AstraZeneca

Abbreviated Clinical Study Report	
Drug substance:	Tesaglitazar
Document No.:	CV.000-441-005
Edition No.:	1.0
Study code:	D6160C00038
Date:	19 May 2008

An Open-Label, Multi-Centre and Long-Term Extension Study to Evaluate the Safety and Tolerability of Oral Tesaglitazar 1 mg in Patients with Type 2 Diabetes Mellitus

GALLEX 1

Abbreviated Clinical Study Report

Study dates: First patient enrolled: 17 March 2005
Last patient discontinued: 15 December 2006

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice.

Drug product:	GALIDA	**SYNOPSIS**	
Drug substance(s):	Tesaglitazar		
Document No.:	CV.000-441-005		
Edition No.:	1.0		
Study code:	D6160C00038		
Date:	19 May 2008		

An Open-Label, Multi-Centre and Long-Term Extension Study to Evaluate the Safety and Tolerability of Oral Tesaglitazar 1 mg in Patients with Type 2 Diabetes Mellitus

GALLEX 1

Study centres

The study was conducted in 973 patients at 164 study centres in 23 Countries (Australia: 20; Canada: 18; Czech Republic: 9; Estonia: 5; Finland: 20; Hong Kong: 1; Hungary: 8; India: 5; Indonesia: 3; Israel: 7; Republic of Korea: 5; Latvia: 1; Malaysia: 1; Netherlands: 8; Philippines: 11; Poland: 5; Russian Federation: 7; Singapore: 3; Slovakia: 4; South Africa: 8; United Kingdom: 35; United States: 10 and Vietnam: 2).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	17 March 2005	Therapeutic confirmatory (III)
Last patient discontinued*	15 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 long-term safety and tolerability of tesaglitazar 1 mg, with or without other oral anti-diabetic drugs, when administered for up to 104 weeks in an extension study from the GALLANT 2/22, 5, 7, 8 and 14 studies in patients with type 2 diabetes by evaluation of:

- 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 rate) and
- Body weight.

Secondary objectives

To evaluate the effect of tesaglitazar 1 mg, with or without other oral anti-diabetic drugs, when administered for up to 104 weeks in an extension study from the GALLANT 2/22, 5, 7, 8 and 14 studies in patients with type 2 diabetes:

1. In modifying glycaemic control by assessment of:

- Changes in glycaemic variables:
  - Fasting plasma glucose (FPG) and
  - Glycosylated haemoglobin A_{1c} (HbA_{1c}).

2. In modifying lipid control by assessment of:

- Changes in lipid variables:
  - Triglycerides (TG),
  - Total cholesterol (TC),
  - Low density lipoprotein-cholesterol (LDL-C),

- High density lipoprotein-cholesterol (HDL-C) and
- non-HDL-C.

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

4. On central obesity by assessment of:

- Waist circumference,
- Hip circumference and
- Waist-hip ratio.

Study design

This study was to be a long-term extension of the GALLANT 2/22, 5, 7, 8 and 14 studies. The GALLEX 1 study evaluated the long-term safety and tolerability of 1 mg tesaglitazar. The study was an open-label, single-arm, multi-centre long-term extension of oral tesaglitazar (1 mg) treatment, with or without other oral anti-diabetic drugs in patients with type 2 diabetes. The total study duration including the treatment period (104 weeks) and follow-up period (3 weeks) was to be a maximum of 107 weeks.

Patients on placebo in preceeding GALLANT studies were switched to tesaglitazar 1 mg when entering GALLEX 1.

Due to the termination of the study, the Investigators were to let the next scheduled visit be the End of Treatment (EOT) Visit. Patients who had completed 12 weeks of GALLEX 1 treatment had to complete an additional two Follow-up Visits, 12 weeks and 24 weeks after the EOT Visit. Subsequently, the study duration could have been a potential maximum of 128 weeks.

Target patient population and sample size

Men and women with type 2 diabetes who participated in and completed the last two visits of the randomised treatment period of the GALLANT 2/22, 5, 7, 8 or 14 studies were considered eligible for the GALLEX 1 study. The patients in GALLANT 2/22 were drug-naïve and those in GALLANT 5 and GALLANT 14 were drug-naïve or previously treated with a single oral anti-diabetic drug. Patients in GALLANT 7 and GALLANT 8 were previously treated with a single oral anti-diabetic drug or combination therapy.

Since GALLEX 1 was an extension study, no formal sample size calculations were made.

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

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

Duration of treatment

The planned duration of treatment was to be 104 weeks with a Follow-up Visit 3 weeks after EOT.

However, due to the termination of the tesaglitazar development programme, additional safety Follow-up Visits were implemented at 12 and 24 weeks after EOT and the maximum duration of the study could be a potential 128 weeks.

Criteria for evaluation (main variables)

For both the Safety and ITT analysis sets Baseline assessments for the different categories of variables are defined as all measurements and derived parameters assessed at the randomisation visit of the relevant GALLANT study.

Efficacy

Efficacy was evaluated by assessing the change from Baseline for HbA_{1c}, FPG, TG, TC, LDL-C, HDL-C, non-HDL-C, ratio LDL-C/HDL-C, ratio TG/HDL-C, CRP and the waist-hip ratio.

Safety

The safety variables included AEs, clinical laboratory values, physical examination, cardiac evaluation (including New York Heart Association [NYHA] classification), hypoglycaemic events, ECG, vital signs (blood pressure and pulse rate) and body weight.

Statistical methods

All analyses were based on observed data only. No imputation was made for missing data. All percentages were calculated based on the total number of patients with available data in the respective treatment group.

No subgroups were defined.

Patient population

Approximately 1500 to 2100 patients were expect to enrol in GALLEX 1, but due to the termination of the tesaglitazar programme, only 973 patients were subsequently enrolled in the GALLEX 1 study. Of the 973 enrolled patients, 931 patients completed the study by attending all 3 Follow-up Visits. Due to the termination of the GALLEX 1 study, all 973 enrolled patients discontinued their participation from the study during the treatment period, with the major reason recorded under 'other'. The first patient entered the study on 17 March 2005, whilst the last patient visit was conducted on 15 December 2006.

The majority of the patients (70.1%) were Caucasian. Slightly more males (53.5%) than females (46.5%) were enrolled in the study. The ages of the patients ranged from 21 years to 92 years, with an overall mean of 57.8 years.

Of the 973 enrolled patients, 967 (99.4%) patients were included in the Safety analysis set and 965 (99.2%) patients in the Intention to Treat (ITT) analysis set.

In total, 5.7% of the patients entered the relevant handling plans. Most of these patients entered the handling plan for serum creatinine (S-creatinine).

Efficacy results

Since this study was a long-term extension of the GALLANT 2/22, 5, 7, 8 and 14 studies, the primary objective was to assess the safety and tolerability of tesaglitazar. The secondary objective was to assess the effect of tesaglitazar by primarily evaluating glycaemic control, lipid control and central obesity in patients enrolled in GALLEX 1.

The results showed that tesaglitazar 1 mg treatment notably improved blood lipids as measured by the relative changes in TG, HDL-C and non-HDL-C. However, since this was a single arm study, no definitive conclusion regarding the effect of tesaglitazar treatment could be drawn from this study alone. Tesaglitazar significantly reduced HbA_{1c} and FPG. The results suggest that 1mg tesaglitazar orally, once daily could be effective in maintaining glycaemic and lipid control during this study.

Safety results

Due to early termination of the GALIDA study programme and subsequently of the GALLEX 1 study, exposure to treatment was shorter than planned. The majority of patients (94.7%) received 1 mg tesaglitazar in GALLEX 1 for less than 1 year instead of the planned 104 weeks (2 years).

The number of patients with serious adverse events (SAEs) (44 [4.6%] patients) was low and the majority of the events was considered not related to tesaglitazar treatment. Three patients died during the study; one patient (acute renal failure) during the treatment period and two patients during the follow-up period (cerebrovascular accident, renal and hepatic failure); none of the events was considered related to tesaglitazar treatment. No safety concerns were raised regarding the number or distribution of AEs, physical examination and cardiac evaluation findings. Similarly, the number of patients (42 [4.3%] patients) who withdrew from the study due to AEs was low.

Overall, 55 (5.7%) of the Safety patients entered a relevant handling plan, primarily serum creatinine (S-creatinine), whilst 17 (1.7%) of these patients were discontinued from the study.

Fifteen patients had serious cardiovascular AEs. None of these events were considered related to tesaglitazar treatment. For 6 patients, new onset or worsening of congestive heart failure (CHF) was recorded.

Changes in clinical laboratory results were generally not notable. However, increases in mean S-creatinine levels and decreases in mean estimated glomerular filtration rate (eGFR) from Baseline to the EOT Visit was observed. Decreases in the mean alkaline phosphatase (ALP) and mean absolute neutrophil count (ANC) levels were also noted. Although increases or

decreases were observed in other laboratory evaluations, the changes were not notable and the majority reversed towards baseline after the EOT Visit.

Only 1 (0.1%) patient had a major hypoglycaemic event and the number of patients with minor hypoglycaemic events was low (38 [3.9%] patients).

Abnormal physical findings observed during the study were mostly ankle oedema and dyspnoea on exertion. A notable increase was noted for mean weight, but mean weight decreased again after the EOT Visit. No clinically notable changes from Baseline were observed for the mean systolic and diastolic blood pressures or pulse rate.

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, and that tesaglitazar consistently increases S-creatinine and decreases in eGFR.