Document Type:	Statistical Analysis Plan
Official Title:	A Study to Evaluate the Effectiveness of Essure Post-NovaSure Radiofrequency Endometrial Ablation Procedure Following a Successful Essure Confirmation Test
NCT Number:	NCT01740687
Document Date:	29-Mar-2021

A Study to Evaluate the Effectiveness of Essure Post-NovaSure Radiofrequency Endometrial Ablation Procedure Following a Successful Essure Confirmation Test

Essure® (Model ESS310) Placement Study

BSP study device	Essure (Model ESS305)		
Study purpose:	The purpose of the study is to evaluate the effectiveness and safety of the Essure System when a NovaSure endometrial ablation (EA) procedure is performed following a successful Essure Confirmation Test.		
Clinical study phase:	Post-approval study (PAS)	**Date:**	29MAR2021
Study No.:	16975	**Version:**	1.2
Authors:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Abbreviations

ADE	Adverse device event
ADL	Activities of daily living
AE	Adverse event
CRF	Case Report Form
D&C	dilatation and curettage
EA	Endometrial Ablation
ECG	electrocardiogram
eCRF	Electronic case report form
EMA	European medicines evaluation agency
FDA	Food and Drug Administration of the United States
GCP	Good clinical practices
HSG	Hysterosalpingogram
HTA	Hydro Thermablator®
ICF	Informed consent form
IEC	Independent ethics committee
IFU	Instructions for Use
IME	Important medical events
IRB	Institutional Review Board
IVRS	Interactive voice response system
LPLV	Last patient last visit
PAS	Post-Approval Study
PMA	Pre-market Approval
SADE	Serious adverse device effect
SAE	Serious adverse event
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
US	United States

1. Introduction

This statistical analysis plan is based on Amendment 6 of the protocol (dated 12 Jul 2016). Statistical analyses will be performed by or under supervision of the responsible statistician at Bayer HealthCare Pharmaceuticals.

The purpose of the study is to evaluate the effectiveness and safety of the Essure System when a NovaSure endometrial ablation (EA) procedure is performed following a successful Essure Confirmation Test. This post-approval study (PAS) is a prospective, multi-center, single-arm observational study.

2. Study Objectives

The objectives of this study are to:

- Evaluate the contraceptive failure rate of Essure when NovaSure is performed following a successful Essure Confirmation Test, and
- Monitor the incidence of adverse events and/or complications associated with the performance of NovaSure in the presence of Essure micro-inserts.

3. Study Design

Design overview

This PAS is a prospective, multi-center, single-arm observational study to monitor and evaluate the effectiveness and safety of Essure when NovaSure is performed following a successful Essure Confirmation Test. The PAS will be conducted at up to 15 sites in the United States. Each site may enroll a maximum of 35 subjects. A minimum of 220 female subjects will be enrolled in the study. Subjects will be followed for a total of 3 years post-NovaSure EA with evaluations to occur at the 1 week, 12 month, 24 month and 36 month follow-up time points. PAS subjects who have been identified as candidates for NovaSure EA and have had a successful Essure Confirmation Test will be considered.

At least 50% of the subjects enrolled in the study must be 45 years of age or younger.

End of study

The primary outcome will be collected after last patient - last visit (LPLV). The end of the study as a whole will be the date when the clean data base is available.

3.1 Primary Endpoint

- Occurrence of confirmed pregnancy at 1 year and 3 years among subjects relying on Essure micro-inserts for permanent birth control when NovaSure is performed following a successful Essure Confirmation Test.

3.2 Secondary Endpoints and Assessments

- Adverse event data

3.3 Study Flowchart

See Section 7.1.1 in the Study Protocol for a schedule of procedures.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA) or R release 3.0.2 or higher (R Foundation for Statistical Computing, Vienna, Austria). Baseline NovaSure EA and follow-up data will be summarized using the appropriate statistical method; continuous variables will be summarized using means, standard deviations, medians and quartiles. Categorical data will be summarized using frequency rates (e.g., count/sample size).

4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject qualified for the study or attempted the NovaSure EA procedure. Dropouts will be analyzed in each analysis set for which they meet the qualifications. Dropouts will not be replaced.

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see above) is regarded a "screening failure".

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

4.3 Handling of Missing Data

In order to achieve the goal of a well conducted clinical trial according to Good Clinical Practice (GCP), every effort will be made to collect all data. i.e., if a subject misses a

scheduled assessment, the site personnel will contact the subject and request her to come to the clinic for a visit. However, despite best efforts, it may be inevitable that missing or incomplete data are reported. Except as noted below, missing data will not be estimated or imputed.

General rules

When appropriate, the following rules will be implemented so as not to exclude subjects from statistical analyses due to missing or incomplete dates:

Table 1 - Imputation rules for missing adverse event start and stop dates

Scenario		
Start date	***Stop date***	***Imputation rule***
Partially Missing	Complete	Imputation of <u>start</u> date: A. If partial date has day and month missing: If the year is same as the year of the NovaSure EA procedure, then the day and month of the NovaSure EA procedure will be assigned to the missing fields If the year is prior to the year of the NovaSure EA procedure, then December 31 will be assigned to the missing fields. If the year is after the year of the NovaSure EA procedure, then January 01 will be assigned to the missing fields. Note: if NovaSure EA procedure date is missing, then there is no need to impute the date as the AE is not treatment emergent. B. If partial date has missing day only: If the month and year are same as the year and month of the NovaSure EA procedure, then the day of the NovaSure EA procedure will be assigned to the missing day.

		If the month and year are before the year and month of the NovaSure EA procedure, then the last day of the month will be assigned to the missing day. If the month and year are after the year and month of the NovaSure EA procedure, then the first day of the month will be assigned to the missing day. If the imputed event start date (after A or B above) is after the event stop date, the start date will be imputed to be equal to the stop date.
Complete	Partially Missing	Imputation of <u>stop</u> date C. If partial date has day and month missing: If the year is same as the year of the NovaSure EA procedure, then the day and month of the NovaSure EA procedure will be assigned to the missing fields If the year is prior to the year of the NovaSure EA procedure, then December 31 will be assigned to the missing fields. If the year is after the year of the NovaSure EA procedure, then January 01 will be assigned to the missing fields. D. If partial date has missing day only: If the month and year are same as the year and month of the NovaSure EA procedure, then the day of the NovaSure EA procedure will be assigned to the missing day. If the month and year are before the year and month of the NovaSure EA procedure, then the last day of the month will be assigned to the missing day. If the month and year are after the year and month of the NovaSure EA procedure, then the last day of the month will be assigned to the missing day.

		If the imputed stop date (after C or D above) is before the event start date, the stop date will be imputed to be equal to the event start date.
Partially Missing	Partially Missing	Impute start date per A and B above Impute stop date per C and D above If start date > stop date, then set start date = stop date = minimum of (imputed start date per A and B, imputed stop date per C and D)
Partially Missing	Completely Missing	Impute start date per A and B above Impute stop date as the study completion date If start date > stop date, then set start date = stop date = imputed start date per A and B
Completely Missing	Partially Missing	Impute start date as the NovaSure EA procedure date. Impute stop date per C and D above If start date > stop date, then set start date = stop date = minimum of (imputed start date per A and B, imputed stop date per C and D)
Completely Missing	Complete	Impute start date as the NovaSure EA procedure date If start date > stop date, then set start date = (complete) stop date
Completely Missing	Completely Missing	Impute start date as the NovaSure EA procedure date Impute stop date as the study completion date

4.4 Interim Analyses

Interim PAS status reports will be submitted at least annually from the date of the pre-market approval (PMA) letter or other negotiated starting date (i.e., PAS initiation). Ongoing interim PAS status reports will be submitted until the final PAS report is written after the termination or completion of the PAS. The ongoing interim reports and final PAS report will include information related to PAS methodology and results/endpoints including the following:

- Occurrence of confirmed pregnancy at 1 and 3 years after NovaSure EA among subjects relying on Essure inserts for permanent birth control when NovaSure is performed following a successful Confirmation Test.

- Adverse event data.

4.5 Data Rules

Repeated measurements

If there are repeated measurements at one time point, the following rules apply :

- at screening and at baseline the last measurement (based on the specimen collection date and time), ie, the measurement, which is the closest to the attempted NovaSure EA procedure, will be used,

- during or after the attempted NovaSure EA procedure, the first measurement (based on collection date and time) will be used, provided the data are of equal quality.

4.6 Validity Review

Assignment of subjects to the analysis set described in Section 5 will be discussed and documented. In addition, protocol deviations will be discussed, reviewed, and categorized. Any changes to the statistical analysis prompted by the results of this meeting will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

Primary effectiveness cohort

All subjects who sign a study-specific ICF and undergo insertion of the NovaSure device transcervically

Primary safety cohort

All subjects who sign a study-specific ICF and in whom a NovaSure procedure is attempted (e.g., subject who comes to the study site with the intent of having the procedure performed).

Enrolled cohort

The enrolled cohort includes any subject who signs the study-specific ICF.

6. Statistical Methodology

Variables measured on metrical scales will be summarized by use of descriptive statistics (number of subjects with non-missing observations, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum). Variables measured on ordinal or nominal scales will be summarized by use of frequency tables showing the number and percentage of subjects falling within a particular category.

6.1 Population characteristics

Subject enrollment and disposition will be summarized for the following via the enrolled cohort:

- Enrollment by site and overall
- Disposition (completed study (Y/N), etc.)
- Summary of all reasons for early termination
- Subject validity
- Visit accountability (enrolled subjects not screen failures)

The following demographic and baseline characteristics will be summarized descriptively for the Safety Cohort:

- Demography – Race, ethnicity, age, age groups (18-27, 28-33, >34, and also ≤45, >45), weight [kg], height [cm], and body mass index [kg/m²]
- Medical History – Primary method of contraceptive used immediately prior to the Essure placement procedure, gravidity (both categorical and continuous), parity (both categorical and continuous), vaginal births (categorical only), cesarean births (categorical only), total abortions (categorical only), ectopic pregnancies (categorical only), days from last delivery/termination of pregnancy to NovaSure procedure, days from Essure procedure to NovaSure procedure, days from Essure confirmation test to NovaSure procedure, did Essure confirmation test show both micro-inserts in the

proper location (Y/N), did Essure confirmation test show both fallopian tubes occluded (Y/N), number of previous abdominal surgeries (continuous only), days from most recent abdominal surgery to NovaSure procedure,

- Pelvic exam (unremarkable/remarkable)

The following procedure data will be summarized descriptively for the Primary Effectiveness Cohort:

- NovaSure Procedure – Duration (minutes), anesthesia type (inhaled, IV, IM, oral, regional, local, other), uterine positions (Anteverted, Retroverted, Midpositional), cervical dilation required (Y/N), treatment time (seconds), power setting (continuous), was the ablation procedure interrupted during the treatment cycle (Y/N), was a restart of the endometrial ablation necessary (Y/N), was resistance encountered during withdrawal of the NovaSure device (Y/N), was an Essure micro-insert attached to the array upon removal (Y/N), was the endometrial ablation completed successfully (Y/N)

- Frequency summary of discharge medications

- Follow-up at 1 week, 1 year, 2 years and 3 years – has either Essure insert been expelled (Y/N), patient's rating of comfort of wearing the micro-insert, patient's rating of overall satisfaction with the micro-insert, patient's rating of overall satisfaction with the treatment plan of Essure permanent birth control and confirmation test followed by NovaSure treatment

Protocol deviations will also be summarized by category of deviation for the enrolled cohort.

6.2 Efficacy

6.2.1 Primary Efficacy Analysis

The primary effectiveness endpoint of this study is the 1-year and 3-year pregnancy rates. The rates will be calculated as done in prior Essure studies, as described below.

Each woman-month of follow-up represents a "Bernoulli trial" of the Essure device. A woman contributes as many women-months as her participation in the post-approval study. Upon observing f failures (pregnancies) in w women-months, the posterior distribution of the monthly failure rate, r, is calculated as:

r = beta(a+f, b+w-f)

where a and b = 0.5, representing a non-informative prior distribution. The upper Bayesian credible interval of r is easily calculated from the inverse beta function. A 1-year failure rate can be calculated as:

$$1\text{-year rate} = 1-(1-r)^{12}$$

The 1-year rate will be calculated when all participating women have reached at least 1 year of follow-up.

As an additional related calculation, the 3-year failure rate will be determined as:

$$3\text{-year rate} = 1-(1-r)^{36}$$

- For example, if there are 0 failures in 200 × 12 = 2,400 women-months, the posterior distribution of the monthly failure rate is beta(0.5, 0.5 + 2400). The upper Bayesian credible interval is (in Excel) betainv (.975, 0.5, 0.5 + 2400) = 0.00105. The upper 95% credible interval for the 1-year rate is $1-(1-0.00105)^{12} = 0.0125$ or 1.25%. This value meets the pre-determined study success threshold of 2.1% for the 1-year rate. 2.1% refers to the Upper Confidence Limit of the Adiana 1-year failure rate and 2.8% refers to the Upper Confidence Limit of the Adiana 3-year failure rate. (from Table 5: Contraceptive Failure Rates, Adiana Permanent Contraception Instructions For Use, AW-03216-001 Rev. 003);

The analysis population is the Primary Effectiveness Cohort.

The primary objective of the PAS is to evaluate the contraceptive failure rate of Essure when NovaSure EA is performed following a successful Essure Confirmation Test and to demonstrate that the failure rate is reasonably low (see details below). Consistent with prior Essure clinical studies, a Bayesian approach will be used. The study will be considered a success if the posterior probability (PPr) that the observed failure rate at 1 year (rate1y) is <2.1% is at least 97.5%, i.e.:

$$PPr(rate1y < 0.021) > 0.975\ *$$

* i.e., a Type 1 error rate of 5%

This equation provides the posterior probability that the one-year pregnancy rate is less than 2.1% given trial data is at least 97.5%. If the posterior probability that the 1-year rate is <0.021 exceeds 97.5%, we have shown with a high degree of confidence that the rate is at least as good as that which FDA has found acceptable for Adiana Permanent Contraceptive (PMA P070022).

For the three-year rate, the same procedure is followed with the only exception that the threshold value is 2.8%, rather than the 2.1% specified for the one-year rate.

As a supportive analysis, the pregnancy rate will be also calculated using Kaplan-Meier method.

Assumptions

The following assumptions were used to calculate the PAS sample size and power for the 1- and 3-year hypothesis:

- Participants in this PAS are women who have undergone the Essure procedure followed by a successful Essure Confirmation Test showing satisfactory micro-insert location and bilateral tubal occlusion;
- Contraceptive failure rates after Essure are very low (no pregnancies identified in References 4 and 5 (two retrospective studies) in the clinical study protocol)) for the PAS population as demonstrated by prior clinical studies;
- For the purposes of power calculations, the one-year pregnancy rate is modeled as r=beta(0.5+a, 0.5+b), where beta(0.5,0.5) is a non-informative prior and a=0, b=600, roughly the size of the Essure Phase II and Pivotal clinical trial relying cohorts in the Essure premarket studies;
- Multiple clinical trials are simulated with the underlying pregnancy rate of r;
- The one-sided upper Bayesian credible interval of the observed one-year failure rate amongst n=200 is calculated in 5000 simulated clinical trials using an underlying pregnancy rate of r;
- Power for the 1-year hypothesis is the probability (based on 5000 simulated clinical trials) that the Upper Credible Interval of the 1-year rate is <2.1%, where 2.1% is the Upper Confidence Limit of the Adiana 1-year failure rate (from Table 5 in the clinical study protocol: Contraceptive Failure Rates, Adiana Permanent Contraception Instructions For Use, AW-03216-001 Rev. 003);
- Power for the 3-year hypothesis is the probability that the Upper Credible Interval of the 3-year rate is <2.8%, the Upper Confidence Limit of the Adiana 3-year failure rate (Table 5: Contraceptive Failure Rates, Adiana Permanent Contraception Instructions For Use, AW-03216-001 Rev. 003).

Given the assumed underlying failure rate for a successful Essure procedure followed by a confirmatory Essure Confirmation Test, a study of n=200 women has an 86% chance of showing that the Upper Credible Interval of the 1-year failure rate will be <2.1%. The table below shows detailed results.

Expected number of failures at 1 year	Probability	2-sided upper credible interval

0	0.861	0.012
1	0.112	0.023
2	0.020	0.031
3	0.006	0.039
4	0.002	0.047
5	0.0004	0.054

6.2.2 Secondary Endpoint Analyses

The secondary endpoint in the PAS is the incidence of adverse events when NovaSure EA is performed in the presence of Essure micro-inserts. There is no specific study hypothesis. Instead, the safety profile will be analyzed using summary statistics on the Safety Cohort as described in Section 6.3.

6.2.3 Other Endpoint Analyses

6.2.3.1 Summary of subject evaluations

The following evaluations will be summarized descriptively for the Primary Effectiveness Cohort for 1-week, 1-year, 2-years and 3-years of follow-up:

- Subject's rating of comfort of wearing the micro-insert
- Subject's rating of overall satisfaction with the micro-insert
- Subject's rating of overall satisfaction with the treatment plan of Essure permanent birth control and Essure Confirmation Test, followed by NovaSure Treatment

6.3 Safety

The safety variables to be investigated in this study include the following:

- Adverse Events
    - Adverse events related (an AE that is at least possibly related to the Essure or NovaSure device/procedure) to Essure and/or NovaSure
    - Adverse events of special interest
    - Most common AEs (≥ 1%)
- Serious Adverse Events (SAE)

- Most common SAEs (≥ 1%)

- Device events for Essure and/or NovaSure
  - Device events leading to AEs
  - Device events that resulted in SAEs
  - Device events that could lead to SAEs

- Device removals
  - Number of subjects with removals
  - Removal procedures – days from last insert procedure to removal procedure, removal intended, primary reason for intentional device removal, procedures performed at time of device removal, number of devices removed per procedure
  - Essure inserts removed – insert location, complete device removal, device removed intact

The safety profile will be analyzed using summary statistics on the Safety Cohort.

6.3.1 Adverse Events

All AEs will be coded using MedDRA.

Frequency tables showing an overall summary of the number of events (where possible) and the number of subjects with AEs by system organ class (SOC) and preferred term (PT) will be given for the following types of AEs:

- All AEs
- AEs (possibly, probably, definitely) related to:
  - Essure device
  - NovaSure device
  - NovaSure procedure
  - Pre-existing condition
- AEs by intensity (mild, moderate, severe)
- AEs by outcome

- AEs of special interest
    - Defined as follows (updated annually by Medical Experts):

AE of Special Interest	Description	AEDECOD (PT)	AELLT
Abnormal Uterine Bleeding	Set to Y if AEDECOD equal to any of values in Column C:	Dysfunctional uterine bleeding	
		Genital hemorrhage	
		Genital haemorrhage	
		Menometrorrhagia	
		Menorrhagia	
		Metrorrhagia	
		Polymenorrhoea	
		Uterine hemorrhage	
		Uterine haemorrhage	
		Vaginal hemorrhage	
		Vaginal haemorrhage	
		Amenorrhea	
		Amenorrhoea	
		Hypomenorrhea	
		Hypomenorrhoea	
		Oligomenorrhea	
		Oligomenorrhoea	
		Bleeding anovulatory	
		Menstrual disorder	
		Menstruation delayed	
		Menstruation irregular	
Lower Abdominal Pelvic and Back Pain	Set to Y if AEDECOD='Back pain' and AELLT='Low back pain', otherwise set to Y if AEDECOD equal to any of values below:	Back pain	Low back pain
		Abdominal pain	
		Abdominal pain lower	
		Abdominal tenderness	
		Abdominal discomfort	
		Incision site pain	
		Implant site pain	
		Medical device discomfort	
		Medical device pain	
		Medical device site discomfort	
		Medical device site pain	
		Suprapubic pain	
		Visceral pain	
		Post ablation tubal ligation syndrome	
		Pubic pain	

		Groin pain	
		Genito-pelvic pain/penetration disorder	
		Uterine cervical pain	
		Ovulation pain	
		Pelvic pain	
		Pelvic discomfort	
		Dyspareunia	
		Adnexa uteri pain	
		Uterine tenderness	
		Uterine pain	
		Uterine spasm	
		Dysmenorrhoea	
		Menstrual discomfort	
		Premenstrual cramps	
Perforation	Set to Y if AEDECOD equal to any of values in Column C:	Fallopian tube perforation	
		Uterine perforation	
Upper genital tract infections	Set to Y if AEDECOD equal to any of values in Column C:	Endometritis	
		Salpingitis	
		Salpingo-oophritis	
		Pelvic inflammatory disease	
Expulsion or migration or unintentional removal of Essure inserts	Set to Y if AEDECOD equal to any of values in Column C:	Device dislocation	
		Device expulsion	
		Unintentional medical device removal	
Potential allergy/hypersensitivity to Essure inserts	Set to Y if AEDECOD equal to any of values in Column C:	Allergy to animals	
		Allergy to chemicals	
		Allergy to metals	
		Hypersensitivity	
		Multiple allergies	
		Pruritus	
		Rash	
		Rash pruritic	
		Seasonal allergy	
		Urticaria	
Auto-immune	Set to Y if AEDECOD equal to any of values in Column C:	Autoimmune disorder	
		Autoimmune thyroiditis	
		Multiple sclerosis	
		Multiple sclerosis relapse	
		Rheumatoid arthritis	

- AEs occurring in at least 1% of subjects

The same AE tables listed above will be repeated for treatment-emergent serious AEs, except for AEs of special interest.

6.3.1.1 Adverse Device Events

All adverse device events that are also adverse events constitute adverse device effects (ADEs). ADEs are defined as AEs that are at least possibly related to the Essure or NovaSure device/procedure)

All adverse device effects (ADEs) will be summarized for the primary safety cohort. All ADEs will be coded using MedDRA.

Frequency tables showing an overall summary of the number of events (where possible) and the number of subjects with ADEs by system organ class (SOC) and preferred term (PT) will be given for the following types of ADEs:

- All adverse device events
- Adverse device events leading to AEs
- ADEs that are serious adverse events (SAEs)
- Adverse device events that could lead to SAEs
- Adverse device events by category (device deficiency, device failure, device malfunction, medical device report (MDR) reportable event, important medical events and events of special interest, unknown, and other)

6.3.2 Pregnancies

A listing of women who became pregnant after the NovaSure EA procedure will be provided.

7. Document history and changes in the planned statistical analysis

- 15Apr2015 – Version 1.0 by PPD
- 15Dec2020 – Version 1.1 by PPD

8. References