AstraZeneca

Abbreviated Clinical Study Report	
Drug substance	Tesaglitazar
Document number	CV.000-441-008
Edition number	1.0
Study code	D6160C00047
Date	19 May 2008

A Parallel-Group, Multi-Centre, Active-Controlled (Glibenclamide) Long Term Extension Study to Evaluate the Safety and Tolerability of Oral Tesaglitazar Therapy in Patients with Type 2 Diabetes Mellitus

GALLEX 4

Abbreviated Clinical Study Report

Study dates: First patient enrolled: 31 October 2005
Last patient discontinued: 14 December 2006

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice.

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Study centres

The study included 35 study centres and a total of 227 patients were enrolled in Belgium, Hong Kong, Hungary, Malaysia, Philippines, Poland, Slovakia, South Africa and Thailand.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	31 October 2005	Therapeutic confirmatory (III)
Last patient discontinued	14 December 2006	

* Note: The GALIDA studies were terminated prematurely because AstraZeneca discontinued the tesaglitazar development programme as the overall benefit/risk profile was unlikely to offer patients significant advantage over current available therapy.

Objectives

Primary objective

To monitor the long-term safety and tolerability of tesaglitazar (0.5 mg and 1 mg) versus glibenclamide (2.5 mg, 5 mg, 10 mg and 15 mg), with or without oral anti-diabetic treatments, when administered for up to 100 weeks in an extension study from the GALLANT 4 study in patients with type 2 diabetes by evaluating:

- Adverse events (AEs),
- Laboratory variables,
- Physical examination,
- Cardiac evaluation (including New York Heart Association [NYHA] status),
- Hypoglycaemic events,
- Electrocardiogram (ECG),
- Vital signs (blood pressure [BP] and pulse) and
- Body weight and height.

Secondary objectives

To evaluate the effect of tesaglitazar (0.5 mg and 1 mg) versus glibenclamide (2.5 mg, 5 mg, 10 mg and 15 mg), with or without other oral anti-diabetic treatments, when administered for up to 100 weeks in an extension study from the GALLANT 4 study in patients with type 2 diabetes:

1. In modifying and maintaining durable glycaemic control by assessment of:
   - Time to treatment failure and
   - Change in glycaemic variables:
     - Glycosylated haemoglobin A_{1C} (HbA_{1C}) and
     - Fasting plasma glucose (FPG).
2. On markers of insulin resistance by assessment of changes in:
   - Insulin and
   - Homeostasis Model Assessment (HOMA).

3. In preserving β-cell function by assessment of changes in:

   - Proinsulin/insulin ratio and
   - C-peptide/FPG ratio.

4. Modifying lipid control by assessment of:

   - Change in lipid variables:
     - Triglycerides (TG),
     - Total cholesterol (TC),
     - High-density lipoprotein-cholesterol (HDL-C),
     - Non-HDL-C,
     - Low-density lipoprotein-cholesterol (LDL-C),
     - LDL-C/HDL-C ratio and
     - Apolipoprotein (Apo) B/ApoA-1 ratio.

5. On inflammatory and coagulation markers by assessment of changes in:

   - C-reactive protein (CRP),
   - Fibrinogen,
   - Tumour necrosis factor-α (TNF-α) and
   - Intracellular adhesion molecule-1 (ICAM-1).

6. On urine albumin excretion by assessment of:

   - Proportion of patients with microalbuminuria.

7. On central obesity by assessment of:

   - Waist-hip ratio.

Study design

This study was a long-term extension of the GALLANT 4 study and evaluated the safety and tolerability of oral tesaglitazar (0.5 mg and 1 mg) as compared to glibenclamide (2.5 mg, 5 mg, 10 mg and 15 mg), with or without other oral anti-diabetic treatments, in patients with type 2 diabetes.

The total study duration including the randomised treatment period (maximum of 100 weeks) and Follow-up Visit (3 weeks after the End of Treatment [EOT] Visit) was to be a maximum of 103 weeks. Due to termination of the tesaglitazar programme two additional Follow-up Visits (at 12 weeks and 24 weeks after the EOT Visit) were implemented (Clinical Study Protocol Amendment D6160P1 [Appendix 12.1.1]). The total duration of the study could thus have been a maximum of 124 weeks.

The treatment was administred in a blinded fashion until the unblinding of GALLEX 4. GALLEX 4 was unblinded and the placebo doses removed after the unblinding of GALLANT 4.

Target patient population

Male and female patients with type 2 diabetes who participated in and completed Visit 20 and Visit 21 of GALLANT 4. The patients in GALLANT 4 were either anti-diabetic treatment naïve, or previously treated with either a single oral anti-diabetic treatment or low dose combination of two oral anti-diabetic treatments.

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

Investigational product: Tesaglitazar 0.5 mg or 1 mg once daily in oral form (film-coated tablets).

Comparator: Glibenclamide 2.5 mg, 5 mg, 10 mg or 15 mg daily divided into morning and evening doses in oral form (encapsulated tablets).

Placebo: Matching either tesaglitazar or glibenclamide once daily (or twice daily, where applicable) in oral form.

* Note: After unblinding of GALLEX 4 placebo tablets to maintain the blind were no longer dispensed and glibenclamide was no longer encapsulated. Both tesaglitazar and glibenclamide patients could have been up- and down titrated. However, the dose on which they entered GALLEX 4 was considered the minimum dose.

Duration of treatment

The planned duration of the randomised treatment period was a maximum of 100 weeks.

The total study duration including randomised treatment period (maximum of 100 weeks) and Follow-up Visits (3 weeks, 12 weeks and 24 weeks after the EOT Visit) was to be a maximum of 124 weeks.

Criteria for evaluation (main variables)

Safety

- AEs, laboratory variables, physical examination, cardiac evaluation, hypoglycaemic events, ECG evaluation, vital signs, body weight and height.

Efficacy

- Time to treatment failure, absolute change from Baseline (defined as Visit 5 of GALLANT 4) in HbA_{1C} and FPG, and relative change (%) from Baseline in insulin, HOMA, proinsulin/insulin ratio, C-peptide/FPG ratio, TG, TC, HDL-C, non-HDL-C, LDL-C, LDL-C/HDL-C ratio, ApoB/ApoA-I ratio, CRP, fibrinogen, TNF-α, ICAM-1, proportion of patients with microalbuminuria and waist-hip ratio.

Statistical methods

Due to the termination of the tesaglitazar programme only two analysis sets were defined, namely Safety and Intention to Treat (ITT). Efficacy results were analysed using the ITT analysis set and the safety results using the Safety analysis set. Furthermore, due to the termination of the study programme, the randomised treatment period could have been less than the 100 weeks specified in the Clinical Study Protocol (CSP).

Results were only descriptively analysed for the change from Baseline by treatment group and visit and no inferential statistics were performed. For HbA_{1C} and FPG, the absolute change from Baseline to each scheduled GALLEX 4 visit is presented, whilst for all other efficacy variables, the relative (%) change from Baseline is presented.

Since no Per Protocol (PP) analysis set was defined, no protocol violations were summarised and presented.

Although a considerable amount of missing data was expected, no last observation carried forward (LOCF) was imputed and only observed data were analysed.

Compliance to treatment was calculated as the patient's compliance to the active investigational product, and compliance with the placebo was not included.

* Note: Due to the possibility of up- or down-titration of the treatment dose, the different dose level groups were merged within each treatment for the two tesaglitazar (0.5 mg and 1 mg) and the four glibenclamide (2.5 mg, 5 mg, 10 mg and 15 mg) dose levels; thus all data is presented for two treatment groups, namely a tesaglitazar and a glibenclamide treatment group (as specified in the Statistical Analysis Plan [SAP] [30 August 2007]).

Patient population

Existing GALLANT 4 study centres that agreed to participate in GALLEX 4 asked their GALLANT 4 patients who had completed Visit 20 and Visit 21 of GALLANT 4 to participate in this long-term extension study (GALLEX 4). The total duration of participation in the

long-term extension study, including the randomised treatment period and Follow-up Visits could potentially have been a maximum of 124 weeks.

Due to termination of the study programme by AstraZeneca, the planned number of patients were not enrolled into the GALLEX 4 study. In total, 227 patients were enrolled at 35 study centres in Belgium, Hong Kong, Hungary, Malaysia, Philippines, Poland, Slovakia, South Africa and Thailand. The first patient entered the study on 31 October 2005, whilst the last patient visit was conducted on 14 December 2006.

Patients who had their EOT Visit at or after 08 May 2006 and who had received at least 12 weeks of randomised treatment were to complete the two additional Follow-up Visits (12 weeks and 24 weeks after the EOT Visit).

A total of 222 (97.8%) patients completed the study by attending all three Follow-up Visits and 5 (2.2%) patients prematurely discontinued their participation from the study during the follow-up period.

The majority of patients were Caucasian. The ages of the patients ranged from 25 years to 77 years, with an overall mean age of 56.6 years.

All 227 (100.0%) enrolled patients were included in the Safety and ITT analysis sets.

Only one patient (Patient E1901401, tesaglitazar) entered a handling plan (creatine kinase handling plan).

Safety results

Due to the early termination of the GALIDA study programme and subsequently of the GALLEX 4 study, exposure to tesaglitazar treatment was shorter than anticipated.

No patients died during the study with reports of SAEs being generally low; 10 (4.4%) patients in total (1 [0.9%] patient during the randomised treatment period, 1 [0.9%] patient during the main study follow-up period [Part A] and 8 [3.5%] patients during the extended follow-up period [Part B]). None of the SAEs were regarded as by the Investigator as causally related to the investigational products. Two patients treated with tesaglitazar discontinued due to AEs during the randomised treatment period, with no patients discontinuing during the follow-up periods.

No safety concerns were raised regarding the number or severity of AEs. The overall AE profile associated with tesaglitazar treatment was similar to that observed with glibenclamide treatment.

No major hypoglycaemic events occurred, with the number of patients with minor hypoglycaemic events being lower in the tesaglitazar treatment group (1 [0.9%] patient) compared to the glibenclamide treatment group (6 [5.3%] patients).

No notable changes from Baseline in the physical examination, cardiac evaluation or vital signs were observed.

No patient in the tesaglitazar group and one patient in the glibencliamide group had an AE report of CHF.

In accordance with previous findings in the phase III programme, a mean increase in serum creatinine and a mean decrease in eGFR remained during the long term extension.Three patients had renal AEs (increased serum creatinine), considered causally related to the investigational product by the Investigator.

A greater mean increase in CK from Baseline to the EOT Visit was observed in the tesaglitazar treatment group. One patient (Patient E1901401 [tesaglitazar]) entered and completed the CK handling plan. There were no AEs of myositis reported.

Efficacy results

Since this study was a long term extension of GALLANT 4, the primary objective was to assess the long-term safety and tolerability of tesaglitazar.

The secondary objective was to evaluate the effect of tesaglitazar (0.5 mg or 1 mg) versus glibenclamide (2.5 mg, 5 mg, 10 mg or 15 mg), with or without additional oral anti-diabetic treatments, when administered for up to 100 weeks in an extension study from the GALLANT 4 study in patients with type 2 diabetes.

A similar mean decrease in HbA_{1C} from Baseline to the EOT Visit was observed for the tesaglitazar (0.491%) and glibenclamide (0.431%) treatment groups and in concordance with results from the GALLANT 4 study.

Mean decreases from Baseline to the EOT Visit for insulin levels (19.63%), HOMA (20.32%), proinsulin (29.06%) and C-peptide (13.21%) were observed for the tesaglitazar treatment group, compared to mean increases observed in the glibenclamide treatment group (26.43% [insulin level], 22.12% [HOMA], 21.53% [proinsulin] and 22.78 [C-peptide]).

Treatment with tesaglitazar resulted in a mean decrease of 20.60% in TG levels, of 31.11% in the TG/HDL-C ratio and of 17.68% in the ApoB/ApoA-1 ratio as well as a mean increase of 25.04% in HDL-C levels from Baseline to the EOT Visit.

Mean decreases from Baseline to the EOT Visit for the tesaglitazar treatment group was observed for CRP (17.60%) and fibrinogen (21.54%).

Overall, 37 (18.7%) patients had microalbuminuria at Baseline. Fewer patients in the tesglitazar treatment group had microalbuminuria at the EOT Visit (8 [9.5%] patients) compared to the glibenclamide treatment group (16 [16.8%] patients).

No notable change from Baseline to the EOT Visit was observed for the waist-hip ratio.

The efficacy results indicated that neither tesaglitazar nor glibenclamide was effective in decreasing HbA_{1C}. Increased lipid control was observed for the tesaglitazar treatment group during the study.