# Clinical Trial Protocol

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| **Clinical Trial Protocol Number** | MS 700623_0009 |
| **Title** | A multicentre, prospective randomised controlled, interventional clinical investigation to assess the clinical safety and performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during Assisted Reproductive Practice **(ENDOMEDE)** |
| **Short Title** | ENDOMEADE |
| **Study Type** | Post Marketing follow-up study<br>Merck-Sponsored Investigation on endometrial washing medical device CE 0546 |
| **Coordinating Investigator** | PPD |
| **Sponsor** | Merck Serono S.p.A.<br>Via Casilina 125, 00176 Rome, Italy |
| **Sponsor Legal Representative in the European Union** | Merck KGaA<br>Frankfurter Strasse 250<br>64293 Darmstadt, Germany |
| **Medical Device Manufacturer** | PPD |
| **Clinical Trial Protocol Version** | December 9, 2016<br>Version 1 |
| **Replaces Version** | Not applicable |

[redacted]

## Table of Contents

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## List of Abbreviations

| | |
|---|---|
| AE | adverse event |
| ART | assisted reproductive technique |
| ASRM | American Society for Reproductive Medicine |
| CER | clinical evaluation report |
| COS | controlled ovarian stimulation |
| CPR | clinical pregnancy rate |
| CRF | case report form |
| DMC | data monitoring committee |
| eCRF | electronic case report form |
| ECG | Electrocardiogram |
| $E_2$ | Estradiol |
| ESHRE | European Society of Human Reproduction and Embryology |
| FGF-1 | fibroblast growth factor-1 |
| FSH | follicle-stimulating hormone |
| GMP | Good Manufacturing Practice |
| HCG | human chorionic gonadotropin |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| ICSI | intracytoplasmic sperm injection |
| IEC | independent ethics committee |
| IFU | instructions for use |
| IUI | intrauterine insemination |
| IVF | in vitro fertilization |
| OPR | ongoing pregnancy rate |
| OPU | oocyte pick-up |
| $P_4$ | Progesterone |
| PCOS | polycystic ovary syndrome |
| PET | post embryo transfer |
| POR | poor ovarian response |

| | |
|---|---|
| PP | per protocol |
| PR | post randomisation |
| HCG | human chorionic gonadotropin |
| RIF | repeated implantation failure |
| SAE | serious adverse event |
| SAF | safety set |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOD | superoxide dismutase |

# 1 Synopsis

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| **Clinical Trial Protocol Number** | MS 700623_0009 |
| **Title** | A multicentre, prospective, randomised, controlled, interventional clinical study to assess the clinical safety and performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during Assisted Reproductive Practice **(ENDOMEDE)** |
| **Short Title** | ENDOMEDE |
| **Study Type** | Post Marketing follow-up study<br>Merck-Sponsored Investigation on **ENDO**metrial Washing **ME**dical **DE**vice (CE 0546) |
| **Coordinating Investigator** | PPD |
| **Sponsor** | Merck Serono S.p.A.<br>Via Casilina 125, 00176 Rome, Italy |
| **Medical Device Manufacturer** | PPD |
| **Sponsor Legal Representative in the European Union** | Merck KGaA<br>Frankfurter Strasse 250<br>64293 Darmstadt, Germany |
| **Trial centres/countries** | At least six clinical sites in Italy will participate |
| **Planned trial period (first subject in-last subject out)** | March 2017 to December 2018 |

**Objectives:**

The Primary Objective of the study is to evaluate the implantation rate increase in women undergoing Assisted Reproductive Technique (ART) by using Forielle, an endometrial wash that restores favourable conditions of endometrial "milieu" after Controlled Ovarian Stimulation (COS).

Secondary objectives are to:

- Determine the Pregnancy Rate at PET Day 14
- Determine the Ongoing Pregnancy Rate during PET Days 70 to 84
- Assess the safety of Forielle by report of device incidents

**Methodology:**

This is a multicentre, prospective randomised controlled, interventional investigation to assess the safety and clinical performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during ART. The study protocol consists of assessing the clinical performance of Forielle in restoring favourable condition of endometrial milieu after COS. Clinical performance will be measured by comparing implantation rate in the treated arm compared to the control. The trial aims to enrol 2,156 women from at least six centres in Italy.

Infertile females aged ≤ 41 years with no more than one previous implantation failure will be assessed for eligibility for the trial after providing written informed consent. Subjects will undergo COS according to standard of care clinical practice. There is no limitation in the gonadotrophin stimulation protocols used; however, triggering must be done with HCG. Eligible subjects will be randomised to receive either the intervention (Forielle endometrial washing) or no endometrial washing following oocyte retrieval on Study Day 0, the HCG Triggering day, in a 1:1 ratio. Oocyte retrieval and endometrial washing (Forielle-treated group) will occur during the same surgical procedure. The entire ART cycle will be performed according to clinical practice of the centre based on each subject's clinical profile.

Retrieved oocytes will be fertilized per ICSI standard clinic practice and the embryology lab will calculate the fertilization rate for each subject. Beginning approximately 24 hours after ICSI, the embryology lab will evaluate embryo for quality daily, with the most viable embryos selected for implantation, which would be Day 5 Post Randomisation (PR) for embryos transferred in the cleavage stage and Day 7 PR for embryos transferred in the blastocyst stage. Luteal support/endometrial preparation will be administered daily, beginning at the Oocyte Retrieval Visit (Day 2 PR). At the Embryo Transfer visit (Day 5 PR or Day 7 PR), a maximum of 2 fertilized embryos or blastocysts will be transferred and luteal support (daily administration of 600 mg of vaginal progesterone) will continue.

All subjects must have a serum β-HCG pregnancy test performed 14 days after embryo transfer (PET Day 14). Subjects may have this assessment performed by another physician; however, the pregnancy test report must be provided to the investigator. In these cases, all other PET Day 14 assessments may be performed with the subject via telephone.

If the PET Day 14 serum β-HCG pregnancy test is negative, the PET Days 21-28 and PET Days 70-84/Weeks 10-12 visits may occur by telephone with the PET Days 70-84/Weeks 10-12 visit serving as the final study contact. In these cases, the PET Days 21-28 visit and PET Days 70-84 visits may be performed via telephone and the investigator will enter negative ultrasound results for ultrasound assessments that would have been performed at PET Days 21-28 and PET Days 70-84.

If the PET Day 14 serum β-HCG pregnancy test is positive, the subject must return to the site 21 to 28 days after embryo transfer (PET Days 21-28), to determine the number of gestational sacs present and calculate the implantation rate, the primary endpoint. The primary endpoint, the subject implantation rate, is defined as the number of intrauterine gestational sacs divided by the number of embryos transferred.

If the subject returns to the site on PET Days 21-28 for transvaginal ultrasound and does not have any gestational sacs present, the investigator will enter a negative result for the PET Days 70-84/Weeks 10-12 obstetric ultrasound (transvaginal or abdominal). In these cases, the PET Days 70-84/Weeks 10-12 final study visit may occur by telephone.

Subjects who return to the site at PET Days 21-28 and have gestational sacs present on transvaginal ultrasound will have a final obstetric ultrasound (transvaginal or abdominal) on PET Days 70-84 to verify the Ongoing Pregnancy Rate (OPR).

In the event a subject cannot return to the site for the PET Days 70-84 visit, ultrasound report confirming ongoing pregnancy details required (number of foetuses, confirmation of foetal vitality based on the presence of foetal heartbeat and confirmation of the development of normal pregnancy for each foetus present on ultrasound) may be provided to the investigator. In these cases, final study procedures may be performed via telephone and the investigator will enter ultrasound results from the report provided.

**Total Planned number of subjects:** 2,156

**Primary endpoint:** Subject implantation rate is defined as number of intrauterine gestational sacs divided by the number of embryos transferred, as assessed at PET Days 21 to 28.

**Secondary endpoints:**

- Subject pregnancy result (positive/negative) at PET Day 14
- Subject with confirmed ongoing pregnancy (yes/no) at PET Days 70 to 84
- Device incidents

**Key inclusion and exclusion criteria:**

*Inclusion Criteria*

- All infertile women treated with ICSI/FIVET
- $\leq 1$ previous failed embryo transfer
- Eumenorrheic normo-gonadotropic women
- Age $\leq 41$ years of age
- Basal FSH $\leq 12$ IU/L
- AMH $> 1.1$ ng/ml
- Ovarian Reserve: number of antral follicles (2 mm ) between $6 \leq AFC \leq 16$
- Follicles $> 16$ mm at the triggering day between 5-14
- Body Mass Index between $18 \leq BMI \leq 27$ kg/m$^2$
- Indication for Fresh Embryo transfer
- Normal uterine cavity on ultrasound exam (e.g., no presence of hydrosalpinx)
- Undergoing ART and oocyte maturation by HCG triggering
- $P_4$ serum level at the HCG triggering day $\leq 1.5$ ng/mL (Day 0/Randomisation)
- $E_2 \leq 3000$ pg/mL at the HCG triggering day (Day 0/Randomisation)
- Subjects must have read and signed the Informed Consent Form prior to study-specific procedures not part of standard of care

*Exclusion Criteria*

- Clinically significant systemic disease (such as diabetes, metabolic syndrome, immunological diseases, diagnosed thrombophilia, porphyria, or any other medical condition requiring the use of low-molecular weight heparin therapy)
- Polycystic ovary syndrome (PCOS) according to Rotterdam Consensus Criteria (ESHRE/ASRM, 2003)
- Poor ovarian response (POR) according to the European Society of Human Reproduction and Embryology (ESHRE) Criteria
- RIF (repeated implantation failure), defined as ≥ 2 previous failed embryo transfers
- Endometriosis III-IV stage or adenomyosis
- Clinically significant findings on exam or ultrasound, such as salpingitis, hydrosalpynx or evidence of ovarian cysts
- Known hypersensitivity to any of the components of the solution
- Known hypersensitivity to vaginal progesterone or its excipients

**Medical Device:**

Forielle is a Merck Medical Device CE 0546, in the form of a sterile isotonic solution, intended to be used as intrauterine solution for washing and inactivation of the exudates present in the uterine cavity and/or generated during COS in women undergoing fertility treatment with medically assisted reproduction cycles.

**Reference therapy: dose/mode of administration/dosing schedule:** Not Applicable

**Statistical methods:**

**Determination of sample size:**

The main aim of the study is the evaluation of the clinical performance of Forielle in restoring favourable condition of endometrial milieu, after Controlled Ovarian Stimulation. For this purpose, clinical performance will be measured by assessing the difference in implantation rate in the treated arm compared to the control (standard clinical practice). Generally, the average implantation rate of ART is considered of about 25% (Nastri et al. 2013). Several works in the literature suggested the key role of endometrial receptivity on the ART outcomes (Evans et al. 2012). An improvement of about 6% in implantation rate from the usual ART outcome is clinically relevant difference. Thus, for the calculation of sample size, a clinically important difference of 6% was assumed and an interim clinical performance analysis assuming that 2 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries. Sample sizes of 916 each arm achieve 80% power to detect a difference of 0,06 between the group proportions of 0,25 and 0,31 at a significance level (alpha) of 0,050 using a two-sided z-test with continuity correction and allocation ratio of 1:1. The total number of women to be randomised is 2,156, considering a drop-out rate of 15%.

| Target Power | Actual Power | N1 | N2 | N | P1 | P2 | Alpha |
|---|---|---|---|---|---|---|---|
| 0.80 | 0.80025 | 916 | 916 | 1832 | 0.25 | 0.31 | 0.05 |

Details when Spending = O'Brien-Fleming, N1=916, N2=916, P1=0,25, P2=0,31, Continuity Correction.

| Look | Time | Lower Boundary | Upper Boundary | Nominal Alpha | Incremental Alpha | Total Alpha | Incremental Power | Total Power |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.5 | -2.96259 | 2.96259 | 0.003 | 0.003 | 0.003 | 0.16425 | 0.164 |
| 2 | 1 | -1.96857 | 1.96857 | 0.049 | 0.047 | 0.047 | 0.63600 | 0.800 |

The required significance level for stopping the study for clinical performance is 0.003 to first look (50% of patients) and 0.049 at second look (final). The overall power is 80%.

***Statistical Analysis***

As appropriate, variables will be summarized descriptively (frequency and percentage will be summarized for categorical variables; mean, standard deviation [SD], median, and maximum will be presented for continuous variables) by study visit and by treatment group. All study data will be listed by subject. A detailed Statistical Analysis Plan (SAP) including dictionaries used for coding and software used will be prepared separately for interim and final analysis. Study final analysis will be performed by PPD and Interim analysis will performed by a PPD independent statistician from a different geographical region. A firewall will be implemented to ensure interim results will not be accessible to any PPD staff except to the independent statistician who will perform interim analysis.

***Forielle Clinical Performance***

The primary endpoint, subject implantation rate, is defined as number of intrauterine gestational sacs divided by the number of embryos transferred, as assessed at PET Days 21 to 28. Mean subject implantation rate, as assessed at PET Days 21 to 28 in subjects treated with Forielle endometrial washing procedure, will be compared to the mean subject implantation rate in subjects who receive no endometrial washing (control group) following COS.

For the primary endpoint analysis addition to summary statistics, differences in mean subject implantation rate between study procedure and control procedure will be investigated and compared using Gamma/log normal regression model. The analysis model will include treatment procedure as the fixed effect and Embryo Transfer Day (Day 5 PR or Day 7 PR), age, number of follicles at baseline and number of embryos transferred per subject as covariates.

To evaluate the treatment comparison, estimated mean differences will be presented together with two-sided 95% confidence intervals and p-values. Appropriate distribution will be decided based on good ness of fit (residual sum of squares) value. This primary clinical performance endpoint analysis will be tested by planned group sequential design with O'Brien-Fleming type spending function. The study for clinical performance will be stopped at significance level of 0.003 in first (50% of subjects) interim analysis and at significance level 0.049 in final analysis.

***Safety***

Device incidents will be summarized using frequency and percentages for two treatment groups.

## Table 1-1 Schedule of Assessments

| Activity/ Assessment | Screening/ Enrolment Visit (Day -15 to Day -12) | COS (Day -12 to Day 0) | | | Oocyte Retrieval Visit (Day 2 PR) | Embryo Transfer (Day 5PR or Day7PR) [5] | Post Embryo Transfer Day 14 (PET Day 14) | Post Embryo Transfer Days 21 to 28 (PET Days 21-28) [6] | Study Exit Visit (PET Days 70-84/ PET Weeks 10-12) |
|---|---|---|---|---|---|---|---|---|---|
| | | Start of Stimulation (Day -12 to -10) | COS Control (Day -8) | HCG Triggering (Randomisation/ Day 0) | | | | | |
| Informed Consent | X | | | | | | | | |
| Assess Eligibility Criteria | X | X | X | X | | | | | |
| Evaluate hormone levels for eligibility | X | | | X | | | | | |
| Demographics, BMI, Social History | X | | | | | | | | |
| Medical, gynaecological, infertility, and social history | X | | | | | | | | |
| Perform fertility assessments | X | | | | | | | | |
| COS Follicular/Endometrial Assessment | | X | X | X | | | | | |
| HCG injection | | | | X | | | | | |
| Oocyte Retrieval | | | | | X | | | | |
| Endometrial washing (Forielle group) | | | | | X | | | | |
| Device Incident Recording (Forielle group) | | | | | X | X | X | X | X |
| Provide Luteal support | | | | | X | X | | | |
| Perform ICSI (Day 2) and daily embryo evaluation 24 hours after ICSI [2] | | | | | X | | | | |
| Calculate Fertilization Rate [2] | | | | | | X | | | |
| Transfer embryos/blastocysts (≤ 2) | | | | | | X | | | |
| Serum pregnancy test (β-HCG) [3] | | | | | | | X | | |
| Ultrasound [4] | | | | | | | | X | X |
| Study Exit Pregnancy Assessment | | | | | | | | | X |
| Adverse Event Recording | | X | X | X | X | X | X | X | X |
| Record medication use | X | X | X | X | X | X | X | X | X |

**PR: Post Randomisation** **PET: Post Embryo Transfer**

[1] Luteal support should be continued until different clinical indication or discontinued if the subject is determined not to be pregnant (PET Day 14 or PET Days 21 to 28).
[2] The embryology lab will perform these procedures and will be blinded to the endometrial washing procedure (Forielle or no endometrial washing).
[3] Serum β-HCG may be performed by another physician with the report provided to the investigator. In these cases, the PET Day 14 visit may be completed via telephone. If the subject is not pregnant at PET Day 14,telephone visits will be conducted for PET Days 21-28 and PET Days 70-84/Weeks 10-12 and the investigator will enter negative ultrasound results for PET Days 21-28 and PET Days 70-84/Weeks 10-12 ultrasound assessments. If the subject is pregnant at PET Day 14, she must return to the centre at PET Days 21-28.
[4] At PET Days 21-28, transvaginal ultrasound will be performed; at PET Days 70-84, obstetric ultrasound (transvaginal or abdominal) will be performed.
[5] Embryo transfer will occur on Day 5 PR if embryos are transferred in the cleavage stage and will occur on Day 7 PR if embryos are transferred in the blastocyst stage.
[6] If the subject has no gestational sacs present on transvaginal ultrasound at PET Days 21-28, the PET Days 70-84/Weeks 10-12 visit will be a telephone visit and the investigator will enter negative ultrasound results for the PET Days 70-84/Weeks 10-12 ultrasound assessment.
[7] The PET Days 70-84/Weeks 10-12 obstetric ultrasound (transvaginal or abdominal) may be performed by another physician with remaining PET Days 70-84/Weeks 10-12 assessments performed by telephone. In these cases, the ultrasound report must be provided to the investigator and include the following: number of foetuses, confirmation of foetal vitality based on the presence of foetal heartbeat and confirmation of the development of normal pregnancy for each foetus present on ultrasound.

## 2 Sponsor, Investigators, and Trial Administrative Structure

This clinical trial will be sponsored by Merck Serono S.p.A, Italy. The trial will be conducted in at least six (6) sites in Italy. Centres to be used for the trial include sites currently using ART, including public clinical centres, private centres with public authorization and private centres.

The Coordinating Investigator, PPD represents all Investigators for decisions and discussions regarding this trial. The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix I.

The trial will be managed by PPD PPD. Services to be provided by PPD include: project management, trial management and monitoring, data management, safety reporting, start-up, regulatory, biostatistics, and medical writing. Study final analysis will be performed by PPD and Interim analysis will performed by a PPD independent statistician from a different geographical region. A firewall will be implemented to ensure interim results will not be accessible to any PPD staff except to the independent statistician who will perform interim analysis. Merck Serono, S.p.A. Italy will provide Forielle to sites for use in the trial. Forielle will be stored in a refrigerator (2 to 8°C), distributed, resupplied and accounted for by PPD PPD.

Details of structures and associated procedures will be defined in a separate Study Manual, which will be prepared under the supervision of the Clinical Trial Leader.

## 3 Background Information

Implantation is a key step towards a successful pregnancy and it is influenced by several critical factors. The developing embryo has, in each cycle, a narrow window of time suitable for proper implantation, depending on endometrial receptivity. In this short period of time, several changes occur in the endometrium involving both its structure and function (Evans 2012), which are very complex, since endometrium displays a series of periodic transitions, characteristic to this mucosal tissue. These transitions include: rapid proliferation, secretory transformation, physiological angiogenesis, interstitial oedema, and menstrual shedding (Kitaya 2014). As soon as the embryo is implanted, it starts a close interaction with the surrounding endometrial tissue through reciprocal secretions (Evans 2012). In natural reproductive cycles, hormones secretion synchrony with ovulation and embryo migration from Fallopian tubes to uterus lumen increases the possibility that endometrium becomes receptive when the embryo reaches it. In ART, the time for transferring the embryo in the uterus depends on the achievement of an appropriate stage of blastocyst development, regardless of endometrium receptivity. On top of embryo

transfer possibly outside the implantation window, another issue that makes implantation in ART very challenging is the impact of ovarian stimulation on endometrial receptivity.

Major lines of evidence confirmed that ovarian stimulation reduces endometrial receptivity, even if, recently, some authors reported that this happens only in high responders, while in low and average responders it does not (Yeh 2014). Starting from genes expression (Blockeel 2011; Mariee 2012; Haouzi 2014) to histology (Evans 2012; Li 2013), from immunologic mechanisms (Evans 2012) to vascularity (Kim 2014), transcriptomics (Haouzi 2009; Detti 2011; Blesa 2014; Díaz-Gimeno 2014), proteomic (Garrido-Gómez 2014) and secretomic (Hannan 2010; Cheong 2013; Galliano 2014), all these aspects of endometrium biology may affect its receptivity in ART cycles. As a result, Garcia-Flores et al. (Garcia-Flores 2013) found that some patients have a delayed window of implantation, others have an advanced one, and others show unusually short windows of receptivity. This problem has been hypothesized to be related with a particular pattern of progesterone and estrogen receptors expression, found in oocyte donors during an ART cycle (Detti 2011) and other authors, more recently, confirmed these evidences (Tapia-Pizzarro 2014). Thin endometrium is a problem often related to implantation failure and its assessment and management have been proposed as approaches aimed at improving pregnancy rates (Lebovitz 2014) in ART, even if some authors published data that contradicted this argument (Gingold 2014). Revel et al. and Evans et al. suggested a role for MicroRNAs as diagnostic markers and therapeutic tools for implantation disorders in ART (Revel 2011; Evans 2012), while a well-established line of research studied profiles of genes expression related to endometrium receptivity. In particular, HOXA-10, leukemia inhibitory factor, and cleavage stimulation factor genes expression has been showed to correlate with endometrium receptivity and with clinical pregnancy as well (Garcia-Flores 2013). Moreover, Sak et al., comparing fibroblast growth factor-1 (FGF-1) gene expression in patients who underwent in vitro fertilization (IVF) and had repeated implantation failure, with fertile patients, found that the expression of this gene was reduced in patients and concluded that growth factors, such as FGF-1, could be relevant in promoting implantation (Sak 2013). Other authors found that IL-15 expression is related to higher risk of implantation failure (Mariee 2012). On the other hand, Boomsma et al., in 2009, already showed that changes in cytokines profile expression in endometrial aspirates was so characteristic in stimulated cycles, that assessment of these modifications were proposed as a marker of endometrial receptivity (Boomsma 2009). Aflatoonian et al. in 2014 reviewed the negative effects of some of these proteins and cytokines on implantation (Aflatoonian 2014). Changes in genes expression induced by ovarian stimulation protocols depend even on the protocols used. In fact, some authors found that with GnRH antagonist the profile of genes expression related to endometrial receptivity is more similar to the one of natural cycles, compared with GnRH agonist protocols (Haouzi 2010). These findings contradicted previous studies that emphasized the negative effects of GnRH antagonists on endometrium receptivity (Rackow 2008).

In recent years, a specific test has been developed, based on the analysis of expression of 238 genes, coupled to a computational predictor, capable of diagnosing a functionally receptive endometrium, regardless of its histological appearance (Ruiz and Simon 2014). Among the molecules secreted in the endometrial fluid, PGE2 and PGF2α are so strictly related to the window of implantation, that have been proposed as biomarkers of human embryonic

implantation (Vilella 2013). In a tissue that undergoes profound transformations in each menstrual cycle and where a complex interaction with the embryo develops, peaks of superoxide radicals are envisaged and, in the normal human endometrium, Superoxide Dismutase (SOD) concentration increases in the mid-secretory phase, during the preimplantation period (Shavell 2012). SOD is an antioxidant with isoforms detected in the cytosol (SOD1), mitochondria (SOD2), and extracellular matrix (SOD3). It scavenges superoxide radicals that cause tissue damage (Du Plessis 2008). Shavell et al. revealed increases of SOD3 levels and worsening of oxidative stress state in the endometrium during the pre-implantation period in women who underwent ovarian stimulation (Shavell 2012). Oxidative stress is involved in all steps of reproductive function: from oocytes maturation to follicles developments, from embryo early life to endometrial receptivity (Du Plessis 2008). Evaluating endometrial biopsies collected in pre-receptive and receptive phase, differences were found in expression of genes related to mechanisms aimed at free radicals scavenging (Riesewijk 2003).

An aspect that remains to be elucidated is the role of inflammation and repair mechanisms in implantation. Several studies suggested that mechanical damages induced in the endometrium, increase implantation rate and, overall, ART procedures outcomes (Gnainsky 2010; Nastri 2013; Buzzi 2014; Gnainsky 2015). In a review by Dekel et al. it has been hypothesized that the injury-derived inflammation stimulates dendritic cells that, in turn, enhance, in the endometrium, the expression of mediators that facilitate the interaction between the embryo and the uterine epithelium (Dekel 2014). Besides, more recently, Melnick et al. and Werner et al. found that endometrial biopsy didn't impact on endometrial receptivity, in a particular subgroup of patients that have failed to sustain the transfer of morphologically normal euploid embryos, suggesting that variations in endometrial injury technique may alter outcomes (Melnick 2014; Werner 2015). Finally, other authors pointed out the need to clarify aspects of this approach such as patient selection, timing, technique and number of endometrial biopsies needed (Ashrafi et al. 2014).

Uterine cavity washing has been used successfully to remove different kinds of molecules located in the lumen and of the endometrium surface: many papers illustrated how complete and accurate the collection of these substances was. Designing a device aimed at washing potentially detrimental compounds from uterine cavity, it was important to include in the lavage solution components aimed at inactivating that compounds while they are washed away. Methionine, arginine and melatonin have been carefully selected referring to the action that they showed in many experiments in vitro and in vivo. Robust evidences support the direct scavenging effect of methionine and melatonin and the stabilizing effect of arginine, in particular on proteins and other molecules that are expected to be collected by the lavage. All these available information corroborate Forielle clinical performance and reason to use in the routine of assisted reproductive technique with the aim to remove possible altered exudate and to restore condition favourable to embryo implantation.

## 3.1 Benefit-Risk Assessment

The analysis of the risks and benefits of Forielle demonstrated that Forielle met its safety and clinical performance requirements and the device fulfilled its intended use as claimed by Ares

Trading S.A.. Following is a description of potential (expected) risks and benefits that may be associated with the use of Forielle. Forielle received the CE marking as a class IIa medical device.

### 3.1.1 Risks Related to Forielle

The Risk Analyses (Product Risk Analysis, Human Factor Risk Analysis and Clinical Risk Analysis) conducted during the whole product lifecycle process to establish the safety and the clinical performance of Forielle have not evidenced and not identified any Human factor and Clinical risks, the residual Product Risk was determined acceptable based on risk benefit analyses Product risk, identified as medium or low level, is related to device sterility that could be impacted during Medical Device Production. The related contingency plan was set as per Good Manufacturing Practice (GMP) for Sterile Product.

### 3.1.2 Benefits of Forielle

No market feedback data currently support directly and objectively the clinical performance benefit of Forielle, due to fact that this device has to be introduced into the market for the first time in the field of Fertility therapeutic area. Indirect evidence, from equivalent solution and equivalent methodology, suggests that Forielle might benefit patients and medical professionals by improving the environmental conditions and facilitating interventions for the preparation of the ART. This study is being conducted in order to determine the extent of beneficial effects and to confirm the clinical safety of Forielle use in standard clinical practice.

## 4 Trial Objectives

### 4.1 Primary Objective

The primary objective of this study is to evaluate the implantation rate increase in women undergoing Assisted Reproductive Technique (ART) by using Forielle, an endometrial wash that restores favourable conditions of endometrial "milieu" after Controlled Ovarian Stimulation (COS).

### 4.2 Secondary Objectives

The secondary objectives of the study are to:

- Determine the Pregnancy Rate at PET Day 14
- Determine the Ongoing Pregnancy Rate during PET Days 70 to 84
- Assess the safety of Forielle by report of device incidents

# 5 Investigational Plan

## 5.1 Overall Trial Design and Plan

This is a multicentre, prospective randomised controlled, interventional investigation to assess the safety and clinical performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during ART.

The study protocol consists in assessing the clinical performance of Forielle in restoring favourable condition of endometrial milieu after COS. Clinical Performance will be measured by comparing implantation rate in the treated arm compared to the control. The trial aims to enrol 2,156 women from at least six centres in Italy.

Infertile females aged ≤ 41 years with no more than one previous implantation failure will be assessed for eligibility for the trial after providing written informed consent. Subjects will under COS according to standard of care clinical practice. There is no limitation in the gonadotrophin stimulation protocols used; however, triggering must be done with HCG. Eligible subjects will be randomised to receive either the intervention (Forielle endometrial washing) or no endometrial washing following oocyte retrieval on Study Day 0, the HCG Triggering day, in a 1:1 ratio. Oocyte retrieval and endometrial washing (Forielle-treated group) will occur during the same surgical procedure. The entire ART cycle will be performed according to clinical practice of the centre based on each subject's clinical profile.

Retrieved oocytes will be fertilized per ICSI standard clinic practice and the embryology lab will calculate the fertilization rate for each subject. Beginning approximately 24 hours after ICSI, the embryology lab will evaluate embryo for quality daily, with the most viable embryos selected for implantation (Day 5 PR for embryos transferred in the cleavage stage and Day 7 PR for embryos transferred in the blastocyst stage).

Luteal support/endometrial preparation will be done with progesterone (100 mg intramuscular injection at the Oocyte Pick Up [OPU] day and 600 mg of vaginal progesterone from the day after OPU and administered daily). At the Embryo Transfer visit (Day 5 PR or Day 7 PR), a maximum of 2 fertilized embryos or blastocysts will be transferred; luteal support (daily administration of 600 mg of vaginal progesterone) will continue.

All subjects must have a serum β-HCG pregnancy test performed 14 days after embryo transfer (PET Day 14). Subjects may have this assessment performed by another physician; however, the pregnancy test report must be provided to the investigator. In these cases, all other PET Day 14 assessments may be performed with the subject via telephone.

If the PET Day 14 serum β-HCG pregnancy test is negative, the PET Days 21-28 and PET Days 70-84/Weeks 10-12 visits may occur by telephone with the PET Days 70-84/Weeks 10-12 visit serving as the final study contact. In these cases, the PET Days 21-28 visit and PET Days 70-84 visits may be performed via telephone and the investigator will enter negative ultrasound results for ultrasound assessments that would have been performed at PET Days 21-28 and PET Days 70-84.

If the PET Day 14 serum β-HCG pregnancy test is positive, the subject must return to the site 21 to 28 days after embryo transfer (PET Days 21-28), to determine the number of gestational sacs present and calculate the implantation rate, the primary endpoint. The primary endpoint, the subject implantation rate, is defined as the number of intrauterine gestational sacs divided by the number of embryos transferred.

If the subject returns to the site on PET Days 21-28 for transvaginal ultrasound and does not have any gestational sacs present, the investigator will enter a negative result for the PET Days 70-84/Weeks 10-12 obstetric ultrasound (transvaginal or abdominal). In these cases, the PET Days 70-84/Weeks 10-12 final study visit may occur by telephone.

Subjects who return to the site at PET Days 21-28 and have gestational sacs present on transvaginal ultrasound will have a final obstetric ultrasound (transvaginal or abdominal) on PET Days 70-84/Weeks 10-12 to verify the Ongoing Pregnancy Rate (OPR). In the event a subject cannot return to the site for the PET Days 70-84/Weeks 10-12 visit, ultrasound report confirming ongoing pregnancy details required (number of foetuses, confirmation of foetal vitality based on the presence of foetal heartbeat and confirmation of the development of normal pregnancy for each foetus present on ultrasound) may be provided to the investigator. In these cases, final study procedures may be performed via telephone and the investigator will enter ultrasound results from the report provided.

## 5.2 Discussion of Trial Design

The prospective, randomised design selected for this trial was defined based on the need to assess the clinical performance and the safety of Forielle in clinical practice setting by collecting real-life clinical data of Forielle use endometrial washing and comparing them to a control (no endometrial washing) in restoring favourable endometrial conditions. Implantation rate is defined as an appropriate endpoint to evaluate endometrial receptivity; indeed, additional downstream steps to implantation rate assessment are strongly affected by embryo quality and health besides endometrial receptivity. This study is being conducted as a commitment agreed upon with the Certifying Body during the CE Mark authorization procedure.

## 5.3 Selection of Trial Population

Only potential subjects meeting all eligibility criteria may be randomised to participate in the trial. Prior to performing any study assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

### 5.3.1 Inclusion Criteria

To be included in the study, potential subjects must meet the following inclusion criteria:

- All infertile women treated with ICSI/FIVET
- ≤ 1 previous failed embryo transfer
- Eumenorrheic normo-gonadotropic women

- Age ≤ 41years of age
- Basal FSH ≤12 IU/L
- AMH > 1.1 ng/ml
- Ovarian Reserve: number of antral follicles (> 2 mm ) between 6 ≤ AFC ≤ 16
- Follicles > 16 mm at the triggering day between 5-14
- Body Mass Index between 18 ≤ BMI ≤ 27 $kg/m^2$
- Indication for Fresh Embryo transfer
- Normal uterine cavity on ultrasound exam (e.g., no presence of hydrosalpinx)
- Undergoing ART and oocyte maturation by HCG triggering
- $P_4$ serum level at the HCG triggering day ≤ 1.5 ng/mL (Day 0/Randomisation)
- $E_2$ ≤ 3000 pg/mL at the HCG triggering day (Day 0/Randomisation)
- Subjects must have read and signed the Informed Consent form prior to study-specific procedures not part of standard of care

### 5.3.2 Exclusion Criteria

If any of the following exclusion criteria are met, potential subjects may not participate in the trial:

- Clinically significant systemic disease (such as diabetes, metabolic syndrome, immunological diseases, diagnosed thrombophilia, porphyria, or any other medical condition requiring the use of low-molecular weight heparin therapy)
- PCOS according to Rotterdam Consensus Criteria (ESHRE/ASRM, 2003)
- POR according to ESHRE Criteria
- RIF, defined as ≥ 2 previous failed embryo transfers
- Endometriosis III-IV stage or adenomyosis
- Clinically significant findings on exam or ultrasound, such as salpingitis, hydrosalpynx or evidence of ovarian cysts
- Known hypersensitivity to any of the components of the solution
- Known hypersensitivity to vaginal progesterone or its excipients

## 5.4 Criteria for Initiation of Trial Treatment

Potential subjects will provide written informed consent at a screening visit and then undergo approximately 10 to 12 days of COS, following standard of care for women undergoing ART for infertility. Once the potential subject has met standard practice criteria for oocyte maturation (Day 0) and all other eligibility criteria, she will be randomised in a 1:1 ratio to receive Forielle (endometrial washing) or no endometrial washing after oocyte retrieval and will undergo HCG triggering (Day 0/Randomisation). Subjects who do not meet the eligibility criteria will not be included in the study and will continue the IVF cycle as standard clinical practice of the Centre.

Following standard of care, the subject will return to the site for oocyte retrieval approximately 2 days after HCG triggering. After oocytes are retrieved, the subject will receive endometrial washing with Forielle or no endometrial washing, per the randomisation schedule. Although the subject and the investigator will be aware of the subject's randomisation and endometrial washing condition, the embryology lab performing ICSI will not be aware of the endometrial washing condition and randomisation schedule. Potential subjects who do not meet the hormonal requirements for HCG triggering and a fresh embryo transfer (E2 > 3000 pg/ml; $P_4$ > 1,5 ng/ml) will be considered a screening failure, will not be randomised into the study and will continue the IVF cycle as standard clinical practice of the Centre.

## 5.5 Criteria for Subject Withdrawal

The Investigator will make every reasonable attempt to complete the study. Subjects may be withdrawn from the study at any time for reasons including the following:

- Due to adverse event or device incident
- At their own request (withdrawn consent)
- Lost to follow-up (every effort will be made to ensure subjects return for Study Exit procedures in the event of early termination)
- If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being; or
- At the specific request of the Sponsor

In all cases, the reason for withdrawal will be recorded in the subject's electronic case report form (eCRF). If the reason is not known, attempts to contact the subject will be made to establish the reason for withdrawal. Every effort will be made to complete all examinations scheduled for the study follow-up visit for all subjects who participate in the study, but who do not complete the study according to the protocol. If the dropout rate exceeds 15%, replacement subjects may be required.

Note: negative ultrasound results will be entered into the eCRF for ultrasound assessments that would have occurred if the subject had been pregnant at the time of a planned visit. In these cases, the subject's final study assessment of adverse events, concomitant medications and device incidents may occur prior to the date of the recording of ultrasound result.

## 5.6 Premature Stopping of the Trial

The study is planned to stop early for significant clinical performance evidence based on interim analysis evaluated 50% of patients using group sequential design O'Brien-Fleming spending function. Prospective interim analyses will be conducted by an independent statistician as part of a group sequential design as described in Section 8. Based on the interim finding, the DMC recommend to stop the subject enrolment early for clinical performance considerations or to continue the study as planned. No further results of the interim analysis will be made available by the DMC until final analysis is done..

The trial may be prematurely discontinued or suspended at the request of Competent Authorities or if new information leads to an unfavourable risk benefit judgement for the investigational device. The sponsor may prematurely discontinue the trial if it becomes unjustifiable for medical or ethical reasons, due to enrolment issues, recalls and/or product issues associated with the use of Forielle. If the trial is prematurely discontinued, Competent Authorities and Independent Ethics Committees (IECs) will be informed in accordance with applicable regulations.

## 5.7 Definition of End of Trial

This clinical trial protocol may not be considered closed as long as visits specified by the protocol are still taking place and/or procedures or interventions are still being undertaken in any subject.

For subjects who are not pregnant at PET Day 14, the PET Days 21-28 and PET Days 70-84/Weeks 10-12 visits may occur by telephone, with negative ultrasound results entered for the ultrasound assessments that would have been performed at these visits. In this cases, the PET Days 70-84/Weeks 10-12 telephone visit will be the last study contact.

Subjects who are pregnant at the PET Day 14 visit will return to the centre at PET Days 21-28 for transvaginal ultrasound and pregnancy confirmation. If no gestational sacs are present at PET Days 21-28, negative ultrasound results will be entered for the PET Days 70-84/Weeks 10-12 obstetric ultrasound (transvaginal or abdominal) and the study exit visit at PET Days 70-84/Weeks 10-12 visit will be a telephone visit.

Subjects who have a confirmed pregnancy at PET Days 21-28 will have a final obstetric ultrasound (transvaginal or abdominal) performed at PET Days 70-84/Weeks 10-12 to confirm ongoing pregnancy. Subjects may have this assessment performed by another physician; however, ultrasound report confirming ongoing pregnancy details (number of foetuses, confirmation of foetal vitality based on the presence of foetal heartbeat and confirmation of the development of normal pregnancy for each foetus present on ultrasound) must be provided to the investigator and all other study assessments at PET Days 70-84 performed via telephone.

# 6 Medical Device and Other Drugs Used in the Trial

## 6.1 Description of the Medical Device

Forielle is a Class IIa medical device according to rule 5, paragraph 2.1of Annex IX of European Directive 93/42 EEC as amended by 2007/47/EC. The Notified Body chosen for the conformity assessment is Certiquality, identification number 0546. Forielle obtained the CE mark on 29 December 2015. The use of Forielle in this clinical trial is fully conform to the released authorization and the approved Instructions for Use (IFU).

Forielle is a single-use medical device in the form of sterile water solution in a prefilled glass syringe. Forielle is designed to perform a uterine washing with lavage and dilution of endometrial secretions present in the uterus or produced during COS in medical assisted

reproduction cycles, such as intrauterine insemination, IVF, intra-cytoplasmic sperm injection (ICSI), zygotes intra-fallopian transfer, gametes intra-fallopian transfer.

Forielle washes and dilutes oxidizing substances, cytokines, proteins, and enzymes that may be detrimental for embryo implantation in stimulated or natural cycles by irrigation of the endometrial wall. The purpose of the medical device is that of washing oxidizing substances, cytokines, proteins, and enzymes secreted in response to the ovarian stimulation preceding the ART techniques and thus helping to restore the physiological composition of the endometrial exudate. The objective is reducing the impact of such oxidizing substances and secreted products on embryo implantation in women undergoing ART. The use of buffer salts and amino acids is provided for setting a pH comprised between 7-8, preferably between 7.5 and 7.8, for replicating the uterine micro-environment suitable for the embryo. The addition of melatonin and methionine exerts an antioxidant effect and a protective action versus endometrial cells, towards the oxidative damage due to toxic radicals and other catabolic products. Moreover, arginine has been added mainly for its anti-aggregative action on proteins.

### 6.1.1 Syringe and connector

Forielle is contained in a 3 mL pre-filled borosilicate glass syringe with conical lock fittings (male Luer lock), and plunger stopper and plunger rod filled with 2.7 mL of solution to deliver at least 1.5mL. The pre-filled syringe shall be connected to any intra-uterine flexible catheter with single terminal hole (Luer lock female) by the health care specialist.

### 6.1.2 Components Properties

Components are aimed at facilitating the endometrial secretion elimination and neutralization:

- N-acetyl-5-methoxytryptamine
- L-methionine
- L-Arginine HCl
- NaCl
- Phosphate
- Polysorbate 20
- WFI q.s to final volume

## 6.2 Dosage and Administration

Forielle is intended to wash and dilute the uterine secretions that are produced after COS which may create an unfavourable environment for embryo implantation. The Forielle medical device is intended for intra-uterine use in women during medically assisted reproduction and ovulation induction cycles. It is only to be used by qualified medical professionals operating in assisted reproduction centres.

## 6.3 Assignment to Treatment Groups

Subjects will be randomised in a 1:1 ratio to receive endometrial washing with Forielle or no endometrial washing (control group); randomised subjects will be stratified by age (< 32 years of age; 32 to 37 years of age; 38 to 41 years of age) and number of follicles >16 mm (5 to 9 follicles >16 mm; 10 to 14 follicles >16 mm). Although the subject and the investigator and site staff will be aware of the endometrial washing condition, the embryology lab will be blinded to the randomisation procedure and will not know the endometrial washing condition.

## 6.4 Non-investigational Medicinal Products to be Used

Oocyte maturation may only be completed by HCG, other methods for triggering oocyte maturation will not be allowed. Vaginal Progesterone (600 mg) will be the only luteal support therapy allowed from the Day after Oocyte retrieval visit (Day 2 PR).

## 6.5 Concomitant Medications and Therapies

All medications taken by the subject during the trial, from the date of signature of informed consent to the study exit visit, are to be recorded in the appropriate section of the CRF, noting the name, dose, duration, and indication of each drug. Changes to a concomitant medications and other interventions that are not considered standard of care procedures for women undergoing ART should be recorded in the CRF. Standard of care procedures for ART (e.g., $E_2$, $P_4$, HCG oocyte retrieval, luteal support) will not be recorded as concomitant therapies and medications.

### 6.5.1 Permitted Medicines

Subjects will be instructed to check with their physician to ensure that any medications taken during the study are safe for women who are pregnant. All medications used will be recorded in the case report form.

### 6.5.2 Prohibited Medicines

There are no medications contraindicated for use with this medical device; however, if a subject has any medical condition that requires the use of low-molecular weight heparin, she should not be enrolled into the study. Subjects will be instructed to check with their physician to ensure that any medications taken during the study are safe to use during pregnancy.

### 6.5.3 Other Interventions

Subjects will follow standard of care instructions for women undergoing ART.

### 6.5.4 Special Precautions

No additional precautions are necessary for the subjects to undertake during this study.

### 6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

There are no adverse events expected with the use of this device except hypersensitivity to the Forielle components, as indicated in the IFU. If hypersensitivity to Forielle occurs, the Investigator will follow the IFU and standard of care treatment.

## 6.6 Packaging and Labelling of the Medical Device

Forielle will be packaged and labelled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

## 6.7 Preparation, Handling, and Storage of the Medical Device

Prior to shipment to the investigative centre, Forielle will be stored in a secure, limited-access, temperature-controlled refrigerated storage area of PPD PPD. Once Forielle is sent to the study centre, the centre must store Forielle in a locked, refrigerated area with access limited to study personnel. Forielle usage instructions and required storage conditions will be provided to the centre in a detailed pharmacy manual.

## 6.8 Medical Device Accountability

The Investigator is responsible for ensuring Forielle accountability, including reconciliation of the medical device, and maintenance of records.

- Upon receipt of Forielle, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialling and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Forielle dispensing will be recorded on the appropriate device accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial site Forielle accountability records will include the following:
  - Confirmation of Forielle receipt, in good condition and in the defined temperature range
  - The inventory of Forielle provided for the clinical trial and prepared at the site
  - By-subject accountability of Forielle used
  - The disposition of all unused Forielle
  - Dates, quantities, batch numbers, expiry dates, and the individual subject trial numbers

The Investigator site should maintain records which adequately document the investigational product details of Forielle received by subjects randomised to the Forielle procedure. Unused Forielle must not be discarded or used for any purpose other than the present trial. A Trial Monitor will verify Forielle accountability records.

## 6.9 Assessment of Medical Device Compliance

Not applicable due to the nature of the study design (e.g., medical device will be used once under the direction of the investigator).

## 6.10 Blinding

The subject, the investigator and site staff will be aware of the endometrial washing condition; however, the embryology lab will be blinded to the randomisation procedure and will not know the endometrial washing condition when preparing and/or evaluating embryos.

## 6.11 Emergency Unblinding

Not applicable; although the embryology lab will be blinded to the use of Forielle, it is not anticipated unblinding of the embryology lab would need to occur in any situation.

## 6.12 Treatment of Overdose

Due to the nature of the study design and Forielle packaging, overdose is not applicable.

## 6.13 Medical Care of Subjects after End of Trial

The Sponsor will not provide any additional care to subjects after they leave the trial as such care should not differ from what is normally expected for women undergoing ART.

# 7 Trial Procedures and Assessments

This is a multicentre, prospective, randomised, controlled, interventional investigation to assess the safety and clinical performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during ART.

## 7.1 Schedule of Assessments

Table 1-1 presents the Schedule of Assessments. A summary of assessments and procedures to be performed at each study visit is described in detail in the following sections.

### 7.1.1 Screening Visit (Day -15 to -12)

The screening visit should occur 15 to 12 days prior to the anticipated randomisation date (HCG Triggering Day). The following assessments and procedures will be performed at Screening:

- Potential subjects will provide written informed consent prior to any study-specific procedures
- Record demographics (age, race, ethnicity), weight and height to calculate BMI

- Record medical history, gynaecological history, infertility history, and social history (alcohol, tobacco and illicit drug use)
- Perform standard of care fertility assessments (e.g., measure ovarian reserve markers, assess fallopian tube patency, seminal liquid parameters, thyroid functioning)
- Local laboratory evaluation of eligibility labs (see Inclusion and Exclusion criteria)
- Record the use of any pre-study medications
- Assess eligibility and schedule COS Start of Stimulation Visit (Day -12 to Day -10)

### 7.1.2 Controlled Ovarian Stimulation Visits (Days -12 to Day 0)

COS will be performed over the course of three clinic visits. The following procedures and assessments will occur at each of the COS visits.

#### 7.1.2.1 Start of Stimulation (Day -12 to Day -10)

COS will begin approximately 10 to 12 days prior to HCG Triggering (Randomisation/Day 0). Potential subjects will present to the study site and the following assessments and procedures will occur at the start of COS:

- Follicular assessment, to include follicle counts, measure of the follicles overall size (two diameters of circumference required)
- Endometrial assessment, to include measurement of endometrial thickness
- Record adverse events and concomitant medications
- Verify continued eligibility and schedule COS Control Visit (Day -8)

#### 7.1.2.2 Stimulation Control (Day -8)

Potential subjects will return to the study site approximately 2 days after the start of stimulation (Day -8) for a COS Control Visit. At the COS control visit, the following assessments and procedures will occur:

- Follicular assessment, to include follicle counts, measure of the follicles overall size (two diameters of circumference required)
- Endometrial assessment, to include measurement of endometrial thickness
- Record adverse events and concomitant medications

#### 7.1.2.3 HCG Triggering/Randomisation (Day 0)

Based on standard of care hormone level monitoring, potential subjects will return to the study site for follicular assessment and hormone level assessment to verify eligibility. If potential subjects meet the follicle requirements and required $E_2$ and $P_4$ levels, they will be randomised into the study and HCG triggering will occur. At the HCG Triggering/Randomisation (Day 0) visit, the following assessments and procedures will occur:

- Follicular assessment; confirm number of follicles > 16mm (between 5 and 14 required in order to proceed with patient eligibility); if follicular requirements are not met, potential subjects will not be randomised and will be considered a screen failure even if they continue the IVF cycle as standard clinical practice of the Centre.
- Ensure hormone levels ($E_2$ and $P_4$) meet eligibility criteria required for HCG triggering; if hormone levels for eligibility are not met, the potential subject will not be randomised and will be considered a screen failure even if they continue the IVF cycle as standard clinical practice of the site
- Randomise subject to receive endometrial washing procedure with Forielle or no endometrial washing (control group) at the Oocyte Retrieval Visit
- Administer HCG (based on standard of care procedures)
- Record adverse events and concomitant medications
- Schedule Oocyte Retrieval Visit (Day 2 PR)

### 7.1.3 Oocyte Retrieval Visit (Day 2 Post Randomization)

Subjects will return to the site approximately 34-36 hours after HCG triggering for oocyte retrieval and, when applicable based on randomisation, endometrial washing with Forielle for the Day 2 Post Randomisation (PR) visit. The following assessments and procedures will occur at the Oocyte Retrieval Visit (Day 2 PR):

- Oocyte retrieval (based on standard of care practices)
- Subjects randomised to Forielle will undergo endometrial washing per the Forielle IFU
- Provide luteal support/endometrial preparation (with 100 mg of intramuscular progesterone)
- Record adverse events, device incidents and concomitant medications
- Embryology lab will perform ICSI on oocytes retrieved
- Approximately 24 hours after ICSI, the embryology lab will perform daily embryo culture assessments to determine the embryo vitality and fertilization rate.
- The Embryology lab with the Doctor will determine how many embryos will be transferred and at which stage (e.g., either Day 5 PR or Day 7 PR), based on standard laboratory and clinical parameters. Definition of Embryo Transfer Visit should occur at this time point

### 7.1.4 Embryo Transfer Visit (Day 5 or Day 7 Post Randomization)

Subjects will return to the site 3 to 5 days after oocyte retrieval for embryo transfer. If the embryologist determines the embryos should be transferred at the cleavage stage, embryo transfer will occur on Day 5 Post Randomization. If the embryologist determines the embryos should be transferred at the blastocyst stage, embryo transfer will occur on Day 7 Post Randomization.

The following procedures will occur at the Embryo Transfer Visit:

- Embryo transfer (maximum of 2 embryos will be transferred); if no embryos are available for transfer, the subject will exit the study and study exit procedures, as applicable, will be performed
- Provide luteal support/endometrial preparation (600 mg vaginal progesterone to be used daily from the day after Oocyte Pick Up day)
- Calculate the fertilization rate (number of zygotes divided by the number of mature (MII) oocytes inseminated)
- Record adverse events, device incidents and concomitant medications
- Schedule the Post Embryo Transfer Visit 1 (Day 14 Post Embryo Transfer)

### 7.1.5 Post Embryo Transfer Day 14 Visit (PET Day 14)

The following study assessments will be performed 14 days after embryo transfer at the Post Embryo Transfer (PET) Day 14 visit:

- Serum β-HCG pregnancy test
- Record adverse events, device incidents and concomitant medications

Serum β-HCG pregnancy test may be performed by another physician; however, the pregnancy test report must be provided to the investigator. In these cases, all other PET Day 14 assessments may be performed via telephone.

If the serum β-HCG pregnancy test is negative at PET Day 14, luteal support will be discontinued and the investigator will enter negative ultrasound results for ultrasound assessments that would have been performed at the PET Days 21-28 and PET Days 70-84/Weeks 10-12 visits.

If the serum β-HCG pregnancy test is positive at PET Day 14, luteal support will continue, remaining PET Day 14 assessments will be performed and the subject will be instructed to return to the centre for the PET Days 21-28 visit.

### 7.1.6 Post Embryo Transfer Days 21 to 28 Visit (PET Days 21-28)

Subjects with a negative serum β-HCG pregnancy test at PET Day 14 will be contacted via telephone 21 to 28 days after embryo transfer for the PET Days 21-28 visit. During this telephone visit, adverse events, device incidents and concomitant medications will be recorded. The investigator will ensure negative ultrasound results are recorded for ultrasound assessments that would have been performed at PET Days 21-28 and PET Days 70-84/Weeks 10-12.

Subjects with a positive serum β-HCG pregnancy test at PET Day 14 will return 21 to 28 days after embryo transfer for the PET Days 21-28 visit. At this visit, the following procedures will occur:

- Confirm pregnancy via transvaginal ultrasound
- Record the number of gestational sacs present
- Record adverse events, device incidents and concomitant medications
- Schedule the PET Days 70-84/Weeks 10-12 visit

For subjects with no gestational sacs present on transvaginal ultrasound at PET Days 21-28, the investigator will enter a negative result for the PET Days 70-84/Weeks 10-12 obstetric ultrasound (transvaginal or abdominal) and the study exit visit at PET Days 70-84/Weeks 10-12 will be a telephone visit.

### 7.1.7 Post Embryo Transfer Days 70-84/Weeks 10-12 (Study Exit)

The study exit visit will occur 70 to 84 days (10 to 12 weeks) after embryo transfer. For subjects who are not pregnant at the PET Days 14 or PET Days 21-28 visits, the Days 70-84/Weeks 10-12 visit will be a telephone visit to record adverse events, device incidents, and concomitant medications. The investigator will ensure negative ultrasound results are entered for ultrasounds that were not performed due to the subject not being pregnant.

For subjects with an ongoing pregnancy at the PET Days 21-28 visit, the following assessments will occur at the visit PET Days 70-84/Weeks 10-12 visit:

- Confirm ongoing pregnancy via obstetric ultrasound (transvaginal or abdominal)
- Confirm the number of foetuses, confirm foetal vitality based on the presence of foetal heartbeat(s) and confirm the development of normal pregnancy (assessments to be made for each foetus present on ultrasound)
- Record adverse events, device incidents and concomitant medications

In the event a subject cannot return to the site for the PET Days 70-84 visit, ultrasound report confirming ongoing pregnancy details required (number of foetuses, confirmation of foetal vitality based on the presence of foetal heartbeat and confirmation of the development of normal pregnancy for each foetus present on ultrasound) may be provided to the investigator. In these cases, final study procedures may be performed via telephone and the investigator will enter ultrasound results from the report provided.

## 7.2 Demographic and Other Baseline Characteristics

At screening, demographics (age, race, ethnicity), BMI, medical history, gynaecological history, infertility history, social history (alcohol, tobacco and illicit drug use), gynaecological exam, and fertility assessment will be performed.

## 7.3 Clinical Performance Assessments

Clinical Performance of Forielle will be determined by comparing the implantation rate in subjects receiving endometrial washing with Forielle after oocyte retrieval compared to subjects

who receive no endometrial washing after oocyte retrieval. Clinical performance is defined as behavior of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s). The primary endpoint of the study is the subject implantation Rate, defined as the number of intrauterine gestational sacs divided by the number of embryos transferred. Additional Forielle clinical performance assessments include the number of pregnancies continuing past the first trimester of pregnancy.

Serum samples will be collected for Estradiol ($E_2$) and Progesterone ($P_4$) at the HCG Triggering day to be analysed locally by the centre for the purposes of confirming eligibility criteria (serum $P_4 \leq 1.5$ ng/mL and $E_2 \leq 3000$ pg/ml). If potential subjects do not meet $E_2$ and $P_4$ eligibility criteria, they will be considered screen failures and will not undergo HCG triggering and randomisation within the protocol study conditions. Each site will collect an extra serum sample for $P_4$ evaluation to be carried out by the central laboratory (PPD ) to validate local laboratory evaluation of $P_4$ retrospectively to verify subject eligibility and inclusion in planned analyses.

## 7.4 Assessment of Safety

Safety of Forielle will be assessed through the recording and reporting of medical device incidents.

In addition, any Adverse Event (AE) or Serious Adverse Event (SAE) related to the conduct of the study that would occur in a subject participating in the clinical trial will be recorded and reported through AE CRF. The analysis of these AEs/SAEs should be used to update the Forielle Risk Assessment as well as Instruction For Use.

Of note, given the design of this study and the reporting period for safety surveillance, assessment of serious adverse device effects in offspring of subjects participating in the clinical trial is not applicable (see Section 7.4.1).

### 7.4.1 Definition of the Safety Surveillance Reporting Period

The reporting period for overall safety surveillance begins when the subject is included in the clinical trial (date of first signature of informed consent) and continues through the Study Exit (PET Days 70-84/Weeks 10-12). Differences in the recording and assessment of AEs related to the conduct of the study and medical device incidents may be found in Sections 7.4.2.3 and 7.4.3.2, respectively. There is no pregnancy follow-up planned in the study. Hence, any abnormal pregnancy outcome and/or congenital anomaly/birth defect that would be reported to the Sponsor by the investigator will be collected, processed and followed-up by the Sponsor's Global Drug Safety Department as a spontaneous case report

### 7.4.2 Clinical Trial Adverse Events

AEs related to the conduct of the study will be recorded as described below.

### 7.4.2.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects participating in a clinical trial. Incidents with the Forielle device will be reported as detailed in Section 7.4.3.

### 7.4.2.2 Definition of Serious Adverse Events

Serious Adverse Events are defined as AEs that:

a) Led to death
b) Led to serious deterioration in the state of health of the subject, that either resulted in
    a. A life-threatening illness or injury, or
    b. A permanent impairment of a body structure or a body function, or
    c. In-patient or prolonged hospitalization, or
    d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c) Led to foetal distress, foetal death or a congenital abnormality or birth defect

### 7.4.2.3 Method of Recording and Assessing Adverse Events

At each visit after enrolment, from Start of stimulation at Day -12 up to Study Exit (PET Days 70-84/PET Weeks 10-12) or final study contact, the subject will be queried on changes in her condition. During this reporting period of the study any AE related to the conduct of the study will be recorded and assessed on an AE case report form (CRF) (distinct from the Device Incident CRF) whether reported by the subject to the investigator or observed by the investigator.

The assessment by investigator shall include a description of the event, its duration (onset and resolution), dates its severity and seriousness, its relationship with the conduct of the Study, any other potential causal factors, any treatment given or other action taken (including withdrawal to the study) and its outcome.

## 7.4.3 Medical Device Incidents

Device Incidents will be reported as described below.

### 7.4.3.1 Definition of Medical Device Incident (MEDDEV 2.12-1, Rev. 8, adapted to definitions above)

A medical device incident is 'any malfunction or deterioration in the characteristics and/or clinical performance of a device, as well as any inadequacy in the labelling or the IFU which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health'. A medical device incident that would require reporting include:

a) Serious public health threat: Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action (MEDDEV 2.12-1 rev.8).
b) Death or UNANTICIPATED serious deterioration in state of health of a subject that resulted in
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c) Other events: events that have an established link between the device and the event

#### 7.4.3.2 Method of Recording and Assessing Medical Device Incidents

At each visit from Day 2 PR up to Study Exit (PET Days 70-84/Weeks 10-12), the subject will be queried on medical device incident associated with the use of Forielle. During this reporting period any medical device incident will be recorded and assessed on the Device Incident CRF, whether reported by the subject to the investigator or observed by the investigator.

The assessment by the investigator shall include the determination of the seriousness of the incident and its relationship with the medical device.

### 7.4.4 Procedure for reporting Serious adverse events and/or Medical Device Incident

Investigator MUST Report all medical device incidents to the sponsor using Manufacturing Incident Report Form within 24 hours.

The sponsor shall:

- Inform within 24 hours all other investigators of medical device incident reports and SAE related to the conduct of the study
- Notify the manufacturer of all medical device incidents within 24 hours

The manufacturer shall:

- Conduct an investigation of the medical device incident and determine whether the risk analysis needs to be updated and whether corrective actions are required.
- Report all medical device incidents to the competent authority in accordance with the Meddev 2.12-1, Rev. 8 guidance.

### 7.4.5 Monitoring of Subjects with Medical Device Incidents and/or Adverse Events related to the conduct of the study

Any medical device incident that would require reporting, as defined in Section 7.4.3.1, and AE related to the conduct of the study, must be monitored and followed up by the Investigator or Sub-Investigator until stabilization of the subject health's condition or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented.

It is also the responsibility of the Investigator or Sub-Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. The Sponsor will actively follow-up and collect information on any SAEs related to the conduct of the study.

### 7.4.6 Clinical Laboratory Assessments

Serum samples will be collected for $E_2$ and $P_4$ at the HCG Triggering day to be analysed locally by the centre for the purposes of confirming eligibility criteria. Each site will collect an extra serum sample for $P_4$ evaluation to be carried out by the central laboratory (PPD PPD ) to validate local laboratory evaluation of $P_4$ retrospectively to validate subject inclusion in planned analyses.

## 8 Statistics

### 8.1 Sample Size

The main aim of the study is the evaluation of the clinical performance of Forielle in restoring favourable condition of endometrial milieu, after Controlled Ovarian Stimulation. For this purpose, clinical performance will be measured by assessing the difference in implantation rate in the treated arm compared to the control (standard clinical practice). Generally, the average implantation rate of ART is considered of about 25% (Nastri et al. 2013). Several works in the literature suggested the key role of endometrial receptivity on the ART outcomes (Evans et al. 2012). An improvement of about 6% in implantation rate from the usual ART outcome is clinically relevant difference. Thus, for the calculation of sample size, a clinically important difference of 6% was assumed and an interim clinical performance analysis assuming that 2 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries. Sample sizes of 916 each arm achieve 80% power to detect a difference of 0,06 between the group proportions of 0,25 and 0,31 at a significance level (alpha) of 0,050 using a two-sided z-test with continuity correction and allocation ratio of 1:1. The total number of women to be randomised is 2,156, considering a drop-out rate of 15%.

| Target Power | Actual Power | N1 | N2 | N | P1 | P2 | Alpha |
|---|---|---|---|---|---|---|---|
| 0.80 | 0.80025 | 916 | 916 | 1832 | 0.25 | 0.31 | 0.05 |

Details when Spending = O'Brien-Fleming, N1=916, N2=916, P1=0,25, P2=0,31, Continuity Correction.

| Look | Time | Lower Boundary | Upper Boundary | Nominal Alpha | Incremental Alpha | Total Alpha | Incremental Power | Total Power |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.5 | -2.96259 | 2.96259 | 0.003 | 0.003 | 0.003 | 0.16425 | 0.164 |
| 2 | 1 | -1.96857 | 1.96857 | 0.049 | 0.047 | 0.047 | 0.63600 | 0.800 |

The required significance level for stopping the study for clinical performance is 0.003 to first look (50% of patients) and 0.049 at second look (final). The overall power is 80%.

## 8.2 Randomisation

Eligible subjects will be randomised to receive either the intervention (Forielle endometrial washing) or no endometrial washing following oocyte retrieval on Study Day 0, the HCG Triggering day, in a 1:1 ratio.

At the HCG triggering day, on study day 0 all eligible women subjects will be randomised in ratio of 1:1 to one of two parallel treatment groups:

- Forielle
- Control (No endometrial washing)

Women subjects will be stratified with respect two factors:

- Age (age <32; 32 ≤ age <38; 38 ≤ age ≤ 41)
- n° of follicles (>16mm) (5 ≤ n° follicles ≤ 9; 10 ≤ n° follicles ≤ 14)

## 8.3 Endpoint

### 8.3.1 Primary Endpoint

Subject implantation rate is defined as number of intrauterine gestational sacs divided by the number of embryos transferred, as assessed at PET Days 21to 28.

### 8.3.2 Secondary Endpoints

- Subject pregnancy result (positive/negative) at PET Day 14
- Subject with confirmed ongoing pregnancy (yes/no) at PET Days 70 to 84
- Device incidents

## 8.4 Analysis Sets

Intent-to-Treat (ITT) set: The ITT set will include all randomised subjects. In this population, procedure (Forielle /Control) will be assigned based upon the procedure arm to which subjects were randomised regardless of which procedure they actually received.

Per Protocol set (PP): The PP set will include all subjects who do not have major protocol violations that would affect the evaluation of the primary clinical performance endpoint.

Protocol deviations categories with severity will be described in statistical analysis plan document. Before interim/final analysis, all reported protocol deviations will be reviewed and evaluated for any impact on primary endpoint analysis.

Safety set (SAF): The SAF population will include all randomised subjects on whom the intrauterine washing procedure was attempted (even if not completed). In this population, procedure (Forielle/Control) will be assigned based upon the procedure subjects actually received, regardless of the procedure arm to which they were randomised.

## 8.5 Description of Statistical Analyses

### 8.5.1 General Considerations

The study data will be reported using summary tables, figures, and data listings. Continuous variables will be summarized using mean, standard deviation (SD), coefficient of variation (CV%, as appropriate), median, minimum, maximum, and, as appropriate, geometric mean.

Descriptive statistics will be presented for key outcome measures. Categorical data will be summarized with the number of non-missing values and the numbers of values equal to each of the possible values. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding analysis population, unless stated otherwise.

Unless otherwise specified, all formal statistical tests will be two-sided at the 5% significance level. Point estimates of treatment differences will be accompanied with two-sided 95% confidence intervals (CIs) where applicable. P-value will be used to draw statistical significant conclusions only for primary endpoint and for secondary endpoints all statistical estimates will be used for descriptive comparison.

In the case of normality assumption violations, appropriate non-parametric methods will be used for analysis.

All data will be presented in by-subject listings.

The statistical analysis will be performed using SAS® Version 9.2 or higher.

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in a separate Statistical Analysis Plan (SAP) document developed by separately for interim and final analysis.

Study final analysis will be performed by PPD and Interim analysis will performed by a PPD independent statistician from a different geographical region. A firewall will be implemented to ensure interim results will not be accessible to any PPD staff except to the independent statistician who will perform interim analysis.

### 8.5.2 Analysis of Primary Endpoints

The primary endpoint subject implantation rate is defined as number of intrauterine gestational sacs divided by the number of embryos transferred, as assessed at PET Days 21 to 28.

Mean subject implantation rate as assessed at PET Days 21-28 in subjects treated with Forielle endometrial washing procedure will be compared to the mean subject implantation rate in subjects who receive no endometrial washing (control group) following COS.

For the primary endpoint analysis addition to summary statistics, differences in mean subject implantation rate between study procedure and control procedure will be investigated and compared using Gamma/log normal regression model. The analysis model will include treatment procedure as the fixed effect and Embryo Transfer Day (Day 5 PR or Day 7 PR), age, number of follicles at baseline and number of embryos transferred per subject as covariates.

To evaluate the treatment comparison, estimated mean differences will be presented together with two-sided 95% confidence intervals and p-values. Appropriate distribution will be decided based on good ness of fit (residual sum of squares) value.

This primary endpoint analysis will be tested by planned group sequential design with O'Brien-Fleming type spending function. The study for clinical performance will be stopped at significance level of 0.003 in first (50% of subjects) interim analysis and at significance level 0.049 in final analysis.

### 8.5.3 Analysis of Secondary Endpoints

For the secondary endpoints, subject pregnancy result (positive/negative) and subject with confirmed pregnancy (yes/no), the pregnancy rate at PET Day 14 and ongoing pregnancy rate at PET Days 70-84 will be estimated and compared using logistic regression model including Embryo Transfer Day (Day 5 PR or Day 7 PR), age and number of follicles at baseline as covariates. Estimates of odds ratio, confidence intervals and relevant p-values will be presented for each endpoint.

### 8.5.4 Analysis of Safety and Other Endpoints

Device incidents will be summarized using frequency and percentages for two treatment groups.

Clinical laboratory assessments ($E_2$ and $P_4$, etc.) will be presented in listings appropriately.

## 8.6 Interim and Additional Planned Analyses

One interim analysis is planned and a Data Monitoring Committee (DMC) will review and give advice to the sponsor regarding the study conduct. The DMC will be comprised of a statistician and physician not part of the study and will be appointed prior to the planned interim analysis. The purpose of the DMC is to verify the reliability of the primary endpoint since the study is unblinded to the study investigator. Detailed procedures will be described in a DMC charter.

Interim analysis on PET Days 21 to 28 data will be conducted when 1,078 subjects have been through treatment procedure and followed for 21 to 28 days after embryo transfer for the primary analysis. An O'Brien-Fleming type boundary will be used to determine the nominal significance level with overall 5% two-sided significance level i.e., the nominal significance level for the interim analysis will be 0.003. Based on the interim finding, the DMC may recommend to stop the subject enrolment early for clinical performance considerations or to continue the study as planned. No further results of the interim analysis will be made available by the DMC until final analysis is done.

The final analysis will be done when 2,156 subjects have been through treatment procedure and followed for 70 to 84 days post embryo transfer and complete all the protocol planned procedures and the O'Brien-Fleming boundary will be used to determine the nominal significance level with overall 5% two-sided significance level i.e. the nominal significance level for the final analysis will be 0.049.

# 9 Ethical and Regulatory Aspects

## 9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the sites and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

## 9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with local regulations and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject

will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

Only the Investigator and sub-investigators may inform the subject about the trial and sign the Informed Consent Form (ICF), as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator.

The signed and dated declarations of informed consent are to remain at the Investigator's site, and must be safely archived so that the forms can be reviewed during study monitoring and auditing. A copy of the signed and dated ICF should be provided to the subject.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IEC for review and opinion. Using the approved revised subject information sheet and other written information, The Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

## 9.3 Subject Identification and Privacy

A unique number will be assigned to each subject immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the sites. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but patient confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

## 9.4 Emergency Medical Support and Subject Card

Subjects will be provided with an Emergency Medical Support card by the Sponsor for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the subject. The Investigator agrees to provide his or her emergency contact information on the card

for this purpose. If the Investigator is available when an event occurs, they will answer any questions and any subsequent actions will follow the standard process for Investigator oversight.

## 9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for the country participating in the trial, as per local and country legislation. Insurance conditions shall meet good local standards, as applicable.

## 9.6 Independent Ethics Committee

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the responsible IEC for its favourable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Trial Master File.

The IEC will be asked to document the date of the meeting at which the favourable opinion or approval was given and the members and voting members present. Written evidence of favourable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC, before implementation of substantial changes (see Section 10.6). Relevant safety information will be submitted to the IEC during the course of the trial in accordance with national regulations and requirements.

## 9.7 Competent Authorities

The clinical trial protocol and any applicable documentation (e.g., IFU and ICF) will be submitted or notified to the Competent Authorities in accordance with local and national regulations.

# 10 Trial Management

## 10.1 Protocol Deviation and Deviation Reporting

A protocol deviation occurs when an investigator and/or trial site personnel do not conduct the trial according the clinical protocol. Investigators must maintain accurate, complete and current records related to the trial This includes source documents showing the dates and reasons for each deviation from the clinical protocol. Depending upon the nature of the protocol deviation, expedited reporting to the reviewing IEC, according to the reporting requirements of the IEC, and prior approval from the sponsor may be required.

If the sponsor or its designate determines that an investigator is not complying with the executed clinical research agreements, the clinical protocol, applicable regulations, or the requirements of

the reviewing IEC, prompt action will be taken to secure compliance. In addition, the participation of an investigator may be terminated.

## 10.2 Case Report Form Handling

Refer to the Study Manual for eCRF handling guidelines. The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible, and timely manner. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to the Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing in accordance with PPD data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

## 10.3 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible:

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial

All documents containing source data must be filed, including, but not limited to: transvaginal ultrasound results, hormones administered and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation

of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

## 10.4 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits, and for inspection by Competent Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

## 10.5 Monitoring, Quality Assurance, and Inspection by Competent Authorities

This trial will be monitored in accordance with Good Clinical Practices and all other applicable local and national regulations. The site Monitor will perform visits to the trial sites at regular intervals. The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical study report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Competent Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed CRFs, all device and device accountability records, and the original medical records or files for each subject.

## 10.6 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Competent Authorities and to the relevant IEC for approval or favourable opinion. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC or to Competent Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

## 10.7 Clinical Trial Report and Publication Policy

### 10.7.1 Clinical Trial Report

The completed clinical trial will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study and interpretation of the findings.

### 10.7.2 Publication and Disclosure

The first publication will be a publication of the results of the analysis of the Primary Endpoints that will include data from all study sites. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspaper, oral presentations, etc.), either in whole part or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

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# 12 Appendices

## Signature Page – Protocol Lead

| | |
|---|---|
| **Trial Title** | A multicentre, prospective randomised controlled, interventional clinical investigation to assess the clinical safety and performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during Assisted Reproductive Practice **(ENDOMEDE)** |
| **Clinical Trial Protocol Date/ Version** | December 9, 2016/Version 1 |

**Protocol Lead responsible for designing the clinical trial:**

I approve the design of the clinical trial:

PPD PPD

Signature PPD Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: Merck Serono S.p.A.

Address: Via Casilina 125, 00176 Rome, Italy

Telephone number: PPD

Fax number: PPD

E-mail address: PPD

## Signature Page – Coordinating Investigator

| | |
|---|---|
| **Trial Title** | A multicentre, prospective randomised controlled, interventional clinical investigation to assess the clinical safety and performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during Assisted Reproductive Practice **(ENDOMEDE)** |
| **Clinical Trial Protocol Date/ Version** | December 9, 2016/Version 1 |

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments and all applicable Competent Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

PP

Name, academic degree: PPD

Function / Title: Coordinating Principal Investigator

Institution: PPD

Address: PPD

Telephone number: PPD

Fax number: PPD

E-mail address: PPD

[redacted]

## Signature Page – Principal Investigator

| | |
|---|---|
| **Trial Title** | A multicentre, prospective randomised controlled, interventional clinical investigation to assess the clinical safety and performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during Assisted Reproductive Practice **(ENDOMEDE)** |
| **Clinical Trial Protocol Date/ Version** | December 9, 2016/Version 1 |
| **Centre Number** | |
| **Principal Investigator** | |

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments and all applicable Competent Authority requirements and national laws.

Signature

Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

## Sponsor Responsible Persons not Named on the Cover Page

| | |
|---|---|
| **Trial Title** | A multicentre, prospective randomised controlled, interventional clinical investigation to assess the clinical safety and performance of Forielle, a medical device for endometrial washing, in restoring favourable endometrial condition to implantation after COS during Assisted Reproductive Practice **(ENDOMEDE)** |
| **Clinical Trial Protocol Date/ Version** | December 9, 2016/Version 1 |

I approve the design of the clinical trial:

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function / Title: PPD

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