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Clinical Study Report

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Dose-finding, Efficacy, and Safety of AZ 242 in Subjects with Type 2 Diabetes

TITLE PAGE

Study dates:	First patient enrolled: 30 April 2002 Last patient completed: 20 June 2003
Phase of development:	Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice.

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Drug product: Drug substance(s): Study code: Date:	Tesaglitazar Tesaglitazar SH-SBD-001 03 November 2003	**SYNOPSIS**	

Dose-Finding, Efficacy, and Safety of AZ 242 in Subjects with Type 2 Diabetes

Study centre(s)

This study was conducted in the USA (99 centers), Canada (11 centers), France (13 centers), and Mexico (4 centers).

Publications

N/A

Study dates		**Phase of development**
First patient enrolled	30 April 2002	Therapeutic exploratory (II)
Last patient completed	20 June 2003	

Objectives

Primary:

to investigate the dose-response relationship of AZ 242 (tesaglitazar) in subjects with type 2 diabetes. The dose-response will be analyzed by the assessment of the effects of each of five doses of AZ 242 (0.1, 0.5, 1, 2, and 3 mg) to placebo with respect to fasting plasma glucose (FPG) after 12 weeks of randomized treatment.

Secondary:

(a) to estimate the effect of AZ 242 versus that of open-label ACTOS® (pioglitazone) on the reduction of FPG levels

(b) to compare the effects of AZ 242 with that of placebo and estimate the effect of ACTOS versus that of placebo on the following fasting lipid parameters: total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C) non-HDL-C (total cholesterol [TC] minus HDL-C), apolipoproteins (ApoAI, ApoB, and ApoCIII), triglycerides (TG), and free fatty acids (FFAs)

(c) to compare the effects of AZ 242 with that of placebo and estimate the effect of ACTOS versus that of placebo on glucose and insulin values during an oral glucose tolerance test.

(d) to compare the effects of AZ 242 with that of placebo and estimate the effect of ACTOS versus that of placebo on the reduction of insulin and hemoglobin A1c (HbA1c) levels.

(e) to compare the effects of AZ 242 with that of placebo on the proportion of FPG responders (ie, subjects with a decrease in FPG ≥30 mg/dL [≥1.7 mmol/L]). In addition, the proportion of subjects in each group who achieve FPG ≤140 mg/dL and ≤126 mg/dL (≤7.8 mmol/L and ≤7.0 mmol/L) will be described.

(f) to compare the effects of AZ 242 with that of placebo on the proportion of HDL-C responders (ie, subjects with an increase in HDL-C ≥5%) and TG responders (ie, subjects with a decrease in TG ≥15%).

(g) to evaluate the pharmacokinetics of AZ 242 in subjects with type 2 diabetes

(h) to assess the safety and tolerability of AZ 242 compared to placebo

(i) to assess the burden of type 2 diabetes mellitus in patients through the administration of the SF-36 health survey and the Well-Being Questionnaire (W-BQ12) and comparing the study population data to published national and international normative data for exploratory purposes

(j) to evaluate diabetes-specific instruments, Audit of Diabetes Dependent Quality of Life (ADDQoL) and The Diabetes Treatment Satisfaction Questionnaire (DTSQ) (s and c) in the study population and estimate the effect size of the instruments in patients receiving AZ 242, placebo, ACTOS for exploratory purposes

Study design

This was a randomized, double-blind, parallel group, multicenter study to determine the optimal dose of tesaglitazar (0.1, 0.5, 1, 2, and 3 mg) and to further define the efficacy, safety, and pharmacokinetics of tesaglitazar in comparison to placebo during a 12-week period of treatment in patients with type 2 diabetes mellitus. Open-label pioglitazone was also included in this study.

Target patient population and sample size

Male and female patients, 30 to 80 years of age, with type 2 diabetes mellitus
A total of 364 randomized and evaluable patients (52 per treatment group) with type 2 diabetes mellitus, derived from an estimated 400 recruited patients, were required for 90% power of detecting a 10% difference between groups with respect to change in logarithms of FPG from baseline to the end of the 12-week randomized treatment period.

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

Tesaglitazar (AR-H039242XX, AZ 242, GALIDA™) 0.1, 0.5, 1, 2, or 3 mg orally once daily (batch numbers H 1465-02-01-01, H 1434-03-01-01, H 1467-02-01-01, H 1427-03-01-01, and H 1493-02-01-01, respectively); placebo (batch H 1428-03-01-01) orally once daily; open-label pioglitazone 45 mg once daily (batch number 45157ZA). It should be noted that pioglitazone was not available in France so patients at sites in France were not randomized to this treatment.

Duration of treatment

12 weeks

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable was the change in the fasting level of plasma glucose from the randomization visit to the last randomized treatment evaluation (12-week treatment period).

- Secondary variables were changes from baseline in TG, TC, HDL-C, non-HDL-C, ApoAI, ApoB, ApoB/ApoAI, ApoCIII, LDL-C, VLDL-C, FFA, HbA1c, fasting plasma insulin (FPI), homeostatis model assessment (HOMA) model for insulin resistance index, and glucose and insulin after an oral glucose tolerance test (OGTT).

Safety

The safety variables were adverse events, clinical laboratory variables, vital signs, ECG, and physical findings.

Statistical methods

The primary efficacy analysis compared each of the 5 doses of tesaglitazar (0.1, 0.5, 1, 2, and 3 mg) to placebo with respect to ΔFPG measured at the end of the double-blind treatment period. The change from baseline in FPG was analyzed in a linear model using a fixed-effect analysis of covariance (ANCOVA).

Patient population

A total of 500 patients were randomized to treatment. The majority of randomized patients were Caucasian (>80% for each treatment group) and under 65 years of age, with slightly more men randomized to tesaglitazar than women (57.5% men versus 42.5% women). The age range of the patients was 30 to 80 years. Overall, the treatment groups were similar for demographic and baseline characteristics.
The disposition of the patients in the study, as well as the analysis groups evaluated in this CSR, is presented in Table S1.

Table S1 Patient disposition

		Tesaglitazar						
Population	**Placebo**	**0.1 mg**	**0.5 mg**	**1 mg**	**2 mg**	**3 mg**	**Total**	**Pio 45 mg**
Randomized	**70**	**72**	**73**	**70**	**70**	**73**	**358**	**72**
N of patients who completed	57	58	58	51	41	29	237	56
N of patients who discontinued	13	14	15	19	29	44	121	16
N analyzed for safety	70	72	72	70	70	73	351	72
N analyzed for efficacy (ITT)	67	71	72	69	69	69	350	68
N analyzed for efficacy (PP)	45	49	55	42	35	31	212	45

One randomized patient (tesaglitazar 0.5 mg) received no study treatment and was not included in the safety population; thus only 499 patients were evaluated for safety. Of these, 485 were analyzed for efficacy in the intent-to treat (ITT) population and 302 in the per protocol (PP) population.

A total of 121 patients (24.2%) randomized to treatment with tesaglitazar discontinued the study during the randomized treatment period, compared with 13 patients (18.6%) for placebo and 16 patients (22.2%) for pioglitazone. The most common reason for discontinuation was adverse events. The majority of adverse events leading to withdrawal were due to laboratory abnormalities categorized by the investigator as adverse events, including creatinine increased, hemoglobin decreased, and white blood cells decreased. It should be noted the original protocol was amended to specify investigators were required to discontinue patients who had a >50% increase in creatinine, a >2 g/dL decrease in hemoglobin, or an absolute neutrophil count (ANC) $<1.0 \times 10^9$ whether or not the absolute value remained within safe or normal limits or was associated with signs and symptoms of an adverse event.

Efficacy results

A dose-dependent reduction in FPG levels was observed following 12 weeks of treatment with tesaglitazar. The dose-response for FPG reductions was clinically relevant and statistically significant from tesaglitazar 0.5 mg up to 3 mg and did not appear to reach a plateau. Placebo-corrected FPG reductions of at least 30 mg/dL were observed starting with the 0.5-mg dose of tesaglitazar, increasing to 41 mg/dL with 1 mg, and 55 mg/dL with 2 mg to a maximum reduction of 61 mg/dL at the 3-mg dose. The estimate of FPG reduction with pioglitazone 45 mg was 39 mg/dL. This result suggests that reductions in FPG with the 1-mg dose of tesaglitazar were approximately equal with those observed with the maximum marketed dose of pioglitazone.

A dose-dependent reduction in serum TG levels was observed with tesaglitazar that appeared to reach a plateau at the 2.0 mg dose. The results were clinically relevant and statistically significant from tesaglitazar 0.5 mg up to 3 mg. Significant, placebo-corrected, percent change from baseline reductions in serum TG levels were observed starting with 17% at

tesaglitazar 0.5 mg, up to 33% at 1 mg, to a maximum of 41% at 2 and 3 mg. The estimate of TG reduction (8%) with 45 mg pioglitazone lies between the 0.1 mg (5%) and 0.5 mg (17%) doses of tesaglitazar.

A dose-dependent reduction in non-HDL-C levels was observed with tesaglitazar. Statistically significant, placebo-corrected, percent change from baseline reductions in non-HDL-C levels were observed starting with 13% at 1 mg, up to 22% at 2 mg, to a maximum of 25% at 3 mg of tesaglitazar. The estimate of non-HDL-C reduction (2%) with pioglitazone 45 mg lies below the 0.1 mg (3%) dose of tesaglitazar.

A dose-dependent increase in HDL-C levels was observed with tesaglitazar that appeared to reach a plateau at the 1-mg dose of tesaglitazar. Placebo-corrected percent change from baseline increases were statistically significant at 15%, 13% and 13% for the 1-, 2-, and 3-mg doses of tesaglitazar, respectively. The estimate of HDL-C increase (6%) with pioglitazone 45 mg is similar to the 0.5-mg (5%) dose of tesaglitazar.

Tesaglitazar improved the handling of an oral glucose load with a downward shift in glucose excursion on an OGTT after 12 weeks of treatment.

Pharmacokinetic results

A population pharmacokinetic (PK) analysis was performed to characterize the PK properties of tesaglitazar. Two Phase IIb studies (SH-SBD-0001 and SH-SBT-0001) were pooled and analyzed simultaneously.

The PK of tesaglitazar was well described by a 1-compartment model. The oral clearance (CL/F) was found to be positively correlated to renal function, assessed as $CLCr_{LBW}$ (Cockroft-Gault formula using lean body weight as measure of body weight). Oral clearance at steady state was 0.12 L/h for an individual with a $CLCr_{LBW}$ of 76 mL/min. The overall between-patient variability in exposure was approximately 37%. When renal function was accounted for, remaining unexplained variability in CL/F was 28%. A small decrease in CL/F with increasing doses was found. Also a small decrease in CL/F with time was identified. Neither the dose nor the time effect on CL/F had any major affect on between-patient variability in CL/F. The apparent volume of distribution (V_z/F) was 10.7 L and the between-patient variability was 37 %. The median terminal half-life was 61 hours. Other covariates tested, ie, patient population, gender, age, body weight, albumin, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphokinase (ALP), gamma-glutamyl transferase (GGT) and smoking were judged as being of no clinical relevance when renal function was taken into account.

Safety results

The study treatments were well tolerated. A presentation of the adverse events reported is presented in Table S2. The overall frequency of adverse events associated with each treatment was relatively similar for placebo, pioglitazone, and doses of tesaglitazar up to and including 1 mg. The frequencies of adverse events associated with the 2- and 3-mg doses were higher. There were no deaths in the program and the number of SAEs was low. Discontinuations due to adverse events were higher in the tesaglitazar 1-, 2- and 3-mg dose groups, but this was likely due to the requirement to discontinue patients with changes in particular laboratory evaluations. The most frequently reported adverse events are shown in Table S3.

Treatment with tesaglitazar was associated with a dose-dependent decrease in mean hemoglobin, white blood cell count (WBC), and absolute neutrophil count (ANC), as well as a dose-dependent increase in mean serum creatinine that was not observed in either the placebo or pioglitazone treatment groups.

Table S2 Number (%) of patients who had an adverse event in any category (safety population)

Category	Placebo	Tesaglitazar						Pioglitazone
		0.1 mg	0.5 mg	1 mg	2 mg	3 mg	Total	45 mg
	(N=70)	(N=72)	(N=72)	(N=70)	(N=70)	(N=73)	(N=357)	(N=72)
		n (%) of patients who had an adverse event						
Any adverse event (AE)	48 (68.6)	42 (58.3)	47 (65.3)	46 (65.7)	63 (90.0)	61 (83.6)	259 (72.5)	47 (65.3)
Serious AEs	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	3 (4.3)	3 (4.1)	9 (2.5)	3 (4.2)
Serious AEs leading to death	0	0	0	0	0	0	0	0
Serious AEs not leading to death	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	3 (4.3)	3 (4.1)	9 (2.5)	3 (4.2)
Discontinuations of study due to AEs	0	3 (4.2)	3 (4.2)	12 (17.1)	23 (32.9)	36 (49.3)	77 (21.6)	6 (8.3)
Other significant AEs	0	0	0	0	0	0	0	0
		Total number of adverse events						
Any adverse event	118	126	153	150	172	169	770	118
Serious AEs	1	2	1	1	3	4	11	5
Other significant AEs	0	0	0	0	0	0	0	0

Table S3 N (%) of patients with the most common[a] adverse events

Preferred term[b]	Placebo	Tesaglitazar						Pioglitazone
		0.1 mg	0.5 mg	1 mg	2 mg	3 mg	Total	45 mg
	(N=70)	(N=72)	(N=72)	(N=70)	(N=70)	(N=73)	(N=357)	(N=72)
N (%) of patients with any adverse event (AE)	**48 (68.6)**	**42 (58.3)**	**47 (65.3)**	**46 (65.7)**	**63 (90.0)**	**61 (83.6)**	**259 (72.5)**	**47 (65.3)**
Hemoglobin decreased	0	0	2 (2.8)	6 (8.6)	16 (22.9)	22 (30.1)	46 (12.9)	2 (2.8)
Blood creatinine increased	0	0	1 (1.4)	7 (10.0)	13 (18.6)	9 (12.3)	30 (8.4)	0
Nasopharyngitis	5 (7.1)	7 (9.7)	4 (5.6)	4 (5.7)	5 (7.1)	4 (5.5)	24 (6.7)	4 (5.6)
Headache	4 (5.7)	6 (8.3)	7 (9.7)	2 (2.9)	4 (5.7)	2 (2.7)	21 (5.9)	3 (4.2)
Weight increased	2 (2.9)	2 (2.8)	3 (4.2)	2 (2.9)	5 (7.1)	8 (11.0)	20 (5.6)	4 (5.6)
Edema peripheral	2 (2.9)	3 (4.2)	3 (4.2)	4 (5.7)	3 (4.3)	5 (6.8)	18 (5.0)	3 (4.2)
Upper respiratory tract infection NOS	4 (5.7)	5 (6.9)	3 (4.2)	3 (4.3)	1 (1.4)	4 (5.5)	16 (4.5)	2 (2.8)
Neutropenia	0	2 (2.8)	1 (1.4)	2 (2.9)	4 (5.7)	6 (8.2)	15 (4.2)	2 (2.8)
Arthralgia	3 (4.3)	3 (4.2)	3 (4.2)	0	2 (2.9)	6 (8.2)	14 (3.9)	1 (1.4)
Fatigue	2 (2.9)	4 (5.6)	2 (2.8)	4 (5.7)	0	4 (5.5)	14 (3.9)	0
Dizziness	3 (4.3)	1 (1.4)	3 (4.2)	3 (4.3)	4 (5.7)	2 (2.7)	13 (3.6)	2 (2.8)
Back pain	1 (1.4)	2 (2.8)	2 (2.8)	1 (1.4)	4 (5.7)	3 (4.1)	12 (3.4)	3 (4.2)
Blood creatine phosphokinase increased	4 (5.7)	0	3 (4.2)	2 (2.9)	5 (7.1)	2 (2.7)	12 (3.4)	2 (2.8)
Nausea	2 (2.9)	1 (1.4)	2 (2.8)	1 (1.4)	4 (5.7)	0	8 (2.2)	1 (1.4)
Vomiting NOS	4 (5.7)	1 (1.4)	0	0	1 (1.4)	0	2 (0.6)	3 (4.2)

[a] Only those adverse events with incidence >5% in any treatment group are shown.
[b] MedDRA terms.
NOS not otherwise specified

Date of the report

03 November 2003