*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

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| Sponsor / Company: Sanofi<br>Drug substance(s): HMR1726 (Teriflunomide) | Study Identifiers: NCT02046629, UTN U1111-1152-4217<br>Study code: PKM12788 |
| Title of the study: An open-label, single-dose study to evaluate the pharmacokinetic profiles of 14 mg teriflunomide tablet in healthy Chinese subjects | |
| Study center: 1 center in China | |
| Study period:<br>Date first subject enrolled: 28/May/2014<br>Date last subject completed: 22/Jul/2014 | |
| Phase of development: Phase 1 | |
| Objectives:<br>Primary: To assess the pharmacokinetic (PK) parameters of teriflunomide after a single oral dose of 14 mg administration in Chinese healthy subjects.<br>Secondary: To assess the safety and tolerability after a single oral dose of 14 mg teriflunomide in Chinese healthy subjects. | |
| Methodology: Phase 1, single-center, open-label, single oral dose study in healthy adult Chinese subjects. | |
| Number of subjects: Planned: 12<br>Treated: 12<br>Evaluated:<br>Safety: 12<br>Pharmacokinetics: 12 | |
| Diagnosis and criteria for inclusion: Healthy male and female Chinese subjects, between 18 and 45 years of age, inclusive (at least 30% of each gender). | |
| Study treatments<br>Investigational medicinal product: Teriflunomide<br>Formulation: Film coated tablet of 14 mg teriflunomide<br>Route(s) of administration: Oral route in the fasted condition<br>Dose regimen: Single dose of teriflunomide 14 mg | |
| Noninvestigational medicinal product: Cholestyramine<br>Formulation: Powder packs containing 4 g<br>Route(s) of administration: Oral route in fed condition, in a glass of fruit juice, milk, soup, apple sauce or water<br>Dose regimen: 8 g administered with meals, 3 times per day from Day 27 to Day 30 for 4 consecutive days | |

Duration of treatment: Single dose

Duration of observation: Up to maximum of 9 weeks including screening (2 to 21 days before inclusion), institutionalization period (6 days including 1 treatment day), follow-up (7 to 10 days) and end of study (Day 38 to Day 41).

Criteria for evaluation:

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

Pharmacokinetics:

The following PK parameters were calculated using noncompartmental methods from teriflunomide plasma concentrations:

Primary: Maximum plasma concentration observed ($C_{max}$), area under the plasma concentration versus time curve from time zero to 624 hours ($AUC_{0-624}$), area under the plasma concentration versus time curve from time zero to the real time ($AUC_{last}$), area under the plasma concentration versus time curve extrapolated to infinity (AUC).

Secondary: Time to reach $C_{max}$ ($t_{max}$), terminal half-life associated with the terminal slope ($t_{1/2z}$), time corresponding to the last concentration above the limit of quantification ($t_{last}$), apparent volume of distribution at steady state ($V_{ss}/F$), apparent total body clearance (CL/F).

Pharmacokinetic sampling times and bioanalytical methods: Blood samples for the determination of teriflunomide concentrations in plasma were collected at the following times: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 288, 456, and 624 hours after teriflunomide dosing. At least 1 additional sample was taken at the end of cholestyramine treatment (Day 31). Plasma teriflunomide concentrations were determined using a validated liquid chromatography coupled with tandem mass spectrometry method with a lower limit of quantification of 0.01 µg/mL.

Statistical methods:

Safety: The safety analysis was based on the review of AEs, descriptive statistics (summary tables) and individual data (potentially clinically significant abnormalities [PCSAs]) for clinical laboratory, vital sign, and ECG parameters AEs were coded using the Medical Dictionary for Regulatory Activities version 17.0, and the numbers of subjects with treatment-emergent adverse events (TEAEs) were summarized by System Organ Class (SOC) and Preferred Term (PT). Potentially clinically significant abnormalities (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.

Pharmacokinetics: Teriflunomide plasma concentrations and PK parameters were summarized using descriptive statistics.

Summary:

Safety results:

There were no serious TEAEs or TEAEs leading to study discontinuation reported during the study. Six out of the 12 subjects had TEAEs. All TEAEs were of mild intensity and recovered within 4 weeks. The most frequently reported TEAEs were hypertriglyceridemia (4 out of 12 subjects) during teriflunomide treatment period and the Investigator considered these AEs as not related to the teriflunomide, although none of triglycerides values in these subjects reached PCSA limits. Gastrointestinal events (nausea and constipation) were most frequently reported in one subject after cholestyramine treatment, and the Investigator considered these AEs as not related to the teriflunomide or cholestyramine. The incidence of PCSAs in clinical laboratory parameters and vital signs was low, and none of these PCSAs were considered clinically relevant by the Investigator.

Pharmacokinetic results:

Mean ± SD (geometric mean) (CV%) of teriflunomide PK parameters

| Parameter | 14 mg Teriflunomide |
|---|---|
| N | 12 |
| $C_{max}$ (µg/mL) | 2.05 ± 0.348 (2.02) [17.0] |
| $t_{max}$[a] (h) | 2.00 (0.75 - 5.00) |
| $t_{last}$[a] (h) | 624 (624- 624) |
| $AUC_{0-624}$ (µg.h/mL) | 630 ± 106 (621) [16.8] |
| AUC (µg.h/mL) | 730 ± 165 (712) [22.7][b] |
| $t_{1/2z}$ (h) | 352 ± 138 (326) [39.2] |
| CL/F (mL/h) | 20.2 ± 5.56 (19.7) [27.5][b] |
| $V_{ss}$/F (L) | 7.34 ± 0.848 (7.30) [11.6][b] |

[a] Median (Min - Max)
[b] n=7 due to area extrapolation >30% in 5 subjects

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