Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
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:	23 AUG 2007
Study title:	A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the safety, tolerability and efficacy of the CCR1 antagonist ZK 811752, given orally in a dose of 600 mg three times daily, for the treatment of endometriosis over 12 weeks
Sponsor's study number:	91399
NCT number:	NCT00185341
EudraCT number:	2004-000630-37
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	This study was designed as a proof-of-concept trial to evaluate safety, tolerability, and the efficacy of 1800 mg (ZK 811752 600 mg given orally three times daily) over 12 weeks for the treatment of endometriosis-associated pelvic pain (EAPP) in comparison to placebo.
Test drug:	CCR-1 Receptor Antagonist (BAY 86-5047, ZK 811752)
Name of active ingredient(s):	CCR-1 Receptor Antagonist
Dose:	2 x 300 mg tablets, 3 times daily
Route of administration:	Oral
Duration of treatment:	84 days (12 weeks)
Reference drug:	Placebo
Dose	2 tablets, 3 times daily
Route of administration	Oral
Duration of treatment	84 days (12 weeks)
Indication:	Endometriosis
Diagnosis and main criteria for inclusion:	• Symptomatic female subjects suffering from visually proven endometriosis, age 18-45 years inclusive, fertile and non-fertile • Women with cyclic menstrual bleeding • Good general health • Willingness to use a barrier contraceptive method such as condoms but no hormonal contraception • Willingness to use only up to 3 ibuprofen 400 tablets as pain killer for endometriosis-related pelvic pain
Study design:	The study was conducted in a multicenter, double-blind, randomized,

	placebo-controlled, parallel-group design in women of reproductive age.
Methodology:	EAPP was assessed by a composite parameter, consisting of the reading of the visual analog scale (VAS) and the intake of rescue medication, each covering an observation period of 4 weeks preceding the respective time point of assessment. Several other medical parameters (Biberoglu & Behrman severity profile for symptoms and findings, or B&B) and non-medical parameters (global assessment of efficacy) were also assessed. Safety aspects monitored throughout the study were adverse events (AEs), electrocardiogram (ECG) monitoring, bleeding pattern, gynecological safety, and laboratory evaluations.
Study center(s):	The study was conducted at four centers in Czech republic, two centers in Denmark, six centers in Spain, six centers in Finland, one center in France, three centers in Netherlands, and six centers in Sweden
Publication(s) based on the study (references):	None at the time of report creation
Study period:	**Study Start Date:** 08 FEB 2005 **Study Completion Date:** 15 FEB 2007
Number of subjects:	**Planned:** 116 subjects **Randomized:** 110 subjects **Analyzed:** 110 subjects
Criteria for evaluation	
Efficacy:	The *primary efficacy variable* was the two-dimensional vector defined by the following two constituents, from Visit 2 (baseline) to Visit 7 (end of treatment or EOT) of the individual absolute change in EAPP determined by: • Change in VAS (in mm) • Intake of rescue medication *Secondary efficacy* variables were as follows: • Individual absolute EAPP change between Visits 2 and 7, by evaluating VAS change • Individual change in rescue medication intake between Visits 2 and 7 • VAS for EAPP taken at Visit 2, every 4 weeks throughout the treatment period, and at Visit 7 • Intake of rescue medication due to EAPP as recorded in the subject diaries • B&B score recorded at Visits 2, 7, and 8 • Global assessment of efficacy by subject and investigator at Visit 7

	in accordance with the Clinical Global Impressions (CGI) scale
Safety:	• Adverse events (AEs) • Laboratory evaluations (urinalysis, serum chemistry, coagulation, hematology, thyroid profile, glucose, HbA1c, human immunodeficiency virus, and hepatitis serology) • ECG monitoring • Vital signs (heart rate, blood pressure) • Physical and gynecological examinations (including breast palpation and cervical smear) • Pregnancy tests • Bleeding pattern assessment
Statistical methods:	**Primary efficacy:** The approximate likelihood ratio (ALR) test according to Tamhane and Logan, and a sensitivity analysis using a 3-step hierarchical testing procedure according to Röhmel et al., step 1 being non-inferiority tests of both single variables, step 2 using Läuter's standard sum test, and step 3 being superiority tests of each variable were used. **Secondary efficacy:** Superiority analysis of change in EAPP from Visits 2 and 7, and for B&B scores; descriptive statistics for VAS values at Visits 2 and 7, for intake of rescue medication, and for CGI scores at Visit 7; descriptive statistics and responder analysis for B&B scores at Visits 2, 7 and 8 were used. **Safety:** Tabulation of AEs, pregnancies and ECGs, descriptive statistics for laboratory values, vital signs, physical and gynecological examinations, and bleeding pattern were used.
Substantial protocol changes:	Amendment 1 from 22 NOV 2004 introduced the following changes: • Substitution of the condition 'histologically proven endometriosis' by the condition 'visually proven endometriosis' in the inclusion criteria • Determination of an additional laboratory parameter (CA125) and postponement of the determination of the immunological parameter. • Decision to use electronic data capture (EDC) and an electronic diary within this study

Subject disposition and baseline

From 157 screened subjects, 110 subjects (54 on placebo / 56 on ZK 811752) were randomized and comprised the full analysis set (FAS), the analysis set of choice for the primary efficacy variable. The per protocol set (PPS) comprised 90 subjects without any major protocol deviations (48 on placebo / 42 on ZK 811752), among whom 84 subjects (47 on placebo / 37 on ZK 811752) had taken at least 80% of study medication.

Ninety-one subjects (48 on placebo/43 on ZK 811752) completed the study medication intake. Study medication was prematurely discontinued by 19 subjects (6 on placebo/13 on ZK 811752), either due to AEs (4 on placebo/11 on ZK 811752), protocol deviation (1 on placebo), loss to follow-up (1 on placebo), pregnancy (1 on ZK 811752), or desire for pregnancy (1 on ZK 811752). Twelve subjects prematurely discontinued the study course during the follow-up phase (3 on placebo/9 on ZK 811752) for "other" reasons described as AEs (nausea, vertigo, abdominal pain, blackout episodes, tiredness, cold), prolonged QT-time, pregnancy, or journey abroad.

The study population was largely Caucasian (108 subjects or 98.2% of FAS) with similar demographic and baseline characteristics across both treatment groups.

Efficacy evaluation

All evaluations for primary and secondary endpoints failed to show any difference between ZK 811752 and placebo after 12 weeks of treatment.

The primary efficacy variable whereby the null hypotheses of no effect in both components was tested with Tamhane and Logan's ALR test, at a level of significance of alpha = 0.05 against the one-sided alternative of a non-zero effect in at least one component, failed to show a statistical significant difference between ZK 811752 and placebo (p-value for FAS = 0.7500) after 12 weeks of treatment (see Table 1).

The 3-step sensitivity analysis according to Röhmel et al (testing hypotheses H_{20}, H_{30}, and H_{40}) also failed to show superiority of ZK 811752 against placebo (p-value for FAS = 0.6665). For the PPS only, non-inferiority (hypothesis H_{20}) could be demonstrated for VAS (difference below pre-specified margin of 15 mm), but not for rescue medication intake (difference not below 6 tablets). As step 2 testing failed (hypothesis H_{30}), step 3 testing was not performed.

Table 1: Primary efficacy variables after 12 weeks of treatment: Test statistics and p-values – FAS and PPS

	Analysis set	Value of test statistic	p-value
Tamhane-Logan statistic for ALR test (H_{10})	FAS	0.00	0.7500
	PPS	0.06	0.6470
Läuters test statistic (H_{30}) according to Röhmel et al.'s test procedure	FAS	0.43	0.6665
	PPS	0.24	0.5952

FAS = full analysis set; PPS = per-protocol set; ALR = approximate likelihood test

The calculation of the ALR test statistic needed the assumption of normality for the changes to baseline in VAS and rescue medication intake. This assumption was tested and holds true for VAS (Shapiro Wilk test p-value = 0.096) but not for rescue medication intake (Shapiro-Wilk test p-value = 0.000; as the intake of ibuprofen was very low, no change at all could be noted for most subjects).

The secondary efficacy variable, change in VAS compared to baseline, evaluated by testing the null hypothesis H_{50}: $V_Z < V_{placebo}$ against the one-sided alternative H_{5A}: $V_Z \geq V_{placebo}$ (where V_Z and $V_{placebo}$

denote the mean V scores assessed at end of treatment for ZK 811752 and placebo, respectively), also failed to show a statistical significant difference between ZK 811752 and placebo (p-value for FAS = 0.4536); see Table 2.

Table 2: Secondary efficacy: t-tests evaluating treatment difference (ZK 811752 - placebo) for VAS and rescue medication intake after 12 weeks of treatment - FAS and PPS

	Analysis set	Mean difference	p-value	95%-CI
VAS (H_{50})	FAS	3.89	0.4536	[-6.42, 14.21]
	PPS	-0.41	0.9393	[-11.10, 10.28]
Rescue medication intake	FAS	0.84	0.8227	[-6.47, 8.14]
	PPS	1.36	0.6402	[-4.63, 7.35]

VAS = Visual Analog Scale, CI = confidence interval; FAS = full analysis set; PPS = per protocol set

Note that changes to baseline for both VAS and rescue medication intake were typically negative. However, the calculations shown in the table above take into consideration the treatment difference (ZK 811752 – placebo) of the changes. Hence, a positive mean value (above) indicates that the decrease was greater in the placebo group compared to the ZK 811752 group. The standard deviation of the difference was approximately 27 mm, which is well below the assumption made when determining sample size for this study.

The B&B score did not show any significant differences between ZK 811752 and placebo, neither in its total score (p-value = 1) nor its categories (see Table 3 below).

Table 3: Secondary efficacy: t-tests evaluating treatment difference for B&B scores after 12 weeks of treatment - FAS only

	N_T / N_P	Mean difference	p-value	95% CI
Total B&B score	51 / 51	0	1	[−0.34 , 0.34]
Pelvic pain	51 / 51	0.12	0.4618	[−0.20 , 0.43]
Dysmenorrhea	51 / 51	−0.04	0.8172	[−0.37 , 0.30]
Dyspareunia	48 / 43	0.33	0.0793	[−0.04 , 0.70]
Pelvic tenderness	51 / 51	0.06	0.6839	[−0.23 , 0.35]
Induration	51 / 51	0.12	0.4333	[−0.18 , 0.41]

Abbreviations: N_T / N_P = Number of subjects on ZK 811752 / number of subjects on placebo; B&B = Biberoglu & Behrman severity profile; CI = confidence interval; FAS = full analysis set; PPS = per-protocol set

For responder analysis using B&B scores (a subject was considered to be a responder if 3 out of 5 categories of the B&B questionnaire showed improvement), there were 9 responders from the placebo group compared to 5 responders from the ZK 811752 group, ie, placebo: total 54 subjects; proportion 16.67%; CI [8.3%, 25.0%]; ZK 811752: total 56 subjects; proportion 8.93%; CI [2.7%, 15.2%].

Global assessment of efficacy using the CGI questionnaire did not show a treatment difference, neither for assessments by subjects (eg, much satisfied 38.5% for placebo; 39.2% for ZK 811752) nor by investigators (eg, much improved 28.5% for placebo; 33.3% for ZK 811752).

Result for secondary efficacy variables VAS for EAPP taken at Visit 2, every 4 weeks throughout the treatment period, and at Visit 7 and intake of rescue medication due to EAPP as recorded in the subject diaries, are not available.

Safety evaluation

There were no deaths during this study.

AEs which led to dose reductions occurred mainly in the ZK 811752 group (20 AEs for 11 subjects vs 1 AE for 1 subject on placebo). These AEs were most commonly gastrointestinal disorders, ie, nausea (8 subjects/14.3%) and vomiting (3 subjects/5.4%).

Study medication was prematurely discontinued due to AEs for 15 subjects: 4 subjects / 4 AEs for placebo, 11 subjects / 17 AEs for ZK 811752. Gastrointestinal disorder was also the commonest cause for withdrawals, ie, nausea (4 subjects / 7.1% ZK 811752) and vomiting (3 subjects / 5.4% ZK 811752).

Eight nonfatal serious AEs (SAEs) were reported for 5 subjects: using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms vertigo and headache (2 SAEs for 1 subject), dysmenorrhea (reported as 3 SAEs for 1 subject), carcinoma in situ (CIN III), abortion spontaneous, and ankle fracture. All except for 2 of these subjects (ankle fracture and vertigo with headache) had completed the full course of the study medication. Three SAEs for 2 subjects were considered by the investigator to be possibly related to study medication, ie, vertigo and headache for 1 subject on placebo, and cervical dysplasia for 1 subject on ZK 811752. All other SAEs were not considered to be related to the study medication.

Five pregnancies were reported, one of which ended in miscarriage and was reported as an SAE (subject on placebo).

Clinical laboratory investigations and other safety examinations (bleeding pattern, physical and gynecological examinations, cervical smear, vital signs, ECG) gave no reason for concern.

Overall conclusions:

- Efficacy analysis of the visual analog scale and rescue medication intake failed to show any treatment difference between ZK 811752 and placebo, given orally 3 times daily over 12 weeks in subjects with endometriosis. As none of the efficacy criteria for proof of concept were met, the development of this project was terminated.

- No significant safety concerns arose. The pattern of AEs was expected and the dose of 3 x 600 mg daily was well tolerated.