TITLE PAGE

Clinical Study Report

Study Title:	A Post-Marketing Observational Study of Implanon® Radiopaque among Chinese Women Aged 18 and Older Requesting Contraception		
Study Drug:	Implanon® Radiopaque	**Protocol Number:**	MK-8415-038-02
Indication:	Contraception	**Clinical Phase:**	Phase IV
Date of Enrolment:	29 Mar 2016	**Date of Completed:**	28 Jul 2021
Sponsor:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.		
Principal/Coordinating Investigator:	Signature: Name: PPD Hospital: Wuhan Tongji Reproductive Medical Hospital		
Principle research center	Hospital: Wuhan Tongji Reproductive Medical Hospital		
Statistician:	Signature: Name: PPD Company: Hangzhou Tigermed Consulting Co., Ltd.		
Statistic Company:	Hangzhou Tigermed Consulting Co., Ltd.		
Sponsor's Responsible Medical Officer:	Signature: Name: PPD Tel: PPD		
Applicant:	Company Name: Organon (Shanghai) Pharmaceutical Technology Co., Ltd. Signature: (Stamp)		
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1 ABSTRACT

Title	A Post-Marketing Observational Study of Implanon® Radiopaque among Chinese Women Aged 18 and Older Requesting Contraception
Report version and date	Version 0.27, 6-Jun-2022
Keywords	Implanon® Radiopaque, Contraception, Post-Marketing Observational Study
Rationale and background	Implanon® is a single rod contraceptive implant. Data from clinical studies as well as from marketed use have shown that Implanon® is a safe, well-tolerated, and highly efficacious contraceptive method for up to 3 years of use. To better ensure successful placement of Implanon®, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. developed a radio-opaque version of Implanon® that can be detected by two-dimensional X-ray imaging. This new radiopaque implant was approved in 2013 in China. This post-approval observational study in Chinese women aimed to collect data on overall and topical safety, subject and physician satisfaction, and contraceptive effectiveness in clinical practice settings.
Research question and objectives	The primary objective was to evaluate overall safety profile of Implanon® Radiopaque. The secondary objectives were: • To evaluate topical safety profile of Implanon® Radiopaque • To assess the subject and physician satisfaction with Implanon® Radiopaque • To estimate overall contraceptive effectiveness of Implanon® Radiopaque
Study design	This is a single arm, multicenter, open-label, uncontrolled post-marketing observational study in the setting for routine clinical practice in China to evaluate the safety, subject and physician satisfaction and the effectiveness of Implanon® Radiopaque contraceptive implant for 3-year duration.
Setting	31 investigational sites in China
Subjects and study size, including dropouts	A total of 1909 subjects aged 18 and older who decided to use Implanon® Radiopaque for contraception were screened, and 1901 subjects were enrolled.
Variables and data sources	**Primary Endpoint (safety):** • All Serious Adverse Events (SAEs) regardless of assessed relationship to Implanon® Radiopaque

	• All non-serious drug-related AEs (as assessed by the investigators[1]) • All topical AEs The investigator or qualified designee would ask the subject about adverse experiences at each telephone contact and report all non-serious Adverse Events (AEs) considered by the investigator to be related to Implanon® Radiopaque and to report all Serious Adverse Events (SAEs) (regardless of assessed relationship to Implanon® Radiopaque). **Secondary Endpoint:** • Subject and physician satisfaction (as measured by questionnaires) Subject satisfaction was to be evaluated by the subject satisfaction questionnaire. • Contraceptive effectiveness Contraceptive effectiveness was to be assessed based on reports of pregnancies with an estimated conception date within the treatment period following a general practice.
Results	Among the 1901 enrolled subjects, 864 (45.45%) subjects completed 36 months of product use and 1037 (54.55%) discontinued the study prematurely. Overall, 651 subjects (34.25%) discontinued due to an AE as the primary reason, followed by planning pregnancy (147 subjects, 7.73%), other (137 subjects, 7.21%), lost to follow-up (98 subjects, 5.16%), withdrew informed consent (3 subjects, 0.16%) and pregnancy (1 subject, 0.05%). The mean [±Standard Deviation (SD)] exposure duration was 783.7 (±388.7) days (5.0 to 1610.0 days). **Characteristics** The enrolled study population consisted of 1901 Chinese females, the mean (±SD) age, height, weight, body mass index (BMI) were 32.1 (± 5.6) years old, 160.7 (± 5.0) cm, 56.1 (± 8.3) kg and 21.7 (± 3.0) kg/m^2, respectively. **Overall Safety** In the study, drug-related AEs (excluding topical AEs) were reported by 911 (47.9%) subjects, and SAEs were reported by 20 (1.1%) subjects. The drug-related AEs or SAEs leading to discontinuation of study drug were reported by 650 (34.02%) subjects, including 646 (34.0%) subjects with

[1] In this report, "investigator" and "physician" are interchangeable.

	drug-related AE and 6 (0.3%) subjects with drug-related SAE. The 5 most frequently reported (≥ 5% of subjects) drug-related AEs by Preferred Term (PT) included vaginal haemorrhage (15.6%), heavy menstrual bleeding (8.0%), amenorrhoea (6.7%,), menstrual disorder (6.3%) and weight increased (5.9%). The most frequently reported (> 0.1% of subjects) SAEs by PT were abnormal uterine bleeding (0.3%) and uterine leiomyoma (0.2%). The most frequently reported (≥ 5% of subjects) drug-related AEs leading to discontinuation of study drug by PT were vaginal haemorrhage (10.5%), heavy menstrual bleeding (5.5%) and menstrual disorder (5.0%). **Topical safety** In the study, topical AEs were reported by 197 (10.4%) subjects. The most frequently reported (> 2% of subjects) topical AEs by PT were implant site bruising (4.6%), implant site pruritus (4.2%), and implant site pain (2.5%). **Subject Satisfaction** *Insertion-Related Satisfaction* Among 1890 subjects completing the initial satisfaction questionnaire at Day 10, 1216 (64.3%) and 649 (34.3%) reported that they experienced no pain or mild pain during implant insertion. Only 3 (0.2%) subjects reported experiencing severe pain during insertion. Most (1737 subjects, 91.9%) reported that the insertion procedure was less painful than or as painful as expected. After insertion, 57 (3.0%) subjects reported "significant problems" in their arm with the implant. The most commonly reported AEs following insertion were bruising (40 subjects, 2.1%), weakness or pain when moving the arm (6 subjects, 0.3%), and other reported problems (12 subjects, 0.6%). *General Satisfaction* At 6 months after insertion, 1704 subjects (89.6%) completed the follow-up questionnaire, of whom 908 (53.3%) subjects were satisfied, 380 (22.3%) subjects were very satisfied, 330 (19.4%) subjects were neutral 79 (4.6%) subjects were dissatisfied and 7(0.4%) subjects were very dissatisfied with the implant. Most (1337 subjects, 78.5%) were willing to recommend Implanon® Radiopaque to others.

	At 36 months after insertion or premature removal, 1740 subjects completed the general satisfaction-related questionnaire, of whom 676 (38.9%) subjects were satisfied,412 (23.7%) subjects were very satisfied, 423 (24.3%) subjects were neural, 205 (11.8%) subjects were dissatisfied and 24 (1.4%) subjects were very dissatisfied with the implant. Most (1176 subjects, 67.6%) subjects were willing to recommend Implanon® Radiopaque to others. *Removal Satisfaction* Removal satisfaction questionnaires assessing pain and satisfaction with the removal procedure, the reason for implant discontinuation, and willingness to use the implant in the future were completed by 891 (50.8%) at premature removal and 864 (49.2%) subjects removal at month 36. Most subjects (1721 subjects, 98.1%) reported no pain (1118 subjects, 63.7%) or mild pain (603 subjects, 34.4%) during the removal procedure, and the majority (1286 subjects, 73.3%) reported that the removal procedure was less painful than expected. **Physician Satisfaction** *Insertion Satisfaction* Physician Insertion Satisfaction was assessed by questionnaires given after completing the first and fifth insertion procedures. Ninety-six physicians completed questionnaires following their first insertion procedure. All but 4 physicians (95.8%) were satisfied following their first insertion procedure. Overall, 7 (7.3%) physicians reported difficulties or minor complications during the first insertion procedure; some reported more than one. The most common difficulty in removing the protection cap from the applicator was reported by 4 (4.2%) physicians. The difficulty in sliding needle to its full length into skin was reported by 3 (3.1%) physicians, difficulty in unlocking purple slider was reported by 2 (2.1%) physicians. Satisfaction after the fifth insertion was evaluated in 74 (90.2%) physicians who completed 5 insertion procedures, and 8 (9.8%) physicians who completed less than 5. All but 1 physician (98.8%) were satisfied following their fifth or less than fifth insertion, and no physician reported dissatisfaction after the fifth insertion, although 1 (1.2%) physician reported being neither satisfied nor dissatisfied. Five (6.1%) physicians reported challenges or minor complications, including difficulty in removing protection cap (4 physicians, 4.9%), difficulty in sliding needle to its

	full length into skin (1 physician, 1.2%), implant partially sticking out of skin after insertion (1 physician, 1.2%), and difficulty in unlocking purple slider (1 physician, 1.2%). *Removal Satisfaction* Ninety-five physicians completed questionnaires following their first implant removal. All but one physician (98.9%) reported satisfaction following their first removal procedure, of whom 62 (65.3%) physicians were very satisfied and 32 (33.7%) physicians were satisfied. Satisfaction after the fifth implant removal was evaluated in 53 (86.9%) physicians who completed 5 removal procedures and 8 (13.1%) physicians who completed less than 5. All physicians (100.0%) were satisfied, of whom 38 (62.3%) physicians were very satisfied, and 23 (37.7%) physicians were satisfied and did not report any complications with their fifth procedure. **Contraceptive effectiveness** Among 1901 subjects with Implanon® Radiopaque insertion, 1 (0.05%) pregnancy was conceived during the treatment period. The subject decided to have an induced abortion, which occurred on 28-SEP-2017. The same day the implant was removed.
Conclusion	The results of this post-approval study revealed no new safety signals in relation to Implanon® Radiopaque use in the approved indication of contraception in Chinese females in routine clinical practice. The type and incidence of topical and general AEs observed in this study are consistent with those reported during the clinical development of the contraceptive implant. No unexpected safety findings were observed. The majority of subjects were satisfied with the product and were willing to recommend it to others. The majority of physicians were satisfied with Implanon® Radiopaque insertion and removal procedures. Implant insertion and removal complications were rare. The observed overall safety profile including topical safety is consistent with the information already included in the Core Company Data Sheet and the Chinese package insert of Implanon® Radiopaque. The benefit-risk balance of Implanon® Radiopaque remains favorable.
Marketing Authorisation Holder(s)	N.V.Organon
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators and sites participating in the study are listed in Section 16.1.4.

2 LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reactions
AST	All Subject Treated
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CSR	clinical study report
DMP	Data Management Plan
ECD	Estimated Conception Date
ENG	Etonogestrel
EU	European Union
EVA	Ethylene Vinyl Acetate
hCG	human Chorionic Gonadotropin
ICF	Informed Consent Form
ID	identifier
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LMP	Last Menstrual Period
MRI	Magnetic Resonance Imaging
NMPA	China National Medical Products Administration
PASS	Post-Authorization Safety Study
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TFL	table figure listing
US	Ultrasound
USA	the United States of America

3 ETHICS, INVESTIGATORS, AND STUDY ADMINISTRATIVE STRUCTURE

3.1 Ethics

3.1.1 Independent Ethics Committee or Institutional Review Board

The protocol and protocol amendment were reviewed and approved by each study site's Independent Ethics Committee (IEC) before the start of the study. A list of IECs consulted can be found in Section **16.1.3**.

3.1.2 Ethical Conduct of the Study

The study was carried out within an approved indication in accordance with guidelines and regulations of China National Medical Products Administration (NMPA) and applicable local law(s) and regulation(s).

3.1.3 Patient Information and Consent

An informed consent form (ICF) explaining the study's procedures, including the potential hazards, was reviewed and approved by the IECs before its use. Only after the patient signed the ICF was she able to enter the study. If the patient could not provide a signature, an oral statement of consent could be given in the presence of a witness. Each patient or representative received a signed and dated copy of the ICF.

A sample ICF and written information are given to the patients are provided in Section **16.1.3**.

3.2 Investigators and Study Administrative Structure

The study operations, data management and statistical analysis were outsourced to a contract research organization (CRO) (Tigermed, Inc.).

The study was conducted at 31 study sites in China. At each center, the coordinating investigator was responsible for the study. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study product.

Contact details of the principal and/or coordinating investigators for each site participating in the study are listed in Section **16.1.4**. The signatures of the principal investigators are located in Section **16.1.5**.

4 OTHER RESPONSIBLE PARTIES

Shared Responsibilities	Contact Person
1. Sponsor: Merck/MSD Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA	PPD
2. CRO: Tigermed Consulting Ltd. Floor16, Building A Shengda Science Park, No. 19 Jugong Road, Binjiang District, Hangzhou, Zhejiang, China	PPD

5 MILESTONES

Milestone	Actual date
Start of data collection	29-Mar-2016
End of data collection	30-Nov-2021
Registration in China Center for Drug Evaluation register	02-Dec-2013
Interim report of study results	22-Jun-2018
Final report of study results	6-Jun-2022

6 RATIONALE AND BACKGROUND

6.1 Background

Implanon® is a 4 cm long and 2 mm in diameter single-rod contraceptive implant. Implanon® contains 68 mg etonogestrel (ENG) (Org 3236, 3-ketodesogestrel), dispersed in a matrix of ethylene vinyl acetate (EVA), surrounded by an EVA membrane. ENG is the active metabolite of desogestrel, the progestagen used in combination with oral contraceptives like Marvelon and Mercilon®.[1]

The ENG dose released by Implanon® amounts to about 60-70 µg/day shortly after insertion and decreases to about 40 µg/day at the beginning of the second year, and to about 25-30µg/day at the end of the third year. This release rate results in ENG serum levels that are sufficient to provide ovulation inhibition. Data from clinical studies as well as from marketed use have shown that Implanon® is a safe, well-tolerated, and highly efficacious contraceptive method for up to 3 years of use.[1] Since the marketing introduction of Implanon®, the Sponsor has received reports related to the unsuccessful localization of Implanon®. This may occur when insertion has not been performed as instructed in the product's labeling and includes errors during insertion such as wrong insertion site, too deep insertion, and non-insertion. When properly inserted, the implant should be immediately palpable. If the implant is not palpable by the subject, ultrasound (US) or Magnetic Resonance Imaging (MRI) could be used to localize the implant. If all localization measures fail, serum ENG levels may be determined to verify the presence of an Implanon® implant in the body.

To further improve upon Implanon®, MSD developed a radio-opaque version of Implanon® that can be detected by two-dimensional X-ray imaging.[2] Implanon® Radiopaque is a radiopaque, non-biodegradable, progestagen-only, flexible implant preloaded in a sterile, ready for-use, disposable applicator. The innovative applicator is designed to be operated with one hand and help facilitate correct subdermal insertion of the implant.[3, 4] This new radiopaque implant was approved in 2010 in the European Union (EU) and 2011 in the United States of America (USA). China approval was achieved based on the demonstration of bioequivalent with Implanon® (non-radiopaque) implant in December 2013 with an Agency requested commitment to conduct a Post-Authorization Safety Study (PASS). This postmarketing observational study aimed to observe and collect data on subject and physician satisfaction, overall and topical safety, and contraceptive effectiveness in clinical practice settings.

6.2 Rationale

This observational study in Chinese women was to be conducted in clinical practice settings and focused on subject and physician satisfaction, safety, evaluated by all SAEs and drug related AEs including topical AEs, the condition of the insertion site, as well as information associated with insertion or removal of the implant. Contraceptive effectiveness data were also collected and evaluated.

As this is a post-approval observational study, subjects were to be treated with prescribed Implanon® Radiopaque according to the product label without any other intervention. All data were to be collected during normal use of the product.

7 RESEARCH QUESTION AND OBJECTIVES

This postmarketing observational study aimed to observe and collect data on subject and physician satisfaction, overall and topical safety, and contraceptive effectiveness in clinical practice setting.

7.1 Primary Objective

- To evaluate overall safety profile of Implanon® Radiopaque.

7.2 Secondary Objectives

- To evaluate topical safety profile of Implanon® Radiopaque.
- To assess subject and physician satisfaction with Implanon® Radiopaque.
- To estimate overall contraceptive effectiveness of Implanon® Radiopaque.

8 AMENDMENTS AND UPDATES

The original protocol had been amended once. The latest protocol and amendment are provided in Section **16.1.1**.

The following significant changes to the protocol have been made:

Section Number(s)	**Section Title(s)**	**Description of Change(s)**	**Rationale**
Section 4.2	Secondary Measurements	Inserted a description for removal satisfaction for Physician Satisfaction Questionnaire	The Physician Satisfaction Questionnaire includes questions for insertion and removal of Implanon® Radiopaque, respectively, but in the main text of the protocol, the description for the questionnaire missed the wording for the removal.
Section 5	Study Flow Chart	1. Inserted a "X" at the removal visit for Physician Satisfaction Questionnaire 2. Updated footnote 'k'	The same reason as above.
Section 6.1.2.3	Implanon® Removal	Added description for removal satisfaction for Physician Satisfaction Questionnaire	The same reason as above.
Section 6.1.3.1	Earlier discontinuation	Added information for Physician Satisfaction Questionnaire for removal in case of discontinuation	Keep accuracy for data collection.

9 RESEARCH METHODS

9.1 Study Design

This postmarketing observational study was intended to evaluate subject and physician satisfaction, SAEs, drug-related AEs including topical AEs, and overall contraceptive effectiveness in standard clinical practice. The primary data were safety data; therefore, an open-label, uncontrolled, and observational design was considered to be sufficient.

Study data were to be collected from outpatient clinics in about 50 hospitals. Subjects were to be registered after signing the ICF. No data was to be obtained or recorded for this observational study until after the ICF had been fully executed. The ICF was provided to patients for their review after the treatment decision (the decision with the use of Implanon® Radiopaque) had been made by the trained physician and the patient. Information about insertion and removal was to be collected. A subject satisfaction-related questionnaire was to be completed at 10 days, 6-month visit (call), and at the time of removal of the implant.

After insertion, subjects were to be followed by the investigator via telephone contact per the schedule outlined in the Study Flow Chart (**Table 9-1**) until Implanon® Radiopaque was to be removed. During telephone contact, the investigator was to collect all SAEs and potential drug-related AEs, including topical AEs, following the use of Implanon® Radiopaque. A topical AE referred to any AE in the insert arm proximate to the insertion site or, based on the investigator's assessment, was potentially a topical AE related to Implanon® Radiopaque.

The investigator would instruct the subject to observe the insertion site and report any AEs.

The subject satisfaction questionnaire was to be answered by the subject at telephone contact and filled out by the investigator. Pregnancy status and estimated conception date (ECD) were also to be collected at every telephone contact. The conception date was to be determined by ultrasound result (if available) or estimated using LMP only if ultrasound was not available. If pregnancy was reported, the subject was informed to come back and remove Implanon® Radiopaque.

One month post-implant removal, subjects were to be followed by the investigator via telephone to collect any potential AEs related to Implanon® Radiopaque and follow up with SAEs.

Before subject recruitment, training was to be provided to investigators by video and on-site training.

Table 9-1 Study Flow Chart

Assessment	Screen & Implant Insertion	Follow Up					Implant Removal	Post Removal
	to Day1[a]	Day10	3 months	6 months	12 months	24 months	36 months[b]	37 months[c]
Visit number	Screen & Implant Insertion (clinic)	V1[d] (telephone)	V2 [d] (telephone)	V3 [d] (telephone)	V4 [d] (telephone)	V5 [d] (telephone)	V6 [d] (clinic)	V7 (telephone)
Informed consent[e]	×							
Age, height, weight	×						×	
Inclusion criteria	×							
Urine pregnancy test[f]	×[g]						×	
Pregnancy status[h]	×	×	×	×	×	×	×	×
Breastfeeding status	×	×	×	×	×	×	×	×
Subject report of topical AEs [i]	×	×	×	×	×	×	×[j]	
Physician palpation of the implant	×						×[j]	
Physician satisfaction	×[k]						×[k]	
Subject satisfaction		×		×			×	
All SAEs and potential drug-related AEs	×	×	×	×	×	×	×	×

a. Day1 refers to the day for the insertion of Implanon® Radiopaque.
b. Or earlier in case of premature discontinuation.
c. To be performed 1 month after implant removal, by telephone.
d. V1, ±3 days; all other visits refer to section 6.1.2.2 of the clinial study protocol.
e. The ICF was provided to patients for their review after treatment (the decision with the use of Implanon® Radiopaque) was made by the trained physician and the patient.
f. The first pregnancy test was conducted in clinic to confirm the pregnancy status (in the same clinic of insertion). Anytime during the observational study if pregnancy was suspected, urine pregnancy test was done by subject and reported to investigator.
g. To be done just before implant insertion.
h. During telephone visit, physician asked for subject's menstruation status. If pregnancy was suspected, subject was asked to do urine pregnancy test to confirm; subject can do a pregnancy test anytime for suspected pregnancy and report to physician.
i. The subject would be asked to report if they have any local complaints (or see any changes in the region of the implant).

j. To be done before implant removal.
k. This questionnaire would be completed by investigator after insertion and the removal for the first and the fifth (or fifth+) subject. If the investigator did not enroll 5 subjects, the survey should be completed for the last insertion and for the last removal.

9.2 Setting

This China-only Post-Authorization Safety Study (PASS) started after Implanon® Radiopaque was authorized and made commercially available in China. At the time of the final clinical database lock (30-Nov-2021), a total of 1901 subjects were enrolled under the responsibility of the investigators across 31 sites in China.

This post-marketing observational study was conducted from 29-MAR-2016 (first subject, first visit) to 28-JUL-2021 (last subject, last visit).

9.3 Subjects

9.3.1 Study Population

This observational study was to enroll approximately 1900 women ≥ 18 years of age at the time of screening requesting contraception at approximately 50 sites throughout China. The identification of eligible subjects was to be based on standard clinical practice and the product labeling. All investigators were to be trained to insert Implanon® Radiopaque. Subjects who were willing to join this survey and sign the ICF were to be enrolled and followed, and the decision of the subject to use the Implanon® Radiopaque would have been made prior to the decision to be involved in the observational study.

9.3.2 Inclusion Criteria

All inclusion criteria were reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

- Women ≥18 years of age at the time of screening requesting contraception;
- Capable to answer the questionnaire;
- Decided to use Implanon® Radiopaque for contraception;
- Willing to participate in the survey and give informed consent in writing.

9.4 Variables

Primary Measurement

The investigator or qualified designee would ask the subject about adverse experiences at each telephone contact and report all non-serious AEs considered by the investigator to be related to Implanon® Radiopaque and to report all SAEs (regardless of assessed relationship to Implanon® Radiopaque).

Secondary Measurements

Subject and physician satisfaction:

Subject satisfaction was to be evaluated by the subject satisfaction questionnaire, which was to be answered by subjects at 10 days and at 6-months after the insertion, and at the time of removal of Implanon® Radiopaque through telephone contact and filled out by investigator. Physician satisfaction was to be evaluated by the physician satisfaction questionnaire, which was to be completed after insertion and after removal of the first and the fifth subject by

investigator. If the investigator did not enroll 5 subjects, the survey should be completed for the last insertion and for the last removal.

Contraceptive effectiveness:

In this study, contraceptive effectiveness is the only effectiveness variable. Contraceptive effectiveness was to be assessed based on reports of pregnancies with an estimated conception date within the treatment period following a general practice. To exclude pre-treatment pregnancy, per routine clinical practice, a pregnancy test (urinary hCG, human chorionic gonadotropin) was to be performed right before implant insertion on the same day in the clinic; to confirm post-treatment non-pregnancy, another test was to be performed at implant removal. At every contact, the investigators/their designees would ask the subject her pregnancy status, including pregnancy date (i.e., estimated date of conception), outcome, ultrasound test date and results, and other pertinent pregnancy information by filling out a pregnancy form provided by the Sponsor. The conception date was to be determined by ultrasound result (if available), or LMP was to be asked, physician estimated the conception date based on LMPif ultrasound was not available. The first pregnancy test was to be conducted in the clinic to confirm the pregnancy status if pregnancy was suspected. Anytime during the observational study, urine pregnancy test might also be performed by subject if subject suspected pregnancy. If urine pregnancy test was done by subject, the information should be collected by the investigator.

9.4.1 Exposure

Subjects were to be exposed to Implanon® Radiopaque for three years.

9.4.2 Outcome

Subject and physician satisfaction was to be determined by questionnaires. All SAEs and drug-related AEs, including topical AE, and information about insertion and removal were to be reported. The overall contraceptive effectiveness was to be assessed based on self-reported pregnancies to investigators trained to prescribe the product.

9.4.3 Covariates

Not applicable.

9.5 Data sources and measurement

The investigators collected demographic and clinical characteristics and treatment-related data during scheduled visits. Each subject was identified by a unique central subject identification code, which was only used for study purposes. The investigator documented the study-relevant data for each subject in the CRF. The sample CRF is included in Section 16.1.2.

9.5.1 Study Procedures

The Study Diagram (**Table 9-1**) summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. If deemed clinically necessary

by the investigator, it might be necessary to perform these procedures at unscheduled time points. Furthermore, additional evaluations/testing might be deemed necessary by the Investigator/Sponsor for reasons related to subject safety.

9.5.1.1 Administrative Procedures

General Informed Consent

Eligible volunteers were to be fully informed of the nature of the study. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the Institutional Review Board/ Independent Ethics Committee (IRB/IEC)'s approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information became available that might be relevant to the subject's willingness to continue participation in the study. The communication of this information was to be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a study and the study population were to be added to the consent form template at the protocol level.

The informed consent would adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor's requirements.

All the potential adverse drug reactions (ADRs), study duration, follow-up duration, and data which would be collected should be listed in the ICF. Investigators should explain all the detailed information on the ICF to the subject.

9.5.1.2 Clinical Procedures/Assessments

Implant Insert

The implant must be inserted in compliance with local label following routine clinical practice. The insertion should only be performed if the proper insertion and handling of the applicator has been followed. The following routine clinical practice must be done at the implant insertion visit:

1. Check the occurrence of adverse events since the screening assessment

2. Perform urine pregnancy test before implant insertion

• The subject should only start with the insert if the test is negative. If the pregnancy test is positive, the subject must not have implant inserted.

3. Determine breastfeeding status

4. Insert the implant (see "How to insert this product" in appendices A of the clinical study protocol for detailed procedure)

5. Localize the implant by palpation.

• If implant is not palpable, the implant could be localized by two-dimensional X- ray (if determined by physician as needed)

6. Inspection of the implantation site would be done for any abnormalities (e.g. no abnormalities, swelling, redness, pain, hematoma, expulsion).

7. Report any issues during insertion procedure by the physician (if applicable).

9.5.1.3 Treatment Assessment (Telephone Visit)

The investigator must telephone visit the subject at the following time-points after implant insertion: 10 (±3) days, 3 (±0.5), 6 (±0.5), 12 (±1), 24 (±1) and 36 (±1) months. At each of these time-points information was to be collected includes:

1. Check the occurrence of any SAE and potential drug related AE since the previous assessment;

2. Ask patients if they have any complaints in the area of the Implanon® insertion (e.g., discomfort and any local change in appearance)

3. If any suspicion of pregnancy, the subject would perform a urine pregnancy test (if positive, the implant must be removed) to comply with the local label.

4. Check breastfeeding status

5. Complete Subject Satisfaction Questionnaire at 10 days, Month 6 after the implant and removal of the implant.

9.5.1.4 Insertion Assessment

After insertion, the investigator should complete the Physician Satisfaction Questionnaire for the first and the fifth (or 5+) subject. If the investigator did not enroll 5 subjects, the survey should be completed for the last insertion.

9.5.1.5 Implant Removal

At implant removal (which is either at the scheduled Month 36 (±1) assessment or earlier in case of premature discontinuation), the assessment includes:

1. Check the occurrence of any SAE and potential drug related AE since the previous assessment.

2. If any suspicion of pregnancy, performance of urine pregnancy test would be done in comply with local label (if positive, localize implant before removal if needed, collect pregnancy data and end of trial data)

3. Determination of breastfeeding status

4. Remove the implant (cross reference the label "How to remove the implant")

After removal, the investigator should complete the Physician Satisfaction Questionnaire for the first and the fifth (or 5+) subject. If the investigator does not experience 5 subjects for removal, the survey should be completed for the last removal.

9.5.1.6 Post Treatment

The post-treatment contact might be done by telephone and was to be scheduled to take place at 1 month after implant removal (Month 37 or earlier in case of premature discontinuation). The post-treatment assessment includes:

1. Check the occurrence of any SAE and potential drug related AE since the previous assessment

2. Return of the menstrual cycle (not applicable if the subject has initiated a hormonal contraceptive method immediately after implant removal, or is (still) breastfeeding)

3. Pregnancy status (and pregnancy data if pregnant)

4. Breastfeeding status

9.5.1.7 Other Procedures

Earlier discontinuation

In case a subject discontinues treatment before the scheduled end of treatment (Month 36), all assessments described for the Implant Removal Visit and Post treatment Contact (appropriately timed relative to implant removal) must be performed (including the Physician Satisfaction Questionnaire for removal if the investigator performs removal. If the subject underwent removal elsewhere, every effort should be made to get the Subject General Satisfaction Questionnaire after removal). If the subject discontinues due to pregnancy, pregnancy status should be followed.

9.6 Bias

Several sources for bias may exist (ie, selection biases in subject recruitment, information bias due to missing values, and recall bias if the information was not in the medical chart and the investigator needed to ask the subject for family medical history). To reduce subject selection bias, investgators documented subjects who had Implanon® Radiopaque inserted and provided informed consent. Missing data are a common methodological problem in registries due to the observational nature of this study type. 100% source data verification was performed in all the study sites to check for the documented data's completeness, accuracy, plausibility, and validity to decrease information bias. The distribution of missing values is reported for each variable in the analyses. No missing values were imputed.

9.7 Study size

A total of 1900 healthy female subjects aged 18 and older were to be recruited in China. The sample size along with global data provided a reasonable understanding of the safety profile in Chinese females.

A total of approximately 1900 subjects were expected to be recruited to have at least 1500 subjects that were interviewed at least once to account for a lost to follow up rate of up to 20%. A total of 1500 subjects were sufficient to observe an event that occurs with a true rate of

0.31% at least once with a probability of more than 99%. In case that a specific event was not observed in 1500 subjects the upper 95% confidence limits for the event rates would be 0.246%, it could be assumed that the true event rate is lower than 1 out of 400 subjects.

According to previous Periodic Safety Update Report (Period covered: Sep. 2, 2013 to Jan. 3, 2014), it is assumed that the expected, overall AE rate could be 0.5%. With this AE, using the exact (Clopper- Pearson) method,[5, 6] **Table 9-2** shows the 95% Confidence Intervals (CIs) when AE rates vary with sample size of 1500.

Table 9-2 95% CIs for the AE under different AE rates with sample size of 1,500

AE rate	Precision	95% CI Lower limit	95% CI Upperlimit
0.4%	0.7%	0.1%	0.9%
0.5%	0.8%	0.2%	1.0%
0.6%	0.9%	0.3%	1.1%

9.8 Data transformation

Subject data consistency checks, derived variables, coding of medical terms, and concomitant medication were described in detail in the Data Management Plan (DMP).

Statistical transformations including calculated variables and proposed format and content of tables were detailed in the Statistical Analysis Plan (SAP).

9.8.1 Data management

A CRO was selected and assigned for clinical database (oracle clinical) development. The paper format of Case Report Form (CRF) were collected from Investigational Sites, and DM double entered them into the oracle clinical system. Information on the oracle clinical system was to be available upon request. Detailed information on data management, including procedures for data collection, data review, and query handing, is provided in the DMP, which will be available upon request.

One hundred percent source document verification was conducted on all study data. The purpose was to review the documented data for completeness and plausibility, adherence to the study protocol, and verification with source documents. To accomplish this, monitors accessed medical records on site for data verification. Detailed measures for quality reviews were described in the Site Monitoring Plan.

9.9 Statistical methods

The separate SAP was to be finalized prior to the final DBL (Data Base Lock). Statistical analyses were conducted by using the software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All collected variables and outcome parameters were analyzed descriptively with appropriate statistical methods.

All CIs are two-sided 95% CIs, which were calculated by the Wilson Score method. For continuous variables, the number of subjects (n), mean (SD), and median (minimum, maximum) were presented. The numbers of observations with frequencies or proportions were presented in terms of categorical variables.

9.9.1 Main summary measures

Primary Objective

All SAEs and Implanon® Radiopaque-related AEs were to be summarized. The main safety endpoints are: the subjects proportion of (1) drug-related AE; (2) SAE; (3) discontinued treatment due to drug-related AE or SAE. These safety endpoints were to be summarized by count, point estimate, and corresponding 95% confidence interval.

The safety analysis were to be performed on the All Subject Treated (AST) population. The AST population includes all subjects who had Implanon® Radiopaque inserted.

Secondary Objectives

Topical safety profile:

Frequency of the overall and each component of topical AEs were summarized via point estimate and corresponding 95% confidence interval of the event rate. Topical safety were characterized by inclusion of all drug-related AEs that were classified to the Skin and Subcutaneous Tissue Disorders System Organ Class and/or were localized to the implant arm (i.e., “right arm pain” or “right arm swelling” if implant was inserted in the right arm).

The analysis for topical safety profile was performed on the AST population.

Subject and physician satisfaction:

Subject and physician satisfaction was assessed by the count and percentage of every score for each question. Questions without a score were listed.

The subject satisfaction analysis was performed on the population consisting of subjects who were in AST population and answered the Subject Satisfaction Questionnaire.

The physician satisfaction analysis for insertion was performed on the population consisting of all physicians who performed at least one insertion and answered the Physician Satisfaction Questionnaire.

The physician satisfaction analysis for removal was performed on the population consisting of all physicians who performed at least one removal and answered the Physician Satisfaction Questionnaire.

Contraceptive effectiveness:

Contraceptive effectiveness was evaluated by summarizing pregnancies of pre-treatment, in-treatment and post-treatment as specified below:

Pre-treatment pregnancy: Defined as pregnancy with the estimated date of conception prior to Implanon® Radiopaque insertion.

In-treatment pregnancy: Defined as pregnancy with the estimated date of conception after Implanon® Radiopaque insertion and before its removal.

Post-treatment pregnancy: Defined as pregnancy with the estimated date of conception after Implanon® Radiopaque removal. Data was collected through the safety follow-up visit at approximately 1 month after removal.

The effectiveness analysis will be performed on the AST population.

9.9.2 Missing values

Missing values were not addressed.

9.9.3 Sensitivity analyses

No sensitivity analysis was done in this study.

9.9.4 Amendments to the statistical analysis plan

There were no changes to the planned analyses. The final version of SAP is 1.0.

9.10 Quality control

The Sponsor was responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures to ensure that studies were conducted and data were generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable local laws, and rules and regulations relating to the conduct of the study.

Before the study started at the sites, all investigators were sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators had the chance to discuss and develop a common understanding of the study protocol and the CRF.

A CRO was assigned for study operation and project management. All subject data relating to the study were recorded on CRFs. Clinical Research Associates performed ongoing source data verification to confirm that data recorded into the paper CRF by authorized site personnel were accurate, complete, and verifiable from source documents and that the study was being conducted in accordance with the protocol and any other study agreements.

An CRO was selected and assigned for clinical database (oracle clinical) development, quality control, verification of the data collection, data analysis, and data transfer to the Sponsor.

All outcome variables were recorded in a standardized CRF. After data entry, missing or implausible data were queried, and the data were validated. A check for multiple documented patients was done.

Detailed information on checks for completeness, accuracy, plausibility, and validity was given in the DMP. The plan specified measures for the handling of missing data and permissible clarifications. The DMP is available upon request.

10 RESULTS

10.1 Participants

10.1.1 Subject Disposition

A total of 1909 subjects were screened, and 1901 subjects were enrolled. The main reasons for screen failure were other (4 subjects), withdrawal of informed consent (2 subjects), non-compliance with inclusion criteria (1 subject), and Investigator's decision (1 subject) [TFL Table 2]. A by-subject listing of screen failure is provided in TFL Listing 1.

A total of 864 (45.45%) subjects completed the study, and 1037 (54.55%) subjects discontinued the study prematurely. Overall, 651 (34.25%) subjects discontinued due to AEs as the primary reason, followed by planning pregnancy (147 subjects, 7.73%), other (137 subjects, 7.21%), lost to follow-up (98 subjects, 5.16%), withdrew informed consent (3 subjects, 0.16%) and pregnancy (1 subject, 0.05%) [**Table 10-1**].

Table 10-1 Subjects Disposition
(All Subjects)

	n (%)
Number of subjects screened	1909
Number of all treated subjects	1901
Number of subjects who completed the study	864 (45.45)
Number of subjects who prematurely discontinued the study	1037 (54.55)
Adverse events	651 (34.25)
Pregnancy	1 (0.05)
Protocol violation	0 (0)
Lost to follow-up	98 (5.16)
Withdrawal of informed consent	3 (0.16)
Planning Pregnancy	147 (7.73)
Investigator's decision	0 (0)
Study termination by the sponsor	0 (0)
Death	0 (0)
Others	137 (7.21)
Missing	0 (0)

Note:This table presents subject counts according to their main reason for premature study discontinuation. The denominator of the percentage is the number of all subjects who had Implanon® Radiopaque inserted. Two subjects who prematurely discontinued from study mainly in order to plan pregnancy (and accounted into that category) also reported experiencing adverse events leading to study drug discontinuation. The reason 'Others' for discontinuation includes subject personal reason, shifting to other contraceptive methods, logistics (time, hard to get, remember) and health concerns.
Source: TFL Table 1.

10.1.2 Protocol Deviations

Protocol deviations were classified as per the ICH E3 classification of protocol deviations as important (those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant’s rights, safety, or well-being) or not important.

At least one protocol deviation was reported for 1018 (53.6%) subjects in this study. Of these, 12 (0.6%) subjects had important deviations and 1011 (53.2%) subjects had non-important deviations documented [**Table 10-2**]. By-subject listings of protocol deviations, including important deviations and non-important deviations, are provided in TFL Listing 3.1 and TFL Listing 3.2, respectively.

None of the deviations were expected to affect safety or effectiveness conclusions.

Table 10-2 Summary of Protocol Deviation
(All Subjects Treated)

	(N=1901) n (%)
Number of subjects with at least one protocol deviation	1018 (53.6)
Important protocol deviation	12 (0.6)
Informed consent	2 (0.1)
Inclusion/exclusion criteria	0 (0)
Safety report	10 (0.5)
Study operation/procedure	0 (0)
Non-important protocol deviation	1011 (53.2)

Source: TFL Table 3.

10.2 Descriptive data

10.2.1 Demographic and Baseline Characteristics

The enrolled study population consisted of 1901 Chinese females, the mean (±SD) age, height, weight and body mass index (BMI) were 32.1 (± 5.6) years old, 160.7 (± 5.0) cm, 56.1 (± 8.3) kg and 21.7 (± 3.0) kg/m^2, respectively [**A** by-subject listing of demographic and baseline characteristics is provided in TFL Listing 4.

Table 10-3]. A by-subject listing of demographic and baseline characteristics is provided in TFL Listing 4.

Table 10-3 Demographic and Baseline Characteristics
(All Subjects Treated)

		All Subject Treated (N=1901)
Age (year)	Number of subjects observed	1901
	Mean (SD)	32.1 (5.6)
	Median (minimum, maximum)	32.0 (18.0, 52.0)
Height (cm)	Number of subjects observed	1901
	Mean (SD)	160.7 (5.0)

		All Subject Treated (N=1901)
	Median (minimum, maximum)	160.0 (142.0, 178.0)
Weight (kg)	Number of subjects observed	1901
	Mean (SD)	56.1 (8.3)
	Median (minimum, maximum)	55.0 (39.0, 101.0)
BMI (kg/m^2)	Number of subjects observed	1901
	Mean (SD)	21.7 (3.0)
	Median (minimum, maximum)	21.2 (15.4, 38.5)

Source: TFL Table 4.

10.2.2 Concomitant Medications and Therapy

A total of 300 (15.8%) subjects had taken at least one concomitant medication with the study product. The most frequently reported (>1%) concomitant medication categories included genito urinary system and sex hormones (10.0%), various (4.4%) anti-infectives for systmic use (3.7%), blood and blood forming organs (2.6%) and nerous system (1.5%). The most frequently reported (>1%) concomitant medications were mifepristone (3.0%), drospirenone and ethinylestradiol (1.8%), tranexamic acid (1.3%) and callicarpa nudiflora leaf (1.1%) [TFL Table 5.2].

A total of 150 (7.9%) subjects had reported concomitant medication related to AE at least once. The most frequently reported (>1%) concomitant medication categories included genito urinary system and sex hormones (5.5%), various (2.2%), and blood and blood forming organs (1.6%). The most frequently reported (>1%) concomitant medications was mifepristone (2.1%) [TFL Table 5.1]. A by-subject listing of concomitant medications related to adverse events is provided in TFL Listing 5.

A total of 13 (0.7%) subjects underwent surgical procedures or operations related to AE. A summary of surgical Operation or surgery is provided in TFL Table 6.

10.2.3 Lactation

At each telephone visit, subjects were asked if they were breastfeeding. A total of 151 (7.9%) subjects were exposed to product during lactation. At the last visit, 11 (0.6%) subjects were still breastfeeding. No AE or SAE were reported for infants breastfed by subjects during treatment. A summary of lactation is provided in TFL Table 8. By-subject listings of breastfeeding is provided in TFL Listing 14.

10.2.4 Implantation Duration

The mean (±SD) duration of exposure was 783.7 (±388.7) days (5.0 to 1610.0 days). The exposure duration of 1605 (91.3%) subjects was more than 180 days, and the exposure duration of 152 (8.7%) subjects was less than or equal to 180 days [**. No** pregnancies were observed among those subjects.

Table 10-4]. A by-subject listing of implant exposure duration is provided in TFL Listing 6.

In this study, 592 (33.7%) subjects still had implant in place beyond the approved 3-year duration of use. Investigators advised such subjects to use an additional non-hormonal contraceptive measure (eg, condoms). No pregnancies were observed among those subjects.

Table 10-4 Summary of Implant Use Duration (All Subjects Treated)

		All Subject Treated (N=1901)
Implant use duration (days)	Number of subjects observed*	1757
	Mean (SD)	783.7 (388.7)
	Median (Q1, Q3)	1032.0 (401.0, 1104.0)
	Minimum, Maximum	5.0, 1610.0
	Number of subjects with ≤ 180 days after implantation	152 (8.7)
	Number of subjects with > 180 days after implantation	1605 (91.3)
	Number of subjects with ≥ 3 years (1095 days) after implantation	592 (33.7)

Note: Implant use duration = removal date - insertion date + 1
* Subjects with both insertion and removal dates.
Source: TFL Table 9.

10.3 Outcome data

The numbers of subjects across categories of the main outcomes are presented in Section **10.4**.

10.4 Main results

10.4.1 Safety Results

Safety analyses were performed in AST population of all subjects.

10.4.1.1 Overall Summary of Adverse Events

In the study, drug-related AE (excluding topical AEs), SAEs, topical AEs were reported by 911 (47.9%), 20 (1.1%) and 197 (10.4 %), respectively. Drug-related AEs or SAEs leading to discontinuation of study drug were reported by 650 (34.02%) subjects, including 646 (34.0%) subjects with drug-related AE and 6 (0.3%) subjects with drug-related SAE. No deaths were reported [**Table 10-5**].

Most subjects experienced AEs that were mild in severity [**Table 10-6**].

By-subject listings of AEs, SAEs, drug-related AEs and SAEs, topical AEs and AEs leading to discontinuation of study drug are provided in TFL Listing 7, TFL Listing 8, TFL Listing 9, TFL Listing 10, TFL Listing 11 and TFL Listing 12, respectively.

Table 10-5 Overall Summary of Adverse Events (All Subjects Treated)

	All Subject Treated (N=1901) n (%)	95% CI
Number of subjects with at least one drug-related AE (excluding topical AEs) #	911 (47.9)	(45.7, 50.2)
Number of subjects with at least one SAE	20 (1.1)	(0.7, 1.6)
Number of subjects with at least one drug-related SAE	7 (0.4)	(0.2, 0.8)
Number of subjects with at least one topical AE	197 (10.4)	(9.1, 11.8)
Number of subjects with at least one drug−related AE or SAE leading to discontinuation of study drug *	650 (34.2)	(32.1, 36.4)
Number of subjects with at least one drug-related AE leading to discontinuation of study drug #	646 (34.0)	(31.9, 36.1)
Number of subjects with at least one drug-related SAE leading to discontinuation of study drug	6 (0.3)	(0.1, 0.7)
Number of deaths	0 (0)	(0.0, 0.2)

Note:All causality assessments (as related or unrelated) that are presented in this table were made by the investigators.
Subjects with drug-related serious adverse events are included. A topical AE refers to any AE in the insert arm that is proximate to the site of insertion or, based upon the assessment of the investigator, is potentially a topical AE related to Implanon® Radiopaque. All such AEs are considered possibly related to study product by the Sponsor. Of note, no serious topical AEs were reported in this study.
* All drug related non-serious and serious adverse events as well as all unrelated serious adverse events leading to discontinuation are included in this count.
Source: TFL Table 10.

Table 10-6 Summary of Adverse Events by Severity (All Subjects Treated)

	All Subject Treated (N=1901) n (%)
Number of subjects with at least one drug-related AE (excluding topical AEs) #	911 (47.9)
Mild	744 (39.1)
Moderate	155 (8.2)
Severe	11 (0.6)
Missing	1 (0.1)
Number of subjects with at least one SAE	20 (1.1)
Mild	4 (0.2)
Moderate	7 (0.4)
Severe	9 (0.5)
Number of subjects with at least one drug-related SAE	7 (0.4)

	All Subject Treated (N=1901) n (%)
Mild	3 (0.2)
Moderate	2 (0.1)
Severe	2 (0.1)
Number of subjects with at least one topical AE	197 (10.4)
Mild	188 (9.9)
Moderate	7 (0.4)
Severe	2 (0.1)
Number of subjects with at least one drug-related AE or SAE leading to discontinuation of study drug *	650 (34.2)
Mild	514 (27.0)
Moderate	124 (6.5)
Severe	11 (0.6)
Missing	1 (0.1)
Number of subjects with at least one drug-related AE leading to discontinuation of study drug #	646 (34.0)
Mild	514 (27.0)
Moderate	124 (6.5)
Severe	7 (0.4)
Missing	1 (0.1)
Number of subjects with at least one drug-related SAE leading to discontinuation of study drug	6 (0.3)
Mild	3 (0.2)
Moderate	2 (0.1)
Severe	1 (0.1)

Note: All causality assessments (as related or unrelated) were made by the investigators.
Subjects with drug-related serious adverse events are included.
A topical AE refers to any AE in the insert arm that is proximate to the site of insertion or, based upon the assessment of the investigator, is potentially a topical AE related to Implanon® Radiopaque. All such AEs are considered possibly related to study product by the Sponsor. Of note, no serious topical AEs were reported in this study.
* All drug related non-serious and serious adverse events as well as all unrelated serious adverse events leading to discontinuation are included in this count.
If there were events of different severity reported in a subject, then this subject was only be counted into the highest severity.
Source: TFL Table 11.

10.4.1.2 Drug-Related AEs

In the study, drug-related AE (excluding topical AEs) was reported by 911 (47.9%) subjects [**Table 10-5**]. The most frequently reported (≥ 5% of subjects) drug-related AE by SOC were reproductive system and breast disorders (34.2%, 650 subjects), and investigations (5.9%, 112 subjects). The most frequently reported (≥ 5% of subjects) drug-related AE by PT were vaginal hemorrhage (15.6%, 297 subjects), heavy menstrual bleeding (8.0%, 153 subjects),

amenorrhoea (6.7%, 127 subjects), menstrual disorder (6.3%, 119 subjects) and weight increased (5.9%, 112 subjects) [**Of** note, there were no specific topical AEs reported in ≥ 5% of subjects [**Table 10-11**].

Table 10-7]. Of note, there were no specific topical AEs reported in ≥ 5% of subjects [**Table 10-11**].

Table 10-7 Summary of Drug-related Adverse Events by System Organ Class and Preferred Term (Incidence ≥ 5%)
(All Subjects Treated)

	All Subject Treated (N=1901) n (%)	95% CI
Reproductive system and breast disorders		
Vaginal haemorrhage	297 (15.6)	(14.1, 17.3)
Heavy menstrual bleeding	153 (8.0)	(6.9, 9.4)
Amenorrhoea	127 (6.7)	(5.6, 7.9)
Menstrual disorder	119 (6.3)	(5.3, 7.4)
Investigations		
Weight increased	112 (5.9)	(4.9, 7.0)

Note: None of the events presented in this table were serious adverse events.
Source: TFL Table 12.

10.4.1.3 SAEs and drug-related SAEs

In the study, SAEs were reported by 20 (1.1%), including 7 (0.4%) subjects with drug-related SAEs [**Table 10-5**]. The most frequently reported (> 0.1% of subjects) SAEs by PT were abnormal uterine bleeding (0.3%, 5 subjects) and uterine leiomyoma (0.2%, 3 subjects) [**Table 10-8**].

Table 10-8 Summary of Serious Adverse Events by System Organ Class and Preferred Term
(All Subjects Treated)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Number of subjects with at least one SAE	20 (1.1)	(0.7, 1.6)
Reproductive system and breast disorders	9 (0.5)	(0.2, 0.9)
Abnormal uterine bleeding	5 (0.3)	(0.1, 0.6)
Adenomyosis	1 (0.1)	(0.0, 0.3)
Breast mass	1 (0.1)	(0.0, 0.3)
Ovarian cyst	1 (0.1)	(0.0, 0.3)
Uterine enlargement	1 (0.1)	(0.0, 0.3)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Vaginal haemorrhage	1 (0.1)	(0.0, 0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (0.3)	(0.1, 0.7)
Uterine leiomyoma	3 (0.2)	(0.1, 0.5)
Lung neoplasm malignant	2 (0.1)	(0.0, 0.4)
Fibroadenoma of breast	1 (0.1)	(0.0, 0.3)
Intraductal papilloma of breast	1 (0.1)	(0.0, 0.3)
Blood and lymphatic system disorders	2 (0.1)	(0.0, 0.4)
Anaemia	2 (0.1)	(0.0, 0.4)
Gastrointestinal disorders	2 (0.1)	(0.0, 0.4)
Abdominal pain	1 (0.1)	(0.0, 0.3)
Chronic gastritis	1 (0.1)	(0.0, 0.3)
Oesophageal ulcer	1 (0.1)	(0.0, 0.3)
Stomach mass	1 (0.1)	(0.0, 0.3)
Endocrine disorders	1 (0.1)	(0.0, 0.3)
Adrenal disorder	1 (0.1)	(0.0, 0.3)
Eye disorders	1 (0.1)	(0.0, 0.3)
Eye swelling	1 (0.1)	(0.0, 0.3)
General disorders and administration site conditions	1 (0.1)	(0.0, 0.3)
Asthenia	1 (0.1)	(0.0, 0.3)
Hepatobiliary disorders	1 (0.1)	(0.0, 0.3)
Cholelithiasis	1 (0.1)	(0.0, 0.3)
Injury, poisoning and procedural complications	1 (0.1)	(0.0, 0.3)
Joint dislocation	1 (0.1)	(0.0, 0.3)
Nervous system disorders	1 (0.1)	(0.0, 0.3)
Headache	1 (0.1)	(0.0, 0.3)
Skin and subcutaneous tissue disorders	1 (0.1)	(0.0, 0.3)
Urticaria	1 (0.1)	(0.0, 0.3)

Source: TFL Table 13.1.

The most frequently reported drug-related SAE was abnormal uterine bleeding (0.3%, 5 subjects), respectively［**Table 10-9**］. Reported bleeding irregularities are further discussed in section 10.4.1.6.

Table 10-9 Summary of Drug-related Serious Adverse Events by System Organ Class and Preferred Term (All Subjects Treated)

	All Subject Treated (N=1901) n (%)	95% CI
Number of subjects with at least one drug-related SAE	7 (0.4)	(0.2, 0.8)
Reproductive system and breast disorders	6 (0.3)	(0.1, 0.7)
Abnormal uterine bleeding	5 (0.3)	(0.1, 0.6)
Breast mass	1 (0.1)	(0.0, 0.3)
Blood and lymphatic system disorders	2 (0.1)	(0.0, 0.4)
Anaemia	2 (0.1)	(0.0, 0.4)
Eye disorders	1 (0.1)	(0.0, 0.3)
Eye swelling	1 (0.1)	(0.0, 0.3)
Gastrointestinal disorders	1 (0.1)	(0.0, 0.3)
Abdominal pain	1 (0.1)	(0.0, 0.3)
General disorders and administration site conditions	1 (0.1)	(0.0, 0.3)
Asthenia	1 (0.1)	(0.0, 0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	(0.0, 0.3)
Uterine leiomyoma	1 (0.1)	(0.0, 0.3)
Nervous system disorders	1 (0.1)	(0.0, 0.3)
Headache	1 (0.1)	(0.0, 0.3)

Source: TFL Table 13.2.

10.4.1.4 Drug-related AEs and Topical AEs

Topical AEs are presented in this section separately from other AEs because topical safety profile was one of secondary endopoints in this study.

Drug-Related AEs (excluding topical AEs)

In the study, drug-related AEs (excluding topical AEs) were reported by 911 (47.9%) subjects The most frequently reported (≥ 5% of subjects) drug-related AEs (excluding topical AEs) by SOC were reproductive system and breast disorders (42.6%, 810 subjects) and investigations (6.0%, 114 subjects). The most frequently reported (≥ 5% of subjects) drug-related AEs by PT were vaginal haemorrhage (15.6%, 297 subjects), heavy menstrual bleeding (8.0%, 153 subjects), amenorrhoea (6.7%, 127 subjects), menstrual disorder (6.3%, 119 subjects) and weight increased (5.9%, 112 subjects) [**Table 10-10**].

Table 10-10 Summary of Drug-Related Adverse Events (Excluding Topical AEs) by System Organ Class and Preferred Term (All Subjects Treated)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Number of subjects with at least one drug-related AE (excluding Topical AEs) #	911 (47.9)	(45.7, 50.2)
Reproductive system and breast disorders	810 (42.6)	(40.4, 44.8)
Vaginal haemorrhage	297 (15.6)	(14.1, 17.3)
Heavy menstrual bleeding	153 (8.0)	(6.9, 9.4)
Amenorrhoea	127 (6.7)	(5.6, 7.9)
Menstrual disorder	119 (6.3)	(5.3, 7.4)
Menstruation irregular	59 (3.1)	(2.4, 4.0)
Abnormal uterine bleeding	36 (1.9)	(1.4, 2.6)
Menstruation delayed	32 (1.7)	(1.2, 2.4)
Oligomenorrhoea	29 (1.5)	(1.1, 2.2)
Breast pain	24 (1.3)	(0.8, 1.9)
Hypomenorrhoea	19 (1.0)	(0.6, 1.6)
Intermenstrual bleeding	13 (0.7)	(0.4, 1.2)
Polymenorrhoea	11 (0.6)	(0.3, 1.0)
Breast mass	3 (0.2)	(0.1, 0.5)
Breast swelling	3 (0.2)	(0.1, 0.5)
Adnexa uteri cyst	2 (0.1)	(0.0, 0.4)
Adnexa uteri mass	1 (0.1)	(0.0, 0.3)
Menstrual discomfort	1 (0.1)	(0.0, 0.3)
Nipple pain	1 (0.1)	(0.0, 0.3)
Ovarian cyst	1 (0.1)	(0.0, 0.3)
Suppressed lactation	1 (0.1)	(0.0, 0.3)
Vaginal discharge	1 (0.1)	(0.0, 0.3)
Vulvovaginal dryness	1 (0.1)	(0.0, 0.3)
Vulvovaginal pruritus	1 (0.1)	(0.0, 0.3)
Investigations	114 (6.0)	(5.0, 7.2)
Weight increased	112 (5.9)	(4.9, 7.0)
Blood pressure increased	1 (0.1)	(0.0, 0.3)
Transaminases increased	1 (0.1)	(0.0, 0.3)
Skin and subcutaneous tissue disorders	43 (2.3)	(1.7, 3.0)
Acne	26 (1.4)	(0.9, 2.0)
Alopecia	3 (0.2)	(0.1, 0.5)
Pigmentation disorder	3 (0.2)	(0.1, 0.5)
Rash	3 (0.2)	(0.1, 0.5)
Ephelides	2 (0.1)	(0.0, 0.4)
Seborrhoeic dermatitis	2 (0.1)	(0.0, 0.4)
Alopecia areata	1 (0.1)	(0.0, 0.3)
Dermatitis allergic	1 (0.1)	(0.0, 0.3)
Hair growth abnormal	1 (0.1)	(0.0, 0.3)
Hypertrichosis	1 (0.1)	(0.0, 0.3)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Skin haemorrhage	1 (0.1)	(0.0, 0.3)
Urticaria	1 (0.1)	(0.0, 0.3)
Nervous system disorders	25 (1.3)	(0.9, 1.9)
Dizziness	13 (0.7)	(0.4, 1.2)
Headache	13 (0.7)	(0.4, 1.2)
Somnolence	2 (0.1)	(0.0, 0.4)
Migraine	1 (0.1)	(0.0, 0.3)
Psychiatric disorders	19 (1.0)	(0.6, 1.6)
Libido decreased	7 (0.4)	(0.2, 0.8)
Anger	3 (0.2)	(0.1, 0.5)
Depression	3 (0.2)	(0.1, 0.5)
Poor quality sleep	2 (0.1)	(0.0, 0.4)
Affect lability	1 (0.1)	(0.0, 0.3)
Anxiety	1 (0.1)	(0.0, 0.3)
Dysphoria	1 (0.1)	(0.0, 0.3)
Mental disorder	1 (0.1)	(0.0, 0.3)
Orgasmic sensation decreased	1 (0.1)	(0.0, 0.3)
Gastrointestinal disorders	14 (0.7)	(0.4, 1.2)
Abdominal pain	4 (0.2)	(0.1, 0.5)
Nausea	4 (0.2)	(0.1, 0.5)
Abdominal distension	2 (0.1)	(0.0, 0.4)
Abdominal pain lower	2 (0.1)	(0.0, 0.4)
Constipation	1 (0.1)	(0.0, 0.3)
Gastrointestinal disorder	1 (0.1)	(0.0, 0.3)
General disorders and administration site conditions	10 (0.5)	(0.3, 1.0)
Asthenia	3 (0.2)	(0.1, 0.5)
Chest discomfort	3 (0.2)	(0.1, 0.5)
Axillary pain	1 (0.1)	(0.0, 0.3)
Chest pain	1 (0.1)	(0.0, 0.3)
Fatigue	1 (0.1)	(0.0, 0.3)
Swelling face	1 (0.1)	(0.0, 0.3)
Blood and lymphatic system disorders	7 (0.4)	(0.2, 0.8)
Anaemia	7 (0.4)	(0.2, 0.8)
Musculoskeletal and connective tissue disorders	5 (0.3)	(0.1, 0.6)
Back pain	4 (0.2)	(0.1, 0.5)
Myalgia	1 (0.1)	(0.0, 0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.3)	(0.1, 0.6)
Uterine leiomyoma	5 (0.3)	(0.1, 0.6)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Infections and infestations	3 (0.2)	(0.1, 0.5)
Measles	1 (0.1)	(0.0, 0.3)
Oral herpes	1 (0.1)	(0.0, 0.3)
Rhinitis	1 (0.1)	(0.0, 0.3)
Eye disorders	2 (0.1)	(0.0, 0.4)
Dry eye	1 (0.1)	(0.0, 0.3)
Eye pain	1 (0.1)	(0.0, 0.3)
Eye swelling	1 (0.1)	(0.0, 0.3)
Hepatobiliary disorders	2 (0.1)	(0.0, 0.4)
Hepatic function abnormal	2 (0.1)	(0.0, 0.4)
Cardiac disorders	1 (0.1)	(0.0, 0.3)
Palpitations	1 (0.1)	(0.0, 0.3)
Immune system disorders	1 (0.1)	(0.0, 0.3)
Hypersensitivity	1 (0.1)	(0.0, 0.3)
Metabolism and nutrition disorders	1 (0.1)	(0.0, 0.3)
Increased appetite	1 (0.1)	(0.0, 0.3)
Product issues	1 (0.1)	(0.0, 0.3)
Device breakage	1 (0.1)	(0.0, 0.3)
Vascular disorders	1 (0.1)	(0.0, 0.3)
Hot flush	1 (0.1)	(0.0, 0.3)

Note: # Subjects with drug-related serious adverse events are included.
Source: TFL Table 13.3.

Topical AEs

In the study, topical AEs were reported by 197 (10.4%) subjects. The most frequently reported (> 2% of subjects) topical AEs by PT were implant site bruising (4.6%, 87 subjects), implant site pruritus (4.2%, 79 subjects), and implant site pain (2.5%, 48 subjects) [**Table 10-11**]. There were no topical SAEs reported in this study.

In the single case of device dislocation reported in this study, the implant was reported to have moved by 1 cm. Subject did not experience any complications related to this event, and no actions were required regarding the study treatment, which was continued for another year.

Table 10-11 Summary of Topical Adverse Events by Preferred Term (All Subjects Treated)

Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Number of subjects with at least one topical AE	197 (10.4)	(9.1, 11.8)
Device dislocation	1 (0.1)	(0.0, 0.3)
Impaired healing	1 (0.1)	(0.0, 0.3)
Implant site bruising	87 (4.6)	(3.7, 5.6)
Implant site erythema	16 (0.8)	(0.5, 1.4)
Implant site extravasation	1 (0.1)	(0.0, 0.3)
Implant site haematoma	1 (0.1)	(0.0, 0.3)
Implant site haemorrhage	5 (0.3)	(0.1, 0.6)
Implant site hypoaesthesia	5 (0.3)	(0.1, 0.6)
Implant site infection	1 (0.1)	(0.0, 0.3)
Implant site mass	1 (0.1)	(0.0, 0.3)
Implant site nodule	2 (0.1)	(0.0, 0.4)
Implant site pain	48 (2.5)	(1.9, 3.3)
Implant site papules	1 (0.1)	(0.0, 0.3)
Implant site paraesthesia	2 (0.1)	(0.0, 0.4)
Implant site pruritus	79 (4.2)	(3.3, 5.1)
Implant site rash	1 (0.1)	(0.0, 0.3)
Implant site reaction	2 (0.1)	(0.0, 0.4)
Implant site scar	2 (0.1)	(0.0, 0.4)
Implant site swelling	13 (0.7)	(0.4, 1.2)

Note: A topical AE refers to any AE in the insert arm that is proximate to the site of insertion or, based upon the assessment of the investigator, is potentially a topical AE related to Implanon® Radiopaque.
Source: TFL Table 14.

10.4.1.5 Drug-related AEs and SAEs Leading to Discontinuation of Study Drug

In the study, drug-related AEs leading to discontinuation of study drug were reported by 646 (34.0%) subjects. The most frequently reported (≥ 5% of subjects) drug-related AEs leading to discontinuation of study drug by PT were vaginal haemorrhage (10.5%, 199 subjects), heavy menstrual bleeding (5.5%, 105 subjects) and menstrual disorder (5.0%, 96 subjects) [**Table 10-12**].

Table 10-12 Summary of Analysis of Subjects with Drug-related AEs Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term (All Subjects Treated)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Number of subjects with at least one drug-related AE leading to discontinuation of study drug #	646 (34.0)	(31.9, 36.1)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Reproductive system and breast disorders	582 (30.6)	(28.6, 32.7)
Vaginal haemorrhage	199 (10.5)	(9.2, 11.9)
Heavy menstrual bleeding	105 (5.5)	(4.6, 6.6)
Menstrual disorder	96 (5.0)	(4.2, 6.1)
Amenorrhoea	81 (4.3)	(3.4, 5.3)
Menstruation irregular	43 (2.3)	(1.7, 3.0)
Abnormal uterine bleeding	32 (1.7)	(1.2, 2.4)
Menstruation delayed	13 (0.7)	(0.4, 1.2)
Breast pain	11 (0.6)	(0.3, 1.0)
Hypomenorrhoea	11 (0.6)	(0.3, 1.0)
Oligomenorrhoea	11 (0.6)	(0.3, 1.0)
Intermenstrual bleeding	9 (0.5)	(0.2, 0.9)
Polymenorrhoea	8 (0.4)	(0.2, 0.8)
Breast mass	2 (0.1)	(0.0, 0.4)
Adnexa uteri cyst	1 (0.1)	(0.0, 0.3)
Ovarian cyst	1 (0.1)	(0.0, 0.3)
Vaginal discharge	1 (0.1)	(0.0, 0.3)
Vulvovaginal dryness	1 (0.1)	(0.0, 0.3)
Investigations	62 (3.3)	(2.6, 4.2)
Weight increased	62 (3.3)	(2.6, 4.2)
Skin and subcutaneous tissue disorders	21 (1.1)	(0.7, 1.7)
Acne	12 (0.6)	(0.4, 1.1)
Pigmentation disorder	2 (0.1)	(0.0, 0.4)
Rash	2 (0.1)	(0.0, 0.4)
Alopecia	1 (0.1)	(0.0, 0.3)
Alopecia areata	1 (0.1)	(0.0, 0.3)
Dermatitis allergic	1 (0.1)	(0.0, 0.3)
Ephelides	1 (0.1)	(0.0, 0.3)
Hair growth abnormal	1 (0.1)	(0.0, 0.3)
Urticaria	1 (0.1)	(0.0, 0.3)
Nervous system disorders	15 (0.8)	(0.5, 1.3)
Headache	9 (0.5)	(0.2, 0.9)
Dizziness	8 (0.4)	(0.2, 0.8)
Migraine	1 (0.1)	(0.0, 0.3)
Psychiatric disorders	15 (0.8)	(0.5, 1.3)
Libido decreased	6 (0.3)	(0.1, 0.7)
Depression	2 (0.1)	(0.0, 0.4)
Poor quality sleep	2 (0.1)	(0.0, 0.4)
Anger	1 (0.1)	(0.0, 0.3)
Anxiety	1 (0.1)	(0.0, 0.3)
Dysphoria	1 (0.1)	(0.0, 0.3)
Mental disorder	1 (0.1)	(0.0, 0.3)
Orgasmic sensation decreased	1 (0.1)	(0.0, 0.3)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Gastrointestinal disorders	5 (0.3)	(0.1, 0.6)
Abdominal pain	2 (0.1)	(0.0, 0.4)
Abdominal pain lower	1 (0.1)	(0.0, 0.3)
Gastrointestinal disorder	1 (0.1)	(0.0, 0.3)
Nausea	1 (0.1)	(0.0, 0.3)
General disorders and administration site conditions	5 (0.3)	(0.1, 0.6)
Implant site pruritus	2 (0.1)	(0.0, 0.4)
Implant site swelling	2 (0.1)	(0.0, 0.4)
Asthenia	1 (0.1)	(0.0, 0.3)
Fatigue	1 (0.1)	(0.0, 0.3)
Implant site erythema	1 (0.1)	(0.0, 0.3)
Implant site extravasation	1 (0.1)	(0.0, 0.3)
Implant site pain	1 (0.1)	(0.0, 0.3)
Blood and lymphatic system disorders	4 (0.2)	(0.1, 0.5)
Anaemia	4 (0.2)	(0.1, 0.5)
Infections and infestations	3 (0.2)	(0.1, 0.5)
Measles	1 (0.1)	(0.0, 0.3)
Oral herpes	1 (0.1)	(0.0, 0.3)
Rhinitis	1 (0.1)	(0.0, 0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.2)	(0.1, 0.5)
Uterine leiomyoma	3 (0.2)	(0.1, 0.5)
Musculoskeletal and connective tissue disorders	2 (0.1)	(0.0, 0.4)
Back pain	2 (0.1)	(0.0, 0.4)
Hepatobiliary disorders	1 (0.1)	(0.0, 0.3)
Hepatic function abnormal	1 (0.1)	(0.0, 0.3)
Immune system disorders	1 (0.1)	(0.0, 0.3)
Hypersensitivity	1 (0.1)	(0.0, 0.3)
Product issues	1 (0.1)	(0.0, 0.3)
Device breakage	1 (0.1)	(0.0, 0.3)
Vascular disorders	1 (0.1)	(0.0, 0.3)
Hot flush	1 (0.1)	(0.0, 0.3)

Note: # Subjects with drug-related serious adverse events are included.
Source: TFL Table 15.1.

In the study, drug-related SAE leading to discontinuation of study drug were reported by 6 (0.3%) subjects. The most frequently reported drug-related SAEs leading to discontinuation of

study drug by SOC and PT were reproductive system and breast disorders (0.3%, 6 subjects) and abnormal uterine bleeding (0.3%, 5 subjects) , respectively [**Table 10-13**].

Table 10-13 Summary of Analysis of subjects with Drug-Related SAEs Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term (All Subjects Treated)

System Organ Class Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Number of subjects with at least one drug-related SAE leading to discontinuation of study drug	6 (0.3)	(0.1, 0.7)
Reproductive system and breast disorders	6 (0.3)	(0.1, 0.7)
Abnormal uterine bleeding	5 (0.3)	(0.1, 0.6)
Breast mass	1 (0.1)	(0.0, 0.3)
Blood and lymphatic system disorders	1 (0.1)	(0.0, 0.3)
Anaemia	1 (0.1)	(0.0, 0.3)
Gastrointestinal disorders	1 (0.1)	(0.0, 0.3)
Abdominal pain	1 (0.1)	(0.0, 0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	(0.0, 0.3)
Uterine leiomyoma	1 (0.1)	(0.0, 0.3)

Source: TFL Table 15.2.

Further analysis of subjects with drug-related AE or SAE of bleeding irregularities and bleeding irregularities leading to discontinuation of study drug was conducted.

10.4.1.6 Bleeding irregularities

In the study, bleeding irregularities were reported by 790 (41.6%) subjects, including 6 (0.3%) subjects with SAE.[**Table 10-14**]

Five (0.3%) subjects reported serious bleeding irregularities leading to discontinuation of study drug [TFL Table 17.2].

Table 10-14 Summary of Drug-Related Adverse Event of Bleeding Irregularities by Preferred Term (All Subjects Treated)

Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Bleeding irregularities total	790 (41.6)	(39.4, 43.8)
Abnormal uterine bleeding	36 (1.9)	(1.4, 2.6)
Amenorrhoea	127 (6.7)	(5.6, 7.9)
Heavy menstrual bleeding	153 (8.0)	(6.9, 9.4)
Hypomenorrhoea	19 (1.0)	(0.6, 1.6)

Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Intermenstrual bleeding	13 (0.7)	(0.4, 1.2)
Menstrual disorder	119 (6.3)	(5.3, 7.4)
Menstruation delayed	32 (1.7)	(1.2, 2.4)
Menstruation irregular	59 (3.1)	(2.4, 4.0)
Oligomenorrhoea	29 (1.5)	(1.1, 2.2)
Polymenorrhoea	11 (0.6)	(0.3, 1.0)
Vaginal haemorrhage	297 (15.6)	(14.1, 17.3)

Note: Subjects with drug-related serious adverse events are included.
Source: TFL Table 16.1.

Table 10-15 Summary of Serious Adverse Event of Bleeding Irregularities by Preferred Term (All Subjects Treated)

Preferred Term	All Subject Treated (N=1901) n (%)	95% CI
Bleeding irregularities total	6 (0.3)	(0.1, 0.7)
Abnormal uterine bleeding	5 (0.3)	(0.1, 0.6)
Vaginal haemorrhage	1 (<0.1)	(0.0, 0.3)

Source: TFL Table 16.2.

In the study, the cumulative discontinuation rates with Implanon® Radiopaque owing to bleeding irregularities were 14.5% after 1 year , 25.5% after 2 years and 30.0% after 3 years [**Table 10-16**].

Table 10-16 Bleeding Irregularities Leading to Discontinuation of Study Drug (All Subjects Treated)

	Up to 1 Year (N=1901) n (%)	Up to 2 Years (N=1901) n (%)	Up to 3 Years (N=1901) n (%)
Number of subjects with bleeding irregularities	275 (14.5)	484 (25.5)	571 (30.0)
Number of subjects with favorable bleeding pattern	60 (3.2)	104 (5.5)	114 (6.0)
Amenorrhoea	43 (2.3)	76 (4.0)	81 (4.3)
Hypomenorrhoea	5 (0.3)	8 (0.4)	11 (0.6)
Menstruation delayed	11 (0.6)	12 (0.6)	13 (0.7)
Oligomenorrhoea	2 (0.1)	9 (0.5)	11 (0.6)

	Up to 1 Year (N=1901) n (%)	Up to 2 Years (N=1901) n (%)	Up to 3 Years (N=1901) n (%)
Number of subjects with unfavorable bleeding pattern	223 (11.7)	395 (20.8)	473 (24.9)
Abnormal uterine bleeding	16 (0.8)	26 (1.4)	32 (1.7)
Heavy menstrual bleeding	43 (2.3)	84 (4.4)	105 (5.5)
Intermenstrual bleeding	7 (0.4)	9 (0.5)	9 (0.5)
Menstrual disorder	34 (1.8)	74 (3.9)	96 (5.0)
Menstruation irregular	18 (0.9)	34 (1.8)	43 (2.3)
Polymenorrhoea	4 (0.2)	8 (0.4)	8 (0.4)
Vaginal haemorrhage	110 (5.8)	176 (9.3)	199 (10.5)

Note: The term bleeding irregularities has been used to include all disturbances of bleeding and as follows: favorable patterns include amenorrhea, infrequent (oligomenorrhoea), menstruation delayed and hypomenorrhoea; unfavorable patterns include frequent bleeding (polymenorrhoea), heavy menstrual bleeding, prolonged menstrual bleeding and spotting, menstruation irregular, intermenstrual bleeding, abnormal uterine bleeding, vaginal haemorrhage and menstrual disorder. The denominator of the percentage is the number of all treated subjects.
Source: TFL Table 27.

As shown in **Table 10-17**, overall discontinuation (15.4% to 100.0%) and discontinuation due to bleeding irregularities (7.7% to 60%) were highly variable among investigational sites.

Table 10-17 Bleeding Irregularities and Discontinuation Due to Bleeding Irregularities by Site (All Subjects Treated)

Site Number	Overall Discontinuation n (%)	Bleeding Irregularities n (%)	Discontinuation Due to Bleeding Irregularities n (%)	Proportion* of Bleeding Irregularities Leading to Discontinuation (%)
All Sites (N=1901)	1037 (54.6)	790 (41.6)	571 (30.0)	72.3
Site 0001 (N=20)	12 (60.0)	18 (90.0)	12 (60.0)	66.7
Site 0003 (N=59)	26 (44.1)	31 (52.5)	11 (18.6)	35.5
Site 0004 (N=20)	15 (75.0)	13 (65.0)	7 (35.0)	53.8
Site 0007 (N=40)	26 (65.0)	22 (55.0)	18 (45.0)	81.8
Site 0008 (N=19)	8 (42.1)	6 (31.6)	5 (26.3)	83.3
Site 0011 (N=115)	72 (62.6)	36 (31.3)	36 (31.3)	100.0
Site 0014 (N=200)	134 (67.0)	105 (52.5)	74 (37.0)	70.5
Site 0019 (N=60)	38 (63.3)	33 (55.0)	17 (28.3)	51.5
Site 0021 (N=82)	37 (45.1)	18 (22.0)	16 (19.5)	88.9
Site 0028 (N=16)	7 (43.8)	5 (31.3)	4 (25.0)	80.0
Site 0030 (N=26)	4 (15.4)	5 (19.2)	2 (7.7)	40.0
Site 0032 (N=27)	20 (74.1)	15 (55.6)	13 (48.1)	86.7
Site 0037 (N=40)	24 (60.0)	11 (27.5)	7 (17.5)	63.6

Site Number	Overall Discontinuation n (%)	Bleeding Irregularities n (%)	Discontinuation Due to Bleeding Irregularities n (%)	Proportion* of Bleeding Irregularities Leading to Discontinuation (%)
Site 0038 (N=40)	25 (62.5)	23 (57.5)	14 (35.0)	60.9
Site 0041 (N=96)	44 (45.8)	33 (34.4)	20 (20.8)	60.6
Site 0042 (N=80)	55 (68.8)	26 (32.5)	24 (30.0)	92.3
Site 0045 (N=60)	22 (36.7)	15 (25.0)	13 (21.7)	86.7
Site 0046 (N=99)	52 (52.5)	45 (45.5)	36(36.4)	80.0
Site 0049 (N=80)	52 (65.0)	31 (38.8)	31 (38.8)	100.0
Site 0050 (N=77)	35 (45.5)	53 (68.8)	30 (39.0)	56.6
Site 0053 (N=150)	44 (29.3)	70 (46.7)	21 (14.0)	30.0
Site 0060 (N=39)	28 (71.8)	19 (48.7)	19 (48.7)	100.0
Site 0061 (N=51)	31 (60.8)	23 (45.1)	22 (43.1)	95.7
Site0062 (N=214)	122 (57.0)	65 (30.4)	60 (28.0)	92.3
Site 0063 (N=4)	4 (100)	2 (50.0)	2 (50.0)	100.0
Site 0076 (N=40)	23 (57.5)	20 (50.0)	17 (42.5)	85.0
Site 0078 (N=52)	26 (50.0)	14 (26.9)	12 (23.1)	85.7
Site 0086 (N=47)	27 (57.4)	22 (46.8)	20 (42.6)	90.9
Site 0087 (N=1)	1 (100)	1 (100)	1 (100)	100.0

Site Number	Overall Discontinuation n (%)	Bleeding Irregularities n (%)	Discontinuation Due to Bleeding Irregularities n (%)	Proportion* of Bleeding Irregularities Leading to Discontinuation (%)
Site 0093(N=36)	16 (44.4)	10 (27.8)	7 (19.4)	70.0
Site 0095(N=11)	7 (63.6)	0	0	0.0

Note: The term bleeding irregularities has been used to include all disturbances of bleeding and as follows: favorable patterns include amenorrhea, infrequent (oligomenorrhoea), menstruation delayedand hypomenorrhoea; unfavorable patterns include frequent bleeding (polymenorrhoea), heavy menstrual bleeding, prolonged menstrual bleeding and spotting, menstruation irregular, intermenstrual bleeding, abnormal uterine bleeding, vaginal haemorrhage and menstrual disorder.
* Calculated by the number of subjects who discontinued due to bleeding irregularities (Column 3) over the number of subjects who reported bleeding irregularities (Column 2).
Source: TFL Table 28.

10.4.2 Satisfaction Results

Subject insertion satisfaction and general satisfaction were respectively evaluated in 1890(99.4%) subjects at 10 days and 1704 subjects (89.6%) at 6-months after the insertion. At 36 months after implantation or at the time of premature implant removal, 1740 (91.5%) and 1755 (92.3%) subjects completed the general satisfaction questionnaire and removal satisfaction questionnaire, respectively.

Ninety-six physicians performed implant insertion (or implantation) during the study. All physicians (100.0%) completed the satisfaction questionnaire following their first insertion, and 82 (85.4%) physicians completed the questionnaire after their fifth insertion.

Ninety-five physicians performed implant removal in the study. All physicians (100.0%) completed the removal satisfaction questionnaire after their first removal, and 61 (64.2%) physicians completed the satisfaction questionnaire following their fifth removal［**Table 10-18**］.

Table 10-18 Summary of Subject and Physician Satisfaction Related Questionnaire

	n (%)
All subjects implanted	1901
Completed insertion satisfaction questionnaire (10 days after implantation)	1890 (99.4)
Completed general satisfaction questionnaire (6 months after implantation)	1704 (89.6)
Completed general satisfaction questionnaire (36 months after implantation or at the time of premature removal)	1740 (91.5)
Completed removal satisfaction questionnaire (36 months after implantation or at the time of premature removal)	1755 (92.3)
All physicians who performed implantation	96
Having experience in implantation of Implanon® (non-radiopaque)#	66 (71.7)
No experience in implantation of Implanon® (non-radiopaque)#	81 (88.0)
Completed insertion satisfaction questionnaire (after completing the first insertion procedure)	96 (100.0)
Completed insertion satisfaction questionnaire (after completing the fifth insertion procedure*)	82 (85.4)
All physicians who performed removal	95
Completed removal satisfaction questionnaire (after completing the first removal procedure)	95 (100.0)
Completed removal satisfaction questionnaire (after completing the fifth removal procedure*)	61 (64.2)

*: This questionnaire was completed by investigator after insertion and the removal for the first and the fifth (or fifth+) subject. If the investigator did not enroll 5 subjects, the survey would be completed for the last insertion and for the last removal.
#: % Percentages are based on the total number of physicians who provided valid answers.

Source: TFL Table 18.

10.4.2.1 Subject Satisfaction

Insertion-Related Satisfaction

Among 1890 subjects completing the initial satisfaction questionnaire at Day 10, 1216 (64.3%) and 649 (34.3%) of the subjects reported that they experienced no pain or mild pain during implant insertion, respectively. Only 3 (0.2%) subjects reported experiencing severe pain during insertion.

Most subjects (1737 subjects, 91.9%) reported that the insertion procedure was less painful than or as painful as expected, including 1388 (73.4%) subjects answered "Less painful than expected" and 349 (18.5%) subjects answered "As expected". After insertion, 57 (3.0%) subjects reported "significant problems" in their arm with the implant. The most commonly reported significant problems following implant insertion were bruising (40 subjects, 2.1%), weakness or pain when moving the arm (6 subjects, 0.3%), and other reported problems (12 subjects, 0.6%). [**Table 10-19**]. Topical AEs (as assessed by the physician) are discussed earlier in this report (see Section **10.4.1.4**).

Table 10-19 Summary of Insertion-Related Satisfaction -- 10 Days after Insertion (All Subject Treated Who Answered the Insertion-Related Satisfaction Questionnaire)

Question Answers	All Subject Treated (N=1890) n (%)
Q1 Did you experience any pain during the insertion of the Implant?	1890 (100.0)
1 No pain	1216 (64.3)
2 Mild pain	649 (34.3)
3 Moderate pain	22 (1.2)
4 Severe pain	3 (0.2)
Q2 How did the Implant insertion procedure compare to your expectations?	1890 (100.0)
1 Less painful than expected	1388 (73.4)
2 As expected	349 (18.5)
3 More painful than expected	35 (1.9)
4 Did not have expectations	118 (6.2)
Q3 Have you experienced any significant problems in your "implant arm" since the implant was inserted?	1890 (100.0)
0 No	1833 (97.0)
1 Yes	57 (3.0)
Severe pain	0 (0)
Bruising	40 (2.1)
Pins and needles/numbness in the arm/hand/fingers	1 (0.1)
Weakness or pain when moving the arm	6 (0.3)
Others	12 (0.6)

Note: n is the number of subjects who answered the corresponding questions; the denominator of percentage is the total number of subjects who completed the Insertion-Related Satisfaction Questionnaire on 10th day after implantation among all treated subjects.

Source: TFL Table 19.

General Satisfaction

At 6 months after insertion, 1704 subjects completed the follow-up questionnaire, of whom 908 (53.3%) subjects were satisfied, 380 (22.3%) subjects were very satisfied, 330 (19.4%) subjects were neutral, 79 (4.6%) subjects were dissatisfied and 7(0.4%) subjects were very dissatisfied with the implant. Most (78.5%) subjects were willing to recommend Implanon® Radiopaque to others, including 596 (35.0%) subjects answered "Yes, absolutely" and 741 (43.5%) subjects answered "Yes, most probably" [**Table 10-20**].

Table 10-20 Summary of General Satisfaction -- 6 Months after Insertion (All Subject Treated Who Answered the General Satisfaction Related Questionnaire)

Question Answers	All Subject Treated (N=1704) n (%)
Q1 In general, how satisfied are you with the implant?	1704 (100.0)
1 Very satisfied	380 (22.3)
2 Satisfied	908 (53.3)
3 Neutral	330 (19.4)
4 Dissatisfied	79 (4.6)
5 Very dissatisfied	7 (0.4)
Q2 Would you recommend this Implant to others?	1704 (100.0)
1 Yes, absolutely	596 (35.0)
2 Yes, most probably	741 (43.5)
3 Undecided	278 (16.3)
4 No, probably not	73 (4.3)
5 No, absolutely not	16 (0.9)

Note: n is the number of subjects who answered the corresponding questions; the denominator pf percentage is the total number of subjects who completed the General Satisfaction questionnaire in the 6th month after implantation among all treated subjects.
Source: TFL Table 20.

At 36 months after insertion or premature removal, 1740 subjects completed the general satisfaction-related questionnaire, of whom 676 (38.9%) subjects were satisfied, 412 (23.7%) subjects were very satisfied, 423 (24.3%) subjects were neural, 205 (11.8%) subjects were dissatisfied and 24 (1.4%) subjects were very dissatisfied with the implant. Most subjects (67.6%) were willing to recommend Implanon® Radiopaque to others, including 509 (29.3%) subjects answered "Yes, absolutely" and 667 (38.3%) subjects answered "Yes, most probably" [**Table 10-21**].

Table 10-21 Summary of General Satisfaction -- 36 Months after Insertion or Premature Removal
(All Subject treated Who Answered the General Satisfaction Related Questionnaire)

Question Answers	All Subject Treated (N=1740) n (%)
Q1 In general, how satisfied are you with the implant?	1740 (100.0)
1 Very satisfied	412 (23.7)
2 Satisfied	676 (38.9)
3 Neutral	423 (24.3)
4 Dissatisfied	205 (11.8)
5 Very dissatisfied	24 (1.4)
Q2 Would you recommend this Implant to others?	1740 (100.0)
1 Yes, absolutely	509 (29.3)
2 Yes, most probably	667 (38.3)
3 Undecided	346 (19.9)
4 No, probably not	170 (9.8)
5 No, absolutely not	48 (2.8)

Note: n is the number of subjects who answered the corresponding questions; the denominator of percentage is the total number of subjects who completed the General Satisfaction Questionnaire in the 36th month after implantation or at the time of premature removal.
Source: TFL Table 21.

Removal Satisfaction

Removal satisfaction questionnaires assessing pain and satisfaction with the removal procedure, the reason for implant discontinuation, and willingness to use the implant in the future were completed by 891 (50.8%) and 864 (49.2%) subjects at premature removal and removal at month 36, respectively.

Of the subjects that completed satisfaction questionnaires (1721 subjects, 98.1%), the majority reported no pain (1118 subjects, 63.7%) or mild pain (603 subjects, 34.4%) during the removal procedure. Most (1286 subjects, 73.3%) reported that the removal procedure was less painful than expected.

The most common reasons for the implant removal or attempted removal were that the implant had been in place for 36 months (864 subjects, 49.2%), menstrual/bleeding problems (576 subjects, 32.8%), others (226 subjects, 12.9%), and planning pregnancy and/or contraception no longer needed (155 subjects, 8.8%). A total of 831 subjects (47.4%) were willing to continue to use Implanon® Radiopaque as their method of contraception, including 391 subjects (22.3%) answered “Yes, absolutely” and 440 subjects (25.1%) answered “Yes, most probably” [**Table 10-22**].

Table 10-22 Summary of Removal Satisfaction
(All Subject treated Who Answered the Removal Satisfaction Questionnaire)

Question Answers	All Subject Treated (N=1755) n (%)
Premature removal	891 (50.8)
Removal at month 36	864 (49.2)
Q1 Would you be willing to continue to use of this Implant as your method of contraception?	1741 (99.2)
1 Yes, absolutely	391 (22.3)
2 Yes, most probably	440 (25.1)
3 Undecided	360 (20.5)
4 No, probably not	356 (20.3)
5 No, absolutely not	194 (11.1)
Q2 What was the reason for the implant removal or attempted removal?	1754 (99.9)
1 The implant had been in place for 3 years	864 (49.2)
2 Planning pregnancy and/or contraception no longer needed	155 (8.8)
3 Became pregnant despite use Implanon® Radiopaque	1 (0.1)
4 Problem with implant	6 (0.3)
5 Menstrual/bleeding problems	576 (32.8)
6 Others	226 (12.9)
Q3 Did you experience any pain during the removal of the Implant?	1739 (99.1)
1 No pain	1118 (63.7)
2 Mild pain	603 (34.4)
3 Moderate pain	16 (0.9)
4 Severe pain	2 (0.1)
Q4 How did the Implant removal procedure compare to your expectations?	1739 (99.1)
1 Less painful than expected	1286 (73.3)
2 As expected	335 (19.1)
3 More painful than expected	31 (1.8)
4 Did not have expectations	87 (5.0)

Note: n is the number of people who answered the corresponding questions; the denominator of percentage is the total number of subjects who completed the Removal Satisfaction Questionnaire among all treated subjects.
Source: TFL Table 22.

10.4.2.2 Physician Satisfaction

Insertion Satisfaction

Physician Insertion Satisfaction was assessed by questionnaires given after completing the first and fifth insertion procedures. Ninety-six physicians completed questionnaires following their

first insertion procedure. Most physicians (95.8%) were satisfied following their first insertion procedure, of whom 55 (57.3%) physicians were very satisfied and 37 (38.5%) physicians were satisfied. Overall, 7 (7.3%) physicians reported difficulties or minor complications during the first insertion procedure; some reported more than one.

The most commonly reported difficulty was removing the protective cap from the applicator, which was reported by 4 (4.2%) physicians. Three (3.1%) physicians reported there was difficulty in sliding needle to its full length into skin, 2 (2.1%) physicians reported difficulty in unlocking purple slider, and 3 physicians reported each of the following issues: implant (partially) sticks out of the skin after insertion (1 physician, 1.0%), a needle inserted too deep (1 physician, 1.0%) and difficulty in moving purple slider fully to the back (1 physician, 1.0%) [**Table 10-23**].

Table 10-23 Summary of Physician Insertion Satisfaction after Completing the 1st Insertion Procedure
(All Physician Who Completed the Insertion Satisfaction Questionnaire)

Question Answers	Physician Completing Implantation Operation (N=96) n (%)
Q1 Taking all things into account, how satisfied are you with the insertion this time?	96 (100.0)
1 Very satisfied	55 (57.3)
2 Satisfied	37 (38.5)
3 Not satisfied nor dissatisfied	2 (2.1)
4 Dissatisfied	2 (2.1)
5 Very dissatisfied	0 (0)
Q2 Did you encounter any issues during insertion procedure this time?	96 (100.0)
1 No	89 (92.7)
2 Yes	7 (7.3)
Difficulty removing protection cap	4 (4.2)
Needle inserted too superficial	0 (0)
Difficulty sliding needle to its full length into skin	3 (3.1)
Implant (partially) sticks out of skin after insertion	1 (1.0)
Needle stick injury	0 (0)
Injury to nerve or blood-vessel	0 (0)
Difficulty unlocking purple slider	2 (2.1)
Needle visible after insertion (not fully retracted)	0 (0)
Needle inserted too deep	1 (1.0)
Difficulty moving purple slider fully to the back	1 (1.0)
Others	0 (0)

Note: n is the number of physicians who answered the corresponding questions; the denominator of percentage is the total number of physicians who completed the Physician Insertion Satisfaction Questionnaire after completing the 1st insertion procedure.
Source: TFL Table 23.

Satisfaction after the fifth insertion was evaluated in 74 (90.2%) physicians who completed 5 insertion procedures, and 8 (9.8%) physicians who completed less than 5. Most physicians physicians (81 physicians, 98.8%) were satisfied following their fifth or less than fifth insertion, of whom 55 (67.1%) physicians were very satisfied and 26 (31.7%) physicians were satisfied. No physician reported dissatisfaction after the fifth insertion, although one (1.2%) physician reported being neither satisfied nor dissatisfied.

Five (6.1%) physicians reported challenges or minor complications, including difficulty removing protection cap (4 physicians, 4.9%), difficulty in sliding needle to its full length into skin (1 physician, 1.2%), implant partially sticking out of the skin after insertion (1 physician, 1.2%), and difficulty in unlocking purple slider (1 physician, 1.2%) [**Table 10-24**].

Table 10-24 Summary of Physician Insertion Satisfaction after Completing the 5th Insertion Procedure
(All Physician Who Completed the Insertion Satisfaction Questionnaire)

Question Answers	Physician Completing Implantation Operation (N=82) n (%)
Less than 5 insertion procedures were done	8 (9.8)
5 Insertion procedures were done	74 (90.2)
Q1 Taking all things into account, how satisfied are you with the insertion this time?	82 (100.0)
1 Very satisfied	55 (67.1)
2 Satisfied	26 (31.7)
3 Not satisfied nor dissatisfied	1 (1.2)
4 Dissatisfied	0 (0)
5 Very dissatisfied	0 (0)
Q2 Did you encounter any issues during insertion procedure this time?	82 (100.0)
1 No	77 (93.9)
2 Yes	5 (6.1)
Difficulty removing protection cap	4 (4.9)
Needle inserted too superficial	0 (0)
Difficulty sliding needle to its full length into skin	1 (1.2)
Implant (partially) sticks out of skin after insertion	1 (1.2)
Needle stick injury	0 (0)
Injury to nerve or blood-vessel	0 (0)
Difficulty unlocking purple slider	1 (1.2)
Needle visible after insertion (not fully retracted)	0 (0)
Needle inserted too deep	0 (0)
Difficulty moving purple slider fully to the back	0 (0)
Others	0 (0)

Note: n is the number of physicians who answered the corresponding questions; the denominator of percentage is the total number of physicians who completed the Physician Insertion Satisfaction Questionnaire after completing the 5th insertion procedure.

*: This questionnaire was completed by investigator after insertion and the removal for the first and the fifth (or fifth+) subject. If the investigator did not enroll 5 subjects, the survey would be completed for the last insertion and for the last removal.
Source: TFL Table 24.

Removal Satisfaction

Ninety-five physicians completed questionnaires following their first implant removal. Most physicians (94 physicians, 98.9%) reported satisfaction following their first removal procedure, of whom 62 (65.3%) physicians were very satisfied and 32 (33.7%) physicians were satisfied. One (1.1%) physician reported being neither satisfied nor dissatisfied [**Table 10-25**].

In the one case of neither satisfied nor dissatisfied, the physician reported complications making removal difficult, including that the implant was encased in fibrotic tissue, the implant migrated approximately 1 cm, and multiple attempts were required for successful removal.

Table 10-25 Summary of Physician Removal Satisfaction after Completing the 1st Removal Procedure
(All Physician Who Completed the Removal Satisfaction Questionnaire)

Question Answers	Physician Completing Removal Operation (N=95) n (%)
Q1 Taking all things into account, how satisfied are you with the insertion this time?	95 (100.0)
1 Very satisfied	62 (65.3)
2 Satisfied	32 (33.7)
3 Not satisfied nor dissatisfied	1 (1.1)
4 Dissatisfied	0 (0)
5 Very dissatisfied	0 (0)
Q2 Were there any complications during the removal procedure this time?	95 (100.0)
1 No	94 (98.9)
2 Yes	1 (1.1)
Possible injury to nerve/blood vessel	0 (0)
Implant encased in fibrotic tissue making removal difficult	1 (1.1)
Implant located too deep	0 (0)
Implant migrated	1 (1.1)
Implant not found	0 (0)
Multiple attempts required	1 (1.1)
Others	0 (0)

Note: The numerator is the number of physicians who answered the corresponding questions; the denominator is the total number of all physicians who completed the Removal Satisfaction Questionnaire of physician after completed the 1st removal procedure.
Source: TFL Table 25.

Satisfaction after the fifth implant removal was evaluated in 53 (86.9%) physicians who completed 5 removal procedures and 8 (13.1%) physicians who completed less than 5. All physicians (100.0%) were satisfied, of whom 38 (62.3%) physicians were very satisfied and

23 (37.7%) physicians were satisfied and no physicians reported any complications with their fifth procedure [**Table 10-26**].

Table 10-26 Summary of Physician Removal Satisfaction after Completing the 5th Removal Procedure (All Physician Who Completed the Removal Satisfaction)

Question Answers	Physician Completing Removal Operation (N=61) n (%)
Less than 5 removal procedures were done	8 (13.1)
5 Removal procedures were done	53 (86.9)
Q1 Taking all things into account, how satisfied are you with the insertion this time?	61 (100.0)
1 Very satisfied	38 (62.3)
2 Satisfied	23 (37.7)
3 Not satisfied nor dissatisfied	0 (0)
4 Dissatisfied	0 (0)
5 Very dissatisfied	0 (0)
Q2 Did you encounter any issues during insertion procedure this time?	61 (100.0)
1 No	61 (100.0)
2 Yes	0 (0)
Possible injury to nerve/blood vessel	0 (0)
Implant encased in fibrotic tissue making removal difficult	0 (0)
Implant located too deep	0 (0)
Implant migrated	0 (0)
Implant not found	0 (0)
Multiple attempts required	0 (0)
Others	0 (0)

Note: n is the number of physicians who answered the corresponding questions; the denominator of the percentage is the total number of all physicians who completed the Physician Removal Satisfaction Questionnaire after completing the 5th removal procedure.
*: This questionnaire was completed by investigator after insertion and the removal for the first and the fifth (or fifth+) subject. If the investigator did not enroll 5 subjects, the survey should be completed for the last insertion and for the last removal.
Source: TFL Table 26.

10.4.3 Contraceptive Effectiveness Results and Pregnancies

10.4.3.1 Contraceptive Effectiveness Results

At each telephone visit, subjects were asked if they were pregnant. Among 1901 subjects with Implanon® Radiopaque insertion, 1 (0.05%) pregnancy was conceived during the treatment period.

The in-treatment pregnancy was reported by a 25-year-old subject. The pregnancy and conception date was confirmed by urine pregnancy test strips and ultrasound, respectively. The Implanon® Radiopaque was implanted on 29-MAR-2017, and the estimated conception date was 1-Aug-2017. The subject had experienced vaginal hemorrhage and was treated with mifepristone for 23 days (from 4-AUG-2017 to 23-AUG-2017). For the in-treatment pregnancy, the conception date was estimated to be 4 months after Implanon® Radiopaque insertion. The subject decided to have an induced abortion, which occurred on 28-SEP-2017. The same day the implant was removed.

10.4.3.2 Pregnancies

Twelve (0.63%) pregnancies had been reported in subjects who participated in this study. According to the estimated date of conception, 3 (0.16%) pregnancies were conceived prior to Implanon® Radiopaque insertion, 1 (0.05%) pregnancy was conceived during the treatment period, 2 (0.11%) pregnancies were conceived within 2 weeks of removal, 3 (0.16%) pregnancies were conceived after over 2 weeks of removal and 3 (0.16%) pregnancies were conceived at an uncertain time after removal [**Table 10-27**].

All 4 subjects who conceived prior-to-treatment or in-treatment pregnancies had induced abortion. One of the 2 subjects conceived pregnancies within 2 weeks of removal delivered a healthy infant and the other had induced abortion. One of the 3 subjects who conceived pregnancies over 2 weeks of removal delivered a healthy infant and the other 2 subjects had induced abortion. All the 3 subjects who conceived pregnancies on uncertain dates after removal had induced abortion or unknown pregnancy outcomes. No fetal-related AEs were reported.

One of the two post-treatment pregnancies (within 2 weeks of removal) was reported by a 24-year-old subject. The implant was removed on 26-MAR-2018, and the estimated date of conception was 1-APR-2018. The pregnancy and conception date was confirmed for this in-treatment pregnancy by urine pregnancy test strips. Subject had an induced abortion.

The other post-treatment pregnancy (within 2 weeks of removal) was reported by a 30-year-old subject . The implant was removed on 9-OCT-2018, and the estimated date of conception was 20-OCT-2018. She confirmed pregnancy by using pregnancy test strips and subsequently delivered a healthy baby boy.

Table 10-27 Summary of Pregnancy
(All Subjects Treated)

	All Subject Treated (N=1901) n (%)
Total number of pregnancies	12 (0.63)
Presumed time of conception	
Pre-treatment pregnancies	3 (0.16)
In-treatment pregnancies	1 (0.05)

	All Subject Treated (N=1901) n (%)
Post-treatment pregnancies	8 (0.42)
Within 2 weeks after removal	2 (0.11)
Over 2 weeks after removal	3 (0.16)
Other (time uncertain)	3 (0.16)

Note: In-treatment period (efficacy analysis): The period from implant insertion up to and including the day of implant removal. Pre-treatment pregnancies are pregnancies with an estimated date of conception before the implant insertion. In-treatment pregnancies are pregnancies with an estimated date of conception within the in-treatment period, i.e. from the day of implant insertion up to and including the day of implant removal.; Post-treatment pregnancies are pregnancies with an estimated date of conception after the in-treatment period.
Source: TFL Table 7.

10.5 Other analyses

All tables for the analyses not described in the main body of the clinical study report (CSR) but defined in the SAP will be provided in Section **14.**

10.6 Adverse events/adverse reactions

Please see Section **10.4.1**.

11 DISCUSSION

11.1 Key results

This study was conducted from 29-MAR-2016 (first subject, first visit) to 28-JUL-2021 (last subject, last visit). A total of 1909 subjects were screened, and 1901 subjects were enrolled. Thus, all of the 1901 enrolled patients (100.0%) were evaluable for the safety analysis. No other datasets were defined. Safety data collection was based mainly on solicited collection.

Among the 1901 enrolled subjects, 864 (45.45%) subjects completed 36 months of product use and 1037 (54.55%) discontinued the study prematurely. Overall, 651 subjects (34.25%) discontinued due to an AE as the primary reason, followed by planning pregnancy (147 subjects, 7.73%), others (137 subjects, 7.21%), lost to follow-up (98 subjects, 5.16%), withdrew informed consent (3 subjects, 0.16%) and pregnancy (1 subject, 0.05%). The mean (±SD) exposure duration was 783.7 (±388.7) days (5.0 to 1610.0 days).

Characteristics

The enrolled study population consisted of 1901 Chinese females, the mean (±SD) age, height, weight, body mass index (BMI) were 32.1 (± 5.6) years old, 160.7 (± 5.0) cm, 56.1 (± 8.3) kg and 21.7 (± 3.0) kg/m^2, respectively.

Overall Safety

In the study, drug-related AEs (excluding topical AEs) were reported by 911 (47.9%) subjects, and SAEs were reported by 20 (1.1%) subjects. The drug-related AEs or SAEs leading to discontinuation of study drug were reported by 650 (34.02%) subjects, including 646 (34.0%) subjects with drug-related AE and 6 (0.3%) subjects with drug-related SAE. No deaths occurred.

The 5 most frequently reported (≥ 5% of subjects) drug-related AE (excluding topical AEs) by PT included vaginal haemorrhage (15.6%), heavy menstrual bleeding (8.0%), amenorrhoea (6.7%,), menstrual disorder (6.3%) and weight increased (5.9%).

The most frequently reported (> 0.1% of subjects) SAEs by PT were abnormal uterine bleeding (0.3%) and uterine leiomyoma (0.2%).

The most frequently reported (≥ 5% of subjects) drug-related AEs leading to discontinuation of study drug by PT were vaginal haemorrhage (10.5%), heavy menstrual bleeding (5.5%) and menstrual disorder (5.0%).

Topical safety

In the study, topical AEs were reported by 197 (10.4%) subjects. The most frequently reported (> 2% of subjects) topical AEs by PT were implant site bruising (4.6%), implant site pruritus (4.2%), and implant site pain (2.5%).

Subject Satisfaction

Insertion-Related Satisfaction

Among 1890 subjects completing the initial satisfaction questionnaire at Day 10, 1216 (64.3%) and 649 (34.3%) reported that they experienced no pain or mild pain during implant insertion. Only 3 (0.2%) subjects reported experiencing severe pain during insertion. Most (1737 subjects,

91.9%) reported that the insertion procedure was less painful than or as painful as expected. After insertion, 57 (3.0%) subjects reported "significant problems" in their arm with the implant. The most commonly reported AEs following insertion were bruising (40 subjects, 2.1%), weakness or pain when moving the arm (6 subjects, 0.3%), and other reported problems (12 subjects, 0.6%).

General Satisfaction

At 6 months after insertion, 1704 subjects completed the follow-up questionnaire, of whom 908 (53.3%) subjects were satisfied, 380 (22.3%) subjects were very satisfied, 330 (19.4%) subjects were neutral, 79 (4.6%) subjects were dissatisfied and 7(0.4%) subjects were very dissatisfied with the implant. Most (1337 subjects, 78.5%) were willing to recommend Implanon® Radiopaque to others.

At 36 months after insertion or premature removal, 1740 subjects completed the general satisfaction-related questionnaire, of whom 676 (38.9%) subjects were satisfied, 412 (23.7%) subjects were very satisfied, 423 (24.3%) subjects were neural, 205 (11.8%) subjects were dissatisfied and 24 (1.4%) subjects were very dissatisfied with the implant. Most (1176 subjects, 67.6%) subjects were willing to recommend Implanon® Radiopaque to others.

Removal Satisfaction

Removal satisfaction questionnaires assessing pain and satisfaction with the removal procedure, the reason for implant discontinuation, and willingness to use the implant in the future were completed by 891 (50.8%) and 864 (49.2%) subjects at premature removal and removal at month 36, respectively. Most subjects (1721 subjects, 98.1%) reported no pain (1118 subjects, 63.7%) or mild pain (603 subjects, 34.4%) during the removal procedure, and the majority (1286 subjects, 73.3%) reported that the removal procedure was less painful than expected.

Physician Satisfaction

Insertion Satisfaction

Physician Insertion Satisfaction was assessed by questionnaires given after completing the first and fifth implant insertion procedures. Ninety-six physicians have completed questionnaires following their first insertion procedure. All but 4 physicians (95.8%) were satisfied following their first insertion procedure. Overall, 7 (7.3%) physicians reported difficulties or minor complications during the first insertion procedure; some reported more than one.

The most common difficulty reported by 4 (4.2%) physicians was related to removing the protection cap from the applicator. The difficulty in sliding needle to its full length into skin was reported by 3 (3.1%) physicians, difficulty in unlocking purple slider was reported by 2 (2.1%) physicians, and each of implant (partially) sticks out of skin after insertion (1 physician, 1.0%), needle inserted too deep (1 physician, 1.0%) and difficulty in moving purple slider fully to the back was reported by 1 (1.0%) physician, respectively.

Satisfaction after the fifth insertion was evaluated in 74 (90.2%) physicians who completed 5 insertion procedures, and 8 (9.8%) physicians who completed less than 5. All but 1 physician (98.8%) were satisfied following their fifth or less than fifth insertion, and no physician reported dissatisfaction after the fifth insertion, although 1 (1.2%) physician reported being neither satisfied nor dissatisfied.

Five (6.1%) physicians reported challenges or minor complications, including difficulty in removing protection cap (4 physicians, 4.9%), difficulty in sliding needle to its full length into skin (1 physician, 1.2%), implant partially sticking out of skin after insertion (1 physician, 1.2%), and difficulty in unlocking purple slider (1 physician, 1.2%).

Removal Satisfaction

Ninety-five physicians completed questionnaires following their first implant removal. All but one physician (98.9%) reported satisfaction following their first removal procedure, of whom 62 (65.3%) physicians were very satisfied and 32 (33.7%) physicians were satisfied.

Satisfaction after the fifth implant removal was evaluated in 53 (86.9%) physicians who completed 5 removal procedures and 8 (13.1%) physicians who completed less than 5. All physicians (100.0%) were satisfied, of whom 38 (62.3%) physicians were very satisfied, and 23 (37.7%) physicians were satisfied and did not report any complications with their fifth procedure.

Contraceptive Effectiveness Results

Among 1901 subjects with Implanon® Radiopaque insertion, 1 (0.05%) pregnancy was conceived during the treatment period. The subject decided to have an induced abortion, which occurred on 28-SEP-2017. The same day the implant was removed.

11.2 Interpretation

During the use of Implanon® Radiopaque, some women may have changes in their menstrual bleeding pattern. These may include the occurrence of an irregular bleeding pattern (absent, less, more frequent or continuous), and changes in bleeding volume (reduced or increased) or duration. Amenorrhoea was reported in about 1 of 5 women while another 1 of 5 women reported frequent and/or prolonged bleeding.[3] Occasionally, heavy bleeding has been reported.[2] Changes in the menstrual bleeding pattern including bleeding irregularities are the most common adverse effect of progestogen-only contraception and constitute the most important reason that women discontinue these progestin only methods.[8]

It is reported that Implanon® use was associated with amenorrhoea (22.2%) and infrequent (33.6%), frequent (6.7%), and/or prolonged bleeding (17.7%).[8] In this study, bleeding irregularities were reported by 790 (41.6%) subjects, including 127 (6.7%) subjects with amenorrhoea, 29 (1.5%) subjects with oligomenorrhoea, 11 (0.6%) subjects with polymenorrhoea and 153 (8.0%) subjects with heavy menstrual bleeding [**Table 10-14**]. The incidence of bleeding irregularities were somehow lower than the incidences reported in previous Implanon® clinical studies.[7]

In the study, the cumulative discontinuation rates with Implanon® were 14.5% after 1 year, 25.5% after 2 years and 30.0% after 3 years [**Table 10-16**]. The most frequently reported drug-related reason for discontinuation of Implanon® was vaginal haemorrhage (10.5%, 199 subjects), heavy menstrual bleeding (5.5%, 105 subjects) and menstrual disorder (5.0%, 96 subjects). These rates of discontinuation due to bleeding irregularities are not too disimilar to those reported in the literature.[8] The overall discontinuation (15.4% to 100.0%) and discontinuation due to bleeding irregularities (7.7% to 60%) were highly variable among investigational sites [**Table 10-17**]. These changes in the bleeding pattern have no serious effects on health; however they may interfere with daily activities and have an impact on

general well-being. Amenorrhoea was reported by 127 (6.7%) subjects in the study, which were somehow lower than the incidences (22%) reported in previous Implanon® clinical studies.[3,8] Eighty-one (4.3%) subjects reported amenorrhoea leading to discontinuation of study drug, which were somehow higher than it reported in previous studies (about 0.8%).

Since irregular vaginal bleeding and amenorrhea is an expected outcome, effective counseling provides reassurance that the absence of bleeding does not signify pregnancy or other problems leading to high continuation rate and high level of patient satisfaction. Clear and accurate counselling before insertion of Implanon® on the possible changes in bleeding patterns is pivotal to improving the woman's acceptance of a bleeding pattern, satisfaction with this contraceptive method and potentially improve continuation rates.

11.3 Generalisability

In this study, subjects were inserted Implanon® Radiopaque according to routine clinical practice conditions. The non-interventional nature of the study allowed collection of real-life data, without influencing the physicians' treatment decisions.

The study was non-controlled with limited on-site monitoring and was performed during the COVID-19 (Coronavirus Disease 2019) pandemic. Therefore, it might be subject to missing, inaccurate, or incomplete data and physician/selection bias. The centers that participated in the study were all very experienced with subject management and most investigators had previous experience with the use of Implanon® Radiopaque.

Since clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical practice of a drug cannot be directly compared to rates in the clinical trials of the same drug and may not reflect the rates observed in clinical trials.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

The results of this post-approval study revealed no new safety signals in relation to Implanon® Radiopaque use in the approved indication of contraception in Chinese females in routine clinical practice.

The type and incidence of topical and general AEs observed in this study are consistent with those reported during the clinical development of the contraceptive implant. No unexpected safety findings were observed.

The majority of subjects were satisfied with the product and were willing to recommend it to others. The majority of physicians were satisfied with Implanon® Implant insertion and removal complications were rare.

The observed overall safety profile including topical safety is consistent with the information already included in the Core Company Data Sheet and the Chinese package insert of Implanon® Radiopaque. The benefit-risk balance of Implanon® Radiopaque remains favorable.

14 TABLES AND FIGURES

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Table 15.3 Summary of Analysis of subjects with Drug-unrelated AEs Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term Table 16.1 Summary of Drug-Related Adverse Event of Bleeding Irregularities by System Organ Class and Preferred Term

Table 16.2 Summary of Serious Adverse Event of Bleeding Irregularities by System Organ Class and Preferred Term

Table 17.1 Summary of Drug-Related Bleeding Irregularities Leading to Discontinuation of Study Drug

15 REFERENCES

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16 LIST OF APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

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16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs

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