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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:** U1111-1170-3686, NCT02536937 **Study code:** POP13778
Title of the study: An open-label two-stage pharmacokinetic and tolerability study of eliglustat tartrate given as a single dose in subjects with mild, moderate and severe renal impairment, and in matched subjects with normal renal function.	
Study centers: Three sites in the United States	
Study period: Date first subject enrolled: 22/Sep/2015 Date last subject completed: 26/Jan/2017	
Phase of development: Phase 1	
Objectives: Primary: To study the effect of mild, moderate, and severe renal impairment (RI) on the pharmacokinetics (PK) of eliglustat. Secondary: To assess the tolerability of eliglustat tartrate given as a single dose in subjects with mild, moderate, and severe RI in comparison with matched subjects with normal renal function.	
Methodology: A phase 1, open-label, 2-stage, pharmacokinetic and tolerability study of single dose eliglustat tartrate in subjects with RI (mild, moderate, and severe) and subjects with normal renal function, matched to RI subjects by age, weight, and cytochrome P450 [CYP] 2D6 phenotype. Approximately 32 subjects were planned to be enrolled in 2 stages: Stage 1 comprised of 8 subjects with severe RI and 8 subjects with normal renal function, matched by CYP2D6 phenotype, weight, and age. Subjects with mild and moderate RI would have been enrolled in Stage 2 if the results in subjects with severe RI showed a substantial effect of reduced renal function on eliglustat PK compared to the matched normal function subjects. Stage 2 was to include 8 subjects with mild and 8 subjects with moderate RI. Allowed concomitant medications included no more than one weak CYP3A inhibitor and one weak CYP2D6 inhibitor, alone or in combination. 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: 32 Treated: 16 **Evaluated:** Safety: 16 Pharmacokinetics: 16	
Diagnosis and criteria for inclusion: For RI subjects: Male (body weight between 50.0 and 125.0 kg, inclusive) and female (body weight between 40.0 and 110.0 kg, inclusive) subjects between 18 and 79 years, with a body mass index (BMI) between 18.0 and 37.0 kg/m2, inclusive, having mild, moderate or severe RI determined by a creatinine clearance (CrCl), calculated by Cockcroft-Gault formula, of 50-80 mL/min, 30-50 mL/min or <30mL/min, respectively. Normal renal function subjects: Male or female subjects, between 18 and 79 years, inclusive, body weight within 15% of the body weight of matched subject with RI, BMI between 18.0 and 37.0 kg/m^2 and a CrCl of >80 mL/min. Healthy subjects were also matched by age and CYP2D6 predicted phenotype based on genotype.	

Study treatments

Investigational medicinal products: Eliglustat tartrate 50 mg and 100 mg

Formulation: Eliglustat tartrate 50 mg (equivalent to 42.2 mg of eliglustat) or 100 mg (equivalent to 84.4 mg of eliglustat) capsules. Each capsule formulation contained 84.35% of the free base.

Route of administration: Oral administration

Dose regimen:

A single 100 mg capsule of eliglustat tartrate was to be administered to CYP2D6 EM or IM subjects with RI and matching healthy subjects.

A single 50 mg capsule of eliglustat tartrate was to be administered to CYP2D6 PM subjects with RI 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: Plasma eliglustat concentrations were used to determine the following PK parameters using noncompartmental methods: Maximum plasma concentration observed (C_{max}), first time to reach C_{max} (t_{max}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the time corresponding to the last concentration above the limit of quantification, t_{last} (AUC_{last}), area under the plasma concentration time curve extrapolated to infinity (AUC), terminal half-life associated with the terminal slope λz ($t_{1/2Z}$), apparent total body clearance of a drug from plasma (CL/F), and apparent volume of distribution during the terminal phase (VZ/F).

Safety: Adverse events (AEs) spontaneously reported by the subject or noted by the Investigator; standard clinical laboratory (biochemistry, hematology, urinalysis); vital signs (heart rate, systolic and diastolic blood pressure); and 12-lead electrocardiogram (ECG; automatic readings).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

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

Eliglustat concentrations in plasma were determined using a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification (LLOQ) 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. Estimate and 90% confidence interval (CI) for the geometric mean of each population group and for the geometric mean ratio of severe RI group versus the normal control group were provided from this model for each parameter.

Safety

The safety evaluation was based on the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables). All safety analyses were performed using the safety population and based on the on-treatment phase (defined as the start time of investigational medicinal product [IMP] administration up to Day 3 visit).

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

Summary:

Population characteristics:

A total of 16 subjects were enrolled: 8 subjects were enrolled into the severe RI cohort and 8 into the healthy matched cohort. For each cohort, 7 subjects were CYP2D6 EMs and 1 subject was CYP2D6 IM. Since Stage 1 did not show a substantial effect of severe RI on eliglustat PK compared to the matched normal renal function in EMs, Stage 2 of the study was not undertaken. Five EM subjects in the severe RI cohort were concomitantly taking a weak CYP3A inhibitor (amlodipine) and 1 IM subject in the severe renal impairment cohort was taking both a weak CYP2D6 inhibitor (escitalopram) and a weak CYP3A inhibitor (amlodipine). None of the healthy matched subjects were taking CYP2D6 or CYP3A inhibitors.

Pharmacokinetic results:

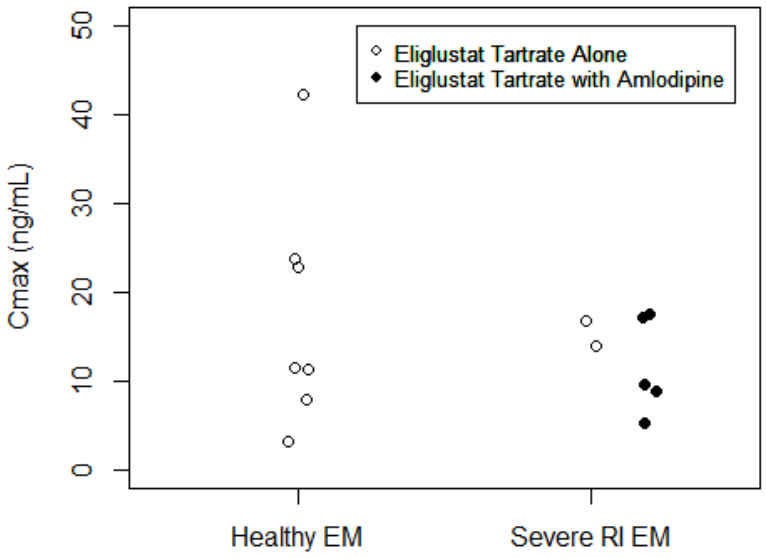
Mean ± SD (Geometric Mean) [CV%] plasma PK parameters of eliglustat after a single oral dose of 100 mg eliglustat tartrate

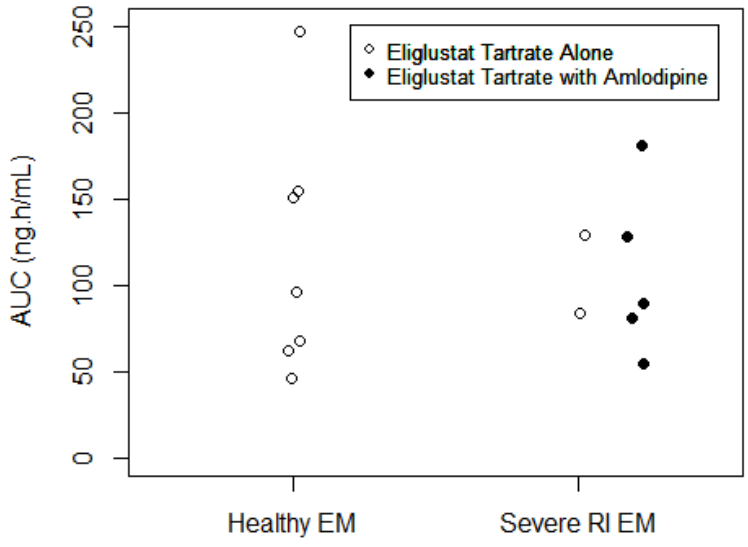
Parameter	CYP2D6 EM Subjects		CYP2D6 IM Subjects	
	Healthy	Severe RI	Healthy	Severe RI
N	7	7	1	1
C_{max}	17.6 ± 13.2	12.7 ± 4.85	54.7	220
(ng/mL)	(13.4) [75.2]	(11.8) [38.1]		
t_{max}[a]	1.50	4.00	3	4
(h)	(0.50 - 6.00)	(1.00 - 6.00)		
AUC_{last}	112 ± 68.7	102 ± 41.7	520	3590
(ng•h/mL)	(96.0) [61.1]	(95.5) [40.7]		
AUC	118 ± 71.1	107 ± 42.1	559	NRb
(ng•h/mL)	(101) [60.3]	(99.8) [39.5]		
$t_{1/2z}$	8.50 ± 1.51	6.56 ± 0.876	9.59	NRb
(h)	(8.39) [17.8]	(6.51) [13.3]		
CL/F	963 ± 532	903 ± 354	151	NRb
(L/h)	(834) [55.2]	(845) [39.2]		
Vz/F	11700 ± 6710	8480 ± 3190	2090	NRb
(L)	(10100) [57.5]	(7940) [37.7]		
t_{last}[a]	36.00	36.00	36.00	36.00
(h)	(24.00 - 36.00)	(24.00 - 36.00)		

a Median (Min - Max)

b NR: not reported. AUC, CL/F, $t_{1/2}$ and V_z/F values were not reported due to % AUC extrapolation greater than 20% of total AUC

Individual eliglustat C_{max} and AUC values after a single oral dose of 100 mg eliglustat tartrate in CYP2D6 EM subjects





Point estimates of geometric mean ratio with 90% CI in CYP2D6 EM subjects			
Comparison	**Parameter**	**Estimate**	**90% CI**
Severe RI vs Healthy	C_{max}	0.878	(0.462 to 1.669)
	AUC_{last}	0.994	(0.608 to 1.627)
	AUC	0.986	(0.609 to 1.597)
	$t_{1/2z}$	0.776	(0.671 to 0.898)
	CL/F	1.014	(0.626 to 1.643)
	Vz/F	0.787	(0.485 to 1.275)

Note: The analysis model is log(PK parameter)=Population and conducted for EM subjects (7 severe RI and 7 Healthy).

POPTYP = Population

PGM=PRODOPS/GZ385660/POP13778/CSR_01/REPORT/PGM/pk_pop13778.sas OUT=REPORT/OUTPUT/pk_fr_k_t_2_i.rtf (09MAR2017 - 3:29)

Eliglustat geometric mean C_{max} and AUC values were similar in subjects with severe RI and healthy matched subjects with CYP2D6 EM phenotype (0.878 and 0.986 fold, respectively). Coadministration of a single weak CYP3A inhibitor (amlodipine) in CYP2D6 EM subjects with severe RI (N=5, geometric mean [CV%] for C_{max} and AUC: 10.6 ng/mL [46.6] and 98.3 ng.h/mL [45.9] , respectively) did not appear to result in an increase in eliglustat exposures compared to severe RI EM subjects receiving eliglustat tartrate alone (N=2, geometric mean [CV%] for C_{max} and AUC: 15.2 ng/mL [12.9] and 104 ng.h/mL [30.3], respectively). Mean $t_{1/2z}$ values were shorter in severe RI subjects than in healthy subjects (6.56 versus 8.50 hours) and t_{max} values were longer (4.0 versus 1.5 hours).

No definitive conclusion can be drawn for the effect of RI in CYP2D6 IMs as only one CYP2D6 IM with severe RI taking concomitant medications was included. The substantially higher AUC_{last} values in this subject compared to CYP2D6 IM healthy subject (6.90-fold) or to either healthy CYP2D6 EMs (32.1-fold) or CYP2D6 EM with severe RI (35.2-fold) is attributed, at least in part, to the combined effect of 2 coadministered CYP inhibitors, a CYP2D6 inhibitor (escitalopram) and a CYP3A inhibitor (amlodipine).

Safety results:

A total of one mild treatment-emergent adverse event (TEAE) was observed in 1 subject, and was considered related to study drug by the investigator: fatigue in a healthy subject. No serious adverse events were reported, and there were no deaths or withdrawals due to 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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