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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	15105	NCT01295294
Study Phase:	IV Interventional	
Official Study Title:	International, prospective, double-blind, 3-arm comparative, randomized, placebo-controlled phase IV study on the effect of counseling and either tranexamic acid or mefenamic acid or placebo, on the management of bleeding/spotting in women using the levonorgestrel-releasing intrauterine system (MIRENA) for contraception.	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	Tranexamic acid or mefenamic acid	
Name of Active Ingredient:	Tranexamic acid or mefenamic acid	
Dose and Mode of Administration:	Tranexamic acid, 500 mg 3 times daily orally during bleeding/spotting episodes Mefenamic acid, 500 mg 3 times daily orally during bleeding/spotting episodes	
Reference Therapy/Placebo		
Reference Therapy:	Placebo	
Dose and Mode of Administration:	3 times daily orally during bleeding/spotting episodes	
Duration of Treatment:	90 days	
Studied period:	Date of first subjects' first visit:	04 Mar 2011
	Date of last subjects' last visit:	19 December 2011
Premature Study Suspension / Termination:	NA	
Substantial Study Protocol Amendments:	NA	
Study Centre(s):	6 recruiting study centers in Denmark, 3 in Ireland, and 3 in Norway	
Methodology:	Subject diary to assess the number of bleeding / spotting days during the initial 120 days of levonorgestrel-releasing intrauterine system use	

	The double-blind treatment period with oral blinded study drug treatment was planned to last for 90 days, followed by a 30 day follow-up period without oral blinded study drug treatment while levonorgestrel-releasing intrauterine system use was continued. Oral blinded study drug treatment was initiated upon occurrence of a bleeding / spotting episode until bleeding / spotting stopped. Oral blinded study drug treatment was re-started upon occurrence of a new bleeding / spotting episode during the 90 day double-blind treatment period. The oral blinded study drug treatment was not allowed to be used during the 30 day follow-up period.
Indication/ Main Inclusion Criteria:	Contraception Fertile healthy women aged 18 to 45 years inclusive, who were planned to have insertion of the levonorgestrel-releasing intrauterine system for contraception Interval insertion (within 7 days of the onset of menstruation / withdrawal bleeding) Regular menstrual cycles (length of cycle 21 to 35 days)
Study Objectives:	Overall: Not Applicable Primary: To investigate if tranexamic acid and / or mefenamic acid were superior to placebo in the management of bleeding / spotting during the first 90 days of levonorgestrel-releasing intrauterine system use Secondary: To detect/exclude the possibility that the active oral blinded study drug treatment for bleeding / spotting would only postpone initial bleeding / spotting, to compare the number of bleeding / spotting days during the 30 day follow-up period in the 3 treatment groups, and the change in the number of bleeding / spotting days between Day 60 and Day 90 of levonorgestrel-releasing intrauterine system use (last 30 days on oral blinded study drug) and the 30 day follow-up period in the 3 treatment groups To investigate subject satisfaction and continuation rate with tranexamic acid, mefenamic acid, or placebo treatment for bleeding / spotting To investigate subject satisfaction and continuation rate with the levonorgestrel-releasing intrauterine system in women treated with tranexamic acid, mefenamic acid, or placebo for bleeding / spotting To investigate the safety of tranexamic acid and mefenamic acid in the management of bleeding / spotting during the first 90 days of levonorgestrel-releasing intrauterine system use To investigate the occurrence of dysmenorrhea before and after levonorgestrel-releasing intrauterine system insertion in women

	treated with tranexamic acid, mefenamic acid, or placebo for bleeding / spotting and the effect of oral blinded study drug treatment for bleeding / spotting on the need fo pain medication for dysmenorrheal.
Evaluation Criteria:	Efficacy (Primary): The cumulative number of bleeding / spotting days during the 90 day double-blind treatment period. Efficacy (Secondary): Number of bleeding-only days Number of spotting-only days Number of bleeding / spotting episodes Length of bleeding / spotting episodes Number of bleeding days with heavy intensity Number of days and number and length of episodes of oral blinded study drug treatment during the 90 day treatment period Number of bleeding / spotting days, number of bleeding-only days, number of spotting-only days, number of bleeding / spotting episodes, and number of bleeding days with heavy intensity, during the 30 day follow-up period Change in the number of bleeding / spotting days between Day 60 and Day 90 of levonorgestrel-releasing intrauterine system use (last 30 days on oral blinded study drug) and the 30-day follow-up period Satisfaction with oral blinded study drug treatment for bleeding / spotting Continuation rate with the oral blinded study drug treatment during the 90 day treatment period Continuation rate with levonorgestrel-releasing intrauterine system including the 30 day follow-up period Satisfaction with levonorgestrel-releasing intrauterine system Occurrence of dysmenorrhea before and after levonorgestrel-releasing intrauterine system insertion Number of days of pain medication for dysmenorrhea during the 90 day treatment period

	Safety: Adverse event collection
Statistical Methods:	Efficacy (Primary): The cumulative number of bleeding / spotting days during the 90 day observation period in the placebo group was compared pairwise with the 2 active oral blinded study drug treatment groups with a 1-sided non-parametric Wilcoxon rank sum test. To take the multiplicity testing into account, the alpha level was adjusted using the Bonferroni-Holm procedure. Efficacy (Secondary): In addition to the primary analysis comparing tranexamic acid vs. placebo and mefenamic acid vs. placebo, a direct comparison of tranexamic acid vs. mefenamic acid was performed using a 2 sided Wilcoxon rank sum test providing the P value, Hodges-Lehmann estimate, and corresponding 95% confidence interval. This analysis was descriptive only, therefore no adjustment had to be performed. Descriptive statistics of the cumulated number of B/S days were provided for each treatment group for the 90 day double-blind treatment period and each 30 day RP. Point estimates and 95% confidence intervals (Hodges-Lehmann estimates) for the number of B/S days for each treatment group were provided for the 90-day double-blind treatment period and each 30-day RP. Box plots and histograms were presented. Descriptive analyses of the primary efficacy variable were provided using the FAS and, in addition, the PPS, based on the 90-day RP as well as on each 30-day RP. For each of those analyses, only subjects with valid corresponding RP were considered. Safety: Individual listings of adverse events (including age, weight, height, adverse event as reported, start, duration, severity, relation to study drug) were provided by treatment group for the FAS only. The incidences of treatment-emergent adverse events and treatment-emergent, drug-related adverse events, respectively, were summarized by treatment group using MedDRA.
Number of Subjects:	204 subjects

Study Results

Results Summary — Subject Disposition and Baseline

A total of 204 subjects were enrolled in this study, 93 subjects in 6 study centers in Denmark, 34 subjects in 3 study centers in Ireland, and 77 subjects in 3 study centers in Norway.

Following successful MIRENA insertion, 187 subjects were randomized to receive tranexamic acid (n=63), mefenamic acid (n=63), or placebo (n=61) as oral blinded study drug. 170

subjects of the FAS completed the 90 day treatment period and 167 subjects completed the 30 day follow-up period

Results Summary — Efficacy

In the main analysis of the primary efficacy variable in the full analysis set, both active oral treatments turned out to be not superior to placebo, i.e. both null hypotheses were retained and the Bonferroni-Holm procedure stopped after the first comparison. Based on the number of bleeding / spotting days during the 90 day treatment period, tranexamic acid tended to be superior to placebo with a Hodges-Lehmann estimate for the difference of 6 days, which is a clinically relevant difference although not statistically significant.

Results for the secondary variables were predominantly similar in all 3 treatment groups without clear evidence for an advantage of one particular oral blinded study drug over the 2 others. Nonetheless, tranexamic acid tended to be superior to placebo concerning some secondary variables.

Results Summary — Safety

Overall, the combination of MIRENA use together with tranexamic acid or mefenamic acid use upon occurrence of bleeding / spotting episodes was safe and well tolerated during the first 90 days after MIRENA insertion. The safety profiles of those treatments corresponded to the well-known safety profiles of their components.

Conclusion(s)

Neither treatment with tranexamic acid and mefenamic acid resulted in ≥ 25% reduction in the bleeding/spotting days during initial 3 months of MIRENA use. However, tranexamic acid tended to be associated with fewer bleeding/spotting days, shorter bleeding/spotting episodes and greater satisfaction, compared with mefenamic acid or placebo.

The satisfaction rates and continuation rates with MIRENA were equally high in all three treatment groups. Treatments were well tolerated.

Publication(s):	Not Applicable
Date Created or Date Last Updated:	1 March 2013

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Mirena
Brand/Trade Name(s) ex-US	Mirena LNG
Generic Name	Levonorgestrel
Main Product Company Code	BAY86-5028
Other Company Code(s)	
Chemical Description	Levonorgestrel: (-)-13-Ethyl-17-hydroxy-18,19-dinor-17alpha-pregn-4-en-20-yn-3-one
Other Product Aliases	

Date of last Update/Change: 14 Aug 2014