AstraZeneca

Clinical Pharmacology Study Report

Drug Substance	Tesaglitazar
Study Code	D6160C00058
Date	19 May 2008

A Randomized, Double-blind, Placebo-controlled, Cross-over Study to Evaluate the Effect of Tesaglitazar 1 mg Once Daily on the Pharmacokinetics of Metformin Following Addition of Tesaglitazar to Metformin Treatment Twice Daily in Patients with Type 2 Diabetes

Abbreviated report

Study dates: First patient enrolled: 22 March 2006
Last patient completed: 22 August 2006

Phase of development: Clinical Pharmacology (I)

This study was performed in compliance with Good Clinical Practice

Drug Substance(s)	Tesaglitazar	**SYNOPSIS**	(For national authority use only)
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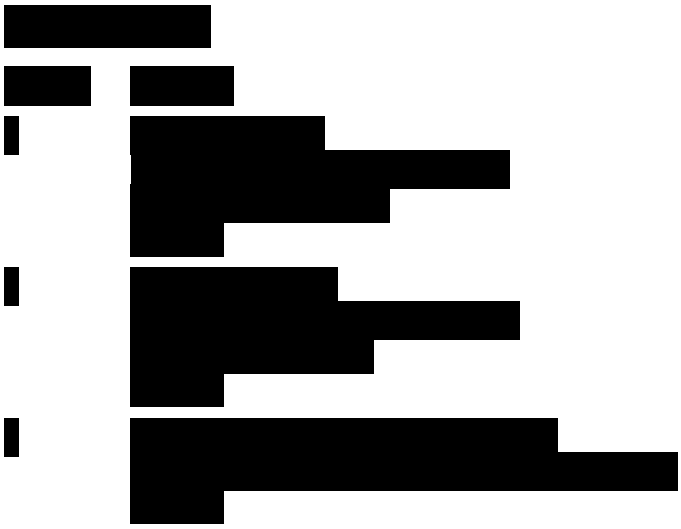
Abbreviated report

Reason for writing an abbreviated report

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



Study dates		**Phase of development**
First patient enrolled	22 March 2006	Clinical pharmacology (I)
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Objectives

The **primary objective** of the study was to compare the effect of 1 mg tesaglitazar once daily versus placebo once daily given as add-on therapy to metformin on the steady-state exposure (area under the plasma concentration-time curve during a dosing interval at steady-state; AUC_{ss}) of metformin in patients with type 2 diabetes with a serum creatinine within normal range and a calculated creatinine clearance (CrCL) >70 mL/min or CrCL ≤70 to ≥50 mL/min, by assessment after a 12-week randomised treatment period.

The **secondary objectives** of the study were:

1. To compare the effect of 1 mg tesaglitazar once daily versus placebo once daily given as add-on therapy to metformin on the pharmacokinetics of metformin in patients with type 2 diabetes with a serum creatinine within normal range and having a CrCL >70 mL/min or CrCL ≤70 to ≥50 mL/min, by assessment of the observed maximum plasma concentration at steady-state ($C_{ss,max}$), the time to reach peak or maximum concentration during any dosing interval at steady-state ($t_{ss,max}$), the minimum (trough) steady-state drug concentrations in plasma during the dosing interval ($C_{ss,min}$), renal clearance (CL_R), apparent plasma clearance (dose/AUC; CL/F) and elimination half-life ($t_{½}$) of metformin, after a 12-week randomised treatment period.

2. To compare the effects of 1 mg tesaglitazar once daily versus placebo once daily given as add-on therapy to metformin on glomerular filtration rate (GFR), in patients with type 2 diabetes with a serum creatinine within normal range and having CrCL >70 mL/min or CrCL ≤70 to ≥50 mL/min, by assessment of plasma clearance of ^{51}Cr-ethyl-enediaminetetraacetic acid (^{51}Cr-EDTA), and endogenous CrCL after a 12-week randomised treatment period.

3. To evaluate the safety and tolerability of 1 mg tesaglitazar once daily given as add-on therapy to metformin, by assessment of adverse events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure, hypoglycaemic events, body weight and physical examination.

Study design

This was a randomised, double-blind, placebo-controlled, cross-over study to evaluate the effect on metformin exposure when tesaglitazar was added to metformin therapy in male and female patients with type 2 diabetes with a Serum creatinine within normal range and with CrCL >70 mL/min or CrCL ≤70 to ≥50 mL/min, estimated at the enrolment visit according to the Cockcroft–Gault equation:

For males (mL/min):

$$CrCL = \frac{(140\text{-age}) \text{ (weight kg)}}{72 \times S_{cr} \text{ (mg/dL)}}$$

For females (mL/min):

$$CrCL = \frac{(140\text{-age}) \text{ (weight kg)}}{72 \times S_{cr} \text{ (mg/dL)}} \times 0.85$$

Patients were eligible if, for at least 3 months prior to entry to the study, they had been treated with metformin or metformin and one additional oral anti-diabetic agent in a low dose (not a thiazolidinedione). The low dose of additional anti-diabetic medication was defined as a maximal daily dose of sulphonylurea comparable to glibenclamide/glyburide 5 mg (corresponding to 3.5 mg of Swedish microcrystal form of glibenclamide), meglitinide comparable to repaglinide 1.5 mg or alpha-glucosidase inhibitors comparable to acarbose 150 mg.

It was planned that patients would receive tesaglitazar and placebo in two 12-week treatment periods separated by a 3- to 5-week wash-out period. Following early termination of the study, less than the planned number of 36 patients were enrolled and none of the randomised patients received the second treatment in the planned sequence.

Target patient population and sample size

Male and female patients, ≥18 years of age, diagnosed with type 2 diabetes and treated for at least 3 months prior to entry to the study with metformin or metformin and one additional oral anti-diabetic agent in a low dose.

A total of 36 patients (18 with calculated CrCL >70 mL/min and 18 with CrCL ≤70 to ≥50 mL/min) were planned to be enrolled to ensure that at least 24 patients (12 in each group) completed the study.

A total of 9 male and female volunteers (54 to 81 years of age) were enrolled , including starting treatment period for 6 patients who received placebo and 3 who received tesaglitazarbefore the study was terminated.

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

Tesaglitazar 1 mg tablets or matching placebo tablets, taken once daily (1 mg/day) in the morning, orally.

Metformin hydrochloride 500 mg, 850 mg and 1000 mg tablets, taken twice daily 12 hours apart (minimum daily dose 1 g, maximum daily dose 2.7 g), orally.

Duration of treatment

Tesaglitazar, 1 mg tablets, or placebo once daily in the morning as add-on therapy to metformin. The study was to include two 12-week treatment periods and a wash-out period of 3 to 5 weeks between the treatment periods.

Metformin (Glucophage®) tablets were taken as 2 equal doses (500 mg twice daily up to 500 + 850 mg twice daily) throughout the study (patients continued taking metformin during the wash-out period).

The total study duration including enrolment, randomised treatments, wash-out and follow-up was planned to be 39 to 41 weeks.

Variables

Primary

Pharmacokinetic

- AUC_{ss} of metformin during the last day-time 12-hour dosing interval after 12 weeks treatment with metformin and tesaglitazar as compared to treatment with metformin and placebo in patients with type 2 diabetes with a serum creatinine within normal range and having CrCL >70 mL/min or CrCL ≤70 to ≥50 mL/min.

Secondary

Pharmacokinetic

- $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, CL_R, CL/F and $t_{½}$ of metformin during the last day-time 12-hour dosing interval after 12 weeks treatment with metformin and tesaglitazar as compared to treatment with metformin and placebo in patients with type 2 diabetes with a serum creatinine within normal range and having CrCL >70 mL/min or CrCL ≤70 to ≥50 mL/min.

Safety

- GFR, measured as plasma clearance of ^{51}Cr-EDTA and endogenous CrCL, after 12 weeks treatment with metformin and tesaglitazar as compared to treatment with metformin and placebo in patients with type 2 diabetes with a serum creatinine within normal range and having CrCL >70 mL/min or CrCL ≤70 to ≥50 mL/min.

- AEs, laboratory values, ECG, pulse, blood pressure, hypoglycaemic events, body weight and physical examination including cardiac evaluation.

Statistical methods

Following the early termination of the study, no statistical analyses of the primary and secondary pharmacokinetic variables were performed.

Analysis of secondary variables – Safety

All safety data are presented descriptively.

Patient population

Twenty-one (21) patients with type 2 diabetes were enrolled. Ten (10) patients were randomised, of whom 9 (5 male and 4 female) received treatment and were included in the safety analysis set. All 9 patients were Caucasians. None of the 9 patients completed the study. Demographic characteristics are shown in Table S1.

Table S1 Demographic characteristics (Safety analysis set, N=9)

	Age (years)	**Height** (cm)	**Weight** (kg)	**BMI** (kg/m^2)
Mean	65.1	174.4	88.58	29.15
SD	8.96	7.38	13.478	4.526
Minimum	54	161	64.8	23.23
Median	64.0	177.0	91.50	29.48
Maximum	81	184	105.6	36.97

SD Standard deviation.

Extent of exposure

Ten (10) patients were randomised into the study. Of the 10 patients, 9 received at least 1 dose of study treatment and had post-dose data available and were included in the safety analysis set.

As the study was prematurely discontinued, none of the patients received the second treatment in the planned sequence (tesaglitazar or placebo) and none of the patients completed the study. Only 3 patients received tesaglitazar treatment.

Summary of safety results

There were no serious AEs or discontinuations of study treatment due to AEs. Diarrhoea and paraesthesia were the only AEs reported by more than one patient overall (both AEs were reported by 2 patients overall). There were no clinically relevant changes in laboratory results or vital signs during the study. One patient who received placebo, had an abnormal ECG (partial right bundle branch block) at the end of the study.