewed a TQT study for Genz-112638 (eliglustat). Genz-112638 increased the QTc and PR intervals in a dose- and concentration-dependent manner. For QTcF, the largest upper bounds of the 2-sided 90% CI for the mean difference between GENZ-112638 (200 mg and 800 mg) and placebo were below 10 ms. For PR, the largest upper limits of the 2-sided 90% CI for the mean difference between Genz- 112638 (200 mg and 800 mg) and placebo were 5.8 ms and 16.4 ms, respectively.

Sponsor's Proposed Label

12.2 Pharmacodynamics

Electrocardiographic Evaluation

(b) (4)

(b) (4)

(b) (4)

4 Contraindications[1]

(b) (4)

Warning and Precautions

5.1 Drug-Drug Interactions

(b) (4)

[1] 2.5 Section 3.2.1, Table 2

[redacted]

5.2 [redacted]

Use of CERDELGA in patients with pre-existing cardiac conditions has not been studied during clinical trials. Because CERDELGA is predicted to cause [redacted] increases in ECG intervals at substantially elevated eliglustat plasma concentrations, use of CERDELGA [redacted] in patients with cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, and in combination with Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications.

QT-IRT suggested label

The following text is our suggestion for labeling. We defer all labeling decisions to the review division.

12.2 Pharmacodynamics

QTc interval prolongation was studied in a double-blind, single dose, placebo- and positive-controlled crossover study in 42 healthy subjects. At a dose 4 times the recommended dose, CERDELGA did not prolong the QT interval to any clinically relevant extent.

For PR, the largest upper limits of the 2-sided 90% CI for the mean difference between CERDELGA (169 mg and 675 mg) and placebo were 5.8 ms and 16.4 ms, respectively. Two subjects whose baseline PR was less than 200 ms experienced a maximum change of 18 ms.

5.1 Drug-Drug Interactions

CERDELGA is contraindicated in patients taking a strong (e.g., paroxetine, fluoxetine, quinidine) or moderate (e.g., duloxetine, terbinafine) CYP2D6 inhibitor concomitantly with a strong (e.g., clarithromycin, itraconazole) or moderate (e.g., erythromycin, fluconazole) CYP3A inhibitor. Under these conditions both major metabolic pathways for CERDELGA metabolism are impaired, with predicted substantially elevated eliglustat plasma concentrations [see Contraindications (4), and Pharmacokinetics (12.3)]. Based on PK/PD modeling, eliglustat

plasma concentrations 11-fold those expected at the indicated dose are predicted to increase the PR, QRS, and QTc intervals (by 25% upper bound of 26, 10 and 19 msec, respectively).

SAFETY

From Integrated Electrocardiogram analyses (ISS, section 3.1.2, page 39)

The ECG data available for this ISS were collected in 5 studies as follows:

- TQT Study, a completed Phase 1 study in healthy subjects;
- Phase 2, a study in treatment-naïve patients with GD1: data from the 52-week Primary Analysis Period, 3 years of Extension Period data, and up to the ISS cut-off date of 31 January 2013;
- ENGAGE, a Phase 3 study in treatment-naïve patients with GD1: data from the 39-week Primary Analysis Period and Long-term Treatment Period data up to the ISS cut-off date (31 January 2013);
- ENCORE, a Phase 3 study in GD1 patients switching from ERT: data from the 52-week Primary Analysis Period and Long-term Treatment Period data up to the ISS cut-off date (31 January 2013);
- EDGE, a Phase 3b study in patients with GD1: available data from the ongoing Lead-in Period up to the ISS cut-off date (31 January 2013).

With the exception of EDGE, all ECG and Holter recordings for the other 4 studies were centrally read by a core laboratory, (b) (4)

Electrocardiograms

ECGs Results from Phase 2 and 3 Studies

The effect of eliglustat on ECG parameters was further investigated in the population of adult GD1 patients and after repeated therapeutic dosing at 50, 100 or 150 mg BID during the Phase 2 and 3 studies.

The primary safety database supporting this application contains pooled data from 393 patients with GD1 who received eliglustat in an ongoing Phase 2 study (GZGD00304), and 2 ongoing Phase 3 studies (GZGD02507 [ENGAGE], GZGD02607 [ENCORE], and 1 ongoing Phase 3b study GZGD03109 [EDGE; Lead-In Period only]);

Table 2- Patients With Select Potentially Clinically Significant Abnormalities in Electrocardiogram QTcF and PR Parameters – Phase 2 Study and Phase 3 Studies

Criterion/ Study	Patient ID#	Duration in Study (last visit evaluated)	Number of Time Points with Liability	Baseline	ECG Highest Values*				PK Conc. at Time of Highest Value (ng/mL)	Highest Conc. Overall Study (ng/mL)
					Raw value	Delta	% Change	Visit/Time		
QTcF Interval >480 msec post Baseline and Baseline ≤480 msec (n=2 patients)										
EDGE	33903	Wk 26	1/19	461.7	502.0	40.3	8.7	Wk 26 T1H	1.70**	10.2
	35704	Wk 26	1/26	463.4	482.7	19.3	4.2	Day 1 T2H	<LLOQ**	50.5
QTcF Interval Increase from Baseline >60 msec (n=6 patients)										
EDGE	30501	Wk 26	5/20	350.9	427.4	76.5	21.8	Wk 2 T4H	0.77**	33.3
	31613	Wk 78	1/29	379.2	441.2	62.0	16.3	Wk 78 T3H	9.68**	18.9
	32804	Wk 26	1/21	362.7	434.6	71.9	19.8	Wk 26 T2H	13.8	14.5
	32806	Wk 26	2/19	362.6	432.0	69.3	19.1	Wk 2 T3H	1.31**	10.5
	38401	Wk 26	2/30	340.0	451.0	111.0	32.6	Wk 2 T1H	21.9	22.58
	38402	Wk 78	1/39	353.6	414.8	61.2	17.3	Wk 8 Pre	6.66	140.09
PR Interval >200 msec and Increase from Baseline ≥ 25% (n=7 patients)										
ENCORE	2103	Wk 91	3/40	397.7	568.0	170.3	42.8	Wk 13 T4H	32.6	62.8
	2703	Wk 130 / Mo 30	2/48	154.0	208.0	54.0	35.1	Wk 52 T1H	29.9	63.2
	5801	Wk 130 / Mo 30	1/50	137.3	206.0	68.7	50.0	Wk 13 Pre	23.7	111
	5957	Wk 52	3/25	155.0	205.0	50.0	32.3	Wk 52 T2H	40.4	84.4
EDGE	31002	Wk 52	6/23	120.0	220.0	100.0	83.3	Wk 13 T1H	4.53	32.3
								Wk 13 T2H	20.8	
								Wk 26 Pre	2.97	
								Wk 52 T1H	4.93	
								Wk 52 T2H	23.0	
	34501	Wk 52	1/24	160.0	240.0	80.0	50.0	Wk 2 T1H	2.41**	28.5
	38401	Wk 26	1/30	206.7	260.0	53.3	25.8	Day 1 T3H	5.61	22.58

Criterion/ Study	Patient ID#	Duration in Study (last visit evaluated)	Number of Time Points with Liability	Baseline	ECG Highest Values*				PK Conc. at Time of Highest Value (ng/mL)	Highest Conc. Overall Study (ng/mL)
					Raw value	Delta	% Change	Visit/Time		
QRS Interval ≥ 120 msec (n=18 patients)										
ENGAGE	0105	Wk 156 / Mo 36	1/65	104.0	120.0	16.0	15.4	Wk 143 T3H	7.33**	24.7
	2401	Wk 130 / Mo 30	14/57	106.0	127.0	21.0	19.8	Wk 4 T2H	21.7	31.3
ENCORE	5706	Wk 65	2/29	104.7	122.0	17.3	16.6	Day 1 T4H	4.82	81.6
EDGE	30402	Wk 52	2/24	112.7	129.0	16.3	14.5	Wk 52 T1H	24.0**	29.1
	30406	Wk 26	8/23	113.0	126.0	13.0	11.5	Wk 13 T1H	6.43	6.43
								Wk 26 T1H	4.71**	
	30903	Wk 26	1/19	100.7	122.0	21.3	21.2	Wk 13 Pre	2.03	16.8
	32201	Wk 26	3/19	105.7	134.0	28.3	26.8	Wk 26 T1H	7.91**	28.28
	32606	Wk 26	1/16	100.0	124.0a	24.0	24.0	Wk 6 Pre	6.32	31.9
EDGE	32804	Wk 26	4/21	113.3	120.0	6.7	5.9	Day 1 T1H	-	14.5
								Day 1 T2H	2.64	
								Day 1 T3H		
								Day 1 T4H		
	32806	Wk 26	1/19	100.0	120.0	20.0	20.0	Day 1 T4H	0.73**	10.5
	32901	Wk 52	2/24	80.0	120.0	40.0	50.0	Wk 2 T2H	11.6	59.6
								Wk 26 T1H	59.6**	
	32916	Wk 26	1/19	100.0	120.0	20.0	20.0	Wk 26 Pre	-	16.8
	33902	Wk 26	14/18	103.3	134.0	30.7	29.7	Wk 26 T1H	5.97**	34.7
	34801	Wk 26	19/19	133.0	141.0	8.0	6.0	Wk 2 T3H	2.27**	18.0
	35706	Wk 26	1/21	106.0	122.0b	16.0	15.1	Wk 2 T4H	4.55**	37.9
	37901	Wk 52	2/25	116.7	120.0	3.3	2.9	Wk 13 Pre	2.55	12.1

Criterion/ Study	Patient ID#	Duration in Study (last visit evaluated)	Number of Time Points with Liability	Baseline	ECG Highest Values*				PK Conc. at Time of Highest Value (ng/mL)	Highest Conc. Overall Study (ng/mL)
					Raw value	Delta	% Change	Visit/Time		
								Wk 13 T1H	12.12	
	38401	Wk 26	6/30	66.7	240.0	173.3	260.0	Wk 2 Pre	6.42	22.58
EDGE	38402	Wk 78	6/39	120.0	120.0	0.0	0.0	Day 1 T1H	7.84	140.
								Wk 2 Pre		
								Wk 2 T1H		
								Wk 2 T2H		
								Wk 2 T3H		
								Wk 2 T4H		

Source: PGM=DEVOPS/GENZ112638/POOL/ISS_2013/REPORT/PGM/pool_pd_egpcsa_s_t.sas OUT=REPORT/OUTPUT /pool_pd_egpcsa_s_t_a_t_i.rtf (28JUN2013 - 9:50) (modified)
All data up to cutoff date (31 Jan 2013) are taken into account; for EDGE study, only the lead-in data are considered.
Delta=Change from Baseline; %change=Percent change from Baseline; "pre"=predose value.
The number of time points with liability is calculated using all post-Baseline time points.
a. Reporting error detected by the independent cardiologist expert after the cutoff date: QRS value=100 msec
b. Reporting error detected by the independent cardiologist expert after the cutoff date: QRS value=112 msec
* The highest values correspond to the highest raw or delta value, depending on the abnormality definition.
** Genz-99067 concentration available at that visit for ECG time point with no concomitant PK sample.
Some values in GZGD03109 study were corrected after the cutoff date (Jan 31 2013) following additional queries; this output takes into account these modifications.

From ISS, adapted from Table 25 (NDA, module 2.7.4)

Reviewer's comments
With the exception of the EDGE study, all ECGs and Holter recordings were centrally read by a core laboratory. No clinically relevant changes in QTcF were reported in these studies. Seven subjects had PR intervals > 200 ms and increase from baseline ≥ 25%. One had a clinically meaningful PR prolongation. Subject 2103, a participant in the ENCORE study had a PR clinically meaningful at baseline (398 ms) and a post-baseline increase of 170 ms (568 ms). Eighteen subjects had a post-baseline QRS ≥ 120 ms, two of them had postbaseline increases of 30 and 50%, which are clinically meaningful.

Cardiac Disorders (Section 6.6.3, ISS)

6.6.3.1 Cardiac Arrhythmias
Table 6-17 and Table 6-18 summarizes the incidence of cardiovascular TEAEs by HLGT in the pooled Eliglustat Safety Set by study and overall. A total of 4% of patients (15/393) reported cardiac arrhythmia events by HLGT or high level term (HLT).
The most frequent TEAE by HLT were Cardiac conduction disorders (6/393 patients [2%]), Supraventricular arrhythmias (4/393 patients [1%]), and Ventricular arrhythmias and cardiac arrest (4/393 patients [1%]); one patient reported a TEAEs in the HLGT Rate and rhythm disorders not elsewhere classified (NEC). The TEAEs considered related to study drug by the investigators were: Atrioventricular block second degree (3/393 patients [1%]); Ventricular tachycardia (2/393 patients [1%]); and Supraventricular tachycardia (2/393 patients [1%]) (Statistical Table 6.1.4.1). One patient temporarily discontinued study drug but remained in the study (GZGD02507/4905; a dose adjustment was made afterward) and 2 patients (GZGD0304/0302 and GZGD0304/0202) withdrew from the study due to a cardiovascular event, and 6 patients (2%) experienced SAEs in the Cardiac disorders SOC (Statistical Table 6.1.5.1 and Statistical Listing 6.1).

Table 3- Summary of Patients With Treatment-Emergent Cardiac Arrhythmia Adverse Events by MedDRA High Level Term and Preferred Term by Study and Overall - Eliglustat Safety Set

MedDRA High Level Term MedDRA Preferred Term	GZGD00304 (N = 26)		GZGD02507 (N = 40)		GZGD02607 (N = 157)		GZGD03109 (N = 170)		All Eliglustat (N = 393)	
	Events n(/100py) [a]	Patients n (%) [b,c]	Events n(/100py) [a]	Patients n (%) [b,c]	Events n(/100py) [a]	Patients n (%) [b,c]	Events n(/100py) [a]	Patients n (%) [b,c]	Events n(/100py) [a]	Patients n (%) [b,c]
Total patients with events	3 (3)	2 (8)	4 (7)	3 (8)	7 (3)	6 (4)	4 (3)	4 (2)	18 (3)	15 (4)
Cardiac conduction disorders	0 (0)	0 (0)	3 (5)	2 (5)	5 (2)	4 (3)	0 (0)	0 (0)	8 (1)	6 (2)
Atrioventricular block second degree	0 (0)	0 (0)	2 (3)	2 (5)	3 (1)	2 (1)	0 (0)	0 (0)	5 (1)	4 (1)
Atrioventricular block	0 (0)	0 (0)	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (<1)
Atrioventricular block first degree	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	1 (0)	1 (<1)
Sinoatrial block	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	1 (0)	1 (<1)
Supraventricular arrhythmias	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (3)	4 (2)	4 (1)	4 (1)
Supraventricular tachycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)	2 (0)	2 (1)
Arrhythmia supraventricular	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (<1)
Atrial Tachycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (<1)
Ventricular arrhythmias and cardiac arrest	3 (3)	2 (8)	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)	0 (0)	5 (1)	4 (1)
Ventricular tachycardia	3 (3)	2 (8)	0 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	4 (1)	3 (1)
Ventricular extrasystoles	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	1 (0)	1 (<1)
Rate and rhythm disorders NEC	0 (0)	0 (0)	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (<1)
Tachycardia	0 (0)	0 (0)	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (<1)

Source: Statistical Table 6.1.7.2
HLGT = High Level Group Term; HLT = High Level Term; NEC = Not elsewhere classified; PT = Preferred Term; py = patient-years
[a] The adverse event counts are accompanied by normalized counts per 100 person years (/100 py).
[b] If a patient had more than one adverse event for a particular HLT/PT, he/she is counted only once for the HLT/PT.
[c] Patient percentages are based on the total number of patients treated with eliglustat for each column in the pooled studies: GZGD00304, GZGD02507, GZGD02607, and GZGD03109 (open-label Lead-in Period only).

Source: ISS, Table 1-18

Table 4-Summary of Treatment-Emergent Adverse Events Leading to Permanent Study Drug Discontinuation and Study Withdrawal - Eliglustat Safety Set

Patient ID	Sex/Age (yrs)[a]	Dose[b] (mg)	MedDRA System Organ Class[c] / Preferred Term	Time from 1st Dose (days)	Event Duration (days)	Severity/SAE/ Outcome	Relationship to Study Drug	Other Action Taken
Phase 2 Study GZGD00304								
GZGD 00304/ 0105	F/31	--[d]	Musculoskeletal and connective tissue disorders/ Osteonecrosis	365	--	Moderate/No/ Not recovered	Not related	None
GZGD 00304/ 0202	F/56	100 BID	Cardiac disorders/ Ventricular tachycardia	1	1	Mild/No/ Recovered	Remote; unlikely	None
			Cardiac disorders/ Ventricular tachycardia	2	1	Mild/No/ Recovered	Remote; unlikely	None
GZGD 00304/ 0302	M/60	50 QD	Cardiac disorders/ Ventricular tachycardia	1	1	Mild/Yes/ Recovered	Possible	Hospitalization

Source: 2.7.4, table 22 (adapted)

Reviewer's comments:

The pooled Eliglustat Safety Set contained 393 patients, 26 patients from the Phase 2 study, 40 patients from ENGAGE, 157 patients from ENCORE, and 170 patients from EDGE. No sudden cardiac deaths, Torsade de pointes or clinically meaningful AV-block cases were reported.

Subject GZGD00304/0302 was withdrawn from the study after the first dose of Eliglustat due to a ventricular tachycardia episode that required hospitalization and was considered by the investigator to be possibly related to Eliglustat. Three patients had non-sustained ventricular tachycardia episodes that were asymptomatic. Four patients reported 2nd-degree AV block that were asymptomatic and taken from unscheduled Holter monitoring.

Thank you for requesting our input into the development of this product under NDA 205494. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 205494
Drug Name	Eliglustat Tartrate (Genz-112638)
Proposed Indication	Long-term treatment of adults patients with Gaucher Disease type 1
Clinical Division	CDER/ODEIII/DGIEP
PBPK Consult request	Elizabeth Shang, Ph.D. Apparaju Sandhya , Ph.D.
Primary PBPK Reviewer	Yuzhuo Pan, Ph.D.
Secondary PBPK Reviewer	Ping Zhao, Ph.D
Sponsor	Genzyme Corporation

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Objectives

The main purposes of this review memo are (a) to review sponsor's physiologically-based pharmacokinetic (PBPK) reports entitled "Quantitative Prediction Of The Systemic Exposure Of Genz-112638 Using Prior In Vitro And In Vivo Data: Potential For Drug- Drug Interactions As A Victim" and "Quantitative Prediction Of Drug-Drug Interactions Involving Genz-112638 (As The Victim) And Fluconazole (CYP3A4) And Terbinafine (CYP2D6) As Perpetrators" [1,2] and sponsor's responses to the information requests sent by the FDA during NDA review [3-5]; and (b) to evaluate the effect of CYP2D6 polymorphism and co-medication, either alone or in combination on eliglustat exposure.

1. Background

1.1. Regulatory history on PBPK submission

Eliglustat (Genz-112638) is an oral glucosylceramide synthase inhibitor. It is a substrate reduction therapy (SRT) to treat symptoms of Gaucher disease type 1 (GD1) by reducing the synthesis of glucosylceramide. The proposed dose regimen by the sponsor is oral dose of 100 mg capsules twice daily (b.i.d.) in CYP2D6 extensive metabolizers (EM) and intermediate metabolizers (IM) [6]. A PBPK model was developed by the sponsor as part of the NDA submission [6]. A total of 3 PBPK information requests were sent to the sponsor on Dec 12, 2013 (12122013IR), Jan 10, 2014 (01102014IR), and March 19, 2014 (03192014IR). The responses to these IR were received on Dec 12, 2013, Jan 16, 2014, and March 28, 2014 [3-5]. The information requests can be found in **Appendices 5.2.1-5.2.3**.

1.2. Highlight of drug absorption and disposition

After oral administration, the pharmacokinetic (PK) profile of eliglustat was characterized by a rapid absorption, a very low absolute oral bioavailability (F) due to high first-pass metabolism. Eliglustat has a large apparent volume of distribution (V/F), a moderate plasma protein binding and a moderate distribution to red blood cells. The excretion of the drug is through both liver and kidney, mainly as metabolites. Following multiple doses, eliglustat PK exhibits time- and dose-dependent PK nonlinearity.

Table 1. Summary of eliglustat's absorption, distribution, metabolism and excretion (ADME) and drug-drug interaction potential [6]

Absorption	Rapidly absorbed with Tmax 1-4 hrs
Distribution	Apparent volume of distribution (V/F) is (b) (4) L. In vitro, plasma proteins binding ranged from 76.4 to 82.9% and blood/plasma ratio ranged from 1.3 to 1.4
Metabolism/transport	Eliglustat is extensively metabolized by CYP2D6, and to a lesser extent, CYP3A4. In vitro, eliglustat is a substrate of P-glycoprotein (P-gp)
Excretion	Excretion is via feces (51.4%) and urine (41.8%) primarily in the forms of metabolites. Less than 1% of the parent drug in the mass balance study is excreted in the feces and urine, respectively.
Drug-drug interaction potential	As enzyme/transporter perpetrator: In vitro, eliglustat is an inhibitor of P-gp and a time-dependent inhibitor of CYP2D6. The effects were confirmed in vivo using digoxin and metoprolol as substrate. As enzyme substrate: In healthy subjects, co-administration with a strong CYP2D6 and a weak CYP3A inhibitor paroxetine and a strong CYP3A inhibitor ketoconazole increased steady state eliglustat AUC by (b) (4) respectively; co-administration with a strong CYP3A inducer rifampin decreased steady state eliglustat AUC by (b) (4) for subjects who are not CYP2D6 poor metabolizers, and (b) (4) for poor metabolizers.

Simulation results from sponsor's PBPK reports [1,2] and additional information requested by the Office of Clinical Pharmacology [3-5] were used to evaluate the adequacy of eliglustat PBPK model in predicting eliglustat exposure in subjects with different CYP2D6 genotype and the effect of CYP modulators. The effects of CYP2D6 and CYP3A inhibitors, either alone or in combination, on the exposure of eliglustat in subjects with different CYP2D6 genotypes were predicted using PBPK models to support dose recommendation of eliglustat.

2. Methods

SimCYP® software (Sheffield, UK) [7-8] was used by the sponsor to develop and verify PBPK model. Software's "Healthy volunteer" population was used to define sub populations for subjects with a specific CYP2D6 phenotype according to the abundance of active CYP2D6 [7,8]. The software's default population mean CYP2D6 abundance values are 8, 0, 0, and 16 pmol CYP per mg protein in the liver for extensive metabolizers (EMs), poor metabolizers (PMs), intermediate metabolizers (IMs) and ultra-rapid metabolizers (URMs), respectively; population mean CYP2D6 abundance values are 0.8, 0, 0, and 1.6 pmol CYP per total gut in the gastrointestinal tract, respectively. The universal coefficient of variation (%CV) values of 61% and 60% are assigned to the liver and the gut, respectively. These enzyme abundance values dictate the CYP2D6 mediated metabolism of a given drug molecule according to in vitro-in vivo extrapolation methods established in the software [8].

Two versions of SimCYP have been used by the sponsor: Version 10.1 [1] and Version 11.01 [2-5]. Final drug-dependent parameters and their sources for eliglustat are summarized in **Appendix Tables 1 and 2**, and are the same for both versions. This review only discusses the results generated using Version 11.01, with a focus on the prediction of eliglustat PK in subpopulations with a specific CYP2D6 phenotype.

Unless otherwise noted, all simulations used 10 trials, with each trial "consisting of either the actual number of subjects that were included in specific clinical study being simulated or ten subjects for situations that were not previously assessed in a specific clinical study. The demographic data of the population simulated was matched to the demographics of the actual subjects enrolled in the study, where appropriate" [3]. For simulations of eliglustat PK in a subpopulation with a specific CYP2D6 phenotype, the frequency of the phenotype was set to 1 in the model.

PBPK models of paroxetine, ketoconazole, and metoprolol used for the evaluation of drug-drug interaction with eliglustat were modified by the sponsor from the respective library model files provided in the PBPK software. Modifications are highlighted in **Appendix Tables 3-6**.

2.1. Model building

Results of in vitro ADME experiments and physicochemical properties were used to build eliglustat PBPK model in SimCYP software. Results of several clinical PK studies were used to optimize eliglustat PBPK model before the model was verified with data from additional studies and was applied to predict untested situations. Clinical studies for model optimization are summarized in **Appendix Table 7**.

a. Integration of metabolic pathways of CYP3A and CYP2D6 in eliglustat PBPK model

Clearance (CL) values from PK studies in CYP2D6 EMs (mean systemic CL 85.8 L/h (after intravenous administration of single dose 50 mg eliglustat from 9 EMs and 1 IMs, and a renal CL of 6.2 L/h from Studies GZGD02107 and GZGD0103, respectively [6]) were used to derive hepatic intrinsic clearance (CL_{int}), according to software's built-in retrograde method [7]. In vitro experiment using human liver microsomes shows that at initial eliglustat concentration of 0.1 μM, CYP3A and CYP2D6 contributed to the overall metabolism of eliglustat by 40 and 60%, respectively. The initial fractional hepatic clearance by each CYP ($f_{m,CYP}$) were then assigned as 0.4 and 0.6 for CYP3A4 and CYP2D6, respectively, in the PBPK model. Initial simulation of oral absorption, considering first pass metabolism in the gut and the liver, shows that the model significantly under-estimated PK nonlinearity and over-estimated apparent CL, suggesting that the model should consider greater contribution of CYP2D6. The sponsor used PK parameters obtained from CYP2D6 PM subjects taking oral eliglustat (control arm of rifampin interaction study GZGD02407, [1,6]) to optimize the model with regard to $f_{m,CYP}$ values. The optimized $f_{m,CYP}$ values were 0.14 and 0.86 for CYP3A4 and CYP2D6, respectively. This setup is represented by CL_{int} of 0.95 and 100 μL/min/pmol hepatic CYP isozyme for CYP3A4 and CYP2D6 in the model (**Appendix Table 2**).

In vitro, eliglustat is a time-dependent CYP2D6 inhibitor, with maximal inactivation constant (k_{inact}) and inactivation constant (K_I) of 0.90 /hr and 1.05 μM, respectively. These parameters were integrated into the PBPK model and are responsible for time- and dose-dependent nonlinear pharmacokinetics of eliglustat.

b. Establishment of CYP2D6 IM and URM populations

The sponsor optimized IM and URM abundance values of CYP2D6 in response to FDA's 12122013IR (Appendix 2.1) [3].

For CYP2D6 IM, the sponsor defined a mean CYP2D6 abundance value of 2.5 pmol per mg in the liver and 0.25 pmol per gut in intestine in IMs (%CV remained unchanged, see above). This adjustment was based on eliglustat PK observed in 5 IMs in Study GZGD4112 (eliglustat PK measurement in metoprolol drug interaction study, mistakenly cited as GZGD2407 in reference [3]), and assumed one universal population mean tissue abundance value for all IMs. The selection of hepatic abundance of CYP2D6 in IMs appeared to be supported by literature findings: CYP2D6 abundance "between 0.81 pmol/mg-protein from a *10/*0 genotype (unstable protein/suppressive mutation; Zanger at al. 2001) and 3.5 pmol/mg-protein" [3].

For CYP2D6 URMs, initial simulation using drug model developed in EM and PM (section "*a*" above) underestimated eliglustat CL in URMs. The sponsor increased mean abundance of CYP2D6 from the default value of 16 to 28 pmol per mg in the liver and from 1.6 to 2.8 pmol per gut in intestine in URMs (%CV remained unchanged, see above). This adjustment was based on the following studies: GZGD01807/GZGD02007 (n=1 URMs, two measurements in ketoconazole and paroxetine drug interaction studies, 100 mg b.i.d. for 13 doses) and GZGD02407 (n=5 URMs, control arm in rifampin drug interaction studies, 150 mg b.i.d. for 11 doses) [3]. The adjustment assumed one universal population mean tissue abundance value for all URMs.

Final CYP2D6 abundance values in subjects of different phenotypes used by the sponsor are summarized in **Table 2**.

Table 2. CYP2D6 enzyme abundances used by the sponsor

CYP2D6 abundance	PM	IM	EM	URM
Liver (pmol/mg-protein)	0	2.5	8	28
Gastrointestinal tract (pmol per gut)	0	0.25	0.8	2.8

Percent CV of 61% and 60% for the liver and gut, respectively

2.2. Model verification

Multiple clinical pharmacology studies were used to verify eliglustat PBPK model in subpopulations with a specific CYP2D6 phenotype (See results 3.1)

2.3. Model applications

Multiple scenarios were simulated using the PBPK model of eliglustat in subjects with different CYP2D6 phenotypes, taking eliglustat alone or in combination with CYP inhibitors.

3. Results

3.1. Verification of Eliglustat PBPK Model in CYP2D6 EMs, PMs, IMs and URMs

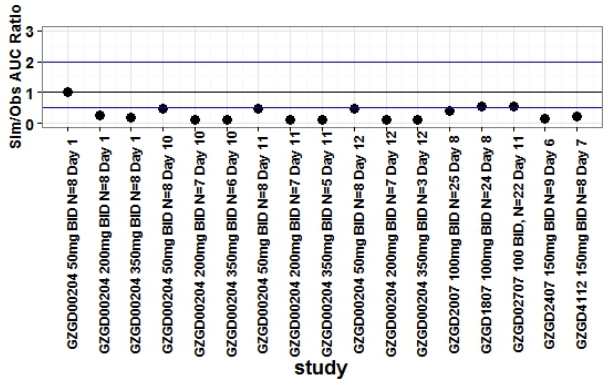
3.1.1. CYP2D6 EMs

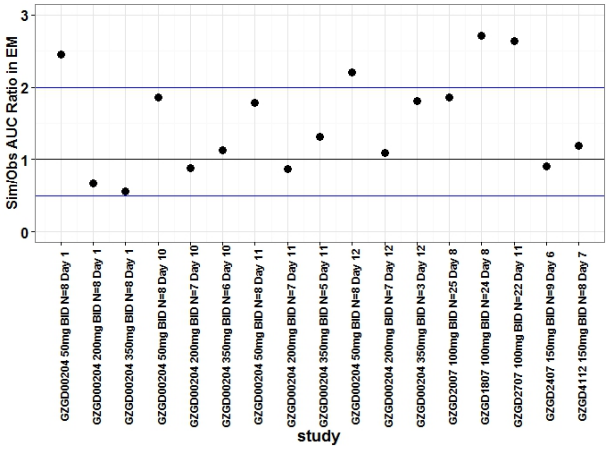
Figure 1 shows the ratio of mean predicted versus observed eliglustat exposure (Sim/Obs ratio) across different studies. When linear pharmacokinetics is assumed, eliglustat exposure extrapolated from 50 mg single dose ($AUC_{0\text{-inf}}$, GZGD00204) systematically under-predicts the observed data (upper panel, Figure 1). The sponsor included time-dependent CYP2D6 inhibition in eliglustat PBPK model in EMs to account for nonlinear pharmacokinetics. The ratio of PBPK predicted versus observed AUC and Cmax are shown in the middle panel and lower panel of Figure 1, respectively. For single dose scenarios (GZGD00204, day 1), the model tends to overestimate eliglustat exposure when the drug is given at a lower oral dose (50 mg), and tends to underestimate eliglustat exposure when the drug is given at a higher oral dose (350 mg). The deviation of model prediction from observation appears to be less when eliglustat is dosed to steady state. However, the model systematically over-predicted eliglustat exposure by approximately 2-fold for studies in in which subjects were given 100 mg b.i.d. dosing (clinical dose. Studies GZGD02007, 01807, and 02707). These findings imply the need for further optimization of eliglustat PBPK model in EMs (Appendix 5.2.1). Specifically, the baseline CYP2D6 intrinsic clearance may be higher than the value currently parameterized in the model.

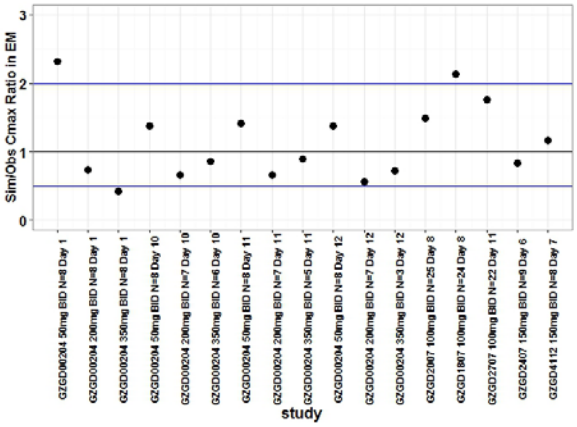
Figure 1. Comparison of the predicted and observed pharmacokinetic parameters (Sim/Obs) for eliglustat in the absence of perpetrators in EMs.

Upper panel: AUC comparison. Predicted AUC values were extrapolated from AUC0-inf after a single oral dose of eliglustat (Study GZGD00204, day 1) assuming linear pharmacokinetics; middle panel: AUC comparison. Predicted AUC using PBPK; lower panel: Cmax comparison. Predicted AUC using PBPK.

PBPK simulation conditions are the same for GZGD02407 and GZGD04112, and the same for GZGD01807/02007 and GZGD02707.







In order to verify the TDI mechanism included in eliglustat PBPK model, sponsor conducted simulations of the effect of eliglustat on the PK of probe CYP2D6 substrate metoprolol, and compared the results from clinical interaction study (GZGD04112) [3]. The FDA reviewer further stratified the simulated results according to CYP2D6 phenotypes. The PBPK predicted metoprolol exposure with and without eliglustat coadministration, and the exposure ratios are summarized in **Table 3**. For CYP2D6 EMs, the models of eliglustat and metoprolol appeared to adequately describe the observed data.

Table 3. PBPK predicted metoprolol exposure with and without eliglustat coadministration, and the exposure ratios versus observed findings from Study GZGD04112 in subjects with different CYP2D6 phenotypes.

CYP2D6 phenotype		Metoprolol alone		Metoprolol + eliglustat		Exposure Ratio	
		Observed	**Predicted**	**Observed**	**Predicted**	**Observed**	**Predicted**
	Cmax (ng/mL)						
EM	Mean	65	64	108	93	1.7	1.5
(N=8)	Minimum, maximum	35, 102	10, 159	87, 156	10, 279	1.11, 2.79	1.1, 2.0
IM	Mean	125	115	144	152	1.2	1.3
(N=5)	Minimum, maximum	90, 169	53, 218	123, 158	62, 315	0.86, 1.41	1.0, 1.7
URM	Mean	25	34	57	43	2.3	1.2
(N=1)	min, max	NA	13, 66	NA	14, 91	NA	1.1, 1.4
	AUC (ng/mL*h)						
EM	Mean	308	356	711	765	2.4	1.8
(N=8)	Minimum, maximum	152, 537	41, 1030	416,1120	45, 4177	1.77, 3.43	1.1, 4.7
IM	Mean	921	928	1440	1890	1.7	1.9
(N=5)	Minimum, maximum	568, 1600	295, 2368	1090, 2030	355, 4441	1.27, 2.06	1.0, 3.3
URM	Mean	85	150	245	203	2.9	1.4
(N=1)	Minimum, maximum	NA	50, 303	NA	55, 471	NA	1.1, 1.6

Simulation used 10 trials with 14 subjects for each trial in healthy volunteers [3]. The subject numbers for the observed and simulated data are 8 and 82, 5 and 50, and 1 and 8 for EMs, IMs and URMs, respectively. Observed values were from Study GZGD04112; simulated values were calculated from FDA analyses of metoprolol simulation submitted as part of reference [3].

Table 4 compares the PBPK predicted and observed exposure ratios (AUCR and CmaxR for AUC and Cmax, respectively) of eliglustat when the drug is co-administered with a strong CYP2D6 inhibitor paroxetine and a strong CYP3A inhibitor ketoconazole in EMs, IMs, and URMs. For EMs, the model adequately describes the drug-drug interaction between eliglustat and enzyme inhibitors. The sponsor also predicted no effect of eliglustat on the PK of paroxetine (also a substrate of CYP2D6) and demonstrated that the observed paroxetine trough concentrations in Study GZGD02007 are within the model predicted range (Figure 2 of reference [3], data not shown).

Table 4. PBPK predicted and observed effects of CYP2D6 inhibitor paroxetine and CYP3A inhibitor ketoconazole on eliglustat in subjects with different CYP2D6 phenotype

CPY2D6 Phenotype	PK Parameter	Exposure ratio with enzyme inhibitors					
		Eliglustat + Paroxetine			Eliglustat + ketoconazole		
		Observed	Simulated	Sim/Obs	Observed	Simulated	Sim/Obs
EM (n=24)	CmaxR	8.2	7.3	0.89	4.3	3.4	0.79
	AUCR	10.0	9.3	0.93	4.4	4.1	0.93
IM (n=8)	CmaxR	4.1	2.5	0.61	3.0	5.1	1.7
	AUCR	5.2	2.9	0.56	4.1	6.6	1.61
URM (n=1)	CmaxR	22.0	NA		2.2	1.6	0.73
	AUCR	28.4	NA		3.0	1.6	0.53

Exposure ratios (CmaxR and AUCR) were calculated for each individual (with or without inhibitor). Mean exposure ratios are summarized in this table. Simulation results were from reference [5]. NA: sponsor did not conduct the simulation.

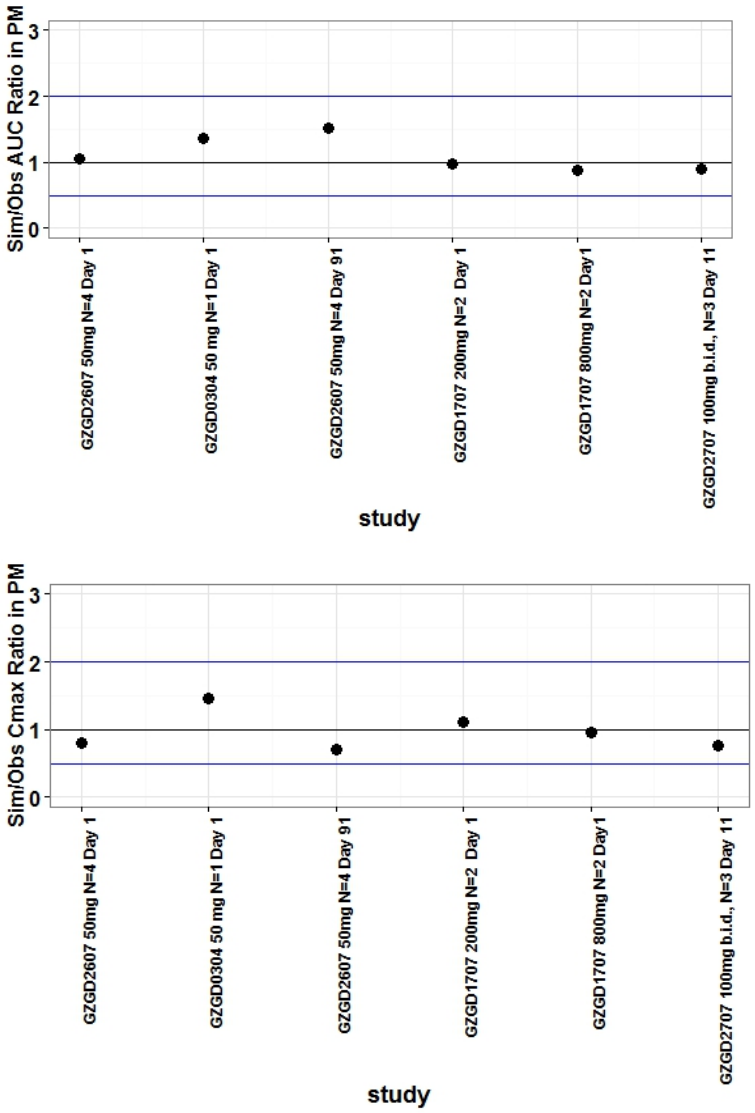
In summary, in CYP2D6 EM subjects, eliglustat PBPK model generally captured the nonlinear PK of eliglustat at steady state and the effect of strong inhibitors, ketoconazole and paroxetine, and its inhibitory effect on a sensitive CYP2D6 substrate metoprolol. The discrepancy between model simulation and observed data is more pronounced at lower doses including the clinical dose (100 mg b.i.d.), suggesting the need to further optimize the PBPK model of eliglustat in EMs. Nonetheless, given the known safety margin from cardiac safety review [reference QBR section], the model can be used to simulate the effect of various CYP modulators and to support dose recommendation (See Section 3.2).

3.1.2. CYP2D6 PMs

Figure 2 shows that the ratio of mean (or geo mean) PBPK predicted versus observed AUC (upper panel) and Cmax (lower panel) across different studies in PM subjects (see Appendix Table A8 for study details). Generally, PBPK model was able to describe the observed eliglustat PK in PMs.

Figure 2. Comparison of PBPK simulated and observed expousre (Sim/Obs) for eliglustat in the absence of perpetrators in CYP2D6 PMs.

Upper panel: AUC comparison; lower panel: Cmax comparison. Simulations for GZGD02807 and GZGD0304 were conducted by the reviewer using sponsor's models. Partial AUC of 0-4 hours was compared for GZGD2607 on day 1. Simulation conditions are the same for GZGD01807/02007 and GZGD02707.



3.1.3. CYP2D6 IMs

Exposure values of CYP2D6 probe substrate metoprolol were predicted using PBPK models of metoprolol and eliglustat in CYP2D6 IMs according to the design of GZGD04112 (**Table 3**). Metoprolol AUC and Cmax, in the absence or in the presence of eliglustat, were well captured by PBPK.

The sponsor also compared simulations to the observed data according to study GZGD02407 (n=2, 11 eliglustat doses at (b) (4) b.i.d.). The FDA reviewer requested PK information stratified for CYP2D6 phenotype [9]. The simulated eliglustat PK in IMs was compared to the control arm of studies GZGD01807 and GZGD02007, and study GZGD02707 (**Table 5**). It appears that the model overestimated the exposure of eliglustat in IMs in studies GZGD02407, GZGD01807 and GZGD02007,

and slightly under predicted exposure for GZGD02707. The comparison revealed large inter-study variability, reflecting a wide range of CYP2D6 activity or CYP2D6 enzyme abundance among IM subjects with different genotypes.

The effects of a strong CYP2D6 inhibitor paroxetine and a strong CYP3A inhibitor ketoconazole on eliglustat in IMs are summarized in **Table 4 (**IM group, Sim/Obs values**)**. There appears to be a trend of over-prediction of the effect of ketoconazole, and an under prediction of the effect of paroxetine. These deviations suggest that baseline intrinsic clearance of CYP2D6 may be higher than the value parameterized currently in the model for EMs (see above discussion for EMs in 3.1.1).

In summary, a mean CYP2D6 abundance derived from study GZGD04112 using eliglustat PK in IMs may not be representative for all IMs. Further refinement of eliglustat drug model in the EM and the system model regarding CYP2D6 abundance in IMs may be needed. Given the known safety margin from cardiac safety review [reference QBR section], the model can be used to simulate the effect of various CYP modulators and to support dose recommendation (See Section 3.2).

Table 5: Observed and predicted pharmacokinetic parameters for eliglustat in CYP2D6 IM population (Values are mean [minimum, maximum])

	Study number	N	Eliglustat dose	Observed	Predicted
Cmax	GZGD02407[$]	2	(b) (4) b.i.d.	57 [42, 72]	97 [9, 388]
	GZGD02007[&]	8	100 mg b.i.d.	30 [5, 54]	62 [6, 278]
	GZGD01807[&]	8	100 mg b.i.d.	41 [21, 68]	
	GZGD02707*	3	100 mg b.i.d.	99 [39, 142]	
AUC	GZGD02407[$]	2	(b) (4) b.i.d.	430 [307, 533]	812 [65, 3650]
	GZGD02007[&]	8	100 mg b.i.d.	194 [31, 346]	527 [39, 2740]
	GZGD01807[&]	8	100 mg b.i.d.	258 [97,503]	
	GZGD02707*	3	100 mg b.i.d.	625 [229, 915]	

[$] *GZGD02407 from reference [3] Simulated mean (minimum, maximum) parameters from simulations comprising of 10 trials, with 10 subjects/trial;* [&] *GZGD02007/1807 Same subjects in these two studies. *GZGD02707 reference [9]. Simulated mean (minimum, maximum) parameters from simulations comprising 10 trails, with 36 subjects/trial [5]; observed data mean (minimum, maximum) parameters from reference [9]*

3.1.4. CYP2D6 URMs and other verifications

Given the small number of subjects evaluated through the development of eliglustat, only two interaction studies (Table 4) can be used to verify eliglustat PBPK model in URMs (1 subject). Predictive performance cannot be evaluated.

In response to 12122013IR, the sponsor provided simulations of the effect of strong CYP3A inducer rifampin [3]. The sponsor demonstrated the capability of software built-in rifampin model "SV-Rifampin" in predicting the exposure of rifampin measured in non-PMs and PMs in Study 02407. Generally, the model under-estimated the effect of rifampin on the exposure of eliglustat. The predicted and observed AUC ratio of eliglusat (0-24 hr) were 0.45 and 0.21 in non-PMs, respectively; the predicted and observed AUC ratio of eliglusat (0-24 hr) were and 0.22 and 0.04 in PMs, respectively. It has been

documented that the rifampin PBPK model may not be optimal with regard to induction potency in the model. PBPK model captured a relatively stronger effect of rifampin on the exposure of eliglustat in CYP2D6 PMs than in non-PMs.

3.2. Application of Eliglustat PBPK Model in Supporting Dosing Recommendations of Eliglustat in Subjects with Specific CYP2D6 Phenotype

In sponsor's draft label submitted in NDA, (b) (4) . In order to gain insight in the effect of CYP inhibitors on eliglustat PK in subjects with a specific CYP2D6 phenotype, the FDA reviewer requested further simulations [3-5].

Figure 3. (b) (4)

Eliglustat PK was simulated under different dosing scenarios that were not evaluated through clinical studies. These scenarios include the administration of q.d. or b.i.d. 100 mg eliglustat alone or in combination with enzyme inhibitors in CYP2D6 EMs, IMs, or PMs. The predicted exposure values, especially C_{max}, are compared to a predefined tolerable margin of 250 ng/mL derived from the thorough QT study [reference QBR section]. The comparison forms the basis of dosing recommendations for different scenarios in the subsequent sections.

3.2.1. Can PBPK provide dosing recommendation for CYP2D6 PMs?

Predicted eliglustat exposure values (steady state C_{max}, AUC_{tau}, and C_{trough}) in CYP2D6 PMs, are shown in **Table 6**, with the exposure in EMs taking 100 mg b.i.d. as reference. Based on the tolerable margin of

250 ng/mL mentioned above, the predicted mean Cmax values are more than 50% lower, suggesting that (b) (4) 100 mg q.d. is acceptable regimen for CYP2D6 PMs.

In response to FDA's information request 01142014IR (Appendix 2.2), the sponsor also provided simulations of elglustat exposure in CYP2D6 PMs taking 50 mg b.i.d.. These data are summarized in **Table 7**.

Table 6. Predicted eliglustat in CYP2D6 PMs under different dosing regimens(Mean [minimum, maximum])

	(b) (4)	**100 mg q.d. in PMs**	**100 b.i.d. in EMs[$]**
C_{max} (ng/mL)		75.2 [6.04, 287]	24.7 [1.67, 221]
AUC (ng/mL h)		956 [49.1, 5290]	185 [11.8, 1800]
C_{trough} (ng/mL)		15.0 [0.117, 152]	6.61 [0.348, 76.1]

[$]Predicted exposures in EMs are used as reference (last column). Simulations used 10 trials, with 36 subjects/trial. Reference [5] Tables 2, 20, 21

Table 7. Predicted eliglustat exposure in PMs taking chronic dosing of 50 mg dose (Mean [minimum, maximum])

Eliglustat dosing	**Inhibitor**	**Cmax (ng/mL)**	**AUC_{tau} (ng/mL h) 0-12h for b i.d. 0-24h for q.d.**	**C_{trough} (ng/mL)**	**Source**
50 mg b.i.d.	NA[a]	49.4 [3.13, 197]	441 [24.6, 2050]	23.0 [0.946, 143]	Table 2, [3]
50 mg q.d.	NA[b]	35.7 [2.54, 121]	441 [24.5, 2060]	6.56 [0.0748, 57.2]	Table 4, [3]
50 mg b.i.d.	Fluconazole[c]	136 [14.3, 466]	1380 [120, 5180]	88.3 [5.27, 384]	Table 3, [3]

[a] 10 trials, with 10 subjects/trial, receiving a single dose of eliglustat on the morning of Day 1 and BID doses of eliglustat from the evening of Day 2 through the morning of Day 8 (13 eliglustat doses).[b] 10 subjects/trial, receiving QD dosing with eliglustat from the morning of Day 1 through the morning of Day 8 (8 eliglustat doses). [c] 10 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with fluconazole (loading dose of 400 mg on day 8, and 200 mg q.d. from day 9-day 18) coadministered from Day 8 to Day 18 (Period 2).

3.2.2. Can PBPK provide dosing recommendation when EM, IM, or PM subjects are taking eliglustat with enzyme inhibitors?

Predicted eliglustat exposure values (steady state C_{max}, AUC_{tau}, and C_{trough}) in CYP2D6 EMs, IMs, and PMs with and without co-administration with enzyme inhibitors are summarized in **Tables 8,9 and 10**, respectively. Accordingly, dosing recommendations are provided for EMs, IMs and PMs in **Tables 11, 12, and 13**, respectively.

Table 8. Predicted eliglustat exposure in EMs in the absence and presence of enzyme inhibitors (Mean [minimum, maximum])

Eliglustat Dose	**CYP Inhibitors**	**Cmax (ng/mL)**	**AUC_{tau} (ng/mL h) 0-12h for b.i.d. 0-24h for q.d.**	**C_{trough} (ng/mL)**	**Tables, [reference]**

Eliglustat Dose	CYP Inhibitors	Cmax (ng/mL)	AUC_{tau} (ng/mL h) 0-12h for b.i.d. 0-24h for q.d.	C_{trough} (ng/mL)	Tables, [reference]
100 mg BID	NA[a]	24.7 [1.67, 221]	185 [11.8, 1800]	6.61 [0.348, 76.1]	Table 2, [5]
100 mg QD	NA[b]	15.4 [1.81, 124]	130 [10.7, 1520]	0.591 [0.00554, 19.1]	Table 5, [5]
100 mg BID	Strong CYP2D6 inhibitors Paroxetine[a]	124 [7.06, 466]	1120 [55.5, 5070]	59.7 [2.14, 363]	Table 2, [5]
100 mg BID	Strong CYP3A4 inhibitors Ketoconazole[c]	98.9 [3.53, 956]	934 [20.0, 10700]	54.1 [0.292, 799]	Table 4, [5]
100 mg BID	Paroxetine and ketoconazole[c]	**412**[$] [101, 1350]	4470 [919, 15300]	319 [45.1, 1172]	Table 6, [5]
100 mg QD	Paroxetine and ketoconazole[b]	**281**[$] [91.0, 742]	4920 [1110, 15400]	112 [5.09, 518]	Table 7, [5]
100 mg BID	Moderate CYP2D6 inhibitor terbinafine[d]	93.9 [6.18, 356]	831 [48.5, 3640]	42.4 [1.87, 235]	Table 10, [4]
100 mg BID	Moderate CYP3A4 inhibitor fluconazole[e]	68.5 [2.42, 429]	593 [17.1, 4210]	29.2 [0.507, 254]	Table 9, [4]
100 mg BID	Terbinafine and fluconazole[f]	**251**[$] [20.7, 655]	2512 [151, 7755]	158 [4.94, 571]	Simulation from [2]
100 mg QD	Terbinafine and fluconazole[g]	165 [18.2, 415]	2510 [156, 7290]	51.9 [0.628, 207]	Table 11, [5]

Values are population mean [minimum, maximum]. Ten trials for each simulation experiment. [a] *36 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 with paroxetine coadministered from Day 9 to Day 18 [5];* [b] *36 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 with paroxetine and ketoconazole coadministered from Day 9 to Day 18[5];* [c] *36 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 15 with ketoconazole coadministered from Day 9 to Day 15 [5];* [d] *10 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with terbinafine coadministered from Day 9 to Day 18 (Period 2) [4];* [e] *10 subjects/trial receiving repeated;* [f] *10 subjects/trial 18 days in the absence and presence of terbinafine (250 mg QD for 10 days) and fluconazole (400 mg on day 9 and 200 mg QD from days 10 to 18) [2];* [g] *10 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with terbinafine and fluconazole coadministered from Day 9 to Day 18 (Period 2) [5].*

[$] *Value exceeding 250 ng/mL threshold*

Table 9. Predicted eliglustat exposure in IMs in the absence and presence of enzyme inhibitors (Mean [minimum, maximum])

Eliglustat Dose	CYP Inhibitors	Cmax (ng/mL)	AUC_{tau} (ng/mL h) 0-12h for b i.d. 0-24h for q.d.	C_{trough} (ng/mL)	Tables, [reference]
100 mg BID	NA[a]	62.8 [5.46, 278]	527 [39.4, 2740]	24.3 [1.23, 188]	Table 12, [5]
100 mg BID	Strong CYP2D6 inhibitors paroxetine[a]	133 [7.12, 520]	1220 [56.0, 5700]	66.4 [2.16, 414]	Table 12, [5]
100 mg BID	Strong CYP3A4 inhibitors Ketoconazole[b]	**274**[$] [17.3, 1050]	2850 [103, 11800]	193 [1.84, 893]	Table 13, [5]
100 mg QD	Strong CYP3A4 ketoconazole[c]	147 [12.0, 589]	2270 [75.2, 11800]	42.7 [0.0565, 374]	Table 14, [5]
100 mg BID	Paroxetine and ketoconazole[d]	**470**[$] [103, 1480]	5170 [937, 16900]	379 [46.2, 1300]	Table 15, [5]
100 mg QD	Paroxetine and ketoconazole[e]	**313**[$] **[101, 811]**	5710 [1180, 17100]	139 [6.97, 587]	Table 16, [5]
100 mg BID	Moderate CYP2D6 inhibitor Terbinafine[f]	97.2 [6.23, 382]	866 [49.0, 3930]	44.9 [1.88, 267]	Table 15, [4]
100 mg BID	Moderate CYP3A4 inhibitor Fluconazole[g]	159 [10.7, 634]	1500 [78.4, 6720]	85.4 [2.56, 461]	Table 14, [4]
100 mg BID	Terbinafine and fluconazole[h]	**261**[$] [20.9, 823]	2630 [153, 9220]	167 [5.00, 690]	Table 16, [4]
100 mg QD	Terbinafine and fluconazole[i]	172 [18.3, 449]	2680 [158, 8950]	58.3 [0.640, 286]	Table 19, [5]

Values are population mean [minimum, maximum]. Ten trials for each simulation experiment. [a] 36 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 with paroxetine coadministered from Day 9 to Day 18 [5]; [b or c] 36 subjects/trial receiving repeated doses (100 mg b.i.d. or q.d.) of eliglustat from Day 1 to Day 15 with ketoconazole coadministered from Day 9 to Day 15 [5]; [d or e] 36 subjects/trial receiving repeated doses (100 mg b.i.d. or q.d.) of eliglustat from Day 1 to Day 18 with paroxetine and ketoconazole coadministered from Day 9 to Day 18 [5]; [f] 10 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with terbinafine coadministered from Day 9 to Day 18 (Period 2) [4] [g] 10 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with fluconazole coadministered from Day 8 to Day 18 (Period 2) [4]; [h] 10 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with fluconazole and terbinafine coadministered from Day 9 to Day 18 (Period 2) [4] [i] 10 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with terbinafine and fluconazole coadministered from Day 9 to Day 18 (Period 2) [5]

[$] *Value exceeding 250 ng/mL threshold*

Table 10. Predicted eliglustat exposure in PMs in the absence and presence of enzyme inhibitors (Mean [minimum, maximum])

Eliglustat Dose	CYP Inhibitors	Cmax (ng/mL)	AUC_{tau} (ng/mL h) 0-12h for b.i.d. 0-24h for q.d.	C_{trough} (ng/mL)	Tables, [reference]
100 mg b.i.d	NA[a]	105 [6.95, 489]	957 [49.1, 5270]	51.3 [1.46, 371]	Table 20, [5]
100 mg q.d	NA[a]	75.2 [6.04, 287]	956 [49.1, 5290]	15.0 [0.117, 152]	Table 21, [5]
100 mg b.i.d	Strong CYP3A4 inhibitors ketoconazole[a]	**478**[$] [119, 1260]	5300 [1100, 14300]	392 [52.3, 1110]	Table 20, [5]
100 mg q.d	Ketoconazole[b]	**321**[$] [114, 709]	5950 [1310, 14700]	147 [6.74, 519]	Table 21, [5]
100 mg b.i.d	Moderate CYP3A4 inhibitor fluconazole[c]	**395**[$] **[29.3, 1939]**	7214 [346, 40979]	300 [11, 1775]	FDA in house analysis
100 mg q.d.	Fluconazole[c]	179 [23.1, 530]	2820 [248, 10500]	63.5 [1.27, 333]	Table 6, [4]

Values are population mean [minimum, maximum]. Ten trials for each simulation experiment. [a] *36 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 15 with ketoconazole coadministered from Day 9 to Day 15 [5];* [b] *36 subjects/trial receiving repeated doses of eliglustat from Day 1 to Day 15 with ketoconazole coadministered from Day 9 to Day 15. [5];* [c] *10 subjects/trial receiving repeated doses of eliglustat (100 mg b.i.d. or q.d.) from Day 1 to Day 18 (Period 1) and repeated doses of eliglustat from Day 1 to Day 18 with fluconazole coadministered from Day 8 to Day 18 (Period 2) [4]*

[$]*Value exceeding 250 ng/mL threshold*

Table 11. Recommendation of eliglustat dosing regimen in the presence of enzyme inhibitors in EMs taking eliglustat 100 mg twice daily

Refer to Table 8 and GZGD02007/GZGD01807 for Cmax values.

Inhibitors	Is predicted Cmax >250 ng/mL?	Recommendations and Comments
Strong CYP2D6 inhibitors (e.g. paroxetine)	☐ Yes ☒ No	(b) (4)
Strong CYP3A4 inhibitors (e.g. ketoconazole)	☐ Yes ☒ No	(b) (4)
Strong CYP2D6 inhibitors+ Strong CYP3A4 inhibitors	☒ Yes ☐ No	**Do not use**
Moderate CYP2D6 inhibitors (e.g. Terbinafine)	☐ Yes ☒ No	(b) (4)
Moderate CYP3A4 inhibitors (e.g. fluconazole)	☐ Yes ☒ No	(b) (4)
Moderate CYP2D6 inhibitors+ Moderate CYP3A4 inhibitors	☒ Yes ☐ No	(b) (4)

Table 12. Recommendation of eliglustat dosing regimen in the presence of enzyme inhibitors in IMs taking eliglustat 100 mg twice daily

Refer to Table 9 and GZGD02007/GZGD01807 for Cmax values.

Inhibitors	Is predicted Cmax >250 ng/mL?	Recommendations and Comments
Strong CYP2D6 inhibitors (e.g. paroxetine)	☐ Yes ☒ No	(b) (4)
Strong CYP3A4 inhibitors (e.g. ketoconazole)	☒ Yes ☐ No	(b) (4)
Strong CYP2D6 inhibitors+ Strong CYP3A4 inhibitors	☒ Yes ☐ No	**Do not use**
Moderate CYP2D6 inhibitors (e.g. Terbinafine)	☐ Yes ☒ No	(b) (4)
Moderate CYP3A4 inhibitors (e.g. fluconazole)	☐ Yes ☒ No	(b) (4)
A moderate CYP2D6 inhibitor+ a moderate CYP3A4 inhibitor	☒ Yes ☐ No	(b) (4)

Table 13. Recommendation of eliglustat dosing regimen in the presence of enzyme inhibitors in PMs taking eliglustat 100 mg (b) (4)

Refer to Table 10 for Cmax values.

Inhibitors	Is predicted Cmax >250 ng/mL?	Recommendations and Comments
Strong CYP3A4 inhibitors (e.g. ketoconazole)	☒ Yes ☐ No	**Do not use**
Moderate CYP3A4 inhibitors (e.g. fluconazole)	☒ Yes ☐ No	(b) (4)

3.3. Predicting the Effect of Eliglustat on the Exposure of other CYP2D6 Substrates

Eliglustat PBPK model considering TDI of CYP2D6 appears to reasonably describe the observed effect on probe substrate metoprolol in CYP2D6 EMs and IMs (**Table 3**). At 100 mg b.i.d. dosing of eliglustat, the effect on metoprolol is expected to be lower than 2-fold in both CYP2D6 EMs and IMs.

4. Conclusion

The sponsor's PBPK model of eliglustat reasonably predicted eliglustat PK in CYP2D6 PMs, the nonlinear PK of the drug at steady state in CYP2D6 EMs, and the effect of strong CYP2D6 inhibitor paroxetine and strong CYP3A inhibitor ketoconazole in CYP2D6 EMs. Verification of eliglustat PK in IMs suggested that the model may need further optimization possibly for CYP2D6 abundance in IMs and relative contribution of CYP2D6 and CYP3A in CYP2D6 EMs. Overall, the model is considered sufficient in providing dose recommendation in subjects taking eliglustat in the absence and in the presence of various CYP inhibitors in CYP2D6 EMs, IMs, or PMs.

5. Appendices

5.1. Abbreviations

ADME, absorption, distribution, metabolism, and excretion; b.i.d., twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; AUC_{tau}, steady state AUC within a dosing interval; B/P, blood to plasma ratio; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; C_{trough}, trough concentration; CL, clearance; CL_{int}, intrinsic clearance; DDI: drug-drug interaction; EM, extensive metabolizers; F, bioavailability; Fa, fraction absorbed; Fg, fraction that escapes intestinal metabolism; fmj, fraction of total clearance mediated by j CYP isoform or renal elimination; fp, fraction unbound in plasma; fu,mic, fraction unbound in microsomes; fu,gut, apparent unbound fraction in enterocytes; GI: gastrointestinal; IM, intermediate metabolizers; IR, immediate release formulation; k_a, first order absorption rate constant; K_i, reversible inhibition constant; LogP, logarithm of the octanol-water partition coefficient; NA, not applicable; ND, not determined; NDA: new drug application; P_{eff}, passive permeability; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; PM, poor metabolizers; q.d., once daily dosing; Q_{gut}, a hypothetical flow term for the intestine absorption model; SRT, substrate reduction therapy; TDI, time-dependent enzyme inhibition; Tmax: time at maximal concentration in plasma; URM, ultra-rapid metabolizers; V_{ss}, volume of distribution at steady state.

5.2. Information requests

5.2.1. Information Request-Clinical Pharmacology Dec 12, 2013 (12122013IR)

After conducting initial assessment of your PBPK study reports SIM0105 and SIM0106, we have the following information requests:

1. You should conduct simulations according to the designs of additional human PK studies and determine the need to optimize the PBPK model of Genz-99067 with regard to its nonlinear PK and its effect on other CYP2D6 substrates. These studies include GZGD00204 (50 mg, 200 mg, and 300 mg twice daily in healthy, non-CYP2D6 PM subjects, with PK data available on day 1, day 10 and day 12 for each dose level), GZGD02007 (specifically the effect of Genz-99067 on pharmacokinetics of paroxetine), and GZGD04112 (the effect of Genz-99067 on pharmacokinetics of metoprolol).
2. You should develop CYP2D6 ultra rapid metabolizer population (URM) and intermediate metabolizer population (IMs) and simulate the pharmacokinetics of Genz-99067 in these groups. The effect of a moderate CYP3A4 inhibitor and/or a moderate CYP2D6 inhibitor (such as fluconazole and terbinafine) on Genz-99067 should be simulated in CYP2D6 IMs. The dose regimens of eliglustat in these simulations can be 50, 100, and 150 mg twice daily. The simulated exposure of Genz-99067 under these conditions should be compared to that from CYP2D6 extensive metabolizers taking eliglustat alone.
3. You should conduct simulations according to Study GZGD02407 (effect of rifampin on Genz-099067).
4. For the simulation of the effect of ketoconazole and the effect of rifampin, you should consider the inhibition and induction effect of active renal secretion of Genz-99067 using your PBPK model.
5. You should justify the calculation of exposure ratios for the effect of paroxetine and the effect of ketoconazole on the exposure of Genz-99067 in report SIM0105.
6. You should provide simulation results on the effect of terbinafine as a moderate CYP2D6 inhibitor on the pharmacokinetics of another CYP2D6 substrate

If you require clarification of the above requests or have any questions/concerns, you may choose to arrange a meeting with us to discuss the issues further. At this meeting, we would request PBPK modeler(s) be in attendance.

5.2.2. Information Request-Clinical Pharmacology Jan 10, 2014 (01102014IR)

1. Please use your PBPK models to simulate eliglustat plasma PK at steady state in the following scenarios:
    a. 50 mg twice daily (B.I.D.) in CYP2D6 poor metabolizers (PMs)
    b. 50 mg B.I.D. in CYP2D6 PMs co-administered with a moderate CYP3A4 inhibitor fluconazole
    c. 50 mg once daily (QD) in CYP2D6 PMs
    d. 100 mg QD in CYP2D6 PMs
    e. 100 mg QD in CYP2D6 PMs co-administered with a moderate CYP3A4 inhibitor fluconazole
    f. 100 mg three times a day (TID) in CYP2D6 ultra-rapid metabolizers (URMs)
    g. 200 mg B.I.D. in CYP2D6 URMs
    h. 100 mg B.I.D. in extensive metabolizers (EMs) taking a moderate CYP3A4 inhibitor fluconazole or a CYP2D6 inhibitor terfinabine

Please summarize simulated population mean eliglustat exposure values (AUC_0-last, Cmax, and Cmin) for these scenarios, and calculate exposure ratios using simulation results of 100 mg B.I.D. in CYP2D6 EMs alone as reference. You can use simulation design presented in your Efficacy Information Amendment submitted on Dec 12, 2013.

Please also provide simulated Cmin values (mean [minimum, maximum]) for scenarios presented in Tables 6, 7, 9, 10, 11, 12, and 13 in your Efficacy Information Amendment submitted on Dec 12, 2013.

These simulations will support further review of eliglustat dose stratification in different patient groups.

2. Clarify how the $AUC_{0\text{-}12h}$ (i.e. AUCtau) on Days 10, 20, Weeks 13, 39, 52, 65, 78, 91, and 104 reported in your Phase 2 study GZGD00304 Clinical Study Report (Table 12-2) were derived when the sampling time point during these PK assessment periods was up to Hour 6 according to your Final Study protocol dated on January 31, 2013. Similarly, please clarify how the reported $AUC_{0\text{-}12h}$ for ENGAGE and ENCORE was derived.
3. You defined Cmin as minimum plasma concentration during a dosing interval and Ctrough as plasma concentration before treatment administration during repeated dosing. Clarify whether if you used the Cmin and Ctrough interchangeably for the following study results:
    a. For ENCORE study, you plotted Ctrough in Week 52 (See Figure 12-6 and Table in CSR) while your supporting dataset (ADPPAV.XPT) submitted on Dec. 20 for this study indicated that Cmin values were for Week 13 and Week 52 and Ctrough values were for other time periods. Clarify if the Cmin for Week13 and Week 52 were same as Ctrough by definition. Similarly, situation occurred for ENGAGE. Clarify if the Cmin for Week 4 and Week 39 were the same as Ctrough by definition. If not, provide each individual's trough concentrations for the period specified above and descriptive statistics stratified by CYP2D6 phenotypes. The individual data should be submitted in .xpt format.
    b. For your Phase 2 study, you reported Cmin. Clarify if they were the same as Ctrough by the definition you provided in your Clinical Study Report (Table 8-5). If not, provide the listing of Ctrough concentrations and descriptive statistics stratified by CYP2D6 phenotypes. The individual data should be submitted in .xpt format.

Please submit these information by COB, Jan 16, 2014.

5.2.3. Information Request-Clinical Pharmacology Mar 19, 2014 (03192014IR)

Please use your PBPK models to simulate eliglustat plasma PK at steady state in the following scenarios:

<u>In CYP2D6 extensive metabolizers</u>

a. 100 mg twice daily (b.i.d) co-administered with paroxetine
b. 100 mg b.i.d co-administered with ketoconazole
c. 100 mg once daily (q.d.) co-administered with ketoconazole

d. 100 mg b.i.d co-administered with paroxetine and ketoconazole
e. 100 mg q.d. co-administered with paroxetine and ketoconazole
f. 100 mg q.d. co-administered with fluconazole
g. 100 mg q.d. co-administered with terbinafine
h. 100 mg q.d. co-administered with terbinafine and fluconazole

In CYP2D6 intermediate metabolizers

a. 100 mg twice daily (b.i.d) co-administered with paroxetine
b. 100 mg b.i.d co-administered with ketoconazole
c. 100 mg once daily (q.d.) co-administered with ketoconazole
d. 100 mg b.i.d co-administered with paroxetine and ketoconazole
e. 100 mg q.d. co-administered with paroxetine and ketoconazole
f. 100 mg q.d. co-administered with fluconazole
g. 100 mg q.d. co-administered with terbinafine
h. 100 mg q.d. co-administered with terbinafine and fluconazole

In CYP2D6 poor metabolizers

a. 100 mg b.i.d co-administered with ketoconazole
b. 100 mg q.d. co-administered with ketoconazole

In CYP2D6 ultra rapid metabolizers

a. 100 mg b.i.d co-administered with quinidine
b. 200 mg b.i.d. co-administered with quinidine
c. 100 mg b.i.d co-administered with ketoconazole
d. 200 mg b.i.d. co-administered with ketoconazole

Please Summarize simulated population mean eliglustat exposure values (AUC_0-last, Cmax, and Cmin) for these scenarios, and calculate exposure ratios using simulation results of 100 mg B.I.D. in CYP2D6 extensive metabolizers alone as reference.

All simulations should be conducted in SimCYP V11.1 as described in your Efficacy Information Amendments submitted on Dec 12, 2013 and Jan 15, 2014. You can use simulation design presented in these two Amendments. For situations of co-administration of ketoconazole and co-administration of combined paroxetine and ketoconazole, simulation designs in study sim0105 can be used.

These simulations will support further review. Please provide the simulation results in 3 business days.

5.3. Appendix tables and figures

Appendix Table 1. Physicochemical parameters of Eliglustat for PBPK model

Input parameter	Value	Unit	Comment
Molecular weight	404.54	g/mol	Genzyme simcyp report-sim 105 Study Report [1]
LogP	2.84		Study Report [1]
Compound Type	Monoprotic Base		Study Report [1]
pKa	8.79		Study Report [1]
Dosage form	Immediate release tablet of 100 mg commercial formulation		

Appendix Table 2. Input parameters of Eliglustat for PBPK model using SimCYP (V11.1)

Parameter	Value	Unit	Comment
Absorption			
Absorption Model	First order		Study Report [1]
fa	0. 93	fraction	Predicted from Caco-2 data
ka	0.95	hr^{-1}	Predicted from Caco-2 data
Papp Caco-2 permeability	21	10^{-6} cm/s	Study Report [1]
Distribution			
B/P (blood to plasma ratio)	1		Study Report [1]
fu plasma	0.239	fraction	Study Report [1] Equilibrium dialysis
Predicted V_{ss}	6.31	L/kg	Fitted using in vivo IV data
Metabolism/Excretion			
$F_{u,gut}$	1		Software default value
fu,mic	1		Software default value
CYP3A4 CLint	0.95	µL/min/pmol protein	Extrapolated from in vivo data, Report - GZGD02407
CYP2D6 CLint	100	µL/min/pmol protein	Extrapolated from in vivo data, Report - GZGD02407
CL_{renal}	6.240	L/h	In vivo data ; Report - GZGD02407
Interaction			
CYP2D6 ki	5.82	µM	Report – DMPK08-R036
CYP2D6 kapp	1.05	µM	
CYP2D6 kinact	0.906	1/h	
CYP2D6 fu,mic	0.86		
CYP3A4 ki	27	µM	

Appendix Table 3. Input parameters of ketoconazole for PBPK model using SimCYP (V11.1)

Process	Parameters	Default SimCyp Library Model	Modified Model
		User input	User input
Absorption	fa	1.0	1.0
	Ka(1/h)	1.9	1.0
Distribution		Minimal PBPK, user input	Minimal PBPK, user input
	Vss(L/kg)	0.345	0.345
Elimination	CL_{po} (L/h)	13.3	7.4
	CL_R (L/h)	0.133	0.133

Appendix Table 4. Input parameters of terbinafine for PBPK model using SimCYP (V11.1)

Process	Parameters	Default SimCyp Library Model	Modified Model

		User input	Predicted from compartmental absorption and transit (CAT) model with Peff man (10^{-4} cm/s) of 3
Absorption	fa	1.0	0.961
	Ka(1/h)	1.2	1.23
Distribution		Minimal PBPK, user input	Full PBPK Predicted with Method 2
	Vss(L/kg)	17.3	11.0
Elimination	CL_{po} (L/h)	68.8	27.2

Appendix Table A5. Input parameters of paroxetine for PBPK model using SimCYP (V11.1)

Process	**Parameters**	**Default SimCyp Library Model (SV-Paroxetine)**	**Modified Model**
	LogP	3.8	3.55
	pKa	9.9	9.66
Elimination	fu,mic for CYP2D6	1	0.914
	fu,mic for CYP2C19	1	0.569
	fu,mic for CYP3A4	1	0.356
	fu,mic for CYP1A2	1	0.229
	fu,mic for CYP3A5	1	0.009
Mechanism based Inhibition	fu,mic for CYP2D6	1	0.2

Appendix Table 6. Input parameters of metoprolol for PBPK model using SimCYP (V11.1)

Process	Parameters	Default SimCyp Library Model	Modified Model
		User input	Predicted from first order absorption and transit model with Peff man (10^{-4} cm/s) of 1.3
Absorption	fa	1.0	0.796
	Ka(1/h)	1.43	0.535
Distribution		Minimal PBPK, user input	Full PBPK Predicted with Method 2
	Vss(L/kg)	4.96	3.1
Elimination	Vmax (pmol/min/mg protein)	Km (uM)	Clint (uL/min/pmol of isoform)
O-demethylatin CYP2D6	300	28.3	Pathway 1 CYP2D6: 4.782
O-demethylatin CYP3A4	1160	1160	Pathway 1 CYP3A4: 0.0210
Alpha-OH CYP2D6	75.9	31	
Alpha-OH CYP3A4	96	874	

Table 3 of reference [3]

Appendix Table 7. Clinical PK studies used for optimization of eliglustat PBPK drug model, and system model for CYP2D6 IM and URM populations

Study number	Description	Parameter optimized
GZGD02107	Intravenous dosing of 50 mg in 10 non-PM subjects	Hepatic CL, Vss
GZGD0103	Single dose escalation in subjects with CYP2D6 phenotype undetermined (0.01-30 mg/kg)	Renal CL, hepatic CL
GZGD02407	Rifampin drug interaction study. Control arm in CYP2D6 PMs 100 mg b.i.d.	$CL_{int,CYP2D6}$ and $CL_{int,CYP3A4}$
GZGD04112	Metoprolol drug interaction study. Control arm in 5 CYP2D6 IMs 150 mg b.i.d.	CYP2D6 abundance in IM
GZGD02407	Rifampin drug interaction study. Control arm in 5 CYP2D6 URMs (b) (4) b.i.d.	CYP2D6 abundance in URM
GZGD01807/2007	Ketoconazole and paroxetine drug interaction studies. Control arms in 1 CYP2D6 URM (receiving 100 mg b.i.d. in both studies, two measurements)	CYP2D6 abundance in URM

Appendix Table A8. Observed (GZGD00204, 01807, 02007, and 02407) and predicted eliglustat PK after oral eliglustat b i.d.

Table 13 of reference [3]

Table 13: Observed (Studies GZGD00204, GZGD01807, GZGD02007 and GZGD02407) and predicted Genz-99067 pharmacokinetic parameters in CYP2D6 EM population after repeated 50-150 mg BID doses of eliglustat

Genz-99067 parameters	Eliglustat Dose	Observed [a]	Predicted [b] (N=100)
C_{max} (ng/mL)	50 mg BID	7.35 [1.09, 13.8] (N=8)	8.98 [0.778, 44.7]
	100 mg BID	19.5 [2.67, 68.4] (N=64)	24.0 [1.67, 142]
	150 mg BID	54.4 [5.10, 116] (N=12)	45.7 [2.63, 248]
AUC_{0-12} (ng·h/mL)	50 mg BID	39.3 [4.61, 71.0] (N=8)	63.7 [5.48, 321]
	100 mg BID	119 [21.2, 503] (N=62)	177 [11.8, 1120]
	150 mg BID	369 [33.2, 727] (N=12)	352 [18.6, 2030]

AUC_{0-12} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (12 hours); BID = twice daily; C_{max} = maximum observed plasma concentration; EM = extensive metabolizer; N = number of subjects.

[a] Observed mean [minimum, maximum] parameters from GZGD00204 (16 eliglustat doses), GZGD02007 (13 eliglustat doses), GZGD01807 (13 eliglustat doses) and GZGD02407 (11 eliglustat doses);

[b] Predicted mean [minimum, maximum] parameters from simulations comprising of 10 trials, with 10 subjects/trial receiving a single dose of eliglustat on the morning of Day 1 and BID dosing with eliglustat from the evening of Day 2 through the morning of Day 8 (13 eliglustat doses).

Appendix Table 9. Observed (GZGD00204) and predicted eliglustat PK after escalating single oral dose repeated oral doses (b i.d.) eliglustat

Table 1 of reference [3]

Table 1: Observed (GZGD00204) and predicted Genz-99067 plasma pharmacokinetic parameters after escalating single and repeated BID doses of eliglustat

Parameters	50 mg BID		200 mg BID		350 mg BID	
	Observed [a]	Predicted [b]	Observed [a]	Predicted [b]	Observed [a]	Predicted [b]
Day 1 [c]						
N	8	80	8	80	8	80
C_{max} (ng/mL)	2.48 [1.32, 3.71]	5.76 [1.02, 22.5]	33.0 [4.10, 85.0]	24.2 [4.26, 99.3]	107 [30.0, 204]	45.8 [10.9, 182]
AUC (ng·h/mL)	19.1 [7.20, 31.8]	46.9 [8.90, 163]	294 [26.0, 952]	197 [37.4, 712]	678 [186, 1330]	380 [85.8, 1350]
Day 10						
N	8	80	7	80	6	80
C_{max} (ng/mL)	7.35 [1.09, 13.8]	10.1 [1.42, 36.4]	119 [12.6, 212]	77.9 [7.33, 366]	231 [149, 355]	197 [19.7, 907]
AUC_{0-12} (ng·h/mL)	39.3 [4.61, 71.0]	72.9 [10.4, 286]	697 [68.5, 1590]	611 [53.9, 3030]	1450 [748, 2430]	1640 [136, 8330]
Day 11						
N	8	80	7	80	5	80
C_{max} (ng/mL)	7.27 [1.62, 13.2]	10.3 [1.43, 36.5]	119 [18.0, 245]	78.7 [7.46, 366]	221 [144, 307]	198 [19.8. 905]
AUC_{0-12} (ng·h/mL)	41.7 [9.76, 81.2]	74.5 [10.5, 291]	715 [93.1, 1470]	618 [54.9, 3030]	1260 [832, 1800]	1650 [137, 8340]
Day 12						
N	8	80	7	80	3	80
C_{max} (ng/mL)	7.64 [1.65, 14.4]	10.5 [1.43, 36.6]	142 [10.6, 260]	79.3 [7.57, 366]	278 [207, 323]	199 [19.8, 906]
AUC_{0-12} (ng·h/mL)	41.9 [11.3, 94.0]	92.3 [12.5, 404]	747 [60.0, 1540]	818 [66.9, 4640]	1290 [978, 1780]	2340 [147, 12700]

AUC = area under the plasma concentration versus time curve extrapolated to infinity; AUC_{0-12} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (12 hours); BID = twice daily; C_{max} = maximum observed plasma concentration; N = number of subjects.

[a] Observed mean (minimum, maximum) parameters in Study GZGD0024, with eliglustat administered on morning of Day 1 and then BID from evening of Day 2 until morning of Day 12;

[b] Predicted mean [minimum, maximum] parameters from simulations comprising of 10 trials, with 8 subjects/trial, according to the design of Study GZGD00204, as described above;

[c] Genz-99067 plasma concentrations measured over 36 hours after dosing on Day 1 in Study GZGD00204.

References

1. Karen Rowland Yeo, Simcyp Ltd. Genzyme Corp, Sanofi Study Number Sim0106: Quantitative Prediction Of Drug-Drug Interactions Involving Genz-112638 (As The Victim) And Fluconazole (CYP3A4) And Terbinafine (CYP2D6) As Perpetrators [Moderate Inhibitors Of CYP3A And CYP2D6]. September 28, 2012.
2. Karen Rowland Yeo, Simcyp Ltd. Genzyme Corp, Sanofi study number SIM0105: Physiologically based PK (PBPK) modeling using SimCYP® software to predict plasma concentration-time profiles of eliglustat with drug-drug interactions [Strong inhibitors of CYP3A and CYP2D6] SEPTEMBER 28, 2012.
3. Genzyme Corp. Response to FDA Information Request from Dec 12, 2013 (Email).
4. Genzyme Corp. Response to FDA Information Request from Jan 10, 2014 (Email).
5. Genzyme Corp. Response to FDA Information Request from Mar 19, 2014 (Email).
6. Genzyme Corp. Eliglustat (Genz-112638) study report: Summary of Clinical Pharmacology Studies, Eliglustat (formerly known as NKTR-118) for the Treatment of Opioid Induced Constipation (OIC). June 31 2013.
7. SimCYP manual: A Guide for IVIVE and PBPK/PD Modeling using the Simcyp Population-based Simulator version 12, CERTARA™ 2013.
8. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp((R)) Population-based ADME Simulator. Expert Opin Drug Metab Toxicol 2009;5(2):211-23.
9. Genzyme Corp. Efficacy Information Amendment: Response to FDA Information Request 2, Agency Request 3 from Jan 10, 2014. Dataset stratified eliglustat PK in subjects with different CYP2D6 phenotypes.

Appendix 4.4

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	205494	Brand Name	Cerdelga
OCP Division (I, II, III, IV, V)	III	Generic Name	Eliglustat Tartrate
Medical Division	DGIEP	Drug Class	Glucosylceramide synthase inhibitors
OCP Reviewers OCP Team Leader	Elizabeth Shang, Ph.D. Sandhya Apparaju, Ph.D. Sue Chih Lee, Ph.D.	Indication(s)	Gaucher Disease Type 1
Pharmacometrics Reviewer Pharmacometrics Team Leader	Anshu Marathe, Ph.D. Nitin Mehrotra, Ph.D.	Dosage Form	Hard Capsules
Pharmacogenomic Reviewer Pharmacogemomic Team Leader	Sarah Dorff, Ph.D. Michael Pacanowski, Pharm.D., M.P.H.	Dosing Regimen	84 mg PO BID
PBPK Team Leader	Ping Zhao, Ph.D.	Route of Administration	PO
Date of Submission	September 20, 2013	Sponsor	Genzyme
Estimated Due Date of OCP Review	February 27, 2014	Priority Classification	Priority
PDUFA Due Date	May 20, 2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	45		28 in vitro studies 17 in vivo studies
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	6		Plasma: Two validation reports (b) (4) 40045 and (b) (4) 141364 (redeveloped method with lower LLOQ); two cross validation report using same assay in (b) (4) 141364; one long-term stability assessment Urine: one validation report (b) (4) 140046
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	4		
Blood/plasma ratio:	X	1		In vitro
Plasma protein binding:	X	1		In vitro
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		Included Thorough QT study
multiple dose:	X	1		
Patients-				

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single dose:				
multiple dose:	X	5		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4		
In-vivo effects of primary drug:	X	3		
In-vitro:	X	16		
Subpopulation studies -				
ethnicity:	X			No dedicated studies. These factors were considered in Population PK analysis.
gender:	X			
geriatrics:	X			
pediatrics:				Request for waiver; orphan drug designation
renal impairment:	X			No studies submitted. Effect of renal impairment is evaluated by population PK analysis. The FDA agreed that these studies could be conducted as PMRs at the Pre-NDA meeting.
hepatic impairment:				
PD -				GL-1 and GM3
Phase 2:	X			Analysis performed on Phase 2 study GZGD00304
Phase 3:	X			Analysis performed on 2 Phase 3 studies and 1 Phase 3b study
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			PK-ECG
Phase 3 clinical trial:	X			PK-PD: % change in spleen volume
Population Analyses -				
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability	X	1		
Relative bioavailability -	X			
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				BCS Class I; BE waiver
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		
Bio-waiver request based on BCS				
BCS class	X			BCS Class I accepted by FDA
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Request for waiver; orphan drug designation
Literature References	X			
Total Number of Studies		45		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment

Appendix 4.4

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?				
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

Appendix 4.4

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

The lists of in vitro and in vivo clinical pharmacology studies are provided in Appendixes 1 and 2, respectively.

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Elizabeth Shang, Ph.D. & Sandhya Apparaju, Ph.D.

Reviewing Clinical Pharmacologists Date

Sue Chih Lee, Ph.D.

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Appendix 1. List of In Vitro Human Biomaterial Studies

Type of Study	Test System	Report Number	Study Report Location
Absorption			
Permeability Caco-2	Cells	DMPK10-R047	4.2.2.2
Simulated human absorption	GastroPlus™ software	DMPK10-R048	5.3.2.3
Distribution			
Plasma protein binding	Human plasma [a]	DMPK11-R031	4.2.2.3
Red blood cell partitioning	Human whole blood [a]	DMPK11-R030	4.2.2.3
Metabolism			
Metabolic stability	Human whole blood [a]	DMPK11-R029	4.2.2.4
	Human liver microsomes [a]	DMPK11-R035	4.2.2.4
	Human hepatocytes [a]	DMPK11-R036	4.2.2.4
Metabolite profile	Human liver microsomes and hepatocytes [a]	DMPK10-R025	4.2.2.4
	Recombinant human CYP2C19, CYP2D6, CYP3A4	DMPK11-R043	4.2.2.4
Metabolic pathway elucidation	Human cryopreserved hepatocytes	DMPK12-R005	4.2.2.4
CYP reaction phenotyping	Recombinant human CYP isozymes and human liver microsomes (eliglustat)	DMPK08-R035, DMPK11-R015	5.3.2.2
	Human liver microsomes from donors with a CYP2D6 PM phenotype (eliglustat)	DMPK11-R034	5.3.2.2
	Recombinant human CYP isozymes (metabolites)	DMPK11-R081	5.3.2.2
Pharmacokinetic Drug-Drug Interaction Potential			
CYP induction	Human cryopreserved hepatocytes (eliglustat)	DMPK08-R040, DMPK08-R048	5.3.2.2

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Type of Study	Test System	Report Number	Study Report Location
	Cultured human hepatocytes (metabolites)	DMPK11-R079	5.3.2.2
CYP direct inhibition	Human liver microsomes with CYP isozyme-selective probe substrates (eliglustat)	DMPK08-R034, DMPK08-R036	5.3.2.2
	Human liver microsomes with CYP isozyme-selective probe substrates (metabolites)	DMPK11-R040	5.3.2.2
CYP time-dependent inhibition	Human liver microsomes with CYP isozyme-selective probe substrates (eliglustat)	DMPK08-R036	5.3.2.2
	Human liver microsomes with CYP isozyme-selective probe substrates (metabolites)	DMPK11-R040	5.3.2.2
CYP2D6 time-dependent inhibition	Recombinant human CYP2D6 (eliglustat)	DMPK11-R033	5.3.2.2
	Human cryopreserved hepatocytes with CYP isozyme-selective probe substrates (eliglustat)	DMPK10-R022	5.3.2.2
P-gp efflux transporter substrate and inhibition	MDCKII-MDR1 cells (eliglustat)	DMPK10-R020	5.3.2.3
	MDR1-expressing LLC-PK1 cells (metabolites)	DMPK11-R080	5.3.2.3
BCRP efflux transporter substrate and inhibition	BCRP-expressing LLC-PK1 cells (eliglustat)	DMPK11-R039	5.3.2.3
	BCRP-expressing LLC-PK1 cells (metabolites)	DMPK11-R080	5.3.2.3
BSEP efflux transporter inhibition	BSEP (eliglustat)	DMPK13-R027	5.3.2.3
	BSEP membrane vesicles from Sf9 cells (metabolites)	DMPK11-R080	5.3.2.3
MRP efflux and OATP, OAT, OCT uptake transporter substrate and/or inhibition	Membrane vesicles from Sf9 (MRP1, MRP2, MRP3), HEK293 (MRP5), or LLC-PK1 (MRP4) cells; OATP1B1, OATP1B3, OCT1, OCT2 and OAT1 expressed in CHO cells; OATP2B1 expressed in MDCKII cells; OAT3 expressed in HEK293 cells (eliglustat)	DMPK10-R019	5.3.2.3

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Type of Study	Test System	Report Number	Study Report Location
	MRP2 membrane vesicles from Sf9 cells; OATP1B1, OATP1B3, OCT1, and OCT2 expressed in HEK293 cells; and OAT1 and OAT3 expressed in S_2 cells (metabolites)	DMPK11-R080	5.3.2.3

BCRP = breast cancer resistance protein; BSEP = bile salt export pump; CHO = Chinese Hamster Ovary CYP = cytochrome P450; MRP = multi-drug resistance protein; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; OCT = organic cation transporter; P-gp = P-glycoprotein; PM = poor metabolizer.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Appendix 2. List of Clinical Pharmacology Studies (In Vivo)

Study Type	Study No.	Eliglustat Dosing Regimen [a] and Duration	No. of Subjects/ Patients Treated with Eliglustat [b]	Study Report Location
Biopharmaceutic Studies in Healthy Adult Subjects c				
Relative bioavailability of Phase 3 and common blend d capsules	GZGD03811	(b) (4) single dose (4 periods)	22	5.3.1.2
Food effect	GZGD00404	300 mg single dose (2 periods)	24	5.3.1.1
Pharmacokinetics, Pharmacodynamics, and Pharmacokinetics/Pharmacodynamics in Healthy Adult Subjects				
Single ascending dose	GZGD00103	0.01, 0.03, 0.1, 0.3, 1.0, 2.0, 3.0, 5.0, 7.0, 10.0, 15.0, 20.0, or 30.0 mg/kg oral solution single dose (Day 1)	74 5.3.3	.1
Multiple ascending dose	GZGD00204	50, 200, or 350 mg (Day 1) 50, 200, or 350 mg BID x 11 days (Day 2 to Day 12)	24 5.3.3	.1
Absolute bioavailability, PK, mass balance, excretion, and metabolism p	GZGD02107 and DMPK09-049	50 mg IV single dose (Day 1) 100 mg (Day 8) 100 mg BID x 6 days (Day 9 to Day 14) 100 mg radiolabeled oral solution (Day 15)	10	5.3.3.1 and 5.3.2.2
Thorough QT/QTc	GZGD01707	200 mg and 800 mg single dose	45	5.3.4.1
Extrinsic Factors in Healthy Adult Subjects				
Ketoconazole (strong CYP3A and P-gp inhibitor)	GZGD01807	100 mg BID x 7 days (2 periods)	36	5.3.3.4
Paroxetine (strong CYP2D6 inhibitor)	GZGD02007	100 mg BID x 7 days followed by 100 mg BID x 10 days	36 5.3.3	.4
Rifampin (strong CYP and P-gp inducer) e, f	GZGD02407	100 or 150 mg g single dose (Day 1 of 2 periods) 100 mg or (b) (4) BID g x 5 days (Day 2 to Day 6 of 2 periods)	25 5.3.3	.4
Antacids h and pantoprazole	GZGD01907	100 mg single dose (4 periods)	24	5.3.3.4

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Study Type	Study No.	Eliglustat Dosing Regimen [a] and Duration	No. of Subjects/ Patients Treated with Eliglustat [b]	Study Report Location
Effect of Eliglustat on Other Drugs in Healthy Adult Subjects				
Digoxin (P-gp substrate) f	GZGD03610 and DMPK11-R084	100 or 150 mg BID g x 7 days (Day 11 to Day 17)	28	5.3.3.4 and 5.3.2.2
Metoprolol (CYP2D6 substrate)	GZGD04112	150 mg BID x 6 days (Day 3 to Day 8)	14 5.3.3	.4
Norethindrone / ethinyl estradiol (oral contraceptive, Ortho-Novum 1/35)	GZGD02707	100 mg BID x 11 days (Day 39 to Day 49)	29 5.3.3	.4
Pharmacokinetics and Pharmacodynamics in GD1 Patients [i]				
Phase 2 study in treatment-naïve patients j, f	GZGD00304 (4 years) k	Through Year 4: 50 mg BID x 20 days (Day 1 to Day 20) followed by 50 or 100 mg BID x 49 weeks (Day 20 to Week 52) followed by 50, 100, or 150 mg BID x 3 years (Week 54 to Year 4)	26 5.3.5	.2
	GZGD03310 (biomarker sub-study)	Through Year 3: See above	21 5.3.4	.2
Phase 3 efficacy/safety study in treatment-naïve patients j	ENGAGE / GZGD02507 (Primary Analysis Period)	Primary Analysis Period: 50 mg BID x 4 weeks followed by 50 or 100 mg BID x 35 weeks	20 5.3.5	.1
Phase 3 efficacy/safety study in patients switching from enzyme replacement therapy	ENCORE / GZGD02607 (Primary Analysis Period)	Primary Analysis Period: [l] 50 mg BID x 4 weeks (Day 1 to Week 4) followed by 50 or 100 mg BID x 4 weeks (Week 4 to Week 8) 50, 100, or 150 mg BID x 44 weeks (Week 8 to Week 52)	106 5.3.5	.1

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Study Type	Study No.	Eliglustat Dosing Regimen [a] and Duration	No. of Subjects/ Patients Treated with Eliglustat [b]	Study Report Location
Phase 3b efficacy/safety study in patients who were treatment-naïve, off prior treatment, or receiving enzyme replacement therapy	EDGE / GZGD03109 (Lead-in Period m)	Lead-in Period: [l, m] 50 mg BID x 4 weeks (Day 1 to Week 4) 50or 100 mg BID (Week 4 to Week 8) 50, 100, or 150 mg BID n (Week 8 up to Week 78)	170 h	NA h
Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Modelling				
Population PK: intrinsic and extrinsic factors influencing PK variability o	POH0373	Dosing regimens for studies in the dataset ° are defined above	405 o	5.3.3.5
Physiologically-based PK (PBPK)-modeling using SimCYP®	SIM0105 SIM0106	NA NA		5.3.3.5
Simulation of exposure by phenotype using population PK model	SIM0124	NA NA		5.3.3.5
Pooled PK/PD-ECG analysis	NA	Dosing regimens for studies in the datasets [p] are defined above	320 to 369	5.3.5.3
PK/PD-efficacy analysis for prediction of efficacy based on phenotype-based recommended dosing	POH0395	Dosing regimens for studies in the datasets (Phase 2, ENGAGE, and ENCORE primary analysis periods) are defined above	105 to 152	5.3.3.5

BID = twice daily; CYP = cytochrome P450; ECG = electrocardiogram; ERT = enzyme replacement therapy; IV = intravenous; PBPK = physiologically-based pharmacokinetics; PD = pharmacodynamic; PK = pharmacokinetic; NA = not applicable; P gp = P-glycoprotein; QT = interval between Q and T waves on ECG; QTc = corrected QT interval

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/s/

ELIZABETH Y SHANG
06/16/2014

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06/16/2014

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	205494/N000
Submission Date:	09/20/13
Brand Name:	Cerdelga
Generic Name:	Eliglustat tartrate
Formulation:	Immediate release (IR) oral capsule
Strength:	100 mg (One strength)
Applicant:	Genzyme
Type of submission:	Original NME (New molecular entity) with Priority (6 months); Major amendment extended it for 3 more months
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Gaucher disease is a rare lysosomal storage disorder (disease) caused by a deficiency of the enzyme, acid beta (β-) glucosidase (also known as glucocerebrosidase), that results in the accumulation of its major natural substrate, glucosylceramide, especially in the liver, spleen, and bone marrow. Eliglustat, is a member of a class of glucosylceramide (GL-1) synthase inhibitors that resemble the ceramide substrate for the enzyme.

Eliglustat reportedly acts as a substrate reduction therapy for Gaucher disease type 1 (GD1). The goal of this approach is to reduce the rate of synthesis of glucosylceramide to match its impaired rate of catabolism in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations.

Development of this product by Genzyme was conducted under IND67589 and Orphan Drug Designation (08-2654) was granted for *treatment of Gaucher disease* on 09/17/08.

Current Submission

On 09/20/13, Genzyme submitted NDA 205494/N000 for an NME, Eliglustat IR 100 mg capsule with a proposed brand name of Cerdelga. A major amendment to the NDA was determined on 01/13/14 and the PDUFA goal date was extended to 08/30/14. During the IND stage, the Agency already determined and accepted that Eliglustat is a BCS (Biopharmaceutical classification system) Class 1 drug substance and product (DS/DP). Please see the Agency's preliminary comments for a Type C meeting on 02/21/12 for details.

Included in the NDA submission were, 1). Complete dissolution development report, 2). Proposed dissolution method with justification and 3). Proposed dissolution acceptance criterion for Cerdelga IR 100 mg capsules. No biowaiver is needed as there is only one strength proposed which was already employed in the pivotal clinical Phase 3 trials and

the clinically tested formulation is the same as the to-be-marketed (TBM) formulation except a minor difference in the capsule shells used. The above dissolution profile data are reviewed here by the Biopharmaceutics/ONDQA

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution development report and the comparative dissolution profile data to support their proposed dissolution method and its acceptance criterion for Eliglustat IR 100 mg capsules.

RECOMMENDATION

From the Biopharmaceutics perspective, the following dissolution method and the dissolution acceptance criterion for Eliglustat IR 100 mg capsule are found acceptable.

Apparatus: **USP II (Paddle) with 75 rpm**
Medium: **0.1 N HCl (pH 1.0), 900 mL at 37 ± 1ºC**
Sinker: **Sotax sinker 19 D 7mm (P/N 8283)**
Acceptance Criterion (Q): **(b)(4)% at 30 min**

No further Biopharmaceutics comments are to be sent to the Applicant at this time.

_____ 05/15/14
Tien-Mien Chen, Ph.D. Date
ONDQA Biopharmaceutics Reviewer

_____ 05/19/14
Tapash Ghosh, Ph.D. Date
ONDQA Biopharmaceutics Team Leader

CC: DARRTS/NDA No.205494/N000\RLostritto

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Gaucher disease is a rare liposomal storage disorder (disease) caused by a deficiency of the enzyme, acid beta (β-) glucosidase (also known as glucocerebrosidase), that results in the accumulation of its major natural substrate, glucosylceramide, especially in the liver, spleen, and bone marrow. Eliglustat, is a member of a class of glucosylceramide (GL-1) synthase inhibitors that resemble the ceramide substrate for the enzyme. Inhibition of glucosylceramide synthase by eliglustat reportedly results in a reduction of the accumulation of glucosylceramide, thereby allowing the patient's residual endogenous acid β-glucosidase levels to clear the substrate.

Eliglustat reportedly acts as a substrate reduction therapy for GD1. The goal of this approach is to reduce the rate of synthesis of glucosylceramide to match its impaired rate of catabolism in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations. Development of this product by Genzyme was conducted under IND67589 and Orphan Drug Designation (08-2654) was granted for *treatment of Gaucher disease* on 09/17/08.

CURRENT SUBMISSION

On 09/20/13, Genzyme submitted NDA 205494/N000 for Eliglustat (an NME) IR 100 mg capsule with a proposed brand name of Cerdelga. A major amendment to the NDA was determined on 01/13/14 and the PDUFA goal date was extended to 08/30/14. During the IND stage, the Agency already determined and accepted that Eliglustat is a BCS Class 1 drug substance and product. Please see the Agency preliminary comments for a Type C meeting which was to be scheduled on 02/21/12, but cancelled.

Included in the NDA submission were, 1). Complete dissolution development report, 2). Proposed dissolution method with justification and 3). Proposed dissolution acceptance criterion for Cerdelga IR 100 mg capsules. No biowaiver is needed for there is only one capsule strength proposed which was already employed in the pivotal clinical Phase 3 trials and the clinically tested formulation is the same as the TBM formulation except a minor difference in the (b) (4) used. The above dissolution profile data are reviewed there by the Biopharmaceutics/ONDQA.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the comparative dissolution profile data in order to support the proposed dissolution method and the proposed dissolution acceptance criterion for quality control of Cerdelga IR 100 mg capsules.

FORMULATION COMPARISONS

The composition and formulation of the proposed Cerdelga (Eligustat tartrate) IR 100 mg capsule is shown below.

Table 1-1. Composition and Formulation of Cerdelga (Eliglustat tartrate) IR 100 mg Capsules

Component	Reference to Quality Standard	Function	Amount (mg/capsule) [a]
Capsule Blend Composition			
Eliglustat[b]	In-house	drug substance	(b) (4)
Microcrystalline cellulose	NF / Ph.Eur.	(b) (4)	
Lactose monohydrate	NF / Ph.Eur.		
Hypromellose	USP / Ph.Eur.		
Glyceryl behenate / (b) (4)	NF / Ph.Eur.		
Capsule			
Size 2 hard gelatin capsules (printed with black ink)[c]	In-house	encapsulation	1 capsule

[a] Target amounts provided. Refer to 3.2.P.3.2 for the ranges for each excipient.
[b] Each capsule contains 84 mg of eliglustat (which is equivalent to 100 mg of eliglustat tartrate)
[c] Refer to Table 2 for the composition of the hard gelatin capsule. Refer to Table 3 for the composition of the black ink.

Table 1-2. Composition and Formulation of Hard Gelatin Capsules

Components	Reference to Quality Standard	Function	Amount (% / capsule[a])	
			Body Composition	Cap Composition
(b) (4)	Ph.Eur. / USP			(b) (4)
	In-house			
	In-house			
	In-house			
				(b) (4)

(b) (4)

Initially, the Applicant proposed (b) (4)

(b) (4)

Upon NDA submission, (b) (4) the pearlescent 100 mg capsule strength was pursued for commercialization.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

Eliglustat is a highly soluble compound which has > 300 mg/mL solubility in water and is a highly permeable compound as well. Eliglustat had been determined by the Agency during the IND development as a BCS Class 1 DS/DP.

Dissolution Development Report:

The Applicant submitted a complete dissolution development report for this BSC Class 1 DS/DP as shown below.

(b) (4)

It is summarized below:

(b) (4)

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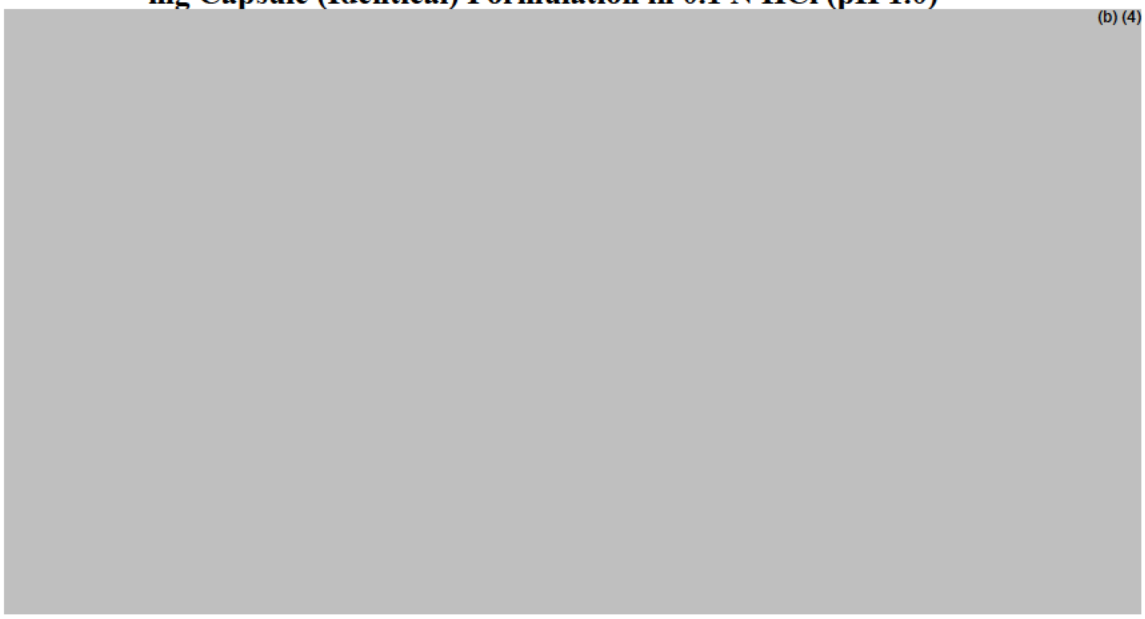
Proposed Dissolution Method and Acceptance Criterion:
The finally proposed dissolution method and its acceptance criterion for the commercial pearlescent 100 mg capsule strength are shown below:

Apparatus: **USP II (Paddle) with 75 rpm**
Medium: **0.1 N HCl (pH 1.0), 900 mL at 37 ± 1°C**
Sinker: **Sotax sinker 19 D 7mm (P/N 8283)**
Acceptance Criterion (Q): **% at 30 min**

The dissolution of Cerdelga (Eliglustat tartrate) IR 100 mg capsule dissolved fast in the proposed dissolution medium of 0.1 N HCl (pH 1.0) showing > % in min (Figure 4 above) which is consistent with its BCS Class 1 properties of the drug.

while that for the TBM capsule formulation is "pearlescent" blue-green opaque cap and pearl white opaque body with mean comparative dissolution profile data between the phase-3 and TBM formulations are slightly different at the initial times as shown below (in dotted- and solid-red; Figure 7 below).

Figure 7. Mean Comparative Dissolution Profile of the Phase 3 and TBM IR 100 mg Capsule (Identical) Formulation in 0.1 N HCl (pH 1.0)



The slight differences in the initial dissolution occurred (b) (4) Please see the complete dissolution development report in Module 3.2.P.5 for details.

Note: (b) (4)

Proposed Dissolution Acceptance Criterion:
The proposed dissolution acceptance criterion is Q= (b) (4) % at 30 min, which is considered acceptable for this is a BCS Class 1 drug product.

Reviewer's Comment:
The mean dissolution profile of Fliglustat IR 100 mg capsule using the proposed dissolution method showed all > (b) (4) % dissolved in (b) (4) min. At the Midcycle meeting dated 12/12/13, a proposal to (b) (4) the dissolution acceptance criterion to either Q= (b) (4) % at 30 min or Q= (b) (4) % at (b) (4) min was considered and discussed. However, no dissolution timepoint at (b) (4) min was available for the registered stability batches. During the internal meeting within the Biopharm team, the Biopharm's proposal for (b) (4) Q= (b) (4) % at 30 min to Q= (b) (4) % at 30 min was dropped as this is a BCS Class 1 DS/DP.

Thus, the Applicant's proposed dissolution method and acceptance criterion are found acceptable, i.e., Q= (b) (4) % at 30 min.

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/s/

TIEN MIEN CHEN
05/19/2014

TAPASH K GHOSH
05/19/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	205494	Brand Name	Cerdelga
OCP Division (I, II, III, IV, V)	III	Generic Name	Eliglustat Tartrate
Medical Division	DGIEP	Drug Class	Glucosylceramide synthase inhibitors
OCP Reviewers OCP Team Leader	Elizabeth Shang, Ph.D. Sandhya Apparaju, Ph.D. Sue Chih Lee, Ph.D.	Indication(s)	Gaucher Disease Type 1
Pharmacometrics Reviewer Pharmacometrics Team Leader	Anshu Marathe, Ph.D. Nitin Mehrotra, Ph.D.	Dosage Form	Hard Capsules
Pharmacogenomic Reviewer Pharmacogemomic Team Leader	Sarah Dorff, Ph.D. Michael Pacanowski, Pharm.D., M.P.H.	Dosing Regimen	84 mg PO BID
PBPK Team Leader	Ping Zhao, Ph.D.	Route of Administration	PO
Date of Submission	September 20, 2013	Sponsor	Genzyme
Estimated Due Date of OCP Review	February 27, 2014	Priority Classification	Priority
PDUFA Due Date	May 20, 2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	45		28 in vitro studies 17 in vivo studies
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	6		Plasma: Two validation reports (b) (4) 140045 and (b) (4) 141364 (redeveloped method with lower LLOQ); two cross validation report using same assay in (b) (4) 141364; one long-term stability assessment Urine: one validation report (b) (4) 140046
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	4		
Blood/plasma ratio:	X	1		In vitro
Plasma protein binding:	X	1		In vitro
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		Included Thorough QT study
multiple dose:	X	1		
Patients-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

single dose:				
multiple dose:	X	5		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4		
In-vivo effects of primary drug:	X	3		
In-vitro:	X	16		
Subpopulation studies -				
ethnicity:	X			**No dedicated studies. These factors were considered in Population PK analysis.**
gender:	X			
geriatrics:	X			
pediatrics:				**Request for waiver; orphan drug designation**
renal impairment:	X			**No studies submitted. Effect of renal impairment is evaluated by population PK analysis. The FDA agreed that these studies could be conducted as PMRs at the Pre-NDA meeting.**
hepatic impairment:				
PD -				**GL-1 and GM3**
Phase 2:	X			**Analysis performed on Phase 2 study GZGD00304**
Phase 3:	X			**Analysis performed on 2 Phase 3 studies and 1 Phase 3b study**
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			**PK-ECG**
Phase 3 clinical trial:	X			**PK-PD: % change in spleen volume**
Population Analyses -				
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability	X	1		
Relative bioavailability -	X			
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				**BCS Class I; BE waiver**
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		
Bio-waiver request based on BCS				
BCS class	X			**BCS Class I accepted by FDA**
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Request for waiver; orphan drug designation**
Literature References	X			
Total Number of Studies		45		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 205494

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?				
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

The lists of in vitro and in vivo clinical pharmacology studies are provided in Appendixes 1 and 2, respectively.
IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Elizabeth Shang, Ph.D. & Sandhya Apparaju, Ph.D.
Reviewing Clinical Pharmacologists Date

Sue Chih Lee, Ph.D.
Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Appendix 1. List of In Vitro Human Biomaterial Studies

Type of Study	Test System	Report Number	Study Report Location
Absorption			
Permeability Caco-2	Cells	DMPK10-R047	4.2.2.2
Simulated human absorption	GastroPlus™ software	DMPK10-R048	5.3.2.3
Distribution			
Plasma protein binding	Human plasma [a]	DMPK11-R031	4.2.2.3
Red blood cell partitioning	Human whole blood [a]	DMPK11-R030	4.2.2.3
Metabolism			
Metabolic stability	Human whole blood [a]	DMPK11-R029	4.2.2.4
	Human liver microsomes [a]	DMPK11-R035	4.2.2.4
	Human hepatocytes [a]	DMPK11-R036	4.2.2.4
Metabolite profile	Human liver microsomes and hepatocytes [a]	DMPK10-R025	4.2.2.4
	Recombinant human CYP2C19, CYP2D6, CYP3A4	DMPK11-R043	4.2.2.4
Metabolic pathway elucidation	Human cryopreserved hepatocytes	DMPK12-R005	4.2.2.4
CYP reaction phenotyping	Recombinant human CYP isozymes and human liver microsomes (eliglustat)	DMPK08-R035, DMPK11-R015	5.3.2.2
	Human liver microsomes from donors with a CYP2D6 PM phenotype (eliglustat)	DMPK11-R034	5.3.2.2
	Recombinant human CYP isozymes (metabolites)	DMPK11-R081	5.3.2.2
Pharmacokinetic Drug-Drug Interaction Potential			
CYP induction	Human cryopreserved hepatocytes (eliglustat)	DMPK08-R040, DMPK08-R048	5.3.2.2

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205494

Type of Study	Test System	Report Number	Study Report Location
	Cultured human hepatocytes (metabolites)	DMPK11-R079	5.3.2.2
CYP direct inhibition	Human liver microsomes with CYP isozyme-selective probe substrates (eliglustat)	DMPK08-R034, DMPK08-R036	5.3.2.2
	Human liver microsomes with CYP isozyme-selective probe substrates (metabolites)	DMPK11-R040	5.3.2.2
CYP time-dependent inhibition	Human liver microsomes with CYP isozyme-selective probe substrates (eliglustat)	DMPK08-R036	5.3.2.2
	Human liver microsomes with CYP isozyme-selective probe substrates (metabolites)	DMPK11-R040	5.3.2.2
CYP2D6 time-dependent inhibition	Recombinant human CYP2D6 (eliglustat)	DMPK11-R033	5.3.2.2
	Human cryopreserved hepatocytes with CYP isozyme-selective probe substrates (eliglustat)	DMPK10-R022	5.3.2.2
P-gp efflux transporter substrate and inhibition	MDCKII-MDR1 cells (eliglustat)	DMPK10-R020	5.3.2.3
	MDR1-expressing LLC-PK1 cells (metabolites)	DMPK11-R080	5.3.2.3
BCRP efflux transporter substrate and inhibition	BCRP-expressing LLC-PK1 cells (eliglustat)	DMPK11-R039	5.3.2.3
	BCRP-expressing LLC-PK1 cells (metabolites)	DMPK11-R080	5.3.2.3
BSEP efflux transporter inhibition	BSEP (eliglustat)	DMPK13-R027	5.3.2.3
	BSEP membrane vesicles from Sf9 cells (metabolites)	DMPK11-R080	5.3.2.3
MRP efflux and OATP, OAT, OCT uptake transporter substrate and/or inhibition	Membrane vesicles from Sf9 (MRP1, MRP2, MRP3), HEK293 (MRP5), or LLC-PK1 (MRP4) cells; OATP1B1, OATP1B3, OCT1, OCT2 and OAT1 expressed in CHO cells; OATP2B1 expressed in MDCKII cells; OAT3 expressed in HEK293 cells (eliglustat)	DMPK10-R019	5.3.2.3

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Type of Study	Test System	Report Number	Study Report Location
	MRP2 membrane vesicles from Sf9 cells; OATP1B1, OATP1B3, OCT1, and OCT2 expressed in HEK293 cells; and OAT1 and OAT3 expressed in S_2 cells (metabolites)	DMPK11-R080	5.3.2.3

BCRP = breast cancer resistance protein; BSEP = bile salt export pump; CHO = Chinese Hamster Ovary CYP = cytochrome P450; MRP = multi-drug resistance protein; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; OCT = organic cation transporter; P-gp = P-glycoprotein; PM = poor metabolizer.

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Appendix 2. List of Clinical Pharmacology Studies (In Vivo)

Study Type	Study No.	Eliglustat Dosing Regimen [a] and Duration	No. of Subjects/ Patients Treated with Eliglustat [b]	Study Report Location
Biopharmaceutic Studies in Healthy Adult Subjects c				
Relative bioavailability of Phase 3 and common blend d capsules	GZGD03811	(b) (4) single dose (4 periods)	22	5.3.1.2
Food effect	GZGD00404	300 mg single dose (2 periods)	24	5.3.1.1
Pharmacokinetics, Pharmacodynamics, and Pharmacokinetics/Pharmacodynamics in Healthy Adult Subjects				
Single ascending dose	GZGD00103	0.01, 0.03, 0.1, 0.3, 1.0, 2.0, 3.0, 5.0, 7.0, 10.0, 15.0, 20.0, or 30.0 mg/kg oral solution single dose (Day 1)	74 5.3.3	.1
Multiple ascending dose	GZGD00204	50, 200, or 350 mg (Day 1) 50, 200, or 350 mg BID x 11 days (Day 2 to Day 12)	24 5.3.3	.1
Absolute bioavailability, PK, mass balance, excretion, and metabolism p	GZGD02107 and DMPK09-049	50 mg IV single dose (Day 1) 100 mg (Day 8) 100 mg BID x 6 days (Day 9 to Day 14) 100 mg radiolabeled oral solution (Day 15)	10	5.3.3.1 and 5.3.2.2
Thorough QT/QTc	GZGD01707	200 mg and 800 mg single dose	45	5.3.4.1
Extrinsic Factors in Healthy Adult Subjects				
Ketoconazole (strong CYP3A and P-gp inhibitor)	GZGD01807	100 mg BID x 7 days (2 periods)	36	5.3.3.4
Paroxetine (strong CYP2D6 inhibitor)	GZGD02007	100 mg BID x 7 days followed by 100 mg BID x 10 days	36 5.3.3	.4
Rifampin (strong CYP and P-gp inducer) e, f	GZGD02407	100 or 150 mg g single dose (Day 1 of 2 periods) 100 mg or (b) (4) BID g x 5 days (Day 2 to Day 6 of 2 periods)	25 5.3.3	.4
Antacids h and pantoprazole	GZGD01907	100 mg single dose (4 periods)	24	5.3.3.4

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Study Type	Study No.	Eliglustat Dosing Regimen [a] and Duration	No. of Subjects/ Patients Treated with Eliglustat [b]	Study Report Location
Effect of Eliglustat on Other Drugs in Healthy Adult Subjects				
Digoxin (P-gp substrate) f	GZGD03610 and DMPK11-R084	100 or 150 mg BID g x 7 days (Day 11 to Day 17)	28	5.3.3.4 and 5.3.2.2
Metoprolol (CYP2D6 substrate)	GZGD04112	150 mg BID x 6 days (Day 3 to Day 8)	14 5.3.3	.4
Norethindrone / ethinyl estradiol (oral contraceptive, Ortho-Novum 1/35)	GZGD02707	100 mg BID x 11 days (Day 39 to Day 49)	29 5.3.3	.4
Pharmacokinetics and Pharmacodynamics in GD1 Patients [i]				
Phase 2 study in treatment-naïve patients j, f	GZGD00304 (4 years) k	Through Year 4: 50 mg BID x 20 days (Day 1 to Day 20) followed by 50 or 100 mg BID x 49 weeks (Day 20 to Week 52) followed by 50, 100, or 150 mg BID x 3 years (Week 54 to Year 4)	26 5.3.5	.2
	GZGD03310 (biomarker sub-study)	Through Year 3: See above	21 5.3.4	.2
Phase 3 efficacy/safety study in treatment-naïve patients j	ENGAGE / GZGD02507 (Primary Analysis Period)	Primary Analysis Period: 50 mg BID x 4 weeks followed by 50 or 100 mg BID x 35 weeks	20 5.3.5	.1
Phase 3 efficacy/safety study in patients switching from enzyme replacement therapy	ENCORE / GZGD02607 (Primary Analysis Period)	Primary Analysis Period: [l] 50 mg BID x 4 weeks (Day 1 to Week 4) followed by 50 or 100 mg BID x 4 weeks (Week 4 to Week 8) 50, 100, or 150 mg BID x 44 weeks (Week 8 to Week 52)	106 5.3.5	.1

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Study Type	Study No.	Eliglustat Dosing Regimen [a] and Duration	No. of Subjects/ Patients Treated with Eliglustat [b]	Study Report Location
Phase 3b efficacy/safety study in patients who were treatment-naïve, off prior treatment, or receiving enzyme replacement therapy	EDGE / GZGD03109 (Lead-in Period m)	Lead-in Period: [l, m] 50 mg BID x 4 weeks (Day 1 to Week 4) 50or 100 mg BID (Week 4 to Week 8) 50, 100, or 150 mg BID n (Week 8 up to Week 78)	170 h	NA h
Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Modelling				
Population PK: intrinsic and extrinsic factors influencing PK variability o	POH0373	Dosing regimens for studies in the dataset ° are defined above	405 o	5.3.3.5
Physiologically-based PK (PBPK)-modeling using SimCYP®	SIM0105 SIM0106	NA NA		5.3.3.5
Simulation of exposure by phenotype using population PK model	SIM0124	NA NA		5.3.3.5
Pooled PK/PD-ECG analysis	NA	Dosing regimens for studies in the datasets [p] are defined above	320 to 369	5.3.5.3
PK/PD-efficacy analysis for prediction of efficacy based on phenotype-based recommended dosing	POH0395	Dosing regimens for studies in the datasets (Phase 2, ENGAGE, and ENCORE primary analysis periods) are defined above	105 to 152	5.3.3.5

BID = twice daily; CYP = cytochrome P450; ECG = electrocardiogram; ERT = enzyme replacement therapy; IV = intravenous; PBPK = physiologically-based pharmacokinetics; PD = pharmacodynamic; PK = pharmacokinetic; NA = not applicable; P gp = P-glycoprotein; QT = interval between Q and T waves on ECG; QTc = corrected QT interval

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/s/

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10/30/2013

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