AstraZeneca

Clinical Study Report

Drug substance	Tesaglitazar
Study code	D6160C09999
Date	2 May 2008

A 16-Week Randomised, Double-blind, Parallel-group, Multicentre, Placebo- and Active- (Metformin) Controlled Study to Evaluate the Effect on Whole Body Insulin Sensitivity of Tesaglitazar Therapy when Administered to Patients with Type 2 Diabetes

ARAMIS

Study dates:	First patient enrolled: 18 October 2005 Last patient enrolled: 15 March 2006
Phase of development:	Phase IIa
International Co-ordinating Investigator:	[redacted]
Sponsor's Responsible Medical Officer:	[redacted]

This study was performed in compliance with Good Clinical Practice.

Drug product	NA	**SYNOPSIS**	
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ARAMIS

International co-ordinating investigator

[redacted]

Reason for writing an abbreviated report

The study was prematurely stopped due to the discontinuation of further development of tesaglitazar.

Study centre(s)

Patients were to be recruited from three centres with Principal Investigators:

[redacted]

[redacted]

[redacted]

Publications

None

Study dates		**Phase of development**
First patient enrolled	18 October 2005	Therapeutic exploratory (IIa)
Last patient completed	31 July 2006	

Objectives

Due to the decision by AstraZeneca to discontinue the tesaglitazar development programme, neither the primary objectives nor the secondary objectives of the study, with the exception of safety, were fulfilled.

The primary objective of this study was to determine the efficacy of tesaglitazar given as monotherapy, as compared to placebo in patients with type 2 diabetes, in improving whole body insulin sensitivity by assessing the index of insulin sensitivity (M value) during high (80mU/m^2/min) insulin level euglycemic hyperinsulinemic clamp.

The secondary objectives of the study were:

1. To determine the efficacy of tesaglitazar given as monotherapy, as compared to metformin in patients with type 2 diabetes, in improving whole body insulin sensitivity by assessing the M value during high (80mU/m^2/min) insulin level euglycemic hyperinsulinemic clamp.

2. To determine the efficacy of tesaglitazar given as monotherapy, as compared to placebo/metformin in patients with type 2 diabetes, in improving hepatic and peripheral insulin sensitivity by assessing the M value during low (20mU/m^2/min) insulin level euglycemic hyperinsulinemic clamp.

3. To assess the effects of tesaglitazar given as monotherapy as compared to placebo/metformin in patients with type 2 diabetes on:

   - basal hepatic glucose output measured by dideuterated glucose in the fasting state and during low insulin level clamp.
   - the plasma profile of glucose, insulin and lipids after a mixed meal
   - calculated insulin secretion
   - liver oxidation after a mixed meal
   - energy expenditure and substrate metabolism by indirect calorimetry
   - body composition using Dual-energy X-ray absorptiometry body composition model (DXA)-scan, abdominal fat distribution using magnetic resonance imaging (MRI), liver fat and muscle fat content using magnetic resonance spectroscopy (MRS)
   - waist and hip circumference
   - laboratory efficacy variables (lipids, inflammatory marker and adipose tissue hormones)

4. To exploratory assess the effects of tesaglitazar on plasma levels of amino acids and different molecular forms of adiponectin.

5. To determine the safety and tolerability of tesaglitazar in patients with type 2 diabetes.

Study design

This was a 16 week randomised, double-blind, parallel-group, multi-centre, placebo- and active- (metformin 1.5 g) controlled study of tesaglitazar (1 mg) in patients with type 2 diabetes. The total study duration including enrolment, run-in, randomised treatment and follow-up was planned to be 29 weeks.

Target patient population and sample size

Men or postmenopausal women who were ≥30 years of age at the enrolment visit (Visit 1), diagnosed with type 2 diabetes and treated with diet alone or on treatment with a single oral anti-diabetic agent or low doses of two agents.

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

Tesaglitazar, 1 mg, once daily in oral form (tablets) and matching placebo.

Metformin, 1.5 g daily divided into morning, lunch-time and evening doses in oral form (tablets) and matching placebo.

Duration of treatment

After a 1-week enrolment period, a 3-week placebo single-blind run in period and 1-week placebo single-blind baseline measurement period the patients were to be given the investigational product for 16 weeks in a double-blind fashion. Metformin was to be titrated up during the first 3 weeks of the double-blind period. Patients were to be counselled on dietary and life-style modifications according to normal clinical routine, with reinforcement throughout the treatment period.

Criteria for evaluation (main variables)

Pharmacokinetics

NA

Efficacy

Due to the decision by AstraZeneca to discontinue the tesaglitazar development programme, no efficacy variables were evaluated in this study.

Primary outcome variables:

- Change from baseline in M value during high (80 mU/m^2/min) insulin level adjusted for lean body mass (mg/min/kg).

Secondary outcome variables:

- Change from baseline in M value during high (80 mU/m^2/min) insulin level adjusted for lean body mass and insulin level (mg/min/kg(mU/L)).
- Change from baseline in M value during low (20 mU/m^2/min) insulin level adjusted for lean body mass (mg/min/kg).
- Change from baseline in M value during low (20 mU/m^2/min) insulin level adjusted for lean body mass and insulin level(mg/min/kg(mU/L)).
- Hepatic glucose output in the fasting state (mg/kg/min).
- Hepatic glucose output during low (20 mU/m^2/min) insulin infusion (mg/kg/min).
- Plasma profile of glucose insulin and lipids after a mixed meal.
- Calculated insulin secretion.
- Plasma concentration of β-OH-butyrate and citrate after a mixed meal.
- Whole-body carbohydrate, lipid and protein oxidation rate and resting energy expenditure.
- Fat and bone free body mass (kg).
- Waist and hip circumference
- Liver fat content.
- Intra Extra Myocellular fat content.
- Laboratory efficacy variables (HbA1c, FPG, insulin, proinsulin, C-peptide, TG, TC, HDL-C, LDL-C, FFA, Apo A-I, Apo B, Apo CIII, adiponectin and leptin)
- Products and ratios of efficacy laboratory values Apo B / Apo A-I, LDL-C/ HDL-C, HOMA-index.
- Values of the exploratory measurements of amino acids.

Safety

- Adverse Events (AE)

- Laboratory values
- ECG
- Vital signs (pulse and blood pressure)
- Hypoglycaemic events
- Body weight
- Cardiac evaluation
- Physical examination

Genetics

NA

Statistical methods

Safety measurements were presented descriptively, by means of tabulations, summaries, and listings. AEs were summarised and presented in tables and listings, as relevant.

Patient population

Characteristic	Age	Weight (kg)	Height (cm)	BMI (kg/m^2)	Waist Hip Ratio	Waist circ.
N	16	16	16	16	15	15
Mean	60.31	87.43	170.88	29.99	0.98	102.47
SD	5.34	12.93	6.67	4.64	0.07	10.62
Min	46.0	66.7	160.0	23.4	0.9	84.0
Median	61.00	85.80	170.50	29.10	1.00	103.00
Max	66.0	110.5	183.0	43.2	1.1	121.0

Characteristic		Tesaglitazar 1.0 mg n	%	Metformin n	%	Placebo n	%
Gender	Male	4	66.67	4	100.00	2	33.33
	Female	2	33.33	0	0.00	4	66.67
Race	Caucasian	6	100.00	4	100.00	6	100.00
Current Smoker	No	5	83.33	4	100.00	4	66.67
	Yes	1	16.67	0	0.00	2	33.33

Characteristic		Tesaglitazar 1.0 mg n	%	Metformin n	%	Placebo n	%
Other Current Nicotine Use	No	6	100.00	4	100.00	6	100.00

Efficacy results

Due to the decision by AstraZeneca to discontinue the tesaglitazar development programme, no efficacy results are reported in this study.

Safety results

Category of adverse event*	Runin Placebo (n = 15)	Tesaglitazar 1.0 mg (n = 5)	Metmorfin (n = 4)	Placebo (n = 6)	Follow-up (n = 15)
Serious AEs leading to death	0	0	0	0	0
Serious AEs not leading to death	0	0	0	0	0
Discontinuation of study treatment due to AEs	0	0	0	0	0
Other AEs	5	4	0	4	5

*Patients with multiple events in the same category are counted only once in each category.
Patients with events in more than 1 category are counted only once in each of those categories.

Category of adverse event*	Runin Placebo (n = 15)	Tesaglitazar 1.0 mg (n = 5)	Metmorfin (n = 4)	Placebo (n = 6)	Follow-up (n = 15)
Any AEs	5	8	0	9	9
Serious AEs	0	0	0	0	0
Discontinuation AEs	0	0	0	0	0
Other AEs	5	8	0	9	9

*Events are counted by preferred term, ie. for patients with multiple events falling under the same preferred term, only occurrence of the event is counted.

[redacted]

Date of the report

2 May 2008