U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA021529
Supplement #:	S-027
Drug Name:	Nexplanon® (etonogestrel implant), 68 mg
Indication(s):	Prevention of pregnancy for up to 5 years.
Applicant:	Organon USA LLC
Date(s):	Stamp Date: 12/16/2024, PDUFA Date: 01/16/2026
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Nadeesri Wijekoon, PhD
Concurring Reviewers:	Solomon Chefo, PhD
Medical Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Clinical Team:	Reviewer: Mary Shuman, CDTL: Ioanna Comstock
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Keywords: Clinical studies, open label, contraceptives, extension studies, Pearl Index

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1 EXECUTIVE SUMMARY

In this supplemental NDA, the applicant seeks to extend the approved duration of use of Nexplanon® (68 mg etonogestrel implant) from 3 years to 5 years for the prevention of pregnancy in women of reproductive age. Nexplanon is a long-acting hormonal contraceptive subdermal implant containing 68 mg of etonogestrel that provides reliable contraception by inhibiting ovulation and altering cervical mucus. The Agency originally approved Nexplanon on May 13, 2011, for pregnancy prevention for up to 3 years.

Efficacy and safety support for extending Nexplanon's duration from 3 to 5 years was based on a Phase 3, multicenter, single-arm, open-label study conducted in the United States and Puerto Rico (Study MK-8415-060 - hereafter referred to as Study 060). The study enrolled 498 eligible women aged 35 or younger with a palpable implant in situ for 36 months (±2 weeks) from the date of insertion and followed them for 24 months to evaluate contraceptive efficacy and safety during Year 4 (from 36 months ±2 weeks to 48 months after insertion) and Year 5 (from 48 months plus one day to 60 months ±2 weeks after insertion) of use. Most enrolled subjects were White (74%) and had a mean age of approximately 27 years (range: 18 to 35 years). The overall discontinuation rate of 46.6% during the 2-year period was consistent with other contraceptive trials and the original 3-year Nexplanon approval study.

The efficacy evaluation in Study 060 was based on the Pearl Index (PI) for on-treatment pregnancies during the 2-year extended use period among 394 participants in the restricted Full Analysis Set (rFAS). Among the 394 participants in the rFAS population with over 6,936 evaluable at-risk cycles, there was no on-treatment pregnancies reported during the 2-year extension period. The estimated PI for Years 4 and 5 combined was 0.0 pregnancies per 100 woman-years (95% CI: 0.00, 0.69). Similarly, the estimated PI for Year 4 alone was 0.0 pregnancies per 100 woman-years (95% CI: 0.00, 1.23) and for Year 5 alone was 0.0 pregnancies per 100 woman-years (95% CI: 0.00, 1.58). The efficacy results were consistent across subgroups including age, Body Mass Index (BMI), race, and ethnicity.

In summary, the zero-pregnancy rate observed during Years 4 and 5 of use in Study 060 demonstrates that Nexplanon maintains its contraceptive effectiveness during the extended use period.

Section 5.1 lists the statistical concerns identified during this NDA review. These concerns include: (1) study design limitations related to enrolling women with existing 3-year implant use rather than following a single cohort from initial insertion, (2) data completeness issues with 20% of enrolled participants excluded from the efficacy analysis at the primary data cutoff date, and (3) considerations regarding the adequacy of 2-year data to support removal of obesity-related labeling warnings for overweight/obese women. This reviewer defers to the DUOG medical review team to consider these concerns in the overall benefit-risk assessment of Nexplanon for the proposed extended use.

2 INTRODUCTION

2.1 Overview

In this supplemental NDA, the applicant, Organon USA LLC, seeks to extend the approved duration of use of 68 mg etonogestrel implant (Nexplanon®) for the prevention of pregnancy in women of reproductive age from 3 to 5 years.

Nexplanon® (OG-8415, formerly MK-8415) is a long-acting, hormonal contraceptive subdermal implant containing 68 mg of etonogestrel (ENG), a progestin which provides reliable contraception by inhibiting ovulation and altering cervical mucus. The Food and Drug Administration (FDA) approved Nexplanon® on May 13, 2011, for the prevention of pregnancy in women of reproductive age for up to 3 years.

Support for the extension of Nexplanon's approved duration from 3 to 5 years was based on a completed 2-year pivotal Phase 3 study 060 (See detail about the study design in Section 3.2.1). This study enrolled women under 35 years of age who had used the implant for 3 years in a real-world clinical practice setting and followed them for an additional 2 years to evaluate safety and efficacy during years 4 and 5.

During the filing review, the Biometrics review team indicated that Study 060 design differs from the typical approach used to extend contraceptive product duration. Standard practice involves enrolling participants at initial product use and following the same cohort continuously from baseline through the entire extended duration period under a single protocol.

In response to the Biometrics review team concern, the DUOG medical review team noted an established precedent for this study design approach. For example, Mirena's approved duration for the prevention of pregnancy was extended from 5 years (initial approval in 2000) to 8 years (approved in 2022) based on a 3-year extension study. This extension study enrolled women who had already been using Mirena for approximately 5 years in a real-world clinical practice, demonstrating DUOG's acceptance of studies that recruit participants with existing product exposure rather than following a single cohort from initial drug use.

2.2 Data Sources

The Applicant has provided the clinical study report (SCR) including the study protocols, statistical analysis plans, and the SAS datasets electronically. These are located at:

- Protocol and SAP: \\CDSESUB1\evsprod\NDA021529\1413\m5\53-clin-stud-rep\535-rep-effic-safety-stud\contracept5y\5352-stud-rep-uncontr\p060v01mk8415
- Data and SAS programs: \\CDSESUB1\evsprod\NDA021529\1413\m5\datasets\p060v01mk8415\analysis\adam

4 STATISTICAL EVALUATION

4.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data and analysis acceptable.

Reviewer's Remark:

Study 060 enrolled a total of 498 eligible women. This NDA submission was based on a data cutoff date of April 8, 2024, and as of this cutoff date, 213 participants had completed the study, 186 had discontinued, and 99 remained active. In the CSR, the applicant provided safety data for 399 participants, comprising the 213 completers and 186 who had discontinued. The applicant's efficacy analysis was based on these same 399 participants, while the 99 ongoing subjects were not included in the efficacy analysis due to the timing of the data cutoff. To provide comprehensive safety information, the applicant's clinical summary of safety included data from all 498 participants using a later data cutoff date of July 25, 2024, offering additional safety context beyond the primary CSR.

Of note, during the pre-NDA meeting held on October 8, 2024, the Division advised the applicant to include data from all participants in the NDA submission, including efficacy data from the 99 ongoing subjects. However, citing the Division's requirement of at least 200 completers for the NDA submission in prior communication, the applicant did not include the requested efficacy data for the 99 ongoing subjects in the NDA. Acknowledging the prior agreement, the Division indicated that an efficacy supplement including data from all participants should be submitted post-approval.

4.2 Evaluation of Efficacy

4.2.1 Study Design and Endpoints

Study 060 was a Phase 3, multicenter, single-arm, open-label study that evaluated the contraceptive efficacy and safety of the ENG implant during extended use in Year 4 (from 36 months ±2 weeks to 48 months after insertion) and Year 5 (from 48 months plus one day to 60 months ±2 weeks after insertion). The study enrolled women 35 or younger with a palpable implant in situ for 36 months (±2 weeks) from the date of insertion at the time of enrollment, willing to continue use for 24 additional months.

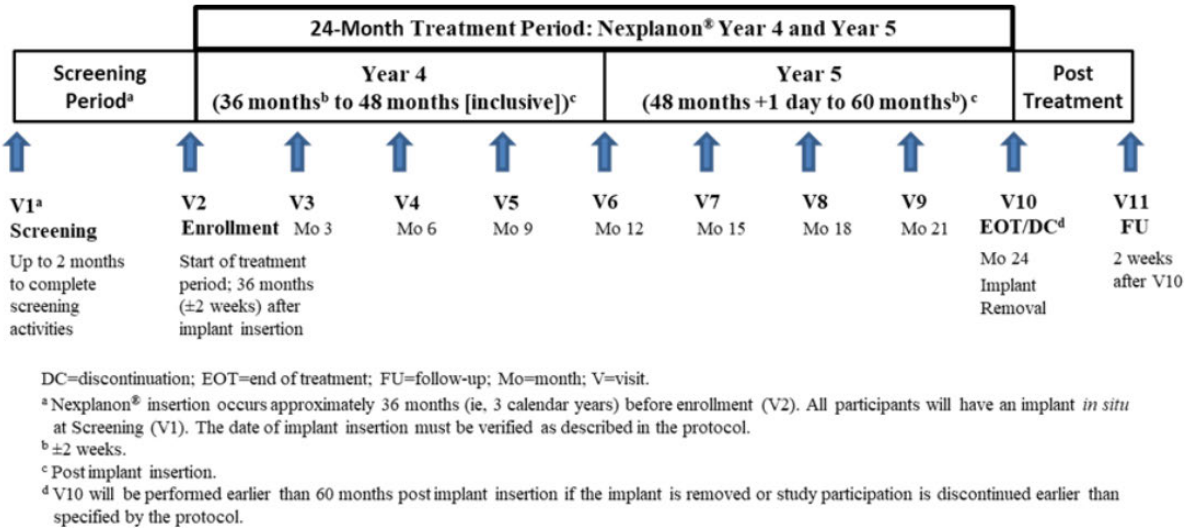
Eligible participants were required to be at risk for pregnancy through regular heterosexual vaginal intercourse at least once monthly with partners who were not known to be subfertile, sterilized, or infertile. Key inclusion criteria included willingness to continue implant use for an additional 24 months without desire for pregnancy during this period, commitment to avoid using additional contraceptive methods (such as condoms) throughout the study duration, and in good physical and mental health as determined by the investigator. Participants were excluded if they had conceived during current or previous contraceptive implant use, had untreated sexually transmitted infections, significant gynecologic abnormalities, cardiovascular risk factors including history of venous or arterial thromboembolism, uncontrolled hypertension, clinically

significant liver disease, or recent use of medications known to affect hormonal contraceptive efficacy.

Figure 1 shows the study schema. As shown, the study comprised of 11 scheduled visits over a 24-month treatment period: a screening visit, an enrollment visit (at Month 0), seven visits at roughly 3-month intervals, an end-of-treatment visit at Month 24, and a post-treatment follow-up visit two weeks later. The screening period lasted up to 2 months, depending on laboratory results, and confirming the participant's implant insertion date based on the Nexplanon user card.

Eligible participants who consented were enrolled at the second visit, marking the start of the treatment period. Throughout the study, an Independent Data Monitoring Committee oversaw subject safety and provided recommendations on trial conduct.

Figure 1: Study Design



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: CSR, page 31

Electronic Diary (eDiary):

In Study 060, participants recorded the status of heterosexual vaginal intercourse and the use of backup contraception monthly and vaginal bleeding or spotting daily using an eDiary. 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.

Reviewer's comment: *Generally, in contraceptive studies, eDiary with shorter recall period (e.g., daily, or weekly) are recommended to record the status of heterosexual vaginal intercourse and the use of backup contraception. In this study, however, a monthly diary was used to record sexual intercourse and backup contraceptive use. Compared to a daily or weekly eDiary use, there is a potential recall bias with the use of a monthly eDiary.*

Primary Efficacy Endpoint:

The primary efficacy endpoint in Study 060 was the rate of on-treatment pregnancy as assessed by PI during the extended use of the ENG implant in women aged ≤35 years at the time of enrollment, with at risk (evaluable) cycle.

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.

At Risk (Evaluable) Cycles was defined as menstrual cycles where a participant had heterosexual vaginal intercourse and used no additional contraception. A cycle was also considered at risk if pregnancy occurred in the cycle regardless of the status of heterosexual vaginal intercourse or the use of additional contraception

Key Secondary Efficacy Endpoints:

Contraceptive Efficacy: Annual on-treatment pregnancies during extended duration of use: PI at Year 4 and PI at Year 5.

Reviewer's comment: *In addition to the above secondary endpoint, the applicant also proposed the following secondary endpoints:*

(b) (4)

However, the Division considered these endpoints not meaningful because (b) (4)

.

The reviewer performed life table analysis to estimate the cumulative pregnancy rate for Year 4 and Year 5 from the start of current study.

4.2.2 Statistical Methodologies

Analysis Populations The following analysis populations were defined in the Statistical Analysis Plan (SAP) for the evaluation of efficacy and safety.

- 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.

Efficacy Analysis

Primary Efficacy Analysis:

The primary efficacy endpoint, pregnancy rate from 4 to 5 years of Nexplanon use as assessed by PI based on confirmed on-treatment pregnancies and evaluable cycles in women aged ≤35 years at the time of enrollment, was calculated using the following formula:

$$PI = \frac{Number\ of\ on\_treatment\ pregnancies\ (n_p)}{Number\ of\ evaluable\ cycles\ (n_E)} * 1300$$

Two-sided 95% confidence interval (CI) estimates for the PI were calculated assuming that events of pregnancy follow a Poisson distribution. The two-sided CI estimates were calculated using the following formulas:

$$CL_{Lower} = \frac{0.5x^2(0.025, 2n_p)}{n_E} * 1300$$

$$CL_{Upper} = \frac{0.5x^2(0.975, 2n_p + 2)}{n_E} * 1300$$

Where $x^2(\alpha, df)$ is the alpha quantile of a chi-square distribution with "*df*" degrees of freedom.

Secondary Efficacy Analysis:

The secondary endpoints of PI at Year 4 and at Year 5 were analyzed similarly to the primary efficacy analysis.

Subgroup Analysis:

The Applicant evaluated the primary PI by the subgroups of body mass index (BMI), race, and ethnicity.

Handling of Missing Data:

Per the SAP, missing values for individual diary entries on intercourse or additional contraception use were handled as follows:

a) Missing information regarding sexual intercourse or the use of additional contraception resulted in exclusion of a cycle from the denominator of the PI calculation except for a cycle in which a pregnancy has occurred.

b) If no pregnancy has occurred, the cycle was assessed as not at risk if there were conflicting information about whether the cycle was truly at risk e.g., one entry reports heterosexual vaginal intercourse with additional contraceptive products (not at risk for pregnancy) and another entry reports heterosexual vaginal intercourse without additional contraceptive products (at risk for pregnancy) for a cycle in which a pregnancy has not occurred, that cycle was determined as not at risk for pregnancy.

c) For subjects that discontinued the study without being pregnant, all at risk cycles prior to study discontinuation were included in the efficacy analyses. The subjects who discontinued due to pregnancy, the cycle with pregnancy occurring and all at risk prior to pregnancy were included in the efficacy analyses.

4.2.3 Patient Disposition, Demographic and Baseline Characteristics

4.2.3.1 Patient Disposition and Protocol deviations

Table 1 summarizes the number of subjects included in each analysis set in Study 060. A total of 498 subjects were treated, but the applicant's primary Clinical Study Report was based on 399 subjects as of the April 8, 2024, data cutoff, with 99 subjects still ongoing. Of the 399 subjects in the safety set, 394 (~99%) were included in the rFAS population, which served as the primary efficacy analysis population.

Table 1: Analysis Populations

	MK-8415 ENG
Total treated subjects	498
Ongoing patients as of the data cutoff date 04/08/24	99
Number of subjects whose information available as of the data cutoff date 04/08/24	399
Safety Set as of the data cutoff date 04/08/24	399 (100)
Full analysis Set (FAS)	395 (99.0)
Restricted Full analysis Set (rFAS)	394 (98.7)
Per-Protocol (PP) Set	393 (98.5)

Source: Applicant's CSR, Table 10-1

Reviewer's comment:

a) *It should be noted that, while 99% (=394/399) of subjects in the safety population (as of the April 8, 2024, data cutoff) were included in the efficacy analysis (rFAS population), this represents only 79% (=394/498) of the total enrolled subjects in the study.*

b) *Five subjects in the safety set were not included in the rFAS population (Subject IDs: (b) (6)). Subject (b) (6) was excluded from the rFAS population because she did not have at least one at-risk treatment cycle. The remaining four subjects were removed from the rFAS population because they did not have at least one cycle of follow-up information.*

The summary of patient disposition and the primary reasons for study discontinuation during the 24-month extended treatment period in Study 060 are shown in Table 2. As shown, a total of 213 (53.4%) participants completed the 2-yearlong study and 186 (46.6%) participants discontinued early.

The most common reasons for study discontinuation were withdrawal by the subject (29.8%) and lost to follow-up (13.5%). Thirty-nine participants (9.8%) discontinued the 2-year study due to adverse events. One death unrelated to the study intervention was reported.

Table 2: Summary of Subject Disposition, safety Set

	Year 4	Year 5	Overall
Status of the Trial			
Safety population	399	292	399
Completed the study [b]	292 (73.2)	213 (72.9)	213 (53.4)
Study Discontinuation	107 (26.8)	79 (27.1)	186 (46.6)
Death	1 (2.5)	0 (0.0)	1a (0.3)
Lost to Follow-Up	35 (8.8)	19 (6.5)	54 (13.5)
Physician Decision	2 (0.5)	3 (1.0)	5 (1.3)
Adverse Events	1 (0.3)	1 (0.3)	2 (0.5)
Adverse event related to vaginal bleeding pattern	0 (0.0)	1 (0.3)	2 (0.5)
Physician Decision	1 (0.3)	1 (0.3)	1 (0.3)
Withdrawal By Subject	65 (16.3)	54 (18.5)	119 (29.8)
Adverse Events	10 (2.5)	6 (2.1)	16 (4.1)
Adverse event related to vaginal bleeding pattern	10 (2.5)	9 (3.1)	19 (4.8)
Withdrawal by subject	35 (8.8)	36 (12.3)	71 (17.8)
Unknown	10 (2.5)	3 (1.0)	13 (3.3)
Other	4 (1.0)	3 (1.0)	7 (1.8)

[a] One death, considered not related to study intervention, was reported.
[b] Completed extended duration of use and had a documented pregnancy test ≥14 days after implant removal (followed the full protocol)
Source: Reviewer's Analysis

Reviewer Comment: *From a statistical perspective, while the overall discontinuation rate of 46.6% in Study 060 can be considered excessive, high discontinuation rates are consistent with other contraceptive trials reviewed by the Division. Further, this discontinuation rate is also consistent with the 3-year discontinuation rates for U.S. subjects observed in the pivotal trial used to support the original approval of Nexplanon (Implanon), which was 48.8%.*

4.2.3.2 Demographic and Baseline Characteristics

The summary of demographic and baseline characteristics for subjects in the Safety population as of the data cutoff date of April 8, 2024, are presented in Table 3. Most female subjects were white (74%), not Hispanic or Latino (70%), and not obese (i.e., BMI <30) (60%). The average age of subjects enrolled in the study was about 27 years (range 18 to 35 years), with 47% of subjects were between 25 to 30 years of age.

Table 3: Baseline Demographics, Safety Set (Data cutoff date April 8, 2024)

	MK-8415 ENG (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 (%)	

	MK-8415 ENG (N=399)
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)
Country, n (%)	
Puerto Rico	14 (3.5)
USA	385 (96.5)
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/m^2	
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/m^2	243 (60.9)
≥ 30 kg/m^2	152 (38.1)
Unknown	4 (1.0)

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

4.2.4 Results and Conclusions

In this section, the efficacy results are discussed. Table 4 displays summary of the overall pregnancy information reported in Study 060. As shown, a total of two pregnancies were reported in the study: one pregnancy occurred during the pre-treatment period, the other pregnancy occurred during the post-treatment period, and no pregnancy was reported during the on-treatment period.

Table 4: Pregnancy Information

Period	MK-8415 ENG Implant N=394, n (%)
Number of Participants with On-treatment Pregnancy	0 (0.0)
Number of Participants with Pre-treatment Pregnancy	1 (0.3)
Number of Participants with Post-treatment Pregnancy	1 (0.3)

Source: Reviewer's Analysis and CSR Table 14.1-1; adsl, adbase
Pre-treatment Pregnacies are defined as estimated conception occurred between the time from screening to one day before enrollment (i.e., <36 months ±2 weeks from implant insertion).
Post-treatment pregnancies are defined as estimated conception occurred after the implant removal (or eDiary deactivation if the implant removal date is not available).

Table 5 presents a summary of treatment cycles in the rFAS population during years 4 and 5. As shown, a total of 7752 exposure cycles were reported during the two years treatment period,

6936 of these cycles were considered as evaluable ("at risk") cycles, and 816 cycles were considered either "not at risk" or "missed" cycles due to a lack of vaginal intercourse, usage of other contraceptive products, or due to lack of relevant information in the eDiary records.

Table 6 displays the Pearl Index estimates for the cumulative pregnancy rate during years 4 and 5 and for the pregnancy rates at year 4 and at year 5 in the rFAS analysis population. As shown, the estimated cumulative PI during year 4 and 5 was 0 pregnancies per 100 women-year (95% CI: 0.00,0.69). Similarly, the estimated PI during year 4 was 0 pregnancy per 100 women-year (95% CI: 0.00,1.23) and during year 5 was 0 pregnancy per 100 women-year (95% CI: 0.00,1.58).

Table 5: Information about Cycles, rFAS population.

	MK-8415 ENG Implant N=394		
	Year 4	*Year 5*	*Overall*
Total Exposure Cycles [a]	4478	3274	7752
Number of On-treatment Cycles at Risk	3894	3042	6936
Number of On-treatment Cycles Not at Risk	210	140	350
No Vaginal Intercourse with a Man	169	121	292
Usage of Other Contraceptive Product	42	20	62
Number of On-treatment Cycles Missed [b]	374	92	466

Source: Reviewer's Analysis.
Two not at-risk cycles reported lack of heterosexual vaginal intercourse with use of additional contraception; these cycles are counted once for each not at-risk subcategory.
[a] The number of expected cycles is calculated as (the analysis end date minus the analysis start date plus 1) divided by 28. The maximum number of expected cycles is 13 per year. If the calculated number of expected cycles exceeds the maximum of a period, it will be set to the maximum for that period e.g., 13 cycles for a year and 26 cycles for two years.
[b] The number of missed cycles is calculated as the number of expected cycles minus the number of cycles at risk minus the number of cycles not at risk. If the calculated number of missed cycles is below 0, it will be set to 0.

Table 6: Primary and Secondary Endpoints, rFAS population.

Endpoints	**Number of on-treatment Pregnancies**	**Number of Total Exposure Cycles**	**Number of at-risk Cycles**	**Pearl Index (95% CI)**
PI at risk Years 4 and 5	0	7752	6936	0.0 (0.0,0.69)
PI at risk Year 4	0	4478	3894	0.0 (0.0,1.23)
PI at risk Year 5	0	3274	3042	0.0 (0.0,1.58)

Source: Reviewer's Analysis and CSR Table 11-3, Table 11-6.

Supporting Analyses for the cumulative PI evaluation using: (i) exposure cycle instead of evaluable cycle as 'at-risk' cycle and (ii) evaluable cycle after excluding 21 additional cycles affected by prohibited concomitant medication resulted in similar efficacy conclusion except for minor numerical differences in the confidence interval estimates.

Further, life-table analysis was performed to calculate pregnancy rates during Years 4 and 5 in the rFAS analysis population. As shown in

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in the appendix, 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).

4.2.1 Efficacy Conclusion

Based on the data available as of the cutoff date of April 8, 2024, the reviewer concludes that the efficacy evidence from Study 060 demonstrates that the application provided substantial evidence for Nexplanon in preventing pregnancies in women who had the implant in situ for three years and continued to use it for an additional two years.

No pregnancies were reported during the 2-year study duration, resulting in an overall Pearl Index of 0 for years 4 and 5.

4.3 Evaluation of Safety

In this study, safety was assessed mainly through exposure to study medication and summary of adverse events (AEs) and serious AEs. Safety data were summarized according to the safety analysis set.

A high-level safety summary for the study 060 was as follows; see the FDA clinical review for a comprehensive safety evaluation of the drug product.

A total of 498 participants were included in the safety population. Of these, 446 participants (89.6%) completed at least 42 months of implant use, 386 participants (77.5%) completed at least 48 months, and 284 participants (57.0%) completed at least 59.5 months of use. There were 218 participants (43.8%) who retained the ENG implant for at least 60 months (±2 weeks). Table **7** shows the overall summary of total exposure for the ENG dose among all participants treated. Of the 498 participants, 305 participants had detectable ENG hormone levels after the implant removal. The median total ENG exposure from the implant was 46.1 mg.

Table 7: Summary of Total Exposure for ENG Dose (mg) (APaT, Snapshot date: 25- Jul-2024**)**

Participants in Population	498
Number of participants whose removed implants had detectable hormone levels remaining.	305
Total ENG Exposure (mg) From the Implant	
Mean (SD)	45.2 (5.6)
Median	46.1
Min, Max	32.3,68.0

Source: Applicant's Clinical Summary of Safety, page 14

Table 8 displays the On-treatment Adverse event summary. As shown, approximately two-thirds of participants (64.7%) experienced at least one on-treatment adverse event.

Table 8: Summary of On-treatment Adverse Reactions (APaT, Snapshot date: 25- Jul-2024)

	MK-8415 ENG Implant		
	n	(%)	(95% CI)[a]
Participants in population	498		
with one or more adverse events	322	(64.7)	(60.3, 68.9)
with no adverse event	176	(35.3)	(31.1, 39.7)
with drug-related adverse events	79	(15.9)	(12.8, 19.4)
with non-serious adverse events	320	(64.3)	(59.9, 68.5)
with serious adverse events	8	(1.6)	(0.7, 3.1)
with serious drug-related adverse events	0	(0.0)	(0.0, 0.7)
who died	1	(0.2)	(0.0, 1.1)
who died due to a drug-related adverse event	0	(0.0)	(0.0, 0.7)
discontinued drug due to an adverse event	38	(7.6)	(5.5, 10.3)
discontinued drug due to a drug-related adverse event	33	(6.6)	(4.6, 9.2)
discontinued drug due to a serious adverse event	0	(0.0)	(0.0, 0.7)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	(0.0, 0.7)

CI=confidence interval.

Every participant is counted a single time for each applicable row.

On-treatment AEs are defined as AEs that started within the date of Visit 2 and the implant removal (or eDiary deactivation if the implant removal date is not available) + 14 days.

If Visit 2 occurred outside of the protocol-specified window (36 months ± 2 weeks from the date of implant insertion), the start of the on-treatment period is set to 36 months – 2 weeks (if it occurred prior to the window), or 36 months + 2 weeks (if it occurred after the window) from the date of implant insertion.

[a] Based on the exact binomial method proposed by Clopper and Pearson.

Based on database snapshot date of 25JUL2024

Source: Applicant's Clinical Summary of Safety, page 18

5 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

5.1 [redacted], Race, Age, and Geographic Region

Table 9 displays summary of the cumulative pregnancy rates based on PI at Years 4 and 5 by the subgroups of age, BMI, race, and ethnicity.

Table 9: Subgroup Analysis based on PI year 4 and 5, rFAS population.

Subgroup	**N**	**Number of Pregnancies**	**At risk Cycles**	**PI (95% CI)**
Overall, 4 and 5 years	394	0	6936	0.00 (0.00,0.69)
Age at Baseline				
18-24	135	0	2267	0.00 (0.00,2.12)
25-30	182	0	3187	0.00 (0.00,1.50)
31-35	77	0	1482	0.00 (0.00,3.24)
BMI (kg/m2)[1]				
< 30	240	0	4345	0.00 (0.00, 1.10)
>= 30	150	0	2573	0.00 (0.00, 1.86)

Subgroup	N	Number of Pregnancies	At risk Cycles	PI (95% CI)
Race[2]				
American Indian or Alaska Native	5	0	121	0.00 (0.00,39.63)
Asian	15	0	355	0.00 (0.00,13.51)
Black or African American	65	0	1058	0.00 (0.00,4.53)
White	293	0	5098	0.00 (0.00,0.94)
Multiple	10	0	197	0.00 (0.00,24.34)
Ethnicity[3]				
Hispanic or Latino	113	0	1878	0.00 (0.00,2.55)
Not Hispanic or Latino	279	0	5009	0.00 (0.00,0.96)

Source: Reviewer's Analysis
[1]4 subjects have unknown BMI
[2] There were only 2 Native Hawaiian or Other Pacific Islanders who contributed 28 at risk cycles and the PI (95% CI) is 0 (0.00, NA). A total of 4 subjects' race information were missing.
[3]Ethnicity information was unknown for two subjects.

Summary of the yearly Pearl Index by these defined subgroups is presented in Table 14 and **Error! Reference source not found.** in the Appendix.

Reviewer's comment: *For contraceptive trials, the Division typically recommends enrolling at least 35% obese female subjects in the study, contributing a minimum of 5,000 evaluable cycles to avoid labeling limitations of use for this subpopulation. The original Nexplanon approval trial excluded women whose ideal body weight was over 130%, resulting in a labeling warning about potential decreased effectiveness in overweight women over time.*

To address this limitation, in Study 060, the applicant enrolled 152 (38%) overweight and obese women, who contributed a total of 2,573 evaluable cycles over the 2-year study period. While the applicant seeks to remove the weight-related warning based on the 2-year efficacy results in this group, the reviewer defers to the medical review team to determine whether the combined real-world use of the product from Years 1-3 and the clinical trial data from Years 4-5 in Study 060 provide sufficient evidence to support (i) a five-year contraceptive efficacy claim without restrictions for overweight and obese women and (ii) warrant removal of the current labeling limitation

5.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

6 SUMMARY AND CONCLUSIONS

6.1 Statistical Issues

The following statistical concerns were identified during the review of this NDA application that may impact the interpretation of the results.

Study Design limitations: The Applicant's request to increase the duration of use of Nexplanon from 3 to 5 years by enrolling women with existing 3-year implant use rather than following a single cohort from initial insertion differs from typical contraceptive extension studies. This approach provides no information about pregnancies, contraceptive use, or sexual activity during the initial three-year period, which may limit the comprehensive understanding of long-term contraceptive performance.

Data Completeness Concerns: Although 498 women were enrolled in Study 060, only 399 participants (80%) were included in the efficacy analysis as of the primary data cutoff date of April 8, 2024, while 99 ongoing participants (20%) were excluded due to data cutoff timing. This raises concern about data completeness and potential bias. During the pre-NDA meeting, the applicant confirmed that there was no reported pregnancy in the ongoing subjects and agreed to submit the complete efficacy data post-approval in an efficacy supplement.

Data Collection Methodology: The use of monthly rather than daily/weekly diaries to record sexual intercourse and backup contraceptive use in Study 060 may have introduced recall bias in efficacy assessments and affected the accuracy of "at risk" cycle determination.

Overweight/obese population considerations: Study 060 enrolled 152 (38%) overweight/obese women, contributing 2,573 evaluable cycles over the 2-year study period. The original three-year approval trial for Nexplanon excluded women who were >130% of ideal body weight, and consequently, the original label included a warning about potential decreased effectiveness in overweight women. Based on the new 2-year data, the applicant has proposed removing this warning from the current label; however, the 2-year study duration may be insufficient to support removal of obesity-related labeling warnings without additional long-term data. This reviewer defers to the DUOG medical review team whether data from only Years 4 and 5 adequately support a five-year contraceptive efficacy claim without restrictions for overweight and obese women.

This reviewer defers to the DUOG medical review team to consider these concerns in the overall benefit-risk assessment.

6.2 Collective Evidence

Efficacy and safety support for extending Nexplanon use from 3 to 5 years for the prevention of pregnancy was based on Study MK-8415-060, a Phase 3, open-label, multicenter, single-arm study conducted in the United States and Puerto Rico.

The collective evidence from Study MK-8415-060 demonstrates that Nexplanon maintains contraceptive efficacy during extended use in Years 4 and 5, with zero on-treatment pregnancies observed among 394 participants in the rFAS population, resulting in a Pearl Index of 0

pregnancies per 100 woman-years (95% CI: 0.00, 0.69). This finding is supported by 6,936 evaluable at-risk cycles over the 2-year extension period, with consistent efficacy observed across both individual years (Year 4: 0.00 [95% CI: 0.00, 1.23]; Year 5: 0.00 [95% CI: 0.00, 1.58]).

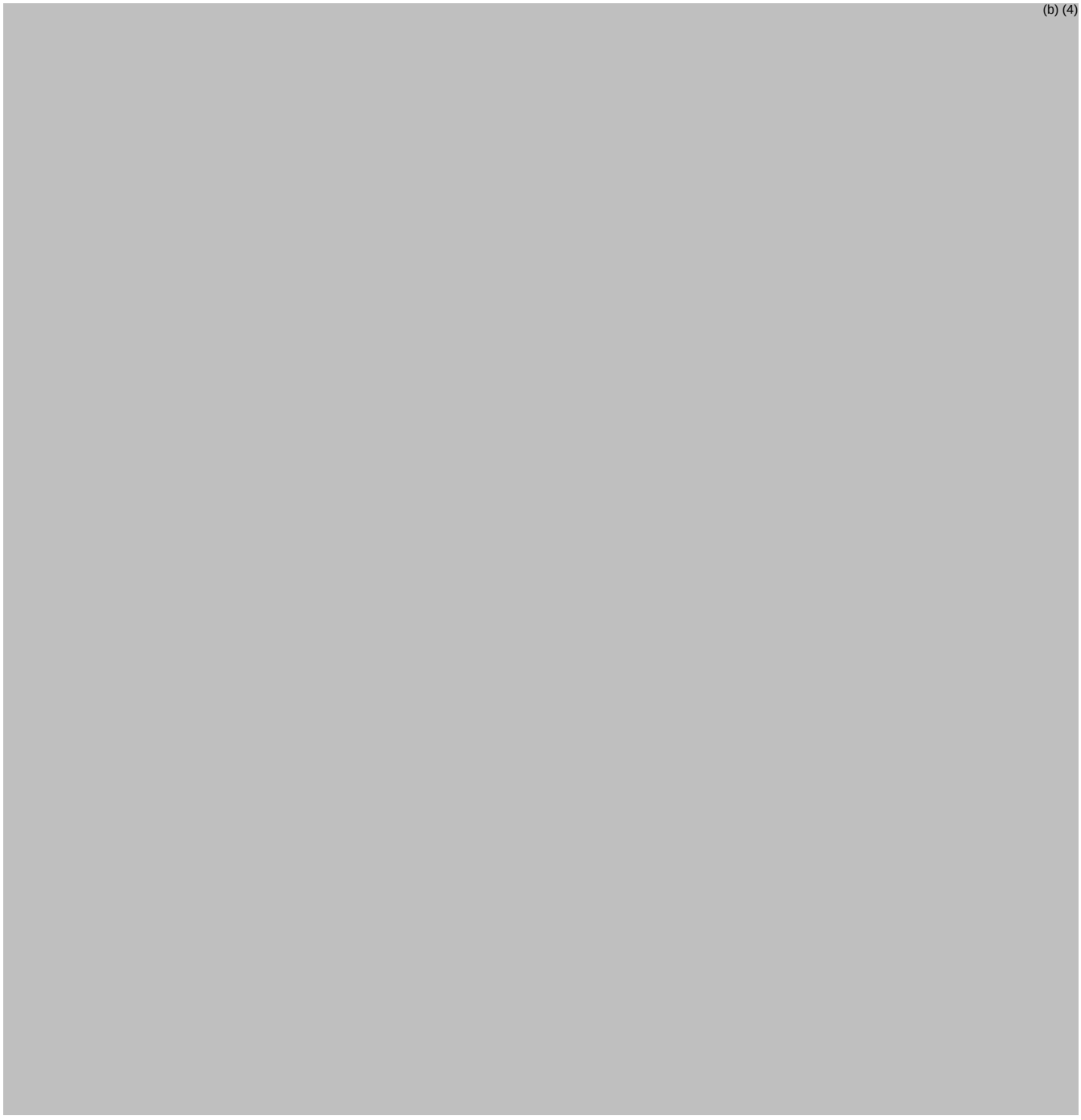
While the study design has limitations, including the lack of data from the initial three years of use and exclusion of ongoing participants from the primary analysis, the efficacy results are consistent with the established high contraceptive effectiveness of etonogestrel implants and support the conclusion that Nexplanon remains effective for pregnancy prevention during the extended use period from 3 to 5 years.

6.3 Conclusions and Recommendations

Based on the collective efficacy evidence from Study 060, the reviewer concludes that the application provided sufficient evidence of efficacy of Nexplanon to extend the duration of use from 3 years to 5 years for prevention of pregnancy.

6.4 Labeling Recommendations

The Applicant proposed to include the following texts in section 14 of the draft label. The reviewer's recommended edits are highlighted in blue font. The reviewer defers to the clinical review team for further edits on this section.



The Applicant also proposed to exclude the following texts in Use in specific population section of the draft label. The applicant's proposed edits are highlighted in pink font.

Nexplanon's original approval excluded women over 130% ideal body weight, resulting in a weight-related effectiveness warning. The applicant now proposes removing this warning based on Study 060 results. The reviewer defers to the medical review team to determine if the combined real-world data (Years 1-3) and clinical trial data (Years 4-5) sufficiently support: (i) five-year efficacy claims without weight restrictions, and (ii) removal of current labeling limitations for overweight/obese women.

APPENDICES

Sample of the Diary used in this study.

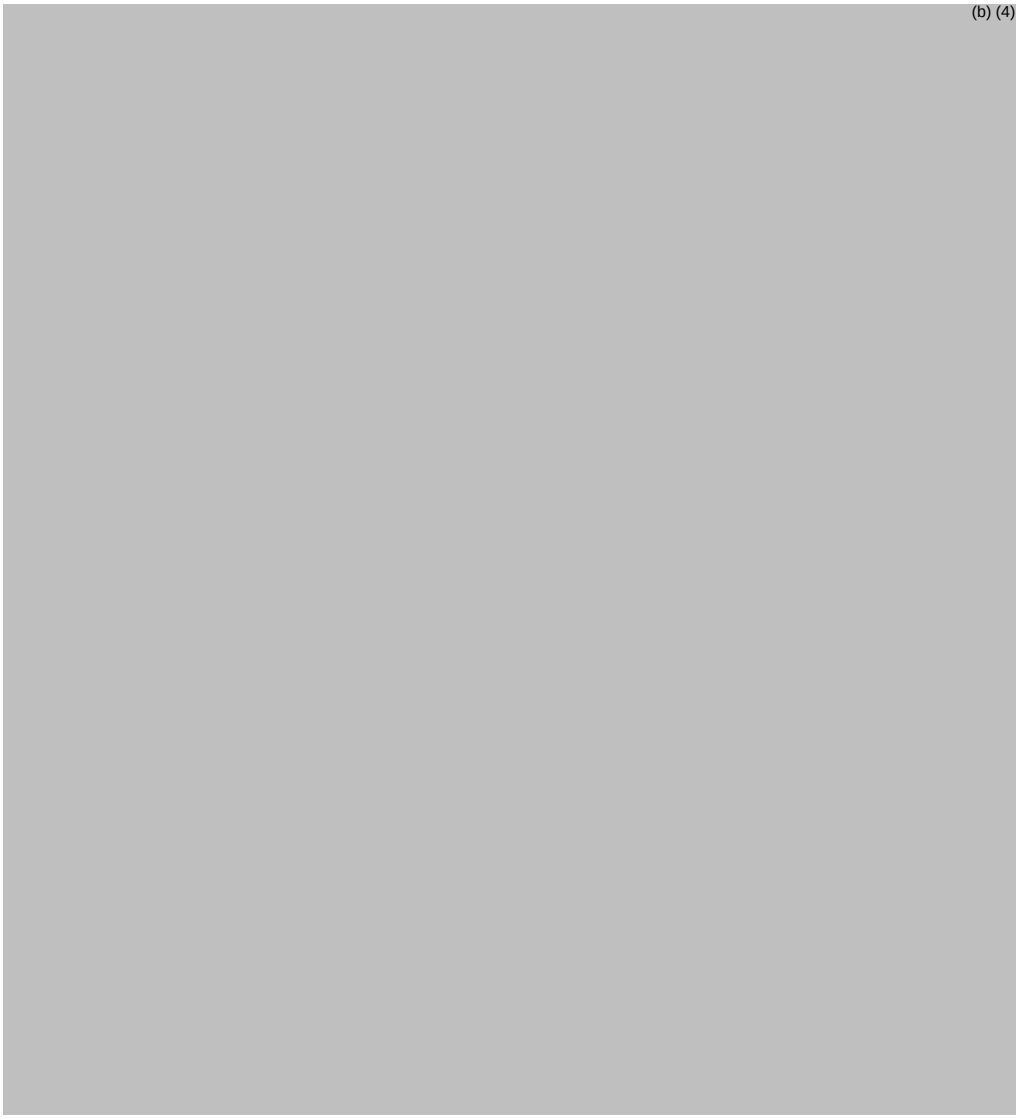


Table 10: Baseline Demographics , Safety Set (data cutoff July,2024)

		MK-8415 ENG Implant N=498
Age, years		
Mean (SD)	Mean (SD)	26.8 (4.12)
Median	Median	27.0
IQR	IQR	24.0, 30.0
Min, Max	Min, Max	18.0, 35.0
Age categories, n (%)		
18-24	18-24	161 (32.3)
25-30	25-30	233 (46.8)
31-35	31-35	104 (20.9)
Race, n (%)		
American Indian or Alaska Native	American Indian or Alaska Native	6 (1.2)
Asian	Asian	24 (4.8)
Black or African American	Black or African American	79 (15.9)
Native Hawaiian or Other Pacific Islander	Native Hawaiian or Other Pacific Islander	2 (<1)
White	White	368 (73.9)
Multiple	Multiple	11 (2.2)
Missing	Missing	8 (1.6)
Country, n (%)		
Puerto Rico	Puerto Rico	17 (3.4)
USA	USA	481 (96.6)
Ethnicity, n(%)		
Hispanic or Latino	Hispanic or Latino	143 (28.7)

Table 11: Disposition of Participants based on the treatment status, APaT/safety Set.

	Overall
Safety population	399
Completed the study treatment	215[b] (53.9)
Discontinued without implant removal	60 (15.0)
- Adverse event	0 (0.0)
- Adverse event related to vaginal bleeding pattern	0 (0.0)
- Death	1 (0.3)
- Lost to Follow-Up	36 (9.0)
- Physician Decision	4 (1.0)
- Withdrawal By Subject	1 (0.3)
- Other (participants refused implant removal)	18 (4.5)
- Pregnancy	0 (0.0)
- Protocol deviation	0 (0.0)
Discontinued with implant removal	124
- Adverse event	18 (4.5)
- Adverse event related to vaginal bleeding pattern	21 (5.3)
- Death	0 (0.0)
- Lost to Follow-Up	0 (0.0)
- Physician Decision	2 (0.5)
- Withdrawal By Subject	76 (19.0)
- Other	2 (0.5)
- Pregnancy	1 (0.3)
- Protocol deviation	4 (1.0)

[b] There were 2 participants (Subject IDs (b) (6)) who did not have a pregnancy test ≥14 days after implant removal, therefore, they were not included in 213 study completers based on the status for trial.

Implant status is completed extended duration of use and had implant removal with or without a documented pregnancy test ≥14 days after implant removal

Table 12: Protocol Deviations, FAS Set

Protocol Deviation Category	MK-8415 ENG
Full Analysis Set	395 (100)
Women with any protocol deviation	353 (89.4)
- Trial Procedures	351 (88.9)
- Inclusion/ Exclusion Criteria	28 (7.1)
- Prohibited Medications	13 (3.3)
- Informed Consent	6 (1.5)
- Safety Reporting	6 (1.5)
Women with Clinically important protocol deviation	130[1] (32.9)
- Trial Procedures	110 (27.8)
- hCG was not collected at EVERY visit for a patient and/or not processed, stored or shipped per lab manual instructions.	82 (20.8)
- No documented pregnancy test (serum or urine) within 14 days (+3) after implant removal or within 14 (+3) days of discontinuation visit (V10) if participant refuses implant removal at V10	55 (13.9)
- Implant not removed or if removed, not returned to Merck after study discontinuation (including lost to follow up).	39 (9.9)
- Inclusion/ Exclusion Criteria	4 (1.0)
- Prohibited Medications	13 (3.3)
- Informed Consent	6 (1.5)
- Safety Reporting	4 (1.0)
Women with Clinically not important protocol deviation	348 (88.1)
- Trial Procedures	347 (87.8)
- The first instance in any reference period in which a participant is non-compliant with their daily dairy for 3 or more consecutive days.	327 (82.8)
- Participant is non-compliant with protocol (ie, used backup contraception or not sexually active) or diary completion such that two consecutive cycles are excluded	96[2] (24.3)
- Implant not removed or if removed, not returned to Merck after study discontinuation (including lost to follow up).	36 (9.1)
- Inclusion/ Exclusion Criteria	25 (6.3)
- Safety Reporting	2 (0.5)

[1] Seven subjects had more than one clinically important protocol deviations.
[2] 95 of the subjects were in the rFAS population which used for the efficacy analysis.
Source: Reviewer's Analysis; CSR Table 14.1-7; sdtm dataset dv.xpt

Table 13: Cumulative Kaplan-Meier Pregnancy Rates, rFAS population

Year	Number of Pregnancies	Number of Evaluable Cycles	Pregnancy rates (95% CI)[a]
Year 4	0	3894	0.0, (0,0.99)
Year 5	0	3042	0.0, (0,1.27)
Year 4 and Year 5	0	6936	0.0, (0,1.12)

Source: Reviewer's Analysis

[a] Due to zero pregnancies observed (100% survival rates), standard Greenwood variance estimation for Kaplan-Meier confidence intervals is not applicable. Alternative upper bound of the 95% confidence intervals were calculated using Poisson approximation (rule of three) method. Lower bound is 0% as no pregnancies were observed.

Confidence intervals are expressed as percentages (×100) to facilitate comparison with Pearl Index estimates in Table 6.

Table 14: Subgroup Analysis based on PI year 4, rFAS set

Subgroup	N	Number of Pregnancies	At risk Cycles	Pearl_Index (95% CI)
Overall, 4 Years	394	0	3895	0 (0,1.23)
Age At Baseline				
18-24	135	0	1,318	0 (0, 3.64)
25-30	182	0	1,797	0 (0, 2.67)
31-35	77	0	780	0 (0, 6.15)
BMI (Kg/M2)				
< 30	240	0	2,470	0 (0, 1.94)
>= 30	150	0	1,423	0 (0, 3.37)
Unknown	4	0	2	0 (0, 4795.54)
Race				
American Indian Or Alaska Native	5	0	64	0 (0, 74.93)
Asian	15	0	182	0 (0, 26.35)
Black or African American	65	0	575	0 (0, 8.34)
Multiple	10	0	102	0 (0, 47.48)
Native Hawaiian or Other Pacific Islander	2	0	12	0 (0, 399.63)
White	293	0	2,921	0 (0, 1.64)
Ethnicity				
Hispanic or Latino	113	0	1,065	0 (0, 4.5)
Not Hispanic or Latino	279	0	2,807	0 (0, 1.71)
Not Reported	1	0	12	0 (0, 399.63)
Unknown	1	0	11	0 (0, 479.55)

Source: Reviewer's Analysis

Table 15: Subgroup Analysis based on PI year 5, rFAS set

Subgroup	N	Number of Pregnancies	At risk Cycles	Pearl_Index (95% CI)
Overall, 5 Years	394	0	3042	0 (0,1.58)
Age At Baseline				
18-24	135	0	951	0 (0, 5.05)
25-30	182	0	1,390	0 (0, 3.45)
31-35	77	0	702	0 (0, 6.83)
BMI (Kg/M2)				
< 30	240	0	1,875	0 (0, 2.56)
>= 30	150	0	1,150	0 (0, 4.17)
Unknown	4	0	18	0 (0, 282.09)
Race				
American Indian or Alaska Native	5	0	57	0 (0, 84.13)
Asian	15	0	174	0 (0, 27.72)
Black or African American	65	0	483	0 (0, 9.93)
Multiple	10	0	96	0 (0, 49.95)
Native Hawaiian or Other Pacific Islander	2	0	16	0 (0, 299.72)
White	293	0	2,179	0 (0, 2.2)
Ethnicity				
Hispanic or Latino	113	0	814	0 (0, 5.9)
Not Hispanic or Latino	279	0	2,202	0 (0, 2.18)
Not Reported	1	0	13	0 (0, 368.89)
Unknown	1	0	15	0 (0, 342.54)

Source: Reviewer's Analysis

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