AstraZeneca

Abbreviated Clinical Study Report

Drug substance:	Tesaglitazar
Document No.:	CV.000-441-023
Edition No.:	1.0
Study code:	D6160C00003
Date:	19 May 2008

A 24-week Randomized, Double-Blind, Parallel-Group, Multi-Center, Active-Controlled (Metformin or Metformin Combined with Fenofibrate) Study to Evaluate the Lipid Metabolic Effects, Safety and Tolerability of Tesaglitazar Therapy in Patients with Type 2 Diabetes and Low HDL-Cholesterol on a Fixed Background Therapy with a Statin

GALLANT 14

Abbreviated Clinical Study Report

Study dates: First patient : 28 March 2005
Last patient discontinued: 16 December 2007

Phase of development: IIIa

This study was performed in compliance with Good Clinical Practice.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Drug product:	GALIDA	**SYNOPSIS**	
Drug substance(s):	Tesaglitazar		
Document No.:	CV.000-441-023		
Edition No.:	1.0		
Study code:	D6160C00003		
Date:	19 May 2008		

A 24-week Randomized, Double-Blind, Parallel-Group, Multi-Center, Active-Controlled (Metformin or Metformin Combined with Fenofibrate) Study to Evaluate the Lipid Metabolic Effects, Safety and Tolerability of Tesaglitazar Therapy in Patients with Type 2 Diabetes and Low HDL-Cholesterol on a Fixed Background Therapy with a Statin

GALLANT 14

Study centre(s)

This study was conducted in Argentina, Brazil, Canada, Finland, France, Germany, Hong Kong, Hungary, India, Indonesia, Malaysia, Norway, Philippines, Portugal, Russia, Singapore, South Africa and Taiwan.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient	28 March 2005	IIIa
Last patient discontinued*	16 December 2007	

* Note that the study was terminated prematurely because the Sponsor (AstraZeneca) discontinued the tesaglitazar development programme. Of the 737 patients who received treatment, 218 completed the 24-week randomised treatment period.

Objectives

The two primary objectives of this study were to assess whether:

- tesaglitazar was superior to metformin in increasing high density lipoprotein-cholesterol (HDL-C)
- tesaglitazar was non-inferior to metformin combined with fenofibrate in increasing HDL-C

in patients with type 2 diabetes and low HDL-C on a fixed background therapy with a statin, as determined by the change in HDL-C from baseline to the end of the randomised treatment period.

The secondary objectives of the study were:

1. To compare the effects of tesaglitazar versus metformin and tesaglitazar versus metformin combined with fenofibrate in improving lipids and lipoproteins in patients with type 2 diabetes and low HDL-C on a fixed background therapy with a statin after a 24-week randomised treatment period, by evaluation of:
   - the change in lipid and lipoprotein variables (triglycerides [TG], non-HDL-C, total cholesterol [TC], low density lipoprotein-cholesterol [LDL-C], lipoprotein particle size and concentration, free fatty acid [FFA], apolipoprotein [Apo] A-I, Apo B and Apo C-III) from baseline to the end of the randomised treatment period
   - the responder rates as determined by the proportion of patients achieving a pre-specified change from baseline to the end of the randomised treatment period, for HDL-C, TG, non-HDL-C and LDL-C
   - the proportion of patients reaching pre-specified target levels for HDL-C, TG, non-HDL-C and LDL-C.
2. To compare the effects of tesaglitazar versus metformin and tesaglitazar versus metformin combined with fenofibrate on risk markers for cardiovascular disease (C-reactive protein [CRP], insulin, Homeostasis Assessment Model [HOMA], LDL-C/HDL-C ratio, very low density lipoprotein-cholesterol [VLDL-C]/LDL-C ratio, Apo B/Apo A-I ratio) in patients with type 2 diabetes and low HDL-C on a fixed background therapy with a statin after a 24-week randomised treatment period.
3. To compare the effects of tesaglitazar versus metformin and tesaglitazar versus metformin combined with fenofibrate on central obesity (waist/hip ratio) in patients with type 2 diabetes and low HDL-C on a fixed background therapy with a statin after a 24-week randomised treatment period.

4. To evaluate the pharmacokinetics of tesaglitazar in patients with type 2 diabetes and low HDL-C on a fixed background therapy with a statin after a 24-week randomised treatment period.

5. To evaluate the safety and tolerability of tesaglitazar in patients with type 2 diabetes and low HDL-C on a fixed background therapy with a statin after a 24-week randomised treatment period by assessment of adverse events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycaemic events, body weight, cardiac evaluation, and physical examination.

Study design

This was a 24-week randomised, double-blind, parallel-group, multi-centre, active-controlled (metformin or metformin combined with fenofibrate) study to determine the lipid metabolic effects, safety and tolerability of tesaglitazar compared to metformin and metformin in combination with fenofibrate, in patients with type 2 diabetes and low HDL-C.

The study comprised a 2-week enrolment period, a 6-week single-blind run-in period, a 24-week double-blind randomised treatment period and a 3-week follow-up. From Visit 2 (run-in) all patients received a standardised dose of statin (rosuvastatin) as background treatment.

Target patient population and sample size

Male and female patients, ≥18 years of age, diagnosed with type 2 diabetes and treated with diet alone or on treatment with a single oral anti-diabetic agent or low doses of two agents, and with diabetic dyslipidaemia (low HDL-C) on concomitant treatment with a statin.

A total of 338 randomised and evaluable patients on tesaglitazar, and metformin and fenofibrate treatment was required to reject the null hypothesis of inferiority of tesaglitazar by 0.05 or more with 90% power using a two-sided t-test at level 0.05 and 156 randomised and evaluable patients on metformin treatment were required to detect a difference, on comparison of tesaglitazar and metformin, of 0.07 with 95% power, using a two-sided t-test at level 0.05.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Tesaglitazar, 0.5 mg or 1 mg, once daily in oral form (tablets) and matching placebo.

Metformin, 1 g, 1.5 g, 2 g, or 2.5 g daily, divided into morning and evening doses in oral form (tablets) and matching placebo.

Fenofibrate (Tricor®), encapsulated into reddish-brown, hard gelatine capsules (160 mg/capsule), once daily in oral form and matching placebo.

Additional drug, dosage and mode of administration

Rosuvastatin (Crestor®) commercial 10 mg tablets, once daily in oral form.

Duration of treatment

After a 2-week enrolment period and a 6-week placebo single-blind run-in period, patients were randomised to receive double-blind treatment for 24 weeks. During the run-in period and throughout the study all patients also received 10 mg rosuvastatin daily (open label) as background treatment. Tesaglitazar and metformin were titrated to optimal effect or highest tolerable dose during the first 12 weeks. After this titration period, and for the next 12 weeks, the dose of tesaglitazar and metformin were to remain constant. Patients were counselled on dietary and life-style modifications according to normal clinical routine, with reinforcement throughout the treatment period.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Change in HDL-C from baseline (Visit 5) to the end of the randomised treatment period (Visit 14).

- Secondary variables:

  Changes from baseline to the end of the randomised treatment period in the following variables:

  – Lipid and lipoprotein variables (TG, non-HDL-C, TC, LDL-C, lipoprotein particle size and concentration, FFA, Apo A-I, Apo B and Apo C-III)

  – Risk markers for cardiovascular disease (CRP, insulin, HOMA, LDL-C/HDL-C ratio, VLDL-C/LDL-C ratio, Apo B/Apo A-I ratio)

  – Waist-hip ratio.

  In addition, the following were evaluated:

  – Responder rates analyses for HDL-C, TG, non-HDL-C and LDL-C according to pre-specified values

  – Proportion of patients reaching pre-specified target levels for HDL-C, TG, non-HDL-C and LDL-C.

Pharmacokinetics

A population pharmacokinetic analysis was planned as part of a pooled analysis across multiple studies, but was not conducted due to the discontinuation of the tesaglitazar programme.

Safety

Standard safety assessments included AEs, laboratory values, ECG, vital signs (pulse and BP),

physical examination, body weight, cardiac evaluation, and hypoglycaemic events. The proportion of patients with microalbuminuria was also assessed under safety.

Genetics

A blood sample for DNA preparation and further genetic analysis was taken from those patients who agreed to participate in the genetic research (optional).

Statistical methods

The primary variable, HDL-C, was analysed in the natural log scale. All secondary efficacy variables, except HbA_{1c} and FPG, were log-transformed to be consistent with the other studies in the programme.

Due to the termination of the study programme, the required number of patients was not recruited into the study. Therefore, no superiority or non-inferiority assessments were performed, descriptive statistics only are provided.

The results of the primary and secondary endpoints are presented using the intention to treat (ITT) analysis set. All analyses were based on observed data only. No imputation based on the last observation carried forward approach was made.

Descriptive statistics are provided for the safety laboratory variables. Adverse events are tabulated. Other safety-related variables are summarised with descriptive statistics, tabulations, and/or listings. The proportion of patients with microalbuminuria and macroalbuminuria are summarised by treatment and time.

Patient population

The study was terminated by the Sponsor because of the decision to discontinue the tesaglitazar development programme. At the time of study termination, enrolment was not yet complete; among the 741 randomised patients, 29.4% of randomised patients had completed 24 weeks of treatment; 8.9% had withdrawn before that time point; and 61.7% were still receiving randomised treatment.

In total, 3230 patients entered the 6-week placebo single-blind run-in period and 741 patients from 46 centres were randomised to treatment. Of these randomised patients, 73.3% attended the follow-up visit (Visit 15), 21.5% transferred to the long-term extension study and 31.4% completed the final follow-up visit (Visit 17). The majority of randomised patients were Caucasian (65.5%, 67.6% and 69.3% of patients in the tesaglitazar, metformin, and metformin and fenofibrate groups, respectively). The male-to-female ratios were similar in the treatment groups; overall, 38.5% of the randomised patients were male and 61.5% were female. The age range of patients in the study was 28.0 to 88.0 years; the overall mean age was 54.8 years. Patients had comparable baseline characteristics, including weight, in the treatment groups, with the exception of the following: the proportion of patients in the metformin group who

had a BMI >30 kg/m^2 or weighed >100 kg (38.8% and 12.2%, respectively) was lower than in the tesaglitazar (45.7% and 18.8%, respectively) or metformin and fenofibrate groups (46.3% and 17.2%, respectively).

The patient population in this study was representative of the target population for tesaglitazar.

Of the 741 randomised patients, 293 were randomised to tesaglitazar, 139 were randomised to metformin and 309 were randomised to metformin and fenofibrate, of whom 100%, 99.3% and 99.0%, respectively, received treatment. The safety and ITT analysis sets comprised 736 patients (99.3%) and 722 patients (97.4%), respectively.

Of the 741 patients randomised to treatment, 60.6% were discontinued during the randomised treatment period. The most common reason for premature discontinuation was recorded as 'other' (50.9%), mainly the Sponsor's decision to terminate the tesaglitazar study programme. The proportion of patients who discontinued study treatment due to AEs was low overall (1.9% of patients).

Mean duration of exposure was similar in the different treatment groups (tesaglitazar 118 days, metformin 114 days, metformin in combination with fenofibrate 121 days). The mean dose at the week 24 visit was tesaglitazar 0.88 mg, metformin alone 1757 mg and metformin in combination with fenofibrate 1822 mg).

Efficacy results

Because the study was terminated prematurely, the per protocol analysis set was not defined. The results of the primary and secondary endpoints are presented using the ITT analysis set. Descriptive statistics only are presented.

For the primary objectives, on comparison of tesaglitazar with metformin, mean HDL-C levels were observed not to deviate much at Week 24 compared to baseline in the metformin group (-0.3 %) while tesaglitazar was associated with a mean increase in HDL-C levels (+21.2 %) from baseline to Week 24. On comparison of tesaglitazar with metformin and fenofibrate, the mean increase in HDL-C levels (+9.0 %) from baseline to Week 24 was greater with tesaglitazar. Tesaglitazar was observed to decrease mean TG levels (-29.6%) from baseline to Week 24, as was metformin and fenofibrate (-24.0 %), compared to a smaller mean increase from baseline observed with metformin (+7.8 %). Greater decreases from baseline in mean non-HDL-C levels were observed with metformin and fenofibrate at Week 24 compared to tesaglitazar and metformin and increases from baseline in mean LDL-C levels were observed with all three treatment groups at Week 24 which were greatest with tesaglitazar.

A reduction was seen in HbA1c and FPG in all treatment arms (tesaglitazar –0.54 % and –2.13 mmol/L, metformin –0.31 % and –1.11 mmol/L, metformin in combination with fenofibrate –0.34 % and –1.26 mmol/L, resp.).

The dyslipidemia typical of patients with insulin resistance or type 2 diabetes on a background

treatment with rosuvastatin was clearly improved by tesaglitazar, and this was better than the effect of fenofibrate in combination with metformin.

Pharmacokinetic results

Because the study was terminated prematurely, the planned analysis of the population pharmacokinetics was not conducted. Pharmacokinetic data are presented as by-patient listings only.

Safety results

The proportion of patients with at least one AE was slightly lower in the tesaglitazar group compared to the metformin, and metformin and fenofibrate groups. No patients died during the study. The majority of AEs were mild to moderate in severity and were considered by the investigator to be unrelated to study treatment. The overall AE profile associated with each treatment group was similar. No patients were reported with major hypoglycaemic events while the proportion of patients with minor hypoglycaemic events was low. The proportion of patients with SAEs was small and similar across the treatment groups. No SAE occurred in more than 1 patient. The proportion of patients with DAEs was small and similar across treatment groups. The only DAE which occurred in ≥0.5% of patients overall was diarrhoea, reported for 1.4% and 1.0% of patients in the metformin, and metformin and fenofibrate groups, respectively. Overall, the proportion of patients discontinuing the study from a handling plans was small, 1.4% of patients in the tesaglitazar group, 2.2% in the metformin group and 1.0% in the metformin and fenofibrate group. No OAEs were identified in the study.

Review of the results of the comprehensive safety monitoring and patient handling plans identified the following:

- No patients had confirmed new/worsening CHF during the study.
- The proportion of patients with a >25 g/L decrease in Hb levels from baseline during the randomised treatment period was higher in the tesaglitazar group (3.4%) compared to the metformin, and metformin and fenofibrate groups (1.4% and 2.0%, respectively). There was little reversibility seen in any of the treatment groups during follow up
- There was a mean increase in S-creatinine from baseline to the end of the randomised treatment period in the tesaglitazar group (+12.7 µmol/L) and in the metformin combined with fenofibrate group (+8.4 µmol/L) compared to an decrease in the metformin group (-2.7 µmol/L). The changes in S-creatinine were reversible during follow up.
- The proportion of patients with an increase from baseline in S-creatinine of >50% from baseline during the randomised treatment period was higher in the tesaglitazar group (4.5%) compared to the metformin, and metformin and fenofibrate groups

(1.4% and 1.6%, respectively).

- There were no other clinically relevant findings.

Changes in laboratory results were generally small and showed no treatment-related trends. There were no marked differences between the treatments in the incidence of haematology-related laboratory findings (Hb <90 g/L or ANC values <1.0 GI/L), hepatic-related laboratory findings (ALT/AST levels > 3 x ULN or ALP levels >3 x ULN) or muscle-related laboratory findings (CK levels >5 x ULN).

There was no obvious trend in the mean changes from baseline in the vital signs data.

The majority of ECGs and cardiac evaluations were unchanged from baseline to the end of the randomised treatment period in the three treatment groups.