Abbreviated Clinical Study Report	
Drug substance:	Tesaglitazar
Document No.:	CV.000-441-019
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Study code:	D6160C00028
Date:	19 May 2008

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

GALLANT 4

Abbreviated Clinical Study Report

Study dates:	First patient enrolled: 01 September 2004 Last patient discontinued: 14 December 2006
Phase of development:	III

This study was performed in compliance with Good Clinical Practice.

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

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Study centre(s)

This study was conducted in Belgium, China (Hong Kong S.A.R.), Hungary, Italy, Malaysia, Mexico, Philippines, Poland, Slovakia, South Africa, Taiwan and Thailand.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	01 September 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 710 patients who received treatment, 275 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 glibenclamide, 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 glibenclamide 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 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)

   - 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 glibenclamide 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 glibenclamide 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 glibenclamide 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 glibenclamide 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 glibenclamide 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 glibenclamide 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 (glibenclamide) study of tesaglitazar in patients with type 2 diabetes, not adequately controlled on diet and lifestyle 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.

Glibenclamide, 2.5 mg, 5 mg, 10 mg or 15 mg daily divided into morning and evening doses in oral form (tablets/capsules) 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 glibenclamide 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

  - Proportion of patients with microalbuminuria

  - 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.

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 glibenclamide 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 glibenclamide 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 712 randomised patients, 38.6% of randomised patients had completed 52 weeks of treatment; 15.7% had withdrawn before that time point; and 45.6% were receiving randomised treatment.

In total, 1119 patients entered the 6-week placebo single-blind run-in period and 712 patients from 40 centres were randomised to treatment. Of these randomised patients, 59.4% attended

the follow-up visit (Visit 22), 31.9% transferred to the long-term extension study and 35.4% completed the final follow-up visit (Visit 24). The majority of randomised patients were Caucasian (67.0% and 65.8% of patients in the tesaglitazar and glibenclamide groups, respectively). The male-to-female ratios were similar in both treatment groups; overall, 47.9% of the randomised patients were male and 52.1% were female. The age range of patients in the study was 25.0 to 85.0 years; the overall mean age was 55.8 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 712 randomised patients, 364 were randomised to tesaglitazar and 348 were randomised to glibenclamide, of whom 99.5% and 100%, respectively, received treatment; 99.6% were analysed for safety and 99.0% were analysed for efficacy in an ITT analysis set. Of the 712 patients randomised to treatment, 60.4% were discontinued during the randomised treatment period. The most common reason for premature discontinuation was recorded as 'other' (45.9%), 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 glibenclamide group (2.9% of patients compared with 1.4% of patients in the tesaglitazar group).

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.

For the primary objective, tesaglitazar demonstrated non-inferiority to glibenclamide, as measured by the absolute change from baseline in HbA_{1c} at the end of the randomised treatment period (Week 52).

For the secondary objectives, tesaglitazar demonstrated significant improvements in blood lipids when compared to glibenclamide, 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 glibenclamide 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 mean duration of exposure was similar in both the tesaglitazar and glibenclamide groups.

The frequency of AEs was similar in both treatment groups. There were three deaths during the study (1 and 2 patients in the tesaglitazar and glibenclamide groups, respectively).One

death was considered by the investigator to be treatment-related: a patient in the tesaglitazar group with abnormal liver function test, increased alpha 1 foetoprotein and malignant hepatic neoplasm. 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. The overall frequency of major hypoglycaemic events was low while the frequency of minor hypoglycaemic events was lower in the tesaglitazar group compared with the glibenclamide group (1.7% of patients compared with 11.5%). The overall frequency of SAEs was low and similar in the treatment groups. No SAE occurred with a frequency of ≥0.5% overall. The overall frequency of DAEs was low and similar in the treatment groups. The only DAE which occurred with a frequency of ≥0.5% overall was decreased neutrophil count, reported for 0.8% and 0.3% of patients in the tesaglitazar and glibenclamide groups, respectively. Overall, the frequency of patients discontinuing the study from a handling plan was low, 1.9% of patients in the tesaglitazar group and 0.6% in the glibenclamide 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 in either treatment group had confirmed new/worsening CHF during the study.

- A greater proportion of patients in the tesaglitazar group had an increase in serum (S)-creatinine meeting pre-specified criteria (increase from baseline of >50%) and a decrease in Hb meeting pre-specified criteria (decrease from baseline >25 g/L) (13.0% and 9.1% of patients, respectively) compared to the glibenclamide group (2.9% and 1.2% of patients, 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). 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 (9.1%) compared to the glibenclamide group (1.2%). The proportion of patients with an increase from baseline in S-creatinine of >50% was higher in the tesaglitazar group (13.0%) compared to the glibenclamide group (2.9%) and there was a mean decrease in estimated GFR from baseline to the end of the randomised treatment period (14.895 mL/min in the tesaglitazar group compared to 4.724 mL/min in the glibenclamide group). Overall, the number of clinically notable elevations was small.

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 both treatment groups.

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