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RESEARCH ARTICLE

Lack of Sex Differences in the Pharmacokinetics of Saroglitazar Magnesium in Healthy Subjects

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ABSTRACT

Background and objective: Saroglitazar magnesium, is indicated to treat patients with diabetic dyslipidemia. Saroglitazar achieves its purported activity via dual PPARαγ agonism, predominant PPARα activity. Its development was carried out with objectives of imparting dyslipidemic and anti-hyperglycaemic effects, and reducing the commonly reported side effects of PPAR modulators. The evaluation of sex differences in pharmacokinetics as a separate standalone study or from a general pooled population pharmacokinetic analysis is now a routine component of drug development to enable dosing considerations, if any. The objective of the analysis was to evaluate if there was a gender difference in the pharmacokinetics of saroglitazar and its metabolite. Such data would not only provide guidance for clinical development but also would support specific label claims for saroglitazar.

Methods: The pharmacokinetic data pertaining to saroglitazar administration under fasting condition from an earlier reported food effect clinical study in male and female subjects (n=54) were used in this analysis. For evaluation of gender effect, saroglitazar and its metabolite were compared in plasma samples collected till 72 h post-dose. Non-compartment approach was used to analyze the pharmacokinetic data.

Results: A total of Fifty-four subjects (1:1 male & female) were enrolled in the study; 24 female and 26 male subjects had completed the study. The observed mean Cmax of saroglitazar in male (259.744±92.499 ng/ml) was similar to those obtained in female (261.055±89.390 ng/ml). The extent of absorption (AUC_{∞}) in male observed as 731.983±238.148 ng x hr/mL whereas in female it was 781.240±231.473 ngxhr/mL. No statistical significant difference was observed for other parameter such as Tmax and T1/2 values of Saroglitazar. Overall Saroglitazar was well tolerated; and there was no adverse event (AE) was reported in fasting period of the study, the reported AEs in fed period were mild in nature.

Conclusion: No PK differences between men vs. women for saroglitazar was observed, which resulted in bioequivalence for saroglitazar. Although the metabolite did not achieve bioequivalence but it has no bearing on the clinical outcome because it is pharmacologically inactive. Overall, based on the

analysis it was concluded that there is no need of dosage adjustment based on gender.

Introduction

Saroglitazar magnesium, has received market approval in India for treating patients with diabetic dyslipidemia [1]. From a pharmacology point of view, saroglitazar achieves its purported activity via dual PPAR agonism, comprising of a predominant PPARα activity coupled with moderate PPARγ activity. The development of saroglitazar, unlike other drugs targeting PPARαvδ/oρ PPARγ was carried out with objectives of imparting dyslipidemic and anti-hyperglycaemic effects, and reducing the commonly reported side effects of PPAR modulators which are typically manifested as peripheral oedema, weight gain etc [2].

A robust preclinical assessment has confirmed both serum triglyceride and glucose lowering properties of saroglitazar including lowering of free fatty acids in various rodent models following oral administration of saroglitazar [3]. In several clinical studies, Saroglitazar has unequivocally demonstrated reduction of several biomarkers which are implicated as cardiovascular risk factors namely: triglycerides (TG), Low density lipoprotein (LDL) Cholesterol, very Low density lipoprotein (VLDL) cholesterol, and non -high density lipoprotein (Non-HDL) Cholesterol and in increase in HDL cholesterol [4,5]. In addition, the dosing of saroglitazar has been shown to display favorable glycemic index since it causes reduction of the fasting plasma glucose and glycosylated hemoglobin in diabetic patients [2].

Saroglitazar has been extensively studied in pre-clinical species to describe pharmacology, pharmacokinetic and pharmacodynamics of the drug in appropriate animal models [3].

Currently, a number of clinical trials of saroglitazar are on-going for different indications like Diabetes mellitus (DM), Nonalcoholic Fatty Liver Disease and/or Nonalcoholic Steatohepatitis (NASH), HIV induced lipodystrophy, dyslipidemia, hypertriglyceridemia, primary biliary cholangitis, Primary Biliary Cirrhosis (PBC) [6-9].

It is now well known that gender differences may affect pharmacokinetics of many drugs and the expanding knowledge of these gender differences in relation with the drug exposure may beneficial for pharmacotherapy for male and female [10-12].

The evaluation of sex differences in pharmacokinetics as a separate standalone study and/or evaluating sex differences from a general pooled population pharmacokinetic analysis is now a routine component of drug development to enable dosing considerations, if any. Also the results for sex differences in pharmacokinetics are usually incorporated in numerous US FDA approved drug labels most notably: liraglutide, golimunab, gemifloxacin, fosamil etc [13-17].

It has been shown that gastric pH is higher in women than men; also, women tend to have longer gastric and bowel transit times as compared to men but it is not known that the such sex differences is clinically relevant [18,19].

Interestingly, the so called inactive excipient such as excipient polyethylene glycol enhances the bioavailability of ranitidine in men by 63 %, whereas the same excipient decreased the bioavailability by 24% in women [20]. Analysis of gender differences in PK and intra-subject variability from reported generic Bioequivalence (BE) studies revealed that despite of there was no gender differences in intra-subject variability; there was a significant difference in PK parameters between male and female [21]. It should also be noted that male have lower percentage of body fat compared to female (approximately 16% male vs. 25 % female), however this difference in body fat may decreases as age increases [22].

The objective of the analysis was to evaluate if there was a gender difference in the pharmacokinetics of saroglitazar and its metabolite saroglitazar sulfoxide. Such data would not only provide guidance for clinical development but also would support specific label claims for saroglitazar.

Key Points:

1. The evaluation of sex differences in pharmacokinetics and/or evaluating sex differences

from a general pooled population pharmacokinetic analysis is now a routine component of drug development to enable dosing considerations, if any.

2. The pharmacokinetic data pertaining to saroglitazar administration under fasting condition from an earlier reported clinical studyin male and female subjects were used in this analysis.

3. The analysis was carried out to clarify whether or not gender differences existed in the pharmacokinetics of saroglitazar when given at the highest therapeutic dose of 4 mg.

4. The results unequivocally confirmed that both absorption rate and extent of absorption of saroglitazar using the surrogates of Cmax and AUCs (AUC0-t and AUC_{∞}) were bioequivalent between male vs. female subjects.

Subjects and Methods

1. Subjects

The study enrolled non-smoking male and female subjects between 18 and 45 years of age (at the pre-study visit) with a body mass index between 18.5 and 30 kg/m^2. Female subjects of childbearing age were not pregnant or breastfeeding and agreed to use of a non-hormonal, barrier birth control method. Prior to enrollment in the study, subjects were assessed on exclusion criteria based on medical history, physical examinations, laboratory safety tests, and Electrocardiogram (ECG) measurements. The study was planned in 54 healthy adult human subjects who were judged as healthy on the basis of a pre-study physical examination and clinical laboratory tests and who provide written informed consent for participation in the study.

2. Study design

The pharmacokinetic data pertaining to saroglitazar administration under fasting condition from an earlier reported clinical study in male and female subjects were used in this analysis [2]. Briefly, clinical study involved enrolment of male and female subjects for the single 4 mg saroglitazar magnesium dose administration under fasting vs. fed conditions [2]. Both male and female subjects were randomized for the appropriate treatment using block randomization schedule (SAS_ statistical software (Version 9.4, SAS Institute Inc., Cary, NC USA). A single oral dose of 4 mg saroglitazar magnesium was administered to male and female subjects (i.e., 2-parallel groups), following an overnight fast (at least 10 h), with approximately 240 ml of water. The subjects continued to remain fasted for at least 4 h post-drug administration, when a standardized meal was served.

In particular, the analysis for gender differences in pharmacokinetic parameters was not statistically powered a-priori. However, the initial sample size of 54 subjects (27 male and 27 female subjects) that was used in the earlier clinical study was considered adequate to fulfill the objective of this analysis.

2.1. Blood samples and concentration determination: Blood samples at pre-dose (0.0 h) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0,8.0, 10.0, 24.0, 36.0, 48.0 and 72.0 h post the single dose administration were collected using vacutainers containing K2EDTA as an anti-coagulant. Plasma was harvested from blood samples and kept frozen at -70° ± -20° C until the analysis of samples.

Both saroglitazar and its sulfoxide metabolite were quantified in plasma by using two independent validated liquid chromatography coupled with a tandem mass spectrometry (LC–MS/MS) method [21]. Briefly, multiple reaction monitoring (MRM) of the transition pairs in a positive mode for saroglitazar and saroglitazar sulfoxide were employed to achieve high specificity and sensitivity to enable the determination of the two analytes in clinical samples [2]. The details of the methodology has been described earlier [2].

3. Pharmacokinetic analysis

A standard non-compartmental model available in the WinNonlin professional software (Phoenix version, 6.4 Pharsight Corporation, Mountain View, CA, USA) was employed for the calculation of various pharmacokinetic parameters. The evaluated parameters included: highest plasma concentration (Cmax); time taken to reach Cmax (Tmax); the plasma concentration vs. time curve (AUC) until the last quantifiable time point "t" (AUC0-t) which was extrapolated to time = infinity (AUC0-inf); the terminal elimination rate constant (Kel) with the

corresponding elimination half-life (T1/2). Both saroglitazar and saroglitazar sulfoxide metabolite data obtained in fasting condition of males and females were subjected to the above described pharmacokinetic analysis.

4. Statistical analysis

Statistical analysis was performed on the primary pharmacokinetic parameters using SAS® statistical software (Version: 9.4, SAS Institute Inc., USA). The assessment of gender effect was performed by using the exposure data (Cmax and AUC_{∞}) of saroglitazar. The 90% confidence intervals of the (male/female) ratios of relative mean (Geometric mean) of saroglitazar was computed for Ln-transformed Cmax and AUC_{∞}. The point estimate and 90% CI was assessed for gender effect as follows:

a) If 90% CIs fell within 80.00-125.00%, lack of gender effect was confirmed.

b) If 90% CIs fell outside 80.00-125.00%, presence of gender effect was confirmed.

Additionally gender effect for saroglitazar sulfoxide (metabolite) was also assessed although it is not pharmacologically active.

5. Safety and tolerability assessment

Safety parameters and laboratory parameters assessment were done at the time of screening. Laboratory parameters were also assessed at the end of the study. All the out of range laboratory parameters were evaluated after end of the study. The laboratory parameters which were labeled as clinically significant by the investigator or physician were documented as an adverse event. The clinical staff based on observation and questioning of the subject determined the severity of each adverse event. The Investigator judged the relationship of the adverse event to the study treatments. None of the adverse events experienced by the subjects during this study were judged as serious (ICH–E2A, Section II-B) [2].

Results

1. Demographics

The study was conducted in Asian male and female population. The 27 male subjects who participated in this study were aged 20 to 42 years (mean age 32 years), weighted 50.1 to 85.8 kg (mean weight 64.7 Kg), and had a Body Mass Index (BMI) in the range of 18.6 to 29.7 kg/m^2 (mean BMI 23.2 kg/m^2). One subject was dropped out due to protocol violation during study, so only 26 out of 27 enrolled male subjects completed both the periods of the study (Figure 1).

The 27 female subjects who participated in this study were aged 22 to 44 years (mean age 32 years), weighed 45.5 to 74.5 kg (mean weight 57.3 Kg), and had a Body Mass Index (BMI) in the range of 19.4 to 29.8 kg/m^2 (mean BMI 24.7 kg/m^2). Two subjects had withdrawn their consent for further participation in the study and one subject was discontinued on medical ground due to adverse event during study, so only 24 out of 27 enrolled female subjects completed both the periods of the study (Figure 1).

Our inclusion criteria were based on age and BMI which showed statistically not significant difference ($p>0.05$) between the two genders (Table 1).

Table 1: Summary of Demographic Data.

PARAMETER	Male	Female	p-value
	Arithmetic mean ± SD (Range)	Arithmetic mean ± SD (Range)	
Age (years)	32.52 ± 6.04 (20 - 42)	31.96 ±5.43 (22 - 44)	0.7238
BMI (kg/m^2)	23.20± 3.43 (18.6 - 29.7)	24.66 ±3.59 (19.4 - 29.8)	0.1327
Weight (kg)	64.66 ± 9.35 (50.1 - 85.8)	57.34 ± 9.19 (45.5 -74.5)	0.0055
Height (cm)	166.96± 4.51 (160 -176)	152.38 ± 4.52 (145 -163)	<0.0001

2. Pharmacokinetics

The gender effect on the concentration profile of saroglitazar was evaluated at an oral dose of 4 mg of saroglitazar magnesium in male and female healthy subjects. The tabular summary of the descriptive statistics and statistical analysis for saroglitazar is given in Table 2. The 90% confidence interval and p-value of in transformed pharmacokinetic data is provided in Table 3. Figure 2 showed plasma concentration of saroglitazar between men vs. women. The observed mean Cmax in male subjects (259.744±92.499 ng/ml) was similar to those obtained in female subjects (261.055±89.390 ng/ml) (Table 2). As evident in Fig. 2, the extent of absorption as measured by AUC_{∞} did not differ

between male and female (male: 731.983±238.148 ng x hr/mL; female: 781.240±231.473 ng x hr/mL; (Table 2). Sign rank Non-Parametric-test was performed for Tmax and T1/2. P-values for Tmax and T1/2 were observed as 0.4858 and 0.5883 respectively; which shows no statistical significant difference between male vs. female under fasting condition for saroglitazar.

Table 2: Summary of Pharmacokinetic Data for Saroglitazar 4 mg (n=50).

PARAMETER	Female (N=24)	Male (N=26)	p-value#
	Arithmetic mean± SD (Range)	Arithmetic mean± SD (Range)	
C_{max} (ng/ mL)	261.055±89.390 (91.630 - 490.600)	259.744±92.499 (96.140 - 475.200)	0.9143
AUC_t (ng·hr/ mL)	777.120±229.952 (298.730 - 1374.600)	727.475±238.016 (413.240 - 1344.300)	0.4369
AUC_∞ (ng·hr/ mL)	781.240±231.473 (302.900- 1385.400)	731.983±238.148 (422.230 - 1346.400)	0.4437
K_{el} (1/hr)	0.121±0.044 (0.038 - 0.206)	0.128±0.038 (0.059- 0.233)	——
$T_{1/2}$(hr)	6.714±3.268 (3.360 - 18.100)	5.943±1.985 (2.970 - 11.850)	——
T_{max} (hr)[a]	1.500 (0.750 - 4.500)	1.500 (0.500 - 4.500)	——

(a) Tmax is presented as Median (Range).
Cmax, maximum concentration; AUCt, area under the concentration time curve from time zero to the last quantifiable concentration; AUC∞, area under the concentration time curve from time zero to infinity; Kel,terminal elimination rate constant; T1/2, elimination half-life; Tmax, time of maximum concentration.
p-value were obtained for gender effect on ln-transformed PK parameter.

Similarly, female vs. male pharmacokinetic evaluation was also carried out for saroglitazar sulfoxide metabolite. Descriptive statistics of pharmacokinetic parameters and 90% confidence interval and p-value of ln transformed data is provided in Table 4 and 5, respectively. Figure 3 showed plasma concentration of saroglitazar between men vs. women. P-values for Cmax and AUC∞ was observed as 0.4478 and 0.6229 respectively whereas P-values for Tmax and T1/2 were observed as 0.4355 and 0.5136 respectively; which shows no statistical significant difference between male vs. female under fasting condition for saroglitazar sulfoxide.

3. Safety results

There was no AE or SAE reported during fasting period of the study, however there were three (03) subjects had experienced Adverse Events (AEs) in fed period of the study which were mild in nature. The two (02) reported AEs (White Blood Cell Count Increased and Blood Glucose Increased) were considered unlikely/remotely related to the drug and one (01) reported AE (Vomiting) was considered possibly related to the drug. Overall, saroglitazar was well tolerated following a single oral dose administration by healthy human subjects.

Discussion

Men and women have different physical and physiological parameters which may influence the drug disposition in to the body, for example female have a higher proportion of body fat, lower total body weight, lower glomerular filtration rate, smaller organ size, a lower muscle mass, lower gastric acid excretion and a lower body surface area. Moreover, hormonal fluctuations during the menstrual cycle may also affect the pharmacokinetic disposition of the drugs. Probably variations in the menstrual cycle, hormonal contraceptive therapy, hormonal changes during menopause and pregnancy influence hematological, renal and cardiovascular systems, which can affect binding of protein with drug and Volume of Distribution (VD). Additionally, there are various molecular factors such as transporter and difference in drug metabolizing enzymes that responsible for gender differences in pharmacokinetics. The drug disposition process may also influenced by various factors like molecular, Physical and physiological [24].

Furthermore, the extent of pharmacokinetic differences if any between men vs. women is often small and may not be clinically relevant. A total of 300 New Drug Applications (NDAs) which was submitted to the United States Food Drug Administration (USFDA) between 1994 to 2000; survey of clinical pharmacology data revealed that out of those 300 NDAs applications 163 NDAs had gender based PK information. Out of the 163 drugs, 51 have a possible gender effect [25]. The clinical pharmacology data survey showed that the most of (90%) the observed gender differences PK were less than 40%, except for one drug having a greater than 40% difference in PK was noted in which women consistently showed higher plasma exposure as

compared to men. Despite of various pathways involved in drug disposition, more than 50 % of the drugs studied displayed less than 20 % differences in PK between men vs. women [25].

If one examines published clinical studies that have evaluate male vs. female subjects pharmacokinetic data, generally a smaller cohort size of 10-15 subjects is chosen for this evaluation [26-28].

Table 3: Geometric least square mean, Ratio, 90% Confidence Intervals and Acceptance Range based on Log-transformed data for Saroglitazar Female Vs. Male (n=50).

Pharmacokinetic parameter	Geometric least square mean		Ratio (%)	Intra-subject CV (%)	90% Confidence Intervals(%)	Gender Effect Acceptance Range %	p-value
	Female	Male					
C_{max} (ng/ mL)	264.654	243.940	98.90	37.341	(83.31; 117.41)	80.00 - 125.00	0.9143
AUC_t (ng×hr/ mL)	6.611	6.541	93.22	32.443	(80.22; 108.33)	80.00 - 125.00	0.4369
AUC_∞ (ng×hr/ mL)	747.136	669.441	93.35	32.282	(80.39; 108.40)	80.00 - 125.00	0.4437

C_{max}, maximum concentration; AUC_∞, area under the concentration time curve from time zero to infinity; CV, coefficient of variation.

Saroglitazar is undergoing global clinical development for several important indications such as PBC, NASH, hypertriglyceridemia etc. Both male and female patients are being dosed with saroglitazar in the planned clinical trials. Hitherto there has been no formal clinical study of saroglitazar that evaluated gender differences in the pharmacokinetic parameters after oral drug administration of therapeutic doses of saroglitazar magnesium. An earlier phase I study that determined the safety, tolerability and pharmacokinetics of saroglitazar had included healthy female subjects at a single dose cohort (i.e., 1 mg dose) for comparative evaluation of the data with male subjects. Although the sample size was limited (n=6) in this comparative evaluation of the pharmacokinetics, the data suggested that there were no appreciable differences in parameters such as Cmax, Tmax and AUC of saroglitazar between male vs. female subjects. However, T1/2 appeared to be faster in female subjects as compared to male subjects [1]. Therefore, the current analysis was carried out to clarify whether or not gender differences existed in the pharmacokinetics of saroglitazar when given at the highest therapeutic dose of 4 mg. Additionally, due to the availability of the concentration data of sulfoxide metabolite, the pharmacokinetics of saroglitazar sulfoxide was included in the analyses.

Hence, there is no precedence of statistical powering of such clinical studies to evaluate gender differences in the pharmacokinetics. Because we extracted the male vs. female subjects' data from an earlier study, there was no a-priori power calculation that supported the n size male and female subjects. However, this dilemma was addressed by performing a post-hoc power calculation of the pharmacokinetic data. While, the post-hoc power performed for Cmax suggested the power to be approximately 70 %, it reached almost 80% for the AUC parameter. Therefore, we believe that the present analysis that encompassed 26 male subjects and 24 female subjects was more than adequate to obtain a confirmation on the influence of gender, if any, on the pharmacokinetics of saroglitazar.

The study results unequivocally confirmed that both absorption rate and extent of absorption of saroglitazar using the surrogates of Cmax and AUCs (AUC0-t and AUC∞) were bioequivalent between male vs. female subjects. However, the lack of achievement of bioequivalence of Cmax and AUC parameters for saroglitazar sulfoxide was noted between male vs. female subjects. Because saroglitazar sulfoxide does not possess pharmacological activity, the lack of bioequivalence between male vs. female subjects for the sulfoxide metabolite should have no bearing on the

clinical outcome of saroglitazar. In addition, there were no statistically significant differences observed in other pharmacokinetic parameters such as Tmax and T1/2 between healthy male vs. female subjects for either saroglitazar or saroglitazar sulfoxide. Therefore, given the relative short half- life of parent/metabolite and the intended once-daily dosing regimen of saroglitazar, it is very unlikely that differential accumulation would occur in male vs. female subjects during chronic therapy of saroglitazar magnesium.

Table 4: Summary of Pharmacokinetic Data for Saroglitazar Sulfoxide (n=50) Dose: Saroglitazar 4 mg.

PARAMETER	Female	Male	p-value#
	Arithmetic mean ± SD (Range)	Arithmetic mean ± SD (Range)	
C_{max} (ng/ mL)	7.595±2.063 (1.644 - 12.890)	7.116±2.718 (3.466 - 15.010)	0.4478
AUC_t(ng×hr/ mL)	33.719±17.396 (8.257 - 95.416)	31.420±16.123 (14.178 - 83.554)	0.5918
AUC_∞ (ng×hr/ mL)	35.438±17.854 (8.847 - 99.455)	33.206±16.415 (15.058 - 84.821)	0.6229
K_{el}(1/hr)	0.289±0.094 (0.105 - 0.446)	0.249±0.088 (0.060 - 0.396)	——
$T_{1/2}$ (hr)	2.833±1.463 (1.560 - 6.600)	3.365±2.240 (1.750 - 11.490)	——
T_{max} (hr)[a]	2.250 (1.000 - 5.000)	2.000 (1.000 - 4.500)	——

(a) Tmax is presented as Median (Range).
Cmax, maximum concentration; AUCt, area under the concentration time curve from time zero to the last quantifiable concentration; AUC∞, area under the concentration time curve from time zero to infinity; Kel,terminal elimination rate constant; T1/2, elimination half-life; Tmax, time of maximum concentration.
p-value were obtained for gender effect on ln-transformed PK parameter.

From a diabetics/dyslipidemia clinical therapy perspective, none of the arsenal of approved mono-therapy drugs and/or combination drugs has been reported to have a differential dosing regimen for male vs. female patients. To underscore this point, the pharmacokinetic data obtained from this analysis for saroglitazar supports the use of same dose of the drug in male vs. female subjects. Hence, in the on-going and planned global clinical studies of saroglitazar magnesium, there is no dose adjustment necessary for food ingestion, which was documented in the earlier published report [2].

Conclusion

In this study, the gender effect on PK, safety and tolerability of saroglitazar were evaluated in healthy, adult, male and female subjects. No pharmacokinetic differences between men vs. women for saroglitazar was observed, which resulted in bioequivalence in rate and extent of absorption for saroglitazar. Although the metabolite, saroglitazar sulfoxide, did not achieve bioequivalence for both Cmax and AUC values, it has no bearing on the clinical outcome because it is pharmacologically inactive. Overall, based on the analysis it was concluded that there is no need of dosage adjustment based on gender.

Table 5: Geometric least square mean, Ratio and 90% Confidence Intervals based on Log-transformed data for Saroglitazar Sulfoxide in Female Vs. Male (n=50).

Pharmacokinetic parameter	Geometric least square mean		Ratio (%)	Intra-subject CV (%)	90% Confidence Intervals (%)	Gender Effect Acceptance Range %	p-value
	Female	Male					
C_{max} (ng/ mL)	1.978	1.901	92.58	36.752	(78.18; 109.62)	80.00 - 125.00	0.4478
AUC_t(ng×hr/ mL)	3.415	3.345	93.32	47.626	(75.30; 115.67)	80.00 - 125.00	0.5918
AUC_∞(ng×hr/ mL)	3.468	3.406	93.99	46.520	(76.17; 115.97)	80.00 - 125.00	0.6229

Cmax, maximum concentration; AUC∞, area under the concentration time curve from time zero to infinity; CV, coefficient of variation.

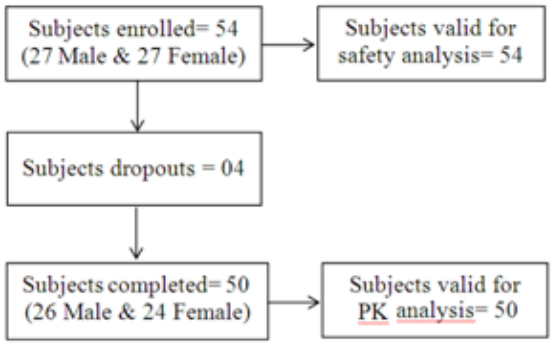

Figure1: Study participation chart.

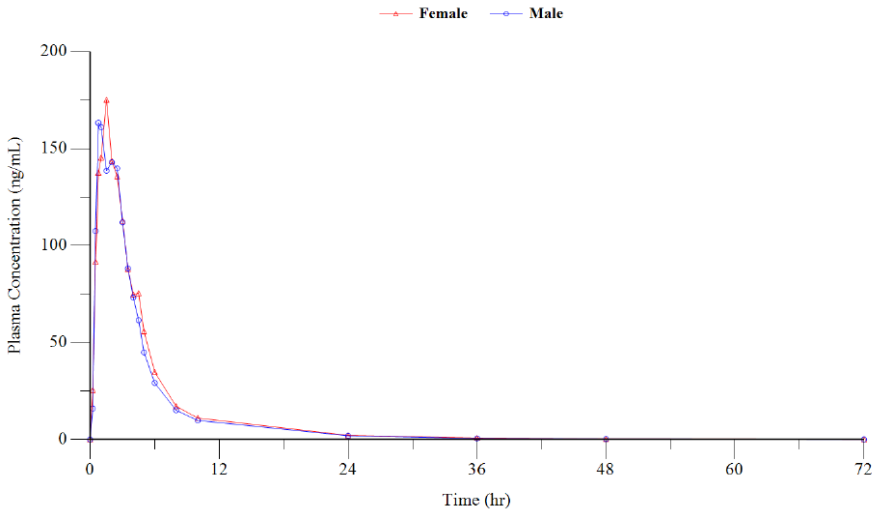

Figure 2: Linear mean concentration-time profile of saroglitazar.

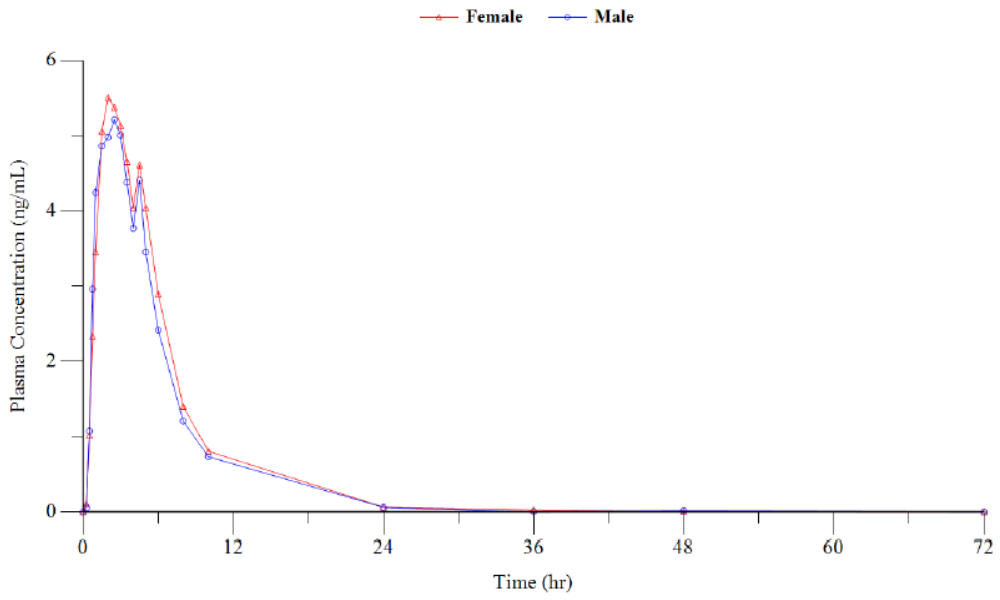

Figure 3: Linear mean concentration-time profile of Saroglitazar Salfoxide.

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Ethical approval

All of the study-related procedures were performed after gaining approval from the Independent Ethics Committee Aditya, Ahmedabad and in accordance with ethical principles stipulated in the Declaration of Helsinki, ICMR ethical guidelines, International Conference on Harmonization (ICH) (Step 5) 'Guidance on Good Clinical Practice' (E6), Schedule Y of Drugs and Cosmetics Act, 2005.

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