AstraZeneca

Clinical Study Report	
Drug substance:	Tesaglitazar
Edition No.:	1
Study code:	D6160C00031
Date:	14 March 2007

A 24-Week Randomised, Double-Blind, Parallel-Group, Multi-Centre, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Tolerability of Tesaglitazar Therapy when Added to the Therapy of Patients with Type 2 Diabetes Poorly Controlled on Metformin Alone

GALLANT 8

Study dates: First patient enrolled: 21 July 2004
Last patient completed: 22 February 2006

Phase of development: Therapeutic confirmatory IIIa

This study was performed in compliance with Good Clinical Practice.

Drug product:	Galida	**SYNOPSIS**	
Drug substance(s):	Tesaglitazar		
Edition No.:	1		
Study code:	D6160C00031		
Date:	14 March 2007		

A 24-Week Randomised, Double-Blind, Parallel-Group, Multi-Centre, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Tolerability of Tesaglitazar Therapy when Added to the Therapy of Patients with Type 2 Diabetes Poorly Controlled on Metformin Alone

GALLANT 8

Study centre(s)

This study was conducted at 114 centres
Australia (15 study centres), Canada (14 study centres),
Finland (10 study centres), Germany (10 study centres), India (4 study centres),
Italy (13 study centres), Malaysia (1 study centres), Philippines (4 study centres),
Singapore (3 study centres), Sweden (10 study centres), UK (30 study centres).

Publications

None at the time of this report

Study dates		**Phase of development**
First patient enrolled	21 July 2004	Therapeutic confirmatory (IIIa)
Last patient completed	22 February 2006	

Objectives

The **primary objective** of this study was to assess the efficacy of tesaglitazar (0.5 and 1 mg) as compared to placebo given as add-on therapy to metformin for 24 weeks in improving glycaemic control in patients with type 2 diabetes as determined by the absolute change in glycosylated haemoglobin A1c (HbA1c), from baseline (visit 7) to the end of the randomised treatment period (visit 13).

Secondary objectives of the study are:

1. To compare the effects of tesaglitazar (0.5 and 1 mg) versus placebo given as add-on therapy to metformin in modifying lipids and lipoproteins in patients with type 2 diabetes after a 24-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 change 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)[1]

   Proportion of patients reaching pre-specified target levels for TG, HDL-C, non-HDL-C and LDL-C [1]

2. To compare the effects of tesaglitazar (0.5 and 1 mg) versus placebo given as add-on therapy to metformin in modifying other markers of glycaemic control in patients with type 2 diabetes after a 24-week randomised treatment period by evaluation of:

   The change in fasting plasma glucose (FPG) and insulin from baseline to the end of the randomised treatment period

   Responder rates and proportion of patients achieving pre-specified target levels, from baseline to the end of the randomised treatment period for both HbA1c and FPG

3. To compare the effects of tesaglitazar (0.5 and 1 mg) versus placebo given as add-on therapy to metformin on the levels of risk markers for cardiovascular disease in patients with type 2 diabetes after a 24-week randomised treatment period

4. To compare the effects of tesaglitazar (0.5 and 1 mg) versus placebo given as add-on therapy to metformin on the waist-hip ratio in patients with type 2 diabetes after a 24-week randomised treatment period

[1] As described in Section **Error! Reference source not found.** Changes to planned analyses, LDL-C and non-HDL-C were not summarized in terms of achievement of target treatment levels and responder rates.

5. To evaluate the pharmacokinetics of tesaglitazar (0.5 and 1 mg) as add-on therapy to metformin

6. To evaluate the safety and tolerability of tesaglitazar (0.5 and 1 mg) as add-on therapy to metformin, by assessment of Adverse Events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure, hypoglycaemic events, body weight, cardiac evaluation and physical examination

Study design

24-week randomised double-blind, parallel-group, multi-centre, placebo-controlled study of tesaglitazar (0.5 mg and 1 mg) given as add-on therapy to metformin in patients with type 2 diabetes, not adequately controlled on optimised metformin treatment and on diet/lifestyle advice during the titration and run-in period.

Target patient population and sample size

Men or women who were ≥18 years of age at the enrolment visit (visit 1), diagnosed with type 2 diabetes, treated with a single or multiple antidiabetic agents.
The primary outcome variable was the absolute change in HbA1c from baseline to the end of the randomised treatment period. To detect a difference of 0.5% in absolute change for HbA1c with 90% power using a two-sided t-test at level 0.05, assuming the standard deviation to be 1.4% required 165 patients in each treatment arm.

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

Tesaglitazar 0.5 or 1 mg once daily in oral form (tablets). Matching placebo once daily in oral form (tablets).
Batch numbers: Tesaglitazar 0.5 mg (H 1434-05-01-01 and H 1434-05-01-05),
Tesaglitazar 1 mg (H 1467-04-01-01 and H 1467-04-01-06),
Placebo (H 1428-05-01-01, H 1428-05-01-02 and H 1428-05-01-03)

Additional drug, dosage and mode of administration

Metformin; 2-2.5 g daily in oral form (Glucophage 500 mg tablet,
Batch numbers: H 1605-01-01-07, H 1605-01-01-08, H 1605-01-01-09, H 1605-01-01-10)

Duration of treatment

After a 6-week metformin titration period and a 2-week single-blind run-in period, the patients were given tesaglitazar/placebo as add-on therapy for 24 weeks in a double-blind fashion. Three weeks after the end of the randomised treatment period (Visit 13), patients who completed the 24-week treatment period and met eligibility criteria were transferred to a long-term extension (LTE) study. Patients not entering the LTE study were to complete a follow-up visit (Visit 14).

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics
Primary variable: Absolute change from baseline to end of the randomised treatment period in HbA1c

Secondary variables: Changes in the following variables:

Lipid parameters (TG, total cholesterol (TC), HDL-C, non-HDL-C, LDL-C, LDL-C/HDL-C ratio), apolipoproteins (Apo A-I, Apo B, Apo B/Apo A-I ratio), glycaemic parameters (FPG, and insulin), C-reactive protein (CRP), waist-hip ratio.

Additionally, the following was evaluated:

Responder analyses for HbA1c, FPG, TG, HDL-C, and non-HDL-C according to pre-specified values and the proportion of patients reaching pre-specified target levels for HbA1c, FPG, TG, HDL-C, and non-HDL-C

Pharmacokinetics

Tesaglitazar plasma concentrations: all plasma concentrations collected during the dosing interval as well as concentrations at trough (16 to 32 hours after last previous intake of tesaglitazar).

Safety

Standard safety assessment included: adverse events (AEs), laboratory values, ECG, vital signs (pulse and blood pressure), hypoglycaemic events, body weight, cardiac evaluation (assessment of cardiac function by history and physical examination, evaluation of signs and symptoms of CHF), and physical examination.

Statistical methods

The change from baseline to the end of the randomised treatment period was analysed with a linear model using fixed-effect analysis of covariance (ANCOVA) with treatment as factor and baseline value as a continuous covariate. Efficacy variables analysed in this model, except HbA1c and FPG, were log-transformed before ANCOVA analysis, unless otherwise indicated in the final statistical analysis plan (SAP). All comparisons between tesaglitazar and placebo were tested with a two-sided t-test at the 0.05 level of significance.
Descriptive statistics were provided for the safety laboratory variables. Adverse events were tabulated. Other safety-related variables, such as pulse, blood pressure, ECG and physical examination, were summarized with descriptive statistics, tabulations and/or listings.

Patient population

In total, 1607 patients were enrolled from 114 centres. Of the enrolled patients, 590 were randomised to treatment. Four patients were excluded from the safety analysis set as either no investigational product was received or no post-baseline safety data were available. All remaining 586 patients were included in the safety analysis set. 585 patients were analyzed for efficacy in a full analysis set and 438 in a per-protocol analysis set. The majority of randomised patients were Caucasian (>81% in each treatment group). The male-to female ratios were similar across the treatment groups; overall 56% men were randomised into the study. The age range of patients in this study was 21 to 87 years with a median age of 60 years. The duration of diabetes in the randomised patients ranged from less than 1 year up to 40 years with a somewhat longer mean duration in the placebo group. The overall number of discontinuations, and the number of patients who discontinued study treatment due to adverse events, was similar between the treatment groups. There were no major differences between

treatment groups in the number of patients who had protocol deviations that were considered serious enough to warrant exclusion of data from the per-protocol analysis. Overall, the treatment groups were comparable for demographic characteristics and baseline characteristics. 295 patients transferred to a long term extension study, according to the CSP these patients did not attend the follow up visit 14 in the present study.

Efficacy and pharmacokinetic results

Compared to placebo as add-on to metformin, treatment with either 1 mg or 0.5 mg of tesaglitazar as add-on to metformin resulted in a statistically significant decrease in HbA1c from baseline to the end of the 24 week treatment period. The mean (CI) absolute change in HbA1c (%) from baseline to end of treatment was -0.82 (-0.92 to -0.72) for tesaglitazar 1 mg + metformin and -0.59 (-0.69 to -0.5) for tesaglitazar 0.5 mg + metformin to be compared to almost no change (-0.1 (-0.2 to 0.0) for placebo + metformin.) Additional analyses on observed data from the PP analysis set confirmed the primary analysis based on the Full analysis set. The lipid variables related to diabetic dyslipidaemia (TG, HDL-C and non-HDL-C) showed statistically significant improvement from baseline to end of treatment in both tesaglitazar + metformin treatment groups as compared to placebo + metformin. These observations were further supported by results in other variables of glycaemic control (FPG and insulin) and lipid and lipoprotein variables as well as risk markers for cardiovascular disease (CRP, LDL-C/HDL-C ratio and Apo B/Apo A-I ratio). There was no statistically significant difference between either dose of tesaglitazar and placebo in the relative change of the waist-hip ratio from baseline to end of treatment.
Similar mean tesaglitazar plasma concentrations (C_{min}) were observed throughout the 24-week treatment period indicating stable pharmacokinetics over time.

Safety results

The extent of exposure was well-balanced across the treatment groups and the mean duration of exposure was adequate for the safety evaluation in this study.
There were more CV AEs in the tesaglitazar + metformin treatment groups than in placebo+ metformin. In the tesaglitazar 0.5 mg+ metformin group 3 patients discontinued the study due to a CV event whilst there were no such DAEs in the other two groups. The number of patients with AEs of oedema peripheral was higher in the tesaglitazar 1 mg + metformin group. There was one patient with exacerbation of cardiac failure in connection with a pneumonia in the tesaglitazar 0.5 mg + metformin group. A dose-related increase in weight from baseline to end of treatment was observed in both tesaglitazar+ metformin treatment groups.
A dose-dependent increase in serum creatinine and decrease in estimated GFR were seen in the tesaglitazar + metformin groups. These changes were not accompanied by any evidence of renal toxicity as judged by urinalysis and blood pressure findings. Haematology laboratory assessments showed a dose-dependent decrease in haemoglobin and ANC in the two tesaglitazar + metformin treatment groups as well as a small dose-related decrease in leucocytes.
The assessment of laboratory data and AEs for potential muscle effects and hepatic effects of tesaglitazar did not raise any safety concerns.

Date of the report

14 March 2007