Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	03 MAY 2013
Study title:	Single-center, randomized, placebo-controlled, double-blind, parallel group study to evaluate whether a single-dose of either 20 mg piroxicam, 40 mg piroxicam or 80 mg piroxicam shows an effect on ovulation after the onset of LH surge compared to placebo in healthy young women
Sponsor's study number:	14835
NCT number:	NCT01320709
EudraCT number:	2010–021195–28
Sponsor:	Bayer HealthCare
Clinical phase:	IIa
Study objectives:	**Primary objective:** • To assess whether piroxicam has an effect on ovulation (delay or inhibition) when given after the onset of luteinizing hormone (LH) surge. **Secondary objectives:** • To describe the course of follicle sizes. • To investigate the course of gonadotropins (follicle-stimulating hormone [FSH] and LH) and ovarian steroids (estradiol [E2] and progesterone). • To investigate the pharmacokinetics (PK) of piroxicam. • To investigate the correlation of serum concentrations of piroxicam and pharmacodynamic (PD) effects (PK/PD analysis), if applicable. • .
Test drug:	Piroxicam (BAY l 1920)
Name of active ingredient(s):	Piroxicam
Dose:	Treatment A: 20 mg, single dose (4 capsules: 1 verum 20 mg, 3 placebo) Treatment B: 40 mg, single dose (4 capsules: 2 verum 20 mg, 2 placebo) Treatment D: 80 mg, single dose (4 capsules: all verum 20 mg)
Route of administration:	Oral
Duration of treatment:	Single dose (after onset of LH surge)

Reference drug:	Treatment C: Placebo; no active comparator
Dose	4 Capsules
Route of administration	Oral
Duration of treatment	Single dose (after onset of LH surge)
Indication:	Emergency contraception
Diagnosis and main criteria for inclusion:	• Healthy female subjects, aged 18-35 years (inclusive) and body mass index (BMI) of 18-30 kg/m² (inclusive) at the first screening visit • No contraindications for the use of non-steroidal anti-inflammatory drugs
Study design:	This was a single-center, parallel-group, randomized, placebo-controlled, double-blind study conducted in healthy women aged 18-35 years over a total of 2 observed menstrual cycles (1 pre-treatment cycle and 1 treatment cycle, separated by up to 4 intermediate cycles).
Methodology:	The complete study comprised a total of 4 study periods: screening, pre-dose (pre-treatment cycle), treatment, and follow-up. **Pharmacodynamics** • Monitoring of follicular development (growth, rupture, and luteinization) by means of transvaginal ultrasound (TVU) during the pre-treatment and treatment cycle • Determination of the ovarian steroids estradiol and progesterone in serum during the pre-treatment and treatment cycle • Determination of the gonadotropins FSH and LH in serum during the pre-treatment and treatment cycle **Pharmacokinetics** • Population pharmacokinetic evaluation of piroxicam serum concentrations **Safety** • Medical, surgical, and gynecological history; physical and gynecological examination; medication history performed at screening • Standard laboratory analyses in blood and urine were performed at screening, day 6 of treatment cycle, and at follow-up. Urine pregnancy test were performed at screening, day 6 of the treatment cycle, follow-up visit, and additionally immediately before study drug administration • Adverse events (AEs) and concomitant medications were monitored throughout the study.

Study center(s):	The study was conducted at one center in Germany
Publication(s) based on the study (references):	None at the time of report creation
Study period:	Study Start Date: 08 MAR 2011 Study Completion Date: 29 MAY 2012
Early termination:	Not applicable
Number of subjects:	Planned: 64 Subjects Analyzed: 72 Subjects
Criteria for evaluation *Clinical pharmacology:*	**Pharmacodynamics:** Primary analysis: Number of responders, defined as subjects with a delay from LH surge to ovulation in the treatment cycle of at least "plus 24 hours" compared with the median duration from LH surge to ovulation in the pre-cycle. Secondary analysis: Number of responders, defined as subjects with a delay from LH surge to ovulation in the treatment cycle of at least "plus 24 hours" compared with the same subject's individual duration from LH surge to ovulation in the pre-cycle. Further analyses: Time-to-event analysis of ovulation, maximum follicle size, and hormones (FSH, LH, estradiol, and progesterone). **Pharmacokinetics:** The population PK model developed in this study in a population PK evaluation was fitted to the data by means of non-linear, mixed-effects modeling. The following PK parameters were determined after single oral administration of 20, 40, or 80 mg piroxicam: • AUC(0-120h): Area under the concentration-time curve from time of piroxicam administration (time 0) to 120 hours after drug administration • AUC(0-t_{last}): Area under the concentration-time curve from time of piroxicam administration (time 0) to last time point (t_{last}) with a piroxicam concentration above the lower limit of quantification (LLOQ) • AUC: Area under concentration-time curve from time of piroxicam administration to infinity calculated from the doses (D) 20, 40, and 80 mg, and the apparent clearance (CL/F) in case of linear kinetics • AUC/D: Dose-normalized AUC • AUC(0-$t_{ovulation}$): Area under the concentration-time curve from time of piroxicam administration (time 0) to sample time point closest to ovulation ($t_{ovulation}$)

	• AUC(0-$t_{no\ ovulation}$): Area under the concentration-time curve from time of piroxicam administration (time 0) to time of next menstruation in the case of no ovulation • $t_{1/2}$: Terminal half-life of piroxicam
Safety:	Adverse events (AEs) and laboratory values
Statistical methods:	**Pharmacodynamics:** The primary and secondary analysis was performed by a hierarchical testing procedure. First, equality of piroxicam and placebo was to be tested. If this first test decided against equality, a second test - for superiority - was to be conducted. The three different doses of piroxicam were also to be tested hierarchically in the order 80 mg, 40 mg, and 20 mg. Other pharmacodynamic variables were analyzed by preparing descriptive statistics. **Pharmacokinetics**: The concentration-time courses of piroxicam were tabulated, separated by treatment including descriptive statistics. **PK/PD Analyses:** Correlation of PK in terms of PK parameters and/or serum concentrations and PD were analyzed using descriptive scatter plots. These analyses were conducted for • correlation of piroxicam concentration at time of maximum follicle size and maximum follicle size • correlation of E2 concentration at time of maximum follicle size and maximum follicle size. **Safety:** Adverse events were listed, and treatment-emergent adverse events were tabulated, to show frequency (numbers of subjects) overall and by treatment group. Quantitative laboratory data were described by the summary statistics, and frequency tables were provided for qualitative data. Abnormal values were listed and tabulated.
Substantial protocol changes:	Protocol version 2 from 06 JUN 2011 introduced the following changes: • An additional single dose of piroxicam, i.e., 80 mg, treatment D, was included in the dose range to be investigated - necessitating an increased number of capsules to be taken (4 capsules instead of 2 capsules). • The determination of the sample size was revised - now ending up with 16 valid cases per treatment and 64 evaluable subjects in total (based on a responder rate under piroxicam of 0.75 instead of 0.7, assuming higher efficacy of the 80 mg dose). • The number of visits during the treatment cycle might be increased in order to allow a clear decision on the subjects' ovulation status. • In cases of proven ovulation, the number of obligatory visits per cycle was reduced slightly.

- The implied definition of inhibition of ovulation was changed from "no ovulation within 5 days post-treatment" to "no ovulation until the next (menstrual) bleeding".
- The pre-treatment and treatment cycle did not have to be consecutive cycles; up to 4 intermediate cycles were permitted.

Subject disposition and baseline

A total of 167 women were screened and, of those, 72 were randomized to receive one of the four study treatments; all received their assigned single-dose treatment, 17 subjects received placebo, 18 subjects received 20 mg piroxicam, 17 subjects received 40 mg piroxicam, and 20 subjects received 80 mg piroxicam. All 72 subjects were eligible for safety (safety set) and PK assessment (PK set); for eight of them major protocol violations involving missing or invalid data were recorded, and these were excluded for the PD population (PD set), which thus comprised 64 subjects (N = 16 for each treatment group). Demographic and baseline data were comparable for all the 4 treatment groups. Mean age of the subjects (N=72) was 28.4 years (SD: 4.1; range: 19-35 years); mean BMI was 22.6 kg/m^2 (SD: 2.5; range: 18.3-29.3 kg/m^2).

Clinical pharmacology evaluation

Pharmacodynamics:
In the primary analysis, for numbers of responders (see Table 1), the null hypothesis of equality between piroxicam and placebo was rejected for all dosing levels (20, 40, and 80 mg). The null hypothesis of "lack of superiority" of piroxicam over placebo was rejected for 80 mg piroxicam only. Therefore, the primary objective of the study was achieved, with a positive result: Piroxicam did indeed show an effect on ovulation when given after the onset of LH surge, with the highest effect observed in the 80 mg group (see Table 2).

Table 1: Responder rates, based on comparison with median duration from luteinizing hormone surge to ovulation in the pre-cycle; PD set

	Placebo *N* = 16	20 mg piroxicam *N* = 16	40 mg piroxicam *N* = 16	80 mg piroxicam *N* = 16
No. (%) of subjects	2 (12.5%)	8 (50.0%)	7 (43.8%)	11 (68.8%)

Table 2: Significant and clinically relevant effects of piroxicam on ovulation in comparison with placebo, based on comparison with median duration from luteinizing hormone surge to ovulation in the pre-cycle; PD set

	20 mg piroxicam vs. placebo *N* = 16	40 mg piroxicam vs. placebo *N* = 16	80 mg piroxicam vs. placebo *N* = 16
p value for equality with placebo	**0.0062**	**0.0180**	**<0.0001**
p value for superiority over placebo (superiority margin = 0.2)	0.1215	0.2252	**0.0054**

p values below 0.05 are emphasized in bold type.

In the secondary analysis, the null hypothesis of equality between piroxicam and placebo was rejected for all dosing levels (20, 40, and 80 mg). The null hypothesis of "lack of superiority" of piroxicam over placebo was rejected for 80 mg and also for 40 mg piroxicam, but not for 20 mg piroxicam. Therefore, this supported the finding of the primary analysis (see Tables 3 and 4).

Table 3: Responder rates, based on comparison with individual duration from luteinizing hormone surge to ovulation in the pre-cycle; PD set

	Placebo *N* = 16	20 mg piroxicam *N* = 16	40 mg piroxicam *N* = 16	80 mg piroxicam *N* = 16
No. (%) of subjects	0	5 (31.3%)	7 (43.8%)	11 (68.8%)

Table 4: Significant and clinically relevant effects of piroxicam on ovulation in comparison with placebo, based on comparison with individual duration from LH surge to ovulation in the pre-cycle; PD set

	20 mg piroxicam vs. placebo *N* = 16	40 mg piroxicam vs. placebo *N* = 16	80 mg piroxicam vs. placebo *N* = 16
p value for equality with placebo	**0.0035**	**0.0002**	**<0.0001**
p value for superiority over placebo (superiority margin = 0.2)	0.1658	**0.0277**	**<0.0001**

p values below 0.05 are emphasized in bold type.

Further analyses, without formal statistical testing, indicated a similar influence of piroxicam:

Time to ovulation: For all subjects, time to ovulation under placebo treatment was ≤3 days. For 20 mg and 40 mg piroxicam, cases of ovulation inhibition occurred, and about 75% of the subjects ovulated within the first 4-5 days. For the 80 mg group, ovulation occurred in about 44% of the subjects within the first 5 days. Assuming a potential fertilization within 5 days after unprotected intercourse, the subjects in the 80 mg group would have had the lowest risk of pregnancy. Table 5 below presents data on duration from LH surge to ovulation by cycle and by treatment in PD analysis set.

Table 5: Duration (hours) from luteinizing hormone surge to ovulation by cycle; PD set

		Placebo *N* = 16	20 mg piroxicam *N* = 16	40 mg piroxicam *N* = 16	80 mg piroxicam *N* = 16
Time from LH surge to ovulation in the pre-treatment cycle	mean median range	47 47 35 – 58	48 47 33 – 72	44 47 24 – 58	58 49 32 – 96
Time from LH surge to ovulation in the treatment cycle	mean median range	55 50 33 – 72	133 65 38 – 416	121 63 37 – 384	219 276 48 – 386
Change in time from LH surge to ovulation (baseline = median pre-cycle)	mean median range	7 3 -15 – 25	85 17 -10 – 368	74 16 -11 – 337	171 228 1 – 338
Change in time from LH surge to ovulation (baseline = individual pre-cycle)	mean median range	8 9 -14 – 24	85 16 -15 – 360	77 20 -2 – 361	161 192 -25 – 337

Follicle size: This was classified according to "maximum follicle size <30 mm" and "maximum follicle size ≥30 mm." In the placebo group - and in all pre-treatment cycles with the exception of one subject on one side - maximum follicle sizes were <30 mm. After active treatment, there were 4 subjects in the category "≥30 mm" in each of the 20 mg and 40 mg piroxicam groups and 10 such subjects in the 80 mg piroxicam group. All but three subjects had luteinized unruptured follicles. As is known from several case reports and clinical studies, cyclo-oxygenase (COX) inhibitors are able to cause an increase in maximum follicle diameter of the dominant follicle and to increase the incidence of luteinized, unruptured follicles.

Hormone levels: Estradiol levels were maintained with larger scatter after dosing for all dose groups. For LH, FSH, and progesterone, no clear effects were seen.

Pharmacokinetics:
A population PK evaluation was performed in order to estimate PK parameters such as the area under the concentration-time curve from the time of piroxicam administration to infinity (AUC). The final population PK model describes the data well.

The piroxicam plasma data from all 55 subjects allocated to active treatment (20 mg piroxicam [N = 18], 40 mg piroxicam [N = 17], or 80 mg piroxicam [N = 20]), were used in the population PK evaluation. The median age was 29 years (range 21–35 years) and the median body weight was 62.8 kg (range 45.0–83.6 kg). The summary statistics of the PK parameters were calculated for all 55 subjects (PK data set), and also for a subset of 48 subjects whose ovulation or lack of ovulation ('no ovulation') was followed according to the study protocol (PD data set). The PK parameters AUC(0–$t_{ovulation}$) and AUC(0–$t_{no\ ovulation}$) could not be determined in one of the 48 women in the PD data set.

No deviation from linear pharmacokinetics within the dose range from 20 mg to 80 mg could be detected. The geometric mean of the apparent clearance (CL/F) was 0.140 L/h, the apparent volume (V/F) was 9.56 L and the half-life of elimination ($t_{1/2}$) was 47.3 h (PK data set). The geometric mean of the AUC values increased approximately linearly from 128 mg·h/L for 20 mg piroxicam to 308 mg·h/L for 40 mg and to 590 mg·h/L for 80 mg (PK data set).

The summary statistics for the derived PK parameters AUC(0–120h), AUC(0–t_{last}), AUC, and AUC/D for the PK data set (N = 55) are listed in Table 6 below.

Table 6: Derived pharmacokinetic parameters (geometric mean and geometric coefficient of variation in parenthesis) estimated based on the final population PK model in the PK data set (N = 55)

Parameter	Units	20 mg (*N*=18)	40 mg (*N*=17)	80 mg (*N*=20)
AUC(0–120h)	mg·h/L	107 (23.3%)	243 (25.0%)	469 (17.1%)
AUC(0–tlast)	mg·h/L	109 (27.5%)	249 (28.2%)	534 (24.5%)
AUC	mg·h/L	128 (32.1%)	308 (35.8%)	590 (24.0%)
AUC/D	h/L	6.39 (32.2%)	7.71 (35.8%)	7.37 (24.0%)

Table 7: Derived pharmacokinetic parameters (geometric mean and geometric coefficient of variation in parenthesis) estimated based on the final population PK model in the PD data set (N = 48)

Parameter	Units	20 mg (*N* = 16)	40 mg (*N* = 16)	80 mg (*N* = 16)
AUC(0–120h)	mg·h/L	107 (23.4%)	242 (25.7%)	470 (17.4%)
AUC(0–tlast)	mg·h/L	109 (28.2%)	249 (29.1%)	542 (25.5%)
AUC	mg·h/L	127 (32.3%)	304 (36.5%)	587 (23.5%)
AUC/D	h/L	6.33 (32.3%)	7.61 (36.5%)	7.34 (23.5%)
$AUC(0-t_{ovulation})$	mg·h/L	58.1 (27.8%) *N* = 12	138 (44.0%) *N* = 13	278 (30.1%) *N* = 7
$AUC(0-t_{no\ ovulation})$	mg·h/L	125 (43.1%) *N* = 4	304 (28.1%) *N* = 3	575 (25.6%) *N* = 8

PK/PD evaluation:
Based on the present data, no meaningful conclusions could be drawn for correlation of PK in terms of PK parameters and/or serum concentrations and PD.

Safety evaluation:
There were no deaths in the study. There was one serious adverse event (endometriotic cyst, left ovary), considered related to the study treatment with 80 mg piroxicam. No AE led to the premature withdrawal of a study subject. One pregnancy in the placebo group was discovered after study treatment; the pregnancy was later terminated by elective abortion.

The most frequent AEs occurring after the start of treatment (number of subjects in the placebo, 20 mg, 40 mg, and 80 mg piroxicam groups, respectively) were anovulatory cycle (0, 4, 5, and 10 subjects, respectively), pelvic pain (1, 1, 3, and 3 subjects, respectively), nasopharyngitis (0, 0, 2, and 4 subjects, respectively), dizziness (1, 1, 2, and 1 subjects, respectively), fatigue, (0, 2, 1, and 1 subjects, respectively), nausea (0, 1, 1, and 2 subjects, respectively), and pelvic discomfort (0, 1, 0, and 3 subjects, respectively). The relatively high incidence of decreased serum ferritin (4, 0, 3, and 3 subjects, respectively) was ascribed to the study procedure. Analysis by MedDRA system organ class revealed higher rates in the higher-dose groups for:

- Reproductive system and breast disorders (1, 4, 4, and 11 subjects in the placebo, 20 mg, 40 mg, and 80 mg piroxicam groups, respectively)
- Endocrine disorders (0, 4, 5, and 10 subjects, respectively)

- Gastrointestinal disorders (1, 1, 2, and 6 subjects, respectively)
- Infections and infestations (0, 1, 3, and 5 subjects, respectively).

The number of subjects with AEs considered causally related to the treatment with piroxicam was greatest in the 80 mg piroxicam group. Specifically, this was the case for anovulatory cycle, pelvic pain/discomfort and ovarian cysts, and for gastrointestinal disorders such as dyspepsia and flatulence.

Laboratory analyses gave no rise to concern about the safety of the study treatment.

Overall conclusions

In this study, all Pharmacodynamic analyses (primary and secondary responder analysis, time to ovulation, maximum follicle size) confirmed that the three dose levels of piroxicam delayed or prevented ovulation in the respective treatment groups, though not all individuals were equally affected, and that the 80 mg dose was the most effective in this respect. Statistical significance for rejection of equality was achieved in the primary analysis for all dose levels, and also for superiority of the 80 mg dose. This finding was supported by the secondary analysis.

Changes in duration from LH surge to ovulation based on the comparison with the median of the pre-cycle were increased by piroxicam (median changes were 3, 17, 16, and 228 hours after treatment with placebo and 20 mg, 40 mg, and 80 mg piroxicam, respectively).

The pharmacokinetic and safety profiles of piroxicam observed in this study corresponded well with those already known and reported.

Linear pharmacokinetics within the dose range from 20 mg to 80 mg were confirmed for piroxicam in a population PK evaluation, with a half-life for elimination of 47.3 hours.