AstraZeneca

Clinical Study Report

Drug substance:	Tesaglitazar
Edition No.:	1
Study code:	D6160C00033
Date:	23 January 2007

A 24-Week Randomised, Double-Blind, 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 Insulin

GALLANT 9

Study dates:	First patient enrolled: 4 August 2004 Last patient completed: 11 January 2006
Phase of development:	Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice.

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Study centre(s)

This study was conducted at 80 centres in the United States.

Publications

None at the time of this report.

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Objectives

Primary Objective

The primary objective of this study was to demonstrate the superior efficacy of tesaglitazar 0.5 mg in combination with insulin compared with placebo in combination with insulin in improving glycaemic control in patients with type 2 diabetes after 24 weeks of treatment as measured by the change in glycosylated haemoglobin A1c (HbA_{1c}) from baseline to end of treatment.

Secondary objectives of the study were as follows:

1. To compare the effects of tesaglitazar (0.5 mg) given in combination with insulin versus placebo given in combination with insulin in modifying lipids and lipoproteins in patients with type 2 diabetes after a 24-week treatment period by evaluation of:

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

- responder rates as determined by the proportion of patients meeting a pre-specified change from baseline to the end of the treatment period for triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), non-high density lipoprotein-cholesterol (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 (0.5 mg) given in combination with insulin versus placebo given in combination with insulin in modifying other markers of glycaemic control in patients with type 2 diabetes after a 24-week treatment period by evaluation of:

   - change in fasting plasma glucose (FPG) from baseline to the end of treatment

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

3. To compare the effects of tesaglitazar (0.5 mg) given in combination with insulin versus placebo given in combination with insulin on the dose of insulin in patients with type 2 diabetes after a 24-week treatment period.

4. To compare the effects of tesaglitazar (0.5 mg) given in combination with insulin versus placebo given in combination with insulin on the levels of risk markers for cardiovascular disease (C-reactive protein [CRP], LDL-C/HDL-C ratio, and apoliprotein B [ApoB]/apoliprotein AI [Apo A-I]) in patients with type 2 diabetes after a 24-week treatment period.

5. To compare the effects of tesaglitazar (0.5 mg) given in combination with insulin versus placebo given in combination with insulin on urinary albumin excretion in patients with type 2 diabetes after a 24-week treatment period.

6. To compare the effects of tesaglitazar (0.5 mg) given in combination with insulin versus placebo given in combination with insulin on the waist-hip ratio in patients with type 2 diabetes after a 24-week treatment period.

7. To compare the effects of tesaglitazar (0.5 mg) given in combination with insulin versus placebo given in combination with insulin on body weight in patients with type 2 diabetes after a 24-week treatment period.

8. To validate the Work Productivity and Activity Impairment-Diabetes Questionnaire (WPAI-Diabetes) and the Diabetes Productivity Impairment Questionnaire (DPIQ) in patients with type 2 diabetes and to explore the effects of tesaglitazar (0.5 mg) on Patient Reported Outcomes (PROs).

9. To evaluate the pharmacokinetics of tesaglitazar (0.5 mg) in combination with insulin.

10. To evaluate the safety and tolerability of tesaglitazar (0.5 mg) in combination with insulin 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, multi-centre, placebo-controlled study of tesaglitazar 0.5 mg in patients with type 2 diabetes who were not adequately controlled on insulin (alone or in combination with 1 or more oral antidiabetic agents in addition to diet and life-style advice).

Target patient population and sample size

Men or women who were ≥ 18 years of age at the enrolment visit (Visit 1) and who had been diagnosed with type 2 diabetes for less than 20 years using clinical criteria. Patients had to also be receiving concurrent treatment with at least 30 U insulin daily, with or without 1 or more oral antidiabetic agents. Patients could not have been treated with thiazolidinediones at least 16 weeks prior to randomisation (Visit 3). HbA_{1c} had to be ≥7.5% and ≤10%.
To detect a difference of 0.5% in change for HbA_{1c} with 90% power using a 2-sided t-test at level 0.05, assuming the standard deviation to be 1.4%, required 166 patients in each treatment arm. To compensate for an assumed 10% discontinuation rate, 185 patients per treatment arm (370 total) were to be randomised.

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

Tesaglitazar 0.5 mg administered once daily in oral form (film-coated tablets). Placebo (matching the investigational product) administered once daily in oral form (film-coated tablets). The following batch numbers were used: tesaglitazar 0.5 mg, H 1434-05-01-01; placebo, H 1428-05-01-02. In addition to receiving either tesaglitazar 0.5 mg or placebo, patients also received concurrent treatment with insulin with or without 1 or more oral antidiabetic medications.

Duration of treatment

Patients entered the study on their current therapy. After a 3-week enrolment period, the patients were given investigational product for 24 weeks in a double-blind fashion. Three weeks after the end of the randomised treatment period (Visit 9), patients who completed the 24-week treatment period and met eligibility criteria were transferred to a long-term extension (LTE) study. Only patients not entering the LTE were to complete the follow-up visit (Visit 10).

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics
Primary variable: Absolute change from baseline to the end of the randomised treatment period (Week 24) in $HbA_{1c.}$

Secondary variables:

Change from baseline to the end of the randomised treatment period (Week 24) in lipid and lipoprotein variables: TG, HDL-C, non-HDL-C, LDL-C, LDL-C/HDL-C, TG/HDL-C, total cholesterol (TC), ApoA-I, ApoB, ApoB/ApoA-I.
Responder rates for TG and HDL-C, as determined by the proportion of patients meeting a prespecified change (A patient was defined as a responder if he/she had a relative decrease from baseline to the end of the randomised treatment period of 30% for TG and a relative increase from baseline to the end of randomised treatment of 10% for HDL-C).
Proportion of patients reaching target levels for TG and HDL-C (American Diabetes Association [ADA] treatment guideline for TG was <150 mg/dL, and for HDL-C was >40 mg/dL for males and >50 mg/dL for females).
Change from baseline to Week 24 in FPG
Change from baseline to Week 24 in dose of insulin.
Responder rates and the proportion of patients reaching prespecified target levels for HbA_{1c} and FPG (A patient was defined as a responder if he/she had an absolute decrease from baseline to the end of the randomised treatment period of 0.7% for HbA_{1c} and 30 mg/dL for FPG). A patient met target treatment goals if he/she reached the ADA guideline for HbA_{1c} (<7.0%) and for FPG (90 to 130 mg/dL) at the end of the randomised treatment period).
Change from baseline to Week 24 in CRP
Change from baseline to Week 24 in urinary albumin/urinary creatinine
Change from baseline to Week 24 in waist-hip ratio
Change from baseline to Week 24 in body weight

Patient reported outcomes (PROs)

Validation analyses of theWPAI-Diabetes and DPIQ questionnaires
Change from baseline to Week 24 on the SF-36

Health economics

Not applicable

Pharmacokinetic

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

Safety assessments included AEs, laboratory values, ECGs, vital signs (pulse and BP), physical examinations, body weight, cardiac evaluation (assessment of cardiac function by history and physical examination, evaluation of signs and symptoms of congestive heart failure [CHF]), and hypoglycaemic events.

Genetic

A blood sample for deoxyribonucleic acid (DNA) preparation and further genetic analysis was taken. Patients who did not wish to participate in the genetic research were still eligible to participate in this Clinical Study. (Genetic analysis was not part of the results for this study).

Statistical methods

The Full analysis set was used for all efficacy analyses, and it constituted the primary evaluation of efficacy. For patients who discontinued participation before the final visit of the treatment period, a last observation carried forward (LOCF) approach was applied. Secondary analyses of HbA1c, FPG, HDL-C, non-HDL-C, and TG were also done using the Per Protocol analysis set.

The change from baseline to the end of the treatment period was analysed with a linear model using a fixed-effect analysis of covariance (ANCOVA) with treatment as a factor and baseline value as a covariate. Efficacy variables analysed in this model, except HbA_{1c} and FPG, were log-transformed before ANCOVA analysis.

The primary outcome variable was the absolute change from baseline in HbA_{1c} after 24 weeks of treatment. Important secondary variables included changes from baseline in TG, HDL-C, and non-HDL-C. A fixed-sequence testing procedure was applied in the analysis of these variables to control the overall significance level.

Analyses of glycaemic and lipid responders were conducted using pre-defined criteria for change. In addition, the proportion of patients reaching target treatment goals according to ADA guidelines were analysed. Treatment group comparisons were performed using logistic regression with adjustment for baseline levels. Subgroup analyses for the change from baseline in HbA_{1c}, FPG, TG, HDL-C, and non-HDL-C at end of treatment were also done. Patient reported outcomes (PROs) were summarized with descriptive statistics and analysed using techniques appropriate for psychometric evaluation.

No hypotheses were proposed a priori for safety-related variables. The safety analysis set was used for all safety analyses. All safety data were analysed and presented according to the treatment received; safety presentations were based on observed cases. Descriptive statistics were presented for all safety variables: AEs, clinical laboratory variables, ECG, vital signs, physical examinations, body weight, cardiac evaluation, and hypoglycaemic events. Adverse events were summarised by the Medical Dictionary for Regulatory Activities (MedDRA) and presented by both system organ class (SOC) and preferred term (PT). The exposure to investigational product and the number of patients entering handling plans and discontinuing from the study due to handling plan-related criteria were also summarised.

Patient population

- In total, 1087 patients from 80 centres entered the study and 392 patients from 74 centres were randomised to treatment. Of these randomised patients, 97 patients (24.7%) attended the follow-up visit (Visit 10) and 241 patients (61.5%) transferred to the LTE study. The first patient was enrolled in the study on 04 August 2004 and the last patient completed the randomised treatment phase on 11 January 2006.

- The majority of randomised patients were Caucasian (76.3%). There were 47.9 % males in the tesaglitazar 0.5 mg + insulin group, compared with 56.0% in the placebo + insulin group; overall, 52.0 % of the randomised patients were men and 48.0 % women. The age range of patients in the study was 20.0 to 83.0 years; the overall median age was 57.0 years. Patients had similar baseline characteristics between the 2 treatment groups, and the patient population enrolled in this study was representative of the target population for tesaglitazar.

- Of the 392 randomised patients, 9 patients were excluded from the safety analysis set, and the remaining 383 patients included in the Safety analysis set. A total of 379 patients were analyzed for efficacy in the Full analysis set and 260 in the PP analysis set.

- The most common reasons for study discontinuation were the patient not willing to continue (7.7%), the development of study specific discontinuation criteria (3.8%), and patient lost to follow-up (3.8%). The frequency of patients who discontinued study treatment due to AEs (3.6%) was higher in the tesaglitazar 0.5 mg + insulin group (4.7%) compared with the placebo + insulin group (2.5%). The number of protocol deviations considered serious enough to warrant exclusion of data was similar between the 2 treatment groups.

Efficacy results

- For the primary objective, tesaglitazar 0.5 mg + insulin treatment resulted in a statistically significant decrease in HbA_{1c} from baseline to the end of the 24 week treatment period relative to placebo + insulin treatment. The mean (confidence interval [CI]) absolute change in HbA1c (%) from baseline to end of treatment was -0.700 (-0.833 to -0.567) for tesaglitazar 0.5 mg + insulin compared with -0.042 (-0.173 to 0.089) for placebo + insulin. Secondary analyses on the PP analysis set were supportive of the primary analysis.

- Tesaglitazar 0.5 mg + insulin was superior to placebo + insulin in improving TG, HDL-C, and non-HDL-C, and also resulted in a statistically significant improvement from baseline to end of treatment in the ratio of LDL-C/HDL-C, as well as ApoA-I, ApoB, and the ratio of ApoB/ApoA-I. No statistically significant difference was observed between the 2 treatment groups in the relative change from baseline in either LDL-C or TC.

- Tesaglitazar 0.5 mg + insulin treatment resulted in statistically significantly higher responder rates for TG and HDL-C at 24 weeks compared with placebo + insulin treatment. Tesaglitazar 0.5 mg + insulin resulted in statistically significantly higher target rates for TG and HDL-C and the combination of TG and HDL-C at 24 weeks compared with placebo + insulin. With respect to the secondary variables for markers of glycemic control, tesaglitazar 0.5 mg + insulin resulted in a statistically significantly lower FPG, statistically significantly higher responder rates for HbA_{1c} and FPG, and a statistically significantly higher rate of patients at target for HbA_{1c} and FPG individually and for the combination of HbA_{1c}, TG, and HDL-C at 24 weeks compared with placebo + insulin.

- Tesaglitazar 0.5 mg + insulin treatment resulted in a statistically significant reduction in insulin dose at 24 weeks compared with placebo + insulin treatment.

- Tesaglitazar 0.5 mg + insulin resulted in statistically significantly lowering of the risk marker for cardiovascular disease of CRP compared with placebo + insulin.

- Tesaglitazar 0.5 mg + insulin treatment resulted in a statistically significant decrease in urinary albumin excretion (ratio U-albumin/U-creatinine) compared with placebo + insulin treatment.

- Waist-hip ratio for patients receiving tesaglitazar 0.5 mg + insulin was not statistically significantly different at 24 weeks compared with patients receiving placebo + insulin.

- Tesaglitazar 0.5 mg + insulin resulted in a statistically significant increase in weight at 24 weeks compared with placebo + insulin.

Patient reported outcomes results

- The WPAI-Diabetes demonstrated concurrent validity with small to moderate correlations with the SF-36 and DPIQ. The DPIQ scale structure as a 7-item single scale was confirmed with excellent model fit. The DPIQ also demonstrated strong internal consistency and concurrent validity with moderate correlations with the SF-36 and WPAI-Diabetes.

- There was little change in the SF-36 scores between Visit 3 and Visit 9 in both treatment groups and within both analysis data sets. Importantly, the majority of change scores were negative, indicating that while of very small magnitude, a general decline in health-related quality of life (HRQL) occurred over time regardless of treatment group.

Pharmacokinetic results

- Concentrations of tesaglitazar 0.5 mg at trough were 0.213 (0.126) µmol/L at Week 4, 0.205 (0.116) µmol/L at Week 12, and 0.221 (0.124) µmol/L at Week 24.

Safety results

- The extent of exposure was well balanced across the treatment dose groups and the mean duration of exposure data was adequate for the evaluation of safety in this study.

- The percentage of patients with an AE, serious adverse event, or an adverse event leading to discontinuation of a patient from study treatment was similar between the 2 treatment groups. No deaths occurred during the study. Overall, the frequency of patients discontinuing the study as a result of handling plans was low and similar between treatments (4 patients [2.1 %] in the tesaglitazar 0.5 mg + insulin group versus one patient [0.5 %] in the placebo + insulin group).

- More hypoglycaemic events were observed for tesaglitazar 0.5 mg + insulin compared with placebo + insulin.

- More patients reported weight gain and oedema-related AEs with tesaglitazar 0.5 mg + insulin treatment compared with placebo + insulin treatment. New onset CHF was reported for 1 patient in the tesaglitazar 0.5 mg + insulin group.

- There was a mean increase in serum creatinine in the tesaglitazar 0.5 mg + insulin group, along with decreases in estimated glomerular filtration rate. The percentage of patients with an increase in serum creatinine of >50% was higher in the tesaglitazar 0.5 mg + insulin group compared with the placebo + insulin group. The pattern of renal-related AEs was similar for both treatment groups.

- Slight decreases in mean haemoglobin and absolute neutrophil count (ANC) values were observed for tesaglitazar 0.5 mg + insulin relative to placebo + insulin. The pattern of AEs related to haemoglobin and ANC was similar for both treatment groups.

- There were no clinically relevant changes in systolic or diastolic BP or pulse between the 2 treatment groups. The majority of ECG evaluations were unchanged from baseline to the end of the randomised treatment period in the 2 treatment groups. No safety concerns were raised for cardiac evaluations across the treatment dose groups.

- There were no clinically relevant differences between the 2 treatment groups for physical examinations.

Date of the report

23 January 2007