AstraZeneca

Clinical Study Report

Drug substance:	Tesaglitazar
Edition No.:	1
Study code:	D6160C00040
Date:	6 April 2007

A 24-week, Randomised, Parallel-Group, Multi-Centre, Open-Label Study of the Renal Effects of Tesaglitazar in Patients with Type 2 Diabetes Mellitus

ARMOR (Analysing Renal Mechanisms of creatinine excretion in patients On tesaglitazaR)

Study dates:	First patient enrolled: 8 September 2004 Last patient enrolled: 29 June 2005
Phase of development:	IIb

This study was performed in compliance with Good Clinical Practice.

Drug product:	Galida	**SYNOPSIS**	
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A 24-week, Randomised, Parallel-Group, Multi-Centre, Open-Label Study of the Renal Effects of Tesaglitazar in Patients with Type 2 Diabetes Mellitus

ARMOR (Analysing Renal Mechanisms of creatinine excretion in patients On tesaglitazaR)

Study centers

19 centers in the US

Publications

None at issue.

Study dates		**Phase of development**
First patient enrolled	8 September 2004	Therapeutic exploratory (IIb)
Last patient completed	29 June 2006	

Objectives

The primary objective of this study was to determine if tesaglitazar reduces renal tubular secretion of creatinine (TSCr).

This study determined the effects of tesaglitazar (2 mg x 12 weeks) on tubular secretion of creatinine in type 2 diabetics as assessed through determinations of:

- glomerular filtration rate (GFR) by iothalamate clearance
- endogenous creatinine clearance (CrCl)

Secondary objectives of the study were:

- To determine the effects of tesaglitazar (2 mg x 24 weeks) on tubular secretion of creatinine in type 2 diabetics as assessed through determinations of:

  - GFR by iothalamate clearance
  - CrCl

- To assess the time course of change in serum creatinine concentration and GFR during a 24-week period of tesaglitazar treatment in type 2 diabetics, by comparisons of serum creatinine concentrations obtained at baseline and at each follow-up visit, as well as comparisons of GFR at baseline vs week 12 and 24.

- To assess the effects of tesaglitazar on urinary protein excretion in type 2 diabetics by comparisons of urinary total protein and albumin excretion rates during each of the timed urine collections performed at baseline and after 12- and 24-weeks of tesaglitazar treatment.

- To assess the effects of tesaglitazar on urinary creatinine excretion in type 2 diabetics by comparisons of urinary total creatinine excretion rates during each of the timed urine collections performed at baseline and after 12- and 24-weeks of tesaglitazar treatment.

- To evaluate the pharmacokinetics of tesaglitazar during 24-weeks of therapy in type 2 diabetics.

- To evaluate the safety and tolerability of tesaglitazar 2 mg per day in type 2 diabetics by assessments of adverse events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), body weight, and physical examination.

Tertiary objectives of the study were:

- To assess the effects of tesaglitazar 2 mg per day on glucose metabolism in type 2 diabetics by evaluation of the absolute change of glycosylated hemoglobin $A1_c$ ($HbA1_c$) and the change in fasting plasma glucose (FPG) from baseline to the end of the treatment period.

- To assess the effects of tesaglitazar 2 mg per day on lipid metabolism in type 2 diabetics by evaluation of the change from baseline to the end of the treatment period in triglycerides (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and non-high density lipoprotein-cholesterol (non-HDL-C) (TC minus HDL-C) levels.

Study design

Prospective, randomized, open-label trial in patients with type 2 diabetes mellitus conducted in 3 parts (enrollment, treatment, and follow-up) designed to investigate the mechanisms responsible for the renal elimination of creatinine (tubular secretion and glomerular filtration) during tesaglitazar treatment. To ensure safety for the individual patient and to ensure that

important and consistent data were collected, handling plans were established for certain laboratory parameters and for congestive heart failure (CHF) to carefully monitor patients who met prespecified criteria.

Target patient population and sample size

Men or women at least 45 years old diagnosed with type 2 diabetes mellitus with serum creatinine levels less than 1.2 mg/dL (106 mmol/L) and $HbA1_c$ levels no more than 8.0% at the enrollment visit. Eligible patients had to have maximum FPG levels of 240 mg/dL with either diet alone or diet plus either a single oral agent or low doses of 2 oral agents at enrollment. To ensure that at least 60 patients completed, 75 patients were planned to be randomized to tesaglitazar, 25 patients to pioglitazone.

Investigational product and control: dosage, mode of administration, and batch numbers

Investigational product: tesaglitazar 2 mg tablet once daily in the morning, with water (batch number H 1427-05-01-02).
Active open-label control: pioglitazone 45 mg tablet once daily in the morning, with water (batch number A10144).

Duration of treatment

Patients participated in the study from 34 weeks to 50 weeks (a 2-week enrollment period plus a 24-week treatment period plus up to 24 [at least 8] weeks of follow-up)

Criteria for evaluation (main variables)

Pharmacodynamics, pharmacokinetics, and efficacy

Primary variable: Change from baseline TSCr (change from baseline in the difference between CrCL and GFR)

Other pharmacodynamic variables: CrCl, GFR, urinary protein excretion, and urinary creatinine excretion

Pharmacokinetic variable: Pharmacokinetic variables of tesaglitazar, with special regards to estimated systemic exposure, area under the plasma concentration-time curve (AUC_τ).

Efficacy variables: $HbA1_c$, FPG, TG, TC, HDL-C, LDL-C, and non-HDL-C

Safety

Safety was assessed from adverse event data, clinical laboratory evaluations, vital signs and body weight measurements, and ECG and physical examination findings.

Statistical methods

There were no proposed statistical comparisons. Data were summarized descriptively by treatment group or listed.

Patient population

All 136 randomized patients received study drug: 98 received tesaglitazar, 38 received pioglitazone; patients were randomized in a 3:1 ratio. Eighty-two (60%) patients completed the study, 54 (55%) who received tesaglitazar and 28 (74%) who received pioglitazone. The most common reasons for premature discontinuations before Week 24 cited by more than 5% of patients were development of a study-specific discontinuation criterion, adverse events, or withdrawal of patient consent. Eighty-four patients attended the Week 48 follow-up visit, 58 (59%) who received tesaglitazar and 26 (68%) who received pioglitazone.

Fifty-two (38%) patients entered at least 1 handling plan, 45 (46%) patients receiving tesaglitazar and 7 (18%) patients receiving pioglitazone; 16 of these patients prematurely discontinued the study, all received tesaglitazar. At least 5% of patients in either treatment group were enrolled into the GFR (24% tesaglitazar, 5% pioglitazone), serum creatinine (SCr) (19% tesaglitazar, 0% pioglitazone), ANC (12% tesaglitazar, 5% pioglitazone), CHF (8% tesaglitazar, 3% pioglitazone), and Hb (2% tesaglitazar, 8% pioglitazone) handling plans. Twelve (12%) patients were discontinued prematurely after enrolling into the GFR handling plan because they met a prespecified safety discontinuation criterion, all received tesaglitazar.

Most patients in each treatment group deviated from the protocol, 84% of patients receiving tesaglitazar and 66% of patients receiving pioglitazone. The most common protocol deviations occurring in at least 35% in each treatment group were out-of-window end-of-treatment visits and administration of prohibited concomitant medications. Data obtained from 118 (87%) patients were analyzed in the renal function evaluable analysis set, from 81 patients who received tesaglitazar and from 37 patients who received pioglitazone.

The population mean (SD) age and baseline body weight, GFR, CrCl, $HbA1_c$, and FPG were 59.1 (8.89) y, 97.42 (23.095) kg, 95.57 (23.442) mL/min/1.73 m^2, 108.02 (26.981) mL/min/1.73 m^2, 6.49 (0.671) %, 128.37 (25.537) mg/dL, respectively. The patient population was nearly balanced in gender; most patients (78%) were Caucasian. There were no appreciable differences between treatment groups in demography. Mean baseline GFR and CrCl were approximately 10 mL/min/1.73 m^2 higher for patients receiving tesaglitazar (98.38 and 110.92 mL/min/1.73 m^2, respectively) relative to pioglitazone (88.45 and 100.66 mL/min/1.73 m^2, respectively).

Pharmacodynamic, pharmacokinetic, and efficacy results

Changes from baseline in median TSCr, as calculated from the difference between CrCl and GFR, were small relative to the variation in measurements. Because the increase in mean SCr (27.70%) in patients receiving tesaglitazar was comparable to the decrease in median GFR (19.86%), increases from baseline SCr are attributed to reductions in GFR rather than to reductions in TSCr. There were minor differences in SCr, GFR, and TSCr between Weeks 12 and 24, indicating little progression beyond 12 weeks of treatment. The decrease in GFR exceeded 35% in 24 (24%) patients receiving tesaglitazar and in 2 (5%) patients receiving pioglitazone. From 4 to 12 weeks after stopping administration of tesaglitazar, GFR and SCr returned toward baseline values; mean changes from baseline SCr were small and comparable between treatment groups. Complete reversal, however, was not demonstrated for all patients

during the 12-week follow-up period. There was no indication of kidney damage in patients receiving tesaglitazar as assessed by the ratio of urine albumin to urine creatinine. There was no increase in creatinine production in patients receiving tesaglitazar as assessed by changes from mean baseline urinary creatinine excretion. Mean trough tesaglitazar plasma concentrations remained nearly constant throughout the study period, from 1.7 µmol/L to 1.9 µmol/L, indicating stable pharmacokinetics over time. Serum glucose levels were sufficiently controlled so as they did not influence GFR measurements. Mean (SD) change from baseline $HbA1_c$ at Week 24 was –0.17% (0.601%) for patients who received tesaglitazar and –0.03% (0.614%) for patients who received pioglitazone. Mean (SD) change from baseline FPG at Week 24 was –1.14 (1.400) mmol/L for patients who received tesaglitazar and –0.21 (1.047) mmol/L for patients who received pioglitazone. Respective relative mean changes from baseline lipid levels at Week 24 for patients randomized to tesaglitazar and pioglitazone were: for TG –27.63% and –4.32%, for TC –7.86% and 2.64%, for HDL-C 11.65% and 8.99%, for LDL-C –5.33% and 2.93%, for non-HDL-C –13.27% and 0.33%.

Safety results

The mean duration of study drug administration was 129.3 days (18 weeks) for patients who received tesaglitazar and 157.1 days (22 weeks) for patients who received pioglitazone. Most patients took study drug until the time of the primary endpoint, 12 weeks; 73 (74%) patients receiving tesaglitazar and 33 (87%) patients receiving pioglitazone.

Approximately 80% of patients in each treatment group experienced at least 1 adverse event, 79 (81%) patients receiving tesaglitazar and 30 (79%) patients receiving pioglitazone. There was no appreciable difference between treatment groups in the distribution of adverse events or in the proportion of patients who experienced adverse events. The most common adverse events experienced by at least 10% of patients overall (frequencies in tesaglitazar and pioglitazone treatment groups, respectively) were peripheral edema (20%, 21%), upper respiratory tract infections (13%, 8%), and increased body weight (13%, 8%). One patient in the tesaglitazar treatment group died; her death was attributed by the investigator to unrelated metastatic lung cancer. The proportion of patients experiencing serious adverse events other than death and adverse events leading to discontinuation of treatment were approximately evenly distributed between treatment groups. Nine patients experienced serious adverse events, 3 patients during tesaglitazar treatment, 3 during the follow-up period up to Week 36 after receiving tesaglitazar, 1 at the Week 48 follow-up visit after receiving tesaglitazar, 1 during pioglitazone treatment, and 1 at the Week 48 follow-up visit after receiving pioglitazone. Two patients withdrew from the study prematurely because of serious adverse events, 1 because of cholelithiasis (tesaglitazar) and another because of exacerbation of anemia (pioglitazone). All serious adverse events that did not have an outcome of death, except for a cerebrovascular accident, resolved. Adverse events that led multiple patients to discontinue study drug in the tesaglitazar treatment group were congestive cardiac failure (3 [3%]) and fatigue (3 [3%]); no adverse event led to multiple discontinuations in the pioglitazone treatment group.

Changes from baseline hematology and clinical chemistry laboratory values were generally small and clinically insignificant. No readily interpretable trends in the analysis of urine

parameters were observed except for changes from baseline levels of N-acetyl beta glucosaminidase. Mean relative changes from baseline urine albumin to urine creatinine ratios were small and variable; large variances in change from baseline means render mean changes from baseline difficult to interpret. Of 12 patients in the tesaglitazar treatment group with microalbuminuria at baseline, 7 had normal urine albumin to urine creatinine ratios at the end-of-treatment visit; in the pioglitazone treatment group, 1 in 4. The mean urinary excretion of N-acetyl beta glucosaminidase approximately doubled at Weeks 12 and 24 in the tesaglitazar treatment group; corresponding increases in the pioglitazone treatment group were smaller. The clinical relevance of these mean changes from baseline N-acetyl beta glucosaminidase is uncertain. In tesaglitazar treated patients attending the Week 48 assessment, mean values for SCr did not differ from baseline, indicating that there was no long term renal injury induced by tesaglitazar treatment.

Decreases from mean systolic blood pressure approximated 3 mmHg at Week 12 and 4 mmHg at Week 24 in the tesaglitazar treatment group; corresponding decreases in diastolic blood pressure approximated 6 and 5 mmHg. Changes from mean blood pressure measurements in the pioglitazone treatment group were smaller than changes in the tesaglitazar treatment group at Weeks 12 and 24. There were no clinically relevant changes from baseline distribution of ECG findings or baseline physical examination findings. Mean body weight increased 3.74 kg in the tesaglitazar treatment group and 3.60 kg in the pioglitazone treatment group.

Date of the report

6 April 2007