Clinical Pharmacology Study Report

Drug Substance	Tesaglitazar
Study Code	D6160C00057
Date	19 May 2008

An Open-label, Non-randomized Study to Evaluate the Effect of Tesaglitazar 1 mg Once Daily Doses on Ovulation Suppression in Healthy Female Volunteers on a Combined Oral Contraceptive Containing Drospirenone and Ethinyl Estradiol

Abbreviated report

Study dates:	First subject enrolled: 18 January 2006
	Last subject completed: 08 June 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)
Study Code	D6160C00057		
Date	19 May 2008		

Abbreviated report

Reason for writing an abbreviated report

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

Study centre(s)

PAREXEL International GmbH, Clinical Pharmacology Research Unit, Klinikum Westend, Haus 18, Spandauer Damm 130, D-14050 Berlin, Germany.

Study dates		**Phase of development**
First subject enrolled	18 January 2006	Clinical pharmacology (I)
Last subject completed	08 June 2006	

Objectives

The **primary objective** of the study was to compare the effect of combined oral contraceptive (COC) treatment alone (Cycle 1) and COC treatment in combination with repeated doses of tesaglitazar (Cycle 3) on the ovulation suppression, by estimating the incidence of ovulations (defined as serum progesterone levels ≥3 ng/mL measured on study Days 19 and 21 in the menstruation cycle).

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

1. to characterise the levels of endogenous hormones by assessment of luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol in serum, during dosing with COC alone and in combination with tesaglitazar

2. to evaluate the follicle size and ovulation by vaginal ultrasonography during dosing with COC alone and in combination with tesaglitazar

3. to evaluate the steady-state pharmacokinetics of drospirenone and ethinyl estradiol (EE) in plasma by assessment of the area under the plasma concentration-time curve during one dosing interval at steady-state (AUC_{τ}), observed maximum plasma concentration at steady-state ($C_{ss,max}$) and time of $C_{ss,max}$ ($t_{ss,max}$) on study Day 21 in Cycle 3 (tesaglitazar + COC), compared to study Day 21 in Cycle 1 (COC alone)

4. to evaluate tesaglitazar's potential effect on cytochrome P450 3A4 by assessment of 6β-hydroxy(OH)-cortisol/cortisol ratio using cortisol and 6β-OH-cortisol in urine (24-hour collection), comparing the ratios from study Day 21 in Cycle 3 (tesaglitazar + COC) and study Day 21 in Cycle 1 (COC alone)

5. to assess cycle control and bleeding pattern by using recorded information from subjects in diary cards during doses with COC alone and in combination with tesaglitazar

6. to evaluate the safety and tolerability of tesaglitazar in combination with a COC by assessment of adverse events (AEs), laboratory variables, pulse rate, blood pressure (BP), electrocardiogram (ECG), physical examination and body weight.

Study design

This was a single centre (Germany), open, non-randomised study. In order to obtain about 60 evaluable subjects, it was planned to enrol approximately 75 subjects. Only subjects that had used a COC (3 mg drospirenone and 0.03 mg EE per tablet) for at least the last three cycles before study start were included. The study was to cover three sequential menstrual cycles for each subject. The subjects were to receive a COC (Yasmin®) once daily on study Days 1 to 21 in all three cycles where the first cycle was a control cycle. Tesaglitazar 1 mg once daily was to be administered from study Day 22 in Cycle 1 until study Day 21 in Cycle 3.

Due to early termination of the study, the study was not fully recruited and only certain subjects participated in the treatment period procedures.

Target subject population and sample size

Approximately 60 patients were planned to be enrolled and treated in the study. However, since the study was prematurely discontinued, only 32 patients were enrolled and 28 patients (females aged 19 to 40 years) received study medication .

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

Tesaglitazar 1 mg tablets taken once daily in the morning, orally, together with the COC.

Yasmin® tablets containing a combination of 3 mg of drospirenone and 0.03 mg of EE per tablet. Tablets were administered orally once daily in the morning.

Duration of treatment

Tesaglitazar 1 mg tablets once daily in the morning for 56 days (Cycle 1: study Days 22-28, Cycle 2: study Days 1-28 and Cycle 3: study Days 1-21).

Yasmin® tablets once daily in the morning from study Day 1 to study Day 21 during three cycles.

The maximum total study duration including pre-entry (within 28 days), three treatment cycles of 28 days, and follow-up of 21 to 28 days was a maximum of 20 weeks.

Variables

Pharmacokinetic

- For drospirenone and EE: AUC_{τ}, $C_{ss,max}$, $t_{ss,max}$ in plasma on study Day 21 in Cycles 1 and 3.
- For tesaglitazar: minimum (trough) steady-state drug plasma concentration during the dosing interval on study Days 1, 14, 19 and 21 in Cycles 2 and 3.
- The urinary 6β-OH-cortisol/cortisol ratio on study Day 21 in Cycles 1 and 3.

Pharmacodynamic

Levels of endogenous hormones:

- progesterone in serum on study Days 19 and 21 in Cycles 1, 2 and 3
- LH and FSH in serum, on study Days 14 in Cycles 1, 2 and 3
- estradiol in serum on study Days 1, 19 and 21 in Cycles 1, 2 and 3.

Safety

Adverse events, laboratory values, pulse rate, BP, ECG, physical examination and body weight.

Statistical methods

Following early termination of the study, no analyses of the pharmacokinetic and pharmcodynamic variables were done.

Analysis of safety variables

All safety data are presented descriptively.

Subject population

Thirty-two (32) female subjects were enrolled. Twenty-eight (28) subjects received treatment and were included in the safety analysis set. All 28 subjects were Caucasians. None of the 28 subjects completed the study. Demographic characteristics are shown in Table S1.

Table S1 Demographic characteristics (Safety analysis set, N=28)

	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Mean	29.1	167.5	64.38	22.86
SD	5.93	6.23	10.32	2.841
Minimum	19	151	48.1	18.64
Median	27.5	168.5	64.95	22.635
Maximum	40	177	89.4	29.87

SD Standard deviation.

Extent of exposure

Thirty-two (32) subjects were enrolled into the study. Of the 32 subjects, 28 received at least 1 dose of study treatment and had post-dose data available and were included in the safety analysis set. (follows in the next paragraph)

As the study was prematurely discontinued, none of the subjects completed the study. Two subjects only received COC treatment (Yasmin®) alone, whereas the remaining 26 subjects started combined treatment with Yasmin® and tesaglitazar.

Summary of safety results

There were no serious AEs. One subject discontinued study treatment due to abdominal pain and nausea, reported as an AE not related to study treatment by the investigator. Adverse events reported for more than 2 patients included: Nasopharyngitis (6 patients), and nausea (3 patients).

Additional adverse events reported for more than 1 patient included: allergic rhinitis 2 patients, headache 2 patients, and metrorrhagia (2 patients). There were no clinically relevant changes in laboratory results or vital signs during the study. Two subjects who had normal ECGs at baseline had ECGs considered abnormal, but not clinically significant, at the end of the study. There were no episodes of spotting and/or breakthrough bleeding. No subjects were recorded as having ovulated and 3 subjects had any follicle size >10 mm (included elevated values for patient E0001020 of 10-13 mm, for patient E0001046 of 11 mm, and for patient E0001061 of 12 mm.