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CADTH COMMON DRUG REVIEW

Clinical Review Report

ETONOGESTREL EXTENDED-RELEASE SUBDERMAL IMPLANT (NEXPLANON)

Merck Canada Inc.

Indication: For the Prevention of Pregnancy

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Abbreviations

AE	adverse event
ASA	all subjects assigned
ASPE	all subjects pharmacokinetically evaluable
ASR	all subjects randomized
AST	all subjects treated
AU	applicator user
$AUC_{0\text{-}6months}$	area under the curve from zero to six months
$AUC_{0\text{-}24months}$	area under the curve from zero to 24 months
$AUC_{0\text{-}36months}$	area under the curve from zero to 36 months
ASQ	Actual Satisfaction Questionnaire
AUC	area under the curve
BMI	body mass index
CDR	Common Drug Review
CI	confidence interval
C_{max}	peak concentration
D&E	dilation and evacuation
ESQ	Expected Satisfaction Questionnaire
GMR	geometric mean ratio
HRQoL	health-related quality of life
ICTRP	International Clinical Trials Registry Platform
ITT	intention to treat
IUD	intrauterine device
LARC	long-acting reversible contraceptive
LLOQ	lower limit of quantification
LTFU	lost to follow-up
NORA	Nexplanon Observational Risk Assessment
PI	Pearl Index
PP	per protocol
PPAU	per-protocol applicator user
PSQ-18	18-item Patient Satisfaction Questionnaire
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
SOGC	Society of Obstetricians and Gynaecologists of Canada
TSQM-II	Treatment Satisfaction Questionnaire for Medication version II

Drug	Etonogestrel extended-release subdermal implant (Nexplanon)
Proposed indication	For the prevention of pregnancy
Reimbursement request	As per indication
Dosage form (and route of administration) and strength	Subdermal implant, 68 mg
NOC date	May 25, 2020
Sponsor	Merck Canada Inc.

NOC = Notice of Compliance.

Executive Summary

Introduction

Canadian women are at risk of an unintended pregnancy for a substantial portion of their life.[1] According to the Society of Obstetricians and Gynaecologists of Canada (SOGC), one in five Canadian women of reproductive age had an unplanned pregnancy in 2016, and one in three of these women reported having an abortion.[2] In a national Canadian study, half the women who reported unintended pregnancies in 2016 were using a method of birth control.[2] Underutilization of effective contraceptive methods is especially pronounced for vulnerable women, including those from low-income families, those with lower education, and immigrants.[1,3]

Throughout their reproductive life span, a third of Canadian women will have an induced abortion.[4] Approximately half of all abortions occur in women between 20 and 29 years of age.[4] A total of 94,030 induced abortions were reported in Canada in 2017 based on data available to the Canadian Institute for Health Information.[5] The actual number of abortions may be underestimated because the data obtained were incomplete for some provinces, and partially based on clinic data where reporting is voluntary. The Canadian data on unplanned pregnancies and abortions demonstrate the substantial burden on the Canadian health care system and the unmet need for effective contraception, particularly for vulnerable women and women in their twenties.

The radiopaque etonogestrel implant is a long-acting hormonal contraceptive containing 68 mg of etonogestrel indicated for the prevention of pregnancy. The dosing recommendations are for a single implant that is inserted subdermally in the upper (non-dominant) arm and can be left in place for three years. The implant should be removed no later than three years after the date of insertion.

The predecessor, a 68 mg non-radiopaque etonogestrel extended-release subdermal implant, is not available in Canada. The radiopaque etonogestrel extended-release subdermal implant differs from the non-radiopaque etonogestrel extended-release subdermal implant according to the following distinctions:

- The radiopaque etonogestrel extended-release subdermal implant contains a small amount of barium sulphate so that the implant can be seen by X-ray or other imaging tools.[6]

- The radiopaque etonogestrel extended-release subdermal implant comes with a new applicator device that has been designed to facilitate correct subdermal insertion.[6]

The non-radiopaque form of the etonogestrel implant has been available since 1998 in other countries; it was approved for use in the US in 2007.

The original non-radiopaque etonogestrel implant received a Notice of Non-Compliance from Health Canada on January 11, 2013, due to safety concerns.[7] The Health Canada Reviewer Report for the radiopaque etonogestrel implant included data from a phase IV Nexplanon Observational Risk Assessment (NORA) study requested by the FDA and post-marketing experience data.[7] These data are considered in brief in the discussion section of this report.

The radiopaque etonogestrel implant received a Notice of Deficiency from Health Canada on January 31, 2020, due to insufficient bioequivalence between the device used in the pivotal studies and the device marketed in Canada.[7] The ethylene vinyl acetate core polymer used in the pivotal studies was supplied by Atofina (Total Petrochemicals USA Inc., Texas, USA), whereas the formulation for the implant in Canada was to be supplied by Celanese (Celanese Corporation, Texas, USA), with the addition of 0.1% magnesium stearate, which was required for a robust manufacturing process.[7] This issue was addressed through an In Vitro-In Vivo Correlation report that adequately predicted etonogestrel plasma concentration levels from two months and onward after implant insertion, and a comparative bioavailability study (P06110) that compared etonogestrel systemic exposure during the first two months after insertion of the implant containing ethylene vinyl acetate from Atofina versus ethylene vinyl acetate (plus 0.1% magnesium stearate) from Celanese.[7] These studies were used by Health Canada as evidence considered in the Notice of Compliance received on May 25, 2020, but were not included in the CADTH submission and are not considered further.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of radiopaque etonogestrel extended-release subdermal implant 68 mg (Nexplanon) for the prevention of pregnancy in women.

Stakeholder Engagement

Patient Input

No patient input was received for this CADTH Common Drug Review (CDR) report.

Clinician Input[a]

Contraception use in Canada is increasing. The most important goal of contraception is effective and reliable prevention of pregnancy using a method that is reversible and allows for rapid return to fertility once the contraceptive is discontinued. The ideal treatment should be easy for patients to access and adhere to and have minimal side effects.

There are several challenges for patients using contraceptives. First, adherence can be challenging. It can be difficult to anticipate a sexual event, publicly acquire the desired method, discuss contraception with a partner, and use the method correctly. Long-acting reversible contraceptives (LARCs) resolve many of these challenges. A second issue for patients is access to different options, especially LARCs. Barriers include attempting to find

[a] This information is based on information provided by the clinical expert consulted by CDR reviewers for the purpose of this review.

a health care provider to counsel and prescribe the desired method and financial barriers for the cost of contraception. Options such as condoms and oral contraceptive pills are not as effective or reliable as intrauterine devices (IUDs). The challenge with IUDs is that they require clinical expertise to insert correctly, are associated with pain and potential harms, and require follow-up. The etonogestrel implant could be used first-line for the prevention of pregnancy in patients who desire this option for contraception. The implant may be particularly useful for younger women, who may not need a speculum exam until they are 21 (age for a first Pap test). Patients who prefer a reliable, discrete, and effective option that does not require recall to use correctly would have the choice of an IUD or implant.

Pregnancy and discontinuation rates are outcomes used in both clinical practice and are typically used in clinical trials. Patients having no pregnancy during treatment would be considered a clinically meaningful response to treatment with contraceptives. The treatment response should be assessed for most patients at the end of the three-year duration of the treatment course of the implant. Patients may choose to discontinue treatment (i.e., have the implant removed) if they desire pregnancy, are no longer sexually active, no longer require contraception, or experience adverse events (AEs). The insertion and removal of the radiopaque etonogestrel implant can be performed in any outpatient clinic by a family physician, nurse practitioner, or gynecologist who has received proper training on the handling of the implant.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Three sponsor-identified studies were included in the CDR. The first study was an integrated analysis that included pooled data from 11 studies that evaluated the non-radiopaque etonogestrel implant (supplied by Atofina) as the intervention in 946 healthy adult women. The objective of the integrated analysis was to present efficacy and safety results from the clinical trials that supported the FDA filing for approval of the non-radiopaque etonogestrel contraceptive implant. Study P05702 was an open-label, non-comparative, single-arm, clinician satisfaction study of 301 adult women treated with the radiopaque etonogestrel implant. The primary objective of Study P05702 was to evaluate the use of the “next-generation” applicator and its instructions for proper insertion of the radiopaque etonogestrel implant. Study 34528 was a double-blind, parallel-group, bioequivalence study in which 108 women were randomized in blocks by centre at a 1:1 ratio for treatment with either the radiopaque etonogestrel implant or the non-radiopaque etonogestrel implant. Patients included in the three studies were healthy women between 18 and 40 years of age with regular menstrual cycles. Contraceptive efficacy was assessed in all three studies. The primary end point was user satisfaction in Study P05702 and bioequivalence in Study 34528.

Efficacy Results

No pregnancies occurred during the treatment periods across all three studies. The overall Pearl Index (PI) was zero contraceptive failures per 100 woman-years (95% confidence interval [CI], 0 to 0.20) for the non-radiopaque etonogestrel implant in the integrated analysis during the treatment period and zero contraceptive failures per 100 woman-years (95% CI, 0 to 0.56) for the radiopaque etonogestrel implant in Study P05702 (user satisfaction study) during the treatment period plus 14 days. The overall PI during the

treatment period of the bioequivalence Study 34528 was zero contraceptive failures per 100 woman-years (95% CI, 0 to 3.04) and zero contraceptive failures per 100 woman-years (95% CI, 0 to 3.06) in the radiopaque etonogestrel implant arm and non-radiopaque etonogestrel implant arm, respectively. Similar results were reported using the annual PI.

Based on findings from Study 34528, the radiopaque and non-radiopaque formulations were bioequivalent with respect to the geometric mean ratio (GMR) of the peak concentration (C_{max}) of etonogestrel (GMR = 1.06; 90% CI, 0.91 to 1.23) and the area under the curve ($AUC_{0\text{-}6months}$) (GMR = 1.00; 90% CI, 0.91 to 1.10); $AUC_{0\text{-}24months}$ (GMR = 0.98; 90% CI, 0.88 to 1.10), and $AUC_{0\text{-}36months}$ (GMR = 1.00; 90% CI, 0.89 to 1.11).

Return of menses to a normal (pre-trial) pattern occurred for 83.5% of patients treated with the radiopaque etonogestrel implant in Study P05702. In Study 34528, 94.4% of patients treated with the radiopaque etonogestrel implant and 90.5% of patients treated with the non-radiopaque etonogestrel implant experienced return of menses to a normal (pre-trial) pattern. This outcome was assessed three months after implant removal for women who were not pregnant, not breastfeeding, and not using post-treatment hormonal contraceptives. Return of menses to a normal pattern was not assessed in the integrated analysis.

Palpability and X-ray visibility of the implant were assessed in studies P05702 and 34528. The radiopaque and non-radiopaque etonogestrel implants were palpable in almost all patients (97.1% to 100%) when assessed at various time points. The radiopaque etonogestrel implant was clearly visible in almost all patients (96.2% to 100%) after insertion and before removal. The product monograph includes a serious warnings and precautions box stating that if the implant is not palpable at any time by the health care professional or the patient, it should be localized as soon as possible and removed as soon as medically appropriate to manage the risks of migration.[8] Implant migration was not assessed in the integrated analysis or Study 34528, although one patient treated with the radiopaque etonogestrel implant in Study P05702 experienced implant migration. The limited data from the pivotal trials on implant migration associated with the radiopaque etonogestrel implant is an important limitation. Findings from post-marketing reports of implants located within the vessels of the arm and the pulmonary artery were suspected to be attributable to deep insertions or intravascular insertion.[8] Real-world evidence has demonstrated implant migration of the radiopaque etonogestrel implant into pulmonary vasculature, with an estimated incidence of 3.17 per 100,000 implants (95% CI, 1.37 to 6.24) based on 2017 data from a study in France.[9] While implant migration may be rare, it can lead to respiratory issues and life-threating conditions, and it highlights the importance of proper insertion by trained clinicians.

In the integrated analysis, the mean insertion time for the non-radiopaque etonogestrel implant was 78 seconds (standard deviation [SD] = 114.0), and the mean removal time was 228 seconds (SD = 294.0). In Study P05702, the mean insertion time for the radiopaque etonogestrel implant was 27.9 seconds (SD = 29.3), and the mean removal time was 119.3 seconds (SD = 120.2). The mean insertion time for the radiopaque etonogestrel implant in Study 34528 was 87.6 seconds (SD = 96.0) and 299.4 seconds (SD = 207.0) for removal. The insertion time for the non-radiopaque etonogestrel implant was 72.6 seconds (SD = 63.6) and the removal time was 264.6 seconds (SD = 241.8). Data from Study P05702 reported that the most common reason for complications during implant removal was the presence of fibrotic tissue around the implant (4.4%).

Frequency results for the User Satisfaction Questionnaire were assessed as the primary efficacy end point in the applicator user (AU) group (investigators) in Study P05702. Generally, as users completed more insertions more users reported being “very satisfied” and fewer users reported being “very dissatisfied,” “dissatisfied,” and “not satisfied nor dissatisfied” based on assessments of design and technical aspects, functionality, safety, used time, and applicator satisfaction. The expected and actual treatment satisfaction for patients treated with the radiopaque etonogestrel implant was assessed in Study P05702. However, aggregate efficacy results were not available and could not be assessed for this review.

Health-related quality of life (HRQoL), an important outcome to patients, was not evaluated in the pivotal studies.

Harms Results

Adverse events were experienced by almost all patients (90.4% to 100.0% based on data from studies P05702 and 34528). Total AEs are a key harms measure and were not reported in the integrated analysis.

Bleeding irregularities were identified by the clinical expert consulted for this review as harms that were important to patients. When examined collectively, bleeding irregularities were the greatest source of AEs across the trials. However, an aggregate measure of AEs related to bleeding irregularities was not reported in any of the studies. The severity of bleeding (mild, moderate, or severe) was also not reported. Specific bleeding-related AEs (including dysmenorrhea, menorrhagia, metrorrhagia, vaginal hemorrhage, and genital hemorrhage) occurred in 5.3% to 28.2% of patients treated with the radiopaque etonogestrel implant in Study P05702, and in 3.8% to 46.2% and 7.1% to 41.1% of patients treated with the radiopaque and non-radiopaque etonogestrel implants, respectively, in Study 34528. A publication related to the integrated analysis reported bleeding patterns for a subset of 780 patients (82%) at two years.[10] Specific bleeding irregularities (including amenorrhea, infrequent, frequent, and/or prolonged bleeding) occurred in 6.7% to 33.6% of patients.[10]

In the integrated analysis, serious adverse events (SAEs) occurred in 5.9% of patients treated with the non-radiopaque etonogestrel implant. In Study P05702, 5.3% of patients treated with the radiopaque etonogestrel implant experienced an SAE, while SAEs occurred similarly for patients treated with the radiopaque (7.7%) and non-radiopaque etonogestrel implant (10.7%) in Study 34528. None of the patients in studies P05702 or 34528 experienced SAEs related to bleeding, although one patient per arm in Study 34528 experienced an SAE related to deep vein thrombosis. In the integrated analysis, one patient experienced an SAE related to the category “platelet, bleeding, and clotting disorder.”

In the integrated analysis, 13.6% of patients stopped treatment due to AEs, with the most common reason attributed to bleeding irregularities (11.1%). In Study P05702, 35.2% of patients treated with the radiopaque etonogestrel implant stopped treatment due to an AE, with bleeding irregularities accounting for 19.3% of the withdrawals. The percentages of patients who stopped treatment due to AEs were similar for those treated with the radiopaque (28.8%) and non-radiopaque etonogestrel implant (30.4%) in Study 34528. Bleeding irregularities accounted for 19.2% of patients treated with the radiopaque etonogestrel implant and 14.3% of patients treated with the non-radiopaque etonogestrel implant. One case of “mild” implant migration was reported.

Table 1: Contraceptive Efficacy, Overall Pearl Index

	Total N			Contraceptive efficacy		
		28-day cycles	Exposure (woman-years)	Pregnancies, n (%)	Overall Pearl Index (95% CI)	P value
Integrated analysis						
Non-radiopaque etonogestrel implant[a]	923	23,883	1,832	0	0 (0 to 0.20)	NA[b]
P05702 (AST)						
Radiopaque etonogestrel implant[c]	301	8,543.9	655.0	0	0 (0 to 0.56)	NA[b]
34528 (AST)						
Radiopaque etonogestrel implant[d]	52	1,585.1	121.5	0	0 (0 to 3.04)	NA[b]
Non-radiopaque etonogestrel implant[d]	56	1,574.3	120.7	0	0 (0 to 3.06)	NA[b]

AST = all subjects treated; CI = confidence interval; NA = not applicable.

[a] Overall Pearl Index calculated for the in-treatment pregnancies.

[b] No statistical testing hierarchy specified in this study.

[c] Overall Pearl Index calculated for the in-treatment pregnancies together with the exact 95% CIs based on a Poisson distribution for the AST population, where in-treatment pregnancies were pregnancies with an estimated date of conception from the day of implant insertion up to and including the day of implant removal extended with a period of 14 days.

[d] Two-sided 95% CI for Pearl Index was calculated by assuming underlying Poisson distribution for the AST population, where in-treatment pregnancies were pregnancies with an estimated date of conception occurring before removal. If Pearl Index = 0 (no pregnancies), an upper confidence limit of 97.5% was used.

Source: Common Technical Document Section 2.5,[11] Clinical Study Reports for P05702[12] and 34528.[13]

Table 2: Summary of Harms

	Integrated analysis (general safety dataset)	P05702 (AST)	34528 (AST)	
	Non-radiopaque etonogestrel implant (N = 942[a])	Radiopaque etonogestrel implant (N = 301)	Radiopaque etonogestrel implant (N = 52)	Non-radiopaque etonogestrel implant (N = 56)
Patients with ≥ 1 serious adverse event				
n (%)	53 (5.9)	16 (5.3)	4 (7.7)	6 (10.7)
Patients who stopped treatment due to adverse events				
n (%)	128 (13.6)	106 (35.2)	15 (28.8)	17 (30.4)
Deaths				
n (%)	0	0	0	0
Notable harms, n (%)				
Vascular disorders	12 (1.3)	8 (2.7)	3 (5.8)	2 (3.6)
Deep vein thrombosis	0	NR	1 (1.9)	1 (1.8)
Peripheral arterial occlusive disease	NR	NR	1 (1.9)	0
Vein disorder	NR	NR	0	1 (1.8)
Neoplasms benign, malignant, unspecified	NR	9 (3.0)	3 (5.8)	2 (3.6)
Benign breast neoplasm	2 (0.2)	2 (0.7)	0	2 (3.6)

	Integrated analysis (general safety dataset)	P05702 (AST)	34528 (AST)	
	Non-radiopaque etonogestrel implant (N = 942[a])	Radiopaque etonogestrel implant (N = 301)	Radiopaque etonogestrel implant (N = 52)	Non-radiopaque etonogestrel implant (N = 56)
Breast ductal carcinoma	1 (0.1)	NR	NR	NR
Weight increase	129 (13.7)	35 (11.6)	4 (7.7)	8 (14.3)
Bleeding irregularities[c]	NR	NR	NR	NR
Dysmenorrhea	NR	16 (5.3)	6 (11.5)	4 (7.1)
Menorrhagia	NR	31 (10.3)	2 (3.8)	9 (16.1)
Metrorrhagia	NR	53 (17.6)	9 (17.3)	9 (16.1)
Vaginal hemorrhage	NR	85 (28.2)	21 (40.4)	18 (32.1)
Genital hemorrhage	NR	NR	24 (46.2)	23 (41.1)
Bone mineral density	0	NR	NR	NR
Implant migration	NR	1 (0.3)[d]	NR	NR
Liver function	0	NR	NR	NR
Serum lipids	0	NR	NR	NR
Suicide risk	NR	NR	NR	NR
Emotional or affect lability	61 (6.5)	2 (0.7)	1 (1.9)	1 (1.8)
Mood altered	NR	14 (4.7)	1 (1.9)	1 (1.8)
Depression	NR	11 (3.7)	1 (1.9)	2 (3.6)

AST = all subjects treated; NR = not reported.

[a] Safety data includes data from 16 breastfeeding women and three patients with no post-baseline assessments.

[b] In this section, the US study is presented separately because the predefined choices of reasons for discontinuation in this study differed from the other studies.

[c] Adverse event aggregate data on bleeding irregularities are not reported.

[d] Implant migration classified as “mild,” no definition provided.

Source: Common Technical Document Section 2.5,[11] Darney et al.,[14] Clinical Study Reports for P05702[12] and 34528.[13]

Critical Appraisal

All three studies assessed contraceptive efficacy; however, only the integrated analysis was designed to evaluate contraceptive efficacy. The individual studies contributing to the integrated analysis were not required to have contraceptive efficacy because the primary end point and only single-arm data for those treated with the non-radiopaque etonogestrel implant were included in the integrated analysis. No adjustments were made for missing data. The integrated analysis was also limited by uncertainty surrounding its methodology and sparse reporting of baseline demographics and characteristics. Study P05702 was limited by the single-arm, open-label study design and the absence of a formal power calculation and statistical assessments for efficacy outcomes.

Across all trials, discontinuations were high, with 35.0% to 48.2% of patients discontinuing the trials over the three-year duration, with most discontinuations attributed to bleeding irregularities and other AEs. The number of discontinuations raises questions about study validity and ability to interpret the results. Theoretically, the three-year duration of the studies was sufficient to determine the effectiveness of etonogestrel. However, the number of discontinuations should be considered when assessing the actual treatment time. Many

patients discontinued the trials in year 1 and year 2, and some of the included trials in the integrated analysis were only two years in duration.

To be included in the studies, women had to be between 18 and 40 years of age. This excludes adolescents and women older than 40 years who would be potentially treated in clinic according to the clinical expert consulted for this review. Based on the three studies, it is unclear if contraceptive efficacy and safety would be different for these subgroups. Additionally, the three studies had inclusion criteria based on "ideal body weight" (integrated analysis) or body mass index (BMI) (studies P05702 and 34528) that excluded women who exceeded 130% of their ideal body weight or had a BMI greater than 35 kg/m^2. The external validity of the studies is limited, as women who do not meet these body measurement criteria would potentially be seen in clinic. Studies P05702 and 34528 required patients to have "good physical and mental health." These criteria are problematic as they are not defined (left to the investigator's discretion), highlighting another feature of the trials that reduces generalizability, as patients not meeting these criteria would potentially be treated in the Canadian clinical setting. All trials had inclusion criteria based on patients having regular menstrual cycles, reducing generalizability of the trials, as patients with irregular menstrual cycles would potentially be included in the patient population in the Canadian clinical setting. Based on results from studies P05702 and 34528, almost all patients included in the two studies were White, which is not representative of the Canadian population. It is unclear if there are differences in efficacy or safety of the etonogestrel implant based on race. Collectively, these eligibility criteria reduce the generalizability to the Canadian clinical population.

Study 34528 was limited by generalizability issues related to the choice of applicator, as all implants (non-radiopaque and radiopaque etonogestrel) were administered using the original applicator associated with the non-radiopaque etonogestrel formulation in an effort to maintain blinding. This is problematic because this applicator is not consistent with the next-generation applicator associated with the radiopaque etonogestrel implant that is expected to be marketed in Canada. The original applicator used in Study 34528 has been associated with AEs (e.g., implant migration) that may not be present with the next-generation applicator.

Other Relevant Evidence

Description of Studies

Four studies were identified that evaluated radiopaque etonogestrel implant use in subgroups indicated as clinically relevant by the clinical expert consulted for this review.[15-18] One study, while observational in design, was summarized because it assessed quality of life, an outcome reported to be important to patients that was not assessed in the pivotal trials.[15] A meta-analysis and two randomized controlled trials (RCTs) assessed radiopaque etonogestrel implant use following immediate versus delayed insertion of the implant in clinically relevant subgroups of patients.[16-18]

One observational study assessed quality of life in 140 patients who received contraceptive counselling on the etonogestrel implant after an abortion for an unplanned pregnancy at 36 weeks.[15] Patients received treatment with the etonogestrel implant or a control (a short-acting contraceptive or non-hormonal contraceptive). The etonogestrel implant was placed on the day of pregnancy termination. Women in the control group who chose to use a short-acting contraceptive method received the prescription at discharge from the hospital.

Quality of life using the Short Form (36) Health Survey (SF-36) and patient satisfaction were assessed.

A systematic review and meta-analysis used data from three RCTs to examine the timing of administration of the etonogestrel implant in patients undergoing medical abortion with mifepristone and misoprostol.[16] Subsequent unintended pregnancies were assessed at three and six months.

The RCT by Byrant et al.[17] investigated the timing of implant insertion in 96 adolescents and young women (14 to 24 years of age) immediately post-partum (i.e., prior to hospital discharge) or delayed (i.e., at the six-week post-partum visit). The primary outcome was contraceptive implant use at 12 months post-partum.

The RCT by Cowett et al.[18] investigated the timing of implant insertion in 148 adult women following an abortion immediately after a dilation and evacuation (D&E) procedure (immediate group), or two to four weeks after a D&E procedure (delayed group). The primary outcome was implant use rate at six months after insertion.

Results

In the observational quality-of-life study, patients in both the etonogestrel and the control groups experienced statistically significant improvements in all physical and mental health subsections of the SF-36 (physical function, physical role, bodily pain, general health, vitality, mental health, social function, emotional role) at 36 months compared to baseline ($P < 0.0001$). Patients in the etonogestrel implant group reported significantly greater improvement compared with the control group ($P < 0.0001$). Of the women treated with the etonogestrel implant, 53 (74.6%) reported they were “very satisfied” with the etonogestrel implant, 12 (16.9%) were “quite satisfied,” and six (8.5%) were “neither satisfied nor dissatisfied.” At 36 months, data were available from 71 patients in the etonogestrel arm (82.6%) and 23 patients in the control arm (42.6%).

In the systematic review and meta-analysis, there was decreased risk of subsequent unintended pregnancy for patients with simultaneous administration of mifepristone and the etonogestrel implant compared with etonogestrel implant administration more than 24 hours after mifepristone at three months (0 of 277, 0% versus 4 of 261, 1.53%; risk ratio = 0.10; 95% CI, 0.01 to 1.94, $P = 0.13$) and at 6 months (3 of 490, 0.61% versus 13 of 474, 2.74%; risk ratio = 0.22; 95% CI, 0.06 to 0.78; $P = 0.02$).

For the RCT by Byrant et al.[17] there was no difference in implant use in adolescents and young women post-partum at 12 months for the immediate group compared with the delayed group (30 of 37, 81% versus 21 of 27, 78%; $P = 0.74$).

For the RCT by Cowett et al.,[18] use of the implant at six months was higher for adult women following an abortion in the immediate group compared with the delayed group (54.5% versus 25.3%; $P < 0.01$).

Critical Appraisal

The baseline characteristics were generally well-balanced between groups in the observational quality-of-life study with the exception of previous elective abortion for patients with three previous abortions, which was greater in the etonogestrel arm (31.4%) compared to the control arm (9.3%). The socioeconomic status of patients at baseline was not directly compared, but 40.7% of women declined the implant at enrolment due to

financial reasons. This difference, coupled with the observational nature of the study, is likely to have created two very different populations that may have differed on other unmeasured confounding factors. The study population included women younger than 18 years, including patients as young as 16, but a subgroup analysis on these patients was not performed. Discontinuation of the study was greater in the control arm (57.4%) compared with the etonogestrel arm (17.4%), with several discontinuations attributed to unintended pregnancies. The differential discontinuation is likely to bias the scores because those who remained in the study are expected to be more satisfied (i.e., have higher scores on the SF-36) than those who discontinued. In addition, the SF-36 scores were not presented in a table, which made it difficult to compare individual results between arms and assess the clinical significance of the results.

The systematic review was generally well performed. However, the review was limited by the use of a single reviewer for the initial literature screening and data extraction. The methods for performing the meta-analysis were sufficient, with clear criteria based on I^2 values specified for guiding the choice of a fixed- or random-effect model. Risk of bias was assessed to be low for the included studies. Sensitivity analyses could not be performed based on limited data.

For the RCT by Byrant et al.,[17] randomization allowed for well-balanced groups, although the sample size was small (n = 48 in each arm). Given that this study was only conducted at one American site, the generalizability to young Canadian women is unknown. Because the results of this study were limited by a small sample size and high loss to follow-up (LTFU) rates, the study was unable to demonstrate a benefit of immediate implant insertion in young women post-partum.

For the RCT by Cowett et al.,[18] randomization allowed for well-balanced comparator groups, and blinding was maintained until after the D&E procedure. Additionally, the study was conducted at a single American centre; therefore, the generalizability to the Canadian population is unknown. The results of the study were also limited by high LTFU rates; 57.3% of women allocated to the delayed-insertion group did not return for implant insertion. Furthermore, 41.1% of participants in the immediate group and 31.3% of participants in the delayed group who received an implant were lost to follow-up by the study completion time (six months post-procedure). Given that the women were receiving interim contraception, it is not known whether women did not return for implant insertion because they were satisfied with their interim contraceptive method, or if they were not using a method at all. Furthermore, using an interim contraceptive method may not be representative of real-world practice. Only eight women (18.6%) who did not return for the implant were contacted at six months and confirmed they were not using the implant, while the remainder were determined LTFU. Sensitivity analysis was not performed; therefore, the effect of the LTFU patients on the primary outcome, which is expected to have a significant effect, was not explored.

Conclusions

Data from three studies suggest that etonogestrel implants are effective in preventing pregnancies in healthy women treated with the radiopaque or non-radiopaque etonogestrel implant over the course of three years. The radiopaque and non-radiopaque formulations of etonogestrel were bioequivalent with respect to parameters in accordance with guidance from Health Canada. The three reviewed studies demonstrated similar and potentially increased frequencies of bleeding irregularities with the etonogestrel implant. There was insufficient evidence to assess the effects of radiopaque etonogestrel implant on quality of life and patient satisfaction.

Key limitations across all studies included concerns about generalizability as the study participants were a selective group when compared to all women of child-bearing age who could potentially receive etonogestrel, and high discontinuation rates often related to bleeding irregularities. The generalizability of the study findings to clinical practice settings in Canada was limited by eligibility requirements that excluded certain patients, including adolescents, patients older than 40 years, those with irregular menstrual cycles, and patients with a BMI greater than 35 kg/m^2. Evidence gaps include an absence of direct and indirect comparisons to relevant contraceptives used in Canada, and the efficacy of the radiopaque etonogestrel implant in subgroups of patients that were excluded in the trials.

Due to critical limitations with the studies on quality of life and the relevant subgroups of patients (post-partum women and young women), the interpretation of the results of these studies was challenging and limited at best.

Introduction

Disease Background

Contraception plays an important role in the reproductive lives of women. In Canada, women are at risk of an unintended pregnancy for a substantial portion of their life.[1] The SOGC states that LARC methods (including contraceptive implants and intrauterine contraception) are the most effective reversible contraceptive methods and have the highest continuation rates.[1] Yet, in Canada, the most common contraceptive methods are condoms (54.3%), oral contraceptives (43.7%), and withdrawal (11.6%).[3] In sexually active women, 14.9% use no contraception and 20% use contraception inconsistently.[3] Data from 2006 and 2016 indicate a decrease in the use of oral contraceptives and an increase in the use of condoms.[2] Misinformation related to the types of contraceptives available and their effectiveness may limit women's ability to choose an appropriate method of contraception.[2] The clinical expert consulted for this review reported that patients are generally concerned with the side effects of contraception typically relating to risk of cancer, stroke, irregular periods, weight gain, sexual discomfort, low libido, and spontaneity. With combined pills, some patients have difficulty remembering to take the medication.

According to the SOGC, one in five Canadian women of reproductive age had an unplanned pregnancy in 2016; one in three of these women reported having an abortion.[2] In a national Canadian study, half the women who reported unintended pregnancies in 2016 were using a method of birth control, which may indicate contraception misuse or failure.[2] Underutilization of effective contraceptive methods is particularly pronounced for vulnerable women, including those from low-income families, lower levels of education, and immigrants.[1,3] Access and adherence issues associated with various contraceptives can also contribute to unintended pregnancies; some of these issues may relate to cost, availability, difficulty remembering to take oral contraceptives, difficulty anticipating sexual events, and lack of education.

Throughout their reproductive life, a third of Canadian women will have an induced abortion.[4] Approximately half of all abortions occur in women between 20 to 29 years of age.[4] A total of 94,030 induced abortions were reported in Canada in 2017 based on data available to the Canadian Institute for Health Information.[5] The actual number of abortions may be underestimated because the data obtained were incomplete for some provinces, and partially based on clinic data where reporting is voluntary. The Canadian data on unplanned pregnancies and abortions demonstrate the substantial burden to the Canadian health care system and the unmet need for effective contraception, particularly for vulnerable women, and those in their twenties.

Standards of Therapy

The choice of contraception used by women is typically made during a counselling session with a health care provider. In Canada, most clinicians follow SOGC clinical practice guidelines on contraception. Contraceptive choices are influenced by several factors that differ on an individual basis. In clinic, the clinician considers an assessment of fit; this includes the woman's views on contraception, what their future fertility plans are, and whether they want permanent contraception (male or female sterilization). The ideal method of contraceptive may differ throughout the patients' reproductive life.

Canadian women had access to only 35% of all contraceptive products available worldwide; comparatively, women in the US had access to 52%.[19] Based on data from a 2006 national survey, common methods of contraception included use of condoms only (54.3%), oral contraceptives (43.7%), withdrawal (11.6%), and LARCs, such as IUDs and implants (4.3%).[3] Other, less common, options for contraception include barriers (female condom, sponge, spermicide, and diaphragm), hormonal methods (patch, ring and injection), fertility awareness (basal temperature monitoring, calendar method, and cervical mucus method), and permanent surgical sterilization (tubal ligation and vasectomy).[3]

Latex condoms used consistently and correctly provide protection against pregnancy and sexually transmitted infections. However, no barrier contraceptive method can provide 100% protection from all STIs. Non-latex male condoms have increased incidences of breakage and slippage.[20]

Oral contraceptives are highly effective with perfect use; typical use failure rates for oral hormonal contraceptives, including the combined oral contraceptive pill, are as high as 9%.[20] Use of oral contraceptives do not provide protection against sexually transmitted infections. Oral contraceptives are associated with increased risk of venous thromboembolism and stroke,[20] and AEs such as spotting, weight gain, and mood changes.

The SOGC states that LARCs (including contraceptive implants and intrauterine contraception) are the most effective reversible contraceptive methods and have the highest continuation rates. Currently in Canada, the only LARCs available are copper-and-progestin IUDs.[1] The AEs associated with IUDs generally occur at the time of insertion and include risk of infection at insertion, pain, perforated uterus, and ectopic pregnancies. LARCs in the form of implants (e.g., non-radiopaque etonogestrel) are available in other countries.

Drug

The radiopaque etonogestrel implant is a long-acting hormonal contraceptive containing 68 mg of etonogestrel indicated for the prevention of pregnancy. The dosing recommendations are for a single implant that is inserted subdermally in the upper (non-dominant) arm and can be left in place for three years. The implant is a sterile, single-rod progestin contraceptive that is individually preloaded in a stainless-steel needle of a disposable applicator. The implant consists of a semi-rigid plastic rod composed of ethylene vinyl acetate measuring 40 mm by 2 mm, and contains 68 mg of the progestin etonogestrel (the 3-keto derivative of desogestrel). The implant is inserted using a unique preloaded disposable applicator. The implant should be inserted and removed by a trained health care professional familiar with the use of the implant. If the implant is not palpable at any time, it should be localized and removed as soon as medically appropriate to manage the risks of migration.

Etonogestrel is released over three years. The release rate is approximately 60 mcg/day to 70 mcg/day in weeks 5 and 6 and decreases to approximately 35 mcg/day to 45 mcg/day at the end of the first year, to approximately 30 mcg/day to 40 mcg/day at the end of the second year, and to approximately 25 mcg/day to 30 mcg/day at the end of the third year. The implant should be removed no later than three years after the date of insertion. The implant also contains barium sulphate so that the implant can be seen by X-ray or other imaging tools.

Etonogestrel is the biologically active metabolite of desogestrel, a progestin widely used in oral contraceptives. Etonogestrel binds with high affinity to progesterone receptors in target organs. The contraceptive effect of etonogestrel is achieved primarily by the inhibition of ovulation. Etonogestrel also causes changes in the cervical mucus, which hinders the passage of spermatozoa.

The non-radiopaque predecessor to the radiopaque etonogestrel implant is not available in Canada. The radiopaque etonogestrel implant differs from the non-radiopaque etonogestrel implant according to the following distinctions:

1. The radiopaque etonogestrel extended-release subdermal implant contains a small amount of barium sulphate so that the implant can be seen by X-ray or other imaging tools.[6]
2. The radiopaque etonogestrel extended-release subdermal implant comes with a new applicator that has been designed to facilitate correct subdermal insertion.[6]

The key characteristics of the radiopaque etonogestrel implant and other LARCs are provided in Table 3.

Table 3: Key Characteristics of Nexplanon, Mirena, and Kyleena

	Radiopaque etonogestrel implant (Nexplanon)	Levonorgestrel (Mirena)	Levonorgestrel (Kyleena)
Mechanism of action	• A metabolite of desogestrel (a progestogen) • Inhibition of ovulation and changes in the cervical mucus	• Consists of a small polyethylene T-shaped frame with a cylindrical reservoir containing levonorgestrel around the vertical arm of the T frame • Produces a strong antiproliferative effect on the endometrium and causes a thickening of the cervical mucus which prevents passage of sperm through the cervical canal • Inhibits ovulation in some women	• Consists of a small polyethylene T-shaped body with a cylindrical reservoir containing levonorgestrel around the vertical stem of the T body • The vertical stem located close to the horizontal arms contains a silver ring to aid in detection by sonography • Mainly local progestogenic effects in the uterine cavity
Indication[a]	Prevention of pregnancy	Contraception control for up to 5 years	Contraception control for up to 5 years
Route of administration	Subcutaneous implant	Intrauterine system	Intrauterine system
Recommended dose	1 implant (containing 68 mg of etonogestrel) removed no more than 3 years after insertion	1 intrauterine system (containing 52 mg of levonorgestrel) for up to 5 years	1 intrauterine system (containing 19.5 mg of levonorgestrel) for up to 5 years
Serious adverse effects or safety issues	• Implant should be inserted and removed by a health care professional familiar with use of the implant. All health care professionals should receive instruction and training prior to performing insertion and/or removal • If at any time the implant is not palpable by the health care	• Uterine perforation may occur with the use of intrauterine contraceptives • Hormonal contraceptives do not protect against STIs • Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels	• Uterine perforation may occur with the use of intrauterine contraceptives • Hormonal contraceptives do not protect against STIs • Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels

	Radiopaque etonogestrel implant (Nexplanon)	Levonorgestrel (Mirena)	Levonorgestrel (Kyleena)
	professional or the patient, the implant should be localized as soon as possible and removed as soon as medically appropriate to manage the risks of migration • Hormonal contraceptives do not protect against STIs		

STI = sexually transmitted infection.

[a] Health Canada indication.

Source: Product monographs for Nexplanon,[8] Mirena,[21] and Kyleena.[22]

Stakeholder Engagement

Patient Group Input

No patient input was received for this CDR.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by one clinical specialist with expertise in obstetrics and gynecology.

Description of the Current Treatment Paradigm

Contraception use in Canada is increasing. At least one-third of Canadian women will have an induced abortion over their reproductive lifespan and there is a decline in birth rates for women younger than 30 years. More than 80,000 abortions are performed in Canada annually and predominantly in women 20 to 24 years old.[23] In women of reproductive age, 14.9% use no contraception and 20% use contraception inconsistently. The most common contraception methods used by Canadian women are oral contraceptive pills (44%), condoms only (54%), the withdrawal method (12%), and LARCs such as IUDs and implants (4.6%).[23] Other options for contraception include barriers (female condom, sponge, spermicide, and diaphragm), hormonal (patch, ring, and injection), fertility awareness (basal temperature monitoring, calendar method, and cervical mucus method), and permanent surgical sterilization (tubal ligation and vasectomy). The choice of contraception requires assessing the “fit” for the patient — they must choose something that is acceptable to them and sometimes that might include what their partner thinks. Different modes of contraception may be necessary throughout a woman’s reproductive life. Canadian women have access to approximately 35% of all the contraceptive products available worldwide (compared to 52% in the US).[19] The single-rod implant LARC is approved in 85 countries but is not yet accessible to Canadians.

There are several challenges for patients using contraceptives. First, adherence can be challenging. It can be difficult to anticipate a sexual event, publicly acquire the desired

method, discuss contraception with a partner, and use the method correctly. As the most efficacious reversible contraception option, LARCs resolve many of these challenges. A second issue for patients is access to different options, and LARCs in particular. Barriers include attempting to find a health care provider to counsel and prescribe the desired method and financial barriers for the cost of contraception. Contraceptives that are the most effective (i.e., LARCS) tend to have higher upfront costs for patients.

Treatment Goals

The most important goal of contraception is an effective and reliable method for the prevention of pregnancy that is reversible and allows for rapid return to fertility once the contraceptive is discontinued. The ideal treatment should be easy for patients to access and adhere to and have minimal side effects.

Unmet Needs

Condoms and oral contraceptive pills are not as effective or reliable as IUDs. The challenge with IUDs is that they require clinical expertise to insert correctly that can be very uncomfortable for some patients: a speculum must be inserted into the vagina, the cervix grasped with a sharp instrument, the size of the uterus is measured, and then the IUD inserted. Once the IUD is inserted, the patient must return four weeks later for another vaginal exam to confirm placement. The patient is then responsible for performing self-vaginal and self-cervical exams intermittently to ensure that they can feel the IUD strings that confirm placement. An alternative treatment is needed that is equally as effective, less uncomfortable to administer, and easier for patients to access.

Place in Therapy

The etonogestrel implant could be used first-line for the prevention of pregnancy in patients who want this option for contraception. The implant may be particularly useful for younger women, who may not need a speculum exam until they are 21 (the age for a first Pap test). Patients who prefer a reliable, discrete, and effective option that does not require recall to use correctly have the choice of an IUD or implant.

Patient Population

Patients best suited for treatment with the radiopaque etonogestrel implant include any patient who wants a LARC. Patients at higher risk of unwanted pregnancies and patients with special circumstances (e.g., physical or cognitive challenges) would be well suited to this method of contraception.

Patients need to self-identify as desiring a mode of contraception to be considered for treatment with the implant. Preventing pregnancy is not a medical condition; therefore, it does not require a diagnosis, laboratory testing, or any diagnostic tool. Patients would need contraceptive counselling to discuss options for treatment to ensure there are no contraindications to different options. Part of this discussion will include how concerned they would be if they “accidentally” got pregnant, as in would it be inconvenient but not terrible or would their quality of life be severely negatively impacted. If the former, then a less-effective option could be considered, but if the latter, the best reversible option should be offered, such as an IUD or implant.

Patients not suitable for treatment with the radiopaque etonogestrel implant are those with contraindications or those who desire pregnancy.

Assessing Response to Treatment

Pregnancy and discontinuation rates are outcomes used in both clinical practice and clinical trials. Patients who do not become pregnant during treatment would be considered a clinically meaningful response to treatment with contraceptives. The treatment response should be assessed for most patients at the end of the three-year duration of the treatment course.

Discontinuing Treatment

Patients may choose to discontinue treatment (i.e., have the implant removed) if they desire pregnancy, are no longer sexually active, or no longer require contraception. Patients may discontinue treatment for reasons related to AEs such as bleeding, mood symptoms, weight changes, and headaches. The diagnosis of other medical conditions, such as progesterone-receptor–positive breast cancer, may cause patients to discontinue treatment.

Prescribing Conditions

The radiopaque etonogestrel implant does not require a specialist to administer. Insertion and removal of the implant can be performed in any outpatient clinic by a family physician, nurse practitioner, or gynecologist.

Additional Considerations

Training should be required for the health care provider, who will need to learn to properly insert and remove the implant. There may also be complications with the implant, such as migration and difficulties with removal.

Clinical Evidence

The clinical evidence included in this review of the radiopaque etonogestrel extended-release subdermal implant is presented in three sections. The systematic review includes pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of radiopaque etonogestrel extended-release subdermal implant, 68 mg, for the prevention of pregnancy in women.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Female patients of reproductive age at risk of pregnancy Subgroups: • Body mass • Breastfeeding mothers • Women advanced in reproductive years (older than 40) • Adolescents • Post-abortion • Perfect versus typical use of contraceptive
Intervention	Etonogestrel extended-release subdermal implant, 68 mg, radiopaque
Comparators	Non-hormonal contraceptives: • Male condom • Female condom • Diaphragm • Sponge • Cervical cap • Withdrawal • Fertility awareness • Spermicide Hormonal contraceptives: • Oral contraceptives • Transdermal patch • Vaginal ring • Injectable contraceptive • Intrauterine contraceptive (progesterone-releasing) Other: • Intrauterine contraceptive (copper-releasing) • Male sterilization • Female sterilization
Outcomes	**Efficacy outcomes:** • Pregnancy[a] (e.g., Pearl Index) • Return to ovulation • Contraceptive discontinuation • HRQoL[a] • Palpation • X-ray imaging • Drug insertion and/or removal characteristics • Patient satisfaction • Clinician satisfaction **Harms outcomes:** • AEs • SAEs • WDAEs • Mortality Notable harms: thromboembolic disorders, arterial thromboembolic disorders, hormone-dependent tumours, weight gain,[a] "spotting" or troublesome bleeding,[a] bone mineral density,[a] implant migration,[a] liver function, serum lipids, suicide risk, mood,[a] depressive symptoms.
Study design	Published and unpublished phase III and IV RCTs

AE = adverse events; HRQoL= health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

[a] Outcomes identified as important to patients according to the clinical expert consulted for the review. No direct patient input received for this review.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[24]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was etonogestrel. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

Search filters were applied to limit retrieval to RCTs or controlled clinical trials. Retrieval was not limited by publication date or language. Conference abstracts were excluded from the search results. See Appendix 1 for detailed search strategies.

The initial search was completed on October 25, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on September 16, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[25] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

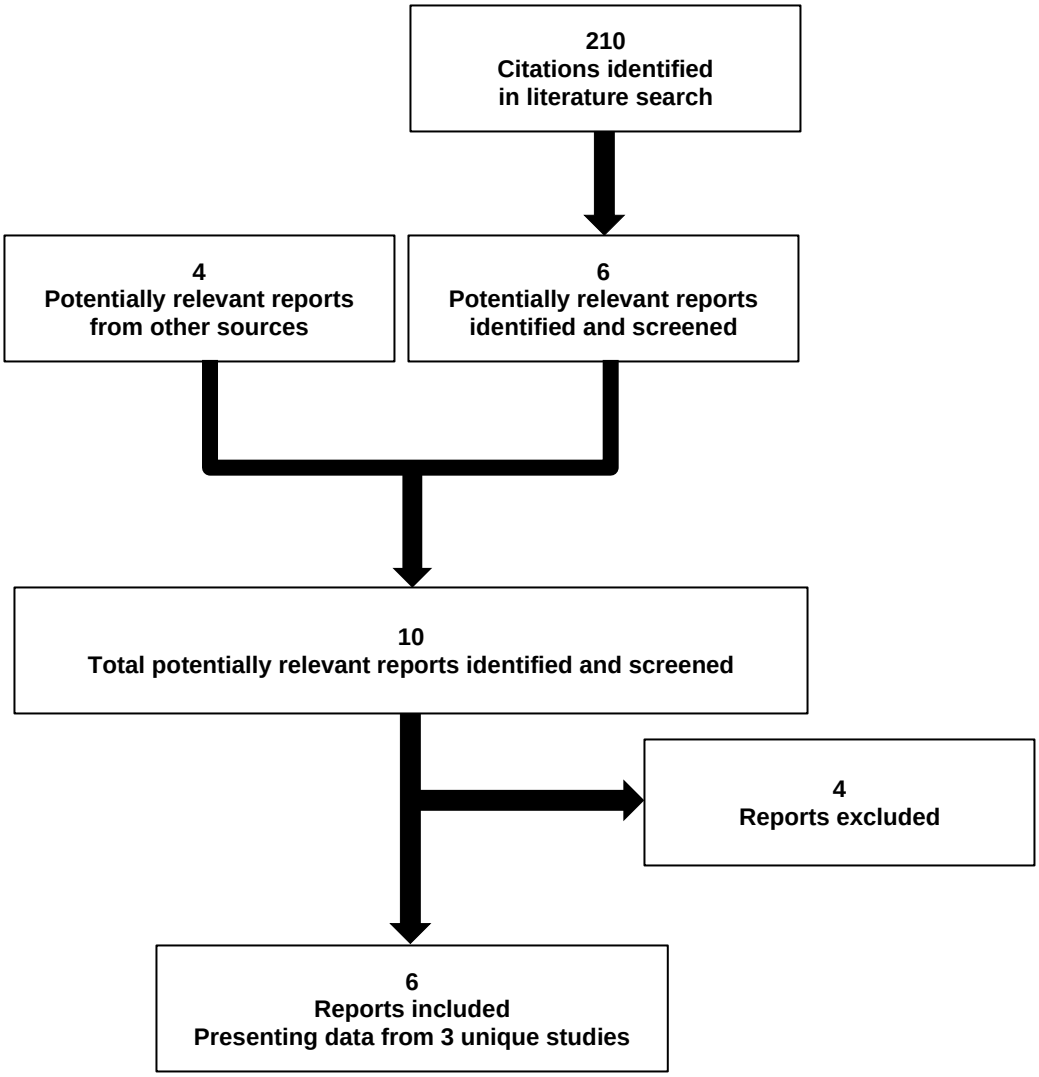

Table 5: Details of Included Studies

		Integrated analysis (non-radiopaque etonogestrel implant)	Study P05702	Study 34528
Designs and Populations	**Study design**	Integrated analysis based on pooled dataset	Open-label, non-comparative	Double-blind RCT, parallel-group, bioequivalence
	Locations	Chile, Europe, Russia, Southeast Asia, US	Australia, Germany, France, UK, Norway, Sweden	France, the Netherlands, Switzerland
	Randomized (N)	946 (treated with non-radiopaque etonogestrel implant)	301 (non-randomized)	108
	Inclusion criteria	Study inclusion: • Contraceptive efficacy evaluated • Scheduled treatment duration of at least 2 years Patient inclusion: • Women ≥ 18 and ≤ 40 years of age • Healthy, sexually active • Within 80% to 130% of their ideal body weight according to the Metropolitan Height and Weight Tables • Child-bearing potential • Normal menstrual cycles (recurring every 24 to 35 days) • Not pregnant or lactating	• Women ≥ 18 and ≤ 40 years of age • Good physical and mental health • Regular cycles with a usual length between 24 and 35 days • Body mass index ≥ 18 kg/m^2 and ≤ 35 kg/m^2	
	Exclusion criteria	Site exclusion: • Not audited or inspected • Insufficient adherence to good clinical practice Patient exclusion: • Women who were breastfeeding (excluded for efficacy analysis only) • Use of an injectable hormonal method of contraception within the preceding 6 months or other hormonal contraceptives within the preceding 2 months • Use of implantable contraception within the preceding 2 months • A delivery, abortion, or miscarriage within 2 months before study entry	• Contraindications (e.g., pregnant, active venous thromboembolic disorder) • Hypertension • A history during pregnancy or during previous use of sex steroids of jaundice and/or severe pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss	
Drugs	**Intervention**	Non-radiopaque etonogestrel implant, 68 mg	Radiopaque etonogestrel implant, 68 mg, containing 15 mg barium sulphate	Radiopaque etonogestrel implant, 68 mg, containing 15 mg barium sulphate
	Comparator	NA	None	Non-radiopaque etonogestrel implant, 68 mg
Duration	**Phase**	NA	IIIb	IIIb
	Run-in	NA	NA	NA
	Double-blind	NA	36 months (treatment period, not blinded)	36 months

		Integrated analysis (non-radiopaque etonogestrel implant)	Study P05702	Study 34528
	Follow-up	NA	3 months	3 months
Outcomes	**Primary end point**	Contraceptive efficacy	User Satisfaction Questionnaire	Bioequivalence
	Secondary and other end points		Secondary: • Insertion characteristics, time for insertion • Removal characteristics, time for removal Other: • Localization of implant • Contraceptive efficacy • Return of menses • Expected Satisfaction Questionnaire • Actual Satisfaction Questionnaires	Other: • Contraceptive efficacy • Return of menses • Palpation • X-ray imaging
Notes	**Publications**	Darney et al.,[14] Graesslin et al.,[26] Blumenthal et al.,[27] Mansour et al.[10]	Mansour et al.[28]	Schnabel et al.[29]

NA = not applicable; RCT = randomized controlled trial.

Note: Two additional reports were included: CADTH Common Drug Review submission[6] and Health Canada Reviewer Report.[7]

Source: Common Technical Document Section 2.5,[11] Clinical Study Reports for P05702[12] and 34528.[13]

Description of Studies

Three pivotal studies identified by the sponsor were included in the systematic review. Four non-pivotal studies providing relevant supplemental information were summarized in brief in the Other Relevant Studies section of the report.

The pivotal studies included an integrated analysis pertaining to the non-radiopaque etonogestrel implant[11] and two studies on the radiopaque etonogestrel implant: P05702 (a non-comparative study)[12] and 34528 (a bioequivalence study)[13]. Although the integrated analysis focused on a drug (non-radiopaque etonogestrel implant) that is not approved as a contraceptive by Health Canada, the integrated analysis will be evaluated in this review as it was identified as pivotal by the sponsor and contains the same active ingredient as the drug under review (radiopaque etonogestrel implant). Two studies evaluating radiopaque etonogestrel implant use in subgroups indicated as clinically relevant by the clinical expert consulted for this review were identified in the literature and are described in the Other Relevant Studies section of the report. The study by Byrant et al.[17] investigated the timing of implant insertion in adolescents and young women post-partum and the study by Cowett et al.[18] investigated the timing of implant insertion in adult women after an abortion procedure.

The integrated analysis included pooled data from 11 studies that included the non-radiopaque etonogestrel implant as the intervention in healthy, adult women. The objective of the integrated analysis was to present efficacy and safety results from the clinical trials that supported the FDA approval of a non-radiopaque etonogestrel contraceptive implant. Studies in the integrated analysis included patients from Chile, Europe, Russia, Southeast

Asia, and the US. The integrated analysis was based on the evaluation of 946 patients treated with the non-radiopaque etonogestrel implant and included individual studies that were performed between 1991 and 2005. Details of the 11 studies are summarized in Appendix 3.

Study P05702 was an open-label, non-comparative, single-arm, clinician satisfaction study of 301 adult women treated with the radiopaque etonogestrel implant. The primary objective of Study P05702 was to evaluate the use of the next-generation applicator and its instructions for proper insertion of the radiopaque etonogestrel implant. Study P05702 included patients from Australia, Germany, France, UK, Norway, and Sweden and took place between April 27, 2007, and October 20, 2010.

Study 34528 was a double-blind, parallel-group, bioequivalence study of 108 adult women. The study's primary objective was to demonstrate the bioequivalence of the radiopaque etonogestrel implant and the non-radiopaque etonogestrel implant. Patients were recruited from France, the Netherlands, and Switzerland. The study took place between May 23, 2005, and February 25, 2009. Patients were randomized in blocks at a 1:1 ratio by centre to treatment with the radiopaque etonogestrel implant and the non-radiopaque etonogestrel implant.

Populations

Inclusion and Exclusion Criteria

The integrated analysis, Study P05702, and Study 34528 had similar patient-eligibility criteria: women between 18 and 40 years of age with regular menstrual cycles with a usual length between cycles of 24 to 35 days. The integrated analysis specified that patients had to be healthy, sexually active, and be within 80% to 130% of their ideal body weight according to the Metropolitan Height and Weight Tables. Studies P05702 and 34528 required patients to be in good physical and mental health (based on investigator discretion) and have a BMI between 18 kg/m^2 and 35 kg/m^2. The integrated analysis required that the individual studies included contraceptive efficacy as an end point and was two years in duration. Individual sites in the integrated analysis were excluded if they were not audited or inspected, and if there was insufficient adherence to good clinical practice. Patients who were breastfeeding were excluded from the integrated analysis. Studies P05702 and 34528 excluded patients who were contraindicated (e.g., pregnant, an active venous thromboembolic disorder) or had hypertension.

Baseline Characteristics

The baseline characteristics were generally balanced between the arms of Study 34528. Across studies the mean age of patients ranged from 26.2 years to 28.2 years. Race was reported in studies P05702 and 34528 and almost all patients included in the two studies were White (94.6% to 95.3%). Across the three studies, the mean BMI ranged from 22.37 kg/m^2 to 23.79 kg/m^2. The percentage of patients with no previous pregnancies ranged from 41.2% to 69.6% based on data from studies P05702 and 34528. Table 6 summarizes the baseline characteristics for the integrated analysis, Study P05702, and Study 34528.

Table 6: Summary of Baseline Characteristics

	Integrated analysis	Study P05702	Study 34528	
	Non-radiopaque etonogestrel implant (N = 942)	Radiopaque etonogestrel implant (N = 301)	Radiopaque etonogestrel implant (N = 52)	Non-radiopaque etonogestrel implant (N = 56)
Age (years), mean (SD)	27.7 (5.4)	28.2 (6.7)	28.0 (7.2)	26.2 (6.0)
18 to 20, n (%)	86 (9.1)	43 (14.3)	11 (21.2)	12 (21.4)
21 to 25, n (%)	278 (29.5)	79 (26.2)	9 (17.3)	18 (32.1)
26 to 30, n (%)	291 (30.9)	64 (21.3)	15 (28.8)	10 (17.9)
31 to 35, n (%)	195 (20.7)	54 (17.9)	6 (11.5)	12 (21.4)
36 to 40, n (%)	92 (9.8)	61 (20.3)	10 (19.2)	4 (7.1)
41 to 45, n (%)	0	0	1 (1.9)	0
Race, n (%)				
Asian	NR	8 (2.7)	1 (1.9)	0
Black or African-American	NR	2 (0.7)	0	1 (1.8)
White	NR	287 (95.3)	50 (96.2)	53 (94.6)
Other	NR	4 (1.3)	1 (1.9)	2 (3.6)
Body mass index (kg/m^2), mean (SD)	23 (3.2)	23.79 (3.73)	22.44 (2.56)	22.37 (2.31)
Number of previous pregnancies,[a] n (%)				
0	NR	124 (41.2)	25 (48.1)	39 (69.6)
1	NR	43 (14.3)	11 (21.2)	4 (7.1)
2	NR	64 (21.3)	11 (21.2)	6 (10.7)
≥ 3	NR	70 (23.3)	5 (9.6)	7 (12.5)
Number of live births, n (%)				
0	NR	156 (51.8)	30 (57.7)	39 (69.6)
1	NR	50 (16.6)	7 (13.5)	3 (5.4)
2	NR	66 (21.97)	10 (19.2)	8 (14.3)
≥ 3	NR	29 (9.67)	5 (9.6)	6 (10.7)
Breastfeeding, n (%)				
No	NR	285 (94.7)	52 (100)	56 (100)

SD = standard deviation.

Note: Baseline characteristics for integrated analysis corresponds to “all patients treated” group.

[a] Including miscarriages and abortions.

Source: Common Technical Document Section 2.5,[11] Darney et al. (2009),[14] Clinical Study Reports for P05702[12] and 34528.[13]

Interventions

Patients in the arms of individual studies who contributed to the integrated analysis were all treated with a single-rod, non-radiopaque etonogestrel implant administered via subdermal insertion into the upper arm using a disposable applicator. The applicator used in this trial is not used in Canada and differs from the applicator associated with the drug under review. The non-radiopaque implant initially releases etonogestrel in vitro at a rate of approximately 60 mcg/day to 70 mcg/day, followed by a gradual decline to approximately 40 mcg/day,

35 mcg/day, and 25 mcg/day to 30 mcg/day at the end of the first, second, and third year, respectively. Implants were removed from patients at the end of the treatment period. Data on concomitant medication use by patients in the integrated analysis were not available. Whether all clinicians in the individual studies contributing to the integrated analysis received training on insertion and removal of the non-radiopaque etonogestrel implant was not specified.

In Study P05702, all patients were treated with a single-rod, radiopaque etonogestrel implant administered via subdermal insertion into the inner side of the non-dominant upper arm. The radiopaque etonogestrel implant was expected to perform similarly to the non-radiopaque implant, which initially releases etonogestrel in vitro at a rate of approximately 60 mcg/day to 70 mcg/day, followed by a gradual decline to about 40 mcg/day, 35 mcg/day, and 25 mcg/day to 30 mcg/day at the end of the first, second, and third year, respectively. The implant was administered using a next-generation applicator. All investigators followed a training session on proper insertion and handling of the next-generation applicator that included an instruction leaflet and video followed by two successful insertions on a training arm. Use of concomitant medications and pre-treatment known to interfere with the investigational product were not permitted and were considered major protocol violations. Implants were removed from patients at the end of the treatment period.

In Study 34528, patients were treated with a non-radiopaque etonogestrel implant or a radiopaque etonogestrel implant. The in vitro etonogestrel-release characteristics of the radiopaque rod are similar to those of the non-radiopaque rod and were described previously. Both the non-radiopaque etonogestrel implant and radiopaque etonogestrel implant were administered subdermally using the applicator designed for the original non-radiopaque etonogestrel implant.[29] Although it was specified that the investigators were trained on procedures of the clinical trial, it is unclear if they were trained on proper insertion and handling of the applicator. Implants were removed from patients at the end of the treatment period.

Outcomes

The efficacy outcomes are described and appraised in detail in Appendix 4.

Contraceptive efficacy was the primary end point in the integrated analysis and an “other” end point in studies P05702 and 34528. In the three studies reviewed, contraceptive efficacy was based on the occurrence of pregnancies with an estimated conception date within the treatment period.[11-13] To exclude pregnancy, a pregnancy test (urinary human chorionic gonadotropin) was performed directly before implant insertion (except in the case of a first-trimester abortion, as long as the implant was inserted after the abortion), at each scheduled visit, and at implant removal. Pregnancy tests were also indicated if a pregnancy was suspected outside of the indicated time points. The extent of exposure to the study drug used in the studies under review was expressed by the treatment duration and total exposure.[12,13] Treatment duration (in days) was defined as the time between the date of insertion, and the date of removal, while the total exposure was calculated in woman-years (one woman-year = 365.25 days) and the total number of 28-day cycles. In cases involving a pregnancy, all exposure following the estimated conception date was not counted in the denominator.[11-13]

Contraceptive efficacy was assessed using the PI, which calculates the failure rate for a contraceptive method per 100 woman-years by dividing the number of unplanned pregnancies (numerator) by the number of months or years of exposure to the risk (denominator). The smaller the PI, the more effective the contraceptive method. The studies assessed the overall PI (which counts the pregnancies during the period between implant insertion and removal), and the annual PI (which counts the pregnancies per year of exposure). Although the PI is the most commonly reported measure of contraceptive failure in clinical studies, it is not widely used in clinical practice.

Return of menses to normal was assessed as an "other" outcome in studies P05702 and 34528. Return of menses to normal (yes/no) was assessed three months after implant removal for women who were not pregnant, not breastfeeding, and not using post-treatment hormonal contraceptives, in which *normal* was defined as the pre-treatment menses pattern.

Palpability of the implant was assessed as an "other" outcome in studies P05702 and 34528. Palpability was assessed as palpable or not palpable.

X-ray visibility of the implant was assessed as an "other" outcome in studies P05702 and 34528. In Study P05702 a subgroup of 50 patients were scheduled for two-dimensional X-ray imaging directly after implant insertion (within one day after insertion) and before implant removal (≤ 15 days). For other patients, X-ray imaging was only to be performed if the implant was not palpable. X-ray imaging was assessed as clearly visible or unclearly/not visible.

The times for insertion and removal of the implant were assessed in the integrated analysis but not categorized as a primary, secondary, or other end point. Timing was assessed as a secondary end point in Study P05702 and as an "other" end point in Study 34528.

User satisfaction (with the radiopaque etonogestrel implant) was assessed as the primary end point in Study P05702. A User Satisfaction Questionnaire was created specifically to evaluate investigator-reported satisfaction with the technical and design, function, and safety features of the applicator, their satisfaction with the total time it takes to perform the insertion, and their overall impression of the applicator. The questionnaire consisted of five overall questions, with sub-items for selected questions, with five possible answers, ranging from very satisfied to very dissatisfied. No evidence regarding the validation, reliability, and responsiveness of the User Satisfaction Questionnaire was identified in the literature.

The expected and actual treatment satisfaction with the radiopaque etonogestrel implant was assessed in Study P05702 using two patient-reported outcome instruments: The Expected Satisfaction Questionnaire (ESQ) and Actual Satisfaction Questionnaire (ASQ). The ESQ and ASQ are 32- and 23-item questionnaires, respectively, covering six domains: physician counselling, insertion and removal of the implant, bleeding patterns, side effects, general characteristics, and overall satisfaction. Each item has five possible responses, with 1 being the most negative experience (i.e., strongly disagree) and 5 being the most positive (i.e., strongly agree).[30] Domain scores are computed by averaging the item scores and multiplying by 10. An overall total score is calculated by summing all domain scores and dividing by six. Possible total scores are between 10 and 50, with higher scores indicating higher levels of satisfaction. The validity of these questionnaires with the radiopaque etonogestrel implant is limited.[3]

Bioequivalence in Study 34528 was determined using the following end points consistent with guidance from Health Canada relating to comparative bioavailability standards:[31] C_{max} of etonogestrel and the AUC for etonogestrel at six, 24, and 36 months ($AUC_{0\text{-}6months}$, $AUC_{0\text{-}24months}$ and $AUC_{0\text{-}36months}$) after insertion assessed via blood sampling. Bioequivalence was to be concluded if the 90% CIs of C_{max}, $AUC_{0\text{-}6months}$, $AUC_{0\text{-}24months}$ and $AUC_{0\text{-}36months}$ were fully contained within the acceptance range of 0.80 to 1.25.

The following pharmacokinetic parameters used to support bioequivalence testing were calculated from the concentrations of etonogestrel using the actual sampling times.

- C_{max} and the time of its first occurrence (t_{max}): The C_{max} and t_{max} were taken from the measured serum concentration data.
- $AUC_{0\text{-}6months}$: The area under the C-t curve from zero to six months was calculated using the linear trapezoidal rule. Pre-insertion concentrations above lower limit of quantification (LLOQ) were set to zero.
- $AUC_{0\text{-}24months}$: The area under the C-t curve from zero to 24 months was calculated using the linear trapezoidal rule. Pre-insertion concentrations above LLOQ were set to zero.
- $AUC_{0\text{-}36months}$: The area under the C-t curve from zero to 36 months was calculated using the linear trapezoidal rule. Pre-insertion concentrations above LLOQ were set to zero.

Harms outcomes assessed across all trials included AEs, SAEs, patients who stopped treatment due to AEs, and deaths.

Statistical Analysis

The integrated analysis was based on a dataset that pooled data from 11 studies that supported the FDA filing for the approval of the non-radiopaque etonogestrel contraceptive implant. Data from the 11 studies on other comparators were not included in the dataset. No statistical methods were used in the pooling of the data.

In the non-comparative Study P05702, analyses were performed using Statistical Analysis Software (SAS) version 9.1.3. For continuous variables, summary statistics included mean, median, SD, minimum, and maximum. For categorical variables, frequency counts and percentages were presented. The primary efficacy end point (user satisfaction) was assessed using a frequency distribution. The assessments for palpability and X-ray visibility were presented with Clopper-Pearson two-sided 95% CIs. The PI was presented with an exact 95% CI based on a Poisson distribution. No formal sample size calculations were performed for Study P05702. However, based on a planned sample of 300 patients, the upper limit of the one-sided 95% CI was estimated at 1.0%. Subgroup analysis based on age at study entry (≤ 35 years and > 35 years) for the PI was performed. Subgroup analysis based on experienced (investigator performed more than 10 non-radiopaque etonogestrel implants within past year) and non-experienced (investigator performed 10 or fewer non-radiopaque etonogestrel implants within past year) investigators was performed for insertion and removal characteristics. Missing data for treatment duration (i.e., exposure) for patients who were lost to follow-up before removal of the implant was defined as the time between the date of insertion and the date of the last assessment.

Although Study 34528 assessed efficacy and safety outcomes as described previously, the main objective of the study was to assess bioequivalence between the non-radiopaque and radiopaque etonogestrel implants. Pharmacokinetics are not typically the focus of a CDR report; however, the study was assessed as it was identified by the sponsor. Statistical analysis was performed using SAS version 9.1.3. Bioequivalence was assessed based on etonogestrel AUC and C_{max}. Based on previous pharmacokinetic studies the coefficient of variation for C_{max} was estimated to be 36. An acceptance range of 0.80 to 1.25 was used for bioequivalence testing, which is consistent with guidance from Health Canada.[31] Bioequivalence was based on the $\log_e$-transformed values of C_{max}, $AUC_{0\text{-}6months}$, $AUC_{0\text{-}24months}$, and $AUC_{0\text{-}36months}$ and concluded if the 90% confidence limits of the parameters were fully contained within the acceptance range. In Study 34528, the sample size was calculated based on the assessment of bioequivalence. An estimated 45 patients per arm were required to achieve 80% power and detect a difference between the radiopaque and non-radiopaque etonogestrel implants.

Analysis Populations

The integrated analysis included the following two analysis datasets:

- The overall contraceptive efficacy dataset included patients who were treated with a non-radiopaque etonogestrel implant and had at least one post-baseline assessment; breastfeeding patients were excluded
- The general safety dataset included patients from the efficacy dataset with the addition of breastfeeding patients.

Study P05702 included the following analysis datasets:

- The all-subjects-assigned (ASA) group consisted of all patients who were assigned a patient number
- The all-subjects-treated (AST) group consisted of all patients who had the radiopaque etonogestrel implant inserted
- The per-protocol (PP) group consisted of all patients from the AST group without any major protocol violation
- The AU group consisted of all investigators participating in the trial who performed at least one insertion
- The per-protocol AU (PPAU) group consisted of all investigators in the AU group who did not have a major protocol violation.

Study 34528 included the following analysis datasets:

- The all-subjects-allocated group consisted of all patients who were allocated a patient number
- The all-subjects-randomized (ASR) with intention-to-treat (ITT) group consisted of all patients who were randomized
- The AST group consisted of all patients who had the investigational product
- The all-subjects-pharmacokinetically-evaluable (ASPE) group consisted of all patients who had at least one pharmacokinetic parameter that could be calculated according to the protocol and who did not have any protocol deviations interfering with pharmacokinetics.

Results

Patient Disposition

Data for the number of patients screened for the integrated analysis, Study P050702, and Study 34528 were unavailable. Discontinuations accounted for 34.9% of patients in the integrated analysis, 48.2% of patients in Study P05702, and 38.5% and 42.9% of patients in the radiopaque and non-radiopaque etonogestrel arms of Study 34528, respectively. Across all trials, the most common reasons for discontinuations were bleeding irregularities (35.0% to 48.2%) and AEs (9.6% to 16.1%). In the integrated analysis, bleeding irregularities included amenorrhea, frequent irregular bleeding, heavy menstrual flow, spotting, and other bleeding problems.[10] For studies P05702 and 34528, bleeding irregularities included frequent irregular bleeding (metrorrhagia), heavy menstrual flow (menorrhagia), prolonged menstrual flow (menorrhagia), spotting, and other bleeding problems. No patients died in any of the three trials.

Table 7: Patient Disposition

	Integrated analysis	Study P05702	Study 34528	
	Non-radiopaque etonogestrel implant	Radiopaque etonogestrel implant	Radiopaque etonogestrel implant	Non-radiopaque etonogestrel implant
Screened, N	NR	NR	NR	NR
Assigned/randomized, N	946	308	52	56
Discontinued, N (%)	330 (35.0)	145 (48.2)	20 (38.5)	24 (42.9)
Bleeding irregularities[a]	105 (11.1)	58 (19.3)	10 (19.3)	8 (14.3)
Adverse events	128 (13.5)	46 (15.3)	5 (9.6)	9 (16.1)
Lost to follow-up	21 (2.2)	4 (1.3)	1 (1.9)	1 (1.8)
Other	76 (8.0)	37 (12.3)	4 (7.7)	6 (10.7)
ASR/ITT, N (%)	NA	301 (97.7)	52 (100.0)	56 (100.0)
AST, N (%)	NA	301 (97.7)	52 (100.0)	56 (100.0)
PP, N (%)	NA	275 (89.3)	NA	NA
Efficacy dataset, N (%)	923 (97.6)	NA	NA	NA
Safety dataset, N (%)	942 (99.6)	NA	NA	NA

ASR = all subjects randomized; AST = all subjects treated; ITT = intention to treat; NA = not applicable; NR = not reported; PP = per protocol.

[a] In studies P05702 and 34528, bleeding irregularities included frequent irregular bleeding (metrorrhagia), heavy menstrual flow (menorrhagia), prolonged menstrual flow (menorrhagia), spotting, and other bleeding problems. In the integrated analysis, bleeding irregularities include amenorrhea, frequent irregular bleeding, heavy menstrual flow, spotting, and other bleeding problems.[10]

Source: Darney et al. (2009),[14] Clinical Study Reports for P05702[12] and 34528.[13]

Exposure to Study Treatments

In all trials the study drugs were administered as a single-rod implant that provided sustained delivery of etonogestrel. The implant was removed after the treatment period in each study.

The mean duration of exposure to etonogestrel in the integrated analysis was reported for 939 patients (99.3% of the ITT population). Why exposure was not calculated based on the ITT population was not reported. The total exposure was 1,869 woman-years with a mean duration of exposure of 727.1 days.

In Study P05702, the total extent of exposure was 655.0 woman-years for the AST group and 597.0 woman-years for the PP group. The mean treatment duration was 794.8 (SD = 365.1) days for the AST group and 792.9 (SD = 368.9) days for the PP group.

In Study 34528, the total extent of exposure was similar between the two treatment arms: 121.5 woman-years for the radiopaque etonogestrel implant arm, and 120.7 woman-years for the non-radiopaque etonogestrel implant arm. The mean treatment duration was 853.5 (SD = 359.8) for the radiopaque etonogestrel implant arm, and 787.1 (SD = 402.0) days for the non-radiopaque etonogestrel implant arm.

In studies P05702 and 34528, no analyses were performed on treatment compliance because it was assumed that compliance was met once the implant was successfully inserted.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below, with the exception of an additional summary of bioequivalence for Study 34528. See Appendix 3 for detailed efficacy data.

Contraceptive Efficacy

No pregnancies occurred during the treatment period (Table 8) across all three studies. The overall PI assessed as a primary end point was zero contraceptive failures per 100 woman-years (95% CI, 0 to 0.20) for the non-radiopaque etonogestrel implant in the integrated analysis during the treatment period. The overall PI (assessed as an “other” end point) was zero contraceptive failures per 100 woman-years (95% CI, 0 to 0.56) for the radiopaque etonogestrel implant in Study P05702 during the treatment period plus 14 days. In Study 34528, the overall PI (assessed as an “other” end point) during the treatment period was zero contraceptive failures per 100 woman-years (95% CI, 0 to 3.04) and zero contraceptive failures per 100 woman-years (95% CI, 0 to 3.06) in the radiopaque etonogestrel implant and non-radiopaque etonogestrel implant arms, respectively. Similar results are presented for the PI in Table 9. The ITT results were similar to the results for the AST group in Study 34528.

In all trials, patients were also assessed for pregnancy 14 days after implant removal; during this period, six pregnancies were reported in the integrated analysis, and one pregnancy was reported in 34528.

The integrated analysis included data on exposure by body weight and duration of implant use that showed 68 women weighing 70 kg or more have been exposed for over two years and 11 women for over three years without any in-treatment pregnancies.

Subgroup data in Study P05702 were available for women 35 years old or younger at screening (N = 240) where the overall PI was 0 (95% CI, 0 to 0.72) and women older than 35 years at screening (N = 61) where the overall PI was 0 (95% CI, 0 to 2.53).

Table 8: Contraceptive Efficacy, Overall Pearl Index

	n/N (%)	28-day cycles	Exposure, woman-years	Contraceptive efficacy		
				Pregnancies, n (%)	Overall Pearl Index (95% CI)	P value
Integrated analysis						
Non-radiopaque etonogestrel implant[a]	923/926 (100)	23,883	1,832	0	0 (0 to 0.20)	NA[b]
Study P05702 (AST)						
Radiopaque etonogestrel implant[c]	301/301 (100)	8,543.9	655.0	0	0 (0 to 0.56)	NA[b]
Study 34528 (AST)						
Radiopaque etonogestrel implant[d]	52/52 (100)	1,585.1	121.5	0	0 (0 to 3.04)	NA[b]
Non-radiopaque etonogestrel implant[d]	56/56 (100)	1,574.3	120.7	0	0 (0 to 3.06)	NA[b]

AST = all subjects treated; CI = confidence interval; NA = not applicable.

[a] Overall Pearl Index calculated for the in-treatment pregnancies.

[b] No statistical testing hierarchy specified in this study.

[c] Overall Pearl Index calculated for the in-treatment pregnancies together with the exact 95% CIs based on the Poisson distribution for the AST population, where in-treatment pregnancies were pregnancies with an estimated date of conception from the day of implant insertion up to and including the day of implant removal extended with a period of 14 days.

[d] Two-sided 95% CIs for Pearl Index were calculated by assuming underlying Poisson distribution for the AST population, where in-treatment pregnancies were pregnancies with an estimated date of conception occurring before removal. If Pearl Index = 0 (no pregnancies), an upper confidence limit of 97.5% was used.

Source: Common Technical Document Section 2.5,[11] Clinical Study Reports for P05702[12] and 34528.[13]

Table 9: Contraceptive Efficacy, Annual Pearl Index

	Year	n/N (%)	28-day cycles	Exposure, woman-years	Contraceptive efficacy		
					Pregnancies, n (%)	Annual Pearl Index (95% CI)	P value
Integrated analysis							
Non-radiopaque etonogestrel implant[a]	Year 1	923/923 (100)	10,866	834	0	0 (0 to 0.44)	NA[b]
	Year 2	743/923 (80.5)	8,581	658	0	0 (0 to 0.56)	NA[b]
	Year 3	533/923 (57.7)	3,441	264	0	0 (0 to 1.40)	NA[b]
Study P05702 (AST)							
Radiopaque etonogestrel implant[c]	Year 1	301/301 (100)	3,603.4	276.2	0	0 (0 to 1.34)	NA[b]
	Year 2	242/301 (80.4)	2,743.1	210.3	0	0 (0 to 1.75)	NA[b]
	Year 3	182/301 (60.5)	2,145.8	164.5	0	0 (0 to 2.24)	NA[b]
Study 34528 (AST)							
Radiopaque etonogestrel implant[c]	Year 1	52/52 (100)	617.1	47.3	0	0 (0 to 7.80)	NA[b]
	Year 2	43/5 (82.7%)	529.0	40.6	0	0 (0 to 9.10)	NA[b]
	Year 3	18/52 (34.6)	432.9	33.2	0	0 (0 to 11.12)	NA[b]

	Year	n/N (%)	28-day cycles	Exposure, woman-years	Contraceptive efficacy		
					Pregnancies, n (%)	Annual Pearl Index (95% CI)	P value
Non-radiopaque etonogestrel implant[c]	Year 1	56/56 (100)	641.9	49.2	0	0 (0 to 7.50)	NA[b]
	Year 2	44/56 (78.6)	494.2	37.9	0	0 (0 to 9.74)	NA[b]
	Year 3	23/56 (41.1)	431.9	33.1	0	0 (0 to 11.14)	NA[b]

AST = all subjects treated; CI = confidence interval; NA = not applicable.

[a] Overall Pearl Index calculated for the in-treatment pregnancies.

[b] No statistical testing hierarchy specified in this study.

[c] Two-sided 95% CI for the Pearl Index was calculated by assuming underlying Poisson distribution. If Pearl Index = 0 (no pregnancies), an upper confidence limit of 97.5% was used. In-treatment pregnancies were pregnancies with an estimated date of conception from the day of implant insertion up to and including the day of implant removal extended with a period of 14 days.

[d] Two-sided 95% CI for Pearl Index was calculated by assuming underlying Poisson distribution for the AST population, where in-treatment pregnancies were pregnancies with an estimated date of conception occurring before removal. If Pearl Index = 0 (no pregnancies), an upper confidence limit of 97.5% was used.

Source: Common Technical Document Section 2.5,[11] Clinical Study Reports for P05702[12] and 34528.[13]

Return of Menses to Normal Pattern

Return of menses to normal (pre-trial) pattern (assessed as an "other" outcome in both trials) occurred for 83.5% of patients treated with the radiopaque etonogestrel implant in Study P05702. In Study 34528, 94.4% of patients treated with the radiopaque etonogestrel implant and 90.5% of patients treated with the non-radiopaque etonogestrel implant experienced return of menses to normal (pre-trial) pattern (Table 10).

Table 10: Return of Menses to Normal (Pre-Trial) Pattern

	Yes, n/N (%)
Study P05702[a] (AST)	
Radiopaque etonogestrel implant	91/109 (83.5)
Study 34528[a] (AST)	
Radiopaque etonogestrel implant	17/18 (94.4)
Non-radiopaque etonogestrel implant	19/21 (90.5)

AST = all subjects treated.

[a] Restricted to non-pregnant subjects with post-treatment assessments who have not used (post-treatment) hormonal contraceptive methods or for whom this was unknown.

Source: Clinical Study Reports for P05702[12] and 34528.[13]

Health-Related Quality of Life

This outcome was not evaluated in the reviewed studies.

Palpability of Implant

In Study P05702, the radiopaque etonogestrel implant was palpable in 99.7% of patients after insertion and in all patients assessed (100%) at the time of implant removal (Table 11). In Study 34528, the radiopaque etonogestrel implant was palpable in all patients (100%) at each time point assessed. The non-radiopaque etonogestrel implant was palpable in all patients assessed at all time points except 12 months and 30 months, when it was palpable in 97.1% of patients. Palpability was assessed as an other outcome in both trials. The ITT results were similar to the results for the AST group in Study 34528.

Table 11: Palpability of Implants

	Actual assessment	n[a]/N (%)	Palpable (%)	Palpability incidence 95% CI
Study P05702 (AST)				
Radiopaque etonogestrel implant	Implant insertion	301/301 (100)	300 (99.7)	98.2 to 100.0
	3 months	269/301 (89.4)	268 (99.6)	97.9 to 100.0
	6 months	223/301 (74.1)	222 (99.6)	97.5 to 100.0
	9 months	251/301 (83.4)	250 (99.6)	97.8 to 100.0
	12 months	230/301 (76.4)	229 (99.6)	97.6 to 100.0
	18 months	197/301 (65.4)	197 (100.0)	98.1 to 100.0
	24 months	176/301 (58.5)	176 (100.0)	97.9 to 100.0
	30 months	147/301 (48.8)	147 (100.0)	97.5 to 100.0
	36 months	146/301 (48.5)	146 (100.0)	97.5 to 100.0
	Implant removal	293/301 (97.3)	293 (100.0)	98.7 to 100.0
	Last measurement	301/301 (100)	301 (100.0)	98.8 to 100.0
Study 34528 (AST)				
Radiopaque etonogestrel implant	Implant insertion	52/52 (100)	52 (100.0)	NR
	2 months	51/52 (98.1)	51 (100.0)	NR
	4 months	48/52 (92.3)	48 (100.0)	NR
	6 months	50/52 (96.2)	50 (100.0)	NR
	8 months	47/52 (90.4)	47 (100.0)	NR
	10 months	41/52 (78.8)	41 (100.0)	NR
	12 months	42/52 (80.8)	42 (100.0)	NR
	15 months	40/52 (76.9)	40 (100.0)	NR
	18 months	42/52 (80.8)	42 (100.0)	NR
	21 months	38/52 (73.1)	38 (100.0)	NR
	24 months	38/52 (73.1)	38 (100.0)	NR
	27 months	36/52 (69.2)	36 (100.0)	NR
	30 months	33/52 (63.5)	33 (100.0)	NR
	33 months	32/52 (61.5)	32 (100.0)	NR
	36 months	34/52 (65.4)	34 (100.0)	NR
	Last measurement	52/52 (100)	52 (100.0)	NR
Non-radiopaque etonogestrel implant	Implant insertion	56/56 (100)	56 (100.0)	NR
	2 months	56/56 (100)	56 (100.0)	NR
	4 months	53/56 (94.6)	53 (100.0)	NR
	6 months	51/56 (91.1)	51 (100.0)	NR
	8 months	47/56 (83.9)	47 (100.0)	NR
	10 months	47/56 (83.9)	47 (100.0)	NR
	12 months	43/56 (76.8)	42 (97.7)	NR
	15 months	42/56 (75.0)	42 (100.0)	NR
	18 months	38/56 (67.9)	38 (100.0)	NR
	21 months	36/56 (64.2)	36 (100.0)	NR
	24 months	35/56 (62.5)	35 (100.0)	NR

	Actual assessment	n[a]/N (%)	Palpable (%)	Palpability incidence 95% CI
	27 months	33/56 (58.9)	33 (100.0)	NR
	30 months	35/56 (62.5)	34 (97.1)	NR
	33 months	33/56 (58.9)	33 (100.0)	NR
	36 months	32/56 (57.1)	32 (100.0)	NR
	Last measurement	56/56 (100)	56 (100.0)	NR

AST = all subjects treated; CI = confidence interval; NR = not reported.

[a] Number of patients with non-missing values.

Source: Clinical Study Report for P05702[12] and 34528.[13]

X-Ray Visibility of Implant

X-ray visibility of the implant was assessed as an "other" outcome in studies P05702 and 34528. In Study P05702, the radiopaque etonogestrel implant was clearly visible in all patients after implant insertion (100%; 95% CI, 94.3 to 100.0) and before implant removal (100%; 95% CI, 93.4 to 100.0) (Table 12). In Study 34528, the radiopaque etonogestrel implant was clearly visible in most patients after implant insertion (96.2%; 95% CI, 86.8 to 99.55) and all patients before implant removal (100%; 95% CI, 92.9 to 100.0). The non-radiopaque etonogestrel implant was not clearly visible after insertion or before removal. The ITT results were similar to the results for the AST group in Study 34528.

Table 12: X-Ray Visibility of Implant

	Clearly visible implant after insertion		Clearly visible implant before removal	
	n/N (%)	n (%, 95% CI)	n/N (%)	n (%, 95% CI)
Study P05702 (AST)				
Radiopaque etonogestrel implant	63/63 (100)	63 (100.0, 94.3 to 100.0)	54/54 (100)	54 (100.0, 93.4 to 100.0)
Study 34528 (AST)				
Radiopaque etonogestrel implant	52/52 (100)	50 (96.2, 86.8 to 99.5)	50/52 (96.2)	50 (100, 92.9 to 100.0)
Non-radiopaque etonogestrel implant[c]	56/56 (100)	0 (0, 0.0 to 0.64)	54/56 (96.4)	0 (0, 0.0 to 0.66)

AST = all subjects treated; CI = confidence interval.

Source: Clinical Study Reports for P05702[12] and 34528.[13]

Implant Insertion and Removal Characteristics

The time for insertion and time for removal of the implants were assessed in the integrated analysis but not categorized as a primary, secondary, or other end point. Timing was assessed as a secondary end point in Study P05702 and as an "other" end point in Study 34528. In the integrated analysis, the mean insertion time for the non-radiopaque etonogestrel implant was 78 seconds (SD = 114.0), and the mean removal time was 228 seconds (SD = 294.0).

Table 13). In Study P05702, the mean insertion time for the radiopaque etonogestrel implant was 27.9 seconds (SD = 29.3), and the mean removal time was 119.3 seconds (SD = 120.2). The mean insertion time for the radiopaque etonogestrel implant in Study 34528 was 87.6 seconds (SD = 96.0) and 299.4 seconds (SD = 207.0) for removal. The insertion time for the non-radiopaque etonogestrel implant was 72.6 seconds (SD = 63.6) and the removal time was 264.6 seconds (SD = 241.8).

Subgroup analysis for experienced investigators (N = 11, those who performed more than 10 non-radiopaque etonogestrel implant insertions within the past year) compared with non-experienced investigators (N = 12, those who performed 10 or fewer non-radiopaque etonogestrel implant insertions within the past year) were available for Study P05702. This analysis showed that experienced investigators took less time to insert the implant compared with non-experienced investigators (18.7 seconds versus 36.1 seconds). Experienced investigators also took less time than non-experienced investigators to remove the implant (97.0 seconds versus 139.2 seconds). Additional frequency data on insertion characteristics are reported in Appendix 3.

Complications during removal reported in Study P05702 were reported in 16 of the 296 evaluated patients (5.4%) (Table 14). The most common cause of complications during implant removal was the presence of fibrotic tissue around the implant (4.4%).

Table 13: Implant Insertion and Removal Time

	Insertion time		Removal time	
	n/N(%)	Mean (SD), seconds	n/N (%)	Mean, seconds (SD)
Integrated analysis				
Non-radiopaque etonogestrel implant	927/942 (98.4)	78 (114.0)	875 (92.9)	228 (294.0)
Study P05702 (AST)				
Radiopaque etonogestrel implant	291/291 (100)	27.9 (29.3)	292/292 (100)	119.3 (120.2)
Study 34528 (AST)				
Radiopaque etonogestrel implant	52/52 (100)	87.6 (96.0)	51/52 (98.1)	299.4 (207.0)
Non-radiopaque etonogestrel implant	56/56 (100)	72.6 (63.6)	55/56 (98.2)	264.6 (241.8)

AST = all subjects treated; SD = standard deviation.

Source: Clinical Study Reports for P05702[12] and 34528.[13]

Table 14: Complications During Removal for P05702 (AST)

	Radiopaque etonogestrel implant, n (%)
No	280 (94.6)
Yes	16 (5.4)
Larger incision required	1 (0.3)
Multiple removal attempts required	2 (0.7)
Presence of fibrotic tissue around the implant	13 (4.4)
Other: second incision proximal end	1 (0.3)
Other: single removal attempt which took longer than usual	1 (0.3)
Other: single removal attempt, however it took longer than usual	1 (0.3)

AST = all subjects treated.

Source: Clinical Study Report for P05702.[12]

User (Investigator) Satisfaction

The frequency results of the User Satisfaction Questionnaire assessed as the primary efficacy end point in the AU group (investigators) in Study P05702 are reported by domain in Table 15. Generally, as users completed more insertions more users reported being "very satisfied" and fewer users reported being "very dissatisfied," "dissatisfied," and "not

satisfied nor dissatisfied," based on assessments for design and technical aspects, functionality, safety, used time, and applicator satisfaction. The frequency results of the User Satisfaction Questionnaire reported by domain were not available for the PPAU group (N = 18 of 23).

Table 15: Frequency Distribution (%) of the User Satisfaction Questionnaire by Domain and Assessment

Domain[a]	Completed after insertion	Missing	Very satisfied	Satisfied	Not satisfied nor dissatisfied	Dissatisfied	Very dissatisfied
Study P05702 (applicator user group; N = 23)							
Design and technical aspects	4	0.0	73.0	23.5	2.6	0.9	0.0
	8	0.0	73.9	23.5	2.6	0.0	0.0
	12	0.0	79.1	20.0	0.9	0.0	0.0
Functionality[b]	4	0.0	53.8	32.8	7.6	4.2	1.7
	8	0.0	64.2	28.3	4.2	2.5	0.8
	12	0.9	69.0	25.9	2.6	1.7	0.0
Safety	4	0.0	87.0	11.6	0.0	0.0	1.4
	8	0.0	91.3	7.2	1.4	0.0	0.0
	12	0.0	89.9	8.7	1.4	0.0	0.0
Used time	4	0.0	82.6	17.4	0.0	0.0	0.0
	8	0.0	91.3	8.7	0.0	0.0	0.0
	12	0.0	82.6	17.4	0.0	0.0	0.0
Applicator satisfaction	4	0.0	60.9	30.4	4.3	4.3	0.0
	8	0.0	69.6	26.1	4.3	0.0	0.0
	12	0.0	69.6	30.4	0.0	0.0	0.0

CI = confidence interval.

[a] The different domains consist of a different number of questions: "Design/technical aspects" consists of five questions, "Functionality" consists of six questions, "Safety" consists of three questions. "Used time" and "Applicator satisfaction" are single questions. The domain frequency of a score (e.g., "Satisfied") is the sum of all questions in that particular domain for that score over all investigators.

[b] If the question "Other" in the domain 'Functionality' was not answered by an investigator, this question for that particular investigator did not contribute to the percentage of that domain.

Source: Clinical Study Report for P05702.[12]

Expected and Actual Patient Satisfaction

The expected and actual patient satisfaction with the radiopaque etonogestrel implant was assessed in Study P05702. Aggregate efficacy results were not available.

Bioequivalence

Bioequivalence was the primary efficacy end point for Study 34528. In this study, the radiopaque and non-radiopaque formulations were bioequivalent with respect to the GMR of C_{max} (GMR = 1.06; 90% CI, 0.91 to 1.23), AUC_{6mo} (GMR = 1.00; 90% CI, 0.91 to 1.10), AUC_{24mo} (GMR = 0.98; 90% CI, 0.88 to 1.10), and AUC_{36mo} (GMR = 1.00; 90% CI, 0.89 to 1.11) (Table 16).

Table 16: Results of Bioequivalence Testing for Study 34528 (ASPE)

Parameter	Geometric mean non-radiopaque etonogestrel (n1 = 53)	Geometric mean radiopaque etonogestrel (n2 = 50)	Point estimate of μ (radiopaque etonogestrel)/μ (non-radiopaque etonogestrel)	90% CI	Conclusion
C_{max} (pg/mL)	1,021	1,083	1.06	0.91 to 1.23	Bioequivalent
AUC 0 to 6 months[a] (pg month/mL)	2,210	2,212	1.00	0.91 to 1.10	Bioequivalent
AUC 0 to 24 months[b] (pg month/mL)	5,874	5,783	0.98	0.88 to 1.10	Bioequivalent
AUC 0 to 36 months[c] (pg month/mL)	7,487	7,453	1.00	0.89 to 1.11	Bioequivalent

μ = population mean; ASPE = all subjects pharmacokinetically evaluable; AUC = area under the curve; CI = confidence interval; C_{max} = peak concentration; pg = picogram.

Note: Bioequivalent = 90% CI within acceptance range 0.80 to 1.25.

[a] n1 = 46; n2 = 46.

[b] n1 = 32; n2 = 37.

[c] n1 = 30; n2 = 32.

Source: Clinical Study Reports for 34528.[13]

Harms

Only those harms identified in the review protocol are reported below. See Table 17 for detailed harms data.

Adverse Events

The total proportion of patients treated with the non-radiopaque etonogestrel implant who experienced an AE in the integrated analysis was not reported. The most common individual AEs in the integrated analysis were attributed to headache (24.9%) and vaginitis (14.5%). In Study P05702, AEs were reported by 90.4% of patients treated with the radiopaque etonogestrel implant, with the most common AEs attributed to vaginal hemorrhage (28.2%), headache (18.6%), and metrorrhagia (17.6%). The AEs occurred similarly for patients treated with the radiopaque (100.0%) and non-radiopaque etonogestrel implant (96.4%) in Study 34528. The most commonly occurring AEs were attributed to vaginal hemorrhage (40.4% radiopaque etonogestrel implant and 32.1% non-radiopaque etonogestrel implant), pharyngitis and/or nasopharyngitis (34.6% and 25.0%, respectively), acne (21.1% and 32.1%, respectively), and implant site hematoma (30.8% and 28.6%, respectively).

An aggregate measure of AEs related to bleeding irregularities (troublesome bleeding) was not reported for any of the studies. Specific bleeding-related AEs (including dysmenorrhea, menorrhagia, metrorrhagia, vaginal hemorrhage, and genital hemorrhage) occurred in 5.3% to 28.2% of patients treated with the radiopaque etonogestrel implant in Study P05702, as well as in 3.8% to 46.2% and 7.1% to 41.1% of patients treated with the radiopaque and non-radiopaque etonogestrel implants, respectively, in Study 34528. A publication related to the integrated analysis reported bleeding patterns for a subset of 780 patients at two years.[10] Specific bleeding irregularities (including amenorrhea and infrequent, frequent, and/or prolonged bleeding) occurred in 6.7% to 33.6% of patients.[10]

Serious Adverse Events

In the integrated analysis, SAEs occurred in 5.9% of patients treated with the non-radiopaque etonogestrel implant. In Study P05702, 5.3% of patients treated with the radiopaque etonogestrel implant experienced an SAE. SAEs occurred similarly for patients treated with the radiopaque (7.7%) and non-radiopaque etonogestrel implant (10.7%) in Study 34528. None of the patients in studies P05702 or 34528 experienced SAEs related to bleeding, although one patient per arm in Study 34528 experienced an SAE related to deep vein thrombosis. In the integrated analysis, one patient experienced an SAE related to the "platelet, bleeding, and clotting disorder."

Withdrawals Due to Adverse Events

In the integrated analysis, 13.6% of patients stopped treatment due to AEs, most commonly attributed to bleeding irregularities (11.1%). In Study P05702, 35.2% of patients treated with the radiopaque etonogestrel implant stopped treatment due to an AE, with bleeding irregularities accounting for 19.3% of the withdrawals. Patients who stopped treatment due to AEs was similar for those treated with the radiopaque (28.8%) and the non-radiopaque etonogestrel implant (30.4%) in 34528. Bleeding irregularities accounted for 19.2% of patients treated with the radiopaque etonogestrel implant and 14.3% of patients treated with the non-radiopaque etonogestrel implant.

Mortality

No deaths occurred throughout any of the three trials.

Notable Harms

Notable harms related to those identified in the protocol for this review included vascular disorders, neoplasms, weight increase, spotting or troublesome bleeding, bone mineral density, implant migration, liver function, serum lipids, suicide risk, emotional lability, mood, and depression. Data were not reported for the following notable harms in the integrated analysis: an aggregate measure related to spotting or troublesome bleeding, implant migration, suicide risk, mood altered, and depression. Data were not reported for the following notable harms in studies P05702 and 34528: an aggregate measure related to spotting or troublesome bleeding, bone mineral density, serum lipids, and suicide risk. Implant migration was reported as a "non-serious" AE in Study P05702.

Those AEs related to the category vascular disorders (including but not limited to deep vein thrombosis, peripheral arterial occlusive disease, and vein disorder) occurred in 1.3% of patients treated with the non-radiopaque etonogestrel implant in the integrated analysis and 2.7% of patients treated with the radiopaque etonogestrel implant in P05702. In Study 34528, AEs related to vascular disorders were reported in 5.8% of patients treated with the radiopaque etonogestrel implant and 3.6% of patients treated with the non-radiopaque etonogestrel implant.

In the integrated analysis, benign breast neoplasms occurred in 0.2% of patients and breast ductal carcinoma occurred in 0.1% of patients. AEs related to the category neoplasms occurred in 3% of patients treated with the radiopaque etonogestrel implant in Study P05702 and in 5.8% and 3.6% of patients treated with the radiopaque and non-radiopaque etonogestrel implants in Study 34528, respectively.

Weight increases occurred in 13.7% of patients treated with the non-radiopaque etonogestrel implant in the integrated analysis, 11.6% of patients treated with the

radiopaque etonogestrel implant in Study P05702, and in 7.7% and 14.3% of patients treated with the radiopaque and non-radiopaque etonogestrel implants in Study 34528, respectively.

An aggregate measure of AEs related to bleeding irregularities (troublesome bleeding) was not reported for any of the studies. Specific bleeding-related AEs (including dysmenorrhea, menorrhagia, metrorrhagia, vaginal hemorrhage, and genital hemorrhage) occurred in 5.3% to 28.2% of patients treated with the radiopaque etonogestrel implant in Study P05702, as well as in 3.8% to 46.2% and 7.1% to 41.1% of patients treated with the radiopaque and non-radiopaque etonogestrel implant in Study 34528, respectively. A publication related to the integrated analysis reported bleeding patterns for a subset of 780 patients at two years.[10] These data (not provided in Table 17) indicate that for this subset, patients experienced amenorrhea (22.2%) and infrequent (33.6%), frequent (6.7%), and/or prolonged bleeding (17.7%).[10]

Emotional or affect lability occurred in 6.5% of patients treated with the non-radiopaque etonogestrel implant in the integrated analysis, in 0.7% of patients treated with the radiopaque etonogestrel implant in Study P05702, as well as in 1.9% and 1.8% of patients treated with the radiopaque and non-radiopaque etonogestrel implants, respectively, in Study 34528.

Altered mood occurred in 4.7% of patients treated with the radiopaque etonogestrel implant in Study P05702, as well as in 1.9% and 1.8% of patients treated with the radiopaque and non-radiopaque etonogestrel implants, respectively, in Study 34528.

Depression occurred in 3.7% of patients treated with the radiopaque etonogestrel implant in Study P05702, as well as in 1.9% and 3.6% of patients treated with the radiopaque and non-radiopaque etonogestrel implants, respectively, in Study 34528.

One case of “mild” implant migration (0.3%) was observed in a patient treated with the radiopaque etonogestrel implant in Study P05702. The migration distance and definition of mild were not provided.

Table 17: Summary of Harms

	Integrated analysis (general safety dataset)	Study P05702 (AST)	Study 34528 (AST)	
	Non-radiopaque etonogestrel implant (N = 942)[a]	Radiopaque etonogestrel implant (N = 301)	Radiopaque etonogestrel implant (N = 52)	Non-radiopaque etonogestrel implant (N = 56)
Patients with ≥ 1 adverse event				
n (%)	NR	272 (90.4)	52 (100.0)	54 (96.4)
Most common events[b]				
Headache	235 (24.9)	56 (18.6)	14 (26.9)	15 (26.8)
Vaginitis	137 (14.5)	NR	NR	NR
Weight increase	129 (13.7)	35 (11.6)	4 (7.7)	8 (14.3)
Acne	127 (13.5)	NR	11 (21.2)	18 (32.1)
Breast pain	121 (12.8)	NR	NR	NR
Upper respiratory tract infection	119 (12.6)	NR	NR	NR

	Integrated analysis (general safety dataset)	Study P05702 (AST)	Study 34528 (AST)	
	Non-radiopaque etonogestrel implant (N = 942)[a]	Radiopaque etonogestrel implant (N = 301)	Radiopaque etonogestrel implant (N = 52)	Non-radiopaque etonogestrel implant (N = 56)
Abdominal pain	103 (10.9)	NR	6 (11.5)	2 (3.6)
Pharyngitis or nasopharyngitis	99 (10.5)	32 (10.6)	18 (34.6)	14 (25.0)
Leukorrhea	90 (9.6)	NR	NR	NR
Influenza or influenza-like symptoms	NR	NR	12 (23.1)	14 (25.0)
Dysmenorrhea	NR	NR	6 (11.5)	4 (7.1)
Nausea	NR	NR	6 (11.5)	8 (14.3)
Amenorrhea	NR	NR	3 (5.8)	6 (10.7)
Menorrhagia	NR	31 (10.3)	2 (3.8)	9 (16.1)
Metrorrhagia	NR	53 (17.6)	9 (17.3)	9 (16.1)
Vaginal hemorrhage	NR	85 (28.2)	21 (40.4)	18 (32.1)
Implant site hematoma	NR	NR	16 (30.8)	16 (28.6)
Implant site pain	NR	NR	4 (7.7)	6 (10.7)
Cystitis	NR	NR	8 (15.4)	4 (7.1)
Gastroenteritis	NR	NR	6 (11.5)	4 (7.1)
Vulvovaginal mycotic infection	NR	NR	3 (5.8)	7 (12.5)
Back pain	NR	NR	11 (21.2)	6 (10.7)
Genital hemorrhage	NR	NR	24 (46.2)	23 (41.1)
Patients with ≥ 1 serious adverse event				
n (%)	53 (5.9)	16 (5.3)	4 (7.7)	6 (10.7)
Patients who stopped treatment due to adverse events				
n (%)	128 (13.6)	106 (35.2)	15 (28.8)	17 (30.4)
Most common events				
Bleeding irregularities	105 (11.1)[c]	58 (19.3)[c]	10 (19.2)[c]	8 (14.3)[c]
Emotional lability	22 (2.3)	NR	NR	NR
Weight increase	22 (2.3)	14 (4.7)	0	1 (1.8)
Menorrhagia	NR	14 (4.7)	1 (1.9)	0
Genital hemorrhage	NR	NR	3 (5.8)	1 (1.8)
Vaginal hemorrhage	NR	11 (3.7)	4 (7.7)	4 (7.1)
Metrorrhagia	NR	41 (13.6)	1 (1.9)	3 (5.4)
Acne	NR	12 (4.0)	1 (1.9)	3 (5.4)
Mood altered	NR	10 (3.3)	1 (1.9)	1 (1.8)
Deaths				
n (%)	0	0	0	0
Notable harms, n (%)				
Vascular disorders	12 (1.3)	8 (2.7)	3 (5.8)	2 (3.6)
Deep vein thrombosis	NR	NR	1 (1.9)	1 (1.8)

	Integrated analysis (general safety dataset)	Study P05702 (AST)	Study 34528 (AST)	
	Non-radiopaque etonogestrel implant (N = 942)[a]	Radiopaque etonogestrel implant (N = 301)	Radiopaque etonogestrel implant (N = 52)	Non-radiopaque etonogestrel implant (N = 56)
Peripheral arterial occlusive disease	NR	NR	1(1.9)	0
Vein disorder	NR	NR	0	1 (1.8)
Neoplasms benign, malignant, unspecified	NR	9 (3.0)	3 (5.8)	2 (3.6)
Benign breast neoplasm	2 (0.2)	2 (0.7)	0	2 (3.6)
Breast ductal carcinoma	1 (0.1)	NR	NR	NR
Weight increase	129 (13.7)	35 (11.6)	4 (7.7)	8 (14.3)
Bleeding irregularities[d]	NR	NR	NR	NR
Dysmenorrhea	NR	16 (5.3)	6 (11.5)	4 (7.1)
Menorrhagia	NR	31 (10.3)	2 (3.8)	9 (16.1)
Metrorrhagia	NR	53 (17.6)	9 (17.3)	9 (16.1)
Vaginal hemorrhage	NR	85 (28.2)	21 (40.4)	18 (32.1)
Genital hemorrhage	NR	NR	24 (46.2)	23 (41.1)
Bone mineral density	0	NR	NR	NR
Implant migration	NR	1 (0.3)[e]	NR	NR
Liver function	0	NR	NR	NR
Serum lipids	0	NR	NR	NR
Suicide risk	NR	NR	NR	NR
Emotional or affect lability	61 (6.5)	2 (0.7)	1 (1.9)	1 (1.8)
Mood altered	NR	14 (4.7)	1 (1.9)	1 (1.8)
Depression	NR	11 (3.7)	1 (1.9)	2 (3.6)

AST = all subjects treated; NR = not reported.

[a] Safety data included data from 16 breastfeeding women and three patients with no post-baseline assessments.

[b] Frequency > 10%.

[c] In studies P05702 and 34528, bleeding irregularities included frequent irregular bleeding (metrorrhagia), heavy menstrual flow (menorrhagia), prolonged menstrual flow (menorrhagia), spotting, and other bleeding problems. In the integrated analysis, bleeding irregularities included amenorrhea, frequent irregular bleeding, heavy menstrual flow, spotting, and other bleeding problems.[10]

[d] Adverse event aggregate data on bleeding irregularities not reported.

[e] Implant migration classified as “mild,” no definition provided.

Source: Common Technical Document Section 2.5,[11] Darney et al. (2009),[14] Clinical Study Reports for P05702[12] and 34528.[13]

Critical Appraisal

Internal Validity

All three studies assessed contraceptive efficacy; however, only the integrated analysis was designed to evaluate contraceptive efficacy. The integrated analysis was composed of single-arm data extracted from 11 studies that supported the FDA filing for the approval of the non-radiopaque etonogestrel contraceptive implant. Details around the selection of the 11 studies were sparsely reported. It is unclear if a comprehensive systematic literature search was performed to identify studies for the integrated analysis. If an electronic

literature search was performed, there was no information available on the search terms used in the search. It is unclear if unpublished or grey literature was searched. The methods used for integrated analysis were sparsely reported. It is unclear if structured data extraction was performed, how many authors extracted the data, and how discrepancies were resolved. The integrated analysis did not include information on baseline characteristics stratified by study, and no analysis on heterogeneity was performed; therefore, it is unclear if the individual studies included in the integrated analysis were suitable for pooling. The integrated analysis was composed of individual studies with varying design elements (i.e., non-comparative, unblinded studies, RCTs). The individual studies contributing to the integrated analysis were not required to have contraceptive efficacy as the primary end point and only single-arm data for those treated with the non-radiopaque etonogestrel implant were included in the integrated analysis. No adjustments were made for missing data. The assessment of subjective outcomes, such as harms outcomes, have the potential to be influenced in studies that were not blinded. No statistical methods were used to combine the data from the individual studies. Although failure to use proper statistical methods is problematic, the impact was less relevant because the event rate in the integrated analysis was zero (i.e., there were no pregnancies).

Study P05702 was a single-arm, open-label "user satisfaction" study. No formal sample size calculations were performed for Study P05702. One outcome (contraceptive efficacy) assessed using subgroups based on age did not appear to be specified a priori.

Study 34528 was a double-blind RCT designed to assess bioequivalence between the radiopaque and non-radiopaque etonogestrel implants. The baseline and demographic characteristics were generally well-balanced in Study 34528. Randomization at a 1:1 ratio was performed in blocks by centre. The details of how randomization and treatment allocation were performed were not provided. To maintain blinding, all implants (non-radiopaque and radiopaque) were administered using the original applicator associated with the non-radiopaque etonogestrel formulation. However, the applicator used in this trial is not used in Canada and differs from the next-generation applicator associated with the drug under review. Study 34528 was designed to assess bioequivalence, thus power calculations for the conduct of the study were based on bioequivalence and not contraceptive efficacy. No formal statistical analysis was planned for the assessment of the efficacy outcomes.

Across all trials, discontinuations were high, with 35.0% to 48.2% of patients discontinuing the trials over the three-year duration, and most discontinuations attributed to bleeding irregularities and AEs. The substantial number of discontinuations raises questions about trial validity and the ability to interpret trial results. It is unclear if the efficacy of non-radiopaque etonogestrel would be the same for the patients who discontinued the trial as those who completed it. Theoretically, the three-year duration of the trials was sufficient to determine the effectiveness for patients; however, the extensive number of discontinuations should be considered when assessing the actual treatment time. Many patients discontinued the trials in year 1 and year 2, and some of the included trials in the integrated analysis ran for only two years.

External Validity

Across the three studies (integrated analysis, Study P05702, and Study 34528) patient-eligibility requirements based on age, weight, physical and mental health, and regularity of menstrual cycles reduced the generalizability of the studies to the Canadian clinical population. To be included in the studies, women had to be between 18 and 40 years of

age. This excludes adolescents and women older than 40 years who would be potentially treated in clinic, according to the clinical expert consulted for this review. Based on the three pivotal studies, it is unclear if contraceptive efficacy and safety differ among these subgroups. Additionally, the three studies had inclusion criteria based on "ideal body weight" (integrated analysis) or BMI (studies P05702 and 34528) that exclude women who exceed 130% of their ideal body weight or have a BMI greater than 35 kg/m^2. The external validity of the studies is limited as women that do not meet these body weight and BMI criteria would potentially be seen in clinic. Studies P05702 and 34528 required patients to have "good physical and mental health." These criteria are problematic as they are not defined (they are left to investigator discretion) and highlight another feature of the trials that reduces generalizability because patients not meeting these criteria would potentially be treated in the Canadian clinical setting. All trials had some inclusion criteria based on patients having regular menstrual cycles, which reduces generalizability of the trials as patients with irregular menstrual cycles would potentially be treated in the Canadian clinical setting. Collectively, these eligibility criteria reduce the generalizability to the Canadian clinical population.

The baseline demographics and baseline characteristics were generally reflective of the Canadian clinical population, with the exception of race. Based on results from studies P05702 and 34528, almost all patients included in the two studies were White, which is inconsistent with the Canadian population. It is unclear if there are differences in efficacy or safety of the etonogestrel implant based on race.

The comparative efficacy of the radiopaque etonogestrel implant with respect to relevant contraceptives used in Canada could not be determined using the evidence available for this review, highlighting a major evidence gap associated with this product.

In Study 34528, all implants (non-radiopaque and radiopaque etonogestrel) were inserted using the original applicator associated with the non-radiopaque etonogestrel formulation in an effort to maintain blinding. This is problematic because this applicator differs from the next-generation applicator associated with the radiopaque etonogestrel implant that is expected to be marketed in Canada.

The total proportion of patients treated with the non-radiopaque etonogestrel implant who experienced an AE in the integrated analysis was not reported. Overall AEs is a key harms measure; its absence limits the ability to make global assessments of the safety of the drug in the integrated analysis and prevents comparisons with other studies. Almost all patients experienced an AE (90.4% to 100% based on data from studies P05702 and 34528). Although many of these AEs were related to bleeding irregularities, some may have been associated with the applicator used in the trial rather than the implant itself. This is problematic because the original applicator was used in the integrated analysis and Study 34528, not the next-generation applicator. The use of the alternative applicator in the integrated analysis and Study 34528 reduces the generalizability of the applicator-related harms data to the Canadian clinical population. Across the three trials, discontinuations accounted for 35.0% to 48.2% of patients. The substantial number of discontinuations raises questions about the actual utility of the radiopaque etonogestrel implant in the clinical setting.

All investigators involved with insertion or removal of the non-radiopaque etonogestrel implant in Study P05702 followed a training session on proper insertion and handling of the next-generation applicator, which included an instruction leaflet and video followed by two successful insertions on a training arm. While written instructions, video demonstrations,

and a training website (where health care providers can register for training sessions) will be available to clinicians in Canada, it is unclear what the uptake will be and if the training received in clinic will be comparable to the training received in Study P05702.

Indirect Evidence

No indirect evidence was submitted by the sponsor. An independent literature search for indirect evidence conducted by CADTH did not identify any evidence that met the inclusion criteria of the CDR review protocol.

Other Relevant Studies

Four studies were identified that evaluated radiopaque etonogestrel implant use in subgroups indicated as clinically relevant by the clinical expert consulted for this review. One observational study assessed quality of life in patients treated with the radiopaque etonogestrel implant after abortion for unplanned pregnancy.[15] Quality of life was an outcome reported to be important to patients; however, it was not reported in the pivotal trials. A meta-analysis and two RCTs assessed radiopaque etonogestrel implant use following immediate versus delayed insertion of the implant. The meta-analysis aimed to examine the timing of administration of the etonogestrel implant in patients undergoing medical abortion with mifepristone and misoprostol.[16] The RCT by Byrant et al.[17] investigated the timing of implant insertion in adolescents and young women post-partum. Although Health Canada has not authorized an indication for pediatric use, a subgroup of adolescents was identified as "of interest" by the clinical expert consulted for this review.[8] The RCT by Cowett et al.[18] investigated the timing of implant insertion in adult women following an abortion procedure.

Quality of Life of Women Using the Etonogestrel Long-Acting Reversible Contraceptive Implant After Abortion for Unplanned Pregnancy (Caruso et al.)[15]

Methods

This study was a prospective observational study in 140 women who received contraceptive counselling on the etonogestrel implant after abortion for an unplanned pregnancy. Patients received treatment with the etonogestrel implant or control (short-acting contraceptive or non-hormonal contraceptive). The study was performed at the Family Planning Centre of the Sexology Research Group, Department of General Surgery and Medical Surgical Specialties, School of Medicine, University of Catania, Italy, between January 2013 and September 2019. The radiopaque etonogestrel implant was approved for use in the European Union in April 2010; therefore, it is assumed (but not confirmed) that the etonogestrel implant used in the study was the radiopaque version consistent with the drug under review. Patients' quality of life was assessed at baseline, and six, 12, 24, and 36 months using the SF-36 and sexual function tools (not reported here).

Population

Baseline characteristics were generally similar between the intervention and control groups. The mean age of patients was 27 years (SD = 8) in the etonogestrel arm and 25 years (SD = 8) in the control arm. Mean BMI was 24.4 (SD = 2.2) and 25 (SD = 2.8) in the etonogestrel and control arms, respectively. Cigarette smoking was similar between arms: smoker (34.9% versus 37.0%), never smoker (16.6% versus 16.7%), and past smoker

(48.8% versus 46.3%) for the etonogestrel and control arms, respectively. Parity was also similar between arms: zero (25.6% versus 31.5%), one (61.6% versus 61.1%), two (11.6% versus 7.4%), and three (1.2% versus 0) for the etonogestrel and control arms, respectively. Previous contraception was similar between arms: none (52.3% versus 50.0%), condom (17.4% versus 20.4%), combined oral contraceptives (16.3% versus 24.1%), levonorgestrel-releasing intrauterine system (3.5% versus 0), and vaginal ring (10.5% versus 5.6%) for the etonogestrel and control arms, respectively. Previous elective abortion for patients with three previous abortions was greater in the etonogestrel arm (31.4%) compared to the control arm (9.3%).

Interventions

The etonogestrel implants were placed on the day of pregnancy termination. Women in the control group who chose to use a short-acting contraceptive method received the prescription at discharge from the hospital.

Outcomes

Quality of life was assessed using the eight subscales of the SF-36 at baseline, and six, 12, 24, and 36 months. Patient satisfaction was assessed as “very satisfied,” “quite satisfied,” “neither satisfied nor dissatisfied,” “dissatisfied,” or “very dissatisfied.”

Statistical Analysis

A Student t-test was used to assess variables between the etonogestrel and control arms. A Wilcoxon rank sum test was used to compare intra-group differences in questionnaire scores. No multivariate analysis was performed. Results were reported with means and SDs. A P value of less than 0.05 was considered statistically significant.

Patient Disposition

A total of 145 patients were invited to participate in the study. Five patients were excluded after choosing the levonorgestrel-releasing intrauterine system after contraceptive counselling. Of the 140 patients in the study, 86 (61.4%) chose the etonogestrel implant and 54 (38.6%) chose a short-acting contraceptive or non-hormonal method. In the etonogestrel implant group, eight patients (9.3%) discontinued due to bleeding and seven (8.1%) discontinued the study due to planning a pregnancy. In the control group, eight patients (14.8%) discontinued due to bleeding, eight (14.8%) discontinued before six months due to unintended pregnancy, and 15 (27.8%) discontinued between six and 12 months due to unintended pregnancies.

Results

At 36 months data were available from 71 patients in the etonogestrel arm (82.6%) and 23 patients in the control arm (42.6%).

Patients in both groups experienced statistically significant improvements in all physical and mental health subsections of the SF-36 (physical function, physical role, bodily pain, general health, vitality, mental health, social function, emotional role) at 36 months compared to baseline ($P < 0.0001$). Patients in the etonogestrel implant group had significantly greater improvement compared with the control group ($P < 0.0001$).

Of the women treated with the etonogestrel implant, 53 (74.6%) reported they were “very satisfied” with the etonogestrel implant, 12 (16.9%) were “quite satisfied,” and six (8.5%) were “neither satisfied nor dissatisfied.”

There were no complications associated with the insertion and removal of the implant.

Critical Appraisal

This observational study was designed to assess quality of life in women using the etonogestrel implant after abortion for unplanned pregnancy. Treatment groups were generally well-balanced. Socioeconomic status of patients was not assessed at baseline; however, it was noted that at enrolment that 40.7% of women declined the implant due to financial reasons. The study population included women younger than 18 years, including patients as young as 16 years. However, subgroup analyses on these patients were not performed. Discontinuation of the study was greater in the control arm (57.4%) compared with the etonogestrel arm (17.4%), with several discontinuations attributed to unintended pregnancies. The differential discontinuation is likely to bias the results. Results of the SF-36 (i.e., SF-36 scores) were not presented in a table, which made individual results challenging to compare between arms and to assess the clinical significance of the results. The results of the study are limited by the observational nature of the study.

Long-acting Reversible Contraception Immediately After Medical Abortion: Systematic Review With Meta-Analyses (Schmidt-Hansen et al.)[16]

Methods

This study included a systematic review and meta-analysis assessing the timing of administration of the etonogestrel implant in patients undergoing medical abortion with mifepristone and misoprostol. The implant used in the included primary studies was either identified directly as the radiopaque etonogestrel implant, or was assumed to be the radiopaque etonogestrel implant based on the initiation date of primary studies (starting after approval of the radiopaque etonogestrel implant) in the country where the study was conducted (i.e., approved for use in the US on May 13, 2011).

Several databases, including Embase, Ovid MEDLINE, the Cochrane Library, CENRAL, CINAHL Plus, and Web of Science Core Collection, were searched until November 2018. Literature screening and data extraction were performed by one reviewer. Final selection of included studies was performed by consensus of three reviewers. Risk of bias was assessed using the Cochrane Collaboration quality checklist for RCTs by one reviewer. Subsequent unintended pregnancy was assessed at three and six months. Outcomes for incomplete and complete abortions were assessed but are not reported here.

Population

Patients treated with the etonogestrel implant administered either simultaneously with mifepristone or more than 24 hours after mifepristone.

Outcomes

Subsequent unintended pregnancy was assessed at three and six months.

Statistical Analysis

Outcomes were analyzed as risk ratios. The meta-analysis was performed using the Mantel-Haenszel statistical method. A fixed-effect model was used because the I^2 value was less than 50%.

Results

There was decreased risk of subsequent unintended pregnancy for patients with simultaneous administration of mifepristone and the etonogestrel implant compared with etonogestrel implant administration more than 24 hours after mifepristone at three months (0 of 277, 0% versus 4 of 261,1.53%; risk ratio = 0.10; 95% CI, 0.01 to 1.94; P = 0.13) and at six months (3 of 490, 0.61% versus 13 of 474, 2.74%; risk ratio = 0.22; 95% CI, 0.06 to 0.78; P = 0.02).

Critical Appraisal

The review was generally well performed. However, the review was limited by the use of a single reviewer for the initial literature screening and data extraction. The methods for performing the meta-analysis were sufficient with clear criteria based on I^2 specified for guiding the choice of a fixed- or random-effect model. Risk of bias was assessed to be low for the included studies. Sensitivity analyses could not be performed based on limited data.

Timing of Implant Insertion in Young Post-Partum Women (Bryant et al.)[17]

Methods

The study was a parallel, non-blinded, single-centre RCT of 96 adolescents and young women receiving the radiopaque etonogestrel implant post-partum at the North Carolina Women's Hospital between August 2012 and April 2015 (NCT01666912). Women were included if they were between the ages of 14 to 24, gave birth to a healthy infant, spoke English or Spanish, and consented to receiving a contraceptive implant. Exclusion criteria were a past or present history of thrombosis or thromboembolic disorders; hepatic tumours; active liver disease; undiagnosed abnormal genital bleeding; known, suspected, or history of carcinoma of the breast; hypersensitivity to the implant; use of hepatic enzyme inducers; maternal intensive care unit admission after delivery; post-partum hemorrhaging requiring a blood transfusion; a hospital stay of more than seven days post-partum; coagulopathy; or hemolysis. Participants were randomized 1:1 to receive the implant immediately, as in before hospital discharge (immediate group), or at six weeks post-partum visit (six-week group). Follow-up data on patient satisfaction, bleeding patterns, breastfeeding, and insertion status were collected by phone or in person every three months for up to one year.

Populations

Baseline characteristics were available for the ITT population. Baseline characteristics such as age (mean = 21 years in each group); parity at admission; race; educational, marital, employment, and financial status; delivery details; and whether the participants were living with parents were generally similar between the two groups.[17] The authors indicated that baseline characteristics were also similar among participants who were LTFU or remained in study, with the exception of age; participants who were LTFU were slightly younger (mean = 20.3 years versus 21.4 years; P = 0.04).[17]

Interventions

The interventions were insertion of a radiopaque etonogestrel implant immediately post-partum (i.e., prior to hospital discharge) or delayed insertion (i.e., at the six-week post-partum visit). There was no crossover between treatment groups.[17]

Outcomes

The primary outcome was contraceptive implant use at 12 months post-partum.[17] Secondary outcomes included satisfaction with implant use, a plan to continue implant use, bleeding patterns, breastfeeding, and rapid repeat pregnancy.

Statistical Analysis

The primary analysis was performed on data from participants who had completed a 12-month follow-up (PP analysis). An ITT analysis was also reported that included all participants who were initially randomized.[17] Sensitivity analyses were conducted on the primary outcome to assess the potential effect of LTFU. Descriptive statistics for secondary analysis of demographic and reproductive health characteristics were also provided in the paper. Student t-tests for continuous variables, and Pearson chi-square tests for categorical variables were reported.

Patient Disposition

A total of 187 women aged 14 to 24 years old were screened, of which 96 met eligibility criteria and were randomized to the immediate group (n = 48), or six-week group (n = 48).[17] A summary of patient disposition over the course of the study is provided in Table 18.

Table 18: Patient Disposition in Bryant et al.17

	Immediate group	6-week group[a]
Randomized, N	**48**	**48**
Received allocated intervention, n (%)	48 (100)	32 (67)
Did not receive allocated intervention, n (%)	0	7 (14.6)
Unknown, n (%)	0	10 (20.8)
Completed 12 months follow-up, n (%)	**37 (77.1)**	**27 (56.3)**
Implant in place at 12 months, n (%)	30 (81)	21 (77)
Discontinued implant by 12 months, n (%)	7 (18.9)	1 (3.7)
Unknown, n (%)	0	6 (22.2)
Lost to follow-up by 12 months, n (%)	**11 (23)**	**21 (44)**
ITT, N (%)	**48 (100.0)**	**48 (100.0)**
PP,[b] N (%)	**37 (77.1)**	**27(56.3)**

ITT = intention-to-treat; PP = per protocol.

[a] There were inconsistencies in the data presented in Figure 1 in Bryant et al.[17] and the in-text data. The data in-text were reported.

[b] Includes participants with at least 12 months of follow-up data.

Results

All women (100%) allocated to the immediate implantation group received their implant before hospital discharge, while 67% of women allocated to the six-week implantation group were confirmed to have a successful implantation (P < 0.0001).[17] Seven women declined to receive an implant at the six-week follow-up visit; two received another contraceptive method, and five did not receive any method. Ten participants were LTFU after enrolment; therefore, it is unknown if they received an implant.

The primary outcome analysis included 64 participants with 12-month follow-up data. At three months, a greater proportion of women in the immediate group had the implant in

place, compared to the six-week group (34 of 37, 92% versus 19 of 27, 70%; P = 0.02). However, there was no difference in implant use at 12 months (30 of 37, 81% versus 21 of 27, 78%; P = 0.74). Using ITT analysis, which assumed that all women LTFU did not use an implant at any point during the post-partum period, no statistical difference between the immediate- and delayed-insertion groups in implant use at 12 months was observed (30 of 48, 63% versus 21 of 48, 44%; P = 0.07, respectively). Overall, 33% of all randomized women were LTFU, with a higher proportion in the six-week group (21 of 48) compared to the immediate group (11 of 48) (P = 0.03).[17]

The authors performed sensitivity analysis to evaluate the effect of LTFU on the primary outcome. Four scenarios were evaluated, varying the proportion of LFTU participants in the two treatment groups.[17] When 100% of the LTFU participants in the immediate group were assumed to have the implant at 12 months, 85% of participants in the immediate group were still using the implant at 12 months, compared to 44% in the six-week group (P < 0.001). In contrast, when 100% of the LTFU participants in the six-week group were assumed to have the implant at 12 months, 63% of participants in the immediate group were still using the implant at 12 months, compared to 88% in the six-week group (P = 0.005). No statistically significant differences were observed in the other two scenarios.[17]

Seven participants in the immediate group and one participant in the six-week group discontinued the implant before 12 months post-partum for reasons including migraines (2), dizziness (1), continuous or excessive bleeding (3), and desired pregnancy (1).[17] At 12 months post-partum, participants from both groups were generally satisfied with their implants (89% in the immediate group and 78% in the six-week group indicated they would recommend the implant to a friend). There were no significant differences in any of the secondary outcomes identified between the two groups with respect to satisfaction with the implant, plans to continue use of the implant, bleeding patterns, breastfeeding, and rapid repeat pregnancy.[17] Although seven unplanned pregnancies were reported during the follow-up period, all occurred in women who did not have the implant inserted, or after it was removed.[17]

Critical Appraisal

This small, single-centre RCT attempted to inform on the optimal insertion timing of a contraceptive implant in post-partum young women. Given the nature of the treatment and treatment allocation, a blinded trial was not feasible. Randomization allowed for well-balanced groups, but the sample size was small (n = 48 in each arm). Given that this study was only conducted at one American site, the generalizability to young Canadian women is unknown. The results of this study were further limited by high LTFU rates, and by missing data in the delayed group. While the results of the primary outcome did not identify a significant difference in implant use at 12 months, sensitivity analysis suggests that implant use at 12 months in each group was highly dependent on the proportion of LTFU patients using the contraceptive implant. At three months, there was a significant difference in implant use, which may suggest that earlier insertion may be more suitable for women more prone to be LTFU. The clinical expert consulted in this review identified young women (aged 14 to 24 years) as a subgroup who would benefit from a long-acting, reversible contraceptive method given their high risk of unplanned pregnancy, especially as it is less invasive than an IUD and therefore preferred for use in younger women. Furthermore, the clinical expert indicated that this subgroup is often difficult to follow up, and therefore immediate implant insertion may result in higher implant use rates, and fewer women LTFU before successful implant insertion. Although limited by a small sample size and high LTFU

rates, this study was not able to demonstrate a benefit of immediate implant insertion in young women post-partum.

Timing of Implant Insertion in Post-Abortion Women (Cowett et al.)[18]

Methods

The conducted study was a single-centre RCT of 148 adult women who opted to receive the radiopaque etonogestrel implant post-partum at a freestanding family planning clinic in Chicago, Illinois, between November 2015 and October 2016 (NCT02037919).[18] Women were included if they were older than 18 years and were seeking an abortion between 14 and 23 weeks of gestation. Women were excluded if they were unable to give consent in English or had contraindications to etonogestrel use. Participants were randomized 1:1 to receive the implant immediately following a D&E procedure, as in while still under sedation (immediate group), or two to four weeks post-D&E procedure, as in at a follow-up visit (delayed group). Randomization was blinded until after the procedure; therefore, participants were not aware of their group allocation until waking up from sedation. Follow-up data on implant placement, current contraceptive method use, method satisfaction, side effects, and repeat pregnancies were collected by telephone six months post-procedure.[18]

Populations

Baseline characteristics were available for the ITT population.[18] Baseline characteristics such as age (immediate group = 25 years, delayed group = 23 years), race, educational and marital status, as well as insurance coverage details and positive smoking status were generally similar between the immediate and delayed groups, with no major differences noted. Clinical characteristics related to the total number of pregnancies, prior abortion rates, indication for D&E, birth control methods used in the past, and history of sexually transmitted diseases were also similar between the two groups.[18] The authors indicated that there were no significant differences in baseline characteristics among participants who were LTFU or completed the study.[18]

Interventions

The interventions were insertion of the radiopaque etonogestrel implant immediately post-D&E procedure (immediate group), or 2 to 4-week post-D&E procedure (delayed group). There was no crossover between treatment groups.[18] Women randomized to the delayed group were given an alternate form of contraceptive in the interim.

Outcomes

The primary outcome was the implant use rate six months after insertion.[18] Secondary outcomes included repeat pregnancy rates and satisfaction with the contraceptive method.

Statistical Analysis

The primary analysis was performed on data from participants who had completed a six-month follow-up (PP analysis). An ITT analysis was also performed, which included all participants who were initially randomized. Statistical significance was tested using Fisher exact tests for continuous variables, and Pearson chi-square tests for categorical variables.

Patient Disposition

A total of 509 women were approached, of which 148 met eligibility criteria and were randomized to the immediate group (n = 73), or delayed group (n = 75).[18] A summary of the patient disposition over the course of the study is provided in Table 19.

Table 19: Patient Disposition in Cowett et al.[18]

	Immediate group	Delayed group
Randomized, N	**73**	**75**
Received allocated intervention, n (%)	73 (100)	32 (42.7)
Did not receive allocated intervention, n (%)	0	43 (57.3)
Unknown	–	–
Completed 6 months follow-up, n (%)	**43 (58.9)**	**30 (38.5)**
Implant in place at 6 months	40 (93)	19 (63.3)
Removed implant by 6 months	3 (7)	3 (10)
Other	0	8 (26.7)[a]
Lost to follow-up by 6 months	**30 (41)**	**10 (13.3)**
ITT, N (%)	**73 (100)**	**75 (100)**
PP,[b] N (%)	**40 (93)**	**30 (38.5)**

ITT = intention-to-treat; PP = per protocol.

[a] Of the 43 participants who did not receive their allocated intervention, eight were contacted at six months (i.e., completed study participation).

[b] Includes participants with at least six months of follow-up data.

Results

All of the women (100%) randomized to the immediate implantation group received their implant, compared to only 42.7% of the women randomized to the delayed-insertion group (two to four weeks post-procedure) (P < 0.01).[18] Of the 43 patients completing the study in the immediate group, 40 participants (93%) still had the implant in place at six months, while three (7%) had the implant removed. In the delayed-insertion group, 22 participants (68.8%) completed the study, 19 (86.4%) still had the implant in place at six months, and three had the implant removed. Eight women who did not have the implant inserted were contacted at six months and were included in the PP analysis. The remaining women who received the implant but did not complete the study (30 in the immediate group and 10 in the delayed group) were deemed LTFU. The authors indicated that the six women who had the implant removed (three in each group) were not using another method of contraception.[18]

The primary outcome analysis included 73 participants (43 in the immediate group and 30 in the delayed group) who completed the study (i.e., completed the six-month follow-up call) (P = 0.02). Using PP analysis, a greater proportion of women in the immediate group had the implant in place at six months compared with the delayed group (93% versus 63.3%; P < 0.002). Using ITT analysis, use of the implant at six months was also higher in the immediate group compared with the delayed group (54.5% versus 25.3%; P < 0.01). There was no difference in implant removal rates between the two groups. One woman in each group experienced a repeat pregnancy; the participant in the immediate group became

pregnant with the implant in place, while the participant in the delayed group was not using contraception.[18]

Critical Appraisal

This small single-centre RCT was designed to compare immediate versus delayed implant insertion in women older than 18 years undergoing an abortion procedure. Randomization allowed for well-balanced comparator groups, and blinding was maintained until after the D&E procedure. The study population included only adult women aged 18 years or older, which is in line with the proposed indication. However, this may limit generalizability to women younger than 18 years of age who are at high risk of an abortion due to unplanned pregnancy. Additionally, the study was conducted at a single American centre, and therefore the generalizability to the Canadian population is unknown. The results of the study were also limited by high LTFU rates; 57.3% of women allocated to the delayed-insertion group did not return for implant insertion. Furthermore, 41.1% of participants in the immediate group and 31.3% of participants in the delayed group who received an implant were lost to follow-up by the study completion time (six months post-procedure). Given that the women were receiving interim contraception, it is not known whether they did not return for implant insertion because they were satisfied with their interim contraceptive method, or if they were not using a method at all. Furthermore, using an interim contraceptive method may not be representative of real-world practice. Only eight women (18.6%) who did not return for the implant were contacted at six months and confirmed they were not using the implant, while the remainder were determined LTFU. Sensitivity analysis was not performed, and therefore the effect of the LTFU patients on the primary outcome, which is expected to have a significant effect, was not explored.

Discussion

Summary of Available Evidence

Three studies identified as pivotal by the sponsor were included in the CDR. The integrated analysis included pooled data from 11 studies that included the non-radiopaque etonogestrel implant as the intervention in healthy, adult women. The objective of the integrated analysis was to present efficacy and safety results from the clinical trials that supported the FDA filing for the approval of a non-radiopaque etonogestrel contraceptive implant. Study P05702 was an open-label, non-comparative, single-arm, clinician satisfaction study of adult women treated with the radiopaque etonogestrel implant. The primary objective of Study P05702 was to evaluate the use of the next-generation applicator and its instructions for proper insertion of the radiopaque etonogestrel implant. Study 34528 was a double-blind, parallel-group, bioequivalence study in which women were randomized in blocks by centre at a 1:1 ratio for treatment with the radiopaque etonogestrel implant or the non-radiopaque etonogestrel implant. Patients included in the three studies were healthy women between 18 to 40 years of age with regular menstrual cycles.

Key limitations across all studies included concerns about generalizability as the study participants were a selective group when compared to all women of child-bearing age who could potentially receive etonogestrel, and high discontinuation rates often related to bleeding irregularities. The generalizability of the study findings to clinical practice settings in Canada was limited by eligibility requirements that excluded certain patients, including adolescents, patients older than 40 years, patients with irregular menstrual cycles, and patients with a BMI greater than 35 kg/m^2. Evidence gaps include an absence of direct and indirect comparisons to relevant contraceptives used in Canada, and the efficacy of the radiopaque etonogestrel implant in subgroups of patients who were excluded from the trials.

Four studies were identified that evaluated radiopaque etonogestrel implant use in subgroups indicated as clinically relevant by the clinical expert consulted for this review. One observational study assessed quality of life in patients treated with the radiopaque etonogestrel implant after an abortion for unplanned pregnancy.[15] Quality of life was an outcome reported to be important to patients: however, it was not reported in the pivotal trials. A meta-analysis and two RCTs assessed radiopaque etonogestrel implant use following immediate versus delayed insertion of the implant. The meta-analysis aimed to examine the timing of administration of the etonogestrel implant in patients undergoing medical abortion with mifepristone and misoprostol.[16] The RCT by Byrant et al.[17] investigated the timing of implant insertion in adolescents and young women post-partum, and the RCT by Cowett et al.[18] investigated the timing of implant insertion in adult women following an abortion procedure.

Interpretation of Results

Efficacy

The non-radiopaque form of the etonogestrel implant has been available since 1998 in other countries; it was approved for use in the US in 2007.

The contraceptive efficacy of the radiopaque etonogestrel implant was demonstrated as no pregnancies occurred during the treatment period of the three-year studies reviewed. Although the evidence from the integrated analysis was based on the non-radiopaque etonogestrel implant, Study 34528 demonstrated bioequivalence with the radiopaque etonogestrel implant based on parameters in accordance with guidance from Health Canada.

The contraceptive efficacy profile of the radiopaque etonogestrel implant may be tied to the inherent adherence to treatment; however, the absence of comparative data reduces the ability to interpret the findings from the three studies.

Almost all patients had their menses return to their normal pre-trial pattern (83.5% of patients treated with the radiopaque etonogestrel implant in Study P05702; 94.4% of patients treated with the radiopaque etonogestrel implant and 90.5% of patients treated with the non-radiopaque etonogestrel implant in Study 34528). In all trials, patients were assessed for pregnancy 14 days after implant removal; during this period, six pregnancies were reported in the integrated analysis, and one pregnancy was reported in Study 34528. The lack of comparative data with other contraceptives makes it difficult to draw concrete conclusions regarding the clinical relevance of this finding.

The etonogestrel implant was palpable in almost all patients at each time point assessed (99.6% to 100% assessed every three months for the radiopaque etonogestrel implant in Study P05702; 100% in the radiopaque etonogestrel implant arm, and 97.1% to 100% in the non-radiopaque etonogestrel implant arm assessed every two months in 34528). The radiopaque etonogestrel was visible using X-ray imaging in all patients at insertion and removal in Study P05702; and was visible in 96.2% of patients after insertion and 100% of patients prior to removal in Study 34528.

The ability to palpate and visualize the implant are key features that reduce the harms related to implant migration. The product monograph included a serious warning and precaution box stating that at any time the implant is not palpable by the health care professional or the patient, the implant should be localized as soon as possible and removed as soon as medically appropriate to manage the risks of migration.[8] Implant migration was not assessed in the integrated analysis or Study 34528, although one patient treated with the radiopaque etonogestrel implant in Study P05702 experienced “mild” implant migration. The migration distance and definition of mild were not provided. The limited data from the pivotal trials on implant migration associated with the radiopaque etonogestrel implant is an important limitation. Post-marketing reports of implants located within the vessels of the arm and the pulmonary artery may be related to deep insertions or intravascular insertion.[8] Real-world evidence has demonstrated implant migration of the radiopaque etonogestrel implant into pulmonary vasculature at an estimated incidence of 3.17 per 100,000 implants (95% CI, 1.37 to 6.24) based on 2017 data from a study in France.[9] While implant migration may be rare, it can lead to respiratory issues and life-threating conditions and highlights the importance of proper insertion by trained clinicians.

Generally, investigators in Study P05702 became more satisfied with the radiopaque etonogestrel implant over time based on assessments of design and technical aspects, functionality, safety, used time, and applicator satisfaction. Descriptive outcomes based on the three studies indicated that the implant took less time to insert than to remove. Subgroup analysis based on Study P05702 showed that experienced clinicians took less time with the implant than inexperienced clinicians. Collectively, these findings highlight a learning curve that clinicians may experience and indicate that clinicians may take some

time to feel satisfied with the implant and may need more time for their first implant insertions and removals.

The expected and actual treatment satisfaction with the radiopaque etonogestrel implant was assessed in Study P05702, although aggregate efficacy results were not available. Evidence from an observational study of patients treated with the etonogestrel implant after a medical abortion reported that most patients (74.6%) were “very satisfied” with the implant, 16.9% were “quite satisfied,” 8.5% were “neither satisfied nor dissatisfied,” and none of the patients were dissatisfied; however, these results were limited by the study design and differential discontinuation.[15]

The timing of implant administration was explored in three other studies on relevant subgroups of patients. Findings from a six-month, single-centre RCT that compared immediate versus delayed placement of the radiopaque etonogestrel implant in patients following an abortion reported greater use of the implant in those treated immediately. This suggests that earlier insertion may allow for higher usage rates in a high-risk, hard-to-follow-up population.[18] The timing of treatment was not found to influence the use of the implant in young women post-abortion based on findings from a 12-month, non-blinded, single-centre RCT.[17] Although Health Canada has not authorized an indication for pediatric use, a subgroup of adolescents was identified as “of interest” by the clinical expert consulted for this review.[8] A systematic review and meta-analysis of patients undergoing medical abortion determined that the risk of subsequent unintended pregnancy was lower for patients treated with the etonogestrel implant simultaneously with mifepristone compared to delayed treatment (more than 24 hours after mifepristone) at three months (risk ratio = 0.10; 95% CI, 0.01 to 1.94; P = 0.13) and six months (risk ratio = 0.22; 95% CI, 0.06 to 0.78; P = 0.02).[16]

Although it is an important outcome to patients, HRQoL was not evaluated in the pivotal studies. Data on HRQoL were available from an observational study of women after an abortion for an unwanted pregnancy.[15] Women were treated with the etonogestrel implant (radiopaque or non-radiopaque not specified) (61.4%) or a control in the form of a short-acting reversible contraception (20%) or no hormonal contraception (18.6%). Patients in the etonogestrel implant group had significantly greater improvement compared with the control group (P < 0.0001); however, these results were limited by anticipated differences between the treatment groups (e.g., socioeconomic status), and differential discontinuation, which may have introduced bias.[15]

The comparative efficacy of the radiopaque etonogestrel implant with relevant contraceptives used in Canada could not be determined based on the evidence available for this review and highlights one of the major evidence gaps associated with this product.

One of the major limitations of the three pivotal studies relates to the high number of discontinuations that occurred, as 34.9% to 48.2% of patients discontinued the trial over the three-year period. The substantial number of discontinuations raises questions about the validity, interpretation, and actual utility of the radiopaque etonogestrel implant in the clinical setting. It is unclear if the clinical efficacy of non-radiopaque etonogestrel would be the same for the patients who discontinued the trial as for those who completed it. Theoretically, the three-year duration of the trials was sufficient to determine the effectiveness for patients; however, the extensive number of discontinuations should be considered when assessing the actual treatment time. Many patients discontinued the trials in year 1 and year 2, and some of the included trials in the integrated analysis were only

two years in duration. The totality of evidence in assessing actual etonogestrel implant use at three years is therefore limited.

The generalizability of the study findings to the Canadian population was limited by study eligibility requirements, which excluded patients that would be seen in the Canadian clinical population (e.g., adolescents, patients older than 40 years, patients with irregular menstrual cycles, patients with a BMI greater than 35 kg/m^2). The long-acting mechanism of action in the radiopaque etonogestrel implant is a feature that makes this form of contraception particularly desirable for patients with special circumstances (e.g., physical or cognitive challenges) and those at higher risk of unwanted pregnancies (e.g., adolescents, post-abortion patients).

Patients included in the three studies were required to be "healthy." Additionally, studies P05702 and 34528 required patients to have "good mental health." These health states were undefined, and it was left to the investigator's discretion to exclude potential participants who, in their opinion, would be at additional risk of experiencing harm by participating or would be unable to fulfill the study requirements. The exclusion of patients not meeting these criteria limits the generalizability to the Canadian clinical population as these patients would be seen in clinic.

Issues pertaining to the exclusion of patients with a BMI greater than 35 kg/m^2 are particularly noteworthy as they go beyond generalizability issues. The radiopaque etonogestrel implant is absorbed rapidly into circulation with the maximum serum concentration reached within one to 13 days, followed by a decline in concentration over time. Patients with higher body weights have lower serum concentrations of the drug compared with patients with a lower body weight. The concentration of the drug is lowest in the third year. None of the studies included subgroup analysis based on BMI; however, the integrated analysis did include some data on exposure by body weight and duration of use of the non-radiopaque etonogestrel implant. In a small set of patients, it was determined that there were no in-treatment pregnancies in 68 women weighing 70 kg or more who had been exposed for more than two years, and 11 in women who had been exposed for more than three years. Based on the totality of evidence reviewed, it is unclear how effective radiopaque etonogestrel implant is in patients with a BMI greater than 35 kg/m^2, especially throughout the third year.

Harms

AEs were experienced by almost all patients (90.4% to 100.0% based on data from studies P05702 and 34528). Total AEs are a key harms measure and were not reported in the integrated analysis; this absence limits the ability to make global assessments on the safety of the drug in the integrated analysis and prevents comparisons to other studies.

Bleeding irregularities were identified by the clinical expert consulted for the review as harms that were important to patients. When examined collectively, bleeding irregularities were the greatest source of AEs across the trials; however, an aggregate measure of AEs related to bleeding irregularities (troublesome bleeding) was not reported for any of the studies. Specific bleeding-related AEs (including dysmenorrhea, menorrhagia, metrorrhagia, vaginal hemorrhage, and genital hemorrhage) occurred in 5.3% to 28.2% of patients treated with the radiopaque etonogestrel implant in Study P05702. In Study 34528, specific bleeding-related AEs occurred in 3.8% to 46.2% of patients treated with the radiopaque etonogestrel implant and 7.1% to 41.1% of patients treated with the non-radiopaque etonogestrel implant. Specific bleeding irregularities (including amenorrhea and

infrequent, frequent and/or prolonged bleeding) occurred in 6.7% to 33.6% of a subset of 780 patients in the integrated analysis at two years.[10] No new safety signals arose in the other relevant studies of post-partum women summarized in brief in this report.

While many of the AEs were related to bleeding irregularities, some AEs observed may have been associated with the applicator used in the trial rather than the contents of the implant. None of the available evidence compared the radiopaque and non-radiopaque etonogestrel implants using the specific applicator designed for each product as the comparative study (34528) used the original applicator for both treatment arms (radiopaque and non-radiopaque etonogestrel implant). The original applicator is associated with the form of etonogestrel implant that previously received a Notice of Deficiency from Health Canada. The type of applicator used is of substantial importance as it defines one of two differences between the non-radiopaque (original) and radiopaque etonogestrel implants. The new next-generation applicator for the radiopaque etonogestrel implant was designed to facilitate correct subdermal insertion. The second difference between the two etonogestrel implants was the addition of barium sulphate to the implant, which was incorporated so that the implant can be seen by X-ray or other imaging tools. This study design choice was considered necessary for the maintenance of blinding, but it is unclear why the next-generation applicator was not used in place of the original version.

Study P05702 was the only trial that utilized the next-generation applicator associated with the radiopaque etonogestrel implant. In this study all investigators involved with insertion or removal of the non-radiopaque etonogestrel implant followed a training session on proper insertion and handling of the next-generation applicator that included an instruction leaflet and video followed by two successful insertions on a training arm. The product monograph includes a serious warning and precaution stating that the implant should be inserted or removed by health care professionals familiar with the use of the implant. It also states that health care professionals should receive instruction and training prior to inserting or removing the implant.[8] Some regions, such as the UK, require training through an accredited program to insert or remove the implant.[32] The sponsor's US-specific website states that only health care professionals who have received a training certificate by completing the Merck Clinical Training Program are authorized to purchase the radiopaque etonogestrel implant.[33] Written instructions, video demonstrations, and a training website (where health care providers can register for training sessions) will be available to clinicians in Canada; however, it is unclear what the uptake will be, if the training will be mandatory, and if the training received in clinic will be comparable to the training received in Study P05702. The training needs of clinicians in Canada will be of great importance as inadequate training may negatively impact the overall safety profile of radiopaque etonogestrel implant in clinic.

The Health Canada Reviewer Report for the radiopaque etonogestrel implant included data from a phase IV NORA study requested by the FDA, and post-marketing experience data.[7] Based on 7,364 insertion procedures in the NORA study, the incidence of incorrect insertions was 12.6 per 1,000 insertions (95% CI, 10.2 to 15.5), where incorrect insertions were included initially unrecognized non-insertions, partial insertions, deep insertions, non-palpability of the implant at insertion, and unsuccessful removals.[34] Based on 5,129 removal procedures in the NORA study, the incidence of unsuccessful removal was 0.2 per 1,000 removal procedures.[34] In the NORA study, there were no reports of implants that migrated more than a few centimetres from the insertion site.[34] Post-marketing experience was obtained on insertion- and/or removal-related events (including implant migration).

Based on 33,821,943 insertions, the worldwide reporting rate of insertion- and/or removal-related events was 0.07%.[7]

One of the major limitations of the three pivotal studies relates to the high number of discontinuations, with many attributed to bleeding irregularities and AEs. The harms data in the integrated analysis do not accurately reflect the three-year duration, as some of the included studies were only two years in duration.

Although the clinical expert consulted for this review suggested that the safety profile of the radiopaque etonogestrel implant is likely to be similar to those of other contraceptives, an absence of direct and indirect comparisons of harms data prevents strong conclusions from being made about the comparative safety of the radiopaque etonogestrel implant with other contraceptives used in Canada.

Conclusions

Data from three studies suggest that etonogestrel implant is effective in preventing pregnancies in healthy women treated with the radiopaque or non-radiopaque etonogestrel implant over the course of three years. The radiopaque and non-radiopaque formulations of etonogestrel were bioequivalent with respect to parameters in accordance with guidance from Health Canada. The three reviewed studies similarly demonstrated potentially increased frequency of bleeding irregularities with the etonogestrel implant. There was insufficient evidence to assess the effects of radiopaque etonogestrel implant on quality of life and patient satisfaction.

Key limitations across all studies included concerns about generalizability because the study participants were a selective group compared with all women of child-bearing age who could potentially receive etonogestrel, and high discontinuation rates often related to bleeding irregularities. The generalizability of the study findings to clinical practice settings in Canada was limited by eligibility requirements that excluded certain patients, including adolescents, patients older than 40 years, patients with irregular menstrual cycles, and those with a BMI greater than 35 kg/m^2. Evidence gaps include an absence of direct and indirect comparisons to relevant contraceptives used in Canada, and the efficacy of the radiopaque etonogestrel implant in subgroups of patients that were excluded in the trials.

Due to critical limitations with the studies on quality of life and the relevant subgroups of patients (post-partum women and young women), interpretation of the results of these studies was challenging and limited at best.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–present) Embase (1974–present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid
Date of search:	October 25, 2019
Alerts:	Bi-weekly search updates until project completion
Study types:	Randomized controlled trials; controlled clinical trials; economic evaluations; costs and cost analysis studies, and quality of life studies
Limits:	Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.ot	Original title
.hw	Subject heading word
.rn	Registry number
.dq	Candidate term word
.nm	Name of substance word
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(implanon* or nexplanon* or ORG 3236 or ORG3236 or ORG 532 or ORG532 or 3-Ketodesogestrel or 3-Oxodesogestrel or 3-Keto-desogestrel or 3-oxo desogestrel).ti,ab,kf,ot,hw,rn,nm.
2	(etonogestrel* or 304GTH6RNH* or UNII304GTH6RNH*).ti,ab,kf,ot,hw,rn,nm. and ((implant* or subdermal* or subcutaneous or rod or rods).ti,ab,kf. or Drug Implants/)
3	(progestin adj2 implant*).ti,ab,kf.

MULTI-DATABASE STRATEGY	
4	or/1-3
5	4 use medall
6	(*etonogestrel/ or etonogestrel*.ti,ab,kw,dq.) and ((implant* or subdermal* or intrauterine).ti,ab,kw. or drug implant/ or progestin implant/)
7	(implanon* or nexplanon* or ORG 3236 or ORG3236 or ORG 532 or ORG532 or 3-Ketodesogestrel or 3-Oxodesogestrel or 3-Keto-desogestrel or (progestin adj2 implant*)).ti,ab,kw,dq.
8	6 or 7
9	(conference abstract or conference review).pt.
10	8 not 9
11	10 use oemezd
12	5 or 11
13	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
14	Randomized Controlled Trial/
15	exp Randomized Controlled Trials as Topic/
16	"Randomized Controlled Trial (topic)"/
17	Controlled Clinical Trial/
18	exp Controlled Clinical Trials as Topic/
19	"Controlled Clinical Trial (topic)"/
20	Randomization/
21	Random Allocation/
22	Double-Blind Method/
23	Double Blind Procedure/
24	Double-Blind Studies/
25	Single-Blind Method/
26	Single Blind Procedure/
27	Single-Blind Studies/
28	Placebos/
29	Placebo/
30	Control Groups/
31	Control Group/
32	(random* or sham or placebo*).ti,ab,hw,kf,kw.
33	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
34	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
35	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
36	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
37	allocated.ti,ab,hw.
38	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
39	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.

MULTI-DATABASE STRATEGY	
40	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
41	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
42	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
43	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
44	or/13-43
45	12 and 44
46	remove duplicates from 45

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: (implanon or nexplanon or etonogestrel)	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: (implanon or nexplanon or etonogestrel)	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.	

Grey Literature

Dates for Search:	October 10-17, 2019
Keywords:	(implanon OR nexplanon OR etonogestrel OR long-acting contraceptives OR contraceptive implant)
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search

Appendix 2: Excluded Studies

Table 20: Excluded Studies

Reference	Reason for exclusion
Bahamondes L, Brache V, Ali M, Habib N, women WHOsgocif. A multicenter randomized clinical trial of etonogestrel and levonorgestrel contraceptive implants with nonrandomized copper intrauterine device controls: effect on weight variations up to 3 years after placement. *Contraception*. 2018;98(3):181-187.[35]	Intervention and comparator
Apter D, Briggs P, Tuppurainen M, et al. A 12-month multicenter, randomized study comparing the levonorgestrel intrauterine system with the etonogestrel subdermal implant. *Fertil Steril*. 2016;106(1):151-157.e155.[36]	Comparator
Bahamondes L, Brache V, Meirik O, et al. A 3-year multicentre randomized controlled trial of etonogestrel- and levonorgestrel-releasing contraceptive implants, with non-randomized matched copper-intrauterine device controls. *Hum Reprod*. 2015;30(11):2527-2538.[37]	Intervention and comparator
Meirik O, Brache V, Orawan K, et al. A multicenter randomized clinical trial of one-rod etonogestrel and two-rod levonorgestrel contraceptive implants with nonrandomized copper-IUD controls: methodology and insertion data. *Contraception*. 2013;87(1):113-120.[38]	Intervention

Appendix 3: Detailed Outcome Data

Table 21: Overview of 11 International Studies of the Non-Radiopaque Etonogestrel Implant

Study	Trial design	Year conducted	Primary end point	Study N	Study duration[a]	Publications
069001	Phase III open-label, non-comparative, multi-centre	1993 to 1996	Contraceptive efficacy, safety	330	Two years	Funk et al.[39]
34502	Phase II single-centre, open-label	1989 to 1995	PK, PD, bleeding pattern	15	Two years	
34505	Phase II open-label, single-centre, non-comparative	1991 to 1996	Contraceptive efficacy, safety, acceptability	100	Two years or up to four years (optional extension period)	Kiriwat et al.[40]
34507	Phase III open-label, multi-centre, non-comparative	1991 to 1996	Contraceptive efficacy, safety, acceptability	636	Two years or up to three years (for a 147-women cohort from two centres)	Croxatto et al.[41] Croxatto et al.[42]
34510	Phase IIIa open-label, bi-centre, RCT, comparative Comparator: Norplant (randomized) and copper IUD (non-randomized)	1992 to 1996	Lipid metabolism	90 (randomized) 45 (non-randomized)	Three years	Suherman et al. (1999)[43]
34511	Phase IIIa open-label, RCT, comparative, single-centre Comparator: Norplant	1992 to 1995	Carbohydrate metabolism	80	Two years	Biswas et al.[44] Biswas et al.[45] Biswas et al.[46] Biswas et at.[47]
34512	Phase III open-label, bi-centre, RCT, comparative Comparator: Norplant	1992 to 1995	Lipid metabolism	80	Two years	
34515	Phase II open-label, single-centre, non-comparative	1994 to 1997	Bioavailability	10	Two years	
34522	Phase II open-label, non-randomized, 3-centre, comparative Comparator: copper IUDs	1994 to 1997	Bone mineral density	79	Two years	Beerthuzien et al.[48]
34525	Phase IIIb open-label, non-comparative, bi-centre	2001 to 2003	Contraceptive efficacy	60	One year or up to three years (upon patient's wish and investigator's decision)	
E1729	Phase IV open-label, non-comparative, multi-centre	2001 to 2005	Contraceptive efficacy	210	Three years	

IUD = intrauterine device; PD = pharmacodynamics; PK = pharmacokinetics; RCT = randomized controlled trial.

[a] Excluding a follow-up period of three months.

Source: Clinical Study Reports for Studies 069001,[49] 34502,[50] 34505,[51] 34507,[52] 34510,[53] 34511,[54] 34512,[55] 34515,[56] 34522,[57] 34525,[58] and E1729,[59]

Table 22: Frequency (%) on Implant Insertion and Removal in P05702

Category	Item	N (%)
Implant insertion	Investigator was not supervised	301 (100)
	Is inserting investigator responsible for all insertions?	301 (100)
Preparation of patient	Position of patient (lying)	300 (99.7)
	Anything unusual during anesthesia (no)	300 (99.7)
Preparing the applicator for insertion	Taking applicator from blister (difficult)	1 (0.3)
	Difficulty in removing protection cap (no)	294 (97.7)
	Difficulties holding applicator at textured surface (no)	300 (99.7)
	Easy to check the presence of the implant in the applicator (no)	1 (0.3)
	Difficult to keep needle and implant sterile (no)	1 (0.3)
Insertion of the implant	Difficulty in puncturing the skin (no)	287 (95.3)
	What angle was the skin punctured (< 45 degrees)	277 (92.0)
	Difficulty in sliding needle in subdermal connective tissue (no)	274 (91.0)
	Was the needle inserted in the correct position? (no)	2 (0.7)
	Was the needle inserted to its full length? (yes)	301 (100)
	Difficulty in unlocking the slider (no)	299 (99.3)
	Was it clear when the slider was arrested in the back? (yes)	301 (100)
	Difficulty in removing the applicator (no)	301 (100)
	Was the needle fully retracted and invisible? (yes)	301 (100)
Outcome of the insertion procedure	In which arm was the implant inserted? (left)	275 (91.4)
	Was the implant inserted in the non−dominant arm? (yes)	301 (100)
	Was the implant clearly palpable? (no)	1 (0.3)
	Where was the implant inserted: above the sulcus bicipitalis medialis (i.e., over the biceps muscle); below the sulcus bicipitalis medialis (i.e., over the triceps muscle); in the sulcus bicipitalis medialis?	 62 (20.6); 38 (12.6); 201 (66.8)
	Was the implant inserted correctly? (yes)	301 (100)
	Was overall insertion easy or difficult? (difficult)	6 (2.0)
	Status at site implant: no abnormalities swelling redness pain haematoma expulsion.	 275 (91.4); 4 (1.3); 12 (4.0); 2 (0.7); 10 (3.3)

Source: Clinical Study Report for P05702.[12]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures included in each study and review their measurement properties (validity, reliability, responsiveness to change, and minimal important differences).

The outcome measures used in each study are summarized in Table 23. The primary outcomes in studies P05702 and 34528 (i.e., user satisfaction and contraceptive efficacy, respectively) are described and appraised in this section. The patient-reported outcomes, the ESQ and ASQ are also reviewed. All other outcomes were either clinical outcomes, such as return of menses or localization of implant, or descriptive outcomes such as time for insertion and removal, and therefore are briefly described, but are not further reviewed in this section.

Table 23: Outcome Measures Included in Each Study

Outcome measure	Integrated analysis (non-radiopaque etonogestrel implant)	P05702	34528
Contraceptive efficacy (Pearl Index)	Primary	Other	Other
User Satisfaction Questionnaire	–	Primary	–
Bioequivalence			Primary
Insertion characteristics (Time for insertion)	Not categorized	Secondary	Other
Removal characteristics (Time for removal)	Not categorized	Secondary	Other
Localization of implant (Palpation and X-ray imaging)	–	Other	Other
Return of menses	–	Other	Other
Expected and Actual Satisfaction Questionnaire	–	Other	–
Drug concentration measurements	–	–	Other

Findings

Table 24: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Contraceptive efficacy (Pearl Index)	Calculated index of the number of contraceptive failures per 100 woman-years of use.[61,62] The lower the index, the more efficacious the contraceptive method.	The Pearl Index is the most commonly reported measure of contraceptive failure in clinical studies, although not widely used in clinical practice. It is limited in that it can vary depending on the exposure time (denominator).[61,62]	NA
User Satisfaction Questionnaire	Product-specific, investigator-reported satisfaction questionnaire evaluating the investigator's satisfaction with the	There is no available evidence on the validation, reliability, and responsiveness of the user satisfaction questionnaire.	NA

Outcome measure	Type	Conclusions about measurement properties	MID
	technical/design, function and safety features of the applicator, as well as the total time it takes to perform the insertion, and their overall impression of the applicator.[12] The questionnaire consists of five overall questions, with sub-items for selected questions, with five possible answers ranging from very satisfied to very dissatisfied.		
Expected and Actual Satisfaction questionnaire	The ESQ and ASQ are 32-item, patient-reported questionnaires designed to evaluate the patient's expected and actual satisfaction of the implant.[30] The questionnaires cover six domains: physician counselling, insertion and removal of the implant, bleeding pattern, side effects, general characteristics, and overall satisfaction. A 5-point Likert scale is used to respond to each item with 1 reflecting the most negative experience, and 5 reflecting the most positive experience. Possible total scores are between 10 and 50, with higher scores indicating higher levels of satisfaction.	Results of initial validation studies conducted with the non-radiopaque etonogestrel implant demonstrated acceptable internal consistency across all domains, with lower internal consistency of the insertion and removal characteristics in the ASQ.[30] The instruments did not correlate with the domains and items of the PSQ-18 and TSQM-11, both at counselling (ESQ) and 3 months after insertion (ASQ). Conversely, the global satisfaction score, and total score of the instruments correlated strongly with the global satisfaction assessed by the TSQM-II.[30] ROC curve analysis performed on the ASQ data indicated that the total score was an excellent predictor of satisfaction, while general characteristics and bleeding patterns were good predictors, and counselling, side effects, and insertion/removal domains were fair predictors.[30]	NA

ASQ = actual satisfaction questionnaire; ESQ = expected satisfaction questionnaire; MID = minimal important difference; NA = not applicable; PSQ-18 = 18-item Patient Satisfaction Questionnaire–18; ROC = receiver operating characteristic; TSQM-II = Treatment Satisfaction Questionnaire for Medication, version II.

Contraceptive Efficacy and the Pearl Index

In clinical guidelines, contraceptive efficacy refers to the number of pregnancies prevented during correct and consistent use of a method (i.e., perfect use of the method).[1] Contraceptive effectiveness is the clinical term used for the number of pregnancies prevented during typical use of a method, where typical use is dependent on adherence to the contraceptive method.[1] In contraceptive studies, contraceptive efficacy is often defined as the number of unplanned pregnancies that occur during a specified period of exposure time while using a contraceptive method.[61] In these cases, the sponsor is generally assuming perfect use of the method, and pregnancy events are therefore measured until the completion of the study, discontinuation of the method, or failure of the method (pregnancy).[62]

The PI, which is one of the most commonly reported measures of contraceptive efficacy in clinical trials, describes the failure rate of a contraceptive method.[61] The PI is defined as the number of contraceptive failures per 100 woman-years of use; it is obtained by dividing the number of unplanned pregnancies (numerator) by the number of months or years of

exposure to the risk (denominator).[62] The smaller the PI, the safer the contraceptive method. Given its ease of calculation, the PI continues to be the most widely used statistical measure of contraceptive failure.[62] However, the clinical expert consulted for this review indicated that the PI is not commonly used in clinical practice.

The PI can be calculated using different exposure times in the studies yielding overall or annual indices. The overall PI counts the pregnancies that occur throughout an overall assessment period while the annual PI counts the pregnancies per year of exposure.

The major limitation of the PI is that it can be misleading, given that failure rates are highly dependent on the length of exposure time evaluated.[61,62] As a result, the PI generally decreases with a longer trial, because the likelihood of an unplanned pregnancy decreases over time, likely due to increased proficiency of use of the method over time. Therefore, PIs can approach zero by extending the length of a trial.[62] For this reason, a comparison of PIs across various contraceptive methods, or of the same method across various studies, may not always be valid.[61,62] However, this issue is more significant in contraceptive methods that are dependent on user adherence, such as oral contraceptive pills.

User Satisfaction Questionnaire

A User Satisfaction Questionnaire developed by the sponsor was completed by a single investigator after the fourth, eighth, and 12th insertions at each clinical study site in Study P05702.[12] The questionnaire was designed to evaluate the efficacy and ease of use of the next-generation applicator for the radiopaque etonogestrel implant. The questionnaire was filled out by both experienced (more than 10 insertions of the previous product, the non-radiopaque etonogestrel implant) and non-experienced investigators (fewer than 10 insertions of the previous product, the non-radiopaque etonogestrel implant), and was completed by the same investigator to allow for an assessment of learning curves.[12]

The User Satisfaction Questionnaire consists of five questions covering the investigator's satisfaction with the technical and design (fit, weight, size, handling, and colour), functional (verification of needle, guiding of needle, and retraction of needle), and safety (protection cap, retraction feature, and visibility of an empty applicator) features of the applicator, as well as satisfaction with the total time it takes to perform the insertion, and the overall impression of the applicator.[12] For each question or item, the respondent chooses from five possible answers: very satisfied, satisfied, not satisfied nor dissatisfied, dissatisfied, and very dissatisfied. A list of the questions and associated items can be found in Table 25.[12] At the time of this review, there was no available evidence on the validation, reliability, and responsiveness of the questionnaire.

Table 25: User Satisfaction Questionnaire Components

Questions	Items
1. How satisfied or dissatisfied are you with the design and technical aspects of the applicator?	• fit of the applicator in the hand • size of the applicator • weight of the applicator • handling of the applicator • colour of the applicator
2. How satisfied or dissatisfied are you with the functional aspects of the applicator?	• verifying the presence of the implant in the needle before insertion • guiding the needle into the correct subdermal position by puncturing the skin, lifting the skin to ensure subdermal position of the needle,

Questions	Items
	horizontal lowering of the applicator ensuring the steering of the needle in the subdermal position • the one-hand action during retraction of the needle • other
3. How satisfied or dissatisfied are you with the safety aspects of the applicator?	• removal of the protection cap from the applicator • full retraction of the needle into the applicator after insertion • difference in colours of the obturator and the implant, to visually verify that the implant is no longer in the applicator
4. How satisfied or dissatisfied are you with the amount of time it takes to perform the insertion?	NA
5. Taking all things into account, how satisfied or dissatisfied are you with the applicator?	NA

NA = not applicable.

Source: Clinical Study Report for P05702.[12]

Expected and Actual Satisfaction Questionnaires

The expected and actual treatment satisfaction with the radiopaque etonogestrel implant was assessed in Study P05702 using two patient-reported outcome instruments, the ESQ and ASQ. The ESQ and ASQ are 32-item questionnaires covering six domains: physician counselling, insertion and removal of the implant, side effects, bleeding patterns, general characteristics, and overall satisfaction. Each item has five possible responses, with 1 being the most negative experience (i.e., strongly disagree) to 5 being the most positive (i.e., strongly agree). The response values depend on the domain (Table 26).[30] Additionally, for the side-effect and bleeding pattern domains, the patients are asked if they expect to experience (ESQ) or have experienced (ASQ) the item. Domain scores are computed if at least half of the items plus one were answered. The item scores for each domain are averaged, and then multiplied by 10. A total score is calculated by summing up all domain scores and dividing by six. Possible total scores are between 10 and 50, with higher scores indicating higher levels of satisfaction.[30]

Table 26: Response Options to the Expected and Actual Satisfaction Questionnaires

Domains	Domain question	Possible responses
Physician counselling and insertion and removal (items 1 to 9)	How strongly do you AGREE or DISAGREE with each of the following statements?	1 = strongly disagree 2 = disagree 3 = neutral 4 = agree 5 = strongly agree
Side effects and bleeding pattern (items 10 to 24)	1) Indicate whether you expect to (ASQ) or have experienced (ESQ) the items. 2) 2) Indicate whether the experiences would have (ASQ) or had (ESQ) an impact on your overall satisfaction with the implant.	1 = very negative impact 2 = negative impact 3 = no impact 4 = positive impact 5 = very positive impact
General characteristics (items 25 to 31)	Do you consider the following characteristics of the implant to have an impact on your overall satisfaction with the implant?	1 = very negative impact 2 = negative impact 3 = no impact 4 = positive impact 5 = very positive impact
Overall satisfaction (item 32)	In general, how satisfied are you with the implant?	1 = very dissatisfied 2 = dissatisfied

Domains	Domain question	Possible responses
		3 = neutral 4 = satisfied 5 = very satisfied

ASQ = actual satisfaction questionnaire; ESQ = expected satisfaction questionnaire.

The questionnaires were initially developed by a contract research organization outside of the clinical study protocol, for validation with the non-radiopaque etonogestrel implant.[12,30] Results of the initial validation studies were provided by the sponsor.[30] Reliability was assessed through internal consistency; acceptable internal consistency (Cronbach's alpha > 0.70) was observed across all ESQ and ASQ domains, with the exception of insertion and removal characteristics in the ASQ (Cronbach's alpha = 0.67).[30] To assess construct validity, scores from the ESQ (n = 104) and ASQ (n = 98) were compared to select questions on the 18-item Patient Satisfaction Questionnaire (PSQ-18) and version II of the Treatment Satisfaction Questionnaire for Medication (TSQM-II). The instruments were not found to correlate with the domains and items of the PSQ-18 and TSQM-II, both at counselling (ESQ) and three months after insertion (ASQ), with Pearson correlation coefficients ranging from –0.08 to 0.37. Conversely, the global satisfaction score and total score of the instruments correlated strongly with the global satisfaction assessed by the TSQM-II (Pearson correlation coefficient = 0.66).[30] Furthermore, the receiver operating characteristic curve analysis performed on the ASQ data demonstrated that the total score was an excellent predictor of satisfaction, while general characteristics and bleeding patterns were good predictors, and counselling, side effects, and insertion and removal domains were fair predictors.[30] Descriptive statistics suggested that some of the bleeding patterns had a high impact on the expected and actual satisfaction of the implant; when a woman expected to experience either positive (such as amenorrhea, less-frequent bleeding and lighter bleeding) or negative (such as spotting and more-frequent bleeding) side effects, and they experienced these side effects, this was correlated with more positive and negative actual satisfaction, respectively. Unpredictable bleeding, dysmenorrhea, and irregular bleeding did not have an effect on the expected satisfaction, but had a negative effect on satisfaction if experienced.[30]

In Study P05702, the ESQ was completed at screening, while the ASQ was completed at visits at months 3, 6, 12, 34, and 36 (implant removal).[12] For validation purposes, selected questions from the PQS-18 and TSQM-II were also filled in by a subset of subjects from Australia, Sweden, and Germany. The PSQ-18 was filled in at screening and at the three-month visit, while the TSMQ-II was filled out at the three-month visit only.[12] Given that these results are collected as part of the clinical trial, and have not gone through a peer-review process, the validity of these questionnaires with the radiopaque etonogestrel implant is limited.[12]

Other Outcomes

The remaining outcome measures used in the clinical studies under review are summarized in Table 27.

Table 27: Additional Outcome Measures

Outcome	Description
Insertion and removal characteristics	• Time for insertion (sec) • Time for removal (sec)
Palpation	• Study P05702: Recorded at implant insertion, and visits scheduled at month 3, 6, 9, 12, 18, 24, 30, and 36 (implant removal) • Study 34528: Recorded at implant insertion, and visits scheduled at month 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, and 36 (implant removal) • In both studies, palpability was recorded as palpable or not palpable
X-ray imaging	• Study P05720: A subgroup of 50 patients were scheduled for two-dimensional X-ray imaging directly after implant insertion (within 1 day after insertion) and before implant removal (≤ 15 days). For all remaining insertions, two-dimensional X-ray imaging was only to be performed in case the implant was not palpable • Study 34528: X-ray imaging was scheduled ≤ 14 days after implant insertion, and ≤ 14 days before implant removal • In both studies, the results of the X-ray were recorded as clearly visible or unclearly/not visible
Return of menses	• A post-treatment evaluation of the return of menses was scheduled three months after implant removal for women who were not pregnant, were not breastfeeding, and were not using post-treatment hormonal contraceptives • In both studies, return of menses to normal was recorded as Yes or No, where normal was defined as the pre-treatment menses pattern
Drug concentration measurements	• Etonogestrel serum concentration measurements were taken pre-treatment and every 3 months post-insertion of the implants to compare pharmacokinetic parameters (t_{max}, C_{max}, $AUC_{0\text{-}6months}$, 6-month concentration, $AUC_{0\text{-}24months}$, 24-month concentration, $AUC_{0\text{-}36months}$, and 36-month concentration) between the non-radiopaque and radiopaque implants

AUC = area under the curve; C_{max} = peak concentration; t_{max} = time of first occurrence.

References

1. Black A, Guilbert E, Costescu D, et al. Canadian Contraception Consensus (part 1 of 4). *J Obstet Gynaecol Can.* 2015;37(10):936-942.
2. Vogel L. Canadian women opting for less effective birth control. *CMAJ.* 2017;189(27):E921-922.
3. Black A, Yang Q, Wu Wen S, Lalonde AB, Guilbert E, Fisher W. Contraceptive use among Canadian women of reproductive age: results of a national survey. *J Obstet Gynaecol Can.* 2009;31(7):627-640.
4. Norman WV. Induced abortion in Canada 1974-2005: trends over the first generation with legal access. *Contraception.* 2012;85(2):185-191.
5. Induced abortions reported in Canada in 2017. Ottawa (ON): Canadian Institute for Health Information; 2017: https://www.cihi.ca/en/induced-abortions-reported-in-canada-in-2017. Accessed 2020 Jan 3.
6. CDR submission: Nexplanon (etonogestrel extended release subdermal implant) [**CONFIDENTIAL** sponsor's submission]. Kirkland (QC): Merck Canada Inc.; 2020 Jun.
7. Health Canada reviewer's report: Nexplanon (etonogestrel) [**CONFIDENTIAL** internal report]. Ottawa (ON): Therapeutics Products Directorate, Health Canada; 2020.
8. Nexplanon (etonogestrel extended release subdermal implant): extended release implant, 68 mg per implant (to deliver up to 70 mcg etonogestrel per day), subdermal [product monograph]. Kirkland (QC): Merck Canada Inc.; 2020 May 25.
9. Simon C, Maurier A, Gaboriau L, et al. Incidence and characteristics of intravascular pulmonary migration of etonogestrel implants: a French nationwide study. *Contraception.* 2020.
10. Mansour D, Korver T, Marintcheva-Petrova M, Fraser IS. The effects of Implanon on menstrual bleeding patterns. *Eur J Contracept Reprod Health Care.* 2008;13 Suppl 1:13-28.
11. Clinical Overview: R&D release report ODIN: INT00065117 [**CONFIDENTIAL** internal sponsor's report]. Kirkland (QC): Merck Canada Inc.; 2010 Mar.
12. Clinical Study Report: P05702. Three-year study in healthy women of at least 18 but not older than 40 years of age at the time of screening with the long-acting radiopaque implant for the indication contraception. [**CONFIDENTIAL** internal sponsor's report]. Kenilworth (NJ): Schering-Plough Research Institute; 2011 Apr 11.
13. Clinical Study Report: 34528. A randomized, double-blind, parallel group, bioequivalence study of Implanon® and radiopaque Implanon. [**CONFIDENTIAL** internal sponsor's report]. Kenilworth (NJ): Schering-Plough Research Institute; 2009 Apr.
14. Darney P, Patel A, Rosen K, Shapiro LS, Kaunitz AM. Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. *Fertil Steril.* 2009;91(5):1646-1653.
15. Caruso S, Vitale SG, Fava V, Pasqua SD, Rapisarda AMC, Cianci S. Quality of life of women using the etonogestrel long-acting reversible contraceptive implant after abortion for unplanned pregnancy. *Eur J Contracept Reprod Health Care.* 2020:1-8.
16. Schmidt-Hansen M, Hawkins JE, Lord J, et al. Long-acting reversible contraception immediately after medical abortion: systematic review with meta-analyses. *Hum Reprod Update.* 2020;26(2):141-160.
17. Bryant AG, Bauer AE, Stuart GS, et al. Etonogestrel-releasing contraceptive implant for postpartum adolescents: a randomized controlled trial. *J Pediatr Adolesc Gynecol.* 2017;30(3):389-394.
18. Cowett AA, Ali R, Cooper MA, Evans M, Conzuelo G, Cremer M. Timing of etonogestrel implant insertion after dilation and evacuation: a randomized controlled trial. *Obstet Gynecol.* 2018;131(5):856-862.
19. Azzarello D, Collins J. Canadian access to hormonal contraceptive drug choices. *J Obstet Gynaecol Can.* 2004;26(5):489-500.
20. Black A, Guilbert E, Costescu D, et al. Canadian Contraception Consensus (part 2 of 4). *J Obstet Gynaecol Can.* 2015;37(11):1033-1039.
21. Mirena (levonorgestrel-releasing intrauterine system): 52 mg to deliver up to 20 mcg levonorgestrel per day [product monograph]. Mississauga (ON): Bayer Inc.; 2019 Jun 14: https://www.bayer.ca/omr/online/mirena-pm-en.pdf. Accessed 2019 Dec 7.
22. Kyleena (levonorgestrel-releasing intrauterine system): 19.5 mg [product monograph]. Mississauga (ON): Bayer Inc; 2019 Jun 7: https://www.bayer.ca/omr/online/kyleena-pm-en.pdf. Accessed 2019 Dec 7.
23. Black A, Guilbert E, Costescu D, et al. No. 329-Canadian Contraception Consensus part 4 of 4 chapter 9: combined hormonal contraception. *J Obstet Gynaecol Can.* 2017;39(4):229-268.e225.
24. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.
25. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Jan 3.
26. Graesslin O, Korver T. The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. *Eur J Contracept Reprod Health Care.* 2008;13 Suppl 1:4-12.

27. Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M. Tolerability and clinical safety of Implanon. *Eur J Contracept Reprod Health Care.* 2008;13 Suppl 1:29-36.

28. Mansour D, Mommers E, Teede H, et al. Clinician satisfaction and insertion characteristics of a new applicator to insert radiopaque Implanon: an open-label, noncontrolled, multicenter trial. *Contraception.* 2010;82(3):243-249.

29. Schnabel P, Merki-Feld GS, Malvy A, Duijkers I, Mommers E, van den Heuvel MW. Bioequivalence and x-ray visibility of a radiopaque etonogestrel implant versus a non-radiopaque implant: a 3-year, randomized, double-blind study. *Clin Drug Investig.* 2012;32(6):413-422.

30. Organon response to November 15 request for additional information regarding etonogestrel review: development and validation of a PRO instrument to assess users' expectations and satisfaction with Implanon® [**CONFIDENTIAL** additional sponsor's information]. Oss (NL): Organon; 2008 Mar 10.

31. Health Canada. Guidance document - comparative bioavailability standards: formulations used for systemic effects. 2018: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bio/comparative-bioavailability-standards-formulations-used-systemic-effects.pdf. Accessed 2019 Dec 5.

32. Medicines and Healthcare products Regulatory Agency. Nexplanon (etonogestrel) contraceptive implants: new insertion site to reduce rare risk of neurovascular injury and implant migration; 2020 Feb 12: https://www.gov.uk/drug-safety-update/nexplanon-etonogestrel-contraceptive-implants-new-insertion-site-to-reduce-rare-risk-of-neurovascular-injury-and-implant-migration. Accessed 2020 Jul 14.

33. Merck Connect. Professional resources. 2019; https://www.merckconnect.com/nexplanon/professional-resources/. Accessed 2020 Jul 14.

34. Clinical Study Report: MK-8451. Nexplanon observational risk assessment study (NORA). [**CONFIDENTIAL** internal sponsor's report]. Whitehouse Station (NJ): Merck Sharp & Dohme Corp.; 2018 Mar 20.

35. Bahamondes L, Brache V, Ali M, Habib N, W. H. O. study group on contraceptive implants for women. A multicenter randomized clinical trial of etonogestrel and levonorgestrel contraceptive implants with nonrandomized copper intrauterine device controls: effect on weight variations up to 3 years after placement. *Contraception.* 2018;98(3):181-187.

36. Apter D, Briggs P, Tuppurainen M, et al. A 12-month multicenter, randomized study comparing the levonorgestrel intrauterine system with the etonogestrel subdermal implant. *Fertil Steril.* 2016;106(1):151-157.e155.

37. Bahamondes L, Brache V, Meirik O, et al. A 3-year multicentre randomized controlled trial of etonogestrel- and levonorgestrel-releasing contraceptive implants, with non-randomized matched copper-intrauterine device controls. *Hum Reprod.* 2015;30(11):2527-2538.

38. Meirik O, Brache V, Orawan K, et al. A multicenter randomized clinical trial of one-rod etonogestrel and two-rod levonorgestrel contraceptive implants with nonrandomized copper-IUD controls: methodology and insertion data. *Contraception.* 2013;87(1):113-120.

39. Funk S, Miller MM, Mishell DR, Jr., et al. Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. *Contraception.* 2005;71:319-326.

40. Kiriwat O, Koetsawang S, Korver T, Bennink HC. A 4-year pilot study on the efficacy and safety of Implanot, a single-rod hormonal contraceptive implant, in healthy women in Thailand. *Eur J Contracept Reprod Health Care.* 1998;3:85-91.

41. Croxatto H, Urbancsek J, Massai R, Bennink HC, Van Beek A. A multicentre efficacy and safety study of the single contraceptive implant Implanon. *Hum Reprod.* 1999;14(4):976-981.

42. Croxatto HB. Clinical profile of Implanon: a single-rod etonogestrel contraceptive implant. *Eur J Contracept Reprod Health Care.* 2000;5(2):21-28.

43. Suherman SK, Affandi B, Korver T. The effects of Implanon on lipid metabolism in comparison with Norplant. *Contraception.* 1999;60(5):281-287.

44. Biswas A, Viegas OA, Bennink HJ, Korver T, Ratnam SS. Effect of Implanon use on selected parameters of thyroid and adrenal function. *Contraception.* 2000;62(5):247-251.

45. Biswas A, Viegas OA, Coeling Bennink HJ, Korver T, Ratnam SS. Implanon contraceptive implants: effects on carbohydrate metabolism. *Contraception.* 2001;63(3):137-141.

46. Biswas A, Viegas OA, Roy AC. Effect of Implanon and Norplant subdermal contraceptive implants on serum lipids--a randomized comparative study. *Contraception.* 2003;68(3):189-193.

47. Biswas A, Biswas S, Viegas OA. Effect of etonogestrel subdermal contraceptive implant (Implanon) on liver function tests -- a randomized comparative study with Norplant implants. *Contraception.* 2004;70(5):379-382.

48. Beerthuizen R, van Beek A, Massai R, Makarainen L, Hout J, Bennink HC. Bone mineral density during long-term use of the progestagen contraceptive implant Implanon compared to a non-hormonal method of contraception. *Hum Reprod.* 2000;15(1):118-122.

49. Clinical Study Report: 069001. An open label, noncomparative efficacy and safety study of Org 32222 (Implanon™), a one-rod contraceptive implant containing Org 3236 (3-ketodesogestrel) in healthy female volunteers, with subsets for pharmacokinetic measurements, ophthalmological assessments, carbohydrate metabolism, lipid metabolism, and endometrial morphology. [**CONFIDENTIAL** internal sponsor's report]. Organon; 2002 Aug.

50. Clinical Study Report: 34502. A pharmacodynamic/pharmacokinetic study with a one-rod implant (Org 32222) containing 3-ketodesogestrel (Org 3236) in healthy female subjects. [**CONFIDENTIAL** internal sponsor's report]. Oss (NL): NV Organon; 1996 Sep.

51. Clinical Study Report: 34505. An open, single centre, pilot efficacy and safety study of an all EVA one-rod implant releasing 60 microgram 3-ketodesogestrel (Org 3236)/day (Org 32222, Implanon®). [**CONFIDENTIAL** internal sponsor's report]. Oss (NL): NV Organon; 1996 Sep.

52. Clinical Study Report: 34507. An open, multicentre, efficacy and safety study of an all EVA one-rod implant (Org 32222, Implanon®) releasing 3-ketodesogestrel (Org 3236) in healthy female volunteers. [**CONFIDENTIAL** internal sponsor's report]. Oss (NL): NV Organon; 1997 Jul.

53. Clinical Study Report: 34510. An open bi-centre randomised comparative study of Implanon® (Org 32222) and Norplant® and with a non-randomised control group of multiload Cu 250 users on lipid metabolism, efficacy and safety in healthy female volunteers [**CONFIDENTIAL** internal sponsor's report]. Oss (NL): NV Organon; 1997 Jan.

54. Clinical Study Report: 34511. An open randomised comparative study of Implanon® (Org 32222) and Norplant® on carbohydrate metabolism, thyroid and adrenal function, in healthy female volunteers [**CONFIDENTIAL** internal sponsor's report]. Oss (NL): NV Organon; 1996 Sep.

55. Clinical Study Report: 34512. An open, randomised, comparative, bi-centre study to evaluate the effects of Implanon® (Org 32222) and Norplant® on lipid metabolism in healthy female volunteers. [**CONFIDENTIAL** internal sponsor's report]. Oss (NL): NV Organon; 1996 Sep.

56. Clinical Study Report: 34515. An open, single-centre, absolute bioavailability study of an all EVA one-rod implant releasing 3-ketodesogestrel (Org 32222, Implanon®) in healthy female volunteers. [**CONFIDENTIAL** internal sponsor's report]. Oss (NL): NV Organon; 1997 Sep.

57. Clinical Study Report: 34522. A non-randomised, group comparative study of an all-EVA one-rod implant (Org32222) releasing Org 3236 and non-hormone medicated IUDs on bone mineral density, in young healthy female volunteers. [**CONFIDENTIAL** internal sponsor's report]. Oss (NL): NV Organon; 1998 May.

58. Clinical Study Report: 34525. An open non-comparative bi-center trial on contraceptive efficacy, safety and acceptability of Implanon™ in healthy female volunteers. [**CONFIDENTIAL** internal sponsor's report]. Organon; 2004 Feb.

59. Clinical Study Report: E-1729. A world-wide, open, non-comparative, multi-center GCP-trial on contraceptive of Implanon™ in healthy, female volunteers efficacy, safety and acceptability. [**CONFIDENTIAL** internal sponsor's report]. Organon; 2006 Nov.

60. Table of studies. IN: CDR submission: Nexplanon (etonogestrel extended release subdermal implant) [**CONFIDENTIAL** sponsor's submission]. Kirkland (QC): Merck Canada Inc.; 2020 Feb.

61. Trussell J, Hatcher RA, Willard C, Stewart FH, Kost K. A guide to interpreting contraceptive efficacy studies. *Obstet Gynecol.* 1990;76(558):558-567.

62. Trussell J, Portman D. The creeping Pearl: why has the rate of contraceptive failure increased in clinical trials of combined hormonal contraceptive pills? *Contraception.* 2013;88(5):604-610.