CLINICAL REVIEW

Application Type	Efficacy Supplement (S-027)
Application Number	NDA 021529
Priority or Standard	Standard
Submit Date	12/16/2024
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Division/Office	DUOG/ORPURM
Reviewer Names	Mary Shuman, MD Ioanna Comstock, MD Audrey Gassman, MD
Review Completion Date	01/15/2026
Established/Proper Name	Etonogestrel implant
(Proposed) Trade Name	Nexplanon
Applicant	Organon USA LLC
Dosage Form	Implant 68 mg
Applicant Proposed Dosing Regimen	Single, radiopaque, rod-shaped implant, containing 68 mg etonogestrel, pre-loaded in the needle of a disposable applicator for up to 5 years of use
Applicant Proposed Indication/Population	Prevention of pregnancy in females of childbearing potential
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Prevention of pregnancy in females of childbearing potential

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
DRM	Division of Risk Management
DUOG	Division of Urology, Obstetrics, and Gynecology
ECG	electrocardiogram
ECI	event of clinical interest
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
ICSR	Individual Case Safety Report
IND	Investigational New Drug Application
IRRE	Insertion and Removal Related Events
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IUS	intrauterine systems
ITT	intent to treat
LARC	long-acting reversible contraception
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
NORA	Nexplanon Observational Risk Assessment
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

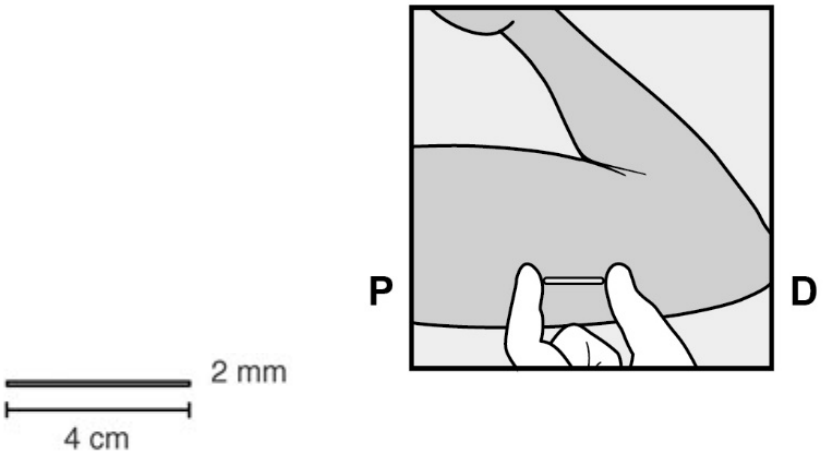
Organon USA, LLC (heretofore referred to as the Applicant) is seeking approval for the etonogestrel implant (Nexplanon) with the proposed indication of prevention of pregnancy for up to 5 years.

The original etonogestrel implant, Implanon, received U.S. approval on July 16, 2006, for a 3-year duration of use. Nexplanon's composition is identical to Implanon except for the addition of 15 mg barium sulfate to the core matrix, (b) (4). Nexplanon was approved as an Implanon replacement on May 13, 2011, and included a new inserter under efficacy supplement S-007 that provided the following benefits over the original Implanon implant:

- Allowance of one-handed insertion by healthcare providers
- A locking mechanism to prevent the implant from falling out of the device
- Less likelihood of the implant not being completely inserted in the proper subdermal location
- Potentially fewer 'deep' insertions.

Nexplanon is a radiopaque, progestin-only containing, flexible subdermal implant. The white/off-white, non-biodegradable implant measures 4 cm in length with a 2 mm diameter. It consists of two ethylene vinyl acetate (EVA) copolymers: an EVA core containing 28% vinyl acetate and an EVA skin (b) (4). Each implant contains an EVA copolymer core containing 68 mg of the progestin etonogestrel and 15 mg barium sulfate (radiopaque ingredient), surrounded by an EVA copolymer skin. Nexplanon is inserted into the inner aspect of the non-dominant arm.

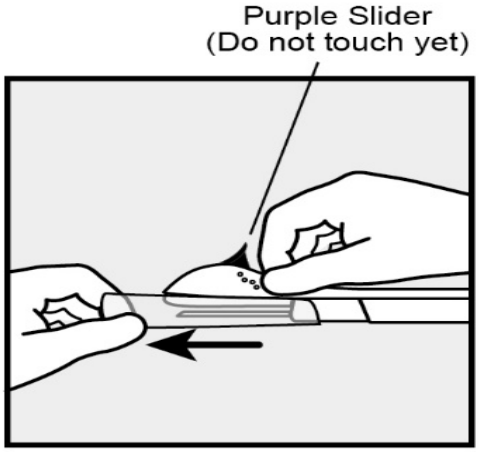
Figure 1: Nexplanon etonogestrel implant



Source: Approved Package Insert, not to scale (September 29,2023)

The inserter provided with Nexplanon is a single-use, disposable, sterile insertion system (Figure 2), preloaded with the Nexplanon implant for subdermal administration.

Figure 2: Inserter for Nexplanon etonogestrel implant



Source: Approved Package Insert (September 29, 2023)

Nexplanon is regulated as a drug-device combination product. While Nexplanon contains a drug substance – etonogestrel, the inserter is considered a device component and necessitates consultative review by the Center for Devices and Radiological Health (CDRH) when changes to the combination product are made.

Nexplanon is the only currently approved etonogestrel implant available in the United States (U.S.) and is approved for up to three years for contraception. This submission (S-027) provides effectiveness and safety data to support extending use through 5 years.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness supporting extension of Nexplanon use from three to five years for the prevention of pregnancy in females of reproductive potential using data from a single trial in their submission dated December 16, 2024. The evidence of clinical efficacy derives from a single adequate and well-controlled Phase 3 clinical investigation (Study MK-8415-060) demonstrating an acceptable primary efficacy endpoint (Pearl Index) that supports use for up to five years of use.

In this submission, the Applicant provided adequate data regarding evaluable cycles to assess the effectiveness of Nexplanon for the extended duration of use from 3 to 5 years. There were no on-treatment pregnancies during the extended duration period in their Phase 3 clinical trial. The individual year (years 4 and 5) Pearl Indices (PI) with 95% confidence intervals (95% CI) and cumulative PI for years 4 and 5 are as follows:

- PI at risk Year 4: 0 (CI: 0.0,1.23)
- PI at risk Year 5: 0 (CI: 0.0, 1.58)
- PI at risk Years 4 and 5: 0 (CI: 0.0,0.69)

The Pearl Indices and 95% confidence intervals for Nexplanon for these additional years of use are similar to those of previously approved LARCs. The clinical data are sufficient to demonstrate substantial evidence of effectiveness for prevention of pregnancy in reproductive age females with the use of Nexplanon for up to 5 years. This extension trial design follows established regulatory precedent for extended use for other approved long-acting reversible contraceptives.

The approval of this efficacy supplement will provide an additional two years of highly effective contraception in females who choose Nexplanon without replacement, thereby improving convenience and reducing healthcare burden while maintaining adequate contraceptive efficacy throughout the extended duration of use.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The Applicant provided substantial evidence of effectiveness to support approval of Nexplanon for the prevention of pregnancy in females of reproductive potential from the approved duration of 3 years of use to up to 5 years of use. The updated effectiveness data from individual year and 5-year cumulative Pearl Indices in this submission are comparable to other long-acting reversible contraceptives (LARCs) on the market and are clinically acceptable.

Acceptable exposure data to extend the duration of use was demonstrated in this submission with 7,752 total cycles of exposure in years four and five of treatment and ≥ 200 female subjects who were ≤ 35 years of age completing the full 5-year extended course of treatment. No new safety signals or trends were identified in the Applicant's pivotal Phase 3 trial (Study MK-8415-060). The number of treatment emergent adverse events (e.g., irregular bleeding and changes in menstrual patterns) were clinically similar to those that occurred in the first 3 years of use. The vaginal bleeding pattern for the participants in years 3 through 5 was consistent with a use of a progestin-only containing LARC. There are no concerns with the clinical benefit of this subdermal product for extended use up to 5 years as it has consistently demonstrated substantial effectiveness and tolerability over the 5-year duration of use with this additional trial data.

While the Benefit-Risk assessment for the submitted clinical trial appears to be favorable, there is a need to mitigate serious safety concerns of risks of insertion and removal related events (IRREs) due to improper insertion and removal techniques among untrained healthcare providers (HCPs). The reader is referred to the REMS review submitted to DARRTS on March 27, 2025, for further information regarding the following:

- Identification of serious IRREs due to improper insertion and removal techniques that were identified during development of the predicate product, Implanon. Serious insertion and removal related events continue to be reported through the post-marketing of Implanon and Nexplanon despite the availability of training from the Applicant.
- Training on the proper insertion and removal of Implanon and Nexplanon that was implemented by the Applicant (referred to as the Clinical Training Program or CTP.
- Findings from a prospective, active surveillance study (NORA study) designed to characterize the frequency of insertion, localization, and removal-related adverse events after the Applicant proposed a change to the inserter. Analyses of the NORA safety findings on IRREs prompted updates and refinements to labeling and the CTP that pertained to implant insertion, removal, and complications.

- Consultation with the Division of Pharmacovigilance II (in the Office of Surveillance and Epidemiology [OSE]) who provided two separate reviews of complications associated with insertion and removal related events from Nexplanon identified through FAERS searches. The review from DPV was signed off on August 16, 2024, and relates to insertion and removal complications.[1] The review that identified the serious safety concerns at insertion despite the ongoing CTP was dated September 3, 2024. This review specifically relates to implant migration to the pulmonary vasculature requiring surgical intervention.[2]

After identifying that serious IRREs continue to be reported in FAERS, DUOG and the Division of Risk Management (DRM) determined it is necessary to require training for HCPs to ensure proper technique on insertion and removal to HCPs prior to first-time use of Nexplanon rather than the current voluntary Applicant led program. On September 19, 2024, the review team (DUOG and DRM) presented the data from the NORA study, and OSE's FAERS results of spontaneous AE reporting, and provided our recommendations for a REMS to the REMS Oversight Committee (ROC). The ROC agreed with the review team's recommendation for a REMS to ensure providers receive training on Nexplanon insertion procedures prior to first use.

There is no other approvability concerns related to the benefit/risk to extend use through 5 years that were identified during this review cycle from the other disciplines. DRM, DMEPA, DMPP, and OPDP have reviewed the submission and have provided comments/recommendations regarding the REMS requirement and labeling for NDA approval.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Unintended pregnancy remains a significant public health concern in the United States, with far-reaching implications across social, economic, and cultural domains. This reproductive health issue affects not only women but also their families and	Nexplanon is an approved progestin-only containing contraceptive product that is indicated for prevention of pregnancy without limitations of use beyond the three-

[1]Chehab M, McCulley L. Pharmacovigilance Memorandum: Nexplanon (etonogestrel) Insertion and Removal Complications. TTT Record ID: 2024-9674. Finalized August 16, 2024. DARRTS Reference ID:5431398.
[2] Kang S, Niak A, Gada N, Brinker A, Jones SC. Pharmacovigilance Memorandum: Implanon (etonogestrel), Nexplanon (etonogestrel), and Migration of Implanon and Nexplanon Implants into the Vasculature, Chest Wall, and Other Body Sites. OSE RCM #2015-2458. Finalized January 29, 2016. DARRTS Reference ID: 3879792.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	broader communities. The consequences of unplanned pregnancies can include disrupted educational and career trajectories, financial strain, and potential health risks for both mother and child. Long-acting reversible contraception methods provide more reliable contraception for females who seek to avoid unintended pregnancy.	year timeframe.
Current Treatment Options	• Current treatment options in the U.S. for long-acting reversible contraceptives (LARCs) include an implant, injection, and six intrauterine systems (two copper-releasing systems and four levonorgestrel (LNG)-releasing systems). These long-acting products vary in terms of duration of use from three months to ten years.	Nexplanon is the only contraceptive implant approved and marketed in the U.S. that provides females of reproductive potential with a new extension to 5-year duration of use. Other long-acting products with this length of duration require intrauterine insertion, which may not be desirable for some patients.
Benefit	• As noted in Section 1.2 of this review, the Applicant has demonstrated substantial evidence of effectiveness for Nexplanon in Study MK-8415-060 through an acceptable pregnancy rate for a progestin-containing subdermal implant. The yearly and cumulative 5-year Pearl Indices are acceptable for this contraceptive product. As a long-acting reversible contraceptive (LARC), this product allows use of a progestin-only containing product with an acceptable pregnancy rate and few provider visits. The ease of use for this product makes it likely that unintended pregnancies will be minimized as daily or regular patient interface with LARCs is not required to maintain effectiveness.	In a large U.S. safety and efficacy single-arm trial (Study MK-8415-060), the Applicant provided evidence of effectiveness expected for a progestin-only containing contraceptive to extend use from 3 years to 5 years. This data in addition to clinical trial data submitted to support the benefit/risk for initial use up to 3 years is sufficient to extend the duration of use. This extended duration of use of Nexplanon offers the following significant benefits to females of reproductive potential:

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• As a long-acting reversible contraceptive (LARC), this product allows use of a contraceptive product with an acceptable pregnancy rate and few provider visits. The ease of use for this product makes it likely that unintended pregnancies will be minimized as daily or regular patient interface is not required to maintain effectiveness.	• Prolonged contraceptive coverage: Users can rely on a single implant for two additional years of highly effective contraception. • Reduced frequency of medical interventions: The extended duration means fewer visits to healthcare providers for implant replacement, which is particularly beneficial for patients with limited access to healthcare services. • Cost-effectiveness: A longer duration of use may reduce the overall cost of contraception for both patients and healthcare systems.
Risk and Risk Management	• The Applicant's safety data in Study MK-8415-060 is acceptable in terms of clinical exposure over a 5-year period for a progestin-only containing subdermal implant. Serious adverse events related to Nexplanon in the submitted clinical study report were similar to those found with other LARCs marketed in the U.S. No new safety signals were identified in the submitted clinical trial or in the 120-day safety report.	The risk of IRREs associated with improper insertion and removal techniques will be elevated to a Boxed Warning in labeling. In addition, DUOG and DRM conclude that a REMS with ETASU is needed for Nexplanon prior to approval of supplemental NDA, S-027 that would extend use for up to 5 years for prevention of pregnancy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Serious insertion and removal related events (IRREs) due to improper insertion and removal techniques were identified prior to approval of Implanon and have persisted through the post-marketing of Implanon and Nexplanon. Questions remain as to whether these IRREs result from a lack of mandatory training. • Training (also referred to as the clinical training program or CTP) on the proper insertion and removal of Implanon is a voluntary program that was initiated in 2006. The Applicant offered training for Implanon and updated the program with the approval of Nexplanon. • The NORA study was a prospective, active surveillance study designed to characterize the frequency of insertion, localization, and removal-related adverse events. In this study, all participating HCPs completed the Applicant's training program. Even with investigator training, difficulties or complications occurred in approximately 2.6% of insertions and 1.5% of removals. Only local migrations (no pulmonary migrations) were reported. Findings from this study were incorporated into labeling in 2019. • Based on recent FAERs reviews by the Division of Pharmacovigilance II, on two separate reviews, dated August 16, 2024, and September 3, 2024concerning and serious IRREs continue to occur. The review team determined that: o Due to the limited data available to the Agency about the operations and compliance with the voluntary CTP, it is possible that some providers who do not receive insertion	Although the current CTP has contributed to an acceptable benefit/risk profile with the incidence of IRREs, serious events continue to be reported. By formalizing the training requirement under our REMS authority, providers who insert and remove the implant will be required to complete training to mitigate the risk of implant and removal related events (i.e., significant damage to neurovascular structures of the arm, breakage of the implant, migration of the implant locally and distally, and unrecognized non-insertion of the implant). In addition, the Agency will be able to assess the REMS and monitor the program to determine whether it is successful in mitigating these errors or whether additional changes to the current program are necessary. The Agency expects implementation of the REMS to have minimal impact on the healthcare system because the Applicant has already required HCP training with restricted distribution.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and removal training could be utilizing the product which may increase the risk of IRREs. o There is no current method for the Agency to assess whether IRREs are related to a lack of training or other factors because we are unable to match IRREs to training. o Lack of required assessments of the current voluntary training program makes it is difficult to determine what improvements need to be made to further mitigate the risk. Increasing the duration of use of the implant could heighten the risk of migration if incorrectly placed, as well as the risk of more difficult removals as additional capsular fibrosis may occur, furthering the importance of adequate HCP training.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

- ☒ The patient experience data that was submitted as part of the application include:
  - ☒ Clinical outcome assessment (COA) data, such as
    - ☒ Patient reported outcome (PRO)
      - eDiary for recording episodes of vaginal bleeding
    - ☐ Observer reported outcome (ObsRO)
    - ☐ Clinician reported outcome (ClinRO)
    - ☐ Performance outcome (PerfO)
  - ☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)
  - ☐ Patient-focused drug development or other stakeholder meeting summary reports
  - ☐ Observational survey studies designed to capture patient experience data
  - ☐ Natural history studies
  - ☐ Patient preference studies (e.g., submitted studies or scientific publications)
  - ☐ Other: (Please specify)
- ☐ Patient experience data that were not submitted in the application, but were considered in this review:
  - ☐ Input informed from participation in meetings with patient stakeholders
  - ☐ Patient-focused drug development or other stakeholder meeting summary reports
  - ☐ Observational survey studies designed to capture patient experience data
  - ☐ Other: (Please specify)
- ☐ Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Pregnancy prevention is an important public health concern because unintended pregnancies can result in significant health, social, and economic hardship on females and their families. In 2019, there were 2,293,000 unintended pregnancies with a rate of 35.9 per 1000 women aged 15-44.[3] Contraception reduces the number of unintended pregnancies and potential unsafe terminations, prevents pregnancy-related health risks for females, and reduces infant morbidity and mortality. Ensuring that females of reproductive potential continue to have access to contraceptive method options, including LARCs, provides significant public health benefits.

2.2. Analysis of Current Treatment Options

Females of reproductive potential (and their partners) have numerous safe and effective options for reversible contraceptive methods to prevent unintended pregnancy:

- Barrier
- Oral Tablets (e.g., tablets, chewable tablets, oral-disintegrating tablets, capsules)
- Transdermal Systems (TDS)
- Vaginal Rings
- Injectable (e.g., Depo-Provera)
- Long-acting reversible contraceptives (LARCs) (e.g., implant, intrauterine systems)

LARC methods, such as intrauterine systems (IUSs) and contraceptive implants, are clinically safe and highly effective forms of reversible contraception. According to the Center for Disease Control (CDC), from 2017 to 2019 in the United States (U.S.), 65% of women 15-49 years of age (47.3 million) used some type of contraceptive method, and of those women, 10.4% (4.9 million) used LARCs (84% of which used IUSs [approximately 4 million] and 2% used the etonogestrel implant [approximately 949,000]). Use of LARCs was highest among women 20-29 (13.7%) and 30-39 (9.7%) years of age, and lower in women 15-19 (5.8%) and 40-49 (6.6%) years of age.[4]

Nexplanon is the only contraceptive implant approved and marketed in the U.S. Outside of the U.S. an identical product is named Implanon-NXT. A 2-rod implant (Jadelle) was approved in the U.S. but never marketed. The nonradiopaque original implant (Implanon) is no longer available worldwide.

Several intrauterine system products are approved in the U.S. These include two copper-releasing intrauterine systems (Paragard and Miudella), and 4 other progestin intrauterine

[3] Lauren Rossen et al. "Updated Methodology to Estimate Overall and Unintended Pregnancy Rates in the United States" *National Vital Statistics Reports* 72, no. 1 (2023).

[4] K. Daniels and JC Abma, "Current Contraceptive Status among Women Aged 15–49: United States, 2017–2019," *NCHS Data Brief*, no. 388 (October 2020).

systems (Mirena, Liletta, Kyleena and Skyla). Table 1 summarizes information about the LARC methods approved for use and marketed in the U.S.

Table 1: Summary of Marketed Long-Acting Reversible Contraceptive Methods in the United States

Product Name	NDA Number	Year of Approval	Duration of Use (Years)	Dose
ParaGard T380A (Copper IUS)	018680	1984	10	380 mm^2 exposed copper
Mirena (levonorgestrel)	021225	2000	8	52 mg LNG
Implanon (etonogestrel)	021529	2006	3	68 mg etonogestrel
Skyla (levonorgestrel)	203159	2013	3	13.5 mg LNG
Liletta (levonorgestrel)	206229	2015	8	52 mg LNG
Kyleena (levonorgestrel)	208224	2016	5	19.5 mg LNG
Miudella (Copper IUS)	218201	2025	3	175 mm^2 exposed copper

Source: FDA-approved labels for drug products
Abbreviations: IUS = intrauterine system; LNG = levonorgestrel
Table adapted from NDA 206229 S008 Clinical Review, Caren Kieswetter, MD MPH, October 18, 2019

There are no other approved contraceptive implant products currently marketed in the U.S.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant submitted this supplemental application (S-027) to extend the duration of use of Nexplanon from up to 3 years to up to 5 years for the prevention of pregnancy indication. The reader is referred to the REMS review submitted to DARRTS on March 27, 2025, for a detailed regulatory and marketing history for Nexplanon and its predecessor, Implanon. The reader is also referred to the Division Director's review dated May 13, 2011, for the approval of Nexplanon and its new inserter for a history of postmarketing requirements associated with the approval of Nexplanon.

3.2. Summary of Presubmission/Submission Regulatory Activity

On October 2, 2019, the Applicant requested a meeting to discuss submission of an efficacy supplement with an extension from 3 to 5 years duration of use. In lieu of a meeting, a Written Response Only (WRO) was provided on December 16, 2019. In this preliminary discussion, clinical trial recommendations and Pearl Index calculations were reviewed. In addition, CMC provided recommendations on development of an acceptable in vitro in vivo correlation (IVIVC).

Pre-sNDA preliminary meeting comments were sent to the Applicant on August 9, 2024, in anticipation of a teleconference on October 8, 2024. In those preliminary comments, it was noted that there were still 99 active participants enrolled in the pivotal trial and the Division's recommendations included the following:

- All narratives of pregnancies and serious adverse events that have occurred up to the time of submission, including those for enrolled participants who have not completed their final visit.
- An assessment of all premature discontinuations in Study MK 8415-060
- An assessment of the impact from the Covid pandemic on subjects in Study MK 8415-060
- An assessment of participants who became amenorrheic or oligomenorrheic initially with the implant who later appeared to show regular menstrual periods
- An assessment of extended duration of use for participants with a BMI > 30 kg/m2
- Any additional medical literature and/or medical society recommendations concerning extended use of the implant
- An effectiveness analysis that includes all participants who have completed the trial and a separate effectiveness analysis of all subjects (including those who have partial cycle data and all participants who are currently ongoing. An analysis including only subjects that have completed the trial could be performed as supporting.

The efficacy supplement (S-27) was submitted on December 16, 2024. Upon submission of S-027, the clinical team identified early in the review cycle that serious IRREs continued to be reported in FAERS, DUOG and the Division of Risk Management (DRM) determined it is necessary to require training for all HCPs to ensure proper technique on insertion and removal to HCPs prior to first-time use of Nexplanon. On September 19, 2024, the review team (DUOG and DRM) presented the data from the NORA study, and OSE's review of FAERS results of spontaneous AE reporting and provided our recommendations for a REMS to the REMS Oversight Committee (ROC). The ROC agreed with review team's recommendation for a REMS to ensure providers receive formal training on Nexplanon insertion procedures prior to first use. The reader is referred to DRM's review dated 01/15/2026 for the Risk Evaluation and Mitigation Strategies (REMS) for further information regarding the REMS requirement.

The efficacy supplement (S-027) included data from a single clinical trial that obtained data from 213 completers who were followed from years three through five. The number of completers fulfilled the agreed-upon 200 participants that was agreed to with the Agency and outlined in the WRO finalized on December 16, 2020.

During the pre-sNDA meeting on October 8, 2024, there was agreement that the Applicant would submit a separate efficacy supplement post approval containing the complete efficacy analysis for all 498 participants (all participants) from study start to last patient visit. The Agency deemed the submission fileable, and an Information Request (IR) for specific participants with IRREs and adverse events was requested and fulfilled.

Due to concerns related to IRREs, a REMS review was conducted early in the review cycle and completed by Ioanna Comstock on March 27, 2025, utilizing data and information from FAERS, DPV, postmarketing information and from previous data submissions to NDA 21529.

At the 120-day safety update, the safety data from the remaining 99 participants were submitted with updated tables and safety analysis. The cumulative dataset now encompassed all 498 participants from study start to last patient visit (database lock: January 23, 2025). There were no clinical concerns at the mid-cycle meeting held on May 15, 2025, and the submission of data from the Applicant fulfilled the clinical team's assessment for approval.

3.3. Foreign Regulatory Actions and Marketing History

Implanon was first approved in Indonesia in 1997. Implanon has not been withdrawn from the market in any country due to safety or efficacy concerns. Implanon has been discontinued from sale in the global market and changed to Nexplanon (which adds barium to allow the implant to be radiopaque). Outside the US, the product is marketed under the tradename Nexplanon or Implanon NXT.

The Medicines and Healthcare products Regulatory Agency (UK regulatory agency) published guidelines to clinicians and the public on amended advice on the insertion site for Nexplanon on February 12, 2020. Within this information, “Up to June 2019, MHRA is aware of 126 reports of implant migration. Of this report 18 mention migration to the lung, with some mentioning multiple instances of implants that have migrated to the lung. Worldwide, a total of 107 cases of migration to the pulmonary artery and chest have been identified by the marketing authorization holder since Nexplanon was launched (between 28 August 1998 to 3 September 2019).”[5] A change in location on the arm was a similar notification process to healthcare providers as was done in the US, with modification in the label and symptoms of migration to

[5]Gov.UK, "Nexplanon (etonogestrel) contraceptive implants: new insertion site to reduce rare risk of neurovascular injury and implant migration," *Drug Safety Update* 13, no. 7 (February 2020): 4 *https://www.gov.uk/drug-safety-update/nexplanon-etonogestrel-contraceptive-implants-new-insertion-site-to-reduce-rare-risk-of-neurovascular-injury-and-implant-migration.*

the lung and chest.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) determined that an on-site inspection of one clinical investigator (Dr. Christy Boraas) was warranted. After inspection of this site, OSI concluded that, "the inspection of Dr. Boraas's site did not reveal significant concerns regarding the conduct of the clinical study or Good Clinical Practice (GCP) or regulatory compliance. Based on the results of this inspection, the data generated by the inspected CI and submitted by the Applicant appear acceptable in support of the proposed indication." The reader is referred to the OSI Review by Regina Zopf dated August 7, 2025, for further information.

4.2. Product Quality

The etonogestrel implant and inserter type used in Study MK-8415-060 is identical to the currently marketed Nexplanon product. No product quality issues were identified during review of this efficacy supplement by the Office of Product Quality. In support of the extended duration of use to 5 years, the applicant provided drug product pharmaceutical development information, product control strategy, critical quality attributes (CQAs), mechanical testing, implant integrity and EVA supplier bridging were performed. This supplement is recommended for approval per CMC reviewer. The reader is referred to OPQ Review by Eturi and Bhattacharyya dated 10/10/2025 for further information.

4.3. Clinical Microbiology

No microbiology issues were identified in review by OPQ.

4.4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology reviewer, Dr. Edna Albuquerque, concluded that new nonclinical studies were not needed to further inform safety considerations for the extended (5-year) clinical use of Nexplanon. No changes were made to the nonclinical labeling section of the approved Nexplanon label. The reader is referred to the Pharmacology/Toxicology review dated November 6, 2025, for further information.

4.5. Clinical Pharmacology

No dedicated clinical pharmacology studies were performed or required for this efficacy supplement. However, a post-hoc analysis was performed to assess the potential impact of baseline body mass index (BMI) on etonogestrel serum concentrations during years 3 to 5 of Nexplanon use.

After review of the etonogestrel serum concentrations, the primary Clinical Pharmacology reviewer, Dr. Li Wang, concluded that "the Office of Clinical Pharmacology has reviewed the information contained in the sNDA and finds the sNDA acceptable from a clinical pharmacology perspective." The Clinical Pharmacology reviewer recommended tables to show concentration updates to the draft physician insert label for the extension to five years as well as the lower concentrations of etonogestrel based on BMI for specific populations in pharmacokinetics section of the label. The reader is referred to the Clinical Pharmacology review dated September 17, 2025, for further information.

4.6. Devices and Companion Diagnostic Issues

CDRH completed their review of the device components of the application and provided feedback on the need for a site manufacturer inspection. CDRH also reviewed the mechanical test results to support a new polymer supplier ((b) (4)) and extended use-life, from year 3 to year 5 for the subject product (Nexplanon). CDRH concluded that based on the inspection history of the firm and the fact that no manufacturing changes are being made as part of this supplement, CDRH does not recommend an inspection of the facility to address the proposed updated to use life and polymer supplier. For the extension, the primary CDRH reviewer, Reginald Avery, concluded that "the Applicant provided mechanical test results in subject products aged and preconditioned appropriately to support a 5-year shelf life and support use of a new EVA polymer supplier. There were no outstanding questions or deficiencies for the applicant to address."

The reader is referred to the CDRH review dated May 07, 2025, for further information.

4.7. Consumer Study Reviews

Not applicable to this submission

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 summarizes the clinical study conducted in support of this application.

Table 2: Clinical Study Conducted in Support of the Benefit-Risk of Nexplanon

Trial	Trial Design	Regimen	Study Endpoints	Treatment Duration	Number enrolled	Study Population	No. of Centers and Countries
Clinical Study to Support Efficacy and Safety							
MK-8415-60	Phase 3 Prospective Single Arm Open Label	Nexplanon In place for three years for duration up to 5 years	Contraceptive Efficacy Safety/Tolerability	Up to 60 months	498	Healthy, Post-menarche, females 18 to 35, wanting to prevent pregnancy	Multicenter 77 Sites US

Source: Clinical Reviewer Table Derived from Applicant's Study Report MK-8415-060

5.2. Review Strategy

The review strategy for the supplemental NDA application included a review of the following data sources and analyses of results from the Applicant.

- Efficacy: Efficacy data from Phase 3 Study MK-8415-060
- Safety: Adverse event data from the safety population in Study MK-8415-060
- The safety review approach for determining the need for a REMS with ETASU for Nexplanon included a review of the following data sources:
  - New FAERS database for adverse event reporting regarding IRREs
  - Worldwide postmarketing information regarding IRREs
  - NORA and the original clinical trial safety database results for context

The reader is referred to REMS review by Dr. Ioanna Comstock dated March 27,2025, for further information regarding the determination for the REMS requirement associated with this application.

Evaluation of efficacy data from Study MK-8415-060 was undertaken by the statistical review team. The reader is referred to the Statistical review by Dr. Nadeesri Wijekoon, PhD dated October 31, 2025, for further information.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study MK-8415-060

6.1.1. Study Design

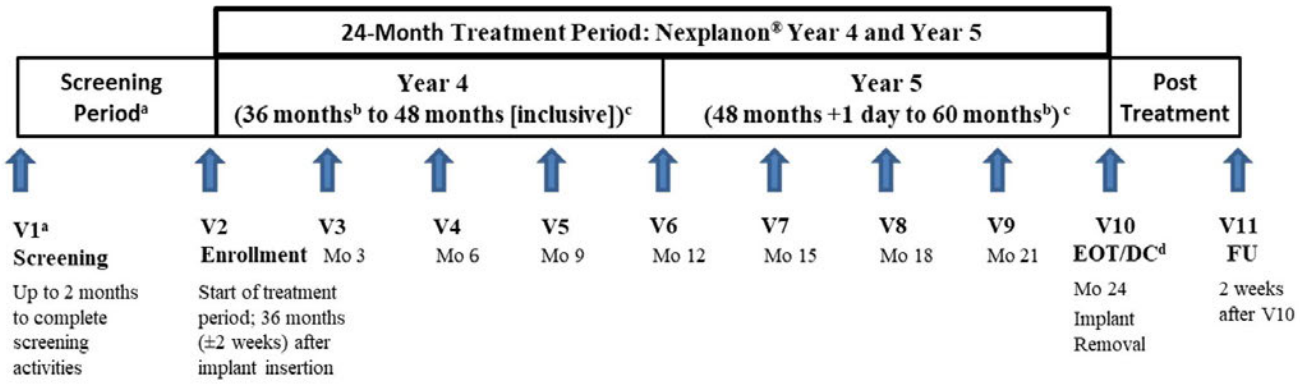
Trial Design

Study MK-8415-060 was a Phase 3, multicenter, open-label, single-arm trial to evaluate the contraceptive efficacy and safety of the etonogestrel (ENG) contraceptive implant during its fourth and fifth years of use. The trial aimed to assess the continued effectiveness and safety profile of the ENG implant beyond its current approved duration of use for two specific time periods.

1. Year 4: From 36 months (±2 weeks) to 48 months after the date of implant insertion
2. Year 5: From 48 months (+1 day) to 60 months (±2 weeks) after the date of implant insertion.

The trial was conducted in 77 clinical sites in the U.S.

Figure 3: Study Design Schema



DC=discontinuation; EOT=end of treatment; FU=follow-up; Mo=month; V=visit.
[a] Nexplanon® insertion occurs approximately 36 months (ie, 3 calendar years) before enrollment (V2). All participants will have an implant *in situ* at Screening (V1). The date of implant insertion must be verified as described in the protocol.
[b] ±2 weeks.
[c] Post implant insertion.
[d] V10 will be performed earlier than 60 months post implant insertion if the implant is removed or study participation is discontinued earlier than specified by the protocol.

Source:MK-8415-060 Study Report Pg 31/327.

Study Population

The study enrolled healthy nulliparous and parous female subjects at risk for pregnancy between ages 18 to 35 with an etonogestrel implant in place for 36 months (±2 weeks). Eligible females provided written consent, underwent screening procedures, and enrolled in this Phase 3 trial in accordance with protocol requirements. An Independent Data Monitoring Committee was engaged to monitor on treatment pregnancies, and participant safety.

Enrollment Criteria

Inclusion/exclusion criteria for this trial were consistent with other trials for hormonal contraceptive products. Key inclusion and exclusion criteria are summarized below.

Inclusion criteria:

1. Is a female, who will be 35 years of age or younger on the date of enrollment (V2) and is before the diagnosis of perimenopause/menopause.
2. Is at risk for pregnancy (i.e., having heterosexual vaginal intercourse at least once a month and not sterilized) with a partner who is not known to be subfertile, sterilized, or infertile, and is seeking contraception.

3. Has a palpable intact ENG implant in situ within the upper inner arm for 36 months (±2 weeks) from the date of insertion at the time of V2 with documentation of the insertion date (i.e., Nexplanon user card or medical record completed on the date of insertion).

   Note: At the time of enrollment and in the opinion of the investigator, there should be no known or anticipated challenges to removing the implant according to the standard technique described in Applicant's prescribing information (PI) (e.g., placement at an incorrect location, failed prior removal). Women known to require imaging or referral to a specialist for a complicated implant removal should not be enrolled. Participants whose implants are placed posteriorly within the upper arm may be enrolled as long as the implant is accessible for removal according to the standard technique with the participant supine as described.

4. Does not desire a pregnancy within the 24 months after V2, is willing to continue use of the implant for an additional 24 months and is not intending to use any other form of contraception (e.g., condoms) from V2 until after implant removal at V10.
5. Is in good physical and mental health, based on the medical judgment of the investigator.
6. Has a history of regular menstrual cycles of 21 to 35 days before the insertion of the ENG implant or before hormonal contraceptive use (which may have preceded the current implant use).
7. Is able and willing (in the opinion of the investigator) to adhere to all required study procedures, including study visits and eDiary entries, and not planning to relocate during the study (such that the participant would not be able to continue participation at the study site).

Reviewer's Comment:
Protocol Amendment 3, implemented in May 2021, restricted enrollment to participants with easily accessible implants. This enrollment criterion may have introduced bias into the study population, creating two distinct cohorts with different risk profiles:

- *Pre-May 2021 cohort: In review, the assumption is that participants enrolled before the amendment included individuals with both easily accessible and difficult-to-access implants, potentially representing a higher-risk population for implant removal-related events (IRREs).*

- *Post-May 2021 cohort: Participants enrolled after the amendment were limited to those with easily accessible and removable implants, potentially representing a lower-risk population for IRREs based on the language of investigator judgment.*

This population shift may have created a best-case scenario in the later study period that does not totally reflect real-world usage patterns. The study design also introduces potential selection bias through open enrollment of existing participants with current Nexplanon devices in situ, subsequently restricting enrollment after Protocol Amendment #3 in May 2021 onward to those with easily removable implants. The study start date was in December of 2020, with 162 participants enrolled by the June 29, 2021, lock date per Annual Report IND 042877, meaning approximately one-third of the final 498 enrolled participants were enrolled prior to the protocol change. There were 12 participants who had Nexplanon in place for 3 years who were deemed screen failures due to these criteria, potentially artificially lowering the IRREs prior to enrollment.

The inclusion criteria had no restrictions on BMI and encouraged enrollment to reflect the US population which was achieved by having approximately 30% of women with a BMI greater than 30 kg/m^2.

Exclusion criteria:

1. Has conceived during use of the current implant or a past contraceptive implant.
2. Has a known or suspected pregnancy. Note: A negative serum hCG test at V1 and a negative urine pregnancy test at V2 are required for a participant to be enrolled in this study.
3. Has a history of subfertility or infertility.
4. Is breastfeeding.
5. Has untreated gonorrhea, chlamydia, or trichomonas or symptomatic vaginitis/cervicitis.
6. Has significantly abnormal cervical cytology (Pap) or pathology results (i.e., ASC-H, squamous intraepithelial lesion [LSIL/HSIL], cervical intraepithelial neoplasia [CIN; any grade], atypical glandular cells [any type], adeno/squamous carcinoma [in situ or invasive]) either (1) at screening (V1) or (2) documented within 36 months before V1 regardless of follow-up results. If testing is performed, the presence of high-risk HPV at V1/Screening (regardless of Pap result) is ALWAYS exclusionary.
7. Is currently using an IUD/IUS.
8. Has any vaginal bleeding/spotting in the 12 months before V1 attributable to underlying pathology (i.e., cervical/endometrial polyp, uterine fibroids) not treated/resolved. The need for treatment is exclusionary; however, if the underlying pathology can be treated and the vaginal bleeding resolved within the enrollment window (36 months [±2 weeks] from the date of implant insertion), the participant may be enrolled.
9. Has in the 12 months before V1 experienced frequent (defined as > 5 episodes in 90 days), prolonged (defined as >14 continuous days), or excessive (in the opinion of the participant or the investigator) vaginal bleeding/spotting not evaluated to detect underlying pathology.
10. Has a history of VTE (i.e., deep vein thrombosis, pulmonary embolism), ATE

(i.e., myocardial infarction, stroke, or peripheral arterial disease), transient ischemic attack, angina pectoris, or claudication.

11. Is at a higher risk of VTE due to recent prolonged immobilization (within 2 weeks before screening, e.g., due to trauma, surgery, or other illness markedly limiting mobility), is planning surgery requiring prolonged immobilization, or has a hereditary or acquired predisposition or elevated risk for venous or arterial thrombosis, such as activated protein C resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (e.g., anticardiolipin antibodies, lupus anticoagulant) or has thrombogenic cardiac valve or rhythm abnormalities of the heart associated with thromboembolism (e.g., atrial fibrillation).
12. Has uncontrolled or severe hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) at V1. If hypertension can be controlled with medications and is no longer severe at enrollment (V2), the participant may be enrolled.
13. Has clinically significant liver disease, including active viral hepatitis or cirrhosis.
14. Has a history of malignancy ≤5 years before signing the informed consent (and assent, if applicable) (except for adequately treated basal cell or squamous cell skin cancer) or any history of sex steroid-influenced malignancies (e.g., genital organs, breasts).
15. Has a history or presence of liver tumors (benign or malignant).
16. Has a known allergy/sensitivity or contraindication to the ENG implant or lidocaine with epinephrine.
17. Has a history (current or within the 24 months before V2) of drug or alcohol abuse or dependence.
18. Has any clinically relevant abnormal laboratory result at V1 as judged by the investigator.
19. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator might expose the participant to risk by participating in the study, confound the results of the study, or interfere with the participant's participation for the full duration of the study (i.e., approximately 24 months).
20. Has more than one ENG implant in situ.

    Has received any treatment listed below more recently than the "last allowable use" indicated and/or needs to continue to receive any treatment listed:

    - Daily/monthly hormonal contraceptives, other sex steroids, or GnRH agonist or antagonist—Last Allowable Use: Three months before V2.
    - Injectable Contraception: Nine months before V2
    - Injectable GnRH agonist with 3 months duration; 10 months before V2
    - Medication that induce liver enzymes: Antiepileptics (e.g., phenytoin, barbiturates, primidone, carbamazepine, oxcarbazepine, topiramate, rufinamide and felbamate), Bosentan, rifampicin and rifabutin: last allowable use 2 months before V2
    - Rifampicin, rifabutin

- Anti-HIV or anti-hepatitis C drugs which decrease serum ENG (e.g., ritonavir, nelfinavir, nevirapine, efavirenz, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, tipranavir/ritonavir, boceprevir, telaprevir)
- Griseofulvin
- Herbal remedies or nonprescription products containing Hypericum perforatum (e.g., St. John's wort)

22. Has used an investigational drug and/or participated in any other clinical study within two months of V2.

Schedule of Events

The trial consisted of a screening visit (V1), enrollment(V2), follow-up visits every 3-months (V3-V10) to palpate implant, and to assess vital signs and serum hCG and serum ENG levels. Removal of the implant occurred at the end of study visit(V10) or at the time of early discontinuation. A follow-up serum hCG was obtained two weeks post implant removal, (visit V11).

The trial Schedule of Events is summarized in Figure 4 in Section 13.3.

Electronic Diary

From the start of the treatment period (visit V2), the subject recorded in the eDiary confirmation of sexual activity for each treatment cycle as well as concomitant contraceptive use including emergency contraception. Diary entries regarding intercourse were recorded monthly.

From the start of the treatment period, subjects also recorded the absence or presence of scheduled (menstrual) or unscheduled (intermenstrual) vaginal bleeding/spotting in the electronic diary on a daily basis.

To ensure data accuracy, the eDiary implemented a 48-hour lockout for daily questions and a 96-hour lockout for monthly questions. Sites contacted participants who were non-compliant with their eDiary entries.

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint of the study was the number of on-treatment pregnancies during the extended use of Nexplanon as assessed by the Pearl Index based on at-risk cycles in subjects aged ≤ 35 years.

An on-treatment pregnancy was defined as a confirmed pregnancy conceived with the implant in situ (or on the day of removal), with an estimated conception date between 36 months (±2

weeks) and 60 months (±2 weeks) from the implant insertion date plus 7 days.

Secondary Efficacy Endpoint

The key secondary endpoint was the annual on-treatment pregnancies during extended duration of use: PI at Year 4 and PI at Year 5.

Other Key Endpoints

Primary Safety Endpoint: Adverse Events (AEs) and discontinuation of study intervention (i.e., implant removed) due to AEs

Secondary Endpoints:

- Vaginal bleeding profile
  Assessed in 90-day reference periods including:
  Number of bleeding days, spotting days, and bleeding/spotting days
  Mean length of bleeding/spotting episodes
  Occurrence of amenorrhea, infrequent bleeding/spotting, frequent bleeding/spotting, normal frequency bleeding/spotting, and prolonged bleeding/spotting

- Implant removal complications
  Failed implant removal (Yes/No)
  Implant site fibrosis (Yes/No)
  Extension of incision >1 cm (Yes/No)
  Removal of a nonpalpable implant (Yes/No)
  Removal of a deeply placed implant (Yes/No)
  Implant removal in an operating room (Yes/No)
  Implant removal requiring general anesthesia (Yes/No)
  Implant removal requiring regional anesthesia (Yes/No)
  Implant removal requiring imaging guidance (Yes/No)
  Nerve injury during implant removal (Yes/No)
  Vascular injury during implant removal (Yes/No)
  Other complications of device removal not previously mentioned

Tertiary/Exploratory Endpoints:

- ENG Serum Concentrations: Pharmacokinetic profile of ENG from beginning of Year 4 to end of Year 5 after insertion.

- ENG (mg) remaining in implant after removal

- Integrity of the ENG implant after removal

  Bent implant (Yes or No)
  Broken implant (Yes or No)
  Implant skin intact (Yes or No)
  Implant core intact (Yes or No)
  Length (mm)
  Diameter (mm)

Statistical Analysis Plan

Analysis Populations (Definitions)

The following analysis populations were defined in the protocol:

- Safety set: consists of all enrolled participants.
- Full Analysis Set (FAS): all participants enrolled with at least one cycle of follow-up information.
- Restricted Full Analysis Set (rFAS): the subset of participants included in the FAS who have at least one "at risk" treatment cycle, or participants with a treatment cycle ("at risk" or not) in which a pregnancy has occurred (i.e., treatment cycle containing an estimated conception date for a pregnancy). This is the primary efficacy analysis set.

The reader is referred to the Statistical review dated October 31, 2025, for further information regarding the statistical analysis plan and approach to analyses for the efficacy endpoints.

Key Protocol Amendments

There were no major protocol amendments that significantly altered the methodology or analyses of primary efficacy and safety outcomes in Study MK-8415-060. However, several minor protocol amendments occurred during the study that included the following revisions:

Amendment 2 (December 15, 2020) - Data Collection Methods
- eDiary and vaginal bleeding analysis updates to accommodate participants using menstrual cups

- Addition of home health visits as an option in exceptional circumstances when clinic visits are not possible, especially for serum PK and end of study collection of pregnancy test 14 days after removal
-Updated the text to define a "completer" as someone who completes the 2-year duration and has a pregnancy test 14 days after removal even if the pregnancy test is performed at home.

Amendment 3 (May 14, 2021)- Inclusion and Exclusion Criteria clarifications
-Interval between V1 and V2 can be no more than 2 months.
-Inclusion criteria # 3 added that participants with palpable implants that can be removed on assessment by the investigator by the standard labeled procedural steps otherwise should not be enrolled.
-Clarified STI screenings

Amendment 4 (October 8, 2021) - Compliance Enhancement

-Implementation of automated cell phone text reminders for overdue eDiary entries to promote compliance.

Amendment 6 (July 3, 2023) - Safety Reporting

-Clarification of concomitant medication data collection associated with serious adverse events (SAE) and events of clinical interest (ECI)

Reviewer's Comment:
The protocol amendments provided appropriate improvements that enhanced data quality and participant safety. However, Amendment 3's refinements to inclusion/exclusion criteria, particularly the addition of an exclusion for participants with anticipated implant removal challenges, may have somewhat altered the study population characteristics compared to earlier enrolled participants (See Key Inclusion criteria). These mid-study eligibility changes could affect the generalizability of results for removal difficulties in the safety population as well as efficacy results, potentially leading to overly optimistic outcomes compared to real world use to five years.

Periodic drug adverse event reports (PADERs) have documented pregnancies in patients with device complications, including migrations, and deep implant placement, which supports concerns about the potential impact of excluding participants with anticipated removal challenges for the five-year duration of use.

6.1.2. Study Results

Compliance with Good Clinical Practices

An attestation to conducting the study in compliance with Good Clinical Practice (GCP) was submitted in this application. The sole study was conducted in accordance with local and national regulations, including all applicable data protection laws, International Council for Harmonization (ICH) Good Clinical Practice guidelines, and ethical principles originating from the Declaration of Helsinki.

Financial Disclosure

The Applicant adequately disclosed financial interests of the clinical investigators. See Financial Disclosure Figure 3 for full details under Appendix 13.2. 8 out of 441 investigators had disclosable financial interests. Most significant payments were made to institutions for investigator-initiated studies rather than direct personal compensation.

One primary investigator was no longer the investigator when he became an employee of the Applicant. That clinical site only enrolled (b) (6) participants, with one screen failure. The 113 uncertified investigators appear to result from administrative nonresponse rather than undisclosed conflict. The Applicant's due diligence efforts are documented with an internal audit. These financial disclosure findings do not affect the clinical approvability assessment of the application. The objective nature of the primary efficacy endpoint and the limited number of investigators with financial interests minimize any potential impact on study conclusions.

Patient Disposition

Table 3 displays the summary of subject disposition for the efficacy population and the primary reasons for discontinuation in Study MK-8415-060. In the study, a total of 656 participants were screened. Of the screened population, initial 399 participants were included in the study population, of which 394 were the efficacy population across 77 U.S. sites. 213 participants completed the study per protocol (i.e., finished year 4 and 5 and had a documented pregnancy test 14 days after implant removal). Of the 186 participants who discontinued from the trial, the most reported reasons were withdrawal by participant (29.8%) and lost to follow up (13.5%). One death was reported in year 4.

Table 3:Participant Disposition (Efficacy Population)

Category	N (%)
Participants in population	399
Completed the study	213 (53.4)
Study Discontinuation	186 (46.6)
Death	1 (0.3)
Drug-related adverse event	33 (8.3)
Lost to Follow-up	54 (13.5)
Withdrawal by Subject	119 (29.8)
Physician Decision and Other Reasons	12 (3.0)

Clinical Reviewer Table Derived from Applicant's Study Report MK-8415-060. Table 10-1. Pg. 44/327.

Protocol Violations/Deviations

The protocol violations and deviations were described from the initial submission of the supplement for efficacy on December 16, 2024. Of the 399 participants, 130 had one or more clinically important protocol deviations. On review of the clinically relevant protocol deviations, the most common clinically important deviations were procedural from the study and included:

- 82 instances in 34 participants: Human chorionic gonadotropin (hCG) sampling was not collected at every visit and/or not processed per laboratory manual instructions
- 55 participants: No documented pregnancy test within 14 days after implant removal
- 39 participants: Implant not removed or returned after study discontinuation (lost to follow up)

Reviewer's Comment:
Missing hCG testing could theoretically lead to undetected pregnancies, but the pregnancy monitoring through multiple visits and follow-up procedures likely mitigated this risk. Very few participants were excluded from efficacy or safety analyses due to protocol deviations. All deviations were tracked and reported comprehensively. While protocol deviations did occur, the primary efficacy conclusion appears robust given the absence of on-treatment pregnancies.

Demographic Characteristics

The Applicant's initial submission was based on 399 subjects as of the April 8, 2024, data cutoff, with 99 subjects still ongoing. Of the 399 subjects in the original safety set, 394 (~99%) were included in the primary efficacy population. Subjects' demographics and baseline characteristics in the efficacy population are shown in Table 4.

Table 4: Demographic Characteristics of Efficacy Population

	N=399 (%)
Age, years	
Mean (SD)	26.7 (4.13)
Median	27.0
IQR	23.0, 30.0
Min, Max	18.0, 35.0
Age categories, n (%)	
18-24	136 (34.1)
25-30	186 (46.6)
31-35	77 (19.3)
Race, n (%)	
American Indian or Alaska Native	5 (1.3)
Asian	15 (3.8)
Black or African American	67 (16.8)
Native Hawaiian or Other Pacific Islander	2 (0.5)
White	296 (74.2)
Multiple	10 (2.5)
Missing	4 (1.0)
Ethnicity, n (%)	
Hispanic or Latino	116 (29.1)
Not Hispanic or Latino	281 (70.4)
Not Reported	1 (0.3)
Unknown	1 (0.3)
BMI at baseline, kg/m2	
Mean (SD)	29.4 (7.74)
Median	27.7
IQR	23.5, 34.4
Min, Max	17.2, 64.3
Missing	4
BMI categories, n (%)	
<30 kg/m2	243 (60.9)
≥ 30 kg/m2	152 (38.1)
Unknown	4 (1.0)

Source: Statistical Reviewer's Analysis and CSR Table 14.1-7; sdtm dataset dv.xpt; IQR: Interquartile range.

Reviewer's comment:
The efficacy population was clinically similar to the intended target US population who would benefit from long-acting contraception. The inclusion of obese participants is particularly relevant given the US obesity prevalence in reproductive age women.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Not applicable.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was not measured as participants had implant already in place at enrollment.

Prior medication use was reported in 69.6% of participants, while concomitant medication use was documented in 95.9% of participants. Ibuprofen emerged as the most used medication, accounting for 14.9% of prior medication use and 22.0% of concomitant medication use when excluding the local anesthetic lidocaine and epinephrine that were administered before implant removal procedures in the full analysis set population.

Additionally, 100 participants (25.3%) received a new contraceptive implant on the same day as their implant removal and were included in the concomitant medication analysis.

Data Quality and Integrity

No concerns regarding data integrity were identified during clinical site inspections or by clinical review of the NDA submission that would affect the approvability of this application. The reader is referred to Section 4.1 Office of Scientific Investigations (OSI) for further information.

Efficacy Results – Primary Endpoint

In Study MK-8415-060, no on-treatment pregnancies were reported. 394 subjects aged ≤ 35 years with at least 1 at-risk cycle in the study reported 6,936 at-risk cycles. The cumulative Pearl Index during years 4 and 5 was 0 per 100 women-years (95% CI: 0.00, 0.69). See Table 5 below. The reader is referred to the Statistical review dated October 31, 2025, for further information regarding the analyses for the efficacy endpoints.

Table 5: Pearl Index in Subjects Aged ≤ 35 Years

Endpoint	Number of Evaluable Cycles	Pearl Index (95% CI)
Year 4 PI at risk	3894	0.0 (0.0, 1.23)
Year 5 PI at risk	3042	0.0 (0.0, 1.58)
Year 4 and 5 PI at risk	6936	0.0 (0.0,0.69)

Source: Table 6 from Biostatistical review, Nadeesri Wijekoon, PhD, dated October 31, 2025, page 13.

Efficacy Results – Secondary and other relevant endpoints

A life-table analysis was performed to calculate pregnancy rates during Years 4 and 5 in the primary efficacy population. Pregnancy rates were 0.0% year 4 (0 pregnancies among 3894 evaluable cycles), year 5 (0 pregnancies among 3042 evaluable cycles), and years 4 and 5 combined (0 pregnancies among 6936 evaluable cycles).

The Pearl Index by subgroup of BMI is presented in Table 6 below. The Pearl Index was numerically similar in subjects with a BMI ≥ 30 kg/m^2 compared to those with a BMI ≤ 30 kg/m^2.

Table 6: Pearl Index by BMI Subgroup

BMI Category	Number of participants	Number of Evaluable Cycles	PI at risk Years 4-5	95% CI
<30 kg/m^2	240	4345	0.00	0.00, 1.10
≥30 kg/m^2	150	2573	0.00	0.00, 1.86

Source: Modified table from Applicant's Clinical Study Report P060V01MK8415. Pg 78/327

Reviewer's Comment:
The PI of 0.00 in BMI **≥30** kg/m^2 *is clinically significant as it demonstrates a maintained efficacy in females with obesity. While the number of evaluable cycles in the obese population was less than 5,000 evaluable cycles that is usually recommended by the Division, the upper bound of the 95% CI at 1.86 is clinically significant and supports effectiveness in this population.*

Dose/Dose Response

Not applicable

Durability of Response

Refer to the Clinical Pharmacology review dated September 17, 2025, for their review on the exposure for ENG Dose in all participants as treated and PK results from Trial MK-8415-060.

Persistence of Effect

Historically, the etonogestrel implant has not demonstrated significant persistence of effectiveness beyond 7 days after removal. There is no evidence from the submitted trial data to alter this determination.

Additional Analyses Conducted on the Individual Trial

Not applicable.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The Applicant conducted a single trial (MK-8415-060) to assess the efficacy and safety for an extension from a duration of use of 3 years to the end of five years. Therefore, an integrated review of efficacy across multiple trials is not pertinent or necessary.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The extension in duration of use from up to 3 to up to 5 years is a relevant benefit to patients who may not have easy access to healthcare providers in the post market setting. The extension from up to 3 years to up to 5 years offers a significant benefit for women who desire a long-acting reversible contraception that does not require placement in the uterus.

7.2.2. Other Relevant Benefits

Long-acting progestin-only contraception may be preferred in noncompliant patients such as adolescents.

7.3. Integrated Assessment of Effectiveness

Efficacy data to support the proposed increased the duration of use for up to 5 years consists of one adequate and controlled Phase 3 clinical investigation (Study MK-8415-060) No other trials were conducted to support this increased duration of use.

There were no on-treatment pregnancies reported in Study MK-8415-060. The cumulative PI for years 4 and 5 was 0.00 (95% CI:0.00, 0.69) per 100 women-years (WY) for a total of 6,936 evaluable cycles. See Section 6.1.2 for review and discussion.

The submitted evidence provides substantial evidence of effectiveness for extending etonogestrel implant use through 5 years. The clinical benefit is highly meaningful, offering women an additional 2 years of highly effective contraceptive protection without device replacement, thereby improving convenience, reducing healthcare burden, and maintaining efficacy throughout the extended duration.

8. Review of Safety

8.1. Safety Review Approach

The safety review of this supplemental NDA consisted of adverse events analyses of the safety population, i.e., all subjects who had existing Nexplanon implants and were candidates for extended Nexplanon use through five years post-insertion.

The safety review incorporated the following data sources to provide comprehensive assessment for the trial:

- Clinical trial safety data from Study MK-8415-060, original submission (n=399) and 120-day safety update report, (safety population, n=498).
- Periodic Adverse Drug Experience Reports (PADERs) and Annual Reports
- Targeted information requests regarding specific IRREs in the US population as well as cumulative IRREs, (device embolization to pulmonary vasculature) global population
- Post marketing surveillance data provided by the Applicant for implants retained beyond three years
- Current labeling with NORA study results and original safety population results.

Given that this submission contained a single pivotal study (MK-8415-060) for the extended duration of use indication, no pooling of clinical trial data was necessary or conducted to assess the risk profile for this increased duration of use.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The overall exposure for the extension from up to year 3 to the end of 5 years of use was acceptable since the Applicant met the Division's requirement of safety and efficacy data for at least 200 subjects completing 5 years of use. A total of 498 participants who had the Nexplanon implant for 3 years were enrolled in Study MK-8415-060. Table 7 lists the duration of exposure for study participants in the full trial to completion in support of this supplemental NDA.

Table 7: Duration of Exposure, Safety Population

Exposure Metric	N (%)
Total enrolled	498 (100%)
Completed ≥42 months	446 (89.6%)
Completed ≥48 months	386 (77.5%)
Completed ≥59.5 months	312(62.7%)
Completed ≥60 months	247 (49.6%)

Source: Clinical Reviewer table modified from Applicant's MK-8415 P060 (ALL Data as of 23Jan2025) 120 Safety Report, Summary of Treatment Duration Exposure Table 2.7. Pg 26/455.

8.2.2. Relevant characteristics of the safety population:

The safety population from Study MK-8415-060 consisted of 498 participants with the following racial composition: 73.9% (n=368) Caucasian, 15.9% (n=79) Black or African American, etc. Participants of Hispanic or Latino ethnicity represented 28.7% (n=143) of the total safety population. These participants contributed at least 7,752 cycles.
The mean baseline BMI of study participants was 29.61 kg/m² with 39.7% (n=198) of study participants having a BMI ≥30 kg/m². The overall proportion of the safety population that was obese aligns closely to the intended population that would use Nexplanon in the US. The demographic characteristics of the safety population in Study MK-8415-060 are shown in Table 8.

Table 8: Safety Population Demographics and Baseline Characteristics

Participants		N (%)
		498
Age		
	Mean years (SD)	26.9 (4.12)
	Median (years)	27.0
	Min, max (years)	18, 35
Age Group		
	18-24 years	161 (32.3)
	25-30 years	233 (46.8)
	31-35 years	104 (20.9)
	Unknown	0 (0.0)
Race		
	White	368 (73.9)
	Black or African American	79 (15.9)
	Asian	24 (4.8)
	American Indian or Alaska Native	6 (1.2)
	Native Hawaiian or Other Pacific Islander	1 (0.2)
	Multiple Race[1]	11 (2.2)
	Missing	8 (1.6)
Ethnicity		
	Hispanic or Latino	143 (28.7)
	Not Hispanic or Latino	349 (70.1)
	Not Reported	3 (0.6)
	Unknown	3 (0.6)
Body Mass Index (BMI)		
	Mean kg/m² (SD)	29.61 (7.933)
	Median kg/m²	28.1
	Min, max kg/m²	17.2, 64.3
BMI Categories		
	<18 kg/m²	3 (0.6)
	≥18 to <25 kg/m²	170 (34.1)
	≥25 to <30 kg/m²	123 (24.7)
	≥30 to <40 kg/m²	147 (29.6)
	≥40 kg/m²	51 (10.2)
	Unknown	4 (0.8)

Notes: [1]Multiple races includes combinations such as Black or African American + Asian, Black or African American + White, etc.
Source: Clinical Reviewer Table Modified from Applicant's MK-8415 P060 (ALL Data as of 23Jan2025) 120 Safety Report from Table 1.11 Participant Characteristics (All Participants as Treated), Page 8-10/455

8.2.3. Adequacy of the safety database:

The primary safety database from Study MK-8415-060 is clinically adequate for this efficacy supplement. The safety database consisted of 498 healthy females of child-bearing potential with at least 7,752 exposure cycles. This provides sufficient safety data from treatment cycles and adverse event reporting to draw general conclusions regarding the tolerability and safety for the extended duration of use of Nexplanon in the U.S. with use beyond three years.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Data integrity concerns were not identified. The quality and integrity of the data submitted in this NDA are acceptable for review.

8.3.2. Categorization of Adverse Events

Adverse events were categorized using MedDRA Version 27.1. Adverse events were categorized appropriately. Definitions of serious adverse events and treatment-emergent adverse events were acceptable and appropriate. IRREs were categorized as events of clinical interest (ECI) in the Applicant's submission and followed closely due to the previous determination for a REMS. Adverse event follow-up, categorization, and causality assessment were adequately described prior to study initiation.

8.3.3. Routine Clinical Tests

Safety measures defined by the protocol, which included medical supervision, physical examination, vital signs, clinical laboratory tests and adverse events (AEs) monitoring were adequate to ensure subjects' safety. Chemistry (glucose) and lipid panel were not done under fasting conditions which could limit interpretation for long-acting contraception effects to five years. However, there were no lipid profile or glucose level changes observed in the original trials supporting the approval of Implanon and no safety trend or signal in the laboratory and vital sign data collected.

8.4. Safety Results

8.4.1. Deaths

One death occurred in a subject enrolled in Study MK-8415-060. The respective case narrative is summarized below:

Participant ID (b) (6):
26-year-old Caucasian female received a Nexplanon implant approximately 3 years prior to study enrollment, day one of study was (b) (6), and death was on day 331, (b) (6)

(b) (6). No further details are known. The Applicant notes that multiple efforts to contact her family yielded no further information. The Applicant deemed the death unrelated to Nexplanon.

Reviewer's Comment:
Due to insufficient information on the circumstances of this patient's death, causality between Nexplanon and the death event cannot be determined.

8.4.2. Serious Adverse Events

Overall, 9 serious adverse events, including one death, were reported in 9 participants (1.8% of safety population) in Study MK-8015-060. Case narratives of these SAEs were carefully reviewed to determine the relationship of the respective SAE to the study drug. Eight were assessed by the reviewer as not related to the study product, and one fatality with unknown causality due to a lack of additional information. Details of the case narratives are discussed below in Table 9.

Table 9:Case Narratives of Serious Adverse Events in Safety Population

Subject ID Study age at enrollment (years)	SAE	Narrative	Relation to Nexplanon
(b) (6) 23	Pyrexia, Liver function test increased	She experienced a severe fever of 102 and went to the ED on day 714 and found to have elevated liver enzymes. She was in the hospital until day 717 and given a diagnosis of Still's disease. Follow-up testing on day 731, showed liver tests resolving and size of liver now normal. Implant removed on day 725 and completion of trial on day 731.	Not related
(b) (6)	Cellulitis	On day 524,	Not related

23		participant fell and hit right arm and hip. She developed cellulitis on right elbow on day 545 and had debridement on day 551. Resolved with IV antibiotics. Implant was in Left arm and not involved in the injury	
(b) (6) 26	Invasive ductal breast cancer	On day of implant removal of 737, she reported that she noted right nipple inversion on day 736. She underwent imaging and biopsy that revealed breast cancer on day 757.	Not related
(b) (6) 33	Acute cholecystitis	Participant with right upper abdominal pain on day 40, underwent surgery on day 51 with resolution. On day 751, participant completed study	Not related
(b) (6) 26	Depression	Participant with history of depression prior to enrollment. On day 484, suicidal ideation admitted to inpatient care. She was released on day 533, with recovery on day 582. Participant completed trial on day 736	Not related
(b) (6) 35	Appendicitis	Participant had right lower quadrant pain	Not related

		and went to the ER and had appendectomy surgery on day 581. Participant finished trial on day 738 with implant removal on day 722.	
(b) (6) 26	Death	See narrative	Unknown
(b) (6) 26	Adnexal mass	Participant experienced complex right adnexal mass on day 50 and had surgery with removal on day 51. No pathology reports available. Participant finished study on day 736 with implant removal.	Not related
(b) (6) 31	Breast abscess/breast cancer	She was initially diagnosed with a breast abscess on day 18 (onset day -11 from the trial). On day 43, invasive ductal carcinoma was diagnosed. On Day 495, the implant was removed due to withdrawal from the trial by the participant. On day 520, last contact with participant.	Not related

Source: Study MK-8415-60 Narratives: Appendix 16.2.7 and 120 Safety Update Report Narratives

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

A total of 39 of 498 (7.8%) participants in the safety population discontinued due to an adverse

event. The most frequently reported preferred terms (PT) leading to discontinuation included irregular menstrual or vaginal bleeding (n=21, 4.2%). 9 participants (1.8%) prematurely discontinued due to psychiatric conditions that included worsening depression, anxiety, or mood swings, and 2 participants (0.4%) discontinued due to weight gain.

Reviewer's Comment:
None of the reported adverse reactions raise a newly identified safety signal or trend as compared to the known risk profile associated with Nexplanon use for up to 3 years. Of note, the clinical events resulting in discontinuation reported in this trial are similar to those reported in the original trial to support 3 years of use.

8.4.4. Significant Adverse Events

Insertion and removal related adverse events are a known risk associated with use of Nexplanon. The significant adverse events associated with improper techniques for insertion and removal procedures for Nexplanon are discussed elsewhere in this review (see Section 8.5.1 for further information). Although some insertion and removal data were collected in this trial, it would not be a useful surrogate as all investigators in this trial were well trained on the procedures involved.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A total of 321 subjects (64.5%) in the safety population experienced at least one treatment-emergent adverse event (TEAE). The most commonly reported PTs related to Nexplanon that were clinically relevant were intermenstrual bleeding (5.6%), heavy menstrual bleeding (5.4%), depression (3.4%), and anxiety (3.2%). The incidences of the most common TEAEs by PT are provided in Table 10.

Table 10:Adverse Events by Preferred Term with Incidence > 2%

Preferred Term	System Organ Class	Cumulative Number of Subject N (%)
COVID-19	Infections and infestations	79 (15.9%)
Upper respiratory tract infection	Infections and infestations	31 (6.2%)
Intermenstrual bleeding	Reproductive system and breast disorders	28 (5.6%)

Heavy menstrual bleeding	Reproductive system and breast disorders	27 (5.4%)
Urinary tract infection	Infections and infestations	27 (5.4%)
Bacterial vaginosis	Infections and infestations	26 (5.2%)
Nausea	Gastrointestinal disorders	18 (3.6%)
Depression	Psychiatric disorders	17 (3.4%)
Anxiety	Psychiatric disorders	16 (3.2%)
Nasopharyngitis	Infections and infestations	14 (2.8%)
Dysmenorrhea	Reproductive system and breast disorders	13 (2.6%)
Acne	Skin and subcutaneous tissue disorders	12 (2.4%)
Menometrorrhagia	Reproductive system and breast disorders	11 (2.2%)
Fatigue	General disorders and administration site conditions	11 (2.2%)
Influenza	Infections and infestations	10 (2.0%)
Attention deficit hyperactivity disorder	Psychiatric disorders	10 (2.0%)
Headache	Nervous system disorders	10 (2.0%)

Source: Clinical Reviewer Table Modified from 120 Safety Update Study Report MK-8415 P060(All Data as of 23JAN2025). Pg30-49/455

The most common adverse events related to study drug were irregular bleeding events consistent with in profile with other progestin only contraception. No new safety signals or trends were identified from the review of TEAEs occurring in the safety population in this study. Of note, adverse events such as headache, fatigue and attention deficit hyperactivity disorder were identified as adverse events. However, there is insufficient information to assess causality of these adverse events given the limitations of available baseline assessment data for these types of contraceptive trials.

Vaginal Bleeding Profiles

Vaginal bleeding profiles are important to hormonal contraceptives users as intermittent spotting and bleeding can result in product discontinuation and unwanted pregnancy. The Applicant evaluated bleeding profiles from the beginning of year 4 to the end of year 5 utilizing 90-day reference periods. This was done by eDiary with daily and monthly entry required of participants. Bleeding was reported only if it was considered bothersome by the study subject, thereby signifying a likely underreporting of intermenstrual, irregular, and spotting by the end of the 24-month duration for the study.

A review of reported vaginal bleeding profiles from EDiary data using 90-day reference periods showed slight increase in irregular spotting as well as normal bleeding frequencies at the end of five years. Women with BMI ≥30 kg/m² experienced numerically fewer bleeding/spotting days compared to women with BMI <30 kg/m² across all reference periods. The findings are from the first reference period to the last reference period (1 to 8 RP):

- Amenorrhea increased slightly: 6.3% to 6.6%
- Infrequent bleeding/spotting (<3 episodes) increased: 16.1% to 17.0%
- Normal frequency bleeding/spotting (3-5 episodes) increased: 53.9% to 58.5%
- Frequent bleeding/spotting (>5 episodes) decreased: 11.0% to 10.4%
- Prolonged bleeding/spotting (>14 continuous days) decreased: 12.2% to 6.6%

None of the abnormal bleeding profiles are unexpected or of concern for a long-acting progestin only contraceptive. The risk of abnormal bleeding with Nexplanon is included in prescription and patient labeling.

8.4.6. Laboratory Findings

Laboratory assessments (e.g., hematology and chemistry parameters) were performed at regular intervals throughout the treatment period in the safety population. Overall, no clinically meaningful changes were observed in hematology or chemistry parameters from baseline over the 24-month study period. No participants met the Hy's Law criteria indicating no cases of drug-induced liver injury were identified.

8.4.7. Vital Signs

Vital sign assessments were performed at regular intervals throughout the treatment period in the safety population. There were no notable differences in mean changes from baseline over time in vital sign measurements, including heart rate, systolic blood pressure or diastolic blood pressure.

8.4.8. Electrocardiograms (ECGs)

No EKG monitoring was performed in this study.

8.4.9. QT

Not applicable.

8.4.10. Immunogenicity

Immunogenicity studies are not required for this drug-device contraceptive efficacy supplement.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Insertion and Removal Related Events

Implant removal and reinsertion events (IRREs) were one of the key adverse events of special interest (AESI), given that these complications represent the primary serious safety concern with extended implant duration. Emphasis was placed on implant removal difficulties for devices remaining in situ longer than three years, as postmarketing reports have identified increased complication rates with prolonged implant duration (see Section 8.9).

A review of the IRREs that occurred in the safety population during participation in Study MK-8415-060 was conducted. Adverse events were collected by investigators by pre-defined terms as discussed in Study Design. The categorization by the Applicant was ECI (events of clinical interest) with Preferred Terms (PT) that included device complications. Overall, implant removal complications occurred at low rates. Table 11 summarizes the complications related to implant removal that were reported in a total of 11 participants, with some participants experiencing more than 1 event.

Table 11: Adverse Events Related to Implant Removal

Event	Number of Participants	Percentage (95% CI)
Event of Clinical Interest (ECI) Associated with Implant Removal		
Nonpalpable Implant	2	0.3%
Implant Migration Beyond the Upper Inner Arm	0	0.0%

Event	Number of Participants	Percentage (95% CI)
ECI Associated with Complications of Implant Removal		
Failed Implant Removal	0	0.0%
Implant Site Fibrosis	2	0.4%
Extension of Incision Greater Than 1 cm During Implant Removal	0	0.0%
Removal of a Nonpalpable Implant	1	0.2%
Removal of a Deeply Placed Implant	4	0.8% (0.2,2.0)
Implant Removal in an Operating Room	2	0.4%
Implant Removal Requiring General Anesthesia	1	0.2%
Implant Removal Requiring Regional Anesthesia	0	0.0%
Removal Requiring Imaging Guidance	4	0.8% (0.2, 2.0)
Nerve Injury During Implant Removal	0	0.0%
Vascular Injury During Implant Removal	0	0.0%
Other Complications of Implant Removal Not Listed Above*	5	1.0% (0.3, 2.3)

Source: Clinical Reviewer Modified Applicant's Table 4.4.1 Analysis Summary of Events of Clinical Interest in 120 Safety Update. Pg 131/455 and Study Report P060V01MK8415. Pg 97/327.
The highest percentage was "Other complications". These were as follows:
1. Implant removal requiring referral to another provider (2 participants).
2. Difficult removal due to scar tissue (1).
3. Implant removal requiring sedation (1).
4. Adhesion to arm (1).

The following two tables (Tables 12 and 13) compare the clinical and laboratory assessments of bent or broken implants. The laboratory assessment category was specifically designed to evaluate implant integrity at and after the time of removal. Bent implants are commonly observed during the removal procedure, which is expected given the flexible nature of the device and the extraction process, so it is not unexpected that the specialized laboratory

revealed a higher number of bent implants after removal than the clinicians in the office. These results provide confidence that the device maintains structural integrity sufficient for consistent drug delivery throughout the full five-year intended duration. However, the laboratory assessment for the 363 implants with intact cores does not differentiate between those from participants who completed the study and those who discontinued early.

Table 12: Implant Integrity Assessment by Clinician

Assessment	Number of Participants	Percentage (95% CI)
Participants with implant removed	433	86.9 (83.7, 89.8)
Before Implant Removal Attempt		
No Broken and Bent Implant Noted	431	99.5% (98.3, 99.9)
Total Broken or Bent Implant Noted	2	0.5% (0.1, 1.7)
Broken Implant Noted	1	0.2% (0.0, 1.3)
Bent Implant Noted	1	0.1% (0.0, 1.3)
During Implant Removal Attempt		
No Broken and Bent Implant Noted	424	97.9% (96.1, 99.0)
Total Broken or Bent Implant Noted	9	2.1% (1.0, 3.9)
Broken Implant Noted	1	0.2% (0.0, 1.3)
Bent Implant Noted	8	1.8% (0.8, 3.6)

Source: Modified Applicant's Table Analysis and Summary of Implant Integrity for Removal by Clinician in 120 Safety Update. Pg 134/455.

Table 13: Implant Integrity Assessment by Specialized Laboratory

Assessment	Number of Implants	Percentage (95% CI)
Participants with implant removed and returned	379	76.1% (72.1, 79.8)
Overall Assessment After Implant Removed		
Breakage of Implant Noted	3	0.8% (0.2, 2.3)
Bent Implant Noted	67	17.7% (14.0, 21.9)
Skin of Device Intact Noted	318	83.9% (79.8, 87.5)
Core of Device Intact Noted	363	95.8% (93.2, 97.6)

Source: Modified Applicant's Table 4.4.4 Analysis and Summary of Implant Integrity Assessed by Specialized Laboratory in 120-day Safety Update. Pg 135/455.

For clinician experience data and insertion and removal related events (IRRE), there was no insertion data to review by clinician or investigator as trial enrollment were only women with an already in place implant for three years that could be removed by standard procedure. For removal data by clinician, there were 52 participants in the population for clinicians who had done less than 5 implant removals in the past year. Among that population, only one participant had four complications with a deep nonpalpable implant that required imaging guidance for removal. For clinicians who had done 5 or more implant removals in the last year, the number of participants was 372, with 15 complications in ten participants included as follows: implant site fibrosis (2), removal of a deeply place implant (3), implant removal in an operating room (2), implant removal requiring general anesthesia (1), removal requiring imaging guidance (3), other complications (4).

> *Reviewer's Comment:*
> *While the Applicant tried to compare device complication rates between inexperienced and experienced clinicians, the findings paradoxically showed that limited surgical removal experience in clinicians led to fewer complications than more experienced clinicians. We suspect that trial clinicians self-selected participants for their removals based on their own surgical limitations or refer to the more experienced clinicians when encountering implants that are perceived on arm exam to be difficult removals, especially in a trial setting. This pattern may not hold in clinical practice where referral options to more experienced clinicians are limited, particularly in rural or resource-constrained settings. In these types of settings, extending the duration of use for up to*

5-years may result in an increase in patient selection of this long-acting product as an option.

8.6. Safety Analyses by Demographic Subgroups

The clinically relevant safety analysis in MK-8415-060 was primarily limited to BMI subgroups, showing no clinically meaningful safety difference. BMI representation was similar to the obese prevalence of the US population. The most clinically pertinent safety categories are listed below. The discontinuations were higher in the non-obese group for drug related adverse events. In clinical practice, Nexplanon is used in higher BMI patients due to its safety profile and efficacy compared to other COCs and progestin only contraception. See Table 14 below.

Table 14: BMI Comparison for Adverse Events

Safety Parameter	BMI <30 kg/m² (n=296)	BMI ≥30 kg/m² (n=198)	BMI Unknown (n=4)
Any adverse events	198 (66.9%) 95% CI: 61.2-72.2	123 (62.1%) 95% CI: 55.0-68.9	0 (0.0%) 95% CI: 0.0-60.2
Drug-related adverse events	51 (17.2%) 95% CI: 13.1-22.0	29 (14.6%) 95% CI: 10.0-20.4	0 (0.0%) 95% CI: 0.0-60.2
Serious adverse events	5 (1.7%) 95% CI: 0.6-3.9	3 (1.5%) 95% CI: 0.3-4.4	0 (0.0%) 95% CI: 0.0-60.2
Discontinued due to drug-related AE	23 (7.8%) 95% CI: 5.0-11.4	11 (5.6%) 95% CI: 2.8-9.7	0 (0.0%) 95% CI: 0.0-60.2

Source: Modified Clinical Table from Applicant's Table 4.1.13, 120-safety update. Pg 66-68.

This study enrolled only females aged 18-35 years precluding full age range analysis. However, it would be expected that effectiveness in terms of the Pearl Index would be similar in women over 35.

The study report does not provide detailed safety breakdowns by race or ethnicity subgroups nor are there sufficient numbers of participants to do a sub-group analysis of effectiveness by demographic and ethnic data. Refer to Section 8.2 for table of the overall trial demographic and ethnic data.

8.7. Specific Safety Studies/Clinical Trials

Not Applicable

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

All preclinical studies were submitted during the first review cycle of NDA 21529/S-000. No new nonclinical data is required to support extending use of Nexplanon through 5 years of use.

8.8.2. Human Reproduction and Pregnancy

One pregnancy that occurred while on Nexplanon was at the end of three years, prior to starting the 4th year of the study and was considered pre-treatment. In the adverse event listing, there was noted one reported event of gestational diabetes which most likely in the same participant who also had obesity. The Nexplanon was removed after her positive pregnancy test. None of this data provides new safety signals or trends that would require updating the pregnancy information or section in the currently approved labeling.

8.8.3. Pediatrics and Assessment of Effects on Growth

Studies in the pediatric population were waived as this product will not be used and is not indicated in males or premenarcheal females. An assessment for adolescent population (12-17) will be extrapolated from efficacy and safety data in adults from this study and from previously available trial data from adolescents using the approved Implanon and Nexplanon products. In addition, the NORA trial results in the adolescent population revealed a similar adverse event profile to adults with irregular vaginal bleeding as most common adverse event.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Division initially identified concerns about IRREs during the initial Implanon approval in 2006. The postmarketing commitment study NORA (PMC 1754-1) demonstrated that IRREs persist even when Nexplanon is inserted, removed or reinserted by highly trained healthcare providers. Results from the NORA trial led to updates to labeling and training materials. For detailed NORA findings, see Dr. Ioanna Comstock's REMS review.

The review of this submission incorporates Dr. Ioanna Comstock's REMS review (March 27, 2025) and an expanded postmarketing clinical analysis beyond the 200-completer efficacy

requirement from Study MK-8415-060. An additional review was also conducted by the drug utilization team in the Division of Epidemiology (December 3, 2025) assessing the specialties and type of healthcare providers inserting and removing Nexplanon. After review of the available safety data, the continued reporting of serious insertion and removal adverse events despite revised training formed the basis of the decision to require elements to assure safe use (ETASU) risk evaluation and mitigation strategy (REMS).

Distribution Context

The Applicant estimates over (b) (4) million etonogestrel implants have been distributed globally through August 2024, representing approximately (b) (4) million women exposed and (b) (4) million woman-years of experience. However, despite this extensive real-world exposure there appear to be critical knowledge gaps which may result from the lack of a requirement for provider training. Given the current distribution patterns of Nexplanon and the voluntary nature of adverse event reporting, the true incidence of IRREs in the clinical setting is unknown.

A summary of the worldwide distribution of Implanon (no longer distributed worldwide) and Implanon NXT (Nexplanon brand name is distributed in the US) for the cumulative period from market introduction to August 31, 2024, is shown below in Table 15.

Table 15: Global Distribution and Patient Exposure of Etonogestrel Implant

Implant Type	Distribution[1,2] (Number of implants)	Patient exposure (Number of women exposed) [3]	Patient-exposure (Women-years) [4,5] (WY)
	Cumulative to 31-AUG-2024	Cumulative to 31-AUG-2024	Cumulative to 31-AUG-2024
Etonogestrel non-radiopaque (Implanon)	(b) (4)		
Etonogestrel radiopaque (Implanon NXT)			
Total[6]			

[1] Patient exposure estimates were calculated based on company's worldwide distribution data derived from the financial systems.
[2] Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The effects of this update may be apparent when comparing current estimates of patient exposure to those of prior reporting periods.
[3] Number of women exposed = Number of implants × [(b) (4)].
[4] Based on the Nexplanon observational risk assessment (NORA) study which showed an implant reinsertion rate of (b) (4)% and average time the implant was in situ was 2.1 years.
[5] Women-Years (WY) = Number of women exposed × 2.1 years.
[6] Due to rounding, the sum of individual – may not be equal to total.

Source: sNDA submission (S-027) under NDA 21529, Summary of Clinical Safety, page 33.

Postmarketing Pulmonary Migration Assessment

The Applicant provided postmarketing IRREs data in response to an Information Request (IR) sent June 26, 2025, focusing on serious IRREs that included vascular migration to the pulmonary space, difficult localizations, and difficult removals. The clinical team's IR was modeled from a French epidemiology study evaluating IRREs for pulmonary migrations since approval in France.[6] The Applicant sent a tabulated summary of all case reports of pulmonary vasculature migrations, and difficult localizations, specific to the rates in the United States and European markets. The Applicant also sent the total number of implants distributed in each market to get a clearer picture of the incidence of serious IRREs obtainable by the Applicant. The Applicant analyzed 10 years of data (January 1, 2015, to December 31, 2024) using MedDRA version 28.0 preferred terms "device dislocation" and "device embolization," supplemented by case narrative review to identify pulmonary artery and/or vascular migrations.

> *Reviewer's Comment:*
> *The preferred terms (PT) used by the Applicant align with the Applicant's PADER global data, which identified 34 device embolizations in the July 2022-July 2023 period, including 5 cases requiring thoracotomy or thoracic surgery for pulmonary removal. No device embolization occurred in Study MK-8415-060 although insertions were performed by trained providers and patients with deep insertions were not enrolled. It is possible that these factors contributed to a lower risk of IRREs than would be seen in clinical practice.*

Methodology and Limitations

The long product shelf life of Nexplanon affects the interpretation of distribution data as a surrogate for clinical use. Alongside the distribution data, the Applicant proposed patient exposure estimates were using a (b) (4)% reinsertion rate adjustment. Using this model, US distribution exceeded (b) (4) implants yearly since 2016 (except 2024: (b) (4)). Critically, voluntary reporting of IRREs occurs predominantly at removal rather than insertion, meaning event onset timing corresponds to implants distributed approximately 2 years prior, not during the same reporting period.

To provide additional information on IRREs, the Applicant provided three analytical approaches: case receipt dates, adverse event onset dates, and pre/post-January 1, 2020, stratification to distinguish cases before and after the 2018 U.S. safety label update requiring insertion away from the sulcus and neurovascular structures.

US Pulmonary Migration Findings

[6] Corinne Simon et al., "Incidence and Characteristics of Intravascular Pulmonary Migration of Etonogestrel Implants: A French Nationwide Study," *Contraception* 102, no. 3 (2020): 186–89

The Applicant's analysis revealed 50 cumulative individual case safety report (ICSR) documenting pulmonary artery or vascular migrations in the US over 10 years. 11 cases had verifiable adverse event onset dates. The Applicant also analyzed and reported that out of these 11 cases, 10 pulmonary migration events were prior to 2020 and only 1 additional case between 2020-2024. The Applicant concluded that the 2018 safety label update to avoid the sulcus may have reduced the risk for pulmonary migration after 2020.

International Perspective

European/UK data showed 86 cumulative ICSRs for pulmonary artery or vascular migration cases among (b) (4) million exposed women over 6 years (2018-2024), compared to fewer reported US cases among (b) (4) million exposed women over 11 years (estimation based on distribution). This disparity likely reflects national insurance data with European reporting practices rather than true regional differences in complication rates.

FAERS Assessment (Conducted by the Division of Pharmacovigilance II)

A review of the FAERS data identified 27 US pulmonary migration case reports (2016-2024), for a similar time period as the Applicant's postmarketing data (2015-2024) including cases requiring thoracotomy for surgical removal. The convergence of Applicant and FAERS data are clinically similar. These data sources confirm persistent serious risks despite voluntary training and labeling mitigation measures. Refer to table 16 below.

Table 16: FAERS Cases from the U.S. of Etonogestrel Implant Migration to the Lungs

Year	Number of Cases
2016	2
2017	5
2018	3
2019	4
2020	3
2021	2
2022	5
2023	1
2024*	2
Total	27

Data through August 15, 2024, Citation: Chehab M, McCulley L. Pharmacovigilance Memorandum: Implant Migration to the Lungs. TTT Record ID: 2024-10629. Finalized September 3, 2024. Page 4. Note: This is modified from the table that appears on page 31 of Ioanna Comstock's FDA REMS Review document, which references the underlying DPV pharmacovigilance memorandum as the data source.

Reviewer's Comment:
The findings from both Applicant and FAERS data sources—50 US Applicant-reported pulmonary cases and 27 FAERS-documented US pulmonary migrations over the past decade—demonstrate persistent serious IRRE risks despite existing voluntary risk mitigation measures and voluntary training. These life-threatening complications, some requiring extensive surgical intervention, underscore the inadequacy of current voluntary training programs and reinforce the compelling need for mandatory REMS implementation. For detailed case narratives of FAERS pulmonary migrations, see Dr. Ioanna Comstock's REMS review (March 27, 2025).

Postmarketing Difficult Removals: Extended Use Safety Review

The safety database to support extended use from 3 years of use to five years of use was assessed in Study MK-8414-060. The safety profile showed no significant IRREs in a population with visible implants and trained providers. Clinical review of difficult removals was expanded to include a review of the Applicant's postmarketing reports due to clinical concerns for increased potential for scarring, fibrosis, and anatomical changes over the longer time in the arm through 5 years of use as well as an assessment of the current providers inserting and removing Nexplanon.

To better assess the risks of difficult removals, the Applicant was asked during this review cycle for a more detailed postmarketing analysis, and a consult was sent to the Office of Surveillance and Epidemiology Drug Use team to determine the numbers of patients who received Nexplanon by year and provider characterization to assess not only who was inserting

Nexplanon but also evaluate a secondary analysis for difficult removals as general surgeons, radiologists, and cardiovascular surgeons are not routine providers of Nexplanon. Both data streams were used to better estimate the risk of difficult removals.

The Applicant's postmarketing analysis through September 1, 2024, revealed concerning patterns with 28,055 ICSRs reporting 55,990 events with sufficient information to determine time to onset (ICSRs provided at least year and month of Nexplanon or Implanon NXT insertion, removal, and AE onset date) with a duration of implant use of up to five years. The number of ICSRs with corresponding duration of Nexplanon use for years 1,2,3, and 4-5 are presented in Table 17 below.

Table 17: Number of ICSRs and Reported AEs by ENG Implant Duration of Use

Duration of ENG implant use	Number of ICSRs	Number of Reported AEs
x ≤ 1 year	19,805	39,618
1 year < x ≤ 2 years	2,979	5,815
2 year < x ≤ 3 years	2,250	4,692
3 years < x ≤ 5 years	3,345	6,924
Total*	28,055	55,990

Source: Applicant's clinical-information-amendment-12jun2025.pdf, Page 1. *Note: The sum of the individual number of ICSRs and events may be greater than the total number of ICSRs and events given that ICSRs may report multiple implant therapies of different durations.

Of the 28,055 ICSRs, there were a total of (b) (4) implants inserted that provided at least year and month of Nexplanon insertion date and removal date up to five years. Again, these are real world cases, which are clinically relevant to assess potential duration concerns. See the total number of implants that correspond with the number of ICSRs (Table 17) to Table 18 below.

Table 18: Number of ENG Implants by Duration of Use

Duration of ENG implant use	Number of ENG implants
x ≤ 1 year	(b) (4)
1 year < x ≤ 2 years	
2 years < x ≤ 3 years	
3 years < x ≤ 4 years	
4 years< x ≤ 5 years	
Total	

Source: Reviewer's Table from Applicant's clinical-information-amendment-12jun2025.pdf, Page 2 and Applicant's clinical-information-amendment 29July2025.pdf, Page 1.

Postmarketing Removals

In the Drug Use Review from the Division of Epidemiology II (updated December 3, 2025), ob/gyn specialists performed the majority of Nexplanon removals. The clinical team asked that the review also examine the involvement of general surgeons and other specialists (including cardiothoracic, radiology, and vascular surgery) in Nexplanon removal procedures. Although the overall number of cases involving these surgical specialties was low, the data revealed no decrease in general surgeon involvement in Nexplanon removals after 2020, in fact there was a slight increase. This finding suggests that complicated removals and/or device migrations continue to occur at consistent rates, requiring specialized surgical intervention beyond routine gynecological care.

Among (b) (4) implants used beyond four years from the Applicant's review, 70 of those (b) (4) implants were difficult removals ((b) (4)%), generating 76 adverse events due to multiple removal attempts. A notable case described by the Applicant involved retention for 4 years and 8 months after multiple failed removal attempts beginning in the first year after insertion, exemplifying how improper insertion technique may lead to prolonged unintended retention past three years of use in the postmarketing reports. See Table 19 for the different cumulative IRREs comparison by duration.

Table 19: Postmarketing Cumulative IRRE for Implants reported to have an AE

Metric	Years 1-3 (≤ 3 years)	Years 4-5 (> 3 to ≤ 5 years)
Number of ICSRs	24,812	3,437
Total Reported AEs	49,461	7,137
Total IRREs	4,212	1,534
Difficult Removals	1,345	720
Difficult Localizations	2,350	733
Implant Migrations	517	81
Percentage of ICSRs with IRRE	16.97%	44.63%
IRREs as % of Total AEs	8.52%	21.49%

Source: Reviewer Table derived from Applicant's Table 2.7.4-contracept5y: 14 (page 37)
Table 2.7.4-contracept5y: 28 (pages 47-48) Applicant's Summary of Clinical Safety. Note: The number of ICSRs was later updated to a correct total to 28,055 in Applicant's information amendment June 12, 2025.

Reviewer's Comments:
The increased reporting rate of IRREs with extended use in the Applicant's report suggests that many of these cases are not a result of off-label use, but rather unintended retention due to procedural complications like deep insertions. Although there are many limitations in evaluating the postmarketing reporting, including an

unreliable denominator for implant use past the approved 3-year duration, the data from PADERs and the Applicant consistently show that removal complexity increases with the duration of use. The most frequently reported adverse events—"incorrect product duration" and "difficult removals"—for implants beyond three years support this view as these preferred terms occur frequently together, indicating the complication likely occurs at insertion but is only recognized at the time of a removal attempt. In addition, the data suggests that increased time since insertion could result in an increase in more complex removal issues.

The continued involvement of general surgeons and other surgical specialists in performing these removals, as documented in real-world data (DEPI II review, December 3, 2025), confirms that a subset of cases is too complicated for routine office-based removal procedures. Clinically, these findings indicate that the current voluntary measures to train providers are inadequate. To ensure patient safety with the proposed five-year extension, a mandatory REMS is needed, which would include enhanced training with a focus on insertion, competency verification, and systematic data collection on IRREs.

8.9.2. Expectations on Safety in the Postmarket Setting

The expectation in the postmarketing setting after the REMS is instituted is that all new providers or providers that have not received formal training will receive a comprehensive training on insertion and removal techniques with Nexplanon. The REMS will be a similar strategy/program to the current Applicant's Comprehensive Training Program (CTP). However, the required periodic assessments of the training program, including audits of healthcare providers and pharmacies, which the Agency is unable to require under the current voluntary CTP, will enable the Applicant and the Agency to assess compliance and accurate data reporting of complications. Assessments will also allow the Applicant and the Agency to determine if improvements to the program, such as updates and revisions to the REMS, are necessary.

8.9.3. Additional Safety Issues from Other Disciplines

None

8.10. Integrated Assessment of Safety

Study MK-8415-060 demonstrated that extended Nexplanon use from use for up to 3 years to use for up to 5 years in 498 participants was clinically effective, with the adverse reaction profile that was clinically similar to those reported in the trials that assessed the first 3 years.

In addition, the bleeding profile of the product with use during years 4 and 5 did not seem to be clinically different from that in the first three years of use.

However, the clinical review team in this review cycle identified critical insertion and removal-related events (IRREs) that impact Nexplanon's benefit-risk profile for five-year extension based on the Agency's review of postmarketing data as well as FAERS reporting. The most serious IRRE involves device migration to pulmonary vasculature, with 27 confirmed US FAERS cases and 50 cases in the Applicant's database, plus 86 EU/UK cases over six years. These life-threatening events require surgical intervention and potential cardiothoracic surgery.

Postmarketing data revealed concerning increases in removal difficulties with extended duration, demonstrating a substantial increase in IRRE rates compared to standard three-year use. Extended five-year duration may significantly increase removal complexity due to capsular fibrosis, tissue integration, and anatomical changes that develop over the prolonged timeframe. The clinical concern is that implants remaining in situ for five years may become more deeply embedded in surrounding tissue, making removal procedures more technically challenging and potentially increasing the risk of neurovascular injury. Unlike other long-acting reversible contraceptives that are placed in the female reproductive system, Nexplanon's safety profile is uniquely dependent on precise insertion technique and thorough knowledge of upper arm anatomy, particularly the location of major neurovascular structures. Serious IRREs continue to occur despite the existing CTP, with anticipated potential in an increased risk due to a five-year extension due to limited healthcare provider experience with long-term implant removal and variable surgical skills across different clinical settings.

The existing CTP lacks adequate mechanisms to audit actual clinical practice, monitor provider competency over time, or ensure adherence to proper insertion and removal training in real-world settings. Given the persistent occurrence of serious IRREs as illustrated in the postmarketing data review, including life-threatening pulmonary migrations requiring surgical intervention, and the demonstrated increase in removal complications with extended duration, implementation of a comprehensive Risk Evaluation and Mitigation Strategy (REMS) is warranted to ensure safe five-year use through enhanced provider training, competency verification, and ongoing safety monitoring. The reader is referred to the DRM review of the REMS dated 01/15/2026 for further information.

9. Advisory Committee Meeting and Other External Consultations

Not applicable as there were no benefit/risk issues that required external expert input.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

This Prescribing Information (PI) review includes a high-level summary of the rationale for the changes to the finalized PI as compared to the Applicant's draft PI. See Table 20 below for this summary review. The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective of the drug, and provides clear and concise information for the healthcare provider.

As an element to assure safe use (ETASU) risk evaluation and mitigation strategy (REMS) was required this review cycle, the prescription labeling was revised to communicate the new required training was under a REMS.

Table 20: Summary of Section Labeling Changes for S-027

Physician Insert Sections	Initial Draft Label Summary	Agreements and Rationale for Finalized Label
HIGHLIGHTS	No Boxed Warning	A boxed warning was added as required by the REMS. The section was also updated to reflect the 5-year duration of use.
1 INDICATIONS AND USAGE	The indication revised to the end of 5 years	The revised 5-year duration of use indication was agreed upon.
2 DOSAGE and ADMINISTRATION	No changes to dose or procedure steps	Agreed to retaining current labeling of procedure steps for insertion and removal
5 WARNINGS AND PRECAUTIONS 5.1	No revision in original draft.	Revision of title for the risk of insertion complications, additional wording in paragraph 3 reiterating the location for insertion and reasoning. Additional information in paragraph 8 on broken implants about a higher release rate of etonogestrel. A conclusion sentence added on proper training to minimize complications, and the REMS was added to 5.1.
5.2	N/A	A new section was added to outline the REMS requirements for training and controlled distribution.
6 ADVERSE REACTIONS	Added most common adverse reactions (b) (4)	The final agreement was updated to reflect data from the full safety population (N=498). The most common adverse reaction was

	(b) (4)	identified as intermenstrual bleeding, consistent with previous findings with Nexplanon. Other subsections remained unchanged.
8 SPECIFIC POPULATIONS		
8.4 Pediatric Use	No revision	A regulatory revision was necessary due to the Nexplanon Observational Risk Assessment (NORA) study, which included women less than 18 years of age in its safety evaluation, thereby contradicting the original label that "no clinical studies have been conducted in women less than 18 years of age" and requiring removal of this inaccurate information.
8.7 Overweight Women	(b) (4)	The original subsection was (b) (4) after labeling negotiations "women with obesity" was provided in a more scientifically appropriate concentration data in Section 12.3 Pharmacokinetics and removed in Section 8.
12 PHARMACOLOGY		
12. 3 Pharmacokinetics (Absorption)	Expanded paragraph to include the mean concentrations (b) (4) for 5-year post insertion data	Per the clinical pharmacology team's recommendation, (b) (4) etonogestrel serum concentrations was (b) (4) a standardized table. This format more clearly presents mean concentrations for both the 3- and 5-year duration of use studies.
12. 3 Pharmacokinetics Specific Population: Women with Obesity	Original draft provided minimal obesity related pharmacokinetic information, (b) (4) "	Clinical pharmacology review team modified and agreed to a final version with numerical data including specific concentration ratios (0.76-0.88) and detailed serum concentration ranges (49.7-455 pg/mL versus 33-363 pg/mL in women ≥ 30 kg/m2), removing clinical interpretation to maintain scientific factual presentation.
13 NONCLINICAL TOXICOLOGY	No revision	Based on Pharmacology/Toxicology review, the sex of the animals (male and female rats) was specified for carcinogenicity studies, and "female" was added to the rats in the fertility study review. No other changes were made.

14 CLINICAL STUDIES		
14.1 Pregnancy	Addition of demographics from trial as well as total from the initial efficacy population (399) with a primary efficacy endpoint listed. PI of 0.00 (95%CI 0.00,0.69)	The demographics description and description of the trial were acceptable from Applicant's draft. The PI language was changed to reflect the total exposure cycles [redacted] (b) (4). "The total exposures expressed as 28-day cycle equivalents by study year were: Year 4: 4478 cycles Year 5: 3274 No pregnancies were reported in years 4 and 5, with a PI of 0.0 (95% CI 0.00, 0.69) pregnancies per 100 women years of use. The rationale to show the number of cycles and data in a factual scientific format.
14.3 Implant Insertion and Removal Characteristics	Original label included detailed insertion timing data (27.9 ± 29.3 seconds), [redacted] (b) (4) .	Following negotiations, several changes were made: • Retained: Insertion timing data, at the Applicant's request. • Removed: [redacted] (b) (4) • Removed: [redacted] (b) (4)

10.2. Nonprescription Drug Labeling

Not Applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

The Agency determined a REMS was necessary to ensure the benefits of Nexplanon outweighs the risk of complications due to improper insertion and removal including migration to the brachial plexus and pulmonary vasculature.[7] The clinical team identified continued post-market reports of serious insertion- and removal-related events (IRREs), including migration to the brachial plexus and pulmonary vasculature, as "new safety

[7] Food and Drug Administration. Division of Urology, Obstetrics, and Gynecology. Nexplanon (etonogestrel implant). NDA 21529. Multi-disciplinary Review and Evaluation, March 28, 2024. Reference ID: 5559531

information" under the FDCA. This risk is potentially heightened by extending the duration of use from 3 to 5-years. The Agency issued a Post-Approval REMS Notification Letter (RNL) on March 28, 2025, requiring the Applicant to develop a REMS with Elements to Assure Safe Use (ETASU) to ensure the benefits of the drug outweigh this risk.

Organon submitted an amendment to S-027 with a proposed REMS consisting of Elements to Assure Safe Use (ETASU), an implementation system, and timetable for submission of assessments. The Agency provided multiple rounds of comments (beginning in April 2025 through January 2026). Organon's existing voluntary Clinical Training Program and Controlled Distribution Program served as the framework for the REMS design, leveraging existing training processes and materials (training slides, videos, in-person practice and competency assessment by a certified trainer) with an improved infrastructure to monitor and evaluate the extent to which HCPs performing procedures with Nexplanon are trained. This REMS includes a REMS assessment plan to assess if the REMS is functioning as designed and to assess if the REMS is meeting its goal and objective. To monitor and evaluate healthcare provider compliance with the certification requirements, the Applicant will conduct claims-based analyses of healthcare providers who perform Nexplanon procedures and the relationship between training status and IRREs, instead of requiring healthcare setting certification and healthcare setting audits to verify healthcare provider compliance with certification requirements. This decision balanced safety oversight with practical considerations including the additional burden on healthcare settings given the large population of HCPs and healthcare settings involved, limited healthcare resources available in practices particularly in rural areas, and potential negative impact on contraceptive access if REMS requirements were overly burdensome. The Agency reviewed the proposed claims-based analysis study design, provided preliminary feedback, and will continue to work with Organon to refine the protocol post approval.

In summary, the goal of the NEXPLANON REMS is to mitigate complications due to improper insertion and removal.

- Objective 1: Healthcare providers who perform NEXPLANON procedures demonstrate proper insertion and removal techniques for NEXPLANON prior to first use.

The REMS design focuses on knowledge, training healthcare providers on the proper insertion and removal techniques prior to first use, as the key risk mitigation strategy to minimize serious IRREs. The REMS elements consist of ETASU, an implementation system, and timetable for submission of assessments as follows:

- ETASU B: Healthcare providers and pharmacies that dispense Nexplanon are specially certified
- ETASU E: Each patient using Nexplanon is subject to certain monitoring

These elements were selected to ensure HCPs are trained on the proper insertion and removal techniques (including successful in-person demonstration of competency with insertion/removal) with Nexplanon prior to first use, and that HCPs assess and report any potential insertion and removal related events to the REMS. Prior to dispensing or

distributing Nexplanon, the pharmacy and wholesaler-distributor must verify that the HCP is certified in the REMS database.

The timetable for submission of assessments is 9 months and 18 months from the date of the initial REMS approval and every 12 months thereafter from the due date of the 18-month submission. The Nexplanon REMS assessment plan was reviewed by the DMAMES and found to be acceptable.

Refer to the DRM review dated 01/15/2026 for further detail on the REMS requirements and training materials for this supplement.

12. Postmarketing Requirements and Commitments

Not Applicable.

13. Appendices

13.1. References

Daniels, K. Abma, JC. *Current Contraceptive Status among Women Aged 15–49: United States, 2017–2019*. NCHS Data Brief, no. 388. Hyattsville, MD: National Center for Health Statistics, (2020).

Gov.UK. “Nexplanon (Etonogestrel) Contraceptive Implants: New Insertion Site to Reduce Rare Risk of Neurovascular Injury and Implant Migration.” *Drug Safety Update* 13, no. 7 (February 2020). https://www.gov.uk/drug-safety-update/nexplanon-etonogestrel-contraceptive-implants-new-insertion-site-to-reduce-rare-risk-of-neurovascular-injury-and-implant-migration.

Reed, Suzanne, Thai Do Minh, Jens A. Lange, Carol Koro, Michelle Fox, and Klaas Heinemann. “Real World Data on Nexplanon® Procedure-Related Events: Final Results from the Nexplanon Observational Risk Assessment Study (NORA).” *Contraception* 100, no. 1 (2019): 31–36.

Rossen, Lauren M., et al. "Updated Methodology to Estimate Overall and Unintended Pregnancy Rates in the United States." *National Vital Statistics Reports* 72, no. 1. Hyattsville, MD: National Center for Health Statistics, (2023).

Simon, Corinne, et al. “Incidence and Characteristics of Intravascular Pulmonary Migration of Etonogestrel Implants: A French Nationwide Study.” *Contraception* 102, issue. 3 (2020): 186–89.

13.2. Financial Disclosure Information from Study MK-8415-060

Covered Clinical Study: MK-8415-060 / Protocol 8415-060 - A Phase 3, Open-label, Multi-center, Single Arm Study to Assess Contraceptive Efficacy and Safety of the Etonogestrel (MK-8415) Implant During Extended Use From 3 Years After Insertion in Females 35 Years of Age or Younger

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 441		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1 (b) (6) (Organon employee as of (b) (6)) was the PI at the (b) (6) until (b) (6)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 8		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 320		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Total Investigators not certified: 113 (all due to investigators not returning request information).

Financial Disclosure Form: The study program for MK-8415 Protocol 060 was originally a study conducted by Merck Sharp & Dohme LLC, a subsidiary of Merck and Co., Inc., Rahway, NJ USA, known as "MSD" outside of the USA and Canada, as well as its affiliates, joint ventures, and subsidiaries. The IND was transferred to Organon USA LLC., a subsidiary of Organon & Co., (Organon) on 03 Jun 2021.

MSD financial disclosure forms were originally collected by MSD and if the investigator left the site before the IND transfer than an MSD only form was collected. Once Organon became a sponsor, investigators were requested to complete an MSD/Organon combination financial disclosure form. Due diligence attempts were made when the combination forms were not received.

Figure 3: Financial Interest Information obtained from Study MK-8415-060

Table of All Clinical Investigators/Sub-Investigators Who Hold Financial Interests and/or Arrangements Requiring Disclosure			
Product/Protocol/Site	**Investigator/Sub-Investigator**	**Role**	**Financial Interest and/or Arrangement**
8415-060 (b) (6)	(b) (6)	Principal	Equity: Comment: Investigator reported equity interest in Organon on (b) (6) . As noted above in Table1, Investigator became an employee of Organon in (b) (6) , after the conclusion of his role as a PI in (b) (6) .
8415-060 (b) (6)	(b) (6)	Principal	Significant Payments of Other Sorts: $ (b) (6) . Comment: (b) (6) (b) (6)
8415-060 (b) (6)	NA	NA	Proprietary Interest: $ (b) (6) Comment: (b) (6) (b) (6)

8415-060 (b) (6)	(b) (6)	Principal	Significant Payments of Other Sorts: $ (b) (6) . Comment: (b) (6) (b) (6)
8415-060 (b) (6)	NA	NA	Significant Payment of Other Sorts: $ (b) (6) Comment: (b) (6) (b) (6)

8415-060 (b) (6)	(b) (6)	Principal	Significant Payments of Other Sorts: $45,715.00. Comment: Investigator received payments inclusive from 2020 in the amount of $45,715.00. MSD provided payments in the amount of $15,815.00 for speaker honoraria and travel. Organon provided payments in the amount of $29,900.00 for speaker honoraria and travel as reported by the investigator on (b) (6).
8415-060 (b) (6)	(b) (6)	Principal	Significant Payments of Other Sorts: $ (b) (6). Comment: (b) (6) (b) (6)

8415-060 (b) (6)	(b) (6)	Principal	Significant Payments of Other Sorts: $ (b) (6) Comment: (b) (6) (b) (6)

13.3 Schedule of Study Activities

Figure 4:Schedule of Activities in Study MK-8415-060

Study Period:	Screen	Treatment Period								Post-Treatment	Notes
Visit Number/Title:	1 Screening	2 Enrollment	3	4	5	6	7	8	9	10 EOT or DC	11 Follow-up	Months are relative to V2 NOT time since implant insertion. V2 must occur 3 calendar years (±2 weeks) from date of implant insertion and be no more than 2 months after V1. V10 should occur 2 calendar years (+1 week) from V2 but no later than 5 calendar years +2 weeks from date of implant insertion, unless the participant discontinues early. For early DC, only V10 and V11 will be performed. Post-treatment assessments should NOT occur before 2 weeks after V10.
Scheduled Month	Up to 2 months before V2	0	3	6	9	12	15	18	21	24	2 weeks after V10	
Scheduled Window			±1 week							+1 week	+3 days	
Administrative Assessments/Procedures												
Informed Consent and Assent (if applicable)	X											
Inclusion/Exclusion Criteria	X	X										
Participant Identification Card	X	X										Card should be updated with treatment (allocation) number at V2.
Medical History	X											Medical history includes illicit drugs, alcohol, and tobacco use.
Gynecologic and Obstetric History	X	X										See Section 8.1.4.1. V1: Obtain a comprehensive obstetric and gynecologic history and review the participant's menstrual bleeding history for the 12 months before V1. V2: Record bleeding profile for the 90 days before V2.
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	
Assignment of Screening Number	X											
Assignment of Treatment (Allocation) Number		X										
Dispense Home Urine Pregnancy Test Kit		X	X	X	X	X	X	X	X	X		Additional test kits can be dispensed as needed. Document LOT number and expiration date for each test kit dispensed. Review instructions with the participant. See Section 8.1.8.
Review Home Urine Pregnancy Test Kit Use and Expiration			X	X	X	X	X	X	X	X		Ensure test kits will not expire before the next scheduled visit.
Dispense/Collect eDiary		X (Dispense)								X (Collect)		Participants should complete their eDiary entries before returning the device. See Section 8.1.9.
eDiary Training		X										Retraining should be conducted as needed. See Section 8.1.9.
eDiary Compliance Review			X	X	X	X	X	X	X	X		eDiary compliance to be monitored between visits. See Section 8.1.9.3.
Check Cycles are "At Risk" as Documented in eDiary			X	X	X	X	X	X	X	X		"At risk" cycles are those with heterosexual vaginal intercourse and nonuse of additional contraception.

Poststudy Contraceptive Counseling									X	X		See Section 8.1.11. Not applicable if pregnancy is desired.
Implant Removal										X		Before and after removal, implant integrity (i.e., bent or broken) will be assessed and recorded on the appropriate CRF. Bent or broken implants are to be reported to the Sponsor. See Section 4.2.1.2. Prespecified events related to implant removal (e.g., implant site fibrosis, failed removal) are to be reported as ECIs (see Sections 4.2.1.2 and 8.4.7). Implants are to be stored and returned to the Sponsor. See the laboratory/procedure manual for instructions.
Initiation of New Contraceptive Method										X		A new contraceptive method may be started immediately after implant removal. Not applicable if pregnancy is desired.
Study Period:	Screen	Treatment Period									Post-Treatment	Notes
Visit Number/Title:	1 Screening	2 Enrollment	3	4	5	6	7	8	9	10 EOT or DC	11 Follow-up	Months are relative to V2 NOT time since implant insertion. V2 must occur 3 calendar years (±2 weeks) from date of implant insertion and be no more than 2 months after V1. V10 should occur 2 calendar years (+1 week) from V2 but no later than 5 calendar years +2 weeks from date of implant insertion, unless the participant discontinues early. For early DC, only V10 and V11 will be performed. Post-treatment assessments should NOT occur before 2 weeks after V10.
Scheduled Month	Up to 2 months before V2	0	3	6	9	12	15	18	21	24	2 weeks after V10	
Scheduled Window			±1 week							+1 week	+3 days	
Efficacy Assessments/Procedures												
Serum hCG	X	X	X	X	X	X	X	X	X	X	X	V1 and V11: Sample for serum hCG will be collected in a 3.5 mL tube (i.e., serum ENG sample is not being collected). Serum will be collected after centrifugation. V2 to V10: Samples for serum hCG and serum ENG will be collected in one 10 mL tube. After centrifugation, serum will be divided into 2 separate samples (i.e., one for hCG [room temperature] and one for ENG [frozen]). See the laboratory manual for detailed instructions.
Urine Pregnancy Test		X										Test must be performed before treatment number assignment. Additional tests may be conducted on-site or at home as needed for suspected pregnancies. Positive urine pregnancy tests must be confirmed by serum hCG. See Section 8.2.1.
Safety Assessments/Procedures												
Focused Physical Examination	X									X		Focused physical examination: heart, lungs, abdomen, and extremities only.
Breast Examination	X					X				X		
Gynecological/Pelvic Examination	X					X				X		

Testing for Gonorrhea and Chlamydia (required), and Trichomonas (if indicated)	X											At V1, all participants will be tested for gonorrhea and chlamydia. Testing for trichomonas is required if a participant has vaginal symptoms (e.g., irritation, odor) or if abnormalities are noted on examination (e.g., abnormal discharge). Testing may be repeated during the study as needed. See Section 8.3.2.1.
Testing for Vaginitis (if indicated)	X											Testing for vaginitis (e.g., yeast, bacterial vaginosis) is required at V1 if a participant has vaginal symptoms (e.g., irritation, odor) or if abnormalities are noted on examination (e.g., abnormal discharge). Testing may be performed as needed during the study. See Section 8.3.2.1.
Cervical Cytology (Pap Test, if indicated)	X											See Section 8.3.2.2.
Palpate Implant	X	X	X	X	X	X	X	X	X	X		Nonpalpable implants (i.e., deeply placed) should be localized and removed as soon as possible to avoid the potential for distant migration.
Height	X											
Weight	X					X				X		
Vital Signs (BP, HR)	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X									X		
Urinalysis	X											
Chemistry	X									X		
Assess Implant Site Following Removal											X	
AE/SAE Review	==========											
Pharmacokinetics												
Serum ENG		X	X	X	X	X	X	X	X	X		Sample will be collected in a 10 mL tube. After centrifugation, serum will be divided into 2 samples (i.e., one for serum ENG [frozen] and one for serum hCG [room temperature]). See the laboratory manual for details. At V10, sample will be collected before implant removal. Sample should be sent even if the visit is performed out of window.

AE=adverse event; BP=blood pressure; CRF=case report form; DC=discontinuation; ECI=event of clinical interest; eDiary=electronic diary; ENG=etonogestrel; EOT=end of treatment.
hCG=human chorionic gonadotropin; HR=heart rate; PAP=Papanicolaou; SAE=serious adverse event; V=visit

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY S SHUMAN
01/15/2026 12:32:18 PM

IOANNA A COMSTOCK
01/15/2026 12:59:05 PM

AUDREY L GASSMAN
01/16/2026 07:45:42 AM
I concur with the recommendations of the clinical team that Nexplanon should be approved for up to 5 years of use