Abbreviated Clinical Study Report	
Drug substance:	Tesaglitazar
Document No.:	CV.000-441-013
Edition No.:	1.0
Study code:	D6160C00026/ D6160C00055
Date:	19 May 2008

A 24-Week Randomised, Double-Blind, Parallel-Group, Multi-Centre, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Tolerability of Tesaglitazar Therapy when Administered as Monotherapy to Drug-Naïve Patients with Type 2 Diabetes

GALLANT 2/22

Abbreviated Clinical Study Report

Study Dates: First patient enrolled: 01 September 2004
Last patient discontinued: 12 December 2006

Phase of Development: Therapeutic confirmatory III

This study was performed in compliance with Good Clinical Practice.

This submission / document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Drug product:	GALIDA	**SYNOPSIS**	
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A 24-Week Randomised, Double-Blind, Parallel-Group, Multi-Centre, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Tolerability of Tesaglitazar Therapy when Administered as Monotherapy to Drug-Naïve Patients with Type 2 Diabetes

GALLANT 2/22

Study centres

The study was conducted at 164 study centres in 15 Countries (Australia: 8; Czech Republic: 10; Estonia: 8; Finland: 16; France: 14; Greece: 3; Hungary: 13; Latvia: 7; Lithuania: 7; Norway: 12; Philippines: 4; Poland: 41; Serbia and Montenegro: 1; Slovakia: 10 and Sweden: 10).

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*	12 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 compare the efficacy of tesaglitazar (0.5 mg and 1 mg) given as monotherapy for 24 weeks to patients with type 2 diabetes with placebo in improving glycaemic control as determined by the absolute change in glycosylated haemoglobin A_{1c} (HbA_{1c}), from Baseline to the end of the randomised treatment period.

Secondary objectives

To compare the effect of tesaglitazar (0.5 mg and 1 mg) monotherapy versus placebo when administered for 24 weeks in patients with type 2 diabetes:

1. 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,
        - Apo CIII,
        - Free fatty acids (FFA) and
        - Lipoprotein particle size and concentration.
2. In modifying other markers of glycaemic control by assessment of:
    - Change in glycaemic variables:
        - Fasting plasma glucose (FPG),
        - Insulin,
        - Proinsulin and
        - C-peptide.

- Insulin sensitivity by assessment of:
  - Homeostasis Model Assessment (HOMA).

3. On risk markers for cardiovascular disease by assessment of:
   - LDL-C/HDL-C ratio,
   - Tumour necrosis factor-alpha (TNF-α) and
   - Intracellular adhesion molecule-1 (ICAM-1).
4. On inflammatory markers by assessment of C-reactive protein (CRP).
5. On thrombosis/coagulation markers by assessment of fibrinogen.
6. On urinary albumin excretion by assessment of:
   - Number of patients with microalbuminuria.
7. On central obesity by assessment of:
   - Waist-hip ratio.
8. On the safety and tolerability of tesaglitazar monotherapy 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 rate) and
   - Body weight.

9. On patient-reported outcomes (PROs) by evaluating, in a sub sample:

- Well-Being Questionnaire (W-BQ12) and
- The Audit of Diabetes Dependent Quality of Life (ADDQoL).

10. To evaluate the pharmacokinetics of tesaglitazar monotherapy (0.5 mg and 1 mg).

Study design

The study design of GALLANT 2 was identical to GALLANT 22 and consequently the two studies were analysed together. The reason for using two different Clinical Study Protocols (CSPs) was administrative. In the GALLANT 2 Clinical Study patients were planned to be recruited from Finland and Poland, in the latter country by screening the population. In the GALLANT 22 Clinical Study the population-screening part was deleted and the patients were recruited from more than 90 study centres in approximately 10 countries.

This study was a 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled study of tesaglitazar (0.5 mg and 1 mg) in patients with type 2 diabetes, not adequately controlled on diet and life-style advice alone during the placebo run-in period.

Target patient population and sample size

Male and female patients with type 2 diabetes who were 18 years of age at the enrolment visit (Visit 1) and had not used any anti-diabetic treatment during the previous 24 weeks.

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 (tablets).

Placebo: Matching placebo once daily in oral form (tablets).

Duration of treatment

The planned treatment duration of the study was to be 24 weeks.

The total study duration including the placebo run-in period (6 weeks), randomised treatment period (24 weeks) and Follow-up visits (3 weeks, 12 weeks and 24 weeks) was to be a potential maximum of 48 weeks (Protocol Amendment 2).

Criteria for evaluation (main variables)

Efficacy

- Primary variable: HbA_{1c}.

- Secondary variables:
  - TG, TC, LDL-C, HDL-C, very low-density lipoprotein cholesterol (VLDL-C), non-HDL-C, ApoB, ApoA-I, ApoCIII, FFA, HDL particle size, LDL particle size, VLDL particle size, HDL particle concentration, LDL particle concentration, VLDL particle concentration, TG/HDL-C ratio
  - Glycaemic control: FPG, insulin, proinsulin, C-peptide, HOMA;
  - Risk markers for cardiovascular disease: LDL-C/HDL-C ratio, TNF-α, ICAM-1;
  - Inflammatory markers: CRP;
  - Thrombois/Coagulation markers: Fibrinogen;
  - Assessment of urinary excretion: Quantitative urine albumin, quantitative urine creatinine;
  - Assessment of central obesity: Waist-hip ratio.

Safety

Safety was assessed by evaluating AEs, hypoglycaemic events, clinical laboratory assessments (haematology, clinical chemistry and urinalysis), ECG, vital signs, cardiac evaluation and physical examination.

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.

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.

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

For both the Safety and ITT analysis sets Baseline assessments for the different categories of variables are defined as Visit 5 GALLANT2/22. If the Visit 5 observation is missing, then Baseline is defined as the last observation before the first administration of the investigational product. If the value of the specified post-baseline visit is missing, no change will be calculated.

The pharmacokinetic analysis was not done due to early termination of the development programme.

Patient population

A total of 1800 patients were planned for enrolment in order to ensure that a total of 555 patients would be randomised at an estimated drop-out rate of 69% during the placebo run-in period. An equal number of patients (185 patients per treatment arm) were to be allocated to each of the 3 treatment arms, 0.5 mg and 1 mg tesaglitazar as well as placebo. Of the 555 randomised patients needed, approximately 80 were to be randomised in GALLANT 2 and approximately 475 in GALLANT 22.

A total of 2276 patients were enrolled in GALLANT 2/22 of which 453 patients were randomised. Overall, 445 (98.2%) of the randomised patients completed the study by completing all three the Follow-up Visits, whilst 310 (68.4%) patients discontinued their participation from the study.

The majority of patients were Caucasian and overall the male to female ratio (49.2% versus 50.8%) was comparable. For the majority of patients a body mass index of > 30 kg/m^2 was calculated, with a maximum of 84 kg/m^2 is this calculation checked and confirmed? in the Tesaglitazar 1 mg treatment group. In total, 96% of patients did not have pre-existing congestive heart failure. The majority of patients did not smoke (82.9%) nor did they use alcohol (62.7%).

Of the 453 randomised patients, 451 (99.6%) patients were included in the Safety analysis set and 450 (99.3%) patients in the ITT analysis set.

Only 2% of the patients entered handling plans, primarily for creatinine kinase and liver function tests.

The study was terminated by the Sponsor (AstraZeneca) because of the decision to terminate the tesaglitazar development programme.

Efficacy results

The primary efficacy data presented in this report show that the absolute change from Baseline to the End of Treatment (EOT) Visit in HbA_{1c} was clinically meaningful in both Tesaglitazar (1 mg and 0.5 mg) treatment groups. The mean change in HbA_{1c} was observed to be dose-related. Furthermore, both Tesaglitazar treatment groups appeared to perform better (larger decrease in HbA_{1c}) than the Placebo treatment group.

Both Tesaglitazar treatment groups showed notable improvements in blood lipids, when compared to Placebo, as measured by the relative change from Baseline in TG, HDL-C and non-HDL-C. The Tesaglitazar 1 mg treatment group showed the largest decrease in TG, the largest increase in HDL-C and the largest decrease in non-HDL-C.

Overall, Tesaglitazar 1 mg treatment showed the greatest efficacy, followed by Tesaglitazar 0.5 mg treatment, when compared to Placebo.

Safety results

The safety data presented in this report generally support findings from previous Phase I-III studies, namely that tesaglitazar is generally safe and tolerated in the patient population studied.

The overall AE profiles were generally similar between the two Tesaglitazar treatment groups and the Placebo treatment group. The number of patients with serious AEs (SAEs) (17 [3.8%] patients) and DAEs (8 [1.8%] patients) during the randomised treatment period was low. There were no deaths during the study.

More patients in the two Tesaglitazar treatment groups than in the Placebo treatment group reported SAEs, and the number of patients with SAEs was similar between the two Tesaglitazar treatment groups. None of the SAEs were considered related to the investigational product, but the majority was considered moderate to severe. More patients discontinued from the study due to AEs (DAEs) in the Tesaglitazar 0.5 mg treatment group compared to Tesaglitazar 1 mg and Placebo treatment groups. Most of the DAEs were considered related to the investigational product.

Changes in clinical laboratory values were more pronounced in the two Tesaglitazar treatment groups compared to Placebo. Increases in S-creatinine levels were larger in the Tesaglitazar 1 mg treatment group compared to Tesaglitazar 0.5 mg, whilst the proportion of patients with increases was comparable between the three treatment groups. Slight dose-related mean decreases in eGFR were noted across the three treatment groups. The mean decrease in eGFR was larger for patients in the two Tesaglitazar treatment groups. The number of patients with renal-related AEs was low and none of the events were considered serious.

No major hypoglycaemic events were recorded and the number of minor events was low (0.7%).

No obvious trend in the mean changes from Baseline was observed for the vital signs data. Although a notable increase in mean weight was observed for patients in the Tesaglitazar treatment groups, the weight values returned to Baseline after EOT.

The proportion of patients with abnormal ECG findings increased from Baseline to EOT in all three treatment groups.