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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** GZ385660	**Study Identifiers:** U1111-1170-3678, NCT02536911 **Study code:** POP13777
Title of the study: An open-label pharmacokinetic and tolerability study of eliglustat tartrate given as a single dose in subjects with mild and moderate hepatic impairment, and in matched subjects with normal hepatic function	
Study center(s): Two centers in the United States	
Study period: Date first subject enrolled: 01/Sep/2015 Date last subject completed: 29/Dec/2016	
Phase of development: Phase 1	
Objectives: Primary: To study the effect of mild and moderate hepatic impairment (HI) on the pharmacokinetics (PK) of eliglustat. Secondary: To assess the tolerability of eliglustat tartrate given as a single dose in subjects with mild and moderate HI in comparison with matched subjects with normal hepatic function.	
Methodology: A multi-center, open-label, single oral dose study of eliglustat tartrate administered to mild or moderate HI and normal hepatic function (healthy) matched (by body weight and cytochrome P450 [CYP] 2D6 phenotype) subjects. Approximately 8 subjects were planned to be enrolled into each HI group (mild or moderate HI) and 8 subjects with normal hepatic function; matched to impaired subjects by weight and CYP2D6 phenotype. CYP2D6 extensive metabolizers (EMs) and intermediate metabolizers (IMs) were to receive a single 100-mg dose of eliglustat tartrate, while CYP2D6 PMs were to receive a single 50-mg dose of eliglustat tartrate.	
Number of subjects**:** Planned: 24 Treated: 24 **Evaluated:** Safety: 24 Pharmacokinetics: 24	
Diagnosis and criteria for inclusion: For HI subjects: Male (body weight between 50.0 and 125.0 kg, inclusive) or female subjects (body weight between 40.0 and 110.0 kg, inclusive) between 18 and 79 years, inclusive, with a body mass index between 18.0 and 37 kg/m^2, inclusive; having stable chronic liver disease assessed by medical history, physical examination, and laboratory values; with moderate (defined as Child- Pugh score of 7 to 9, inclusive) or mild (defined as Child- Pugh score of 5 to 6, inclusive) HI. For healthy subjects: Male or female subjects, between 18 and 79 years, inclusive; body weight within 15% of the body weight of matched subjects with HI, and body mass index between 18.0 and 37 kg/m^2, inclusive; healthy subjects were also matched to HI groups by CYP2D6 phenotype predicted from genotype.	

Study treatments

Investigational medicinal products: Eliglustat tartrate 50-mg and 100-mg capsules

Formulation: Eliglustat tartrate 50-mg (equivalent to 42.2 mg of eliglustat) or 100-mg capsules (equivalent to 84.4 mg of eliglustat)

Route(s) of administration: Oral administration

Dose regimen:

A single 100-mg capsule of eliglustat tartrate was administered to CYP2D6 EM or IM subjects with mild or moderate HI and matching healthy subjects.

A single 50-mg capsule of eliglustat tartrate was to be administered to CYP2D6 PM with mild or moderate HI and matching healthy subjects.

Duration of treatment: 1 day

Duration of observation: Approximately 31 days including screening (2 to 21 days), treatment (1 day), and end-of-study (EOS; 10 days after dosing).

Criteria for evaluation:

Pharmacokinetics: The following PK parameters were calculated for eliglustat plasma concentrations using noncompartmental methods: Maximum plasma concentration observed (C_{max}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the time corresponding to the last quantifiable concentration t_{last} (AUC_{last}), time to reach C_{max} (t_{max}), area under the plasma concentration versus time curve extrapolated to infinity (AUC), terminal half-life associated with the terminal slope λz ($t_{1/2z}$), time corresponding to the last concentration above the limit of quantification (t_{last}), apparent total body clearance of a drug from the plasma (CL/F), and apparent volume of distribution during the terminal (λz) phase (Vz/F).

Safety: Adverse events (AEs) spontaneously reported by the subject or observed by the Investigator; clinical laboratory evaluations (including biochemistry, hematology, and urinalysis); vital signs (heart rate, and systolic and diastolic blood pressure); and 12-lead electrocardiograms (ECGs).

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples were collected at the following timepoints to assess plasma concentrations of eliglustat: predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours postdose

Eliglustat concentrations in plasma were determined using a validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantification of 0.2 ng/mL.

Statistical methods:

Pharmacokinetics

Eliglustat PK parameters were summarized using descriptive statistics for each population group and for each CYP2D6 phenotype.

Safety

The safety evaluation was based upon the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables). All safety analyses were performed using the safety population and were based on the on-treatment phase (defined as the time from investigational medicinal product [IMP] administration up to Day 3 visit, inclusive). For laboratory, vital signs, and ECG data, potentially clinically significant abnormalities (PCSAs) were analyzed using the 24 May 2014 version of the PCSA list. Electrocardiogram parameters were obtained from automatic reading of 12-lead ECGs and were analyzed as raw parameter values and change from baseline. For vital signs, raw data and changes from baseline were summarized using descriptive statistics by population group and time point. All individual data for biochemistry, hematology, and qualitative urinary tests were listed.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA v.19.1).

Summary:

Population characteristics:

Eight subjects were enrolled into each group. Seven CYP2D6 EMs and 1 CYP2D6 IM, each, were enrolled into the moderate impairment group and the healthy matched group, and 6 CYP2D6 EMs and 2 CYP2D6 IMs were enrolled into the mild impairment group.

Pharmacokinetic results:

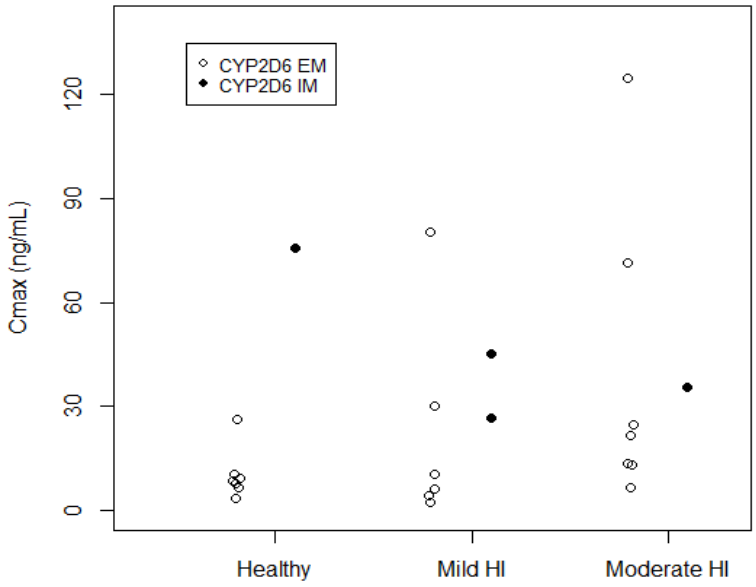
Mean ± SD (Geometric Mean) [CV%] PK parameters of Genz-99067 in CYP2D6 EM subjects after a single oral dose of 100 mg eliglustat tartrate

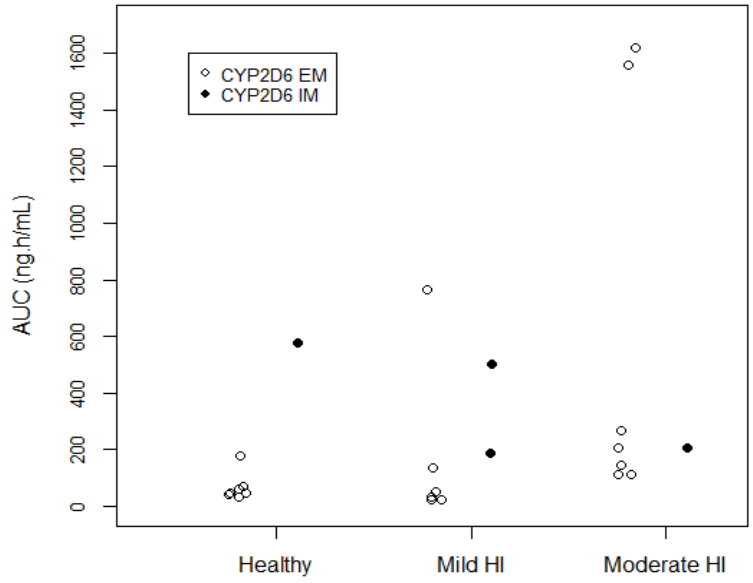
Plasma Eliglustat

	CYP2D6 EM Subjects			CYP2D6 IM Subjects		
Parameter	**Healthy**	**Mild HI**	**Moderate HI**	**Healthy**	**Mild HI**	**Moderate HI**
N	7	6	7	1	2	1
C_{max} (ng/mL)	10.4 ± 7.40 (8.81) [70.9]	22.4 ± 30.2 (10.7) [135.1]	39.5 ± 43.4 (24.8) [110.0]	75.9	35.9 (26.7, 45.1)	35.6
t_{max}[a] (h)	2.50 (1.00 - 3.00)	1.75 (1.00 - 6.00)	4.00 (1.00 - 6.00)	2.50	2.00 (2.00, 2.00)	1.52
AUC_{last} (ng•h/mL)	63.9 ± 47.1 (54.7) [73.7]	166 ± 285 (64.3) [171.3]	536 ± 642 (293) [119.6]	568	334 (187, 481)	197
AUC (ng•h/mL)	69.0 ± 49.1 (59.5) [71.2]	172 ± 293 (68.5) [170.5]	575 ± 696 (307) [121.0]	578	346 (190, 501)	208
$t_{1/2z}$ (h)	7.08 ± 0.881 (7.03) [12.5]	7.25 ± 1.46 (7.13) [20.1]	10.5 ± 2.25 (10.3) [21.4]	8.48	9.34 (8.27, 10.4)	5.87
CL/F (L/h)	1570 ± 628 (1420) [40.1]	1980 ± 1440 (1230) [72.8]	416 ± 295 (275) [70.9]	146	306 (168, 444)	406
Vz/F (L)	16030 ± 6020 (14400) [37.5]	20000 ±15600 (12700) [78.2]	5840 ± 4130 (4090) [70.7]	1790	3910 (2520, 5300)	3430
t_{last}[a] (h)	24.00 (24.00 - 24.05)	30.00 (24.00 - 48.00)	48.00 (36.00 - 48.00)	48.00	48.00 (48.00, 48.00)	24.00

a Median (Min - Max)
b Mean (Min, Max) for N=2

Individual eliglustat Cmax and AUC values after a single oral dose of 100 mg eliglustat tartrate





Point estimates of geometric mean ratio with 90% CI in CYP2D6 EM subjects			
Parameter	**Comparison**	**Estimate**	**90% CI**
C_{max}	Mild HI vs Healthy	1.22	(0.46 to 3.23)
	Moderate HI vs Healthy	2.81	(1.10 to 7.17)
AUC_{last}	Mild HI vs Healthy	1.18	(0.42 to 3.28)
	Moderate HI vs Healthy	5.35	(2.00 to 14.35)
AUC	Mild HI vs Healthy	1.15	(0.41 to 3.19)
	Moderate HI vs Healthy	5.16	(1.93 to 13.74)
$t_{1/2z}$	Mild HI vs Healthy	1.01	(0.85 to 1.21)
	Moderate HI vs Healthy	1.47	(1.24 to 1.74)
CL/F	Mild HI vs Healthy	0.87	(0.31 to 2.41)
	Moderate HI vs Healthy	0.19	(0.07 to 0.52)
Vz/F	Mild HI vs Healthy	0.88	(0.34 to 2.29)
	Moderate HI vs Healthy	0.28	(0.11 to 0.71)

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Compared to healthy CYP2D6 EMs, eliglustat mean C_{max} and AUC was slightly higher in CYP2D6 EMs with mild HI (1.22 and 1.15 fold, respectively) and appreciably higher in subjects with moderate HI (2.81 and 5.16 fold, respectively) following a single 100-mg dose of eliglustat tartrate. Mean $t_{1/2z}$ values were similar in mild HI subjects and healthy subjects, but were prolonged in moderate HI subjects (10.5 hours versus 7.08 hours).

While caution should be exercised in interpretation of the PK results in CYP2D6 IMs due to limited data, eliglustat exposure in CYP2D6 IMs with mild and moderate HI appeared to be similar to CYP2D6 EMs with the same hepatic status.

Safety results:

A total of 6 mild treatment-emergent AEs (TEAEs) were observed in 5 subjects. Four TEAEs in 3 subjects were considered related to study drug by the investigator: dysgeusia in 2 subjects with moderate HI and nausea and headache in 1 healthy subject. No serious adverse events were reported, and there were no deaths or other significant AEs. There were no treatment emergent PCSA that were clinically relevant for the laboratory values or for vital signs and ECGs.

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