AstraZeneca

Abbreviated Clinical Study Report

Drug substance:	Tesaglitazar
Document No.:	CV.000-441-021
Edition No.:	1.0
Study code:	D6160C00029
Date:	19 May 2008

A 52-week Randomized, Double-Blind, Parallel-Group, Multi-Center, Active-Controlled (Metformin) Study to Evaluate the Efficacy, Safety, and Tolerability of Tesaglitazar Therapy when Administered to Patients with Type 2 Diabetes

GALLANT 5

Abbreviated Clinical Study Report

Study dates: First patient enrolled: 18 August 2004
Last patient discontinued: 14 December 2006

Phase of development: III

This study was performed in compliance with Good Clinical Practice.

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Study centre(s)

This study was conducted in 121 centres in Finland, Germany, Israel, The Netherlands, UK and the US.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	18 August 2004	Therapeutic confirmatory (III)
Last patient discontinued*	14 December 2006	

* Note that the study was terminated prematurely because the Sponsor (AstraZeneca) discontinued the tesaglitazar development programme. Of the 775 patients who received treatment, 123 completed the 52-week randomised treatment period.

Objectives

The primary objective of this study was to assess whether tesaglitazar, given as monotherapy, was non-inferior to metformin, given as monotherapy, during 52 weeks in improving glycaemic control in patients with type 2 diabetes, as determined by the absolute change in

glycosylated haemoglobin A_{1c} (HbA_{1c}), from baseline to the end of the randomised treatment period.

The secondary objectives of the study were:

1. To compare the effects of tesaglitazar monotherapy versus metformin monotherapy in modifying lipids and lipoproteins in patients with type 2 diabetes after a 52-week randomised treatment period by evaluation of:

   – the change from baseline to the end of the randomised treatment period in lipid and lipoprotein variables

   – responder rates as determined by the proportion of patients achieving a pre-specified changed from baseline to the end of the randomised treatment period, for triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), non-HDL-C and low density lipoprotein-cholesterol (LDL-C)

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

2. To compare the effects of tesaglitazar monotherapy versus metformin monotherapy in modifying other markers of glycaemic control in patients with type 2 diabetes after a 52-week randomised treatment period by evaluation of:

   – the change in fasting plasma glucose (FPG), insulin, pro-insulin and C-peptide from baseline to the end of the randomised treatment period

   – insulin sensitivity by assessment of change in the calculated variable Homeostasis Assessment Model (HOMA), from baseline to the end of the randomised treatment period

   – the responder rates and proportion of patients achieving pre-specified target levels from baseline to the end of the randomised treatment period for both HbA_{1c} and FPG.

3. To compare the effects of tesaglitazar monotherapy versus metformin monotherapy on the levels of risk markers for cardiovascular disease in patients with type 2 diabetes after a 52-week randomised treatment period.

4. To compare the effects of tesaglitazar monotherapy versus metformin monotherapy on the levels of inflammatory markers in patients with type 2 diabetes after a 52-week randomised treatment period.

5. To compare the effects of tesaglitazar monotherapy versus metformin monotherapy on a marker of thrombosis/coagulation (fibrinogen) in patients with type 2 diabetes after a 52-week randomised treatment period.

6. To compare the effects of tesaglitazar monotherapy versus metformin monotherapy on urinary albumin excretion in patients with type 2 diabetes after a 52-week randomised treatment period.

7. To compare the effects of tesaglitazar monotherapy versus metformin monotherapy on the waist-hip ratio in patients with type 2 diabetes after a 52-week randomised treatment period.

8. To evaluate the pharmacokinetics of tesaglitazar monotherapy.

9. To evaluate the safety and tolerability of tesaglitazar monotherapy 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 52-week randomised, double-blind, parallel-group, multi-centre, active-controlled (metformin) study of tesaglitazar in patients with type 2 diabetes, not adequately controlled on diet and life-style advice alone during the run-in period.

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.

A total of 259 randomised and evaluable patients per treatment arm were required to reject the null hypothesis of inferiority of tesaglitazar by 0.4% or more with 90% power using a two-sided t-test at level 0.05. Taking into account premature discontinuations, it was planned to randomise 580 patients.

Investigational product and comparator: 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.

Duration of treatment

After a 6-week placebo single-blind run-in period, the patients were to be given the investigational product for 52 weeks in a double-blind fashion. Tesaglitazar and metformin were titrated to optimal effect or highest tolerable dose during the first 12 weeks.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Absolute change from baseline to the end of the randomised treatment period in HbA_{1c}.

- Secondary variables:

  Changes in the following variables:

  - Lipid parameters (TG, total cholesterol, HDL-C, non-HDL-C, LDL-C, apolipoproteins [Apo] A-I, Apo B)

  - C-reactive protein, LDL-C/HDL-C ratio and Apo B/Apo A-I ratio

  - FPG, HOMA, insulin, pro-insulin, C-peptide

  - Tumour necrosis factor-alpha, intracellular adhesion molecule-1

  - Fibrinogen

  - Waist-hip ratio.

  In addition, the following were evaluated:

  - Responder analyses for HbA_{1c}, FPG, TG, HDL-C, non-HDL-C and LDL-C according to pre-specified values

  - Proportion of patients reaching pre-specified target levels for HbA_{1c}, FPG, TG, HDL-C, 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 change from baseline to the end of the randomised treatment period was analysed with a linear model including fixed-effects for countries and treatment and baseline value as a continuous covariate. Efficacy variables analysed based on this model, except HbA_{1c} and FPG, were log-transformed before analysis, unless otherwise indicated in the final statistical analysis plan.

The non-inferiority of tesaglitazar as monotherapy versus metformin as monotherapy was assessed by comparing the upper bound of a nominal two-sided 95% confidence interval to a fixed non-inferiority limit of 0.4%. Non-inferiority assessments were limited to the primary efficacy variable.

All main analyses were done with the intention to treat (ITT) analysis set. For patients who discontinued before the final visit of the randomised treatment period, a last observation carried forward approach (LOCF) was applied.

Apart from the non-inferiority comparison for HbA_{1c}, all other comparisons were tested only in the context of superiority using a two-sided test at the 0.05 level, whereas, HbA_{1c} was compared in both contexts.

Descriptive statistics were provided for the efficacy laboratory variables based on LOCF and observed cases approaches for baseline and end of treatment visit and for each scheduled visit, respectively.

Additional analyses assessed the distribution of patients treated with low/high dose of tesaglitazar, and low/high dose of metformin within the treatment groups. The level of FPG by treatment period and by doses of investigational product were also described over time.

Descriptive statistics were provided for the safety laboratory variables. Adverse events were tabulated. Other safety-related variables were summarised with descriptive statistics, tabulations and/or listings. The proportion of patients with microalbuminuria and macroalbuminuria were 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 complete; among the 779 randomised patients, 15.8% of randomised patients had completed 52 weeks of treatment; 25.7% had withdrawn before that time point; and 58.5% were receiving randomised treatment.

In total, 1560 patients entered the 6-week placebo single-blind run-in period and 779 patients from 121 centres were randomised to treatment. Of these randomised patients, 71.4% attended the follow-up visit (Visit 22), 14.6% transferred to the long-term extension study and 36.5% completed the final follow-up visit (Visit 24). The majority of randomised patients

were Caucasian (91.2% and 92.6% of patients in the tesaglitazar and metformin groups, respectively). The male-to-female ratios were similar in both treatment groups; overall, 50.1% of the randomised patients were male and 49.9% were female. The age range of patients in the study was 20.0 to 86.0 years; the overall median age was 58.4 years. Patients had comparable baseline characteristics in the treatment groups and the patient population enrolled in this study was representative of the target population for tesaglitazar.

Of the 779 randomised patients, 387 were randomised to tesaglitazar and 392 were randomised to metformin, of whom 99.5% in each treatment group received treatment; 99.1% were analysed for safety and 97.4% were analysed for efficacy in an ITT analysis set. Of the 779 patients randomised to treatment, 80.2% were discontinued during the randomised treatment period. The most common reason for premature discontinuation was recorded as 'other' (58.7%), mainly the Sponsor's decision to terminate the tesaglitazar study programme. The frequency of patients who discontinued study treatment due to AEs was higher in the metformin group (7.1% of patients compared with 4.7% of patients).

Efficacy results

Because the study was terminated prematurely, the per protocol analysis set was not defined. Efficacy results are presented using the ITT analysis set of 779 patients. Using the LOCF approach, there were more than the 259 patients per treatment group required to have sufficient power to reject the null hypothesis of inferiority.

For the primary objective, tesaglitazar met non-inferiority criteria compared with metformin, as measured by the absolute change from baseline in HbA_{1c} at the end of the randomised treatment period (Week 52). However, there was a small but statistically significant difference in favor of metformin in reducing HbA_{1c}.

For the secondary objectives, tesaglitazar demonstrated significant improvements in blood lipids when compared to metformin, as measured by the relative change from baseline to the end of the randomised treatment period (Week 52) in TG, HDL-C and non-HDL-C. Tesaglitazar resulted in statistically significantly greater decreases from baseline in TG and non-HDL-C and a statistically significantly greater increase from baseline in HDL-C compared to metformin at the end of the randomised treatment period.

Pharmacokinetic results

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

Safety results

The extent of exposure was similar in both the tesaglitazar and metformin groups and the mean duration of exposure data was also similar, with the majority of patients in both treatment groups being exposed to investigational product for 39 to <52 weeks.

The frequency of AEs was similar in both treatment groups. There were four deaths during the study, none considered by the investigator to be treatment-related. 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 the treatment groups was similar. There were no major hypoglycaemic events and the number of minor hypoglycaemic events was low and similar in the two treatment groups. Given the small number of hypoglycaemic events, it is not possible to draw any conclusions on the time to onset between treatment groups. The overall frequency of SAEs was low and similar in the treatment groups. No SAE occurred with a frequency of ≥0.5%. The overall frequency of DAEs was low and similar in the treatment groups. The only DAEs occurring with a frequency of ≥1% were increased blood creatinine (reported for 2.3% and 0% of the patients in the tesaglitazar and metformin groups, respectively) and diarrhoea (reported for 0% and 2.1% of patients, respectively). Overall, the frequency of patients discontinuing the study from a handling plan was low, with more patients from the tesaglitazar group. No OAEs were identified in the study.

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

- The proportion of patients with confirmed new/worsening CHF was low (0.5% overall): 3 and 1 patients in the tesaglitazar and metformin groups, respectively, were confirmed with new onset CHF during the study, while 2 patients (tesaglitazar group) were confirmed with worsening of pre-existing CHF during the study.

- A greater proportion of patients in the tesaglitazar group compared to the metformin group had renal AEs (3.4% compared to 0.8%). In the tesaglitazar group, all the patients with renal AEs had AEs of increased blood creatinine compared to no subjects in the metformin group.

- 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). The proportion of patients with a >25 g/L decrease in Hb levels from baseline to the end of the randomised treatment period was higher in the tesaglitazar group (7.8%) compared to the metformin group (3.1%). The proportion of patients with an increase from baseline in S-creatinine of >50% was higher in the tesaglitazar group (10.2%) compared to the metformin group (0.5%) and there was a mean decrease in estimated GFR (eGFR) from baseline to the end of the randomised treatment period (11.426 mL/min in the tesaglitazar group compared to a mean increase of 2.227 mL/min in the metformin group).

There was no obvious trend in the mean changes from baseline in the vital signs data. An increase in weight from baseline to Week 52 was evident in the tesaglitazar group while, in

the metformin group, a decrease from baseline to Week 52 was observed.

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