This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2.0 SYNOPSIS

SCHERING-PLOUGH RESEARCH INSTITUTE, A DIVISION OF SCHERING CORPORATION, A SUBSIDIARY OF MERCK & CO., INC. (hereafter referred to as Merck) SCH 900342 Etonogestrel-releasing medicated intrauterine system Contraception	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A RANDOMIZED, MULTICENTER, EXPLORATIVE TRIAL TO EXPLORE THE SAFETY, ACCEPTABILITY AND VAGINAL BLEEDING PATTERN OF THREE DOSES OF AN ETONOGESTREL-RELEASING MEDICATED INTRAUTERINE SYSTEM (ENG-MIUS, SCH 900342, ORG 3236) VERSUS A COPPER-RELEASING INTRAUTERINE DEVICE (IUD) (Protocol No. P06060) #P06060

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter: 4 centers in Germany and The Netherlands

PRIMARY THERAPY PERIOD: 03 Dec 2009 – 26 Jul 2011 | **CLINICAL PHASE:** 2

DURATION OF TREATMENT: After a screening phase of maximally 2 months, each subject was to receive assigned treatment for 6 months with a possible extension (dependent on the subject's choice) to 12 months. After the end of (extended) treatment each subject was to be followed for 2 months.

OBJECTIVE(S):

Primary Study Objective:

To explore safety and acceptability of three doses of an etonogestrel-releasing medicated intrauterine system (ENG-MIUS) as compared to Multiload-cu 375® (Multiload).

Secondary Study Objectives:

To explore the effect of three doses of ENG-MIUS as compared to Multiload on the following:
- Vaginal bleeding pattern
- Ovarian function
- Cervical mucus and endometrial thickness
- Contraceptive efficacy

To explore for three doses of ENG-MIUS the following:
- ENG serum pharmacokinetics
- In vitro-in vivo correlation (IVIVC)

STUDY DESIGN: Explorative, randomized, active-controlled, parallel-group, multicenter, single-blind study

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SUBJECT DISPOSITION: A total of 86 female subjects (age range 19 to 40 years) were randomized and treated, 21 subjects to the low dose ENG-MIUS, 22 subjects to the intermediate dose ENG-MIUS, 21 subjects to the high dose ENG-MIUS, and 22 subjects to Multiload. Fourteen subjects (16%) discontinued the treatment phase, 16 subjects completed the treatment phase and stopped after 6 months, and 56 subjects entered the extended treatment phase (11 subjects in the low dose ENG-MIUS group, 13 subjects in the intermediate dose ENG-MIUS, 14 in the high dose ENG-MIUS, and 18 in the Multiload). The majority of subjects who did not enter the extended treatment phase (13 of 16 subjects) were part of the PK/PD subgroup, which had a more extensive visiting schedule in the first 6-months as compared to the rest of the subjects. Six subjects discontinued the extended treatment phase and 50 subjects completed it.

DOSAGE/FORMULATION NOS.:

Test Product, Dose, Mode of Administration, Batch No(s):

Medicated intrauterine system containing an ENG-releasing [redacted] with three different daily release rates of ENG (SCH 900342) as determined by the thickness of the outer ethylene vinyl acetate (EVA) layer ('skin') in combination with the ENG content:

- Low dose: 38 mg ENG with a skin thickness of approximately 350 µm (Batch no: [redacted]
- Intermediate dose: 61 mg ENG with a skin thickness of approximately 140 µm (Batch no: [redacted]
- High dose: 72 mg ENG with a skin thickness of approximately 50 µm (Batch no: [redacted]

[redacted] The ENG-MIUS was inserted on the day of randomization by the investigator or qualified designee.

Reference Therapy, Dose, Mode of Administration, Batch No:

Multiload (Batch no: [redacted]

The IUD was inserted on the day of randomization by the investigator or qualified designee.

DIAGNOSIS/INCLUSION CRITERIA: Healthy female subjects in need of contraception were to be selected to participate in the study. Each subject was ≥18 to ≤40 years of age at screening, in need of contraception, had given birth to at least one child (gestational age ≥28 weeks), and had a uterus with a measured length between 6.0 and 9.0 cm (extremes included) from external os to fundus uteri.

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EVALUATION CRITERIA:

Efficacy variables: Bleeding and spotting were to be recorded daily by the subject in the electronic diaries. Vaginal bleeding pattern parameters included number of bleeding/spotting days, number of bleeding days, number of spotting days, length of bleeding/spotting episode, length of bleeding episode, length of spotting episode, all per 30 days and per 91-day reference period, and the occurrence of amenorrhea per 91-day reference period. Ovarian function as determined by follicle growth using transvaginal ultrasound and by measurement of hormone serum levels of progesterone, 17β-estradiol (E2), luteinizing hormone (LH), and follicle stimulating hormone (FSH). Cervical mucus receptivity as assessed by the Insler score. Endometrium thickness as assessed by transvaginal ultrasound. Contraceptive efficacy by pregnancy reporting.

Safety / Acceptability variables: MIUS/IUD insertion and removal characteristics by means of an investigator questionnaire. (Serious) Adverse Event ([S]AE) reporting (including device/subject events and incidents). Subject's satisfaction with the MIUS/IUD by means of a subject questionnaire, and by determination of discontinuation rates, reason for discontinuation or not proceeding with extended treatment phase, and continuation rates after 6 months of treatment. Routine laboratory assessments, vital signs, body weight, cervical cytology, endometrium histology, and ultrasound position of the MIUS/IUD.

Pharmacokinetics: Blood samples from the Pharmacokinetics/Pharmacodynamics (PK/PD) subgroup for the assessment of ENG serum levels and estimation of PK parameters.

Technical Inspection of the Removed MIUS/IUD: All removed MIUSs/IUDs were to be sent to the sponsor for technical inspection.

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STATISTICAL PLANNING AND ANALYSIS:

Efficacy Analysis:

The primary efficacy endpoint for this study was the vaginal bleeding pattern defined as the number of bleeding and/or spotting days in the second reference period of 91 days. This was analyzed for the Full Analysis and Per Protocol data sets. Summary statistics are presented by treatment group. No statistical tests were performed.

The secondary efficacy endpoints for this study are as follows: other vaginal bleeding pattern parameters; and ovarian function and mucus receptivity (Insler score), which were only assessed in the PK/PD subgroup. The incidence of suspected ovulation was based on ultrasound or on progesterone levels measured during Month 1 and Month 5/6; endometrial thickness; contraceptive efficacy, which was expressed as the number of in-treatment pregnancies. All parameters were analyzed for the Full Analysis and Per Protocol data sets. Summary statistics are presented for continuous parameters, and frequency tables are provided for categorical parameters. No statistical tests were performed.

Safety Analysis:

The descriptive safety endpoints related to the primary study objective were insertion and removal characteristics, (serious) adverse event reporting, and subject's satisfaction. The primary analysis was done after 6 months of treatment, and the secondary analysis was done after 12 months of treatment.

Other descriptive safety endpoints included routine laboratory assessments, vital signs, body weight, cervical cytology, endometrium histology, and ultrasound position of the ENG-MIUS. The safety endpoints were analyzed for the All Randomized data set. Summary statistics are presented for continuous variables and frequency tables for categorical variables. No statistical tests were performed.

Other Analyses:

Pharmacokinetics: The main PK parameters calculated after ENG-MIUS administration were the peak concentration (Cmax) and its time of occurrence (tmax), the area under the curve (AUC5mnt, AUC6mnt and AUC12mnt), and the average concentration ($C_{avg\ 5mnt}$, $C_{avg\ 6mnt}$ and $C_{avg\ 12mnt}$). Descriptive statistics for the pharmacokinetic parameters of ENG were calculated. Individual overlay and mean concentration-versus-time plots by dose were made.

Technical inspection findings of the removed MIUS/IUD are described.

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RESULTS:

Demographics and Other Baseline Characteristics:

The demographics of the subjects were similar between the treatment groups with respect to age, race and ethnicity. Overall, the mean (SD) age was 31.6 (5.4) years with 65% of the subjects being 30 years or older. All subjects were white and not Hispanic or Latino. Body weight and BMI were lower in the high dose ENG-MIUS group as compared to the other groups. Overall, the mean BMI (SD) was 25.26 (4.57) kg/m^2 and the median 24.15 kg/m^2. The demographics of the subjects who entered the extended treatment phase were similar to the demographics of the entire group of subjects.

Most gynecological data were similar between the treatment groups; the majority of subjects (at least 71% per treatment group) had moderate volume of menstrual flow. The majority of subjects had one or two pregnancies in the past, and had one or two children (74% and 91%, respectively). Almost all subjects (99%) used some form of contraception before the study. Nine subjects (10.5%), at least one in each treatment group, were breastfeeding at the time of screening.

Efficacy:

The low and high dose ENG-MIUS groups show a favorable bleeding pattern (with respect to bleeding/spotting as well as bleeding alone) as compared to the intermediate dose ENG-MIUS group and the Multiload group. The mean number of bleeding/spotting days in the second reference period was 10.4 and 6.8 days in the low and high dose ENG-MIUS groups, respectively, and consisted mainly of spotting days. In the intermediate dose ENG-MIUS group and the Multiload group, the mean number of bleeding/spotting in the second reference period was 29.1 and 25.1 days, respectively. The mean number of bleeding/spotting days clearly decreased from Month 3 onwards to very low means in Month 6 in the low and high dose ENG-MIUS group (3.5 and 1.0 days, respectively), whereas only a slight decrease was observed in the other two treatment groups. The mean number of bleeding/spotting days remained low towards Month 12 in the low and high dose ENG-MIUS groups.

In the second reference period, amenorrhea occurred in all ENG-MIUS groups but not in the Multiload group. The percentage of subjects with amenorrhea was highest in the high dose ENG-MIUS group, ie, 41.7%. Of the subjects who entered the extended treatment phase, more than 50% in the low and high dose ENG-MIUS groups had amenorrhea in reference period 4, but the numbers were small.

Suspected ovulation, as assessed by ultrasound, was observed in almost all subjects in the Multiload group (10 of 11 subjects (90.9%) in both Month 1 and Month 5/6). None of the subjects in the high dose ENG-MIUS group had suspected ovulation in Month 1 and only 1 (11.1%) in Month 5/6. In the low and intermediate dose ENG-MIUS groups, suspected ovulation was reported more often, with higher numbers in the low dose ENG-MIUS group in both Month 1 (50% vs 9%, respectively) and Month 5/6 (87.5% vs 44%, respectively). None of the subjects in the high dose ENG-MIUS group had a progesterone value >5 ng/mL and in the intermediate dose group only 1 subject in each assessment period. In the low dose ENG-MIUS group, 70% of the subjects had at least once a progesterone value >5 ng/mL in both assessment periods combined, compared to all subjects in the Multiload group.

The mean maximum follicle diameter in Month 1 was lowest in the high dose ENG-MIUS group (15.2 mm), compared to 29.9 mm in the low dose ENG-MIUS group, 27.8 mm in the intermediate dose ENG-MIUS group, and 19.1 mm in the Multiload group. In Month 5/6, the mean maximum

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follicle diameter was similar in the low and high dose ENG-MIUS groups, and in the Multiload group (range 17.9 to 18.9 mm). In the intermediate dose ENG-MIUS group, the mean maximum follicle diameter was large in Month 5/6 (33.3 mm).

In the high dose ENG-MIUS group, progesterone and E2 values were clearly suppressed to mean values below 0.5 ng/mL and around 50 pg/mL, respectively, LH values were decreased compared to the Multiload group (mean value around 4 mU/mL), whereas FSH values were higher in the six-month treatment phase. The E2 values were still suppressed to below 50 pg/mL at the 12-month time point. Also in the intermediate dose ENG-MIUS group, progesterone values were suppressed to mean values below 1.6 ng/mL. However, E2 values were higher than in the Multiload group, with peak mean values up to 250 pg/mL in Month 1 and very fluctuating values in Month 5/6. The LH surge seemed to be suppressed in the intermediate dose ENG-MIUS group. In the low dose ENG-MIUS group, reasonably high progesterone values were observed with a mean peak value of 4.7 ng/mL in Month 1. Mean E2 values were in the range of the values in the intermediate dose ENG-MIUS group in Month 1 and similar to the values in the Multiload group in Month 5/6. The peak mean LH value was 6.9 mU/mL in Month 1, which was similar to the value in the intermediate dose ENG-MIUS group (7.1 mU/mL). In the Multiload group, the hormone patterns were compatible with a normal ovulatory cycle.

The mean endometrial thickness tended to be somewhat larger in the Multiload group as compared to the ENG-MIUS groups. At Month 3 and Month 6, the mean endometrial thickness was largest in the Multiload group (7.0 mm) (Full Analysis Set). In the ENG-MIUS groups, the largest mean endometrial thickness in Month 3 was measured in the high dose ENG-MIUS group (6.5 mm) and in Month 6 in the intermediate dose ENG-MIUS group (5.6 mm), but the differences were small especially at Month 6. After Month 6, the endometrial thickness did not change remarkably in any of the treatment groups. In general, the endometrial thickness increased from Day 1 to Day 11 or Day 15 in Month 1, after which the thickness more or less stabilized in all treatment groups (PK/PD Subgroup).

Cervical mucus receptivity (PK/PD Subgroup) seemed to be decreased in the ENG-MIUS groups as compared to the Multiload group. The majority of the subjects in the Multiload group had a maximum Insler score of >9 in both Month 1 (72.7%) and Month 5/6 (63.6%). In contrast, only one (11.1%) of the subjects in the high dose ENG-MIUS group had a maximum Insler score of >9 in Month 1 and none in Month 5/6. In Month 5/6, the percentage of subjects having a maximum Insler score of >9 was lower in the low dose ENG-MIUS group (12.5%) as compared to the intermediate dose ENG-MIUS group (44.4%), whereas this was similar in Month 1 (50% vs 40%, respectively).

Safety:

The number of subjects who reported at least one AE ranged from 76% (high dose ENG-MIUS group) to 95% (Multiload group) during the six-month treatment phase, and was lower in the extended treatment phase (range 43% to 55%). The number of subjects who discontinued due to an AE during the six-month treatment phase was lowest in the high dose ENG-MIUS group (1 subject) and highest in the low dose ENG-MIUS group (5 subjects). Four subjects (3 in intermediate and 1 in high dose ENG-MIUS group) discontinued due to an AE in the extended treatment phase. Drug-related AEs were reported for 52% to 67% of the subjects per treatment group, and device-related AEs for 43% to 52% of the subjects in the six-month treatment phase. These percentages were clearly lower in the extended treatment phase.

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Two in-treatment SAEs were reported, ie, 'pelvic inflammatory disease' and 'drug abuse'. The SAE 'pelvic inflammatory disease' (intermediate dose ENG-MIUS) started at Day 29, 1 day after removal of the ENG-MIUS, and was judged as being unlikely related to the study drug and possibly related to the device. The subject recovered. The SAE 'drug abuse' was reported at Day 6. The SAE was judged as unlikely related to both the drug and the device. The outcome of this SAE is unknown.

Adverse events were reported most frequently in the SOCs ‘reproductive system and breast disorders’ and ‘infections and infestations’ in both treatment phases. In the six-month treatment phase, the lowest percentages of subjects with an AE in these SOCs were reported in the high dose ENG-MIUS group. In the extended phase, this was also the case in the ‘reproductive system and breast disorders’ SOC, whereas in the ‘infections and infestations’ SOC no clear difference was seen between the treatment groups. The most frequently reported AEs were 'pelvic pain', 'nasopharyngitis', 'headache', and 'ovarian cyst' in the six-month treatment phase and 'nasopharyngitis', 'influenza', and 'ovarian cyst' in the extended treatment phase. For 'ovarian cyst', the numbers of subjects were clearly lower in the high dose ENG-MIUS group and the Multiload group as compared to the other two treatment groups. For the other AEs, no clear difference between the treatment groups was found.

The most frequently reported drug-related AEs (ie, AEs related to the drug etonogestrel) were 'pelvic pain', 'ovarian cyst', and 'headache'. The most frequently reported device-related AE was 'pelvic pain'.

A total of 10 subjects (12%) in the six-month treatment phase and 4 subjects (7%) in the extended treatment phase reported AEs which led to study discontinuation. The most frequently reported AEs were ‘device expulsion’ or 'device dislocation' (n=7), and ‘menstruation irregular’ (n=4). 'Device expulsion' occurred at least once in each treatment group. 'Menstruation irregular' was only reported as discontinuation reason in the low dose ENG-MIUS group (n=2) and the intermediate dose ENG-MIUS group (n=2).

None of the hematological or biochemical parameters showed notable differences between treatment groups with respect to median relative changes from baseline to endpoint value. For the majority of parameters, median relative changes from baseline were less than 10% in all treatment groups. Almost all laboratory values were within the reference ranges. In general, only a few subjects had a downward or upward shift for the hematological and biochemical parameters from baseline to endpoint value.

The mean body weight changes from baseline were small and no relevant differences between the treatment groups were found at the different assessments. From baseline to endpoint value, the mean (SD) changes in the ENG-MIUS groups varied between -0.1 (1.6) kg in the high dose ENG-MIUS group to +0.3 (4.8) kg in the low dose ENG-MIUS group. In the Multiload group, the mean (SD) change was 0.4 (3.5) kg. For the subjects who entered the extended treatment phase, mean (SD) body weight change from baseline to endpoint value varied in the ENG-MIUS groups between 0.1 (1.6) kg in the high dose ENG-MIUS group to 1.1 (3.4) kg in the intermediate dose ENG-MIUS group. In the Multiload group, the mean (SD) change was 0.4 (3.8) kg.Also for blood pressure and heart rate, the mean changes from baseline were small and there were no notable differences between the treatment groups.

Cervical cytology and endometrial biopsy did not reveal any safety concerns.

Overall, the insertion was rated as easy by the investigator in almost all insertions with no difference between ENG-MIUS or Multiload. As reported by the subjects, 73% to 79%

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experienced pain during the insertion and about 50% of the subjects experienced less pain during insertion than expected. Also removal was rated as easy by the investigator in almost all removals, with low resistance when removing the device in the majority (75%) of cases. The duration of treatment did not seem to have an influence on the easiness of removal or resistance during removal.

The subjects were least satisfied with their bleeding pattern in the Multiload group compared to the ENG-MIUS groups. In general, an increase in satisfaction was observed in all ENG-MIUS groups from Month 1-2 to Month 5-6 regarding the questions on bleeding pattern, whereas this was generally not the case in the Multiload group. For most of the questions on bleeding pattern, the subjects in the intermediate dose ENG-MIUS group were the least satisfied as compared to the other two ENG-MIUS groups. Subjects in the high dose ENG-MIUS group tended to be somewhat more satisfied with their bleeding pattern compared to the low-dose group. Overall, in Month 5-6, 82% of the subjects in the high dose ENG-MIUS group were (very) satisfied with their menstruation, compared to 69% in the low dose group, 63% in the intermediate dose group, and 25% in the Multiload group. Satisfaction with bleeding pattern at Month 11-12 was comparable to the satisfaction at Month 5-6.

The overall satisfaction with the ENG-MIUS/Multiload was high. At least 70% in the Multiload group and approximately 80% in the ENG-MIUS groups were (very) satisfied during the six-month treatment phase. The satisfaction was somewhat higher in the high dose ENG-MIUS group in Month 3-4 and Month 5-6 as compared to the other treatment groups. At Month 11-12, 90-100% of the subjects in the ENG-MIUS groups were (very) satisfied, compared to 65% of the subjects in the Multiload group.

Within two months after end of treatment, menses had returned in all women who did not use any post-treatment hormonal contraceptive (n=45, of which 30 in the ENG-MIUS groups).

Other Parameters:

After insertion of the ENG-MIUS, maximum ENG serum concentrations were reached after approximately 2 days for the low and high dose and after 6 days for the intermediate dose. After reaching the maximum concentrations of 138, 247, and 428 pg/mL for the low, intermediate and high dose, respectively, the concentration clearly decreased in the first month, followed by a gradual decrease towards 56 pg/mL, 132 pg/mL, and 191 pg/mL, respectively at 6 months and 55, 148, and 154 pg/mL after 12 months of treatment for the low, intermediate, and high doses. The average concentration over 12 months (Cavg 12mnt) of the intermediate dose was 2.4 times Cavg 12mnt of the low dose. Cavg 12mnt of the high dose was 1.2 times Cavg 12mnt of the intermediate dose and 2.9 times Cavg 12mnt of the low dose.

Technical inspection of all removed MIUS/Multiloads showed that for all except one ENG-MIUSs and for all Multiloads, the frames and implants (only for ENG-MIUS) were fully intact and no deformations were observed. Additionally, the force needed to remove the little cap from the frame of the ENG-MIUS was in the range of unused ENG-MIUS samples. For one removed ENG-MIUS, the lower part of the frame was deformed (not broken) and the implant was not completely enclosed by the frame anymore. This deformation possibly happened during removal of the ENG-MIUS when pulling the threads, which are attached to the lower part of the stem.

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CONCLUSIONS:

The following conclusions can be drawn from this study:

- The safety profile of the ENG-MIUS was comparable between the three doses and there was no remarkable difference with Multiload. The insertion and removal characteristics were similar between the ENG-MIUS groups and Multiload.
- Subjects were more satisfied with their bleeding pattern in the ENG-MIUS groups than in the Multiload group, and highest satisfaction was observed in the high dose ENG-MIUS group.
- The vaginal bleeding pattern was most favorable in the high dose ENG-MIUS group, taking into account bleeding/spotting days and the occurrence of amenorrhea.
- Ovulation inhibition and ovarian function suppression was only observed in the high dose ENG-MIUS group. In the intermediate dose ENG-MIUS group, ovulation inhibition was observed, but ovarian function was not (completely) suppressed. In the low dose ENG-MIUS group, ovulation was not inhibited.
- All ENG-MIUS doses were contraceptive effective, but the number of subjects per treatment group was small.
- The ENG serum profile was as expected, with a mild burst in serum concentrations in the first days followed by a clear decrease in the first month. The low and intermediate doses gradually decreased towards 6 months and remained constant at this level up to and including 12 months. The high dose gradually decreased from the first month onwards to reach the level of the intermediate dose at the 12-month time point.