AstraZeneca

Clinical Study Report

Drug substance:	Tesaglitazar
Edition No.:	1
Study code:	D6160C00032
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 Sulphonylurea Alone

GALLANT 7

Study dates: First patient enrolled: 28 July 2004
Last patient completed: 21 February 2006

Phase of development: Therapeutic confirmatory IIIa

This study was performed in compliance with Good Clinical Practice.

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Study centres

This study was conducted at 112 centres
Australia (18 study centres), France (23 study centres), Israel (8 study centres), Korea (5 study centres), Norway (17 study centres), Philippines (3 study centres), South Africa (5 study centres), Spain (9 study centres), UK (22 study centres), Vietnam (2 study centres)

Publications

None at the time of this report

Study dates		**Phase of development**
First patient enrolled	28 July 2004	Therapeutic confirmatory (IIIa)
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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 sulphonylurea 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 sulphonylurea 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 sulphonylurea 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 sulphonylurea 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 sulphonylurea on adipose tissue hormones in patients with type 2 diabetes after a 24-week randomised treatment period by evaluation of adiponectin and leptin

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

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

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

[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.

Study design

This is a 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 sulphonylurea in patients with type 2 diabetes, not adequately controlled on optimised sulphonylurea treatment and on diet/lifestyle advice during the titration and run-in period.

Target patient population and sample size

Men or women who are ≥18 years of age at the enrolment visit (visit 1), diagnosed with type 2 diabetes, treated with a single or multiple antidiabetic agents were to be randomised into this study.
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, mode of administration and batch numbers

Sulphonylurea; glibenclamide 10-15 mg tablet (H 1589-02-01-01, H 1589-02-01-02) or gliclazide 160-320 mg (Diamicron tablet 80 mg, H 1746-01-01-01, H 1746-01-01-02) or glimepiride 3-6 mg (Amaryl tablet 2 mg, H 1760-01-01-01, H 1760-01-01-02, H 1760-01-01-03, H 1760-01-01-04) or
glipizide 10-20 mg (Minodiab Tablet 5 mg H 1745-01-01-02) daily in oral form (tablets).

Duration of treatment

After a 6-week sulphonylurea 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, and Apo B/Apo A-I ratio); glycaemic parameters (FPG, and insulin), C-reactive protein (CRP), waist-hip ratio, leptin and adiponectin

Additionally, the following was evaluated:

- Responder analyses for HbA1c, FPG, TG and HDL-C according to pre-specified values and the proportion of patients reaching pre-specified target levels for HbA1c, FPG, TG and 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, 1555 patients were enrolled at 112 centres. Of the enrolled patients, 568 were randomised to treatment. Five randomised patients were excluded from the safety analysis set; 3 patients did not receive investigational product and in 2 patients no post-baseline safety data were available. Thus, 563 patients were included in the safety analysis set. 561 patients were analyzed for efficacy in a full analysis set and 433 in a per-protocol analysis set. The majority of randomised patients were Caucasian (>62% in each treatment group). All treatment groups included also a substantial proportion Oriental patients (≥30% in each treatment group). The male- to female ratios were similar across the treatment groups; overall 55% men were randomised into the study. The age range of patients in this study was 26 to 92 years with a median age of 61 years. The duration of diabetes in the randomised patients ranged from less than 1 year up to 42 years. The number of discontinuations, and the number of patients who discontinued study treatment due to development of study-specific discontinuation criteria (especially hypoglycaemic events), was somewhat higher in the tesaglitazar 1 mg + sulphonylurea group than in the other two 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. A total of 325 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 sulphonylurea, treatment with either 1 mg or 0.5 mg of tesaglitazar as add-on to sulphonylurea 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 -0.96 (-1.08 to -0.85) for tesaglitazar 1 mg + sulphonylurea and -0.59 (-0.70 to -0.48) for tesaglitazar 0.5 mg + sulphonylurea to be compared to a small increase (0.34 (0.22 to 0.46)) for placebo + sulphonylurea. 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 + sulphonylurea treatment groups as compared to placebo + sulphonylurea. 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).
The adipose tissue hormones, adiponectin and leptin, increased significantly during randomised treatment with either 1 mg or 0.5 mg tesaglitazar + sulphonylurea compared to placebo + sulphonylurea.
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 were observed throughout the 24-week treatment period indicating stable tesaglitazar steady state pharmacokinetics in combination with sulphonylurea.

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.
For two patients in the tesaglitazar 0.5 mg + sulphonylurea group CHF was reported and confirmed according to prespecified criteria. The number of patients with AEs of oedema peripheral was highest in the tesaglitazar 1 mg + sulphonylurea group (6.2%, 3.7% and 1.1%, respectively).
A dose dependent increase in weight from baseline to end of treatment was observed in the tesaglitazar+ sulphonylurea treatment groups.
A dose-dependent increase in serum creatinine (an increase in mean serum creatinine of approximately 20% in patients in the tesaglitazar 1 mg + sulphonylurea group and approximately 15% in the tesagltazar 0.5 mg + sulphonylurea group) and decrease in eGFR were seen in the tesaglitazar + sulphonylurea 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 in the two tesaglitazar + sulphonylurea 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.