AstraZeneca

Abbreviated Clinical Study Report	
Drug Substance:	Tesaglitazar
Document No.:	CV.000-442-488
Edition No.:	1.0
Study Code:	D6160C00048
Date:	May 19, 2008

A Double-Blind, Multi-Centre, Active-Controlled (15, 30, and 45 mg Pioglitazone) Long-Term Extension Study to Evaluate the Safety and Tolerability of Oral Tesaglitazar (0.5 and 1 mg) in Patients with Type 2 Diabetes Mellitus

GALLEX 6

Abbreviated Clinical Study Report

Study Dates:	First patient enrolled: 22 March 2005 Last patient discontinued: 20 December 2006
Phase of Development:	Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice.

Drug Product:	GALIDA	**SYNOPSIS**	
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A Double-Blind, Multi-Centre, Active-Controlled (15, 30, and 45 mg Pioglitazone) Long-Term Extension Study to Evaluate the Safety and Tolerability of Oral Tesaglitazar (0.5 and 1 mg) in Patients with Type 2 Diabetes Mellitus

GALLEX 6

Study centres

The study included 152 centres in Canada, Finland, Mexico, the United Kingdom (UK) and the United States of America (USA). A total of 823 patients were recruited. Countries implementing the European Union (EU) Clinical Directive recruited approximately 87 patients.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	22 March 2005	Therapeutic confirmatory (III)
Last patient discontinued*	20 December 2006	

* Note that 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 pioglitazone (15 mg, 30 mg and 45 mg), with or without other oral anti-diabetic drugs, when administered for up to 104 weeks in an extension study from the GALLANT 6 study in patients with type 2 diabetes by evaluating:

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

Secondary objectives

To evaluate the effect of tesaglitazar (0.5 mg and 1 mg) versus pioglitazone (15 mg, 30 mg and 45 mg), with or without other oral anti-diabetic drugs, when administered for up to 104 weeks in an extension study from the GALLANT 6 study in patients with type 2 diabetes:

1. In modifying glycaemic control by assessment of:

- Change in glycaemic variables:
  - Glycosylated haemoglobin A1c (HbA_{1C}),
  - Fasting plasma glucose (FPG),
  - Insulin and
  - Homeostasis Assessment Model (HOMA).

2. In modifying lipid control by assessment of:

- Change in lipid variables:
  - Triglycerides (TG),
  - Total cholesterol (TC),
  - Low-density lipoprotein cholesterol (LDL-C),
  - High-density lipoprotein cholesterol (HDL-C),
  - Non-HDL-C,
  - Apolipoprotein (Apo) B/ApoA-I,
  - ApoCIII,
  - Free fatty acids (FFA) and
  - Lipoprotein particle size.

3. On inflammatory markers by assessment of C-reactive protein (CRP).

4. On central obesity by assessment of:
   - Waist circumference,
   - Hip circumference and
   - Waist-hip ratio.

5. On patient reported outcomes (PROs) using the Medical Outcomes Study Short Form-36 (SF-36).

Exploratory objectives

To evaluate the effect of tesaglitazar (0.5 mg and 1 mg) versus pioglitazone (15 mg, 30 mg and 45 mg), with or without other oral anti-diabetic drugs, when administered for up to 104 weeks in an extension study from the GALLANT 6 study in a subset of patients with type 2 diabetes:

1. On inflammatory markers by assessment of:
   - Tumour Necrosis Factor-alpha (TNF-α) and
   - Intracellular adhesion molecule-1 (ICAM-1).

2. On a thrombosis/coagulation marker by assessment of:

   – Fibrinogen.

Study design

This study was a long-term extension of the GALLANT 6 study. The GALLEX 6 study evaluated the safety and tolerability of oral tesaglitazar (0.5 mg and 1 mg) versus pioglitazone (15 mg, 30 mg and 45 mg), with or without other oral anti-diabetic drugs, in patients with type 2 diabetes. The total study duration including treatment (up to 104 weeks) and Follow-up Visits (3 weeks, 12 weeks and 24 weeks) was to be 128 weeks.

Target patient population and sample size

Male and female patients with type 2 diabetes who participated and completed Visit 11 and Visit 12 of the GALLANT 6 study, who were willing to participate in the extension, and were considered eligible for the GALLEX 6 study. The patients in GALLANT 6 were either anti-diabetic drug naïve or previously treated with a single oral anti-diabetic agent or low dose combination of oral anti-diabetic agents.

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

Investigational product: Tesaglitazar 0.5 mg or 1 mg once daily in oral form (film-coated tablets). Batch numbers: Tesaglitazar 0.5 mg, H 1434-05-01-06; Tesaglitazar 1mg, H 1467-04-01-04, H 1467-04-01-06 and H 1467-04-01-07.

Comparator: Pioglitazone 15 mg, 30 mg or 45 mg once daily in oral form (capsules). Batch numbers: Pioglitazone 15 mg, H 1589-01-01-03 and H 1598-01-01-04; Pioglitazone 30 mg, H 1564-03-01-03 and Pioglitazone 45 mg, H 1599-01-01-03.

Placebo: Matching placebo once daily in oral form (film-coated tablets or capsules).

Duration of treatment

The planned duration of treatment was to be 104 weeks.

The total study duration including treatment (104 weeks) and Follow-up Visits (3 weeks, 12 weeks and 24 weeks) was to be a potential maximum of 128 weeks.

Criteria for evaluation (main variables)

- Primary variables: Safety and tolerability (AEs, laboratory variables, physical examination, cardiac evaluation, hypoglycaemic events, ECG, vital signs and body weight).

- Secondary variables: Efficacy (absolute change from Baseline in HbA_{1C} and FPG; relative change from Baseline in insulin, HOMA, triglycerides, total cholesterol, LDL-C, HDL-C, non-HDL-C, ApoB/ApoA-I, ApoCIII, FFA, lipoprotein particle

size, inflammatory markers [CRP]), central obesity (waist and hip circumference and waist-hip ratio) and SF-36. Baseline was defined as visit 6 in GALLANT 6.

- Exploratory variables: TNF-α, ICAM-1 and fibrinogen.

Statistical methods

Due to early termination of the study, only two analysis sets, Safety and Intention to Treat (ITT), were defined. Efficacy results were presented using the ITT analysis set and safety results using the Safety analysis set. Furthermore, due to the termination of the study programme, the treatment duration was less than the 104 weeks specified in the Clinical Study Protocol.

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 nominal GALLEX 6 visit is presented, whilst all other efficacy variables, the relative (%) change from Baseline are presented.

Since no Per Protocol (PP) analysis set was defined, no protocol violations could be summarised and presented. Patient-reported outcomes are presented only as patient data listings and no additional analyses were performed.

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

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

Patient population

Existing GALLANT 6 centres that agreed to participate in GALLEX 6 asked their GALLANT 6 patients who had completed Visit 11 and Visit 12 to participate in this long-term extension study. The total duration of participation for the long-term extension study, including treatment and three Follow-up Visits, could potentially be up to 128 weeks. The study included 152 centres from Canada, Finland, Mexico, the UK and the USA to recruit a total of approximately 1,100 patients. Countries implementing the EU Clinical Directive were to recruit approximately 210 patients.

Due to the termination of the study programme by AstraZenca, the anticipated number of patients was not recruited into the GALLEX 6 study, and hence the realised number of patients recruited was notably less than the former discussion.

The majority of patients who were enrolled in GALLEX 6 completed the study by attending all three the Follow-up Visits (3 weeks, 12 weeks and 24 weeks after the End of Treatment [EOT] Visit). Due to the termination of the tesaglitazar programme, patients who had their EOT Visit at or after 08 May 2006 were asked to complete the two additional Follow-up Visits (12 weeks and 24 weeks after the EOT Visit).

The first patient entered the study on 22 March 2005, whilst the last patient discontinued from GALLEX 6 on 20 December 2006. A total of 823 patients, randomised at Visit 6 GALLANT 6, were subsequently enrolled in GALLEX 6. Eight hundred (97.2%) patients completed the study by attending all three the Follow-up visits and 23 (2.8%) patients prematurely discontinued their participation from the study.

The majority of the patients were Caucasian. Overall, the male to female ratio was even, 50.9% males and 49.1% females. The ages of the patients were from 20 years to 85 years, with an overall mean of 57.3 years.

Of the 823 enrolled patients, 815 (99.0%) patients were included in the Safety analysis set and 808 (98.2%) patients in the ITT analysis set.

In total, less than 5% of the patients entered the relevant handling plans. Most of these patients entered the handling plans for serum creatinine and creatinine kinase (CK).

Safety results

Due to early termination of the GALIDA study programme and subsequently of the GALLEX 6 study, exposure to treatment was shorter than planned; however, the safety data presented in this report supported the findings from the previous Phase I, II and III studies, namely that tesaglitazar is generally safe and well tolerated in patients. The number of patients who had SAEs were (40 [4.9%] of Safety patients, randomised treatment period; 14 [1.7%], main study follow-up period [Part A] and 13 [1.6%] extended follow-up period [Part B]). The majority of SAEs were considered not related to the investigational product.

The overall AE profiles associated with the tesaglitazar treatment groups and the pioglitazone control groups were similar, except for the renal laboratory findings. The number of patients with DAEs was low in all treatment groups (26 [3.2%], randomised treatment period and 7 [0.9%], main study follow-up period [Part A]). There were four deaths during the study (one during the randomised treatment period [Tesaglitazar 1 mg], two during the main study follow-up period and one during the extended follow-up period [Tesaglitazar 0.5 mg]). None of the deaths were considered related to the investigational product by the Investigator.

In total, 35 (4.3%) of the Safety patients entered a relevant handling plan, 5 of these patients discontinued the study.

Only two patients had new or worsening congestive heart failure (CHF), one patient in the Tesaglitazar 1 mg treatment group and one patient in the Pioglitazone 30 mg treatment group. No clinically relevant findings of the special safety topics were observed.

Increases in serum-creatinine levels were observed for patients in both the tesaglitazar and pioglitazone treatment groups, but on average were larger for patients in the tesaglitazar treatment groups. Similarly, decreases in the mean absolute neutrophil count (ANC), hemoglobin and mean alkaline phosphatase (ALP) levels were observed. A dose-dependent decrease in estimated glomerular filtration rate (eGFR) from Baseline was noted for

tesaglitazar treatment. The number of patients with renal-related AEs was low and no serious renal AEs were observed. Although increases or decreases were observed in the laboratory evaluations, the majority stabilised after the EOT Visit and were mostly not clinically notable.

There were no major hypoglycaemic events and only 4 patients overall had minor hypoglycaemic events (2 patients, Tesaglitazar 1 mg; 1 patient, Tesaglitazar 0.5 mg and 1 patient, Pioglitazone 45 mg).

There was no obvious trend in the mean changes from Baseline in the vital signs data. Although a notable increase in weight was observed, this occurred in both the tesaglitazar and pioglitazone treatment groups. The mean weight decreased again after the EOT Visit. No notable change from Baseline was observed for systolic blood pressure (SBP), diastolic blood pressure (DBP) or pulse rate.

Except for the possible renal effects, the safety results suggest that treatment with tesaglitazar was well tolerated by patients and as safe as pioglitazone in the population studied.