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A 24-Week Randomised, Double-Blind, Multi-Centre, Active-Controlled (pioglitazone) Study to Evaluate the Efficacy, Safety and Tolerability of Tesaglitazar Therapy when Administered to Patients with Type 2 Diabetes (GALLANT 6)

Study dates: First patient enrolled: 02 August 2004
Last patient visit: 13 January 2006

Phase of development: Therapeutic confirmatory IIIa

This study was performed in compliance with Good Clinical Practice.

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Drug product:	GALIDA	**SYNOPSIS**	
Drug substance(s):	Tesaglitazar		
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A 24-Week Randomised, Double-Blind, Multi-Centre, Active-Controlled (pioglitazone) Study to Evaluate the Efficacy, Safety and Tolerability of Tesaglitazar Therapy when Administered to Patients with Type 2 Diabetes (GALLANT 6)

Study centre(s)

This global study was conducted at 218 centres located in the United States of America (123 centres), Canada (23 centres), Mexico (13 centres), Brazil (10 centres), Finland (08 centres), Norway (22 centres), and the United Kingdom (19 centres).

Publications

None at the time of this report

Study dates		**Phase of development**
First patient enrolled	02 August 2004	Therapeutic confirmatory (IIIa)
Last patient completed	13 January 2006	

Objectives

The primary objective was to determine, in patients with type 2 diabetes, whether monotherapy with the high dose of tesaglitazar (1 mg) was noninferior to monotherapy with the high dose of pioglitazone (45 mg) in improving glycaemic control, as measured by the absolute change from baseline in glycosylated haemoglobin (HbA_{1c}) after 24 weeks of randomised treatment.

The secondary objectives were:

1. To assess whether the efficacy of monotherapy with tesaglitazar (0.5 mg and 1 mg) is noninferior to the efficacy of monotherapy with pioglitazone (15 mg and 30 mg) in improving glycaemic control as measured by the absolute change in HbA_{1c} from baseline after 24 weeks of randomised treatment. There were 3 comparisons in this objective: tesaglitazar 1 mg vs pioglitazone 30 mg, tesaglitazar 0.5 mg vs pioglitazone 15 mg, and tesaglitazar 0.5 mg vs pioglitazone 30 mg.

2. To compare the effects of tesaglitazar (0.5 mg and 1 mg) monotherapy vs pioglitazone (15 mg, 30 mg, and 45 mg) monotherapy in modifying lipids and lipoproteins in patients with type 2 diabetes after a 24-week randomised treatment period by evaluation of:

   - The change from baseline to the end of the randomised treatment period in lipid and lipoprotein variables

   - Responder rates as determined by the proportion of patients meeting a pre-specified change from baseline to the end of the randomised treatment period, for triglycerides (TG), high density lipoprotein-cholesterol (HDL-C),
     non-HDL-C and low density lipoprotein-cholesterol (LDL-C)

   - Proportion of patients reaching pre-specified target levels for TG, HDL-C, non-HDL-C and LDL-C

3. To compare the effects of tesaglitazar (0.5 mg and 1 mg) monotherapy vs pioglitazone (15 mg, 30 mg, and 45 mg) monotherapy in modifying other markers of glycaemic control in patients with type 2 diabetes after a 24-week randomised treatment period by evaluation of:

   - The change in fasting plasma glucose (FPG) and insulin from baseline to the end of the randomised treatment period

   - Insulin sensitivity by assessment of change in the calculated variable Homeostasis Assessment Model (HOMA) from baseline to the end of the treatment period

   - The responder rates and proportion of patients meeting a pre-specified target levels from baseline to the end of the randomised treatment period for both HbA_{1c} and FPG

4. To compare the effects of tesaglitazar (0.5 mg and 1 mg) monotherapy vs pioglitazone (15 mg, 30 mg, and 45 mg) monotherapy on the levels of CRP and levels of inflammatory markers in patients with type 2 diabetes, as well as on the level of a marker of thrombosis/coagulation (fibrinogen) in a subset of patients, after a 24-week randomised treatment period.

5. To assess the effects of tesaglitazar (0.5 mg and 1 mg) monotherapy vs pioglitazone (15 mg, 30 mg, and 45 mg) monotherapy on the waist-hip ratio in patients with type 2 diabetes after a 24-week randomised treatment period.

6. To assess the effects of tesaglitazar given as monotherapy as compared to pioglitazone as monotherapy in patients with type 2 diabetes on patient-reported outcomes (PROs) using the Medical Outcomes Study Short Form-36 (SF-36).

7. To validate the Work Productivity and Activity Impairment-Diabetes Questionnaire (WPAI-Diabetes) and the Diabetes Productivity Impairment Questionnaire (DPIQ) (US only).

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

9. To evaluate the safety and tolerability by assessment of adverse events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycaemic events, body weight, cardiac evaluation, and physical examination.

Study design

This was a 24-week randomised, double-blind, multi-centre, active-controlled (pioglitazone 15, 30, and 45 mg) study of tesaglitazar (0.5 mg and 1 mg) in patients with type 2 diabetes, who were not adequately controlled on diet and life-style advice alone during the run-in period.

Target patient population and sample size

Men or women who were ≥18 years of age at Visit 1 and had been diagnosed with type 2 diabetes and treated with diet alone or were on treatment with a single oral anti-diabetic agent or low doses of 2 anti-diabetic agents were recruited for this study.
The primary outcome variable was the absolute change in HbA_{1c} from baseline to the end of the randomised treatment period. A total of 259 randomised and evaluable patients per treatment arm with type 2 diabetes, derived from an estimated 1450 randomised patients, were required to reject the null hypothesis of inferiority of tesaglitazar in the absolute percent change of HbA_{1c} by 0.4% or more with 90% power.

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

Tesaglitazar 0.5 or 1 mg once daily in oral form (tablets). Matching placebo once daily in oral form (tablets). Pioglitazone 15, 30, or 45 mg once daily in oral form (capsules). Matching placebo once daily in oral form (capsules). The following batch numbers were used: Tesaglitazar/Placebo H 1428-05-01-01, H 1428-05-01-02, H 1428-05-01-03, H 1428-05-01-11, H 1428-05-01-12; Tesaglitazar 0.5 mg H 1434-05-01-01, H 1434-05-01-05, H 1434-05-01-06; Tesaglitazar 1 mg H 1467-04-01-01, H 1467-04-01-04, H 1467-04-01-06; Pioglitazone 15 mg H 1598-01-01-02, H 1598-01-01-03, H 1598-01-01-04; Pioglitazone 30 mg H 1564-03-01-02, H 1564-03-01-03, H 1564-03-01-04; Pioglitazone 45 mg H 1599-01-01-01, H 1599-01-01-03, H 1599-01-01-06; and, Pioglitazone/placebo H 1600-01-01-03, H 1600-01-01-04, H 1600-01-01-05.

Duration of treatment

After a 6-week placebo single-blind run-in period, patients were randomised at Visit 6 (baseline) and the double-blind investigational product period was initiated. Either tesaglitazar (1 mg, 0.5 mg) or pioglitazone (45 mg, 30 mg, 15 mg) was taken daily for

24 weeks. At the end of the randomised treatment period (Visit 12), patients who completed the 24-week treatment period and met eligibility criteria were transferred to a long-term extension (LTE) study. Patients not entering the LTE were to complete a follow-up visit (Visit 13).

Criteria for evaluation (main variables)

Efficacy and pharmacodynamics

Primary variable: Absolute change from baseline in HbA_{1c} after 24 weeks of treatment (tesaglitazar 1 mg vs pioglitazone 45 mg)
Secondary variables: Absolute change in HbA_{1c} from baseline to after 24 weeks of randomised treatment (3 comparisons: tesaglitazar 1 mg vs pioglitazone 30 mg; tesaglitazar 0.5 mg vs pioglitazone 15 mg; and, tesaglitazar 0.5 mg vs pioglitazone 30 mg)
Change from baseline to the end of the randomised treatment period (Week 24) in lipid and lipoprotein variables: TG, HDL-C, non-HDL-C, LDL-C, LDL-C/HDL-C, TG/HDL-C, total cholesterol (TC), apolipoprotein (Apo)A-I, ApoB, ApoB/ApoA-I, ApoCIII, free fatty acids (FFA), lipoprotein particle size and concentration.
Responder rates for TG and HDL-C, as determined by the proportion of patients meeting a prespecified change (A patient was defined as a responder if he/she achieved a relative decrease from baseline to the end of the randomised treatment period of 30% for TG and a relative increase from baseline to the end of randomised treatment of 10% for HDL-C).
Proportion of patients reaching target levels for TG and HDL-C (American Diabetes Association [ADA] treatment guideline for TG was <150 mg/dL, and for HDL-C was >40 mg/dL for males and >50 mg/dL for females).
Change from baseline to Week 24 in FPG and insulin
Insulin sensitivity as assessed by the change from baseline to Week 24 in HOMA
Responder rates and the proportion of patients reaching prespecified target levels for HbA_{1c} and FPG (A patient was defined as a responder if he/she achieved an absolute decrease from baseline to the end of the randomised treatment period of 0.7% for HbA_{1c} and 30 mg/dL for FPG. A patient achieved target treatment goals if he/she reached the ADA guideline for HbA_{1c} [<7.0%] and for FPG [90 to 130 mg/dL] at the end of the randomised treatment period).
Change from baseline to Week 24 in C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), intracellular adhesion molecule-1 (ICAM-1), and fibrinogen
Change from baseline to Week 24 in waist-hip ratio

Patient-Reported Outcomes (PROs)

Change from baseline to Week 24 on the SF-36
Validation analyses of the WPAI-Diabetes and DPIQ (US centres only)
Pharmacokinetics

Tesaglitazar plasma concentrations: all plasma concentrations collected during the dosing interval as well as concentrations at trough (16 to 32 hours after last previous intake of tesaglitazar).

Safety

Safety assessments included AEs, laboratory values, ECGs, vital signs (pulse and BP), physical examination, body weight, cardiac evaluation (assessment of cardiac function by history and physical examination, evaluation of signs and symptoms of congestive heart failure [CHF]), and hypoglycaemic events.

Genetic

A blood sample for deoxyribonucleic acid (DNA) preparation and further genetic analysis was taken. Patients who did not wish to participate in the genetic research were still eligible to participate in the study. (Genetic analysis was not part of the results for this study).

Statistical methods

The Full analysis set was used for all efficacy analyses. Analyses of HbA_{1c}, FPG, HDL-C, non-HDL-C, and TG were also performed using the Per Protocol (PP) analysis set as a sensitivity analysis to investigate conclusions of the analyses based on the Full analysis set. The robustness of the results of noninferiority comparisons was further assessed by analysis of the Completers set.

Noninferiority assessments were conducted for the primary efficacy variable: absolute change from baseline in HbA_{1c}. All other efficacy comparisons were evaluated in the context of superiority. The absolute change within treatment groups from baseline to the end of the randomised treatment period was analysed with a linear model using fixed-effect analysis of covariance (ANCOVA). A multiple comparison procedure was adopted to control the overall significance level of the study with respect to four key variables (HbA1c, TG, HDL-C, and non-HDL-C). All other tests assumed a 2-sided alternative and were performed at the 0.05 level of significance. All efficacy variables except HbA_{1c} and FPG were log-transformed before the ANCOVA analysis, unless otherwise indicated. Note that absolute change in the logarithmic scale corresponded to relative change from baseline in the nontransformed scale. The results were reported as p-values, estimates, and 2-sided 95% CIs.

PROs (SF-36) were analysed with linear models. The change from baseline to the last visit was analysed using ANCOVA with the baseline value as a covariate. The PRO instruments were scored according to their respective scoring algorithms. Two domains of the SF-36 were deemed primary: Physical Functioning and Vitality. The psychometric properties of both the WPAI-Diabetes and DPIQ instruments in the study population were also evaluated

Tesaglitazar plasma concentrations were presented using descriptive statistics, categorised by dose and visit. (A population pharmacokinetic analysis was planned as part of a pooled analysis across multiple studies, but was not conducted due to the discontinuation of the tesaglitazar programme).

No hypotheses were proposed a priori for safety-related variables. The safety analysis set was used for all safety analyses. All safety data were analysed and presented according to the treatment received; safety presentations were based on observed cases. Descriptive statistics were presented for all safety variables: AEs, clinical laboratory variables, ECG, vital signs, physical examination, body weight, cardiac evaluation, and hypoglycaemic events. Adverse events were summarised by MedDRA and presented by both SOC and

PT. The exposure to investigational product and the number of patients entering handling plans and discontinuing from the study due to handling plan-related criteria were also summarised.

Patient population

In total, 3945 patients entered the 6-week placebo single-blind, run-in period and 1707 patients from 218 centres were randomised to treatment. Of these randomised patients, 738 patients (43.2%) attended the follow-up visit (Visit 13) and 823 patients (48.2%) transferred to the LTE study. The first patient was enrolled in the study on 02 August 2004 and the last patient completed the randomised treatment phase on 08 February 2006. The majority of randomised patients were Caucasian (>87% for each treatment dose group). The male-to-female ratios were similar across the treatment dose groups; overall, 49.3% men and 50.7% women were randomised into the study. The age range of patients in the study was 20.0 to 85.0 years; the overall median age was 58.0 years. Patients had comparable baseline characteristics across the treatment dose groups, and the patient population enrolled in this study was representative of the target population for tesaglitazar.

A total of 15 randomised patients across the treatment dose groups received no study treatment and were not included in the Safety analysis set; thus, 1692 patients were evaluated for safety. Of these, 1666 were analysed for efficacy in the Full analysis set, 1318 were analysed for efficacy in the PP analysis set, and 1391 were analysed for efficacy in the Completers analysis set. Of the 1707 patients randomised to treatment, 330 patients (19.3%) discontinued the study during the randomised treatment period. The most common reasons for study discontinuation were the patient not willing to continue (6.3%) and the development of study specific discontinuation criteria (4.1%). The frequency of patients who discontinued study treatment due to AEs (3.2%) was highest in the tesaglitazar 1 mg and pioglitazone 30 mg dose groups (4.1% for each). The number of protocol deviations considered serious enough to warrant exclusion of data was generally distributed evenly across the treatment dose groups.

Efficacy and pharmacodynamic results

When evaluating the effect of a given dose of tesaglitazar to that of a given dose of pioglitazone, the majority of efficacy variables were assessed by the change from baseline after 24 weeks of treatment. All statistical comparisons were done on the magnitude of change, and the analyses performed did not compare the end of treatment values between the groups. Therefore, when statements regarding statistically significant results are provided in the text, it is implied, for example, that the change from baseline in the tesaglitazar group is greater than that for pioglitazone group or that the change from baseline in the pioglitazone group is greater than that for tesaglitazar group.

Summary statements for the efficacy results below are provided for the 4 main treatment dose comparisons (tesaglitazar 1 mg vs pioglitazone 45 mg, tesaglitazar 1 mg vs pioglitazone 30 mg, tesaglitazar 0.5 mg vs pioglitazone 30 mg, tesaglitazar 0.5 mg vs pioglitazone 15 mg).

The statistical results for HbA1c, TG, HDL-C, and non-HDL-C were based on a Bonferroni-Holm procedure for groups of hypotheses.

For the primary objective, tesaglitazar 1 mg demonstrated noninferiority to pioglitazone 45 mg, as measured by the absolute change from baseline in HbA1c at 24 weeks.

Secondary analyses on the PP and Completers analysis sets were supportive of the primary analyses.
Tesaglitazar 1 mg resulted in statistically significantly lower HbA1c at 24 weeks compared to pioglitazone 30 mg. Tesaglitazar 0.5 mg demonstrated noninferiority to pioglitazone 30 mg and resulted in statistically significantly lower HbA1c compared to pioglitazone 15 mg, as measured by the absolute change from baseline in HbA1c at 24 weeks.
Tesaglitazar 1 mg resulted in statistically significantly lower TG compared to pioglitazone 45 and 30 mg and tesaglitazar 0.5 mg resulted in statistically significantly lower TG at 24 weeks compared to pioglitazone 30 and 15 mg. Tesaglitazar 1 mg resulted in statistically significantly higher HDL-C at 24 weeks compared to pioglitazone 45 and 30 mg; HDL-C was not statistically significantly higher at 24 weeks in the tesaglitazar 0.5 mg dose group than in the pioglitazone 30 and 15 mg dose groups.
Tesaglitazar 1 mg resulted in statistically significantly lower non-HDL-C at 24 weeks compared to pioglitazone 45 and 30 mg, but statistical significance could not be established for non-HDL-C for tesaglitazar 0.5 mg at 24 weeks compared to pioglitazone 30 mg and 15 mg, primarily due to the placement of these treatment comparisons within the hierachial order of the multiple comparison procedure.
but other lipid variables were not statistically significant in favor of tesaglitazar 0.5 for the comparison with the pioglitazone 30 mg and 15 mg doses in the multiple comparison procedure.
All tesaglitazar vs pioglitazone dose group comparisons, with the exception of the tesaglitazar 0.5 mg vs pioglitazone 15 mg comparison, resulted in statistically significantly lower LDL-C for tesaglitazar at 24 weeks. All tesaglitazar vs pioglitazone dose group comparisons, with the exception of the tesaglitazar 0.5 mg vs pioglitazone 30 mg comparison, resulted in statistically significantly lower LDL-C/HDL-C at 24 weeks.
Tesaglitazar resulted in statistically significantly lower TG/ HDL-C at 24 weeks compared with pioglitazone for the 4 treatment dose comparisons. Tesaglitazar resulted in statistically significantly lower TC at 24 weeks compared with pioglitazone for the 4 treatment dose comparisons. Tesaglitazar resulted in a statistically significant increase in ApoA-I at 24 weeks only for the comparison for tesaglitazar 1 mg and pioglitazone 45 mg. Tesaglitazar resulted in statistically significantly lower ApoB, ApoCIII, and ApoB/ApoA-I at 24 weeks for the 4 treatment dose comparisons. Tesaglitazar resulted in a statistically significant decrease in FFA compared to pioglitazone at 24 weeks for all 4 treatment dose comparisons except tesaglitazar 0.5 mg and pioglitazone 30 mg.
Tesaglitazar resulted in a statistically significant increase in lipoprotein particle size (nm) at 24 weeks only for the comparisons of tesaglitazar 1 mg and pioglitazone 30 mg and tesaglitazar 0.5 mg and pioglitazone 30 mg. For particle concentration (number), tesaglitazar resulted in a statistically significant decrease at 24 weeks for all comparisons except tesaglitazar 0.5 mg and pioglitazone 30 mg.
Tesaglitazar resulted in statistically significantly higher responder rates for TG and HDL-C at 24 weeks for all 4 treatment dose comparisons except tesaglitazar 0.5 mg and pioglitazone 30 mg for HDL-C.
Tesaglitazar 1 mg resulted in statistically significantly higher rates for meeting ADA guidelines for TG and HDL-C at 24 weeks compared to pioglitazone 45 and 30 mg; tesaglitazar 0.5 mg resulted in statistically significantly higher rates of achievement for

TG, but not for HDL-C, compared to pioglitazone 30 and 15 mg. All tesaglitazar vs pioglitazone dose group comparisions, with the exception tesaglitazar 0.5 mg vs pioglitazone 45 mg, resulted in statistically significantly higher rates of achievement with tesaglitazar at 24 weeks when combining TG and HDL-C.

Tesaglitazar 1 mg resulted in statistically significantly lower FPG, insulin, and HOMA at 24 weeks compared to pioglitazone 45 and 30; tesaglitazar 0.5 mg resulted in statistically significantly lower FPG, insulin, and HOMA at 24 weeks compared to pioglitazone 15 mg but not compared to pioglitazone 30 mg.

With respect to the responder analyses in patients meeting pre-specified target levels for glycaemic variables, tesaglitazar 1 mg resulted in a statistically significantly higher responder rate for HbA1c at 24 weeks compared to pioglitazone 30 mg, but the responder rate for HbA1c was not significantly higher for tesaglitazar 1 mg compared to pioglitazone 45 mg. Tesaglitazar 0.5 mg resulted in a statistically significantly higher responder rate for HbA1c at 24 weeks compared to pioglitazone 15 mg, but the responder rate for HbA1c was numerically higher for pioglitazone 30 mg than for tesaglitazar 0.5 mg.

Tesaglitazar 1 mg resulted in a significantly higher responder rate for FPG at 24 weeks compared to pioglitazone 45 mg and 30 mg, whereas tesaglitazar 0.5 mg resulted in a significantly higher responder rate for FPG at 24 weeks compared to pioglitazone 15 mg. The responder rate for tesaglitazar 0.5 mg at 24 weeks was lower than that for pioglitazone 30 mg.

With respect to ADA guidelines for glycemic variables, the rate for HbA1c was not statistically significantly higher for tesaglitazar 1 mg compared to the pioglitazone 45 mg group at 24 weeks, but was statistically significant higher for the comparison to pioglitazone 30 mg. Tesaglitazar 0.5 mg resulted in a statistically significantly lower rate for HbA1c at 24 weeks compared to pioglitazone 30 mg, and to a numerically lower rate relative to pioglitazone 15 mg. For tesaglitazar 1 mg, the comparisons to pioglitazone 45 and 30 mg resulted in statistically significantly higher rates when combining HbA1c, TG, and HDL-C, whereas only the tesaglitazar 0.5 mg vs pioglitazone 15 mg dose group comparison resulted in a statistically significantly higher rate for tesaglitazar at 24 weeks when combining glycaemic and lipid guidelines. Tesaglitazar 1 mg resulted in a significantly higher rate for FPG at 24 weeks compared to pioglitazone 45 and 30 mg, but the rate for tesaglitazar 0.5 mg was not statistically significantly different compared to pioglitazone 30 or 15 mg.

Tesaglitazar 1 mg resulted in statistically significant lowering of CRP for cardiovascular disease at 24 weeks compared to pioglitazone 30 mg but not compared to pioglitazone 45 mg. Tesaglitazar 0.5 mg did not significantly lower CRP for cardiovascular disease at 24 weeks compared to pioglitazone 30 or 15 mg. Tesaglitazar did not significantly lower the inflammatory markers TNF-α or ICAM-1 at 24 weeks compared to pioglitazone for any of the 4 treatment dose comparisons. Tesaglitazar resulted in a statistically significant lowering of fibrinogen at 24 weeks compared to pioglitazone for all treatment dose comparisons.

Waist-hip ratio for patients receiving tesaglitazar 1 mg was not statistically significantly different compared to patients receiving pioglitazone 45 or 30 at 24 weeks, and that for patients receiving tesaglitazar 0.5 mg was not statistically significantly different at 24 weeks compared to patients receiving pioglitazone 30 or 15 mg.

PRO results

The SF-36 Physical Function domain met the established non-inferiority criteria for all but 2 of the planned treatment comparisons (tesaglitazar 1 mg vs pioglitazone 15 mg and tesaglitazar 0.5 mg vs pioglitazone 15 mg), whereas the SF-36 Vitality domain achieved non-inferiority for all planned treatment comparisons of tesaglitazar and pioglitazone. The majority of other SF-36 domains (role-physical score, bodily pain score, general health score, social functioning score, role-emotional score, mental health score, PCS score, and MCS score) achieved non-inferiority for the tesaglitazar doses when compared to the pioglitazone doses. The exception was for the tesaglitazar 1 mg dose compared to pioglitazone 15 mg dose on the SF-36 PCS score, where tesaglitazar 1 mg did not achieve non-inferiority.
The SF-36 demonstrated psychometric equivalence across the seven languages examined with alphas ranging from 0.61 to 0.94. Although there were a few baseline differences between countries in the SF-36 domains, correlations among subscales between countries were relatively high and all subscales showed good internal reliability across countries.
The WPAI-Diabetes demonstrated concurrent validity with small to moderate correlations with the SF-36 and DPIQ.
The 20-item DPIQ was reduced to a single 7-item subscale which demonstrated strong internal consistency with a Cronbach's alpha of 0.87 and concurrent validity with moderate correlations with the SF-36 and WPAI-Diabetes.
In both work productivity measures, the DPIQ and WPAI-Diabetes, very little impact on productivity was noted at baseline among the patients. As such, there was little room for improvement as evidenced by the change scores from Visit 6 to Visit 12. It appears that loss of productivity was not an issue for this patient sample.

Pharmacokinetic results

Mean (SD) plasma concentrations of tesaglitazar 0.5 mg at trough were 0.199 (0.102) µmol/L at Week 4, 0.219 (0.114) µmol/L at Week 12, and 0.218 (0.128) µmol/L at Week 24. The corresponding values after the 1.0 mg tesaglitazar dose regimen were 0.435 (0.206) µmol/L at Week 4, 0.509 (0.257) µmol/L at Week 12, and 0.509 (0.268) µmol/L at Week 24.

Safety results

The extent of exposure was balanced across the treatment dose groups, and the mean duration of exposure data was adequate for the evaluation of safety in this study. The frequency of patients experiencing AEs was highest in the tesaglitazar 1 mg dose group (78.7%) and lowest in the tesaglitazar 0.5 mg dose group (64.8%), and was relatively equally distributed across the pioglitazone dose groups. The most frequently reported AEs were oedema peripheral (6.4%), headache (5.7%), upper respiratory tract infection (5.4%), fatigue (5.3%), and back pain (5.2%). Three patients (1 tesaglitazar 1 mg, 2 pioglitazone 30 mg) died during the study; none of the deaths was considered by the investigator to be treatment-related. The frequency of SAEs and DAEs was low overall (3.7% and 5.1%, respectively). The number of patients who experienced hypoglycaemic events (major, minor or suggestive) was low overall (11 tesaglitazar, 7 for pioglitazone). One patient in the tesaglitazar 1 mg group experienced a major hypoglycaemic event, and the number of minor and suggestive hypoglycaemic events overall was slightly higher for

the tesaglitazar dose groups than for the pioglitazone dose groups. There were no clinically relevant differences among the treatment groups with respect to CV AEs. A small excess number of cases of CHF occurred with tesaglitazar 1 mg treatment compared with pioglitazone 45 mg; however, the number of patients represented was small. There were no CHF AEs or confirmed new or worsening cases of CHF for patients in the tesaglitazar 0.5 mg, pioglitazone 30 mg, or pioglitazone 15 mg groups. Patients in the tesaglitazar and pioglitazone groups reported weight gain (mean increase from baseline to Week 24 of 3.14 kg for tesaglitazar 1 mg and 3.27 kg for pioglitazone 45 mg) and oedema-related AEs; these appeared to be dose-dependent for both tesaglitazar and pioglitazone. A dose-dependent mean increase in serum creatinine and reduction in estimated GFR were observed in the tesaglitazar dose groups. Patients in the pioglitazone dose groups also had a mean increase in serum creatinine and reduction in estimated GFR; however, the changes were not dose-dependent and the magnitude of the changes were smaller than those seen with tesaglitazar. The frequency of renal-related AEs was generally low and distributed across the treatment dose groups. Treatment with tesaglitazar and pioglitazone was associated with dose-dependent decreases in haemoglobin and ANC as well as ALT and ALP, although the magnitude of the reductions was generally greater for tesaglitazar than for pioglitazone. Elevations in CK levels and the frequency of muscle-related AEs were generally low and distributed across the treatment dose groups. Patients treated with tesaglitazar 1 mg had a greater reduction in both systolic and diastolic BP from baseline to Week 24 compared to the other treatment dose groups. The majority of ECGs as well as physical examinations and cardiac evaluations were unchanged from baseline to the end of the randomised treatment period across the treatment dose groups.

Date of the report

30 March 2007