CLINICAL REVIEW

Application Type	NDA
Application Number	21-225 (SE1- Applicant submission 027)
Priority or Standard	Priority
Submit Date	March 31, 2009
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Division / Office	Division of Reproductive and Urologic Products (DRUP) / Office of Drug Evaluation III (ODE III)
Reviewer Name	Gerald Willett M.D.
Review Completion Date	September 16, 2009
Established Name	Levonorgestrel-releasing intrauterine system (LNG IUS)
Trade Name	Mirena®
Therapeutic Class	Progestin-containing intrauterine device
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Formulation	Intrauterine device
Dosing Regimen	Insertion into the uterine cavity (5 year contraceptive efficacy)
Indication	Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception
Intended Population	Women of childbearing age

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List of Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
COC	Combined oral contraceptive
CRF	Case report form
DUB	Dysfunctional uterine bleeding
EA	Endometrial ablation
ERS	Endometrial resection
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GGT	Gamma glutamyltransferase
hCG	Human chorionic gonadotropin
HMB	Heavy menstrual bleeding
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IND	Investigational new drug
IRB	Institutional review board
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
IUD	Intrauterine device
IUS	Intrauterine system
LNG	Levonorgestrel
LNG IUS	Levonorgestrel-releasing intrauterine system
LOCF	Last observation carried forward
NSAID	Non-steroidal anti-inflammatory drug
MBL	Menstrual blood loss
MedDRA	Medical Dictionary for Drug Regulatory Activities
MFA	Mefenamic acid
MPA	Medroxyprogesterone acetate
NET	Norethisterone
NETA / EE	Norethindrone acetate / ethinyl estradiol
OC	Oral contraceptive
PBAC	Pictorial blood loss assessment chart
PPS	Per-protocol analysis set
PSUR	Periodic Safety Update Report
SAE	Serious adverse event
SOC	System organ class
TCRE	Transcervical resection of endometrium
TMFL	Total menstrual fluid loss
TXA	Tranexamic acid
TSH	Thyroid stimulating hormone
WHO	World Health Organization

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended for the Applicant's proposed secondary indication for Mirena® (LNG IUS), that of treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.

1.2 Risk Benefit Assessment

The risk benefit assessment is favorable for this secondary indication (heavy menstrual bleeding). There is no evidence from the safety data presented in this application that the use of LNG IUS in women who seek both contraception and bleeding control from the product are at any greater risk than those who seek the contraceptive benefit alone.

In regard to safety for the proposed new indication, the Applicant presented data on 332 women using LNG IUS in 10 company-sponsored studies of heavy menstrual bleeding. The types and frequency of adverse events seen in these studies were similar to that seen with the LNG IUS contraceptive studies and postmarketing safety reports. The overall cumulative safety experience with LNG IUS is very extensive, with an estimated 44.3 million women-years of exposure since 1990. Recent postmarketing safety update reports (PSURs) for LNG IUS have not demonstrated any significant new safety signal emerging. The two most recent PSURs have been reviewed with this application. The time period covered is September 28, 2007 through June 1, 2009.

In the 10 heavy menstrual bleeding studies (also called idiopathic menorrhagia studies) there were no deaths and 12 serious adverse events (SAEs). Of the SAEs, 3 subjects had events (abdominal pain, headache/nausea and ovarian cyst) that are considered by this reviewer to be possibly related to LNG IUS. The frequency of commonly occurring adverse events such as irregular uterine bleeding/spotting, headache, LNG IUS expulsion and ovarian cyst are similar to that reported for LNG IUS when used solely for contraception. In the 13 medical literature studies reviewed in Appendix Section 9.1, there were no new safety findings.

The efficacy results presented by the applicant provide evidence of <u>added</u> benefit when considering the risk/benefit for LNG IUS. The Applicant demonstrated statistically significant efficacy for LNG IUS compared to medroxyprogesterone acetate in their pivotal Study 309849 in regard to menstrual blood loss (Table A) and the proportion of subjects with successful treatment (defined as subjects whose MBL was < 80 mL and who displayed a decrease to a value no greater than 50% of the Baseline MBL – Table B).

Table A: Study 309849 – Absolute Change in Median Menstrual Blood Loss from Baseline (Analysis Set)

Time Point	Treatment Group	n	Median Baseline MBL (mL)	Change from Baseline (mL)	P-value Wilcoxon Test
Mid-Study	LNG IUS	79	147.96	- 115.13	P<0.001
	MPA	81	154.20	- 3.15	
End-of-Study	LNG IUS	79	147.96	- 128.78	P<0.001
	MPA	81	154.20	- 17.77	

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
MBL = menstrual blood loss
Source: Study Report A38313 Text Table 14; page 68 of 126 and Summary of Clinical Efficacy; page 12 of 108.
Note: Table A is identical to Table 22 in the body of this review.

Table B: Study 309849 – The Proportion of Subjects with Successful Treatment (Analysis Set)

Assessment	LNG IUS N =82	MPA N=83	% Difference	95% CI	p-value (b)
Success (a)					
N	79 (100%)	81 (100%)			
Yes	67 (84.8%)	18 (22.2%)	62.6	50.56-74.61	<0.001
No	12 (15.2%)	63 (77.8%)			
End-of-Study MBL < 80 mL					
N	81 (100%)	81 (100%)			
Yes	71 (87.7%)	24 (29.6%)	58.0	45.77-70.28	<0.001
No	10 (12.3%)	57 (70.4%)			
Decrease in End-of-Study MBL ≥50% of Baseline MBL					
N	79 (100%)	81 (100%)			
Yes	67 (84.8%)	22 (27.2%)	57.6	45.14-70.16	<0.001
No	12 (15.2%)	59 (72.8%)			

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
MBL = menstrual blood loss; CI = confidence interval
(a) = Successful treatment is defined as: End-of-Study MBL < 80 mL and decrease in End-of-Study MBL ≥ 50% of Baseline MBL
(b) = Pearson's Chi-squared test. Significance level of the test is 0.05 (two-sided)
Source: Study Report A38313 Text Table 15; page 70 of 126
Note: Table B is a copy of Table 23 from the body of this review

In addition to the pivotal study there is additional supportive evidence of efficacy with the following:

- Supportive secondary efficacy data from the pivotal Study 309849, which showed increases in hemoglobin, hematocrit and ferritin from baseline through cycle 6
- Supportive efficacy data from Study 92549, which showed that LNG IUS was comparable to norethisterone (15 mg daily – days 5-25 of the cycle) in regard to decreasing MBL. A norethisterone (norethindrone) product (Norlutin) with a similar dosage regimen was approved by the FDA many years ago for a bleeding indication, but the product is no longer marketed.
- Supportive efficacy data from Study 94548, which showed that LNG IUS was statistically superior to tranexamic acid in regard to decreasing MBL.

- Supportive efficacy data from Study 93547, which showed that LNG IUS was statistically superior to mefenamic acid in regard to decreasing MBL.
- Supportive efficacy data from Study 302760, which showed that LNG IUS was statistically superior to a combined oral contraceptive (norethindrone 1 mg / ethinyl estradiol 0.02 mg) in regard to decreasing MBL.
- Additional supportive efficacy data was identified in 10 medical literature articles submitted by the Applicant and in 3 medical articles identified by the medical reviewer. No non-supportive medical articles were identified in a literature search by the medical reviewer.
- The 13 supportive studies in the literature provide supportive data for LNG IUS efficacy as evidenced by
    a) decreased blood loss findings (as established by alkaline hematin and PBAC analysis [see Table 77])
    b) increases in hemoglobin and ferritin
    c) the proportion of subjects with amenorrhea developing after LNG IUS insertion
    d) comparable efficacy to endometrial ablation and resection procedures

The only study in which LNG IUS was not superior to or comparable to the comparator was Study 303003. In this study, danazol was significantly better than LNG IUS in reduction of MBL (by PBAC) from baseline to 3 months. Danazol is not approved for heavy bleeding in the U.S., nor is it used off-label for bleeding due to significant drug-related adverse events (weight gain, fluid retention, acne, hirsutism, hot flushes, voice deepening, and unfavorable lipid changes).

The conclusion from Dr. Fang (primary reviewer in the Office of Biostatistics) was that the data from Study 309849 (Report A38313) was adequate and supported the efficacy of LNG IUS in the treatment of heavy menstrual bleeding (for additional comments on this review see Section 4.5)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarketing risk evaluation or mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarketing requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Mirena ® is a progestin-containing intrauterine contraceptive device that was approved by the FDA on December 6, 2000. The approved duration of use for contraceptive efficacy is 5 years. This reviewer will for the most part use the term LNG IUS (levonorgestrel-releasing intrauterine system) for Mirena® throughout this review. Additional historical information for this product includes:

- LNG IUS contains 52 mg of levonorgestrel. The initial release rate is 20 µg per 24 hours. The rate decreases progressively to half that value after 5 years.

- LNG IUS is believed to exert its contraceptive effect locally in the uterus by
  a) thickening the cervical mucus
  b) inhibiting sperm motility and function
  c) preventing the proliferation of the endometrium during the menstrual cycle
  d) inhibiting ovulation is some cycles (seen more often in the first year of use).

- The cumulative 5-year pregnancy rate reported in the current product label is 0.7 per 100 women.

- "Treatment of idiopathic menorrhagia" has been approved as an indication for LNG IUS in over 100 countries. The local release of levonorgestrel abolishes endometrial cyclic changes, which lead to a histologic pattern of small inactive glands and a pseudodecidualized stroma. The endometrial lining becomes thinner. Irregular bleeding and spotting may increase over the short term but the overall blood volume loss has been found to decrease.

- The chance of pregnancy is very low with LNG IUS. However, if a patient becomes pregnant, an ectopic pregnancy should be ruled out.

- If an intrauterine pregnancy results with LNG IUS in place, there are risks for pregnancy loss, septic abortion, septicemia and rarely death.

- Pelvic inflammatory disease and rare cases of Group A Streptococcal sepsis have been seen shortly after LNG IUS insertion.

- LNG IUS use can alter a woman's bleeding pattern (leading to spotting, irregular bleeding, oligomenorrhea and amenorrhea)

- LNG IUS can become embedded in or perforate the uterus. LNG IUS can be either partially or fully expelled from the uterine cavity.

- Enlarged cystic ovarian follicles have been diagnosed in about 12% of patients using LNG IUS. LNG IUS does not have the same inhibitory effect on follicular cysts that is seen with combination oral contraceptives.

2.2 Currently Available Treatments for Proposed Indications

The Applicant's proposed secondary indication for LNG IUS is "Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception."

Heavy menstrual bleeding may occur either in a background of pathological changes (e.g., uterine leiomyomata, polyps, coagulation problems, etc.) or in the absence of pathology. The principal surgical and medical treatments include:

Surgical Treatments

- Hysterectomy
- Myomectomy
- Endometrial ablation/resection
- Uterine artery embolization to treat uterine leiomyomata

FDA Approved Medical Treatments

- Norlutin® (norethindrone) 10-20 mg (daily for cycle days 5-23) "for menstrual irregularity and functional uterine bleeding" [No longer marketed]
- Norlutate® (norethindrone acetate) 2.5-10 mg (daily for cycle days 5-23) for menstrual irregularity and functional uterine bleeding [No longer marketed]
- Aygestin® (norethindrone acetate) 2.5-10 mg for 5-10 days to produce secretory transformation of an endometrium (to treat abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology)
- Provera® (medroxyprogesterone acetate) 5-10 mg for 5-10 days (to treat abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer)

Off-Label Medical Treatments

- Combination oral contraceptives have been frequently used off-label to decrease menstrual bleeding.

2.3 Availability of Proposed Active Ingredient in the United States

Levonorgestrel, the active drug component of LNG IUS, has a long history of use for hormonal indications in the U.S. These indications include both contraception (oral, intrauterine, and implants) and menopausal therapy. The number of marketed IUDs, however, remains small, with only two available (Mirena® and the copper-containing ParaGard®).

2.4 Important Safety Issues with Consideration to Related Drugs

Intrauterine contraceptive devices (IUDs) as a general class have the following safety issues:

- Concern about ectopic pregnancy if the patient becomes pregnant
- Concern about pregnancy loss, septic abortion and septicemia if the patient has an intrauterine pregnancy while carrying an IUD
- Concern about IUD uterine embedment, perforation and expulsion
- Concern about pelvic infections after IUD insertion

Levonorgestrel and the progestins as a whole share many of the same safety issues that are present with estrogens. Progestins alone, however, appear to have fewer thromboembolic adverse events than estrogen products. There are concerns about some classes of progestins in regard to breast cancer risk (especially for menopausal women).

It would be anticipated that local release of a progestin in the endometrial cavity via an IUD would manifest fewer systemic adverse events than would oral progestins. In regard to endometrial safety, progestins have been found to have protective influences on endometrial tissue by lowering the risk for endometrial hyperplasia and endometrial cancer.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The chronology of regulatory activity for this supplemental NDA is as follows:

- December 6, 2000 - The Mirena® intrauterine device was approved for intrauterine contraception

- December 12, 2002 – DRUP met with the Sponsor (then Berlex Inc.) to discuss the addition of idiopathic menorrhagia to Mirena's contraceptive indication. Based on the apparent deficiencies of the completed menorrhagia studies presented by the Sponsor at that time, DRUP's principal recommendations included the following:

1. That the Sponsor strongly consider conducting one additional multicenter clinical trial in which the product is compared to placebo or an approved therapy in the U.S.
2. That the Sponsor account for all intermenstrual bleeding and spotting that occurs during the study
3. That the Sponsor analyze iron supplement use when analyzing hemoglobin and ferritin measurement.

Medical Officer's Comment: These three recommendations were met. Multicenter trial 309849 was performed, which compared Mirena (LNG IUS) to a U.S.-approved comparator (medroxyprogesterone acetate). Intermenstrual bleeding and spotting were incorporated into the blood loss determination and data about iron use was investigated when analyzing hemoglobin and ferritin.

- October 31, 2005 - The Sponsor submitted a Special Protocol Assessment (SPA) for pivotal Study 309849.

- December 16, 2005 – DRUP responded to the SPA with recommendations that included:
    1. Recommended that a term other than (b) (4) be used in the indication (since enrolled women would most likely have very small submucosal fibroids or other undetected pathology responsible for their menorrhagia).
    2. Recommended adding a measurement of serum prolactin at baseline and exclude women with hyperprolactinemia from the study. Elevated prolactin can be a cause of anovulation, which can in turn lead to menorrhagia.
    3. Recommended that the menstrual blood loss during the screening menstrual periods be greater than 80mL in 2 of 2 or 2 of 3 screening cycles.
    4. Recommended that the mean baseline menstrual blood loss should be based on the measured blood loss during each of the cycles included during the Screening Phase and not limited to the mean of the 2 cycles with the greatest blood loss.
    5. Recommended that success for the primary endpoint be defined to include the following:
        - Treatment with Mirena will produce a statistically greater mean reduction in blood loss than treatment with MPA (measured as the change in absolute value from baseline MBL to the end of treatment MBL) and
        - The difference in the point estimates for the mean reduction in MBL between Mirena and MPA should be at least 50 mL

6. Recommended that treatment success (originally a secondary endpoint) should be defined as "MBL ≤ 80mL after Cycle 6 of the treatment phase and a decrease to a value no greater than 50% of the Baseline MBL"
7. Recommended that treatment success as defined in #6 of this section be elevated to a co-primary endpoint
8. Concurred that the proposed active control (MPA) was appropriate.

Medical Officer's Comments:
The term (b) (4) ***has been replaced with the term "heavy menstrual bleeding" in the Applicant's proposed label in NDA 21-225.***

The recommendation about prolactin and hyperprolactinemia was accepted and carried out by the Sponsor in pivotal Study 309849.

Points 3 and 4 concerning menstrual blood loss were carried out in pivotal Study 309849.

The primary endpoints in Study 309849 were revised to include the first bulleted item in #5 in addition to #6. The second bulleted statement in #5 (difference in point estimate) became one of the overall success criteria defined by the Applicant but they specified 30 mL instead of 50 mL as the requisite difference in MBL reduction between treatment arms. The actual difference obtained, however, was over 70 mL and thus DRUP's original request was met.

- December 21, 2006 – DRUP sent a letter to the Sponsor (Berlex) acknowledging that the statistical analysis plan for pivotal Study 309849 was acceptable.

- September 22, 2008 – The new Sponsor (Bayer) requested a pre-NDA meeting to discuss the secondary indication of treatment of heavy menstrual bleeding in women who desire intrauterine contraception. DRUP's principal responses to the Sponsor's questions included:
    1. Agreed with Bayer's submission strategy of utilizing Study 309849 as a pivotal trial and submitting 9 additional supportive studies.
    2. Agreed that narratives for deaths, SAEs and discontinuations due to AEs would not be necessary for comparator drugs not marketed in the U.S.
    3. Agreed that the literature search conducted by the Sponsor could be limited to heavy menstrual bleeding without organic pathology in women using LNG IUS

2.6 Other Relevant Background Information

The relevant background information was conveyed in the preceding sections.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant provided statements in all of their submitted Phase 3 clinical trials (Study protocols 309849, 92549, 94548, 93547, 302760, 303003, 93503, 90528, 92501 and 91539) that the studies met all local legal and regulatory requirements. Protocols and protocol amendments were reviewed and approved by each of the study site's Independent Ethics Committee (IEC) or Institutional Review Board (IRB). The Applicant also provided a debarment certification confirming that none of the investigators were debarred from the practice of medicine while involved with the pivotal Study 309849 or found on the FDA debarment list.

The FDA's Department of Scientific Investigations (DSI) at the request of DRUP investigated the laboratory responsible for determining the menstrual blood loss in the pivotal trial 309849 (b) (4) and one clinical site in the pivotal study (Dr. Simon Yassear – Carmichael, California). Both site inspections were found to be acceptable in support of the application.

3.2 Compliance with Good Clinical Practices

The Applicant provided statements in all of their submitted Phase 3 clinical trials (Study protocols 309849, 92549, 94548, 93547, 302760, 303003, 93503, 90528, 92501 and 91539) that the studies were conducted in accordance with Good Clinical Practice (GCP) and the standard operating procedures for clinical investigation and documentation applicable at Bayer HealthCare Pharmaceuticals (previously Berlex Inc).

3.3 Financial Disclosures

The Applicant submitted a signed Certification: Financial Interests and Arrangements of Clinical Investigators form (OMB No. 0910-0396) in compliance with 21 CFR part 54. The Applicant provided an investigator disclosure table for the pivotal study (309849). There were no investigators listed that marked "yes" regarding disclosable information. The table listed two sub-investigators for whom financial certification / disclosure forms were not collected:

- (b) (6) – Site No. 20 – Indiana
- (b) (6) – Site No. 95 – Mexico

In addition, the Applicant did not specify whether there was disclosable information for the investigators at site 95 in Mexico. However, sites 20 and 95 were sites that did not randomize any subjects and therefore the lack of these forms and disclosable information does not impact the NDA review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable for this submission

4.2 Clinical Microbiology

Not applicable for this submission

4.3 Preclinical Pharmacology/Toxicology

Not applicable for this submission

4.4 Clinical Pharmacology

Not applicable for this submission

4.5 Biostatistics

Dr. Xin Fang reviewed the efficacy of LNG IUS for heavy menstrual bleeding. Concurrence for his review was given by Dr. Mahboob Sobhan. Key findings from Dr. Fang's review include:

- There were no major statistical issues with regard to efficacy analysis
- The impact of protocol violations had little impact on efficacy results since results based on both the FAS and PPS were similar
- In general the two treatment groups (LNG and MPA) had comparable baseline demographic characteristics
- Investigation of missing values appeared to be properly imputed based on the specific rules of the protocol
- LNG IUS demonstrated statistically and clinically significant reductions in menstrual blood loss in women using intrauterine contraception.

- In a subgroup analysis there was no strong evidence of an age effect among women using LNG IUS
- LNG IUS had similar effects among three BMI groups (<25, 25 to <30 and ≥30)
- LNG IUS did not show significant differences between subjects taking iron supplement and subjects not taking iron supplement

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Pivotal Study 309849 (Report A38313)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) Sex Race
A38313 (309849) Jul/2006 Completed Argentina (2) Brazil (2) Canada (10) US (40)	Phase 3 Multicenter Randomized Open-label Parallel group Active control 6 cycles	LNG IUS 20 µg/day MPA 10 mg oral tablet once daily on days 16-25 of each cycle	LNG IUS = 82 MPA = 83 Total = 165	LNG IUS = 26-50 (38.3) MPA = 26-53 (39.3) 165 Females 118 Caucasian 30 Black 12 Hispanic 3 Asian 2 Other

LNG IUS = levonorgestrel intrauterine system; MPA = medroxyprogesterone acetate
Source: Section 5.2, Tabular listing of all clinical studies; page 3 of 13

Table 2: Supportive Study 92549 (Report B088)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) Sex Race
B088 (92549) May/1994 Completed United Kingdom (1)	Phase 3 Randomized Open-label Parallel group Active control 3 cycles	LNG IUS 20 µg/day NET 5 mg oral tablet TID on days 5-25 of each cycle	LNG IUS = 22 NET = 22 Total = 44	LNG IUS = 32-46 (39.2) NET = 31-46 (38.8) 44 Females 44 Caucasian

LNG IUS = levonorgestrel intrauterine system; NET = norethisterone; TID = three times per day
Source: Section 5.2, Tabular listing of all clinical studies; page 4 of 13

Table 3: Supportive Study 92549, Extension Phase (Report A02916)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment group with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
A02916 (92549) May/1994 Completed United Kingdom (1)	Phase 3 Open-label extension Up to 2-3 years	<u>LNG IUS</u> 20 µg/day	LNG IUS = 22 Total = 22	LNG IUS = 32-46 (39.2) <u>22 Females</u> 22 Caucasian

LNG IUS = levonorgestrel intrauterine system
Source: Section 5.2, Tabular listing of all clinical studies; page 5 of 13

Table 4: Supportive Study 94548 (Report A00630)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
A00630 (945489) Dec/1995 Completed Sweden (1)	Phase 3 Randomized Open-label Parallel group Active control 12 cycles	<u>LNG IUS</u> 20 µg/day <u>TXA</u> Oral tablets (2 x 500 mg) QID on bleeding days (maximum 5 days)	LNG IUS = 28 TXA = 30 Total = 58	LNG IUS = 20-47 (38.3) TXA = 22-47 (38.5) <u>58 Females</u> 58 Caucasian

LNG IUS = levonorgestrel intrauterine system; TXA = tranexamic acid;
QID = four times per day
Source: Section 5.2, Tabular listing of all clinical studies; page 6 of 13

Table 5: Supportive Study 93547 (Report A14096)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
A14096 (93547) May/1996 Completed United Kingdom (1)	Phase 3 Randomized Open-label Parallel group Active control Comparative = 6 cycles Follow up extension up to 5 years for LNG IUS	<u>LNG IUS</u> 20 µg/day <u>MFNA</u> Oral 500 mg tablet TID for the first 4 days of each menstrual cycle	LNG IUS = 25 (19 extended) MFNA = 26 Total = 51	LNG IUS = 29-47 (39.4) MFNA = 31-46 (38.5) <u>51 Females</u> 47 Caucasian 3 Black 1 Other

LNG IUS = levonorgestrel intrauterine system; MFA = mefenamic acid; TID = three times per day
Source: Section 5.2, Tabular listing of all clinical studies; page 7 of 13

Table 6: Supportive Study 302760 (Report A36340)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) Sex Race
A36340 (302760) Jan/2000 Completed Canada (9)	Phase 3 Multicenter Randomized Open-label Parallel group Active control 12 Months	LNG IUS 20 µg/day Oral norethindrone acetate (1mg) ethinyl estradiol (20ug) [NETA / EE] 21 days active 7 days placebo	LNG IUS =20 NETA/EE =19 Total = 39	LNG IUS = 30-47 (41.8) NETA/EE = 31-49 (42.4) 39 Females 35 Caucasian 2 Black 1 Hispanic 1 Other

LNG IUS = levonorgestrel intrauterine system; NETA/EE = norethindrone acetate / ethinyl estradiol
Source: Section 5.2, Tabular listing of all clinical studies; page 8 of 13

Table 7: Supportive Study 303003 (Report A00696)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
A00696 (303003) Nov/1999 Completed Canada (16)	Phase 3 Multicenter Open-label Parallel group Active control 6 Months (LNG IUS) 3 Months (danazol) and then 3 Months observation with no treatment	<u>LNG IUS</u> 20 µg/day <u>DNZ</u> Oral tablet 100mg BID	LNG IUS =75 DNZ = 76 Total = 151	LNG IUS = 28-53 (42.2) DNZ = 30-53 (42.2) <u>151 Females</u> 144 Caucasian 2 Black 1 Hispanic 1 Asian 3 Other

LNG IUS = levonorgestrel intrauterine system; DNZ = danazol; BID = twice per day
Source: Section 5.2, Tabular listing of all clinical studies; page 9 of 13

Table 8: Supportive Study 93503 (Report BC71)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) Sex Race
BC71 (93503) Mar/1993 Completed Norway (1)	Phase 3 Randomized Open-label Parallel group Active control 36 Months	LNG IUS 20 µg/day Endometrial resection (ERS)	LNG IUS = 30 ERS = 29 Total = 59	LNG IUS = 33-48 (41.4) ERS = 34-49 (42.1) 59 Females No data on race collected

LNG IUS = levonorgestrel intrauterine system; ERS = endometrial resection
Source: Section 5.2, Tabular listing of all clinical studies; page 10 of 13

Table 9: Supportive Study 90528 (Report B086)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
B086 (90528) Nov/1991 Completed Finland (3)	Phase 3 Multicenter Randomized Open-label Parallel group Active control Mirena = 6 months treat-ment and 6 months follow-up Comparator = 6 months treatment	<u>LNG IUS</u> 20 µg/day <u>Control =</u> Continuation of existing treatment (e.g. TXA, NET, megestrol and NSAIDs)	LNG IUS = 27 Control = 27 Total = 54	LNG IUS = 35-49 (42.7) Control = 28-49 (41.7) <u>54 Females</u> No data on race collected

LNG IUS = levonorgestrel intrauterine system; TXA = tranexamic acid; NET = norethisterone; NSAID = nonsteroidal anti-inflammatory drug
Source: Section 5.2, Tabular listing of all clinical studies; page 11 of 13

Table 10: Summary Table of Study 92501 (Report AY01)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) Sex Race
AY01 (92501) Jul/1993 Early termination due to enrollment difficulties Italy (3)	Phase 3 Open-label 12 Cycles	LNG IUS 20 µg/day	LNG IUS = 15 Total = 15	LNG IUS = 29-45 (39.9) 15 Females Data on race not collected

LNG IUS = levonorgestrel intrauterine system
Source: Section 5.2, Tabular listing of all clinical studies; page 12 of 13

Table 11: Summary Table of Study 91539 (Report AW82)

Report No. (Protocol No.) Start date Completion status Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) Sex Race
AW82 (91539) May/1993 Early termination due to enrollment difficulties United Kingdom (1)	Phase 3 Randomized Open-label Parallel group Active control 12 Cycles	LNG IUS 20 µg/day Endometrial ablation (EA)	LNG IUS = 10 EA = 11 Total = 21	LNG IUS = < 50 EA = < 50 21 Females Data not collected on race

LNG IUS = levonorgestrel intrauterine system; EA = endometrial ablation
Source: Section 5.2, Tabular listing of all clinical studies; page 13 of 13

5.2 Review Strategy

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Pivotal Study 309849 (Report A38313)

5.3.1.1 Study Title and Coordinating Investigator

"A multicenter, randomized, open label, parallel group, active control study to evaluate the efficacy and safety of LNG IUS (Mirena) as compared to medroxyprogesterone acetate during 6 cycles of treatment in patients with idiopathic menorrhagia"

The coordinating investigator was Andrew Kaunitz, MD, who is at the University of Florida College of Medicine in Jacksonville, Florida.

5.3.1.2 Ethics

The Applicant stated that a) this study met all local legal and regulatory requirements, b) this study was conducted in accordance with Good Clinical Practice (GCP), c) this study complied with ethical principles originating in the Declaration of Helsinki, d) the study protocol and amendments were reviewed and approved by each study site's Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before the start of the study or before implementation of the amendment, and e) the study's informed consent form was reviewed and approved by the IECs and IRBs prior to its issue.

5.3.1.3 Investigators and Study Administrative Structure

In the pivotal Study 309849, there were 165 subjects randomized. Of these, there were 103 subjects from the U.S. and 62 subjects from either Canada or Brazil. Study sites in Mexico and Argentina did not randomize any subjects. The study sites for Protocol 309849 are shown for U.S. (38) and Non-US (18) in Table 12 and Table 13 respectively. Study sites that did not randomize any subjects into the trial are listed with "0".

Clinical monitoring at U.S. sites was performed by (b) (4) determination of menstrual blood loss (alkaline hematin method) was performed by (b) (4) . Laboratory assessments for Pap tests, human papilloma virus and endometrial biopsies were performed by (b) (4) . Most of the other clinical lab tests were performed by (b) (4)

Table 12: Study 309849 – US Study Sites with Randomized Subjects

Site #	Principal Investigator	Subjects Randomized
01	Ackerman	5
02	Aqua	3
03	Archer	4
04	Cheng / Bachman	1
05	Ballard	1
06	Borgatta	1
07	Drosman	5
08	Geary	0
09	Goldberg	5
10	Jensen	7
11	Johnson	1
13	Kaunitz	5
14	Kroll	3
15	Moore	3
16	Nelson	2
17	Nicholson	4
18	Poindexter	3
19	Rauskauskas	0
20	Rogers	0
21	Seid	1
22	Andruczyk	5
23	Wolf	3
24	McIntosh	1
25	Pack	1
26	Wolfson	0
27	Berg	0
28	Bruksch	0
29	Hurtado	0
30	Koltun	8
31	Levine	5
32	Muckerman	2
33	Palamara	0
34	Soltes	7
35	Swanson	4
36	Williams	2
37	Mayes	1
38	Banooni	0
39	Yassear	10
		103 total

Source: Study Report A38313, Section 16.1.4

Table 13: Study 309849 – Non-US Study Sites with Randomized Subjects

Site #	Principal Investigator	Country	Subjects Randomized
41	Ayotte	Canada	6
42	Bisonnette	Canada	6
43	Gamache	Canada	2
44	Fortier	Canada	1
45	Moreau	Canada	9
46	LeBouthillier	Canada	0
47	Gorfinkel	Canada	8
48	Tellier	Canada	5
49	Janzen	Canada	4
51	Arndt	Canada	4
61	Bahamondes	Brazil	7
62	Andrade	Brazil	10
71	Santiago / Gil	Argentina	0
72	Heredia	Argentina	0
90	Mayagoitia	Mexico	0
91	Vazquez / Mendez	Mexico	0
92	Ricalde	Mexico	0
95	Aguilar	Mexico	0
			62 Total

Source: Study Report A38313, Section 16.1.4

5.3.1.4 Study Objectives

The primary objectives of the study were:

- To determine the absolute change in menstrual blood loss (MBL) from Baseline to End-of-Study (Cycle 6)
- To determine the proportion of patients with successful treatment (defined in Section 5.3.1.15)

The secondary objectives included the following:

- To determine the absolute change and percent change from Baseline MBL to Mid-Study MBL
- To determine the percent change from Baseline MBL to End-of-Study MBL
- To determine the continuation rate (proportion of subjects who completed the study)
- To determine the total number of days of bleeding, spotting, bleeding and spotting, and total number of bleeding episodes
- To evaluate the percent change in hemoglobin, hematocrit, and serum ferritin from Visit 5 to Visit 8 and from Visit 8 to Visit 11 and from Visit 5 to Visit 11
- To determine the proportion of patients with improvement in the Investigator and Patient Global Assessment Scale at Cycle 3 and Cycle 6

5.3.1.5 Study Design

Pivotal study 309849 was a multicenter, randomized, open-label, parallel group, active control study designed to evaluate the efficacy and safety of LNG IUS compared to MPA tablets for women with heavy menstrual bleeding (previously termed idiopathic menorrhagia).

The study was conducted according to the final approved protocol, dated May 10, 2006 and its amendments (Amendment 1, dated November 16, 2006, and Amendment 2 dated February 26, 2008).

The subject population consisted of parous women 18 years or older, who were not pregnant or nursing, and who had a diagnosis of heavy menstrual bleeding. Women with a normal length menstrual cycle consisting of 21 – 35 days and withdrawal bleeding MBL of ≥80 mL measured in at least 2 of the 3 cycles during the Screening Phase were eligible to enter the study.

Subjects were eligible as soon as the two qualifying MBL measurements were confirmed. Women who had heavy menstrual bleeding with a diagnosed organic cause or contraindications to LNG IUS or MPA were excluded. The MBL measured during the menstrual periods in the Screening Phase was used to determine eligibility.

Qualifying subjects were randomized to either of the two treatment groups:

1. LNG IUS (containing a total of 52 mg levonorgestrel, with an initial levonorgestrel release of 20 µg/24 hours)

2. Medroxyprogesterone acetate tablets 10 mg, oral administration for 10 consecutive days beginning on the 16th day of the menstrual cycle.

LNG IUS was inserted into the uterine cavity within seven days after the onset of menstruation during Cycle 1 of the 6-cycle treatment phase. In the LNG IUS group (because progestin withdrawal bleeding may not always occur), the 6 treatment cycles were designated to contain 30 days each. The first cycle started on the first bleeding day of the Cycle 1 (i.e., the cycle when the LNG IUS was inserted) and was calculated to end on Day 30. Correspondingly, Cycle 3 and Cycle 6 were calculated as Day 61 to Day 90 and Day 151 to Day 180, respectively.

If, during any visit, the LNG IUS system was confirmed to be displaced, partially or totally expelled, the system could be replaced if pregnancy was been ruled out and if the system was not absent for more than 2 weeks. Re-insertion of LNG IUS could be performed only once throughout the Treatment Period

In the MPA group, each menstrual cycle started on the first bleeding day (withdrawal bleeding) and lasted until the last non-bleeding day before next withdrawal bleeding started. In this group, progestin withdrawal bleeding usually occurred within 3 to 7 days after intake of the last tablet in the cycle. The first bleeding episode occurring after the last intake of MPA (Day 25) was considered the expected bleeding episode (withdrawal bleeding). In case a bleeding episode was ongoing on the last day of drug intake (Day 25) and on the following day (Day 26), this bleeding episode was considered the withdrawal bleeding, provided it started no more than 4 days before drug withdrawal (Day 22). All other bleeding episodes (excluding spotting) were considered unexpected (intracyclic bleedings).

If event cycles became irregular in the MPA group, the following rules applied:

- If bleeding occurred within 23 days after the last intake of MPA, the first day of bleeding was considered Day 1 of the next cycle. The subject started a new diary card and took MPA on Day 16 as per protocol.

- If bleeding did not occur within 23 days after last intake of MPA in the cycle (amenorrhea), the subject was discontinued from study drug and considered a treatment success (with 0 mL MBL). The subject remained in the study for a maximum of 180 days (calculated from the first day of Cycle 1) for all relevant safety evaluations. In these cases, the diary data was collected after MPA was discontinued but was not used for bleeding pattern evaluation.

Menstrual blood loss in both treatment groups was measured using the alkaline hematin method. Subjects collected all used sanitary protection (including tampons and pads, excluding panty liners) that were used during the menstrual cycle throughout the Screening Phase and during Cycle 3 and Cycle 6 of the Treatment Phase for central laboratory evaluation of MBL. This included any possible expected and unexpected (intermenstrual) bleeding that occurred during the menstrual cycle.

During the entire study, subjects maintained a daily record of menstrual bleeding using a diary card. During the Screening Phase and Cycle 3 and Cycle 6 of the Treatment Phase subjects noted whether or not all of the sanitary protection used was collected. Subjects randomized to MPA recorded tablet intake during the Treatment Phase in their diaries.

The mean of the MBL (including intermenstrual bleeding) measured during all of the Screening Phase cycles was used as the baseline value in the statistical analysis. This value was compared to the MBL measured during Cycle 3 and Cycle 6 of the Treatment Phase.

The Applicant stated that an open-label design was necessary because it was not technically feasible to blind treatment with the oral administration of MPA tablets and an intrauterine system. The use of a placebo intrauterine system (IUS) for a blinded design was considered not feasible because a placebo IUS could potentially increase menstrual bleeding.

Medical Officer Comment:
This reviewer concurs with the Applicant's justification to conduct an open label study.

5.3.1.6 Inclusion Criteria

The following criteria were used to evaluate subjects for inclusion in the study:

1. Signed informed consent

2. ≥ 18 years of age

3. Able to read and write, as determined by study personnel

4. FSH value was ≤ 30 mIU/mL

5. Has had at least 1 child

6. Was in a stable, mutually monogamous relationship (only one sexual partner)

7. Had withdrawal bleeding MBL of ≥ 80 mL measured in 2 of the 3 cycles during the Screening Phase

8. Was willing to complete diary cards and use and collect sanitary protection (pads and tampons) provided by the sponsor and compatible with the alkaline hematin test throughout study completion

9. Was willing to use barrier contraception (e.g., condoms) from screening through study completion (for patients randomized to MPA)

10. Had a uterine sound-depth of 6 to 9 cm

5.3.1.7 Exclusion Criteria

The following criteria were used for the exclusion of subjects from the study:

1. Had changes in menstrual regularity (e.g., shorter, longer, absent, irregular), hot flashes, sleeping disorder, changes in mood (e.g., depression, nervous tension, and irritability) within the past 3 months

2. Had menstrual cycles less than 21 days or greater than 35 days within the past 3 months

3. Was pregnant or had suspicion of pregnancy

4. Had a congenital or acquired uterine anomaly including fibroids that distorted the uterine cavity or cervical canal (abnormal hysterosonography); three or fewer subserous or intramural fibroids with a total volume of < 5 cm^3 were acceptable

5. Had a history of an organic causality of uterine bleeding such as chronic endometritis, adenomyosis, endometriosis, endometrial polyps (if not successfully removed), endometrial carcinomas, mixed mullerian mesenchymal tumors, leiomyosarcomas, or endometrial stromal tumors

6. Had acute pelvic inflammatory disease or a history of pelvic inflammatory disease unless there had been a subsequent uterine pregnancy

7. Had postpartum endometritis, missed abortion, or infected abortion in the past 3 months

8. Had known or suspected uterine or cervical neoplasia or unresolved, abnormal pap smear at screening - a valid pap smear performed within 6 months of Visit 1 could be used if a report is available

9. Had evidence of malignancy or hyperplasia as determined by endometrial biopsy at screening - a valid endometrial biopsy performed within 6 months of Visit 1 could be used if a report is available

10. Had untreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections

11. Had acute liver disease or liver tumor (benign or malignant)

12. Had conditions associated with increased susceptibility to infections with microorganisms - such conditions included, but were not limited to, leukemia, acquired immune deficiency syndrome (AIDS), and I.V. drug abuse

13. Had genital actinomycosis

14. Had a previously inserted IUS or IUD that had not been removed within 30 days before Visit 1

15. Had used oral contraceptives or intravaginal contraceptives within 30 days prior to Visit 1

16. Was using medication(s) that could affect bleeding (e.g., antifibrinolytics, platelet aggregation inhibitors, anticoagulants)

17. Was using medication(s) that might interact with the study drugs, such as enzyme-inducing or inhibiting drugs

18. Had used nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) during bleeding after Visit 1

19. Had used intramuscular, transdermal or implant contraceptives which were still effective (as defined in the label for each specific product) within 30 days before Visit 1

20. Had used depot MPA within 6 months before Visit 1

21. Had hypersensitivity to any component of LNG IUS or medroxyprogesterone acetate

22. Had a history or current diagnosis of carcinoma of the breast

23. Had a history of ectopic pregnancy or conditions which would predispose to ectopic pregnancy

24. Had von Willebrand disease

25. Had a history of endometrial ablation, or dilatation and curettage within 2 months of Visit 1

26. Was currently lactating

27. Had known or suspected premalignant or malignant disease including malignant melanoma (excluding other successfully treated skin cancers) and acute malignancies affecting blood or leukemias; and recent trophoblastic disease while hCG levels are elevated or a history of these conditions

28. Had abnormal laboratory values that were exclusionary as indicated in the laboratory manual or considered clinically significant at the discretion of the investigator and which gave suspicion of a specific organ or system dysfunction

29. Had uncontrolled hypertension; sitting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg

30. Had uncontrolled thyroid disorders

31. Had known sickle cell anemia

32. Had known, not adequately controlled diabetes mellitus with vascular involvement

33. Had increased frequency or severity of headaches including migraines during previous estrogen therapy or current or history of migraines with focal neurologic symptoms

34. Had history of drug addiction or alcohol abuse (within the last 2 years)

35. Had current or history of clinically significant depression requiring hospitalization

36. Had epilepsy and/or asthma

37. Had received an investigational drug or participated in another clinical trial within 4 months prior to study entry at Visit 1

38. Had any disease or condition that could compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication; altered hepatic or renal function that was 3x the upper limit of normal range

39. Had a history of vascular diseases and coagulation disorders: Presence or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence or history of arterial thromboembolic diseases (e.g., myocardial infarction, stroke)

40. Had a body mass index > 35 kg/m2

41. Had hyperprolactinemia

5.3.1.8 Concomitant therapy

All concomitant medications used during the course of the study were recorded on the CRF. Details, including the dosage, indication, route, and duration were recorded. Iron intake was recorded throughout the study. The following medications were not allowed during the study:

- Insertion of other IUS or IUD
- Oral contraceptives or intravaginal contraceptives
- Intramuscular, depot, transdermal or implant contraceptives
- Aminoglutethimide (Cytadren)
- Use of nonsteroidal anti inflammatory drugs (NSAIDS) during bleeding episodes (if pain relief was necessary, subjects could use NSAID-free products such as acetaminophen)
- Use of medication that could affect bleeding pattern (e.g., anti fibrinolytics, platelet aggregation inhibitors, anticoagulants)
- Use of medication that might interact with the study drugs, such as enzyme-inducing or inhibiting drugs

5.3.1.9 Study Procedures

The study procedures for pivotal Study 309849 are found in Table 14.

Table 14: Study Procedures (Study 309849)

	Screening Phase					Treatment Phase							
Visit number	V1	V2	V3	V4	PT	V5	V6	V7	V8	V9	V10	V11	V12
Treatment cycle						C1		C2	C3	C4	C5	C6	
Informed consent	X												
Demographic data	X												
Physical exam	X					X	X	X	X	X	X	X	X
Height, Weight, Blood Pressure, Heart Rate	X	X	X	X		X	X	X	X	X	X	X	X
Medical history	X												
Entry criteria	X	X	X	X		X							
Gynecological exam	X											X	
Gynecological history	X												
Endometrial biopsy (or schedule)	X											X	
Pap Smear (or schedule)	X												
Transvaginal ultrasound												X	
Hysterosonography (or schedule)	X												
Diary card dispensed	X												
Diary card entries review		X	X	X		X	X	X	X	X	X	X	
Chemistry, ferritin, hematology, urinalysis	X					X			X			X	
FSH, TSH, PRL, vWF, gonorrhea, chlamydia	X												
Dispense sanitary protection	X	X	X	X		X	X	X	X	X	X		
Collect sanitary protection		X	X	X					X			X	
Dispense condoms	X	X	X	X		X	X	X	X	X	X	X	
Subject / Investigator global assessment scale									X			X	
Review of MBL			X	X	X								
Urine hCG	X	X	X	X		X	X	X	X	X	X	X	
Dispense/Review home preg test						X	X	X	X	X	X	X	
Randomization						X							
Study treatment initiated						X							
Pill count (MPA)							X	X	X	X	X	X	
Baseline findings assessment	X	X	X	X		X							
AE assessment						X	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X		X	X	X	X	X	X	X	X

Abbreviations: V = visit; C = cycle; PT = pre-treatment phase; FSH = follicle stimulating hormone; TSH = thyroid stimulating hormone; PRL = prolactin; MBL = menstrual blood loss; hCG = human chorionic gonadotropin; MPA = medroxyprogesterone acetate; vWF = von Willebrand factor
Source: Protocol for Study 309849; page 31 of 77

Medical Officer's Comments:

- ***Visit 4 was omitted if the subject's MBL qualified in the first two cycles.***
- ***Visit 12 was only scheduled if there was a need to resolve any adverse event.***
- ***LNG IUS was inserted into the uterine cavity within seven days of the onset of menstruation. The first tablet of MPA was started on day 16 of the first treatment cycle.***
- ***The physical examinations during the treatment phase included assessments that the LNG IUS was correctly in place. The physical examinations included breast palpation on Visits 1, 5, 8 and 11.***
- ***Height was only measured at Visit 1.***
- ***Endometrial biopsy at Visit 1 was performed if a valid endometrial biopsy had not been performed in the prior 6 months.***
- ***Endometrial biopsy at Visit 11 was performed for any subject with an endometrial double-wall thickness that was > 12 millimeters.***
- ***The labs at visit 8 included only ferritin, hematocrit and hemoglobin.***

5.3.1.10 Definitions of Bleeding

The applicant provided definitions in section 7.5.2.1 of the study protocol:

- A bleeding day was a day when sanitary protection was required.
- A bleeding episode was defined as a light, normal or heavy bleeding during a minimum of one day. Light, normal and heavy were defined relative to an individual patient's usual experience.
- A bleeding-free day was defined as a day with either no bleeding or only spotting reported on the diary card. Spotting was defined as not requiring sanitary protection (except for panty liners)
- A single bleeding episode consisted of all bleeding days separated by no more than one bleeding-free day. Separate bleeding episodes consisted of bleeding days separated by more than one bleeding-free day. An episode stopped with two consecutive bleeding-free days.

5.3.1.11 Alkaline Hematin Method

This laboratory method measures hemoglobin in a fixed amount of alkaline solution with a spectrophotometer.

5.3.1.12 Global Assessments

The protocol included two global assessments, one each by the investigators and the subjects in regard to overall improvement of heavy bleeding symptomatology. The investigator assessment was based on information in the subject diary card, lab data, physical exams and subject interviews. The assessment for both the investigator and subject included 8 possible responses:

0 = not assessed
1 = very much improved
2 = much improved
3 = improved
4 = no change
5 = worse
6 = much worse
7 = very much worse

5.3.1.13 Primary Efficacy Variables

There were two primary efficacy variables:

- The change in absolute value from Baseline MBL to the End-of-Study MBL. The MBL for each cycle included intermenstrual bleeding in addition to withdrawal bleeding. Baseline MBL was the MBL averaged over each of the cycles during the Screening Phase. End-of-Study MBL was measured during Cycle 6 of the Treatment Phase (imputation using last observation carried forward [LOCF], was applied if needed, as described in Section 5.3.1.16).

- The proportion of patients with successful treatment (defined as End-of-Study MBL < 80 mL and a decrease to a value no greater than 50% of the Baseline MBL)

5.3.1.14 Secondary Efficacy Variables

The secondary efficacy variables included the following:

- The absolute change in Baseline MBL to Mid-Study MBL (cycle 3)

- The percent change from Baseline MBL to Mid-Study MBL (cycle 3)

- The percent change from Baseline MBL to End-of-Study MBL
- Continuation rate (proportion of subjects who completed the study in the LNG IUS treatment group)
- Changes and absolute changes from baseline to Cycle 3, from baseline to Cycle 6, and from Cycle 3 to Cycle 6 of the Treatment Phase were calculated for the following bleeding pattern indices:
    - Total number of days of bleeding
    - Total number of days that include spotting or bleeding
    - Total number of days that include spotting only
    - Total number of bleeding episodes
- Percent change in hemoglobin, hematocrit and serum ferritin (these changes were calculated from baseline to Cycle 3, from baseline to Cycle 6 and from Cycle 3 to Cycle 6 of the Treatment Phase)
- Proportion of subjects with improvement in the Investigator Global Assessment Scale during Cycle 3 and Cycle 6 of the Treatment Phase
- Proportion of subjects with improvement in the Subject's Overall Assessment Scale during Cycle 3and Cycle 6 of the Treatment Phase

5.3.1.15 Overall Success of the Study

The applicant stated that the study would be considered successful if:

- Treatment with LNG IUS produced a statistically significantly greater mean reduction in blood loss than treatment with MPA (measured as the change in the absolute value from Baseline MBL to End-of-Study MBL) and
- Treatment with LNG IUS produced a statistically significant greater number of patients with successful treatment than treatment with MPA and
- The difference of the point estimates for the mean reduction in MBL between LNG IUS and MPA was at least 30 mL and

- The point estimate of the mean End-of-Study MBL was at least 50 mL less than the point estimate of the mean Baseline MBL in the LNG IUS group

5.3.1.16 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) was finalized on September 5, 2008. The primary and secondary efficacy variables were previously listed in this section of the review (5.3.1.13 and 5.3.1.14). Additional key elements from the SAP are the following:

Key Points Related to Handling of Missing Data

- For the evaluations of the MBL, the last observation carried forward (LOCF) method was used for imputation purposes. If no MBL data in Cycle 6 was available or Cycle 6 was invalid, MBL data in Cycle 3 was used as End of Study MBL instead. If no MBL data was available in Cycle 6 and Cycle 3 or both cycles were invalid, Baseline MBL was used as End of Study MBL instead.

- Cycles with more than 10 days with completely missing bleeding assessments (recording of bleeding intensity, sanitary protection collected, blood volume data) were invalid and LOCF was applied in these cycles.

- If sanitary protection was correctly collected but there was missing MBL volume data, then volume data was imputed by using the mean MBL volume for properly recorded days in the same bleeding episode.

Other Key Points

- If there was a bleeding episode in which sanitary protection was incompletely collected on all days, then the missing volume data was imputed by using the mean MBL volume of the preceding bleeding episode in the same cycle where sanitary protection was correctly collected. If there was no preceding bleeding episode a succeeding episode was used.

- No interim analysis was planned

- The Medical Dictionary for Regulatory Activities (MedDRA) was used for coding all adverse events. The System Organ Class and Preferred Term were used for each adverse event.

- Analysis of the primary efficacy variables was performed for both the full analysis set (FAS) and per-protocol analysis set (PPS). The FAS was the primary analysis for the efficacy evaluation. The FAS included all randomized subjects. The PPS included all subjects of the FAS who:

1. Met all the inclusion/exclusion criteria
2. Did not take any prohibited medications
3. Had at least 75% overall study drug compliance (for LNG IUS)
4. Had at least 75% study drug compliance for each cycle (for MPA)
5. Had an available End-of Study MBL
6. Had no major protocol violations
7. Completed all End-of-Study procedure

5.3.1.17 Analysis of Safety

Standard safety monitoring was employed in this protocol (medical history, physical exams, vital sign monitoring, pap smears, chemistry, hematology, urinalysis, pregnancy testing, adverse event reporting, etc.).

Chemistry values assessed included creatinine, potassium, sodium, total protein, albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), ferritin, and serum hCG. Special chemistry included FSH, TSH and serum prolactin.

Hematology testing included hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, total neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count and von Willebrand Factor (vWF) activity.

Urinalysis evaluations included pH, protein, glucose and hCG.

Gonorrhea and Chlamydia were tested by cervical swab prior to IUD insertion. Endometrial biopsies and hysterosonographies were assessed at the beginning of the study. Endometrial biopsies were performed for cause (endometrial thickening by transvaginal sonography) at the end of the study. LNG IUS positioning was confirmed at visits during the treatment phase by physical examination.

The Applicant listed specific adverse events which would lead to subjects being immediately terminated from the study:

- First signs of venous inflammation or blood clots (thrombosis, embolism), e.g., marked pain or swelling in the legs, stabbing pain on breathing or cough of unknown origin, pain and a feeling of constriction in the chest
- Scheduled major operations (4 weeks prior), and/or in case of prolonged immobility (e.g., after accidents)
- Migraine headache (hemicranial headache with sudden onset, accompanied by dizziness and vomiting), occurring for the first time or more frequently with unusual severity
- Sudden sensory disturbances (visual, auditory, etc.)

- Motor disturbances (particularly paralysis)
- Documented persistent moderate to severe hypertension or unexplained increase in blood pressure
- Jaundice, itching over the entire body, disturbances of bile drainage (cholestasis), or clinically significant increase in liver function test values (3x upper limit of normal)
- Epileptic seizures
- Partial or total expulsion of the LNG IUS if the system is out of the uterus for more than two weeks during the study
- Pregnancy
- For patients receiving LNG IUS, pelvic infection, acquired immune deficiency syndrome (AIDS), sexually transmitted disease, endometritis, symptomatic genital actinomycosis, intractable pelvic pain, severe dyspareunia, endometrial or cervical malignancy, and uterine or cervical perforation
- Severe arterial disease, such as stroke or myocardial infarction.

5.3.1.18 Protocol Amendments

The study date of the original protocol was May 10. 2006. The first amendment to Protocol 309849 was dated November 16, 2006. This amendment included:

- Allowance of subjects in the trial who were not seeking intrauterine contraception (for example, subjects with a history of tubal ligation or who had a partner with a vasectomy)

Medical Officer Comment:
Although the "heavy menstrual bleeding" indication sought by the Applicant is secondary and applies to women who are using Mirena for intrauterine contraception, all of the subjects in the trial should not necessarily be required to be "seeking intrauterine contraception." Some of these subjects might have had a history of tubal ligation or their partner has had a vasectomy.

The study date of the second and final amendment to Protocol 309849 was dated February 26, 2008. This amendment included:

- Sponsor name changes (Schering AG and Berlex, Inc. to Bayer HealthCare Pharmaceuticals.
- Administrative changes regarding contact information and the interactive voice response system for registration
- Change in the U.S. study drug disposal (b) (4))

5.3.1.19 Disposition of Subjects

Subject disposition in Study 309849 is found in Table 15. Disposition by cycle and treatment group results are found in Table 16.

Table 15: Study 309849 – Overall Subject Disposition

Disposition / Reason	LNG IUS	MPA	Total
Screened			807
Screening failures			642
Full Analysis Set (a)	82 (100%)	83 (100%)	165 (100%)
Per Protocol Set (b)	37 (45.1%)	45 (54.2%)	82 (49.7%)
Safety Analysis Set (c)	80 (97.6%)	82 (98.8%)	162 (98.2%)
Completed the study	73 (89.0%)	72 (86.7%)	145 (87.9%)
Prematurely discontinued from the study	9 (11.0%)	11 (13.3%)	20 (12.1%)
• Withdrawal of consent	1 (1.2%)	3 (3.6%)	4 (2.4%)
• Protocol deviation	0 (0%)	4 (4.8%)	4 (2.4%)
• Adverse event	4 (4.9%)	2 (2.4%)	6 (3.6%)
• Subject lost; no further information	2 (2.4%)	1 (1.2%)	3 (1.8%)
• Other	2 (2.4%)	1 (1.2%)	3 (1.8%)
Study medication never administered	2 (2.4%)	1 (1.2%)	3 (1.8%)
Completed the study medication	73 (89.0%)	69 (83.1%)	142 (86.1%)
Study medication status unknown	2 (2.4%)	2 (2.4%)	4 (2.4%)
Reasons for premature discontinuation from study medication (multiple reasons possible)			
• Withdrawal of consent	1 (1.2%)	3 (3.6%)	4 (2.4%)
• Protocol deviation	0 (0%)	4 (4.8%)	4 (2.4%)
• Adverse event	4 (4.9%)	2 (2.4%)	6 (3.6%)
• Subject lost; no further information	2 (2.4%)	1 (1.2%)	3 (1.8%)
• Early therapeutic success	0 (0%)	2 (2.4%)	2 (1.2%)
• Other	2 (2.4%)	2 (2.4%)	4 (2.4%)

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
a = Defined as all randomized subjects
b = Defined as all randomized subjects who met all the inclusion/exclusion criteria, did not take any prohibited medications, had at least 75% overall study drug compliance, had no major protocol violations, and completed all End-of-Study procedures
c = Defined as all randomized subjects who took at least one MPA tablet or had LNG IUS inserted or attempted insertion
Source: Study Report A38313 Text Table 4; page 56 of 126

Medical Officer's Comment:
Of the 165 subjects randomized in Study 309849, 103 subjects were randomized at 29 U.S. sites and 62 subjects were randomized at 11 foreign sites (9 sites in Canada and 2 sites in Brazil).

Table 16: Study 309849 – Subject Completion by Cycle and Treatment Group

Cycles Completed	LNG IUS (n=82)	MPA (n=83)	Total (n=165)
Cycle 1	79 (96.3%)	81 (97.6%)	160 (97.0%)
Cycle 2	76 (92.7%)	80 (96.4%)	156 (94.5%)
Cycle 3	75 (91.4%)	77 (92.8%)	152 (92.1%)
Cycle 4	74 (90.2%)	74 (89.2%)	148 (89.7%)
Cycle 5	73 (89.0%)	70 (84.3%)	143 (86.7%)
Cycle 6	73 (89.0%)	70 (84.3%)	143 (86.7%)
Cycle 7	NA	16 (19.3%)	16 (9.7%)
Missing	3 (3.7%)	2 (2.4%)	5 (3.0%)

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
a = a seventh cycle was only possible for subjects who received MPA
Source: Study Report A38313 Text Table 5; page 57 of 126

5.3.1.20 Protocol Deviations

Approximately half (50.3%) of the study subjects had at least one major deviation from the protocol and one third (34.5%) had a minor deviation from the protocol. According to the Applicant most deviations were procedural, treatment-related, or involved an error of the inclusion or exclusion criteria at study entry.

Medical Officer's Comment:
The biostatistician Dr. Fang reviewed the impact of the protocol deviations and did not find any impact on the efficacy of LNG IUS.

5.3.1.21 Demographics

Demographic data for Study 309849 is found in Table 17

Table 17: Study 309849 – Demographics and Baseline Characteristics

Disposition / Reason	LNG IUS (n=82)	MPA (n=83)	Total (n=165)
Mean age (years [range])	38.3 [26-50]	39.3 [26-53]	38.8 [26-53]
Age group 18-35 years	19 (23.2%)	13 (15.7%)	32 (19.4%)
Age group > 35 years	63 (76.8%)	70 (84.3%)	133 (80.6%)
Ethnic group			
• Caucasian	56 (68.3%)	62 (74.7%)	118 (71.5%)
• Black	17 (20.7%)	13 (15.7%)	30 (19.4%)
• Hispanic	6 (7.3%)	6 (7.2%)	12 (7.3%)
• Asian	2 (2.4%)	1 (1.2%)	3 (1.8%)
• Other	1 (1.2%)	1 (1.2%)	2 (1.2%)
Mean weight (kg)	73.4	73.4	73.4
Mean height (cm)	164.4	163.8	164.1
Body mass index (kg/m^2)	27.2	27.4	27.3

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
Source: Study Report A38313 Text Table 8; page 61 of 126

5.3.1.22 Medical History (Includes Surgical and Gynecological History)

The distribution of medical and surgical histories by treatment group was similar.

The historical data related to menarche and pregnancy-related events was similar in both treatment arms as shown in Table 18.

Table 18: Study 309849 – Gynecologic / Obstetric History

	LNG IUS (n=82)	MPA (n=83)	Total (n=165)
Mean age at menarche (years) [range]	12.5 [9-17]	12.5 [9-18]	12.5 [9-18]
Mean number of pregnancies [range]	3.0 [1-8]	3.2 [1-7]	3.1 [1-8]
Mean number of births [range]	2.5 [1-5]	2.6 [1-7]	2.5 [1-7]
Mean number of vaginal deliveries [range]	1.7 [0-4]	1.7 [0-5]	1.7 [0-5]
Mean number of abortions [range]	0.5 [0-4]	0.5 [0-6]	0.5 [0-6]
Mean number of Caesarian sections [range]	0.7 [0-4]	0.8 [0-4]	0.8 [0-4]
Mean number of ectopic pregnancies [range]	0.0 [0-0]	0.0 [0-1]	0.0 [0-1]
Mean years since last birth or abortion [range]	8.8 [1-24]	8.9 [0-23]	8.9 [0-24]

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
Source: Study Report A38313 Text Table 10; page 63 of 126

The distribution of contraceptive methods was similar as shown in Table 19.

Table 19: Study 309849 – Contraceptive History over the Previous 30 Days

	LNG IUS (n=82)	MPA (n=83)	Total (n=165)
Contraceptive Method			
• None	0 (0%)	0 (0%)	0 (0%)
• Condom	17 (20.7%)	22 (26.5	39 (23.6%)
• Oral	1 (1.2%)	0 (0%)	1 (0.6%)
• Intrauterine contraceptive device	0 (0%)	0 (0%)	0 (0%)
• Other	56 (68.3%)	50 (60.2%)	106 (64.2%)
• Missing	8 (9.8%)	11 (13.3%)	19 (11.5%)

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
Source: Study Report A38313 Text Table 11; page 63 of 126

All of the randomized subjects in the clinical trial had regular cycles. The following table (Table 20) gives more specifics on the cycle and bleeding information.

Table 20Study 309849 – Descriptive Statistics for Menstrual History by Randomized Treatment Group

	LNG IUS (n=82)	MPA (n=83)	Total (n=165)
Cycle length (days)			
• Mean	27.2	27.3	27.2
• SD	3.39	2.29	2.88
• Range	7*-33	21-32	7*-33
Menstrual duration (days)			
• Mean	6.2	6.3	6.3
• SD	1.64	1.54	1.59
• Range	3-14	4-14	3-14
Intensity of bleeding (n) [%]			
Normal	1 (1.2%)	2 (2.4%)	3 (1.8%)
Heavy	81 (98.8%)	81 (97.6%)	162 (98.2%)
Intercyclic vaginal bleeding (n) [%]			
No	80 (97.6%)	75 (90.4%)	155 (93.9%)
Yes	2 (2.4%)	8 (9.6%)	10 (6.1%)
Dysmenorrhea (n) [%]			
No	34 (41.5%)	33 (39.8%)	67 (40.6%)
Yes	48 (58.5%)	50 (59.4%)	98 (59.4%)

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
SD = standard deviation
* = This unexpectedly low cycle length was been checked against the database. The entry is believed to represent the findings from only 1 subject and is believed to be an entry error that should have represented menstrual duration and not cycle duration, but this cannot be confirmed.
Source: Study Report A38313 Text Table 11; page 63 of 126

Medical Officer's Comment:
It appears from the menstrual history table that slightly more subjects with a history of intracyclic bleeding were randomized to the MPA treatment group.

5.3.1.23 Previous and Concomitant Treatment

Previous medications were used by 52.1% of study participants (in the FAS). The most commonly used (>5% of subjects) previous medications were propionic acid derivatives (14.5%), anilides (10.9%), and imidazole derivatives (7.9%).

Concomitant medications were used by 86.3% of study participants (FAS). The most commonly used (>5% of subjects) concomitant medications were anilides (34.5%), oral bivalent iron (16.4%), multi-vitamins (14.5%), imidazole derivatives (11.5%), propionic acid derivatives (10.3%), other antihistamines (7.3%), thyroid hormones (6.7%), natural

opium alkaloids (6.1%), iron preparations (6.1%), selective serotonin reuptake inhibitors (6.1%), and multi-vitamins with minerals (5.5%).

Medical Officer's Comment:
According to concomitant dataset 6 LNG IUS subjects and 5 MPA subjects used thyroid hormones concurrently during the study. Thyroid abnormalities can rarely be associated with uterine bleeding. Since the number of subjects taking thyroid is approximately equal in both treatment groups, this reviewer would not anticipate any effect on efficacy.

5.3.1.24 Treatment Compliance

In order to monitor compliance for subjects in the MPA treatment group, subjects recorded daily intake in the diary card. At each visit, the diary card entries were reviewed by study site personnel. Additionally, subjects were required to return all unused study drug (MPA) to the study site personnel at every visit for tablet count. The bottle containing the unused tablets was re-dispensed to the subject.

For the MPA treatment group, compliance was calculated as the number of days when subjects took a tablet during 10 consecutive days from the date of the first tablet intake (i.e., Day 16 ±1 day) in each cycle divided by 10 days.

If subjects had shorter menstrual cycles (i.e., <25 days per cycle for the entire study or during Cycle 6) the compliance of Cycle 6 was calculated as follows: If subjects took tablets everyday from the date of first tablet intake (i.e., Day 16 ±1 day) in Cycle 6 to the last date of the diary, compliance was considered to be 100% regardless of the total number of days when tablets were taken.

For the LNG IUS treatment group, compliance was calculated as the number of days when subjects underwent an insertion attempt or retained an inserted LNG IUS (i.e., either End-of-Study medication date or last date in the diary, whichever came first, minus Day 1 of Cycle 1) divided by the treatment duration.

Overall treatment compliance was higher for the LNG IUS compared to the orally administered MPA, with 95.1% versus 71.6% of subjects, respectively, who achieved or exceeded a level of 75% compliance calculated over all treatment cycles.

5.3.1.25 Primary Efficacy Results– The Absolute Change in Baseline MBL to End-of-Study MBL.

The change in MBL from Baseline to Mid-Study and from Baseline to End-of-Study is shown in Table 21. Both the median and mean results are shown.

Table 21: Study 309849 – Summary of Median Menstrual Blood Loss over Time (Analysis Set)

Time Point	Treatment Group	n	Median MBL (mL)	Range (mL)	Mean	SD
Baseline	LNG IUS	79	147.96	68.3 - 431.4	164.92	70.43
	MPA	81	154.20	63.4 – 456.0	170.58	77.67
Mid-Study	LNG IUS	81	30.30	00 – 317.5	55.81	62.10
	MPA	81	136.20	0.0 – 404.8	149.38	88.29
End-of-Study	LNG IUS	81	7.10	0.0 – 1435.6	49.14	166.96
	MPA	81	121.47	0.0 – 437.7	131.57	84.33

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
MBL = menstrual blood loss
Source: Study Report A38313 Text Table 13; page 68 of 126 and Table 21; page 80 of 318

The Applicant calculated p values on changes from Baseline (Wilcoxon Test).
The results for both Mid-Study and End-of-Study were P<0.001 as shown in Table 22.

Table 22: Study 309849 – Absolute Change in Median Menstrual Blood Loss from Baseline (Analysis Set)

Time Point	Treatment Group	n	Median MBL (mL)	Change from Baseline (mL)	P-value Wilcoxon Test
Mid-Study	LNG IUS	79	147.96	- 115.13	P<0.001
	MPA	81	154.20	- 3.15	
End-of-Study	LNG IUS	79	147.96	- 128.78	P<0.001
	MPA	81	154.20	- 17.77	

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
MBL = menstrual blood loss
Source: Study Report A38313 Text Table 14; page 68 of 126 and Summary of Clinical Efficacy; page 12 of 108.

Among the 165 FAS subjects, a total of 160 subjects (79 for LNG IUS and 81 for MPA) were available for the MBL analysis.

Subjects 12505 (LNG IUS) and 135005 and 13216 (MPA) were not included in the analysis due to missing diary data, and Subjects 24723 and 24812 (LNG IUS) were not available due to invalid baseline data.

The results from the Wilcoxon test showed a statistically significant difference in absolute MBL from baseline to End-of-Study between the two treatment groups (median changes of -128.8 mL LNG IUS versus -17.8 mL MPA; $p < 0.001$).

5.3.1.26 Primary Efficacy Results– The Proportion of Subjects with Successful Treatment

Successful treatment was defined as an End-of-Study MBL < 80 mL and a decrease to a value no greater than 50% of the Baseline MBL. The proportion of subjects with successful treatment and the calculated p values are found in Table 23.

Table 23: Study 309849 – The Proportion of Subjects with Successful Treatment (Analysis Set)

Assessment	LNG IUS N =82	MPA N=83	% Difference	95% CI	p-value (b)
Success (a)					
N	79 (100%)	81 (100%)			
Yes	67 (84.8%)	18 (22.2%)	62.6	50.56-74.61	<0.001
No	12 (15.2%)	63 (77.8%)			
End-of-Study MBL < 80 mL					
N	81 (100%)	81 (100%)			
Yes	71 (87.7%)	24 (29.6%)	58.0	45.77-70.28	<0.001
No	10 (12.3%)	57 (70.4%)			
Decrease in End-of-Study MBL ≥50% of Baseline MBL					
N	79 (100%)	81 (100%)			
Yes	67 (84.8%)	22 (27.2%)	57.6	45.14-70.16	<0.001
No	12 (15.2%)	59 (72.8%)			

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
MBL = menstrual blood loss; CI = confidence interval
(a) = Successful treatment is defined as: End-of-Study MBL < 80 mL and decrease in End-of-Study MBL ≥ 50% of Baseline MBL
(b) = Pearson's Chi-squared test. Significance level of the test is 0.05 (two-sided)
Source: Study Report A38313 Text Table 15; page 70 of 126

Although the study protocol called for two primary endpoints, the Applicant also identified two additional success criteria, which are shown in Table 24.

Medical Officer's Comment:
Only the two pre-specified co-primary endpoints are mentioned in the Clinical Study section of the label.

Table 24: Study 309849 – Overall Study Success Criteria (Full Analysis Set)

Success Criteria	Results	Criteria Met?
1. Treatment with LNG IUS produced a statistically significant greater reduction in blood loss than treatment with MPA (measured as the change in the absolute value from Baseline MBL to End-of-Study MBL)	p<0.001	Yes
2. Treatment with LNG IUS produced a statistically significant greater number of subjects with successful treatment than treatment with MPA	p<0.001	Yes
3. The difference of the point estimates for the mean reduction in MBL between LNG IUS and MPA was at least 30 mL (Baseline to End-of-Study)	-75.67 mL	Yes
4. The point estimate of the mean End-of-Study MBL was at least 50 mL less than the point estimate of the mean Baseline MBL in the LNG IUS group	-114.68 mL	Yes

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
MBL = menstrual blood loss
Source: Study Report A38313 Text Table 16; page 71 of 126
Note: Success criteria #1 is expressed as a median value as shown in Table 22

5.3.1.27 Secondary Efficacy Results

The secondary efficacy results are summarized in Table 25.

Table 25: Study 309849 – Secondary Endpoints

Secondary Endpoints	Results
The absolute change from Baseline MBL to Mid-Study MBL compared to MPA	p<0.001 (Wilcoxon Test)
The percent change from Baseline MBL to Mid-Study MBL compared to MPA	p>0.0001 (t test)
The percent change from Baseline MBL to End-of-Study MBL compared to MPA	p>0.0001 (t test)
Continuation rate through 180 days for LNG IUS	90.12%
Mean number of bleeding days (baseline/cycle 3/cycle6) for LNG IUS	5.6/5.9/4.2
Mean number of bleeding days (baseline/cycle 3/cycle6) for MPA	5.6/5.2/5.2
Mean number of bleeding and spotting days (baseline/cycle 3/cycle6) for LNG IUS	6.3/11.9/8.6
Mean number of bleeding and spotting days (baseline/cycle 3/cycle6) for MPA	6.8/6.9/6.9
Mean number of spotting days (baseline/cycle 3/cycle6) for LNG IUS	1.2/7.3/5.4
Mean number of spotting days (baseline/cycle 3/cycle6) for MPA	1.8/2.3/2.2
Overall percent increase in hemoglobin (baseline to cycle 6) for LNG IUS (median)	7.5%
Overall percent increase in hemoglobin (baseline to cycle 6) for MPA (median)	1.9%
Overall percent increase in hematocrit (baseline to cycle 6) for LNG IUS (median)	5.4%
Overall percent increase in hematocrit (baseline to cycle 6) for MPA (median)	0%
Overall percent increase in ferritin (baseline to cycle 6) for LNG IUS (median)	68.8%
Overall percent increase in ferritin (baseline to cycle 6) for MPA (median)	14.3%
Proportion of subjects with improvement on Investigator Global Assessment Scale for LNG IUS at cycle 6	93.6%
Proportion of subjects with improvement on Investigator Global Assessment Scale for MPA at cycle 6	61.0%
Proportion of subjects with improvement on Patients' Overall Assessment Scale for LNG IUS at cycle 6	93.6%
Proportion of subjects with improvement on Patients' Overall Assessment Scale for MPA at cycle 6	67.1%

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
MBL = menstrual blood loss
Source: Study Report A38313 - Table 37 (From study tables section page 98 of 318); Text tables 18, 19, 20, 21, 22, 23, 25, 27, 28, 29 (From study report pages 73-85 of 126)

Medical Officer's Comment:
As demonstrated in the preceding table, all the secondary efficacy endpoints are supportive of the indication except for an increase in bleeding/spotting days for LNG IUS compared to MPA. This reviewer considers the pronounced decrease in blood loss volume to outweigh the disadvantages of having a few more days of mild bleeding or spotting.

5.3.1.28 Safety – Extent of Exposure

The safety analysis (SAF) set included all randomized subjects who received at least 1 dose of the MPA or had LNG IUS inserted or attempted insertion (i.e., insertion failures). This population comprised 162 subjects (98.2% of the randomized subjects), 80 who received treatment with LNG IUS and 82 who received treatment with MPA.

5.3.1.29 Safety – Event Overview

The safety event overview is shown in Table 26.

Table 26: Study 309849 – Overview of the Number (%) of Subjects with Treatment-Emergent Adverse Events (Safety Analysis Set)

Subjects	LNG IUS N = 80 n (%)	MPA N= 82 n (%)	Total N = 162 n (%)
With at least 1 AE	68 (85.0)	52 (63.4)	120 (74.1)
With AE of severe intensity	13 (16.3)	7 (8.5)	20 (12.3)
With AE of moderate intensity	29 (36.3)	29 (35.4)	58 (35.8)
With AE of mild intensity	26 (32.5)	16 (19.5)	42 (25.9)
With drug-related AEs	38 (47.5)	31 (37.8)	69 (42.6)
With SAEs	1 (1.3)	0	1 (0.6)
Who discontinued study drug due to an AE	4 (5.0)	2 (2.4)	6 (3.7)
Who died	0	0	0

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
AE = adverse event; SAE = serious adverse event
Source: Study Report A38313 Text Table 33; page 90 of 126

5.3.1.30 Safety – Common Adverse Events

Common adverse events (>2%) are shown in Table 27.

Table 27: Study 309849 – Number (%) of Subjects with Common (≥2%) Treatment-Emergent Adverse Events by Preferred Term and Descending Frequency of Occurrence in the LNG IUS Treatment Group (Safety Analysis Set)

Preferred Term	LNG IUS N =80 n (%)	MPA N=82 n (%)	Total N = 162 n (%)
Headache	13 (16.3)	9 (11.0)	22 (13.6)
Ovarian cyst	10 (12.5)	2 (2.4)	12 (7.4)
Vaginitis bacterial	9 (11.3)	3 (3.7)	12 (7.4)
Urinary tract infection	6 (7.5)	3 (3.7)	9 (5.6)
Acne	5 (6.3)	5 (6.1)	10 (6.2)
Hypertension	5 (6.3)	1 (1.2)	6 (3.7)
Sinusitis	5 (6.3)	3 (3.7)	8 (4.9)
Upper respiratory tract infection	5 (6.3)	1 (1.2)	6 (3.7)
Breast tenderness	4 (5.0)	3 (3.7)	7 (4.3)
Fatigue	4 (5.0)	2 (2.4)	6 (3.7)
Pelvic pain	4 (5.0)	2 (2.4)	6 (3.7)
Weight increased	4 (5.0)	5 (6.1)	9 (5.6)
Abdominal pain	3 (3.8)	2 (2.4)	5 (3.1)
Abdominal pain lower	3 (3.8)	5 (6.1)	8 (4.9)
Arthralgia	3 (3.8)	4 (4.9	7 (4.3)
Breast cyst	3 (3.8)	1 (1.2)	4 (2.5)
Menorrhagia	3 (3.8)	1 (1.2)	4 (2.5)
Uterine spasm	3 (3.8)	1 (1.2)	4 (2.5)
Back pain	2 (2.5)	1 (1.2)	3 (1.9)
Breast pain	2 (2.5)	0	2 (1.2)
Bronchitis	2 (2.5)	1 (1.2)	3 (1.9)
Coital bleeding	2 (2.5)	0	2 (1.2)
Cough	2 (2.5)	0	2 (1.2)
Depression	2 (2.5)	1 (1.2)	3 (1.9)
Dysmenorrhea	2 (2.5)	3 (3.7)	5 (3.1)
Flatulence	2 (2.5)	0	2 (1.2)
Gastroenteritis	2 (2.5)	1 (1.2)	3 (1.9)
Genital discharge	2 (2.5)	0	2 (1.2)
Intrauterine device complication	2 (2.5)	0	2 (1.2)
Intrauterine device expelled	2 (2.5)	0	2 (1.2)
Irritability	2 (2.5)	0	2 (1.2)
Libido decreased	2 (2.5)	3 (3.7)	5 (3.1)
Metrorrhagia	2 (2.5)	0	2 (1.2)
Nasopharyngitis	2 (2.5)	3 (3.7)	5 (3.1)
Uterine leiomyoma	2 (2.5)	4 (4.9)	6 (3.7)
Vaginal discharge	2 (2.5)	1 (1.2)	3 (1.9)
Viral upper respiratory infection	2 (2.5)	0	2 (1.2)
Vulvovaginal mycotic infection	2 (2.5)	3 (3.7)	5 (3.1)

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
Source: Study Report A38313 Text Table 37; page 94 of 126

Medical Officer's Comment:
The percentage of ovarian cysts (12.5%) is similar to percent listing in the current Mirena® label.

5.3.1.31 Safety – Nonfatal Serious Adverse Events

One SAE was reported in Study 309849. Subject 24514 who received treatment with LNG IUS was found to have an ovarian cyst at the end of the study. Further history about 4 months later included a hysterectomy and bilateral salpingo-oophorectomy for endometriosis. The event was not considered by the Applicant to be related to treatment with study medication.

Medical Officer's Comment:
There was no mention of endometriosis in the case report form for Subject 24514 (recorded as patient 014 at site 245 in Canada). Endometriosis was an exclusionary criterion. The subject was 43 years old and had a history of four pregnancies. Her husband had a history of a vasectomy. The CRF lists a history of moderate dysmenorrhea that had continued for 2 years prior to the study. Her history of moderate menorrhagia had been continuing for 11 years. A 5 cm right ovarian cyst was identified at the end of the study. The cyst did not resolve. The decision regarding hysterectomy and bilateral salpingo-oophorectomy was also influenced by a strong first degree family history of breast cancer. The Applicant did not list any information on genetic studies (e.g., BRCA 1 or 2 mutations). At the time of surgery, the IUD was removed along with the uterus. Pathology revealed endometriosis.

Although it is likely her endometriosis was pre-existing at study entry, this reviewer would not anticipate any impact on overall study efficacy. It also seems unlikely that the LNG IUS would have worsened her endometriosis. Potent progestins can ameliorate endometriosis but the effect of LNG IUS would probably be too distant from the ovarian focus of endometriosis to improve her disease.

5.3.1.32 Safety – Deaths

No deaths were reported during Study 309849.

5.3.1.33 Safety – Discontinuations Due to Adverse Events

The subjects who discontinued for adverse events in pivotal Study 309849 are listed in Table 28.

Table 28: Study 309849: Subjects who Discontinued Study Drug Due to an Adverse Event

Subject Number	Treatment Group	Discontinuation
10101	LNG IUS	Lower abdominal pain
10120	LNG IUS	IUD dislocation, menorrhagia, uterine cramps
12219	LNG IUS	Lower abdominal pain,
12505	LNG IUS	Menorrhagia
10703	MPA	Dizziness
12308	MPA	Fluid retention

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
Source: Study Report A38313; text table 38 page 97 of 126 and IN.TERMIA dataset via JMP

Medical Officer's Comment:
The menorrhagia reported for subject 10120 began on August 2, 2007 and was reported to be resolved on Sept 1, 2007. There was no history of surgery or transfusion. There was a history of small fibroids

The menorrhagia reported for subject 12505 began on Nov 18, 2007 and was reported to be resolved three days later on Nov 20, 2007. There was no history of surgery or transfusion. This subject was also reported to have fibroids.

5.3.1.34 Safety – Clinical Laboratory

Mean serum chemistry values were within normal ranges at all time points for each analyte. Mean changes from baseline to each time point were small and were similar between treatment groups.

The increases in hemoglobin, hematocrit and ferritin were noted in the secondary efficacy findings reported earlier in this review. There were no hematologic lab safety concerns. There were no safety concerns identified in the urinalyses.

5.3.1.35 Safety – Vital Signs

The following vital signs and body metrics were analyzed and summarized at each study visit: weight, systolic and diastolic blood pressure, and heart rate. No differences in mean weight, systolic blood pressure, diastolic blood pressure, or heart rate were noted between treatment groups or over time.

5.3.2 Supportive Study 92549 (Reports A02916 and B088)

5.3.2.1 Supportive Study 92549 - Efficacy

This was an open-label, randomized, comparative, parallel group study on the efficacy and safety of LNG IUS compared with an oral norethisterone (norethindrone) administered as 15 mg/day during the 5th to 25th days of each cycle in the treatment of idiopathic menorrhagia (MBL ≥80 mL per cycle determined using the alkaline hematin method) in healthy 18 to 45-year-old parous women.

The study consisted of a 3-cycle comparative phase (Report B088), and an extension phase (Report A02916). The study was conducted in 1 center in the United Kingdom. The extension phase was planned for 5 years, but due to the small number of subjects (17 subjects) entering the extension phase, the study was discontinued and the subjects were followed up off-treatment for 2 or 3 years.

The primary efficacy variables included a MBL comparative analysis and an analysis of treatment success.

For MBL, the Applicant compared the reduction in MBL in treatment cycle 3 with MBL prior to treatment, and compared the reduction in MBL between the treatment groups. Comparison of reduction was made with the non-parametric Wilcoxon rank sum test. The laboratory analysis of MBL was performed utilizing the alkaline hematin method. Treatment success was defined based on the number of subjects with MBL below 80 mL at cycle 3. Discontinuation of use of either method for any reason was interpreted as failure. The MBL summary is found in Table 29.

Table 29: Study 92549 – Summary of Median Menstrual Blood Loss over Time (Full Analysis Set)

Time Point	Treatment Group	n	Median MBL (mL)	Range (mL)	Mean	SD
Baseline	LNG IUS	22	105.5	82-780	165.3	160.9
	NET	22	119.5	82-336	130.3	60.6
Cycle 1	LNG IUS	19	19.0	0-62	20.7	18.4
	NET	20	46.0	0-213	70.3	66.4
Cycle 3	LNG IUS	21	6.0	0-284	33.4	72.2
	NET	14	20.5	4-137	32.2	35.0

LNG IUS = levonorgestrel-releasing intrauterine system; NET = norethisterone
MBL = menstrual blood loss
Source: Study Report B088 Table E.2.1.12; page 342 of 767

Based on the FAS, the median MBL was reduced from baseline to Cycle 3 by 94% in the LNG IUS group vs. 87% in the NET group, but the difference in the reduction from baseline between the groups was not statistically significant.

The median MBL was statistically significantly lower in the LNG IUS group than in the NET group in Cycle 1 (P=0.010) and in Cycle 3 (P=0.033) as shown in the following table (Table 30). (Note: This was not a prespecified primary endpoint)

Table 30: Study 92549 – Median MBL by Time Point and Treatment (Full Analysis Set)

	Median MBL (mL) (min to max) N = number of subjects		P-value difference between the treatment groups
	Mirena (LNG IUS)	**NET**	**% Difference**
Baseline	106 (82-780)	120 (82-336)	
	N = 22	N = 22	
Cycle 1	19 (0-62)	46 (0-213)	
	N = 19	N = 20	P = 0.010
Cycle 3	6 (0-284)	21 (4-137)	
	N = 21	N = 14	P = 0.033

LNG IUS = levonorgestrel-releasing intrauterine system; NET = norethisterone
MBL = menstrual blood loss; CI = confidence interval
Source: Summary of Clinical Efficacy; Text table 4; page 14 of 108

Treatment was considered successful for 86% (95% confidence interval: 65.1% - 97.1%) of the LNG IUS treated subjects vs. 65% (95% confidence interval: 40.8% - 84.6%) of the NET-treated subjects, but the difference did not reach statistical significance.

Medical Officer's Comment: In this study LNG IUS was compared to a progestin that was given at 15 mg/day for 21 cycle days. In the pivotal Study 309849, MPA was given for 10 days. Norethisterone is the same as norethindrone. Norethindrone is approved in the U.S. as Micronor® and Nor-QD® (0.35 mg daily) for oral contraception. Neither product carries an indication for heavy menstrual bleeding.

Norlutin is an approved 5 mg norethindrone product in the U.S. that is no longer marketed. Norlutin carried indications for menstrual irregularity and functional uterine bleeding. The dosage recommended varied from 5-20 mg per day (cycle days 5-23). Thus the dosage of norethisterone (15 mg/day for cycle days 5-25) is very similar to an approved regimen in the US that was utilized in the 1950-60 time period. Indications in this time period may have been approved on the basis of less stringent efficacy evaluations, so this reviewer does not believe that a

comparison between LNG IUS and a fairly potent progestin used for 21 days should be required to show superiority.

Although the Applicant was not able to show statistical significance either in the difference in the reduction from baseline or in treatment success, this reviewer still believes there is supportive clinical efficacy shown in this study. The statistical benefit shown in comparison of the medians is noteworthy even though this was not a prespecified endpoint. A point estimate median MBL of 6.0 mL at Cycle 3 for LNG IUS is supportive of success on its own. A reduction in blood loss is evident even in the first cycle of use.

In addition, the subject listings from the study are included below in Table 31***. As shown in the listing for LNG IUS, there is only one subject who had more bleeding at Cycle 3 than at baseline. One other subject reduced her bleeding in half but was still greater than 80 mL at Cycle 3. The NET group had one subject who persisted with MBL > 80 mL at Cycle C. The NET group had more failures listed because of early terminations.***

Table 31: Study 92549 – Individual MBL Listings (For Subjects with Recorded MBLs at Baseline and Cycle 3)

Subject Number	Treatment Group	MBL at Baseline	MBL at Cycle 3
103	LNG IUS	780	47
104	LNG IUS	161	20
107	LNG IUS	104	0
108	LNG IUS	117	4
112	LNG IUS	82	0
114	LNG IUS	94	24
115	LNG IUS	93	7
117	LNG IUS	89	12
119	LNG IUS	468	284
123	LNG IUS	98	6
124	LNG IUS	83	0
126	LNG IUS	99	4
127	LNG IUS	149	13
131	LNG IUS	98	14
132	LNG IUS	122	2
134	LNG IUS	192	59
135	LNG IUS	107	0
137	LNG IUS	91	199
139	LNG IUS	114	6
142	LNG IUS	102	0
144	LNG IUS	243	0
102	NET	140	19
105	NET	82	5
106	NET	82	4
113	NET	120	41
118	NET	134	9
121	NET	138	72
122	NET	83	21
125	NET	245	33
128	NET	92	21
130	NET	125	15
133	NET	132	16
138	NET	336	137
140	NET	162	20
141	NET	94	38

LNG IUS = levonorgestrel-releasing intrauterine system;
NET = norethisterone; MBL = menstrual blood loss
Highlight = subjects who failed to drop below 80 ml
Source: Study Report B088; Table E.2.1.20; page 350 of 767

The findings regarding hemoglobin and ferritin were not dramatically different between the two treatment groups. In the ITT population, mean hemoglobin increased 0.5 g/dL and 0.2 g/dL in the LNG IUS and NET treatment groups respectively from baseline to Cycle 3.

5.3.2.2 Supportive Study 92549 – Safety

In the 3-cycle comparative phase of Study 92549 (Report B088) there was only one reported SAE (elective tonsillectomy – subject 131 – LNG IUS) and no deaths.

In the extension phase of Study 92549 (Report A02916) there was only one additional SAE (lymphoma – subject 114 – LNG IUS) and no deaths. The discontinuations are listed below in Table 32.

Table 32: Study 92549: Discontinuations by Treatment Group and Reason

Subject Number	Treatment Group	Discontinuation
	Discontinuations in first 3 cycles	
108	LNG IUS	Spotting
111	LNG IUS	Frequent irregular bleeding
126	LNG IUS	Subject moved from area
127	LNG IUS	Subject did not follow up
135	LNG IUS	Frequent irregular bleeding
137	LNG IUS	IUD expulsion
139	LNG IUS	Frequent irregular bleeding and abdominal pain
144	LNG IUS	IUD expulsion
143	NET	Acne
101	NET	Bleeding problem
110	NET	Other personal
116	NET	Headache
120	NET	Heavy menstrual flow
136	NET	Heavy menstrual flow
	Discontinuations in extension phase	
131	LNG IUS	Leukorrhea
132	LNG IUS	Headache
114	LNG IUS	Non Hodgkins Lymphoma
115	LNG IUS	Back pain
119	LNG IUS	IUD expulsion
123	LNG IUS	Spotting

LNG IUS = levonorgestrel-releasing intrauterine system; NET = norethisterone
Source: Study Report A02916; Appendix 16.2.1; page 6 of 6 and IN.TERMIA dataset via JMP

5.3.3 Supportive Study 94548 (Report A00630)

5.3.3.1 Supportive Study 94548 – Efficacy

This was an open-label, randomized study comparing the efficacy of LNG IUS and oral tranexamic acid for the treatment of idiopathic menorrhagia (MBL ≥ 80 mL) in healthy

women 18 to 47 years of age. The study duration was 12 cycles. The study was conducted in 1 center in Sweden.

The primary efficacy variable was the comparison of the reduction in the MBL measured by the alkaline hematin method during 12 cycles.

In total, 28 subjects started treatment with LNG IUS and 30 subjects with tranexamic acid.

Both treatments effectively reduced MBL from baseline to Cycle 12 (Table 33). It was found that at baseline, the MBL criterion of ≥80 mL was not met by 1 subject in the LNG IUS group (MBL 77.40 mL) and by 6 subjects (MBL from 67.67 mL to 79.66 mL) in the tranexamic acid group. An analysis was performed excluding these subjects and is also shown in Table 33.

The reduction in the MBL from baseline was statistically significantly larger in the LNG IUS group at both time points (FAS: P=0.0007, baseline to Cycle 6 and P=0.0031 baseline to Cycle 12; secondary analysis population: P=0.0062, baseline to Cycle 6 and P=0.021, baseline to Cycle 12). At both the Cycle 6 and 12 time points, the median MBL values were significantly smaller in the LNG IUS group compared to the tranexamic acid population (P<0.0001 at both time points, FAS and secondary analysis population).

Table 33: Study 94548 – Summary of Median MBL by Time Point and Treatment (FAS and Secondary Analysis Excluding Subjects with Baseline MBL < 80 mL)

Time Point	Median MBL (mL) FAS (minimum to maximum)		Median MBL (mL) Secondary Analysis Population (a) (minimum to maximum)		P-value difference between treatments
	LNG IUS	Tranexamic acid	LNG IUS	Tranexamic acid	
Baseline	168.5 (77.4-348.0) N = 28	140.0 (67.7-568.9) N = 30	168.8 (80.2-348.0) N =27	163.8 (84.5-569.0) N =24	
Cycle 6	10.7 (0-150.7) N = 24	53.3 (20.7-528.3) N = 28	10.3 (0-150.7) N = 23	66.7 (30.7-528.3) N = 22	P <0.0001 for both FAS and secondary analysis
Change from baseline	P = 0.0007		P = 0.0062		
Cycle 12	4.5 (0-350.9) N = 23	71.8 (23.2-250.8) N = 27	4.07 (0-350.9) N = 22	86.8 (44.1-250.8) N = 21	P <0.0001 for both FAS and secondary analysis
Change from baseline	P = 0.0031		P = 0.021		

LNG IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss
(a) Subjects with MBL < 80 mL at baseline excluded
Source: Summary of Clinical Efficacy; Text Table 5; page 16 of 108

Medical Officer's Comment: Tranexamic acid has been approved in Europe for many years for the indication of heavy menstrual bleeding and has been recently submitted in the U.S. for marketing approval for a similar indication.

5.3.3.2 Supportive Study 94548 – Safety

No deaths occurred during the study period. One serious adverse event (severe burns after a visit to a solarium) occurred in subject 157 in the tranexamic treatment group. The three most common AEs by subject count in the LNG IUS group were headache, dysmenorrhea and IUD complication (partial and total expulsions of the LNG IUS). In the tranexamic acid treatment group the three most common AEs by subject count were headache, dysmenorrhea and upper respiratory tract infection. The listing of discontinuations for the study is shown in Table 34.

Table 34: Study 94548: Discontinuations by Treatment Group and Reason

Subject Number	Treatment Group	Reason
102	LNG IUS	Failed insertion
106	LNG IUS	Expulsion
107	LNG IUS	Breast enlargement, weight increase, decreased libido
114	LNG IUS	Expulsion
127	LNG IUS	Expulsion
132	LNG IUS	Expulsion
133	LNG IUS	Other personal
144	LNG IUS	Expulsion
158	LNG IUS	Depression
104	TXA	Pregnancy
155	TXA	Non-compliance

LNG IUS = levonorgestrel-releasing intrauterine system; TXA = tranexamic acid
Source: Study Report A00630; Appendix 16.2.1; page 4 of 4 and IN.TERMIA dataset via JMP

Both treatments reduced the number of bleeding days during the study, but in the LNG IUS group the number of days of bleeding was higher during the first 60 days in the study than in the tranexamic acid group. An increase in the number of days of spotting was detected in the LNG IUS group during the first 180 days of the study, but in the latter part of the study there was a trend towards a reduction in the number of the spotting days. In the oral group the number of spotting days decreased during the first 180 days of the study.

5.3.4 Supportive Study 93547 (Report A14096)

5.3.4.1 Supportive Study 93547 – Efficacy

This was an open-label, randomized comparative study on the efficacy of LNG IUS and oral mefenamic acid for the treatment of idiopathic menorrhagia in healthy women aged 18 – 47 years. The study duration was 6 cycles. The study was conducted in one center in the United Kingdom.

The primary efficacy variable was the comparison of the reduction of MBL between treatments measured objectively by the alkaline hematin method.

The MBL was compared between treatment groups at baseline, Cycle 3 and Cycle 6. A subset of subjects in the LNG IUS group underwent an extension phase of 5 years.

Secondary efficacy variables were total menstrual fluid loss measured by the weighing method, MBL measured by PBAC, hemoglobin, ferritin, vaginal bleeding based on the

bleeding diaries, subject's assessment of the treatment, insertion and removal of LNG IUS, termination of study and continuation rates.

Medical Officer's Comment:
The weighing method involves weighing the sanitary products. PBAC is a method whereby the subjects visually assess and record the amount of blood saturation of their sanitary products in addition to clots. This reviewer considers the alkaline hematin method to be the most reliable of the three.

In addition, FSH was evaluated to monitor possible start of perimenopause and estrogen deficiency. Since the study duration was up to 5 years, there was a possibility that a woman could become perimenopausal during the study, if she was at her late fertile-age (inclusion criteria was up to 47 years) when the study treatment started. Subjects with FSH values indicating menopause were excluded from the per-protocol set (PPS).

For the comparative part of the study, 25 subjects in the LNG IUS group and 26 in the mefenamic acid group were analyzed. Nineteen subjects from the LNG IUS group entered the 5-year extension phase.

The decrease in the MBL measured by alkaline hematin method was statistically significantly greater in the LNG IUS group at 3 and 6 months (P<0.001 at both time points). The results are shown in Table 35.

Table 35: Study 93547 – Median MBL (Alkaline Hematin) by Time Point and Treatment (Full Analysis Set)

	Median MBL (mL) (min to max) % Reduction in the median from baseline N = number of subjects		P-value (a) (change in MBL between treatments)
Time point	**LNG IUS**	**Mefenamic acid**	
Baseline	122.0 (81.0-375.0)	121.0 (85.0-389.0)	
	N = 25	N = 25	
Cycle 3	12.0 (0-240)	94.0 (29.0-219.0)	
	90.9%	31.1%	P < 0.001
	N = 22	N = 23	
Cycle 6	5.0 (0-45.0)	99.5 (46.0-168.0)	
	94.6%	23.0%	P < 0.001
	N = 19	N = 20	

LNG IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss
(a) = Wilcoxon rank sum test
Source: Summary of Clinical Efficacy; Text table 6; page 18 of 108

In the LNG IUS group, the PBAC score decreased significantly more from baseline to Cycle 3 (P=0.004) and from baseline to Cycle 6 (P<0.001) than in the mefenamic acid group (see Table 36). In the mefenamic acid group, the median values for the PBAC score were > 100 at Cycles 3 and 6.

Table 36: Study 93547 – Median MBL (By PBAC) by Time Point and Treatment (Full Analysis Set)

	Median PBAC score (min to max) % Reduction in the median from baseline N = number of subjects		P-value (a) (change in PBAC score between treatments)
Time point	**LNG IUS**	**Mefenamic acid**	
Baseline	240 (91-545) N = 25	233 (77-469) N = 25	
Cycle 3	49 (0-286) 77% N = 22	161 (77-262) 37% N = 22	P < 0.004
Cycle 6	25 (0-402) 90% N = 20	159 (50-307) 37% N = 19	P < 0.001
Year 1	13 (1-400) 94% N = 11	N/A	
Year 2	14 (0-377) 94% N = 13	N/A	
Year 3	8 (0-898) 96% N = 11	N/A	
Year 4	7 (0-51) 97% N = 9	N/A	
Year 5	5 (0-91) 98% N = 10	N/A	

LNG IUS = levonorgestrel-releasing intrauterine system;
MBL = menstrual blood loss; CI = confidence interval
(a) = Wilcoxon rank sum test
Source: Summary of Clinical Efficacy; Text table 6; page 18 of 108

5.3.4.2 Supportive Study 93547 – Safety

No deaths occurred during the study period. One serious adverse event with intermittent dizziness, nausea, lower abdominal pain, left-sided symptoms in the arm and fingers and hypertension occurred in the LNG IUS group in one subject before cycle 3. One subject in the LNG IUS group had chlamydial endometritis. The most frequently

reported AEs were headache, abdominal pain, ovarian cyst, breast pain, emotional lability and upper respiratory tract infection in the LNG IUS group. The listing of discontinuations in the LNG IUS group through 5 years is provided in Table 37.

Table 37: Study 93547: Discontinuations by Treatment, Duration in Study and Reason

Subject Number	Treatment	Time of Discontinuation	Reason
103	LNG IUS	Through Cycle 6	IUD expulsion
105	LNG IUS	Through Cycle 6	IUD expulsion
119	LNG IUS	Through Cycle 6	IUD expulsion
127	LNG IUS	Through Cycle 6	IUD expulsion
120	MFA	Through Cycle 6	Non-compliance
132	MFA	Through Cycle 6	Other – ineffective
143	MFA	Through Cycle 6	Non-compliance
129	LNG IUS		Did not enter extension study
148	LNG IUS		Did not enter extension study
136	LNG IUS	Through Year 1	Bleeding
141	LNG IUS	Through Year 1	IUD expulsion
117	LNG IUS	Through Year 3	Planning pregnancy
125	LNG IUS	Through Year 3	Persistent spotting
151	LNG IUS	Through Year 3	Decreased libido
121	LNG IUS	Through Year 4	IUD expulsion
135	LNG IUS	Through Year 4	Irregular bleeding, mood changes, fatigue
146	LNG IUS	Through Year 4	Bleeding, dysmenorrhea
108	LNG IUS	Through Year 5	Persistent spotting

LNG IUS = levonorgestrel-releasing intrauterine system; MFA = mefenamic acid
Source: Study Report A14096; Appendix 16.2.1 page 4 of 5 and IN.TERMIA dataset via JMP

5.3.5 Supportive Study 302760 (Report A36340)

5.3.5.1 Supportive Study 302760 – Efficacy

This was an open-label, randomized, multicenter, 12-month parallel trial comparing the efficacy of LNG IUS and a combined oral contraceptive (COC), Minestrin ® (NET/EE = norethindrone 1mg / ethinyl estradiol 0.02 mg; 21 active tablets, 7 placebo tablets) in reducing MBL in healthy women over 30 years of age with idiopathic menorrhagia (baseline PBAC score ≥ 100). The study was conducted in 9 centers in Canada.

The primary efficacy variable was the comparison of absolute change in the PBAC score from baseline to 12 months between the treatments.

Secondary efficacy variables included hemoglobin and ferritin levels, clinical outcome of the subjects, quality of life, and patient satisfaction.

For the clinical outcome, a PBAC score ≥ 100 or treatment discontinuation were defined as treatment failures.

The full analysis set (FAS) consisted of 39 subjects (LNG IUS group: 20; NET/EE group: 19). In the FAS population, PBAC score decreased from baseline statistically significantly more in the LNG IUS group than in the NET/EE group (P=0.0024) (estimate for median difference -62, 95% CI: -89 to -18). The mean percent change in MBL score at 12 months was -83% in the LNG IUD arm and -68% in the NET/EE arm. The PBAC scores by time point are presented in Table 38.

Table 38: Study 302760: PBAC Scores by Time Point and Treatment (Full Analysis Set)

	LNG IUS					NET/EE				
	N	**Mean**	**SD**	**Median**	**Q1/Q3**	**N**	**Mean**	**SD**	**Median**	**Q1/Q3**
Baseline	20	307	215	228	158/399	19	263	89	290	168/326
3 months	17	61	70	51	9/85	18	70	50	64	31/98
6 month	17	29	44	12	9/33	15	104	81	68	50/128
9 months	16	39	101	13	4/27	13	62	50	47	15/120
12 months	17	62	166	13	3/50	12	82	47	72	50/120

LNG IUS = levonorgestrel-releasing intrauterine system; NET/EE = norethindrone / ethinyl estradiol;
PBAC = pictorial blood loss assessment chart; Q1/Q3 = first and third quartile; SD = standard deviation
Source: Summary of Clinical Efficacy; Text table 8; page 21 of 108

The Applicant found a decrease in median PBAC score from baseline to 12 months, P=0.0024 (LNG IUS vs. NET/EE).

A significantly higher proportion of subjects in the LNG IUS group (80.0%) had treatment success (MBL score <100) than in the NET/EE group (36.8%) (P=0.0095).

5.3.5.2 Supportive Study 302760 – Safety

There were no deaths reported in the study. One SAE was reported during the study. The SAE consisted of inguinal hernia in a LNG IUS patient who recovered following surgery and was judged as having no relationship to study drug. The discontinuations are shown in the following table (Table 39).

Table 39: Study 302760: Discontinuations by Treatment and Reason

Subject Number	Treatment	Reason
012	LNG IUS	Withdrawal of consent – never inserted
013	LNG IUS	Intermittent bleeding
036	LNG IUS	Lost to follow-up
039	LNG IUS	Withdrawal of consent
042	LNG IUS	Withdrawal of consent
003	NET/EE	Vaginal spotting
005	NET/EE	Migraines
014	NET/EE	Weight gain, increased menses duration
025	NET/EE	Longer periods
027	NET/EE	Lost to follow-up
035	NET/EE	Heavier and painful menses
037	NET/EE	Withdrawal of consent – never administered
044	NET/EE	Withdrawal of consent

LNG IUS = levonorgestrel-releasing intrauterine system; NET = norethisterone; EE = ethinyl estradiol
Source: Study Report A36340; Appendix 16.2.1 page 2 of 7 and IN.TERMIA dataset via JMP

The most frequently occurring AEs were intermenstrual bleeding (LNG IUS = 60.0%, NET/EE = 31.6%), menstrual disorder (LNG IUS = 35.0%, NET/EE = 15.8%), headache (LNG IUS = 15.0%, NET/EE = 36.3%) and influenza-like symptoms (LNG IUS = 20.0%, NET/EE = 15.8%).

5.3.6 Supportive Study 303003 (Report A00696)

5.3.6.1 Supportive Study 303003 – Efficacy

This was an open-label, randomized, multicenter study comparing the efficacy and safety of LNG IUS and danazol in the treatment of women over 30 years of age with idiopathic menorrhagia (with an MBL PBAC score ≥100 for 2 consecutive cycles). In the LNG IUS group the treatment was administered for 6 months. In the danazol groups, subjects were treated for 3 months and followed for a 3-month treatment-free period. Subjects were treated with danazol only for 3 months, reflecting the labeling and safety concerns about longer treatment durations with this agent; however, the effect of this drug is expected to be present for at least 4 months after the last dose. The study was conducted in 13 centers in Canada.

The primary efficacy variable was the comparison of the change in PBAC score from baseline to 3 months. PBAC scores are shown in Table 40.

The secondary variables were the change in PBAC score from baseline to 6 months, the change in hemoglobin and ferritin levels from baseline to 3 months and 6 months,

and the subject outcome from baseline to 6 months. The outcome was defined as success if the PBAC score was <100 at 6 months and as failure if the score was ≥100 at 6 months or if the treatment was discontinued. Secondary efficacy variables were menorrhagia severity score (based on the quality of life questionnaire) reported at baseline, 3 months and 6 months, the degree of patient satisfaction rated at 3 months and 6 months, discontinuation rate, and parameters describing insertion procedure.

In the FAS population, 151 subjects were analyzed (75 in the LNG IUS group and 76 in the danazol group). In the FAS, the decrease in PBAC score from baseline to 3 months was statistically better (P=0.023) in the danazol group (estimate for mean difference was 55 score points on PBAC with a 95% confidence interval [CI] of 8 to 103). Both treatments effectively decreased the PBAC from baseline to 3 months, and the decrease within a treatment was statistically significant in both groups (P<0.0001 for both).

Table 40: Study 303003: PBAC Scores by Time Point and Treatment (Full Analysis Set)

	LNG IUS					Danazol				
	N	Mean	SD	Median	Q1/Q3	N	Mean	SD	Median	Q1/Q3
Baseline	75	329	220	288	180/385	76	344	202	275	187/453
3 months	74	106	182	61	19/110	71	54	127	6	0/42
6 month	68	53	109	17	5/47	62	278	312	186	118/352

LNG IUS = levonorgestrel-releasing intrauterine system; PBAC = pictorial blood loss assessment chart; Q1/Q3 = first and third quartile; SD = standard deviation
Source: Summary of Clinical Efficacy; Text table 10; page 23 of 108

5.3.6.2 Supportive Study 303003 – Safety

No deaths occurred during the study. A total of 3 subjects had serious adverse events (SAEs) during the study. One subject in the LNG IUS group had pain due to an ovarian cyst. She had a salpingo-oophorectomy due to the cyst. In one subject in the danazol group, a mass in her left breast was found at a study visit and later the mass was revealed to be a breast cancer. Another subject in the danazol group suffered from pleural pain and shortness of breath and later from hemoptysis.

A total of 462 adverse events (AEs) (LNG IUS: 257, danazol: 205) were reported by 144 (95.4%) subjects; 73 (97.3%) subjects in the LNG IUS group and 71 (93.4%) in the danazol group. Preferred terms 'intermenstrual bleeding,' 'menstrual disorder' and 'abdominal pain' were more frequently reported in the LNG IUS group while 'amenorrhea' was more common in the danazol group.

Table 41: Study 303003: Discontinuations

Subject Number	Treatment	Reason
6	LNG IUS	IUD expulsion
10	LNG IUS	Intermenstrual bleeding
69	LNG IUS	Prolonged menstrual flow, back pain
101	LNG IUS	Withdrawal of consent
117	LNG IUS	IUD could not be inserted
119	LNG IUS	Non-compliance
140	LNG IUS	Left iliac fossa pain
148	LNG IUS	Pelvic pain, fever
151	LNG IUS	Pain, menstrual disorder
1	Danazol	Spotting and menses prolongation
5	Danazol	Night sweats
9	Danazol	Emotional lability
11	Danazol	Depression
22	Danazol	Migraines
24	Danazol	Acne
77	Danazol	Other personal
82	Danazol	Lost to follow-up
83	Danazol	Withdrawal of consent – never administered
89	Danazol	Headaches, water retention
102	Danazol	Fearful of painful menses
107	Danazol	Hot flashes
127	Danazol	Acne, edema, headaches
134	Danazol	Bloating

LNG IUS = levonorgestrel-releasing intrauterine system
Source: Study Report A00696; Appendix 16.2.1 pages 1-10 and IN.TERMIA dataset via JMP

5.3.7 Supportive Study 93503 (Report BC71)

5.3.7.1 Supportive Study 93503 – Efficacy

This was an open-label, randomized study comparing the efficacy of LNG IUS and transcervical resection of the endometrium (TCRE) in the treatment of idiopathic menorrhagia in women 30 to 49 years of age, with confirmed idiopathic menorrhagia (PBAC score >75). The study was conducted in 1 center in Norway. The planned study period was 12 months, which was extended up to a total of 36 months.

The primary efficacy variable was the comparison of the change in MBL as assessed with PBAC. Additional efficacy variables were the assessment of the insertion procedure of LNG IUS and assessment of transcervical resection surgery of the endometrium.

Secondary efficacy variables were the evaluation of treatment success, vaginal bleeding, hemoglobin, ferritin, menopausal symptoms assessed by a visual analogue scale (VAS), the overall tolerability and effectiveness of the given treatment as assessed by both the investigator and the subject, and the continuation rates.

Fifty-nine subjects received treatment: LNG IUS was inserted in 30 women and TCRE surgery was performed on 29 women. Originally, the study was planned for a period of 12 months but was extended for another 24 months (up to a total of 36 months). Twenty-two out of 30 subjects in the LNG IUS group and 27 out of 29 subjects in the TCRE group continued into the extension phase.

The PBAC scores are shown in Table 42. At baseline, the median PBAC score was somewhat higher in the TCRE group than in the LNG IUS group but not statistically significantly different between the groups. The median values at other time points were comparable and well below 100. This showed that treatment with LNG IUS was as effective as the surgical treatment in reducing MBL. The decrease in the MBL from baseline to month 36 was statistically significant in both treatment groups (P< 0.001 for both treatments). At month 12, PBAC score reduction was 95% and 97% for the MIRENA and TCRE, respectively. At month 24, PBAC reduction was 97% for both groups, while at month 36, it was 97% in the LNG IUS group and 99% in the TCRE group. However, 6 out of 29 subjects had a second TCRE surgery and 1 subject had a third surgery during the 3-year duration of the study. Repeated TCRE was considered a treatment failure.

Table 42: Study 93503: PBAC Scores by Time Point and Treatment (Full Analysis Set)

	LNG IUS					TCRE				
	N	**Mean**	**SD**	**Median**	**Q1/Q3**	**N**	**Mean**	**SD**	**Median**	**Q1/Q3**
Baseline	30	389	314	262	191/609	29	424	456	311	205/508
12 months	23	23	29	12	2/35	28	13	30	9	0/10
24 months	18	18	32	9	0/19	25	20	41	10	0/10
36 months	17	13	24	7	0/10	24	13	37	4	0/10

LNG IUS = levonorgestrel-releasing intrauterine system; TCRE = Transcervical resection of the endometrium
PBAC = pictorial blood loss assessment chart; Q1/Q3 = first and third quartile; SD = standard deviation
Source: Study Report BC71; Section 14; page 49 of 270

5.3.7.2 Supportive Study 93503 – Safety

No deaths occurred in the study. Ten SAEs were reported, 2 in the LNG IUS group for one subject (diarrhea and gastric ulcer) and 8 in the TCRE group for 5 subjects (cerebral insult, abdominal pain twice for one subject, bleeding from the lateral vessels of uterus twice for one subject, pain and hematometra for one subject, and fracture of left proximal humerus). The discontinuations are shown in Table 43.

Table 43: Study 93503: Discontinuations by Treatment and Reason

Subject Number	Treatment	Reason
6	LNG IUS	Irregular bleeding
10	LNG IUS	Prolonged menstrual flow
16	LNG IUS	Endometritis
19	LNG IUS	Abdominal pain
36	LNG IUS	Low back pain
37	LNG IUS	Prolonged menstrual flow
38	LNG IUS	Acne
45	LNG IUS	Irregular bleeding
54	LNG IUS	Did not continue into extension
55	LNG IUS	Abdominal pain
56	LNG IUS	Did not continue into extension
4	TCRE	Did not continue into extension
14	TCRE	Did not continue into extension
20	TCRE	Bleeding
34	TCRE	Pain

LNG IUS = levonorgestrel-releasing intrauterine system;
TCRE = transcervical resection of endometrium
Source: Study Report BC71; Appendix 16.2.1; page 4 of 4 and IN.TERMIA dataset

5.3.8 Supportive Study 90528 (Report B086)

5.3.8.1 Supportive Study 90528 – Efficacy

This was an open-label, controlled, randomized clinical study for the treatment of excessive uterine bleeding and dysmenorrhea. A group of subjects treated with LNG IUS was compared with a group of subjects continuing with their ongoing treatment (including, e.g., tranexamic acid, norethisterone, megestrol and NSAID). Duration of the comparative part of the study was 6 months, and the LNG IUS group was followed up for total of 12 months. The study was conducted in 3 centers in Finland.

A total of 54 subjects awaiting hysterectomy due to excessive uterine bleeding or dysmenorrhea were included in the study; 27 in the LNG IUS group and 27 in the control group. All subjects were guaranteed that their position on the hysterectomy waiting list would be maintained despite participation in the study.

The objective was to assess whether LNG IUS could provide a conservative alternative to hysterectomy. The primary efficacy variables were the proportion of subjects canceling their planned hysterectomy and investigators' overall assessment of tolerability of the therapeutic approach.

In the first 6 months of the study, 18 subjects (67%) in the LNG IUS group avoided hysterectomy compared to 4 subjects (15%) in the control group. In the LNG IUS group, 18 subjects were followed up for 12 months, at which time 15 of these subjects wanted to continue with LNG IUS treatment, 1 changed to oral treatment, and 2 made a decision to undergo hysterectomy.

5.3.8.2 Supportive Study 90528 – Safety

No deaths or SAEs were reported in this study. There was just one discontinuation for an adverse event in the LNG IUS group safety dataset. The adverse events listed for this subject (subject 116) were depression, acne and lower back pain.

5.3.9 Supportive Study 92501 (Report AY01)

5.3.9.1 Supportive Study 92501 – Efficacy

The study was an open, non-comparative study with LNG IUS conducted in 3 centers in Italy. The primary efficacy variable was the reduction in MBL measured by alkaline hematin method after LNG IUS use. The total duration of the study treatment was 12 cycles. The planned number of subjects was 80; however, after 2 years; only 17 subjects had been recruited despite the amendments to the protocol to relax the recruitment criteria. The study was subsequently discontinued.

The primary efficacy variable, MBL measured using the alkaline hematin method, was presented by time point in the abbreviated study report, but no other efficacy evaluations were conducted. The median MBL results for the subjects who did enroll are found in Table 44.

Table 44: Study 92501: Median MBL by Time Point (FAS)

Time Point	N	Median MBL (mL) for LNG IUS
Baseline	17	119
Cycle 3	7	35
Cycle 6	8	18
Cycle 12	6	9

LNG IUS = levonorgestrel-releasing intrauterine system;
N = number of subjects
Source: Summary of clinical efficacy; Text table 12; page 28 of 108

5.3.9.2 Supportive Study 92501 – Safety

No deaths or SAEs were reported. Expulsions of the LNG IUS occurred in 3 subjects (Subject # 1, 306 and 310), all of whom discontinued their participation. Subject number

2 discontinued because of urinary incontinence. Only a small number of adverse events were reported overall: spotting (4), fever (1), and dyspepsia (1).

5.3.10 Supportive Study 91539 (Report AW82)

5.3.10.1 Supportive Study 91539 – Efficacy

The aim of this study was to compare the efficacy of the levonorgestrel intrauterine system (LNG IUS) with total endometrial ablation (TEA) in the treatment of confirmed menorrhagia.

The study was discontinued due to difficult and slow subject recruitment. The main reason for slow recruitment was considered to be the laborious MBL measurements requiring the collection of used sanitary material by the study subjects. Despite the protocol amendments aimed at making the inclusion of subjects easier (e.g., by decreasing the number of MBL measurements during the study), the recruitment was not successful. The final number of subjects was 10 in the LNG IUS group and 11 in the TEA group. They were followed up for 12 cycles before the study was discontinued. For these reasons, the present abbreviated report only describes the safety without any specific statistical analyses.

5.3.10.2 Supportive Study 91539 – Safety

No deaths occurred during the study period. One serious adverse event, a suspected fluid embolus, occurred in the total endometrial ablation group. The most common AE in the LNG IUS group was abdominal pain reported three times by two subjects.

Two subjects in the LNG IUS group discontinued the study due to an AE. Subject no. 24 discontinued the study due to pelvic cramps. Subject no. 30 discontinued due to IUD expulsion.

6 Review of Efficacy

Efficacy Summary

6.1 Indication (Treatment of Heavy Menstrual Bleeding)

6.1.1 Methods

Discussion of the methods will be organized into two categories: a) those studies utilizing the alkaline hematin determination of blood loss and b) studies utilizing PBAC

methods of determining blood loss. Each group will be analyzed in tables comparing entry criteria, study design and lab methodology. Study 93547 will be included in both sets since both alkaline hematin and PBAC were utilized.

The comparison of entry criteria in LNG IUS studies utilizing the alkaline hematin are shown in Table 45.

Table 45: Comparison of Entry Criteria in LNG IUS Studies Utilizing Alkaline Hematin Methodology

Criteria	Study 309849 Report A38313	Study 92549 Report B088	Study 94548 Report A00630	Study 93547 Report A14096	Study 92501 Report AY01
Comparator	MPA	NET	Tranexamic acid	Mefenamic acid	None
Age inclusion range (years)	≥ 18	18-45	18-47	18-47	18-45
HMB confirmation during screening	≥ 80 mL in 2 of 3 cycles	≥ 80 mL in 1 cycle in 3 months	≥ 80 mL average of 2 cycles in 3 months	≥ 80 mL in 1 cycle in 4 months	≥ 60 mL in 1 cycle in 3 months
Uterine sound depth	6-9 cm	≤ 10 cm	bimanual and or sonogram	≤ 10 cm	≤ 9 cm or < than "8" week size
Exclusion for fibroids unless	≤ 3 subserous or intramural fibroids with volume < $5cm^3$	Fibroids not mentioned in entry criteria	Insignificant small subserous and intramural fibroids acceptable	≤ 3 subserous or intramural fibroids with volume < $5cm^3$	Only mentions excluding sono-confirmed submucous fibroids
Parity	Parous	Parous	Not mentioned	Not mentioned	Not mentioned
BMI	≤ 35 kg/m^2	Not mentioned	Not mentioned	Not mentioned	Not mentioned

HMB = heavy menstrual bleeding; MPA = medroxyprogesterone acetate; NET = norethisterone; BMI = body mass index
Sources: Study Reports A38313 (pages 21-22); B088 (pages 13-14); A00630 (pages 16-17) ; A14096 (pages 19-20) ; AY01 (pages 13-14)

Medical Officer's Comments (regarding Table 45***):***

- ***The comparator is mentioned to serve as a better reminder than just the study number.***
- ***Although the pivotal Study 309849 did not list an upper age for inclusion, an FSH value ≤30 mIU/mL was required, thus eliminating postmenopausal women.***
- ***All of the studies required that subjects have regular menstrual cycles. The pivotal Study 309849, Study 94548 and Study 93547 also specified that the cycle should be 21-35 days in length.***
- ***All 5 studies excluded subjects with distortions of the uterine and cervical canal.***

- ***Study 94548 utilized a bimanual exam and/or sonography to verify a normal or slightly enlarged uterus.***

The comparison of lab methodologies in the LNG IUS studies utilizing the alkaline hematin methodology is shown in Table 46.

Table 46: Comparison of Lab Methodology Assessing Bleeding in LNG IUS Studies Utilizing Alkaline Hematin

Criteria	Study 309849 Report A38313	Study 92549 Report B088	Study 94548 Report A00630	Study 93547 Report A14096	Study 92501 Report AY01
Comparator	MPA	NET	Tranexamic acid	Mefenamic acid	None
Pads and tampons	Provided Kotex Pads – Overnights & Maxi Tampax Tampons – Super Plus, Super and Regular	Did not mention if provided	Did not mention if provided	Provided Kotex Maxi Super Tampax Super Plus	Did not mention if provided
Alkaline hematin method reference	Hallberg and Nilsson 1964	Hallberg and Nilsson 1964	Hallberg and Nilsson 1964 Modified by Newton 1977	Hallberg and Nilsson 1964 Modified by Newton 1977	Hallberg and Nilsson 1964 Modified by Newton 1977
Other pertinent laboratory testing that could impact efficacy	Hemoglobin Hematocrit Ferritin	Hemoglobin Ferritin	Hemoglobin Ferritin	Total menstrual fluid loss Hemoglobin Ferritin	Hematocrit

HMB = heavy menstrual bleeding; MPA = medroxyprogesterone acetate; NET = norethisterone; BMI = body mass index;
Sources: Reports A38313 (protocol page 33 and central lab procedure manual page 24); B088 (page 17); A00630 (page 25); A14096 (page 30) ; AY01 (page 16)

Medical Officer's Comments:

The types of tampons and sanitary pads have not been issues when performing alkaline hematin analysis. The Newton modification is the utilization of a machine to agitate the sanitary protection products in solution rather than by hand.

The comparison of entry criteria in LNG IUS studies utilizing the PBAC methodology are shown in Table 47.

Table 47: Comparison of Entry Criteria in LNG IUS Studies Utilizing PBAC

Criteria	Study 93547 Report A14096	Study 302760 Report A36340	Study 303003 Report A00696	Study 93503 Report BC71
Comparator	Mefenamic acid	NET / EE	Danazol	TCRE
Age inclusion range (years)	18-47	≥ 30 years	≥ 30 years	30-49
HMB confirmation during screening	≥ 80 mL in 1 cycle in 4 months by alkaline hematin	PBAC ≥ 100 for 2 consecutive cycles	PBAC ≥ 100 for 2 consecutive cycles	PBAC > 75 from 2nd PBAC of screening period
Uterine size or sound depth	≤ 10 cm	"8" week size or less	"8" week size or less	< 10 cm
Exclusion for fibroids unless	≤ 3 subserous or intramural fibroids with volume < $5cm^3$	< 4cm subserous or intramural	< 4cm subserous or intramural	≤ 4cm subserous (intramural not mentioned)
Parity	Not mentioned	Not mentioned	Not mentioned	Not mentioned
BMI	Not mentioned	Excluded > 30 kg/ m^2	Not mentioned	Not mentioned

PBAC = pictorial blood loss assessment chart; HMB = heavy menstrual bleeding; MPA = medroxyprogesterone acetate; NET = norethisterone / ethinyl estradiol; BMI = body mass index; TCRE = transcervical resection of endometrium
Sources: Reports A14096 (pages 19-20); A36340 (pages 19-21) ; A00696 (pages 23-24) ; BC71 (pages 17-18)

The comparison of methodology in LNG IUS studies utilizing the PBAC methodology is shown in Table 48.

Table 48: Comparison of Methodology Assessing Bleeding in LNG IUS Studies Utilizing PBAC

Criteria	93547 Report A14096	302760 Report A36340	303003 Report A00696	93503 Report BC71
Comparator	Mefenamic acid	NET / EE	Danazol	TCRE
Pads and tampons provided	Kotex Maxi Super pad Tampax Super Plus tampon	Provided but brand name not specified in report	Provided but brand name not specified in report	Saba Normal pad O.B. Fleur tampon
PBAC reference	Higham (picture modified to include coin size pictures)	Higham (picture modified to include coin size pictures)	Higham (picture modified to include coin size pictures)	Higham (picture modified to include coin size pictures)
PBAC methodology	Visual chart provided 3 levels each for tampons and pads based on amount filled with blood Coin size correlation for clots Notation for flooding	Visual chart provided 3 levels each for tampons and pads based on amount filled with blood Coin size correlation for clots Notation for flooding	Visual chart provided 3 levels each for tampons and pads based on amount filled with blood Coin size correlation for clots Notation for flooding	Visual chart provided 3 levels each for tampons and pads based on amount filled with blood Coin size correlation for clots Notation for flooding
Other pertinent laboratory testing that could impact efficacy	Total menstrual fluid loss Hemoglobin Ferritin	Hemoglobin Ferritin	Hemoglobin Ferritin	Hemoglobin Ferritin

PBAC = pictorial blood loss assessment chart; HMB = heavy menstrual bleeding; MPA = medroxyprogesterone acetate; NET = norethisterone / ethinyl estradiol; BMI = body mass index; TCRE = transcervical resection of endometrium
Sources: Reports A14096 (pages 30, 31, Appendix 16.1.2, ref: Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990; 97:734-9); A36340 (protocol pages 13,14, 17, sample case report form page 70, ref: Higham as above) ; A00696 (report pages 30,31,35, sample case report form page 86, ref: Higham as above) ; BC71 (pages 24, 25, 26, sample case report from pages 42-44, ref: Higham as above)

Medical Officer's Comment:
This reviewer considers the PBAC methodology to be more variable than the alkaline hematin method due to differences in the sanitary products used and the possible differences in how study populations interpret the degree of saturation. In general though, in the LNG IUS development program, the studies utilizing PBAC showed concurrence in results with the studies employing alkaline hematin.

6.1.2 Demographics

The comparison of demographics in the LNG IUS studies utilizing the alkaline hematin methodology is shown in Table 49.

Table 49: Comparison of Demographic Results in LNG IUS Studies Utilizing Alkaline Hematin Methodology

Criteria	Study 309849 Report A38313	Study 92549 Report B088	Study 94548 Report A00630	Study 93547 Report A14096	Study 92501 Report AY01
Comparator	MPA	NET	Tranexamic acid	Mefenamic acid	None
Mean age (years)	LNG IUS = 38.3 MPA = 39.3	LNG IUS = 39.2 NET = 38.8	LNG IUS = 38.3 TXA = 38.5	LNG IUS = 39.4 MFA = 38.5	LNG IUS = 39.9
Mean body mass index (kg/m^2)	LNG IUS = 27.2 MPA = 27.4	LNG IUS = NA NET = NA	LNG IUS = 25.4 TXA = 25.0	LNG IUS = 28.0 MFA = 25.7	NA

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate; NET = norethisterone; TXA = tranexamic acid; MFA = mefenanic acid; NA = not available
Sources: Summary of clinical efficacy, pages 43-44 of 108

The comparison of demographics in the LNG IUS studies utilizing the PBAC methodology is shown in Table 50.

Table 50: Comparison of Demographic Results in LNG IUS Studies Utilizing PBAC

Criteria	Study 93547 Report A14096	Study 302760 Report A36340	Study 303003 Report A00696	Study 93503 Report BC71
Comparator	Mefenamic acid	NET / EE	Danazol	TCRE
Mean age (years)	LNG IUS = 39.4 MFA = 38.5	LNG IUS =41.8 NET/EE = 42.2	LNG IUS =42.2 DZ = 42.2	LNG IUS =41.4 TCRE = 42.1
Mean body mass index (kg/m^2)	LNG IUS = 28.0 MFA = 25.7	LNG IUS = 24.3 NET/EE = 22.6	LNG IUS = 28.7 DZ = 28.1	LNG IUS = 26.7 TCRE = 25.3

LNG IUS = levonorgestrel-releasing intrauterine system; NET = norethisterone; EE = ethinyl estradiol; DZ = danazol; TCRE = transcervical resection of the endometrium
Sources: Summary of clinical efficacy, pages 43-44 of 108

Medical Officer's Comment: The demographic results from the integrated analysis of the LNG IUS users (N=332) are the following:

- ***Median age = 41 years (range 20-53)***
- ***Median weight (kg) = 72.0 (range 44-125)***
- ***Median BMI = 25.9 (range 17.6-48.3)***

Source: ISS, text table 7, page 15 of 56

6.1.3 Subject Disposition

The comparison of subject disposition in the LNG IUS studies utilizing the alkaline hematin methodology is shown in Table 51.

Table 51: Comparison of Disposition Results (Number of Subjects) in LNG IUS Studies Utilizing Alkaline Hematin Methodology

Criteria	Study 309849 Report A38313	Study 92549 Report B088	Study 94548 Report A00630	Study 93547 Report A14096	Study 92501 Report AY01
Comparator	MPA	NET	Tranexamic acid	Mefenamic acid	None
Started Treatment	LNG IUS = 80 MPA = 82	LNG IUS = 22 NET = 22	LNG IUS = 28 TXA = 30	LNG IUS = 25 MFA = 26	LNG IUS = 15
Completed study medication	LNG IUS =73 MPA = 69	LNG IUS = 20 NET = 16	LNG IUS = 20 TXA = 28	LNG IUS = 21 MFA = 21	LNG IUS = 9
Discontinued for adverse event	LNG IUS = 4 MPA = 2	LNG IUS = 2 NET = 5	LNG IUS = 8 TXA = 1	LNG IUS = 4 MFA = 2	LNG IUS = 3

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate; NET = norethisterone; TXA = tranexamic acid; MFA = mefenamic acid
Sources: Summary of clinical efficacy, pages 45-47 of 108; Report AY01 page 24 of 41

The comparison of subject disposition in the LNG IUS studies utilizing the PBAC methodology is shown in Table 52.

Table 52: Comparison of Disposition Results (Number of Subjects) Results in LNG IUS Studies Utilizing PBAC

Criteria	Study 93547 Report A14096	Study 302760 Report A36340	Study 303003 Report A00696	Study 93503 Report BC71
Comparator	Mefenamic acid	NET / EE	Danazol	TCRE
Started Treatment	LNG IUS = 25 MFA = 26	LNG IUS = 20 NET/EE = 19	LNG IUS =75 DZ = 76	LNG IUS = 30 TCRE = 29
Completed study medication	LNG IUS = 21 MFA = 21	LNG IUS = 17 NET/EE = 12	LNG IUS = 68 DZ = 64	LNG IUS = 19 TCRE = 25
Discontinued for adverse event	LNG IUS = 4 MFA = 2	LNG IUS = 1 NET/EE = 5	LNG IUS = 7 DZ = 11	LNG IUS = 9 TCRE = 2

LNG IUS = levonorgestrel-releasing intrauterine system; NET = norethisterone; EE = ethinyl estradiol; DZ = danazol; TCRE = transcervical resection of the endometrium; MFA = mefenamic acid
Sources: Summary of clinical efficacy, pages 45-47 of 108

6.1.4 Analysis of Primary Endpoint(s)

The comparison of median MBL in the LNG IUS studies utilizing the alkaline hematin methodology is shown in Table 53.

Table 53: Comparison of Median MBL (mL per cycle) for LNG IUS in the Alkaline Hematin Studies

Study / Report	Treatment	Baseline	Cycle 1	Cycle 3	Cycle 6	Cycle 12
309849 / A38313	LNG IUS	147.96		30.30	7.10	
92549 / B088	LNG IUS	105.5	19.0	6.0		
94548 / A00630	LNG IUS	168.5			10.7	4.5
93547 / A14096	LNG IUS	122.0		12.0	5.0	
92501 / AY01	LNG IUS	119.0		34.5	17.7	8.8

LNG IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss
Source: Summary of clinical efficacy, pages 53 & 57 of 108

The comparison of median MBL in the comparators utilizing the alkaline hematin methodology is shown in Table 54.

Table 54: Comparison of Median MBL (mL per cycle) for Comparators in the Alkaline Hematin Studies

Study / Report	Treatment	Baseline	Cycle 1	Cycle 3	Cycle 6	Cycle 12
309849 / A38313	MPA	154.20		136.20	121.47	
92549 / B088	NET	119.5	46.0	20.5		
94548 / A00630	TXA	140.0			53.3	71.2
93547 / A14096	MFA	121.0		94.0	99.5	

LNG IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss
Source: Summary of clinical efficacy, pages 53 & 57 of 108

Medical Officer's Comment:
The data in the two prior tables provide strong clinical support for the efficacy of LNG IUS in reducing bleeding. The amount of bleeding after LNG IUS is only about 5-20% of the amount present at baseline. In Study 92549, the only study to evaluate after one month of treatment, clinical improvement was noted as early as the first cycle of use.

A summary of the statistical analysis for the pivotal and supporting studies is shown in Table 55.

Table 55: Primary Efficacy Endpoints for Pivotal Study 309849 and Supportive Studies

Study	Primary Endpoint	Results
309849	Treatment with LNG IUS produced a statistically significantly greater reduction in blood loss than treatment with MPA(measured as the change in the absolute value from Baseline MBL to End-of-Study MBL)	P < 0.001
309849	Treatment with LNG IUS produced a statistically significantly greater number of subjects with successful treatment than treatment with MPA	P < 0.001
92549	Difference between LNG IUS and norethisterone for reduction in MBL from baseline to Cycle 3	Not statistically different
94548	The reduction in the median MBL from baseline was statistically significantly larger in the LNG IUS group compared to the tranexamic acid group	P = 0.0007 (Cycle 6) P = 0.0031 (Cycle 12)
93547	The reduction in the median MBL from baseline was statistically significantly larger in the LNG IUS group compared to the mefenamic acid group	P < 0.001 (Cycle 3) P < 0.001 (Cycle 6)
303003	Danazol was statistically significantly better than LNG IUS in reduction of PBAC from baseline to 3 months	P = 0.023
302760	Treatment with LNG IUS produced a statistically significantly greater reduction in blood loss (PBAC) than treatment with NETA/EE (measured as the change in the absolute value from Baseline MBL to 12th month MBL)	P = 0.0024

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate
MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart; NETA/EE = norethindrone acetate / ethinyl estradiol
A = Successful treatment is defined as End-of-Study MBL < 80 mL and decrease in End-of-Study MBL ≥ 50% of Baseline MBL
Source: Summary of Clinical Efficacy, pages 15, 18, 55, and 59 of 108

Medical Officer's Comment:
In the previous table, this reviewer focused primarily on the pre-specified primary endpoints of the most important clinical studies in regards to efficacy. As shown in the table, Studies 94548, 93547 and 302760 would qualify as statistical support for the pivotal Study 309849. The study data cannot be combined in any meaningful way because a) alkaline hematin analysis would have been performed in different labs, b) the PBAC results could possibly vary due to different sanitary products and c) different comparators are being used in open label studies

The reason that LNG IUS was superior to NETA/EE in Study 302760 but not against norethisterone in Study 92549 is likely the more potent progestin dosage in Study 92549 (15 mg norethisterone daily for 21 days) compared to Study 302760 (1 mg norethindrone acetate for 21 days). Danazol is also a potent formulation that leads often to amenorrhea and it is not surprising that LNG IUS would not perform as well as danazol.

Although not listed as a primary endpoint, it is noteworthy that LNG IUS was statistically better than mefenamic acid also in the PBAC analysis (P=0.004 at Cycle 3 and P<0.001 at Cycle 6)

6.1.5 Analysis of Secondary Endpoints

An overview of secondary endpoints in 9 studies is shown in Table 56.

Table 56: Overview of Secondary Endpoints in 9 LNG IUS Studies of "Heavy Menstrual Bleeding"

	309849	92549	94548	93547	302760	303003	93503	90528	92501
Hemoglobin	X	X	X	X	X	X	X	X	
Hematocrit	X								
Ferritin	X	X	X	X	X	X	X	X	
LNG IUS insertion assessment		X	X	X	X	X	X		X
Investigator global assessment	X								
Treatment success	X	X	X		X	X	X		
Menorrhagia severity score					X	X			
Vaginal bleeding	X	X	X	X			X		
Patient's overall assessment	X								
Subject satisfaction					X	X			
Overall assessment of tolerability			X	X					

Source: Summary of Clinical Efficacy, page 64 of 108

Medical Officer's Comment:
Of the secondary endpoints in the pivotal and supportive studies, the two analyses that lend themselves the best for an integrative comparative analysis are those of hemoglobin and ferritin monitoring. These comparisons are shown in Table 57 ***and*** Table 58***.***

Table 57: Comparison of Mean Hemoglobin (g/dL) Values from the Pivotal and Supportive Studies

Study	Rx	Baseline	Cycle 3	Cycle 6	1 year	2 years	3 years	4 years	5 years
309849[A]	LNG IUS	12.43	13.01	13.43					
309849[A]	MPA	12.23	12.38	12.51					
92549	LNG IUS	12.8	13.3						
92549	NET	13.0	13.2						
94548	LNG IUS	12.73	12.56	13.01	13.44				
94548	TXA	12.35	12.42	12.49	12.59				
93547	LNG IUS	12.66	12.52	13.06	13.45	13.41	13.61	13.52	13.81
93547	MFA	12.67	12.46	12.30					
302760	LNG IUS	12.6	13.0	13.4	13.4				
302760	NETA/EE	12.5	12.7	13.0	13.5				
303003	LNG IUS	12.67	13.38	13.63					
303003	Danazol	12.79	13.79	13.31					
93503	LNG IUS	12.52		13.34	13.60	13.68	13.47		
93503	TCRE	12.74		13.33	13.60	13.47	13.52		
90528	LNG IUS	12.8		13.8	13.7				
90528	Control	12.9		12.5	13.1				

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate; NET = norethisterone; TXA = tranexamic acid; MFA = mefenamic acid; NETA/EE = norethindrone acetate / ethinyl estradiol; TCRE = transcervical resection of endometrium

A = The figures for the pivotal study were estimated from tables in the study report that provided baseline values and percent change in hemoglobin – Study Tables 59 and 60, pages 129-130 of 318

Sources: In addition to the study tables above, the remainder of the data came from text table 39 pages 71-72 of 108

Table 58: Comparison of Median Ferritin (ug/L) Values from the Pivotal and Supportive Studies

Study	Rx	Baseline	Cycle 3	Cycle 6	1 year	2 years	3 years	4 years	5 years
309849[A]	LNG IUS	19.0	21.6	32.0					
309849[A]	MPA	19.0	19.0	21.7					
92549	LNG IUS	20.0	27.0						
92549	NET	18.5	11.0						
94548	LNG IUS	14.5	17.0	18.0	31.0				
94548	TXA	10.0	8.0	11.0	13.0				
93547	LNG IUS	11.7	13.8	19.2	24.3	35.8	63.3	52.8	47.9
93547	MFA	8.2	10.4	11.7					
302760	LNG IUS	11.0	11.0	23.0	34.0				
302760	NETA/EE	10.0	15.0	13.0	18.0				
303003	LNG IUS	15.0	20.0	28.0					
303003	Danazol	15.0	16.0	33.0					
93503	LNG IUS	13.0		23.0	33.0	33.0	53.0		
93503	TCRE	11.0		48.0	41.0	44.0	56.5		
90528	LNG IUS	15.0		28.0	38.0				
90528	Control	17.0		16.0	35.0				

LNG IUS = levonorgestrel-releasing intrauterine system; MPA = medroxyprogesterone acetate; NET = norethisterone; TXA = tranexamic acid; MFA = mefenamic acid; NETA/EE = norethindrone acetate / ethinyl estradiol; TCRE = transcervical resection of endometrium
A = The figures for the pivotal study were estimated from tables in the study report that provided baseline values and percent change in ferritin – Study Tables 65 and 66, pages 135-136 of 318
Sources: In addition to the study tables above, the remainder of the data came from text table 42, pages 77-78 of 108

6.1.6 Other Endpoints

All the key endpoints were addressed in prior sections.

6.1.7 Subpopulations

Subpopulation analyses were performed for LNG IUS subjects in the pivotal Study 309849 for age, ethnic group, BMI and use of iron preparations.

An analysis of median absolute change in MBL from baseline to End-of-study by age group was conducted for the age groups 18 to <35 and ≥ 35 years of age. No difference in absolute change in MBL was observed for the subgroups treated with LNG IUS.

Among subjects belonging to ethnic groups for which more than 5 subjects per treatment group were available (Caucasians, Blacks, and Hispanics), no difference in absolute change in median MBL from baseline to End-of-study was observed for subjects who received treatment with LNG IUS.

The difference in absolute change in median MBL from baseline to End-of-study for subjects who received treatment with LNG IUS was not different for subjects whose BMI fell into the categories, <25 (-120.3 mL), 25 to <30 (-133.9 mL), or ≥30 (-115.9 mL).

The difference in absolute change in median MBL from baseline to End-of-study for subjects who received treatment with LNG IUS was not different for subjects who received iron supplementation (-142.3 mL) versus those who did not (-118.5 mL).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Since LNG IUS is available only in a single dose level, there is no further clinical analysis required in this section of the review.

6.1.9 Discussion of Persistence of Efficacy

Although only a small number of subjects have been analyzed with alkaline hematin and PBAC methods between 3-5 years after LNG IUS insertion, the determinations performed confirm the persistence of effect. There is no evidence from medical literature from outside of the U.S. or postmarketing reports that heavy bleeding resumes as the release rate becomes lower.

6.1.10 Additional Efficacy Issues/Analyses

Additional efficacy analyses based on medical literature can be found in Section 9.1 of this review.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The 10 clinical studies used to evaluate safety in this NDA submission include: 309849, 92549, 94548, 93547, 92501, 302760, 303003, 93503, 90528 and 91539.

7.1.2 Categorization of Adverse Events

AEs were monitored throughout the clinical studies, and all reported AEs were included in the safety analyses. For the pivotal study (309849) and the integrated database, AEs

were coded using the Medical Dictionary of Regulatory Authorities, MedDRA Version 11.0.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data was pooled across the studies listed in 7.1.1

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Applicant submitted 10 heavy menstrual bleeding (HMB) studies in this NDA submission. The integrated safety analyses presented in this section of the review are based on 332 subjects who either had LNG IUS inserted or who had at least 1 insertion attempt. The total exposure for these 332 subjects was 340.92 women-years. The breakdown of the subjects in regard to treatment completion time is shown in Table 59.

Table 59: Number of Subjects on LNG IUS Treatment over Time (FAS)

Treatment Completion Time	Total Subjects = 332	
	n	%
3 months	305	91.9
6 months	236	71.1
1 year	105	31.6
2 years	47	14.2
3 years	29	8.7
4 years	11	3.3
5 years	7	2.1

LNG IUS = levonorgestrel-releasing intrauterine system
Source: ISS, text table 1, page 11 of 56

7.2.2 Explorations for Dose Response

Exploration for dose response was not required. The approved product was used and development was focused on its use for the secondary indication of heavy menstrual bleeding. The dosing in the approved product provides contraception efficacy (primary indication) for five years.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable for this submission

7.2.4 Routine Clinical Testing

Routine clinical testing, which included safety labs (chemistry, hematology, urinalysis), pregnancy testing and pap smears, was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Routine evaluations for adverse events expected in association with an intrauterine device containing a progestin were performed.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in any of the ten clinical studies in this submission.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events are shown in Table 60.

Table 60: SAEs for LNG IUS Users in the Integrated Safety Analysis (FAS, N =332 Subjects)

Study	Subject No.	SAE(s) Preferred Term
309849	24514	Endometriosis
92549	114	Non-Hodgkin's lymphoma, stage IV
"	131	Tonsillectomy
93547	103	Abdominal pain, mild hypertension, sensory loss
93503	5	Headache, nausea, hypoacusis
"	12	Diarrhea, dyspepsia, gastric ulcer
"	17	Rheumatoid arthritis
"	31	Breast cosmetic surgery
"	36	Endometrial ablation
"	45	Endometrial ablation
302760	26	Inguinal hernia
303003	116	Ovarian cyst, abdominal pain

LNG IUS = levonorgestrel-releasing intrauterine system
Source: ISS, text table 22, page 44 of 56

Medical Officer's Comment:
The SAEs that appear possibly related to LNG IUS use are abdominal pain, headache/nausea, ovarian cyst and the endometrial ablations.

7.3.3 Discontinuations Due to Adverse Events

All of the discontinuations due to adverse events for the 10 HMB studies are listed in Table 61.

Table 61: LNG IUS Subjects with Discontinuations Due to Adverse Events (N =332 Subjects)

Study	Subject No.	Adverse Event (s)		Study	Subject No.	Adverse Event
309849	10101	Abd pain		93547	103	PEXP
"	12219	Abd pain		"	105	PEXP
"	10120	PEXP, HMF		"	108	Spotting
"	12505	HMF		"	119	Expulsion
92549	108	Spotting		"	121	Expulsion
"	111	FIB		"	125	Spotting
"	114	Lymphoma		"	127	Expulsion
"	115	Back pain		"	135	FIB
"	119	Expulsion		"	136	Bleeding
"	123	Spotting		"	141	PEXP
"	131	Leukorrhea		"	146	HMF, dysmenorrhea
"	132	Headache		"	151	Change in libido
"	135	FIB		90528	67	Spotting
"	137	Expulsion		"	72	Spotting
"	139	FIB		"	106	HMF
"	144	PEXP		"	112	Bleeding
93503	6	FIB		"	116	Depression
"	10	PMF		94548	102	Failed insertion
"	16	Endometritis		"	106	Expulsion
"	19	Abd pain		"	107	Libido decrease, WI, BE
"	36	Back pain		"	114	Expulsion
"	37	PMF		"	127	Expulsion
"	38	Acne		"	132	Expulsion
"	45	FIB		"	144	Expulsion
"	55	Abd pain		"	158	Depression
303003	6	Expulsion		92501	1	Expulsion
	10	Bleeding		"	2	Urinary incontinence
	69	PMF		"	306	Expulsion
	117	Failed insertion		"	310	Expulsion
	140	Pelvic pain		91539	24	Pelvic cramping
	148	Pelvic pain		"	30	Expulsion
	151	Bleeding and pain		302760	13	FIB

LNG IUS = levonorgestrel-releasing intrauterine system; Abd = abdominal; PEXP = partial expulsion; HMF = heavy menstrual flow; PMF = prolonged menstrual flow, FIB = frequent irregular bleeding; WI = weight increase; BE = breast enlargement
Source: IN.TERMIA dataset via JMP and Tables for Integrated Summary of Safety, pages 205-220 of 220

Medical Officer's Comment:
In the prior table there are no new safety signals of concern. Most of these adverse events are included in the current label. Lymphoma is not considered to be a treatment-related event for LNG IUS.

7.3.4 Significant Adverse Events

The significant adverse events related to progestin-containing intrauterine devices include the following:

- IUD expulsion (complete and partial)
- IUD perforation
- Ectopic pregnancy
- Breast cancer
- Pelvic inflammatory disease

There were no cases of breast cancer, ectopic pregnancy or IUD perforation in any of the 10 clinical studies submitted to support the secondary efficacy indication of heavy menstrual bleeding. Only 1 case of PID was reported in the 10 HMB studies. The percentage of complete and partial expulsions are listed in the common adverse events in Section 7.4.1

7.3.5 Submission Specific Primary Safety Concerns

Not applicable for this submission (this was an efficacy supplement).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the 332 LNG IUS subjects in the integrated safety analysis, the most common adverse events were metrorrhagia (22.6%), headache (19.6%), menorrhagia (12.7%), dysmenorrhea (7.5%), breast tenderness (6.3%), ovarian cyst (6.0%), back pain (5.7%), abdominal pain lower (5.4%), complete expulsions (5.1%) and partial expulsions (4.2%)

7.4.2 Laboratory Findings

There were no safety issues identified in routine safety labs. As mentioned in the efficacy sections, there were improvements noted in a) decreased blood loss as measured by alkaline hematin determinations, b) increased hemoglobin and c) increased serum ferritin.

7.4.3 Vital Signs

There were no safety issues identified in routing vital sign monitoring

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not required for this NDA submission.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable for this submission

7.4.6 Immunogenicity

Not applicable for this submission

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable – there is only one dose for LNG IUS (Mirena).

7.5.2 Time Dependency for Adverse Events

There are no new findings in this submission regarding time dependency for adverse events.

7.5.3 Drug-Demographic Interactions

There are no new findings in this submission regarding drug-demographic interactions.

7.5.4 Drug-Disease Interactions

The effect of LNG IUS on heavy menstrual bleeding is the subject of the efficacy analysis performed. There are no other findings in this submission regarding drug-disease interactions

7.5.5 Drug-Drug Interactions

There are no new findings in this submission regarding drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is no evidence from clinical studies to date or postmarketing safety data from nearly 20 years of use to suggest a relationship. LNG IUS has been approved in other countries for protection of the endometrium in postmenopausal women taking estrogen, which may result in neoplasia if used unopposed by a progestin.

7.6.2 Human Reproduction and Pregnancy Data

The adverse events related to LNG IUS and pregnancy are presently covered in the product labeling (ectopic pregnancy, sepsis, pregnancy loss etc.) The pregnancy complications in the 7-31-09 safety update are found in Section 7.7. No new additional pregnancy safety issues have been reported that affect this efficacy supplement.

7.6.3 Pediatrics and Assessment of Effects on Growth

This product is not indicated for prepubertal females.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable for this single dose product, which is inserted by the health care provider.

7.7 Safety Updates

7.7.1 Update for September 28, 2007 through September 27, 2008

A periodic safety update report (PSUR) was submitted by the Applicant for NDA 21-225 on 3-31-09 with the efficacy supplement. This PSUR covered the period from September 28, 2007 to September 27, 2008. Summary comments for this PSUR submission include:

- There have been no changes in the worldwide marketing authorization status of Mirena or significant actions by a regulatory agency due to safety reasons.
- The Applicant estimated the patient exposure during this 12 month period to be approximately 7.26 million women-years.
- The Applicant reported 4 fatal cases during this time period:
    - Case 200810244BNE = Streptococcal infection with septic shock

- Case 200812005NA = Pulmonary embolism
- Case 200812248GPV = Death of prematurely delivered newborn (cervical pregnancy 23.5 weeks)
- Case 200813818GPV = Death of newborn secondary to brainstem problem

Medical Officer's Comment:
Streptococcal infection is listed in the Mirena label as a Warning. This case was unusual in that it occurred 6 months post-insertion. There is no indication that LNG IUS represents a risk for venous thromboembolic events (VTE). The patient who had the pulmonary embolism (by reporting of patient's family) weighed 100 kg and was 47 years old. It's possible that higher risk individuals (weight, age, family history, thrombophilia) may be preferentially prescribed Mirena in an attempt to avoid VTEs developing with combination oral contraceptives. Rare cases of cervical pregnancy have been reported with IUD use. It seems unlikely that the brainstem problem is related to an IUD.

- Table 62 is provided as a companion to the Applicant-submitted table in the safety update from 7-31-09 (Table 63), which provides an updated report over a more recent eight-month period. Reporting rates, if found, are included.

Table 62: Medically-confirmed, Unlisted, Serious and Non-serious Adverse Events (> 5 Events - Reported in Time Period from September 28, 2008 through June 1, 2009)

MedDRA Preferred Term	Number of Events	Reporting Rate per 100,000 woman-years
Breast cancer	43	0.60
VTEs (DVT and/or PE)	33	0.39
Leiomyoma	22	NP
Hypertension	19	0.26
Cervical dysplasia	18	0.25
Cerebrovascular disorders	16	0.22
Depression	15	NP
Device breakage	13	NP
Endometrial and uterine cancers	6	0.08
Myocardial infarction	2	0.028

NP = not provided
Source: PSUR (dated Nov. 16, 2008) Section 6, pages 20-73 and Section 9, pages 93-106

Medical Officer's Comment:
The reporting rate for all of these events is small, less than 1.0 per 100,000 woman-years. Causality is not implied in this listing.

- The Applicant's report of the numbers of pregnancy complications in the safety update covering September 28, 2007 – September 27, 2008:

- Pregnancy loss (99 cases)
- Elective termination (not provided)
- Ectopic pregnancies (217 cases)

Medical Officer's Comment:
Thirty-six cases of live birth without complications were also reported.

7.7.2 Update for September 28, 2008 through June 1, 2009

A safety update was submitted by the Applicant for NDA 21-225 on 7-31-09. The last full year PSUR covered the period from September 28, 2007 to September 27, 2008. In this safety update, the Applicant provided safety data that encompassed the time period of September 28, 2008 to June 1, 2009 (8 months). Summary comments for this safety submission include:

- There have been no changes in the worldwide marketing authorization status of Mirena or significant actions by a regulatory agency due to safety reasons.

- The Applicant has made a revision to the 'Dosage and method of administration' section of the label to include the following paragraph:

(b) (4)

- The Applicant estimated the patient exposure during this 8 month period to be approximately 5.4 million women-years.

  "The number of Mirena insertions from 01 October 2008 to 31 May 2009 is estimated to be almost (b) (4) based on the number of Mirena units sold). Including all current users at the end of the last PSUR period, assuming that every unit sold during the period covered by this report has been inserted and assuming a five-year usage time at maximum with a 10% annual withdrawal rate, about (b) (4) women are estimated to have been exposed to Mirena at some point during the period covered by this statement and almost 5.4 million woman-years with Mirena have been gathered during this period."

- The Applicant reported 3 fatal cases during this time period:

  - Case 200911636BNE = Suicide
  - Case 200910421NA = Necrotizing fasciitis
  - Case 200839950NA = Death report but no additional information

Medical Officer's Comment:
The description of the death with the diagnosis of necrotizing fasciitis did not specify the site of the fasciitis or confirm fasciitis as opposed to generalized sepsis. A uterine curettage showed no evidence of infection either on the IUD or the curettings.

- The Applicant provided safety information on medically confirmed, unlisted, serious and non-serious adverse events in patient's with LNG IUS. The listing of the MedDRA preferred term, number of events and reporting rate per 100,000 woman-years is shown in Table 63 (events > 5).

Table 63: Medically-confirmed, Unlisted, Serious and Non-serious Adverse Events (> 5 Events - Reported in Time Period from September 28, 2008 through June 1, 2009)

MedDRA Preferred Term	Number of Events	Reporting Rate per 100,000 woman-years
Breast cancer	38	0.70
Malignant neoplasm apart from breast cancer	15	0.28
Pulmonary embolism	12	0.22
Uterine leiomyoma	9	0.17
Device breakage	9	0.17
Depression	8	0.15
Myocardial infarction	7	0.13
Cervical dysplasia	7	0.13
Deep vein thrombosis	6	0.09

Source: Safety Update Submission, Addendum report, section 6.2, page 9 of 18

Medical Officer's Comment:
The reporting rate for all of these events is small. Causality is not implied in this listing. As mentioned earlier in this section, there has been no indication of increased vascular adverse events with Mirena. As mentioned in the following postmarketing section, the Applicant has not found an increase in breast cancer in a comparative study between LNG IUS and a copper IUD.

- The Applicant reports numbers of pregnancy complications in the safety update covering September 28. 2008 – June 1, 2009:

    - Pregnancy loss (82 cases)
    - Elective termination (46 cases)
    - Ectopic pregnancies (143 cases)

Medical Officer's Comment:
These are rare but known and labeled pregnancy complications from IUD use. The number of cases of pregnancy loss and ectopic are similar to the preceding PSUR. Thirty-seven (37) cases of live birth with normal newborn were also reported.

- The Applicant reported one new comparative study reported in the literature by Theodoridis, in which it was found that LNG IUS decreased the duration of bleeding more than a roller ball endometrial ablation technique.

> Theodoridis TD, Zepiridis L, Zafrakas M, Grimbizis G, Tantsis A, Kyrou D, Bontis JN. Levonorgestrel-releasing intrauterine system vs. endometrial thermal ablation for menorrhagia. Hormones (Athens). 2009 Jan-Mar;8(1):60-4.

8 Postmarket Experience

Mirena (LNG IUS) was developed initially for contraception and its use for this indication has been approved in over 100 countries. The first marketing authorization for contraception was granted in 1990 in Finland. The postmarketing experience with this product is nearly 20 years. There is a cumulative experience with LNG IUS of almost (b) (4) insertions, and more than 44.3 million woman-years of exposure since start of marketing.

In the U.S., NDA 21-225 for Mirena (LNG IUS) was approved by the Division of Reproductive and Urologic Drug Products on December 6, 2000 for intrauterine contraception for up to five years.

In addition to contraception, "idiopathic menorrhagia" and "protection from endometrial hyperplasia during estrogen replacement therapy" are approved indications for LNG IUS in over 100 countries outside the US.

There have been no new significant safety signals in Periodic Safety Update Reports (PSURs) that would impact approval of the secondary indication of heavy menstrual bleeding.

There are no ongoing post-marketing studies with MIRENA in US. Two observational studies are ongoing in Europe.

One study is a prospective cohort study on the risk of perforation of the uterine wall associated with insertion of MIRENA compared with other IUDs. The recruitment is currently ongoing (13,000 patients currently enrolled), total number of subjects planned is 40,000-60,000. The first interim study report that was available in Dec. 2008 showed similar perforation risk in MIRENA and copper IUD users (< 1/1000).

In addition, a case-control study on the breast cancer risk of MIRENA compared with other contraceptive methods was completed recently. Final report was available in Apr. 2009, with 3500 cases and 14,000 controls. The final report did not show an elevated risk of development of breast cancer in LNG IUS users vs. copper IUD users.

A non-comparative observational study in women with idiopathic menorrhagia has recently been conducted in Europe. The clinical phase of the study has been completed, with 1577 women enrolled in the study. Currently, analysis of the data is ongoing. Another observational study (MIRENA or conventional medical treatment for menorrhagia) is ongoing in Asia. Also some smaller observational studies on women with menorrhagia are ongoing in Europe and Asia.

9 Appendices

9.1 Literature Review/References

The publications found in this section were either provided by the Applicant or identified by the reviewer utilizing PubMed. The reference articles are summarized in tabular form (Tables 62-74), with additional medical officer comments where appropriate.

Table 64: Literature Reference Study Information (First Author – Hurskainen)

First Author Year of Publication Study site(s)	Study Design Study Duration	MBL method	Number of Subjects	Comments
Hurskainen R 2001 (Lancet article) Finland	PR, R, C, O, MC 5 year duration	Alkaline hematin (Hallberg method)	LNG IUS = 117 Hysterectomy = 109	This was an early report of the study. The author reported a significant increase in mean hemoglobin and ferritin levels at 1 year
Hurskainen R 2004 (JAMA article) Finland	PR, R, C, O, MC 5 year duration	Alkaline hematin (Hallberg method)	LNG IUS = 117 treated Hysterectomy = 109 treated	A large number of LNG IUS subjects had amenorrhea at 5 years (43 of 57 = 75%) One discontinuation of LNG IUS was due to recurrent thromboembolic disease 42 of 60 women discontinuing LNG IUS reported intermenstrual bleeding

PR = prospective; R = randomized; C = controlled; O = open, MC = multicenter; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; JAMA = Journal of the American Medical Association
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Hurskainen referenced articles (2001 and 2004)

Medical Officer's Comment:

- ***This study, which had an early report in Lancet and final report in JAMA, provides <u>some</u> supportive clinical evidence for LNG IUS effectiveness in reducing MBL. The mean menstrual blood loss at 1 year was 13 mL and the mean menstrual blood loss at 5 years was 17 mL, which is consistent with the clinical studies presented by the Applicant. However, alkaline hematin determinations were performed for only 25 subjects at one year and only 4***

subjects at 5 years. The mean MBL values for this study are shown in comparative Table 77***. Hemoglobin and ferritin were also increased.***

- ***The proportion of subjects with amenorrhea was 53% and 75% at 1 year and 5 years respectively. Quality of life measures constituted the primary outcome measures.***
- ***As opposed to many other similar studies, this trial did not require the baseline MBL of > 80 mL, but solicited subjects who had complaints of menorrhagia. This resulted in a study population where about 58% had MBL > 80 mL.***

Table 65: Literature Reference Study Information (First Author – Xiao)

First Author Year of Publication Study site(s)	Study Design Study Duration Pertinent entry criteria	MBL method	Number of Subjects	Comments
Xiao B 2003 Beijing	PR, NR, O, SC 3 year duration Entry required MBL > 80 mL (average over two cycles)	Alkaline hematin (Hallberg method)	LNG IUS = 34	There were 4 expulsions No serious adverse events were reported After about 6 months, 33% of subjects became amenorrheic Significant increases in hemoglobin and ferritin were noted

PR = prospective; NR = non-randomized; O = open, SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Xiao reference

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL, increasing hemoglobin and increasing ferritin over a 3 year period. The mean MBL values for this study are shown in comparative Table 77***.***

Table 66: Literature Reference Study Information (First Author – Kriplani)

First Author Year of Publication Study site(s)	Study Design Study Duration	MBL method	Number of Subjects	Comments
Kriplani A. 2007 India	PR, NR, O, SC 4 year duration	PBAC (Higham article referenced)	LNG IUS = 63	There were 6 expulsions Intermenstrual bleeding/spotting was noted in 71% of the subjects during the first three months A significant increase in hemoglobin was noted by the author

PR = prospective; NR = non-randomized; O = open; SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Kriplani reference

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL and increasing hemoglobin over a 4 year period. The mean and median MBL values for this study are shown in comparative Table 77***.***

Table 67: Literature Reference Study Information (First Author – Busfield)

First Author Year of Publication Study site(s)	Study Design Study duration	MBL method	Number of Subjects	Comments
Busfield RA 2006 New Zealand	PR, R, C, O, SC 2 year duration	PBAC (Higham article references)	LNG IUS = 40 treated Balloon ablation = 39 treated	Median PBAC scores at 12 and 24 months were significantly lower for LNG IUS users than those of women treated by balloon ablation Two LNG IUS were expelled and two were removed for pain symptoms There was one case with actinomycosis There were no serious adverse events

PR = prospective; R = randomized; O = open, C = controlled; SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Busfield reference

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL over a 2 year period. The mean and median MBL values for this study are shown in comparative Table 77***.***

Table 68: Literature Reference Study Information (First Author – Shaw)

First Author Year of Publication Study site(s)	Study Design Study Duration Pertinent entry criteria (2)	MBL method	Number of Subjects	Comments
Shaw RW et al. 2007 United Kingdom	PR, R, C, O, SC 1 year duration PBAC > 120 mL required (mean of two cycles) – Included those who had failed oral therapy	PBAC (Higham article referenced)	LNG IUS = 33 treated Balloon ablation = 30 treated	Median PBAC score in LNG IUS users was significantly lower compared to balloon ablation-treated subjects at 1 year ($p<0.001$) Irregular bleeding was the most common reason for LNG IUS discontinuation Hemoglobin and ferritin in this study only showed a slight increase Two LNG IUS subject experienced expulsions

PR = prospective; R = randomized; C = controlled; O = open, SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Shaw reference

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL over a 1 year period. As shown later in comparative Table 77***, this study did not identify a MBL < 100 mL till after 6 months duration. This may be partly accounted for based on the enrollment of subjects who all had > 120 mL of blood loss at entry and who had failed oral therapy. Hemoglobin and ferritin increases were modest in comparison to other "literature" studies in this review. This study is the second study (in addition to Busfield et al.) to suggest that LNG IUS may be more effective in reducing MBL than balloon ablation.***

Table 69: Literature Reference Study Information (First Author – Yazbeck)

First Author Year of Publication Study site(s)	Study Design Study Duration	MBL method	Number of Subjects	Comments
Yazbeck C et al. 2006 France	PR, NR, O, SC Planned 3 year duration	PBAC (referenced Higham and Janssen)	LNG IUS = 49 treated	Only 1 year of data reported Significant increases in hemoglobin, iron and ferritin reported

PR = prospective; NR = non-randomized; O = open, SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Yazbeck reference

Medical Officer's Comment:
This study is primarily written in French with an added English abstract. The mean MBL values for this study are shown in comparative Table 77***. The study would have been more helpful if additional PBAC time points had been selected (e.g., 3 & 6 months)***

Table 70: Literature Reference Study Information (First Author – Andersson)

First Author Year of Publication Study site(s)	Study Design Study Duration Pertinent entry criteria	MBL method	Number of Subjects	Comments
Andersson JK et al. 1990 Sweden	PR, NR, O, SC 1 year duration Required MBL ≥ 80 mL for 2 consecutive cycles	Alkaline hematin (reference Hallberg with Newton modification)	LNG IUS = 20	A significant increase in hemoglobin and ferritin was noted at 1 year. The report did not mention any safety findings.

PR = prospective; NR = non-randomized; O = open, SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Andersson reference

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL over a 1 year period. The median MBL values for this study are shown in comparative Table 77***. The author used the Newton modification of the Hallberg alkaline hematin method, which uses a machine to agitate and loosen the blood in the sanitary products over a shorter time period rather than a prolonged time period of soaking.***

Table 71: Literature Reference Study Information (First Author – Milsom)

First Author Year of Publication Study site(s)	Study Design and Pertinent entry criteria	MBL method	Number of Subjects	Comments
Milsom I 1991 Sweden	PR, C, O, SC 1 year duration	Alkaline hematin (reference Hallberg with Newton modification)	LNG IUS = 20 FL / TXA = 15	Author stated that MLB reduction for LNG IUS was greater than FL ($p<0.001$) and TXA ($p<0.01$)

PR = prospective; C = controlled; O = open; SC = single center; LNG IUS = levonorgestrel intrauterine system; FL = flurbiprofen; TXA = tranexamic acid; MBL = menstrual blood loss
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Milsom reference

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL over a 1 year period. The efficacy results against flurbiprofen and tranexamic acid appear similar to the Applicant's clinical studies against mefenamic acid and tranexamic acid. The mean MBL values for this study are shown in comparative Table 77***.***

Table 72: Literature Reference Study Information (First Author – Crosignani)

First Author Year of Publication Study site(s)	Study Design Study Duration	MBL method	Number of Subjects	Comments
Crosignani PG 1997 Italy	PR, R, C, O, SC 1 year duration	PBAC (Higham article referenced)	LNG IUS = 35 Endometrial resection = 35	MBL reduction in LNG IUS group was 79% at year 1. compared to 89% in the endometrial resection group Amenorrhea or hypomenorrhea was present in 65% of the LNG IUS group at year 1 There were 2 partial expulsions of LNG IUS

PR = prospective; R = randomized; C = controlled; O = open; SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Crosignani reference

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL at the year 1 determination. Similar to the Yasbeck study, additional MBL measurements at 3 & 6 months would have been helpful. In the Applicant's supportive Study 93503 (Section 5.3.7) PBAC improvement at year 1 for LNG IUS and endometrial resection was 95% and 97% respectively. The mean MBL values for this study are shown in comparative Table 77***.***

Table 73: Literature Reference Study Information (First Author – Soysal)

First Author Year of Publication Study site(s)	Study Design Study Duration Pertinent entry criteria	MBL method	Number of Subjects	Comments
Soysal M et al. 2002 Turkey	PR, R, C, SC 1 year duration PBAC > 150 mL x 2 consecutive months required for entry	PBAC (referenced Higham)	LNG IUS = 36 treated Balloon ablation = 36 treated	In regard to PBAC scores at year 1, the balloon out-performed the LNG IUS in this study.

PR = prospective; R = randomized; C = controlled; SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Clinical Overview text tables 5&6, pages 36-44 of 67 and Soysal reference

Medical Officer's Comment:
This study provides supportive clinical evidence (clinical evidence of marked drop in PBAC value) for LNG IUS effectiveness in reducing MBL over a 1 year period. This study did not come to same conclusion as the studies by Busfield and Shaw in regard to effectiveness of the balloon ablation therapy compared to LNG IUS. The mean MBL values for this study are shown in comparative Table 77***.***

Table 74: Literature Reference Study Information (First Author – Barrington)

First Author Year of Publication Study site(s)	Study Design Study Duration	MBL method	Number of Subjects	Comments
Barrington J 2003 UK	PR, R, C, O, SC 6 month duration	PBAC (Higham article referenced)	LNG IUS = 25 Endometrial balloon thermal ablation = 25	The author found the two treatment methods to be equally effective

PR = prospective; R = randomized; C = controlled; O = open, SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Barrington referenced article

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL over a 6 month period. The mean MBL values for this study are shown in Table 77***.***

Table 75: Literature Reference Study Information (First Author – Rauramo)

First Author Year of Publication Study site(s)	Study Design Study Duration	MBL method	Number of Subjects	Comments
Rauramo I 2004 Norway	PR, R, C, O, SC 3 year duration	PBAC (Higham article reference)	LNG IUS = 30 Transcervical resection of endometrium = 29	The author found that both treatments efficiently reduced menstrual bleeding

PR = prospective; R = randomized; C = controlled; O = open, SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Rauramo referenced article

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL over a 3 year period. The median MBL values for this study are shown in comparative Table 77***.***

Table 76: Literature Reference Study Information (First Author – Gupta)

First Author Year of Publication Study site(s)	Study Design Study Duration	MBL method	Number of Subjects	Comments
Gupta B 2006 India	PR, C, O, SC 1 year duration	PBAC (Higham article reference)	LNG IUS = 25 Transcervical resection of endometrium = 25	The author found that both treatments were effective

PR = prospective; C = controlled; O = open, SC = single center; LNG IUS = levonorgestrel intrauterine system; MBL = menstrual blood loss; PBAC = pictorial blood loss assessment chart
Sources: Gupta referenced article

Medical Officer's Comment:
This study provides supportive clinical evidence for LNG IUS effectiveness in reducing MBL over a 1 year period. The MBL values for this study are shown in Table 77***.***

Table 77: LNG IUS Menstrual Blood Loss Comparisons in Referenced Articles

Author	Method	Alkaline Hematin and PBAC Results in mL (number of subjects tested) at Multiple Time Points								
		BL	1M	3M	6M	1Y	2Y	3Y	4Y	5Y
Hurskainen (from 2001 and 2004 articles)	AH mean	130 (n=116)				13 (n=25)				17 (n=4)
Xiao 2003	AH mean	124 (n=34)			23 (n=29)	26 (n=29)	3 (n=26)	14 (n=23)		
Kriplani 2007	PBAC median	460 (n=63)	90 (n=60)	30 (n=59)	10 (n=58)	3 (n=53)	2.5 (n=40)	3 (n=18)	2 (n=15)	
Kriplani 2007	PBAC mean	536 (n=63)	155 (n=60)	118 (n=59)	53 (n=58)	12 (n=53)	5 (n=40)	5 (n=18)	4 (n=15)	
Busfield 2006	PBAC Median	NP		52 (n=39)	32 (n=39)	12 (n=39)	12 (n=37)			
Busfield 2006	PBAC mean	490 (n=40)		125 (n=39)	72 (n=39)	41 (n=39)	21 (n=37)			
Shaw 2007	PBAC median	450 (n=33)		172 (n=31)	124 (n=29)	26 (n=23)				
Yazbeck 2006	PBAC mean	333 (n=41)				51 (n=18)				
Andersson 1990	AH median	176 (n=20)		24 (n=19)	15 (n=17)	5 (n=16)				
Milsom 1991	AH mean	203 (n=20)		34 (n=NP)	25 (n=NP)	9 (n=16)				
Crosignani 1997	PBAC mean	185 (n=35)				38 (n=30)				
Soysal 2002	PBAC mean	408 (n=36)				55 (n=31)				
Barrington 2003	PBAC mean	107 (n=25)			31 (n=21)					
Rauramo 2004	PBAC median	262 (n=30)				12 (n=24)	9 (n=20)	7 (n=19)		
Gupta 2006	PBAC	464 (n=25)		60 (n=23)	28 (n=21)	15 (n=17)				

BL = Baseline; M = month; Y = year; AH = alkaline hematin; PBAC = pictorial blood loss assessment chart; MBL = menstrual blood loss; NP = not provided
Sources: Clinical Overview text table 6, pages 36-44 of 67 and referenced articles by Barrington, Rauramo and Gupta

Medical Officer's Comment:
In the above table the last three studies (highlighted) were identified in the literature by the medical reviewer.

Reviewer Summary of Medical Literature Findings

The medical literature findings regarding the use of LNG IUS for controlling heavy bleeding can be summarized in the following bulleted comments:

- All of the medical articles (including those submitted by the Applicant and those identified by the clinical reviewer) provide some supportive evidence of efficacy for LNG IUS in subjects with heavy uterine bleeding. No non-supportive studies were identified.

- The principal efficacy endpoints demonstrating the reduction in bleeding in these studies entailed measurement of blood loss either through the alkaline hematin test or a pictorial blood loss assessment chart. Table 77 shows that the blood loss is well below the 80 mL threshold for menorrhagia in most studies within 3-6 months of treatment with LNG IUS.

- A number of the medical literature studies showed the supportive finding of increase in hemoglobin and ferritin in the LNG IUS-treated subjects.

- Some studies provided additional efficacy reassurance by finding a large proportion of subjects with amenorrhea developing after LNG IUS insertion.

- LNG IUS compared favorably against endometrial ablation and resection procedures.

- Similar to findings in the Applicant's development program, a number of subjects developed irregular mild bleeding/spotting and LNG IUS expulsion as adverse events. No new safety finding related to LNG IUS was noted in these studies

References

Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol 1990;97(8):690-4.

Barrington JW, Arunkalaivanan AS, Abdel-Fattah M. Comparison between the levonorgestrel intrauterine system (LNG IUS) and thermal balloon ablation in the treatment of menorrhagia. Eur J Obstet Gynecol Reprod Biol 2003;108:72–4.

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Hallberg L, Nilsson L. Determination of menstrual blood loss. Scand J Clin Lab Inv 1964; 16: 244–8.

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Hurskainen R, Teperi J, Rissanen P, Aalto A-M, Grenman S, Kivela A, Kujansuu E, Vuorman S, Yliskoski M, Paavonen J. Quality of life and cost effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomized trial. Lancet 2001; 357: 273-277.

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Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. Am J Obstet Gynecol 1991;164(3):879-83.

Rauramo, I., I. Elo, and O. Istre, Long-term treatment of menorrhagia with levonorgestrel intrauterine system versus endometrial resection. Obstet Gynecol, 2004. 104(6): p. 1314-21.

Shaw RW, Symonds IM, Tamizian O, Chaplain J, Mukhopadhyay S. Randomised comparative trial of thermal balloon ablation and levonorgestrel intrauterine system in patients with idiopathic menorrhagia. Aust N Z J Obstet Gynaecol 2007;47(4):335-40.

Soysal M, Soysal S, Ozer S. A randomized controlled trial of levonorgestrel releasing IUD and thermal balloon ablation in the treatment of menorrhagia. Zentralbl Gynakol 2002;124(4):213-9.

Xiao B, Wu SC, Chong J, Zeng T, Han LH, Luukkainen T. Therapeutic effects of the levonorgestrel releasing intrauterine system in the treatment of idiopathic menorrhagia. Fertil Steril 2003;79:963–9.

Yazbeck C, Omnes S, Vacher-Lavenu MC, Madelenat P. [Levonorgestrel-releasing intrauterine system in the treatment of dysfunctional uterine bleeding: A French multicenter study]. Gynecol Obstet Fertil 2006;34(10):906-13.

9.2 Labeling Recommendations

Review notes concerning revised product labeling based on the new indication sought by the Applicant (heavy menstrual bleeding) and concerning the switch to PLR (Physician Labeling Rule) format are found in this section organized by major label headings. Acceptable labeling was agreed upon with the Applicant.

9.2.1 Highlights

This section is new and required in the PLR format. The Highlights section makes note of recent major changes in this label (both with the new indication in the 2009 submission and the numerous changes that were made in the PLR conversion). The new indication of “Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception” is found in the *Indications and Usage* subsection. Information in the *Dosage and Administration* and *Dosage Forms and Strengths* subsections is accurate and derived from the approved 2008 label.

The *Contraindications* subsection of Highlights contains all of the contraindications that are found in the approved 2008 label and that are found in Section 4 of the label. However, some of the contraindications contain shortened wording.

The *Warnings and Precautions* subsection of Highlights contains all the significant safety concerns for this product. The *Adverse Reactions* subsection of Highlights mentions the common adverse reactions that occur in greater than 10% of users. The *Drug Interactions* subsection of Highlights contains a general statement about

progestogen metabolism changes secondary to substances that induce certain liver enzymes.

The *Use in Specific Populations* subsection of Highlights contains the recommendation that Mirena be used in women who have had a child. This recommendation was found in the Indications section of the prior approved 2008 label. This subsection also contains information for nursing mothers and the fact that it is not indicated in premenarchal females.

9.2.2 Contents

This section was found to be acceptable.

9.2.3 Indications and Usage

The new indication of "Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception" has been added.

9.2.4 Dosage and Administration

This section basically remains unchanged from the 2008 approved label.

9.2.5 Dosage Forms and Strengths

This section basically remains unchanged from the 2008 approved label.

9.2.6 Contraindications

This section basically remains unchanged from the 2008 approved label.

9.2.7 Warnings and Precautions

This section basically remains unchanged from the 2008 approved label, except for a new paragraph that explains what happens to bleeding patterns for women with heavy bleeding who are starting to use Mirena. The number of days of bleeding and spotting may increase during initial use but the overall volume of bleeding progressively improves.

9.2.8 Adverse Reactions

The Applicant sent in integrated safety data tables (containing exact percentages) from the prior contraceptives studies that correlated with the adverse events reported in the label.

9.2.9 Drug Interactions

This section has been reformatted in accord with other contraceptive products

9.2.10 Use in Specific Populations

This section basically remains unchanged from the 2008 approved label, except for the addition of the recommendation to use Mirena in women who have had at least one child (this recommendation used to be included with the Indication in the 2008 approved label).

9.2.11 Description

This section basically remains unchanged from the 2008 approved label.

9.2.12 Clinical Pharmacology

Clinical pharmacology has made some revisions in the ADME section of pharmacokinetics compared to the current label.

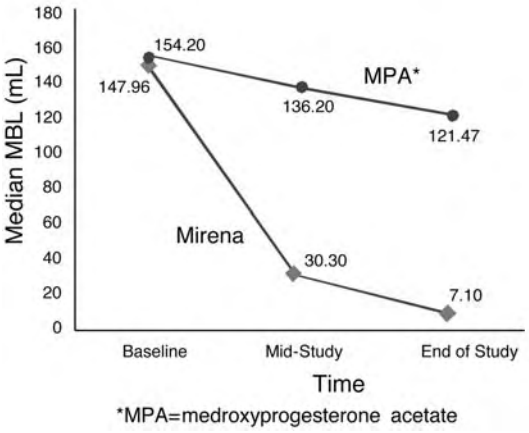
9.2.13 Nonclinical Toxicology

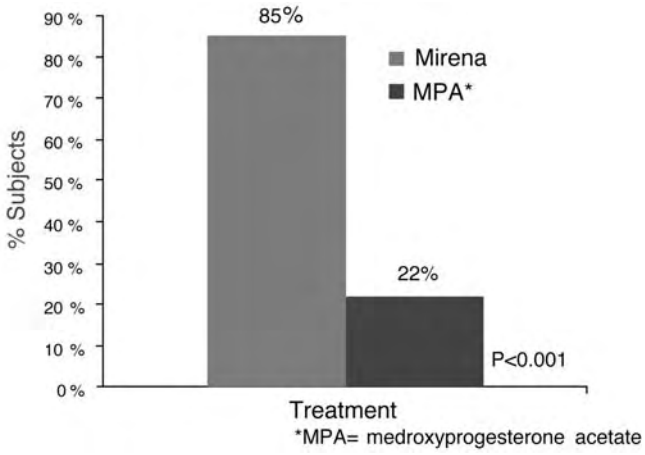
This section basically remains unchanged from the 2008 approved label.

9.2.14 Clinical Studies

This section includes a new paragraph and two figures that illustrate the clinical benefit in regard to heavy menstrual bleeding. The Applicant only provided efficacy information derived from the pivotal Study 309849 and only included the key efficacy data from the two primary co-endpoints.

The two figures are provided below:





9.2.15 How Supplied/Storage and Handling

This section basically remains unchanged from the 2008 approved label.

9.2.16 Patient Counseling Information

There is a new Patient Labeling Section. This section also repeats “when to contact health care provider”.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was determined not to be required for this efficacy supplement, since it concerned only a new indication for an unchanged approved product. No efficacy questions or new safety concerns were identified.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21225	SUPPL-27	BAYER HEALTHCARE PHARMACEUTICALS INC	MIRENA(LEVONORGESTREL RELEASING INTRA-UT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERALD D WILLETT
09/30/2009

LISA M SOULE
09/30/2009
I concur with Dr. Willett's conclusions and recommendation for approval of Mirena for treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception