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Sponsor / Company: Sanofi Drug substance(s): HMR1726/teriflunomide	Study Identifiers: NCT01239459, 2010-022354-16, U1111-11176723 Study code: POP11432
Title of the study: An open-label pharmacokinetic and tolerability study of teriflunomide given as a single 14 mg dose in subjects with severe renal impairment, and in matched subjects with normal renal function (POP11432)	
Study center(s): 1 center in Europe	
Study period: Date first subject enrolled: 11/Nov/2010 Date last subject completed: 23/Mar/2011	
Phase of development: 1	
Objectives: Primary: To study the effect of severe renal impairment on the pharmacokinetics (PK) of teriflunomide. Secondary: To assess the tolerability of teriflunomide given as a single 14 mg dose in subjects with severe renal impairment (SRI) and in matched subjects with normal renal function.	
Methodology: Single-center, open-label, single oral dose study.	
Number of subjects: Planned: 16; randomized: not applicable; treated: 16 Evaluated: Safety: 16 ; pharmacokinetic: 16	
Diagnosis and criteria for inclusion: Male and female subjects with severe renal impairment (defined as creatinine clearance CLcr <30 mL/min, not requiring hemodialysis) and matched healthy subjects (by age, gender and body weight) with normal renal function based on Cockroft-Gault formula.	

Study treatments

Investigational medicinal product(s): Teriflunomide film coated tablet

Dose: 14 mg

Administration: Oral, fasting

Non-investigational product: Cholestyramine, powder packs of 4 g (at least 2 days[Day 54, Day 55], to increase elimination of teriflunomide after the last PK blood sample collection)

Dose: 8 g (might be reduced to 4 g, if not well tolerated), 3 times daily

Administration: Oral, fed

Duration of treatment: Single dose

Duration of observation: 91 to 101 days

Criteria for evaluation:

Safety:

Adverse events (AEs); standard clinical laboratory (biochemistry, hematology, urinalysis); vital signs and electrocardiogram (ECG; automatic readings).

Pharmacokinetics:

The following teriflunomide PK parameters were calculated by non-compartmental analysis:

Primary: Maximum plasma concentration observed (C_{max}), area under the plasma concentration versus time curve from time zero to the real time corresponding to the last concentration above LLOQ (AUC_{last}) and area under the plasma concentration versus time curve from time zero to infinity (AUC).

Secondary: First time to reach C_{max} (t_{max}), terminal half-life ($t_{1/2Z}$), effective half-life ($t_{1/2eff}$), predicted accumulation ratio ($R_{ac,pred}$), apparent clearance (CL/F), apparent volume of distribution at steady state (V_{ss}/F), unbound C_{max} ($C_{max,u}$), unbound AUC (AUC_u) and fraction of unbound drug (f_u).

Pharmacokinetic sampling times and bioanalytical methods:

Sampling: Blood samples were collected for teriflunomide concentrations (ie, total drug) at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 120, 168, 312, 480, 984, and 1272 hours after teriflunomide administration as well as after cholestyramine treatment (washout period). Additionally, blood samples were collected at 2 and 24 hours after teriflunomide administration for the determination of unbound teriflunomide concentrations.

Bioanalytical methods: Teriflunomide concentrations in plasma (total drug) and in retentate samples following equilibrium dialysis were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method, with a lower limit of quantitation (LLOQ) of 0.01 µg/mL. Teriflunomide concentrations in the dialysate samples following equilibrium dialysis (unbound drug) were determined with a validated LC-MS/MS method with an LLOQ of 0.0001µg/mL (0.1 ng/mL).

Statistical methods:

Safety:

The safety analysis was based on the review of descriptive statistics (summary tables) and individual data for AEs, clinical laboratory, vital signs, and ECG parameters. Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 13.1, and the numbers of subjects with treatment-emergent adverse events (TEAEs) were summarized by population group (severe renal impairment and healthy). Potentially clinically significant abnormalities (PCSAs; definitions according to version dated 14 September 2009) for clinical laboratory, vital sign, and ECG data and out-of-normal range values for clinical laboratory data were flagged and summarized in frequency tables by population group.

Pharmacokinetics:

Descriptive statistics for teriflunomide PK parameters (total and unbound) for each population group were provided. Prior to the analyses described below, C_{max}, AUC_{last}, AUC, $t_{1/2z}$, CL/F, unbound C_{max} and unbound AUC for teriflunomide were logtransformed. These parameters were analyzed using a linear fixed effects model with fixed terms for population group (healthy and severe renal impairment) and gender, and with age and weight as covariates, using SAS Proc Mixed®.

For C_{max}, AUC_{last}, AUC, $t_{1/2z}$, CL/F, unbound C_{max} and unbound AUC, estimates and 90% confidence interval (CI) for the geometric mean ratio (severe renal impairment versus healthy) were obtained within the linear fixed effects model framework, and then converted to ratios of adjusted geometric means by the antilog transformation.

All above mentioned analyses were performed with the populations grouped according to the Cockcroft-Gault formula and, in addition, classified according to the abbreviated MDRD (modification of diet in renal disease) equation.

Summary:

Safety results:

There were no SAEs, and no subject discontinued the study due to a TEAE.

Treatment emergent adverse events were reported in 5/8 SRI subjects and 4/8 healthy subjects during teriflunomide alone; and in 5/8 SRI subjects and 3/8 healthy subjects during cholestyramine after teriflunomide.

Few isolated laboratory abnormalities were reported in SRI subjects, which were mainly due to their condition (ie, diabetes, chronic renal failure). One healthy subject presented an episode of creatine phosphokinase (CPK) increase (reported as an AE) following an intramuscular injection to treat a back pain.

No PCSAs were reported for heart rate in either population group. Very few, isolated and not clinically meaningful episodes of systolic or diastolic blood pressure increase which met PCSA criteria were reported.

There were sporadic and fluctuating PCSAs in Q-T interval of electrocardiogram corrected (QTc) intervals for 4/8 SRI subjects. No subjects had prolonged QTc $\geq$500 ms or an increase in QTc from baseline >30 ms.

Pharmacokinetic results:

Pharmacokinetic parameters were similar between SRI subjects and matched subjects with normal renal function.

Mean ± SD (Geometric Mean) [CV%] of teriflunomide PK parameters

	Severe Renal Impairment (N=8)	Healthy (N=8)
C_{max}	1.57 ± 0.137	1.33 ± 0.225
(µg/mL)	(1.56) [8.7]	(1.32) [16.9]
t_{max}[a]	2.00	1.75
(h)	(0.50 - 48.07)	(1.00 - 4.00)
$t_{1/2z}$	297 ± 121	306 ± 77.4
(h)	(274) [40.7]	(296) [25.3]
AUC_{last}	480 ± 195	456 ± 130
(h•µg/mL)	(440) [40.6]	(438) [28.5]
AUC	525 ± 242	495 ± 162
(h•µg/mL)	(472) [46.0]	(470) [32.8]
CL/F	33.6 ± 19.8	31.5 ± 11.9
(mL/h)	(29.6) [59.0]	(29.8) [37.7]
Vss/F	11.3 ± 2.00	12.5 ± 1.48
(L)	(11.1) [17.8]	(12.4) [11.9]
$t_{1/2eff}$	315 ± 185	314 ± 94.8
(h)	(273) [58.8]	(302) [30.2]
$R_{ac,pred}$	19.4 ± 11.1	19.4 ± 5.70
	(17.0) [57.2]	(18.7) [29.4]

[a] Median (Min - Max)

Estimates of group ratio with 90% CI for teriflunomide			
Comparison	Parameter	Estimate	90% CI
Severe Renal Impairment vs. Healthy	C_{max}	1.16	(0.97 to 1.39)
	AUC_{last}	1.02	(0.63 to 1.66)
	AUC	1.03	(0.61 to 1.74)
	$t_{1/2z}$	0.99	(0.65 to 1.52)
	CL/F	0.97	(0.57 to 1.64)
	Unbound C_{max}	1.15	(0.93 to 1.42)
	Unbound AUC_{last}	1.01	(0.64 to 1.60)
	Unbound AUC	1.02	(0.62 to 1.66)

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