AstraZeneca

Abbreviated Clinical Study Report	
Drug substance:	Tesaglitazar
Document No.:	CV.000-442-485
Edition No.:	1.0
Study code:	D6160C00049
Date:	19 May 2008

An Open-label, Multi-Centre, Long-Term Extension Study to Evaluate the Safety and Tolerability of Oral Tesaglitazar 0.5 mg When Added to Insulin Therapy in Patients with Type 2 Diabetes Mellitus

GALLEX 9

Abbreviated Clinical Study Report

Study dates: First patient enrolled: 15 February 2005
Last patient discontinued: 14 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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GALLEX 9

Study centre(s)

This study was conducted in 241 patients in 57 study centres in the United States.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	15 February 2005	Therapeutic confirmatory (III)
Last patient discontinued*	14 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 evaluate the safety and tolerability of tesaglitazar 0.5 mg in combination with insulin, with or without other oral anti-diabetic drugs, when administered for at least 140 weeks in an extension study from the GALLANT 9 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 rate) and
- Body weight.

Secondary Objectives

To evaluate the effect of tesaglitazar 0.5 mg in combination with insulin, with or without other oral anti-diabetic drugs, when administered for at least 140 weeks in an extension study from the GALLANT 9 study in patients with type 2 diabetes:

1. In modifying glycaemic control by assessment of:

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

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, and
- Apolipoprotein (Apo) B/ApoA-1.

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

4. On central obesity by assessment of:

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

5. On urinary albumin excretion by assessment of microalbuminuria.

Study design

GALLEX 9 was to be a long-term extension study for patients who had completed participation in the 400 patient GALLANT 9 study. Both the GALLEX 9 study and the GALLANT 9 study were planned to evaluate the safety and tolerability of tesaglitazar.

The GALLEX 9 study was an open-label, multi-centre study of oral tesaglitazar 0.5 mg in combination with insulin, with or without other oral anti-diabetic drugs, in patients with type 2 diabetes. The total study duration including the treatment period (140 weeks) and follow-up period. The post-treatment follow period was changed by protocol amendment from 3 weeks to 24 weeks.

Patients who had received placebo in GALLANT 9 were switched to tesaglitazar 0.5 mg when entering GALLEX 9.

Target patient population and sample size

Patients who participated in GALLANT 9 and completed Visits 8 and 9 were asked to participate in the GALLEX 9 long term extension study.

The GALLANT 9 study enrolled patients who had been diagnosed with type 2 diabetes less than 20 years prior to screening, and had been treated with at least 30 units (U) of insulin daily, with or without other oral anti-diabetic agents.

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

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

Duration of treatment

The planned study duration of the GALLEX 9 study was to including the treatment period (140 weeks) and the 3 Follow-up Visits (24 weeks), and thus was to be a potential maximum of 164 weeks.

Criteria for evaluation (main variables)

Efficacy

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

Baseline is defined as either Visit 3 during GALLANT 9 (for patients who previously received tesaglitazar) or Visit 1 of GALLEX 9 (for patients who did not receive tesaglitazar previously).

Safety

The safety variables included AEs, laboratory values, physical examination, cardiac evaluation, hypoglycaemic events, ECG, vital signs (BP and pulse), and body weight.

Statistical methods

The time course of safety and pharmacodynamic laboratory variables is described by summary statistics or other methods, as appropriate. Other safety-related variables, such as physical examinations, waist-to-hip ratio and ECG tests are summarised by descriptive statistics, tabulations and/or listings. A detailed description of methods is given in the Statistical Analysis Plan (SAP), 27 November 2007.

Patient population

Existing GALLANT 9 centres that agreed to participate in GALLEX 9 asked their GALLANT 9 patients (who had completed Visit 8 and Visit 9) to participate in this long-term extension study. The GALLEX 9 study included 57 study centres from the United States.

Because the GALLEX 9 study was terminated prematurely by AstraZeneca, the planned enrolment of patients was not achieved.

Of the 241 patients enrolled in GALLEX 9; all patients discontinued their participation from the study during the treatment period, 225 patients completed the follow-up visits, and 187 of those patients discontinued due to AstraZeneca's decision to terminate the tesaglitazar

programme. The first patient entered the study on 15 February 2005, whilst the last patient visit was conducted on 14 December 2006.

The majority of the patients were Caucasian. Slightly more males (53.8%) than females (46.2%) were enrolled in the study. The ages of the patients ranged from 28 years to 82 years, with an overall mean of 56.1 years.

Of the 241 enrolled patients, 238 (98.8%) patients were included in the Safety analysis set and 238 (98.8%) patients in the Intention to Treat (ITT) analysis set.

In total, 7.5% of patients entered the relevant handling plans. Most of these patients entered the handling plan for increased serum creatinine (S-creatinine) levels.

Efficacy results

Due to premature termination of the study, no per protocol analysis set was defined, and efficacy variable were summarized using descriptive statistics for ITT analysis set only. No formal conclusions were made regarding the efficacy data. The secondary objective of the study was to evaluate the effect of 0.5 mg tesaglitazar in combination with insulin, with or without other oral anti-diabetic drugs, when administered for up to 140 weeks in an extension study from the GALLANT 9 study in patients with type 2 diabetes. The efficacy of tesaglitazar was assessed primarily by the glycaemic control, lipid control and central obesity in patients enrolled in GALLEX 9.

An absolute mean decrease from Baseline to the EOT visit for A1c (0.44%) and FPG (1.12 mmol/L) was observed.

A mean decrease from Baseline to EOT of approximately 11% in TG levels was observed. Similarly HDL-C levels showed a mean increase of approximately 10% from Baseline to EOT. A mean decrease of 16% was noted for the TG/HDL-C ration from baseline to EOT. Non-HDL-C levels showed a mean decrease of approximately 7% from Baseline to EOT.

A mean decrease of approximately 10% from Baseline to EOT for CRP was observed. No notable changes from Baseline were observed for the waist-hip ratio.

Safety results

Due to the early termination of the GALIDA study programme and the associated premature termination of the GALLEX 9 study, exposure to treatment was shorter than planned and only descriptive analysis of safety data was performed, and summarized in this report. No formal conclusions were made regarding the safety data.

Eighteen patients had serious adverse events (SAEs) reported during the GALLEX 9 treatment period [7.6%]. The majority of these events were considered by the investigator to

be not causally related to the investigational product. There was 1 patient who died during the post-treatment study follow-up period due to cardiac arrest, which the investigator considered related to tesaglitazar treatment.

.No other safety concerns were raised regarding the number or distribution of AEs, physical examination and cardiac evaluation findings. The number of patients who discontinued from the study due to AEs was low: 10 patients [4.2%] discontinued study participation due to AEs during the treatment period and 4 patients [1.7%] discontinued study participation due to AEs during the 24 week post-treatment follow-up period). In total, 18 (7.5%) of patients entered a relevant handling plan, and 6 of these patients were discontinued from a handling plan.

Increases in mean serum creatinine (S-creatinine) levels and decreases in mean estimated glomerular filtration rate (eGFR) from baseline to the EOT Visit were observed. Decreases in the mean alkaline phosphatse (ALP) and mean absolute neutrophil count (ANC) levels were noted. Changes in laboratory results were generally not clinically significant and reversed toward baseline values during follow up.

None of the renal-related AEs was considered related to tesaglitazar treatment, and only one event was considered serious (acute renal failure). Only 4 (1.7%) patients had major hypoglycaemic events, and 74 (31.1%) patients reported minor hypoglycaemic events.

Abnormal potentially cardiac-related findings observed during the study were mostly ankle oedema and dyspnoea on exertion. An increase in mean weight was observed, which decreased again after the EOT Visit. No clinically notable changes from baseline were observed for mean systolic and diastolic blood pressure or pulse rate.