Clinical Trial Protocol

Trial Protocol Number	EMR700623_545
Title	A Phase IV, prospective, randomized, exploratory, multicenter, Eeva trial (**Ti**me **L**apse **E**eva – TiLE)
Trial Phase	Phase IV
Coordinating Investigator	PPD [redacted]
	PPD [redacted]
	E-mail address: PPD [redacted]
Trial center(s) /country(ies)	Approximately 20 Centers in 8 countries: Canada, Germany, Italy, France, Norway, Sweden, Spain, UK
Sponsor	Merck KGaA, Frankfurter Str. 250 , 64293 Darmstadt, Germany
	Medical Responsible:
	PPD [redacted]
	PPD [redacted]
	Mobile: PPD [redacted]
Protocol Version	21 March 2016/Version 5.0

- Confidential -

Signature Page

Sponsor representatives responsible for the trial:

We approve the design of the trial.

Signature	*Date of Signature*

PPD

PPD, *Medical Responsible*

Merck Serono S.p.A.

Piazza del Pigneto, 9, I-00176 Rome, Italy

Phone: PPD

Mobile: PPD

PPD

Signature	*Date of Signature*

PPD

PPD

Merck KGaA

Frankfurter Str. 250

64293 Darmstadt

Coordinating Investigator

I agree to conduct the trial in accordance with this Protocol and in compliance with all applicable Health Authority requirements and national laws.

Signature *Date of Signature*

PPD

PPD

Telephone number PPD

E-mail address
PPD

Principal Investigator Signature

Trial Title: A Phase IV, prospective, randomized, exploratory, multicenter, Eeva trial (Time Lapse Eeva – TiLE)

Trial Number: EMR700623_545

Protocol Version/Date: Version 5.0 / 21 March 2016

Center Number: 101

Principal Investigator: PPD – PPD

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, International Standard ISO14155 (Clinical investigation of medical devices for human subjects – Good Clinical Practice) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

Signature *Date of Signature*

PPD
PPD
Telephone number PPD

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List of Abbreviations

AE	Adverse Event
AFC	Antral Follicular Count
AMH	Antimullerian Hormone
ART	Assisted Reproductive Technologies
B	Blastocyst
CE	European Community
CRF	Case Report Form
CRO	Contract Research Organization
CSL	Clinical Science Liaison
EB	Early Blastocyst
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EEVA H/M/L	Eeva Predicted High, M: Medium, L: Low
ET	Embryo Transfer
EU	European Union
GP	General Practitioner
hCG	Human Chorionic Gonadotropin
HFEA	Human Fertilisation and Embryology Authority – UK
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
ICSI	Intracytoplasmatic Sperm Injection
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board

ITT	Intention to Treat
IVF	In Vitro Fertilization
NCA	National Competent Authorities
PN	Pronuclei stage
SAP	Statistical Analysis Plan
SPC	Summary of Product Characteristics
USA	United States of America

1 Synopsis

Trial title	**A Phase IV, prospective, randomized, exploratory, multicenter, Eeva trial (Time Lapse Eeva – TiLE)**
Trial number	EMR700623_545
Sponsor	Merck KGaA, Frankfurter Str. 250 , 64293 Darmstadt, Germany
Trial type	Prospective, randomized, multicenter Trial
Coordinating Investigator	PPD
Trial center(s)/country(ies)	Approximately 20 Centers in 8 Countries: Canada, Germany, Italy, France, Norway, Sweden, Spain, UK
Planned Trial period	April 2015 – March 2017
Trial objectives	Primary Objective: To compare the implantation rate for Day 3/5 embryo transfers using Eeva scores plus morphology grading versus Day 3/5 embryo transfers using morphology grading only. Secondary Objectives: To compare the following outcomes from the Eeva trial group to the control group. • Clinical Pregnancy • Ongoing pregnancy rate • Multiple pregnancy rate. • Miscarriage rate. • Utilization rate.
Trial design and plan	Prospective, randomized, exploratory, multicenter trial. When approximately 50% of the subjects have implantation results, an interim analysis will be performed.
Planned number of subjects	1500

Diagnosis and main inclusion and exclusion criteria	All IVF/ICSI patients according to the eligibility criteria: For inclusion in the trial, **all** of the following inclusion criteria **must** be fulfilled: 1. All infertile patients treated with IVF/ICSI. 2. Patient age ≤ 40 years. 3. ≤ 3 failed IVF/ICSI cycles. 4. At least 4 normally fertilized eggs (2PN) in current cycle. 5. Normal uterine cavity. 6. Fertilization using only ejaculated sperm (fresh or frozen). 7. Subject must have read and signed the Informed Consent form. Subjects are not eligible for this trial if they fulfill **any** of the following exclusion criteria: 1. Have clinically significant systemic disease. 2. Have abnormal, undiagnosed gynecological bleeding. 3. Have any contraindication to Controlled Ovarian Stimulation (COS) for ART and to gonadotropins to be used in ART. 4. Egg donor cycle. 5. Planned "freeze all" cycle (oocytes or embryos). 6. Concurrent participation in another clinical trial.

Investigational Medicine Product	Not applicable.
Investigational Medical Device	EEVA, a type-II medical device that received the CE marking in a de novo process as a diagnostic device
Planned duration of observation for each subject	Embryos of consented subjects will be assessed with EEVA System and morphological assessment and after ET will be follow-up until achievement of implantation and confirmation of pregnancy.
Primary endpoint(s)	Implantation rate from embryos transferred on day 3 or 5.
Secondary endpoint(s)	Utilization rate, Clinical pregnancy, Ongoing pregnancy, Multiple pregnancy and Miscarriage.
Estimated Trial calendar	FPI: 29-JUN-2015 LPI: 31-OCT-2016 LPLV: 31-DEC-2016 Trial Report Date: 30-APR-2017

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor(s) of the trial is Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany.

It is planned to perform the trial at approximately 20 sites in about 8 countries from Europe (EU) and Canada (CA).

Principal Investigator: PPD [redacted]

PPD [redacted] is the Contract Research Organization (CRO) appointed for trial management including monitoring activities.

[redacted] PPD [redacted], will provide the database for electronic data capture (EDC), randomization process and electronic case report form (eCRF) management support. Statistical analysis will be done by PPD [redacted].

Trial will be managed by Global Medical Affairs in coordination and with the support from Merck KGaA Global Clinical Operations group and countries Medical Affairs personnel.

3 Background Information and Trial Rationale

This clinical protocol describes the requirements for the Eeva technology (Early Embryo Viability Assessment) EU/CA post-marketing trial. The purpose of this trial is to use Eeva per the approved European commission (CE) mark labeling and gather additional data to evaluate the efficacy to predict embryo implantation potential, for the future development of this technology. This trial will be conducted using a standardized protocol at approximately 20 centers in the European Region and Canada.

As the sponsor of this clinical trial, Merck KGaA has the overall responsibility to conduct this post-marketing trial, including assurance that the trial will be performed according to the clinical protocol, applicable regulations and standards, the Declaration of Helsinki, and elements of Good Clinical Practices (GCP) as may be applied to medical devices.[1,2] The confidentiality provisions of all applicable laws and regulations will apply throughout.

Eeva technology and the Eeva petri dish are classified as a class IIa medical devices in the European Union (CE marked), United States and Canada, commercially available.

Eeva is a time lapse monitoring system with an integrated software, which is able to take photos of embryos every 5 minutes during embryo culture and embryo development. The high quality images collected are automatically analyzed and validated by the software to define precise timing of cell divisions and based on a proprietary algorithm, make a recommendation that is provided to the user to determine the likelihood of whether or not an embryo will develop to the

blastocyst stage. The user has the ability to export image data, embryo reports, and movies. The images are acquired while embryos are developing inside standard incubators. In case of any Eeva malfunction the subsequent development of the embryos will not be affected in any way and the only missing piece will be the automatic recommendation by the computer.

The optimal goal of IVF/ICSI should be the delivery of a healthy singleton baby.[3-5] The clinical dilemma, is how to reduce the number of embryos for transfer to prevent multiple births while at the same time maintaining or improving IVF/ICSI success rates.

Currently, embryos are being selected based on traditional morphology scores developed in the early 1980s, which are based on multiple observations of embryos under regular light microscopes.[6-9] However, it is that traditional morphology grading, which only captures static images at a few time points, is of very limited predictive value. It was reported that only 51% of embryos transferred on Day 5 were pre-selected for transfer on Day 3.[10] In a controlled Trial, embryologists were asked to choose 2 embryos with optimal potential for blastocyst development using traditional morphology grading criteria. Results showed that morphology criteria assessed on Day 3 did not accurately predict blastocyst formation. In 39% of cycles neither choice resulted in blastocyst formation, and in 38% of cycles 1 assessment resulted in a blastocyst transferred. Embryologists were able to pick the best 2 embryos in just 23% of cycles.[11]

Recently, researchers from Stanford University reported results that correlated time-lapse image analysis with gene expression profiling of pre-implantation human embryo development.[12] It was discovered that success in development to the human blastocyst stage can be predicted accurately from dynamic, non-invasive imaging parameters that are observed prior to embryonic genome activation (on Day 3). These parameters can be reliably measured by way of automated image analysis, confirming that successful development follows a set of carefully orchestrated and predictable events. Moreover, image phenotypes reflected underlying molecular programs of the embryo and individual blastomeres. This was the first trial to report that dynamic morphology parameters of embryo development reflect underlying molecular program status and provide a promising platform for early assessment of embryo viability.[12]

Eeva was developed to translate the significant findings from the research trial to the clinical setting.[12] The benefit demonstrated during the clinical investigation of the Eeva System Trial was that Eeva may assist the embryologist in improving embryo assessment accuracy by predicting blastocyst formation at cleavage stage with a specificity of 85%.[13] That is, out of all Non-Blastocyst (arrested) embryos, Eeva was able to identify 85% of them. The main limitation in traditional morphology is its high sensitivity and low specificity. Currently, any embryo with good morphology is considered to be "viable." However, clinical results have shown that many embryos selected by good Day 3 morphology criteria are false positives.[7,8] Embryologists are in need of a test which can discriminate – particularly among the embryos with good morphology – those which *are truly viable and will form blastocysts*. The high specificity of Eeva system's determines which good morphology embryos will actually arrest. Therefore, Eeva is a useful complement to aid the embryologist in identifying the most viable embryos for transfer.

3.1 Benefit-risk assessment

The analysis of the risks and benefits demonstrated that, the Eeva System met its safety and performance requirements and the device fulfilled its intended use as claimed by Merck KGaA Fertility Technologies. Following is a description of potential (expected) risks and benefits that may be associated with use of Eeva technology. Eeva received the CE marking in a de novo process as a diagnostic device.

3.1.1 Risks Related to Eeva

Indeed, there are no risks related with Eeva utilization that could potentially affect embryos survival or quality due to the fact that any malfunction on the Eeva system will only affect its ability to take pictures of the embryos in culture but will not affect in any way the temperature, gas environment and/or culture media conditions to which the embryos will be exposed during the incubation process. In Eeva clinical investigation studies, the average blastocyst formation rate in subjects who had embryo transfers at the blastocyst stage was 47.4%. This demonstrated that embryos imaged by Eeva did not have their development to blastocyst stage altered given the average rate reported in the literature for blastocyst formation is approximately 45.4%.[17]

3.1.2 Benefits of Eeva

The benefit demonstrated during the first clinical investigation was that the Eeva System can assist the embryologist in improving embryo assessment accuracy by predicting blastocyst formation at cleavage stage with a specificity of 85%. That is, out of all arrested embryos, Eeva was able to identify 85% of them.[13]

An additional benefit is that the Eeva System generates consistent and objective data which help embryologists to be more standardized while performing embryo assessments. Furthermore, the Eeva System provides a tool that is fully automated, real-time, and can be easily implemented in the IVF/ICSI laboratory and fit into the work flow.

4 Trial Objectives

The aim of this trial is to use Eeva per the approved, CE mark labeling and gather additional data to evaluate the efficacy to predict embryo implantation potential when combined with morphological assessments.

4.1 Primary

The primary objective of the trial is to compare the rate of implantation for Day 3/5 embryo transfers using Eeva scores plus morphology grading versus Day 3/5 embryo transfers using morphology grading only. Implantation rates are calculated by dividing the number of gestational sacs with fetal heart beat identified by ultrasonography at weeks 5 to 8 by the number of embryos transferred on Days 3 or 5.

4.2 Secondary

The secondary objective is to compare the following outcomes from the combined Eeva + morphology results vs. the control (morphology only) group: Utilization Rate (number of transferred and frozen embryos divided by number of normally fertilized oocytes x100), Clinical Pregnancy (assessed by ultrasonography at weeks 5 to 8), Ongoing pregnancy rate (assessed by ultrasonography at weeks 10 to12), Multiple pregnancy rate (assessed by ultrasonography at weeks 5 to 8) and spontaneous miscarriage.

5 Investigational Plan

5.1 Overall Trial Design and Plan

In general, the Eeva EU/Canadian trial will include 22 investigational sites. Each site will conduct the trial using the same clinical protocol.

Recruitment of patients at each site, with subjects who voluntarily consent to participate, is expected to continue for up to 9 months. Additional follow-up after embryo transfer will take place up to Day 12-18 days to verify biochemical pregnancy and at 5-8 gestational weeks to verify clinical pregnancy. Additionally, pregnancy outcomes will be collected via eCRF for subjects who were pregnant at the 5-8 week gestational follow-up visit (or subsequent ultrasound results). Total duration of the trial, including start up and close out activities, is approximately 19 months. Desired follow-up endpoints and additional collection of outcomes like spontaneous miscarriage is not being considered in the timeline for completion.

5.2 Discussion of Trial Design

The prospective, randomized, exploratory design selected for this trial was defined based on the need to test new diagnostic technologies, like Eeva, to assess embryo viability by collecting real life clinical data and compare it with a control. Implantation rate of individual embryos using the technology will be explored to define realistic confidence intervals utilized for the generation of strong hypothesis to be validated in future RCT.

5.3 Selection of Trial Population

Subjects for this trial are IVF/ICSI patients to be enrolled according to the eligibility criteria.

5.3.1 Inclusion Criteria

For inclusion in the trial, **all** of the following inclusion criteria **must** be fulfilled:

1. All infertile patients treated with IVF/ICSI.
2. Patient age ≤ 40 years.
3. ≤ 3 failed IVF/ICSI cycles.
4. At least 4 normally fertilized eggs (2PN) in current cycle.
5. Normal uterine cavity.
6. Fertilization using only ejaculated sperm (fresh or frozen).
7. Subject must have read and signed the Informed Consent form.

5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill **any** of the following exclusion criteria:

1. Have clinically significant systemic disease.
2. Have abnormal, undiagnosed gynecological bleeding.
3. Have any contraindication to Controlled Ovarian Stimulation (COS) for ART and to gonadotropins to be used in ART.
4. Egg donor cycle.
5. Planned "freeze all" cycle (oocytes or embryos).
6. Concurrent participation in another clinical trial.

5.4 Recruitment of Participants

Subjects will be recruited from patients undergoing IVF/ICSI treatment cycles at the investigators' clinics. Patients will be assessed according the Inclusion/ Exclusion criteria to determine their eligibility for participation.

5.5 Criteria for Randomization

All eligible subjects will be assigned to the group of subjects with embryo transfers using Eeva scores plus morphology grading and to group of subjects with embryo transfers using morphology grading only by randomization. A permuted block randomization with fixed block size and allocation ratio of 2:1 will be used. Further details of the procedure will be described in the EDC related manuals.

An allocation ratio of 2:1 is used since this is an explorative trial. The main objective is to collect data of first experience with the EEVA Time Lapse system. To generate hypotheses in comparison to the 'morphology grading only' group comparable data of the morphology grading only need to be collected.

5.6 Description of Treatment and Definition of Exposure to trial medication

Not applicable as there will be no use of any trial medication. Subjects' embryos will be observed using morphological assessments as standard of practice at the IVF laboratories and a part of the trial patients in an allocation ratio of 2:1 will be assigned to have EEVA Time Lapse system embryos observation and assessments added to their standard assessment. Culture conditions and elements will be the same for all embryos in the laboratory regardless of their allocation at randomization.

5.7 Criteria for Subject Withdrawal

Subjects will be informed that they have the right to withdraw from the trial at any time without prejudice to their medical care, and that they are not obligated to state their reasons. Any withdrawal must be fully documented in the source documents

Subject data will be included in the analyses up to the time that consent was withdrawn. The trial exit electronic case report form should be completed at the time a subject is exited from the trial.

The sponsor reserves the right to discontinue this trial at any time.

6 Trial Endpoints and Assessment Procedures

Embryos will be observed until they are transferred and then subjects' outcomes information will be collected for all subjects until implantation and pregnancy are verified (up to 8 weeks after embryo transfer). Additional follow up to determine final pregnancy outcome may be included if available.

Subjects will be followed up until loss to follow-up, occurrence of an exclusion criterion, or the end of the data collection period, whichever comes first.

6.1 Endpoints

Primary Endpoint: Implantation rate from embryo transfers performed on day 3 or day 5.

Secondary Endpoints: Utilization rate, Clinical pregnancy rate, Ongoing pregnancy rate, Multiple pregnancy rate, Spontaneous miscarriage rate.

Endpoints are defined as follows :

- Implantation rate (number of sacs with fetal heart beat/ total number of embryos transferred)
- Utilization rate (transferred + frozen/ fertilized eggs) X100.
- Clinical pregnancy rate (at approximately 5-8 weeks gestational age)
- Multiple pregnancy rate defined as a clinical pregnancy with ≥ 2 fetal sacs.
- Spontaneous miscarriage rate as a desired follow-up endpoint.

6.2 Potential Confounding Factors

There are no expected major confounding factors that would contribute to determine the outcomes on either one of the arms related to the main variables, that is, use or not of Eeva technology for embryo assessment in addition to standard morphological assessment. Such standard scoring and grading conventions will be provided to sites to capture accordingly in the eCRFs.

6.3 Frequency of Assessments

6.3.1 Baseline Information and hCG Trigger Day

Enrolled subjects in the trial will undergo pre-IVF/ICSI preparations per the standard protocol currently in force for each site. Collection of trial-related information may take place only after the subject and partner, if applicable, has given voluntary, documented, informed consent and will include the following information, which will be recorded on the baseline electronic case report form including:

- Demographics
- Pregnancy history
- Prior ART
- Cycle Day 3 hormones (FSH, AMH, Estrogens, LH, etc)
- Cause of Infertility
- Protocol of Stimulation
- Time of hCG trigger to oocyte retrieval

Data pertaining to the stimulation protocol, stimulation medications, and an evaluation of the endometrium for each subject will be recorded retrospectively on the **ART Treatment** eCRF form.

6.3.2 Oocyte Retrieval, Insemination, and Day 1 Fertilization Check

Oocyte retrieval and insemination will follow the standard protocol in place at each trial site. Data will be recorded on the **Oocyte Retrieval and Insemination/Fertilization** eCRF including:

- Date and time of oocyte retrieval
- Number of oocytes retrieved
- Andrology information
- Insemination method
- Total number of normally fertilized eggs (2PN)
- Culture conditions (including gas phase, media, and protein, etc.)
- Embryo morphological grading may be assessed on Day 2 as per local laboratory standard practice in those subjects randomized to the Morphology group only.

6.3.3 Embryo Day 3

Day 3 embryo morphological grading will be performed according to standard protocol and laboratory procedure manual. Eeva results will be printed and used per the Instructions for Use. Data collected will be recorded on the **Day 3 Laboratory Data** eCRF including:

- Date and time of evaluation
- Type of Eeva Petri Dish (number of micro-wells)

- Eeva micro-well identification
- Cell stage and Morphology grading
- Eeva results
- Number of cells after 42 hours, up to the morning of day 3
- Fate of each embryo (Transferred, Cryopreserved, Discarded or extended culture to Day 5/6)
- Eeva Petri Dish and Scope information
- Culture conditions

6.3.4 Embryo Transfer

Embryo transfer will follow the standard protocol in place at each clinical trial site. Data pertaining to the Day 3 or Day 5/6 embryo transfer procedure will be recorded on the **Transfer and Treatment Outcome** eCRF for all patients (Eeva and non-Eeva ones) including:

- Date and day of transfer
- Luteal phase support
- Use of ultrasound
- Final number of embryos transferred

6.3.5 Embryo Day 5-6

If any embryos are cultured to Day 5 or Day 6, data will be recorded on the **Day 5-6 Laboratory Data** eCRF including:

- Date and time of evaluation
- Type of Eeva Petri Dish (number of micro-wells)
- Eeva micro-well identification
- Development stage and Morphology grading
- Fate of the embryo (Transferred, Cryopreserved, Discarded or extended culture to Day 5/6)
- Eeva Petri Dish and Scope information
- Culture conditions

6.3.6 Post Oocyte Retrieval or Post Transfer Day 12-18

The institution's standard urine or blood serum pregnancy testing results (biochemical pregnancy assessed between days 12 and 18) will be recorded on the **Transfer and Treatment Outcome** eCRF including:

- Date of the biochemical pregnancy test
- Pregnancy test results
- Quantitative βhCG, as applicable

If the result of the pregnancy test is negative, the subject will have completed the trial and be exited at that time (complete **Trial Exit** electronic case report form).

6.3.7 Gestational Age Week 5-8

The first ultrasound to verify clinical pregnancy will be recorded on the **Transfer and Treatment Outcome** eCRF including:

- Date of ultrasound
- Result of initial pregnancy ultrasound
    - Number of intrauterine gestational sacs
    - Number of fetal heartbeats

If the result of the ultrasound is negative, that is, if no fetal heartbeat is detected, then the subject will have completed the trial and be exited at that time (complete **Trial Exit** electronic case report form).

6.3.8 Post-Pregnancy follow-up

Pregnancy outcome will be obtained via clinic visit, telephone contact or from HFEA database review for subjects who were pregnant as of their most recent vaginal ultrasound (5-8 gestational weeks or additional ultrasound if post-5-8 gestational weeks), and a **Post-Pregnancy Follow-up** eCRF.

6.3.9 Additional Ultrasound > 8 weeks (Optional)

Any additional vaginal ultrasounds performed after 8 weeks may be recorded on an **Additional Ultrasound** eCRF. The collection of this data is optional, however encouraged.

Data will include the following:

- Date of ultrasound
- Result of initial pregnancy ultrasound
    - Number of fetal sacs and number of fetal heartbeats

6.4 Assessment of Safety

Safety of Eeva will be evaluated by assessment of device deficiency only.

An adverse event or a serious adverse event, whether or not related to the investigational medical device Eeva, in subjects participating to the study is not applicable. In addition, 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 trial is not applicable (see definitions).

6.4.1 Definitions

6.4.1.1 Specific Definitions

As per the European Guidelines on medical devices (MEDDEV 2.7/3), dated December 2010.

An **Adverse Event (AE)** is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

A **device deficiency** is an "Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

Device Malfunction: A failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.

Use Error: Act or omission of an act that has a different result to that intended by the manufacturer or expected by the operator.

A **Serious Adverse Device Effect** is "an adverse device effects that has resulted in any of the consequences characteristics of a serious adverse event".

A **Serious Adverse Event (SAE)** is an adverse event that:

(In the consented subjects)

a) Led to a death,

b) Led to a serious deterioration in health that either:
   1) Resulted in a life-threatening illness or injury, or
   2) Resulted in a permanent of a body structure or a body function, or
   3) Required in-patient hospitalization or prolongation of existing hospitalization, or
   4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

In the offspring of consented subjects:

5) Led to fetal distress, fetal death or congenital abnormality or birth defect

6.4.1.2 Definition of the reporting period for safety surveillance

The reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues after ET until achievement of implantation and (confirmation of) pregnancy. There is no pregnancy follow-up planned in the frame of this study.

6.4.2 Device Deficiency

6.4.2.1 Methods of recording Device Deficiencies

Any feedback in regard to Eeva will be collected on the **Device Incident** eCRF.

Feedback may consist of any alleged deficiency related to the physical characteristics, identity, quality, durability, reliability, effectiveness, or performance of Eeva.

PPD. Engineering and Quality will investigate device malfunctions/deficiencies and perform an evaluation to determine and document the root cause of any device deficiency. Reports will be filed in the Eeva trial project file and/or in document control. Refer to Section 6.4.1.1. for additional information and definition.

6.4.2.2 Reporting of Device Deficiencies

Investigators are responsible for reporting to Merck KGaA via the eCRF device deficiencies that may affect the assessment process of the embryos during the course of embryo culture through trial completion.

An assessment of the device deficiency by the investigator is not mandatory.

PPD. is responsible for reporting of device deficiencies to NCA (National Competent Authorities) according to applicable legal post-marketing reporting obligations for medical devices.

6.5 Reporting after the defined reporting period for safety surveillance

Beyond the defined reporting period of this study, it is the responsibility of the investigators informed of any serious abnormal pregnancy outcome in subjects who participated to this study, including of any congenital anomalies in the offspring of these subjects, to spontaneously reported the serious adverse events either directly to the marketing holder of EEVA or to their local regulatory health authorities, if necessary, as required by the local ADR reporting guidelines.

7 Data Analysis and Statistics

7.1 Predetermination of Sample Size

7.2 Sample Size

This is an exploratory trial to generate hypotheses for future confirmatory clinical trials.

It is planned to enroll 1000 subjects in the group of subjects with embryo transfers using Eeva scores plus morphology grading and 500 subjects into the control group of subjects with embryo transfers using morphology grading only. Enrollment is non-competitive, each center selected to participate in the study is expected to enroll a minimum number of patients to be defined at site start-up.

Based on this number of subject's precise estimates of the primary endpoint, the rate of implantation for Day 3/5 embryo transfers, is possible.

The following table shows for different implantation rates the distance from the rate (proportion) to the limit of a 95% confidence interval.

Implantation rate	**Distance to limit of 95% CI**	
	500 subjects	1000 subjects
25%	3.8	2.7
30%	4.0	2.8
35%	4.2	3.0
40%	4.3	3.0
45%	4.4	3.1

7.3 Randomization

Subjects will be assigned to the group of subjects with embryo transfers using Eeva scores plus morphology grading and to group of subjects with embryo transfers using morphology grading only by randomization. A permuted block randomization with fixed block size and allocation ratio of 2:1 will be used. Further details of the procedure will be described in the EDC related Manuals.

An allocation ratio of 2:1 is used since this is an explorative trial. The main objective is to collect data of first experience with the EEVA Time Lapse system. To generate hypotheses in

comparison to the 'morphology grading only' group comparable data of the morphology grading only need to be collected.

7.4 Endpoints

7.4.1 Primary Endpoint(s)

The primary endpoint is the Implantation Rate from embryo transfers performed on day 3 or 5. The crude estimate of the implantation for each embryo assessment method (Eeva scores plus morphology grading, morphology grading only) will be calculated as the ratio of the total fetal sacs identified by ultrasonography at weeks 5 to 8 and the number of embryos transferred.

7.4.2 Secondary Endpoint(s)

The secondary endpoints are:

- Clinical Pregnancy (assessed by ultrasonography at weeks 5 to 8)
- Ongoing pregnancy rate (assessed by ultrasonography at weeks 10 to12)
- Multiple pregnancy rate (assessed by ultrasonography at weeks 5 to 8)
- Utilization Rate ([number of transferred and frozen embryos divided by number of normally fertilized oocytes] x100)
- Spontaneous miscarriage (communicated during medical appointment or by telephone contact).

7.5 Analysis Sets

The following sets of subjects will be considered in the analysis:

Intention-to-treat (Full Analysis Set)

The intention-to-treat population includes all randomized subjects. Due to the fact that this is an exploratory trial in contrast to usual definitions of ITT ('presented as randomized') subjects will be presented based on the method used (Eeva scores plus morphology grading, morphology grading only).

Subgroups of Eeva scores plus morphology grading group

The EEVA Time Lapse system assists the embryologist in improving embryo assessment accuracy. Whether the embryologist follows the recommendation made by the system is the decision of the embryologist. Therefore two subgroups will be considered:

- Subjects form Eeva scores plus morphology grading group for whom the embryologist has followed the recommendation of the Eeva system.
  As the principle selection algorithm for the test arm of the study the selection of embryos for transfer is based on the recommendations made by the EEVA system.

- Subjects form Eeva scores plus morphology grading group for whom the embryologist has NOT followed the recommendation of the Eeva system. Every effort at the site will be made to keep this case to a minimum of cases as investigators are encouraged to use their technical expertise and follow the EEVA system recommendations. However, on investigators' discretion and patients' best interests it may be decided to exceptionally disregard the system recommendation when such recommendation contradicts the morphological pre-assessment of the embryos.

7.6 Description of Statistical Analyses

7.6.1 General Considerations

Descriptive statistics for continuous variables will be calculated which will include measures of central tendency, dispersion, summary statistics, and a count of the number of missing values. Categorical variables will be summarized with counts and proportions. Graphical methods will be used as appropriate. No data imputations will be performed. Further details will be specified in the Statistical Analysis Plan (SAP).

7.6.2 Analysis of Primary Endpoint(s)

The crude estimate of the implantation for each embryo assessment method will be calculated as the ratio of the total fetal sacs identified by ultrasonography at weeks 5 to 8 and number of embryos transferred. The approximate 95 % confidence interval of implantation for each embryo assessment method will be calculated. The difference between the methods will be analyzed in an exploratory way using a Poisson regression model. Details regarding the model and analysis approach will be specified in the SAP.

7.6.3 Analysis of Secondary Endpoint(s)

Descriptive statistics for each and all of the secondary endpoints will be provided. The specific exploratory analyses used to assess the endpoints, for example, to examine whether there is a difference in a specific endpoint associated with an embryo assessment method or other relevant assessments will be specified in the SAP.

7.7 Interim Analysis

When half of the patients have completed the study (pregnancy/implantation yes/no) an interim analysis will be done. Primary and secondary endpoints will be analyzed in an explorative way similar as planned for the final analysis. Further details will be specified in the SAP.

7.8 Ethical and Regulatory Aspects

7.9 Estimated Trial Calendar

Trial will begin enrollment on April 2015 and will continue until 1500 subjects will be enrolled or January 31, 2016, whichever comes first. Last patient observation will be recorded by March 31, 2016 and close-out activities and trial final report will follow within 3 months after.

7.10 Protocol Deviations

A protocol/GCP deviation occurs when a clinical investigator and/or trial site personnel do not conduct the trial according to the clinical protocol/GCP.

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/GCP. Depending upon the nature of the protocol deviation, expedited reporting to the reviewing EC according to the reporting requirements of that EC, and prior approval from Merck KGaA may be required.

If Merck KGaA finds that an investigator is not complying with the executed clinical research agreements, the clinical protocol, applicable regulations, or the requirements of the reviewing EC, prompt action will be taken to secure compliance. In addition, the participation of an investigator may be terminated.

7.11 Protocol Modifications

The sponsor will lead all protocol modifications and will provide the final version of the modified protocol to the principal investigator at each investigational site. If applicable, the sponsor will secure any EC or regulatory approvals required.

7.12 Source of Information

Investigators must maintain information in the trial subject's medical records to corroborate data collected on the eCRFs. The following types of information should be maintained and made available as required by Merck KGaA and/or its designees. Shadow charts are not appropriate or adequate source documentation. Medical (clinical and hospital) records may include the following documentation.

- Medical history/physical condition of the patient before involvement in the trial.
- Signed notes in the subject's medical record on the enrollment day that identify and include: the subject's date of enrollment, the trial sponsor (Merck KGaA), the subject-assigned identification number, and documentation and confirmation that the appropriate informed consent was obtained.
- Description of the IVF/ICSI procedure.
- Dated and signed notes for each subject's trial visit.

- Laboratory results.
- Imaging reports, etc.
- Subject's condition upon completion of or withdrawal from the trial.

Data sources will be primarily recorded on patients' charts, laboratory and medical records as part of their standard care, and for the purpose of this Trial the applicable Trial specific information collected will be recorded on the applicable electronic case report forms. Data will be collected to establish eligibility, at baseline, during the stimulation and in vitro fertilization process, during embryo culture, at embryo transfer, at 12-18 days post oocyte retrieval, to verify at 5-8 weeks gestational sacs, to verify implantation and clinical pregnancy, miscarriage and live birth. When half of the patients have completed the trial (pregnancy/implantation yes/no) an interim analysis will be done and when all enrolled subjects have completed or previously exited from the trial, the trial will be closed and a final report generated for EC submission and/or other applicable regulatory purposes.

Merck KGaA will oversee all data management functions such as database development, user training, system maintenance, data queries, and report generation.

7.13 Data Collection

Merck KGaA will use an electronic data capture (EDC) system to collect subject data. The electronic case report forms (eCRFs) are the primary component of EDC that the site personnel will interface with. Training on use of the system will be provided to the trial site personnel. Instructions for completion of the eCRFs also will be provided.

The eCRFs must be completed, saved, and locked via electronic signature by the investigator using a unique ID and password. This ID and password are for the use of the investigator only and may not be used by any other person. Because of the potential for errors or inaccuracies in transcribing data into eCRFs, source documentation must be maintained in each subject's hospital/clinic chart and/or electronic medical record. The eCRFs and source documentation must be available at all times for inspection by the monitors or regulatory inspectors.

Required data will be recorded on the appropriate eCRF at the time of or as soon as possible after the subject visit or embryo assessment. The eCRF data will be processed through an EDC database. Questions about completion of the eCRFs may be directed to the Merck KGaA/PPD clinical trial team.

Eeva embryo pictures (1 picture every 5 minutes of culture over 3/5 days) will be anonymous and collected by Merck KGaA Clinical Application Engineer (CAE) twice during the duration of the study. These pictures will be sent to the bioanalytical department from PPD to explore the possibility to strengthen the predictive algorithm.

Changes made to eCRFs will be electronically recorded in a complete audit trail that cannot be changed, but can be accessed by authorized personnel at any time. All data are transmitted via the internet in an encrypted fashion. When received at the server site, the data are decrypted and stored. Data can be extracted for Merck KGaA review and analysis at any time.

It is the responsibility of the investigators and the trial staff to complete the eCRFs accurately and in a timely fashion. The principal or designated trial investigator will sign and date each eCRF to verify that the data has been reviewed by him/her.

This trial will not have blinding procedures as subject cohorts will be assigned to each arm according to the procedure described.

7.14 Data Monitoring Committee

The trial will not utilize a data monitoring committee, a safety monitoring committee or an adjudication committee.

8 Ethical and Regulatory Aspects

8.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the International Standard ISO14155 (Clinical Investigation of medical devices for human subjects – Good Clinical Practice) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their informed consent are included into the trial.

In addition, Merck KGaA, Inc. confirms that the Eeva System complies with the Essential Requirements of the European directives 93/42/EEC (Medical Device Directive) and that of the Canadian regulation on medical device (SOR/98-282).

The Investigator is responsible for the conduct of the trial at his/her site. He/She will ensure that the trial is performed in accordance with the protocol and will ensure the quality and integrity of data, following the applicable international and national guidelines.

This trial will not interfere with treatment prescription by Investigators. Accordingly, the Investigator will decide in advance the best therapeutic strategy for each patient according to current practice, regardless of the potential participation of this patient in the trial.

The Investigator is responsible for device malfunction recording and reporting, as specified in Section 6.4.2.

The investigator shall submit a progress report and end of trial notification according to the requirements of the reviewing EC, if applicable.

8.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent.

To protect the rights and welfare of trial subjects, the trial will be conducted in conformance with the Declaration of Helsinki and elements of good clinical practices as may be applied to medical devices.[1,2] The confidentiality provisions within all applicable laws and regulations will apply throughout. Obtaining informed consent in accordance with the policy of the EC, this clinical protocol, and applicable regulations is mandatory for subject participation. The sponsor will avoid improper influence on or inducement of the subject for participating in the trial. The subject informed consent document(s) must be provided in a language that the patient reads and understands. All subjects must provide voluntary, written informed consent prior to the start of any trial-related activities. This includes subjects who are the partners of the subjects, if applicable.

Informed consent should be signed prior to the day of oocyte pick up, preferably on the day of the last ultrasonography for assessment of number of follicles available. On day 1 after oocyte pick up and following assessment of the number of 2PNs available, subjects will either be enrolled in the trial or not included in the trial.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language 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 his/her designee will inform the subject verbally of all pertinent aspects of the trial *(the language used in doing so must be chosen so that the information can be fully and readily understood by laypersons)*. Depending on national regulations, a person other than the Investigator may inform the subject and sign the Informed Consent Form.

The Informed Consent Form must be signed and personally dated by the subject and the Investigator. The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator. A copy of the signed and dated information and consent form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be forwarded to each subject in the trial. The Investigator will explain the changes to the previous version.

Merck KGaA and the EC must review and approve the informed consent documentation and any modifications to the consent materials prior to use. The approved informed consent documentation should have a version number or version date. The informed consent process (including time and date of discussion), should be documented in the subject's medical record and signed/dated by the individual (investigator or designee) who recorded it. The original

signed consent form should be filed in the subject's medical record and a copy of the signed informed consent documentation given to the subject.

In the event of a consent form revision, enrolled subjects may be required to re-consent, as determined by the reviewing EC.

8.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, 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.

The Investigator must ensure that the subjects' anonymity is maintained. On the CRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by their assigned identification numbers. If subject names are included on copies of documents submitted to the Sponsor, the names must be obliterated and the assigned subject numbers added to the documents.

The Investigator should keep a separate log of subjects' identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the Sponsor, such as signed Informed Consent Forms, should be maintained in strict confidence by the Investigator.

Only authorized persons will have access to identifiable personal details, if required for data verification. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and Health Authority inspections will be kept strictly confidential. The Investigator agrees to provide direct access to these documents to the Sponsor and to Health Authority representatives. The Investigator is responsible for retrieving information from personal medical records.

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

8.4 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents including informed consent forms to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File (TMF) at Merck KGaA.

The trial must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

8.5 Health Authorities

The clinical trial protocol and any applicable documentation (e.g. Subject Information and Informed Consent Form) will be submitted or notified to the Health Authorities in accordance with the regulations of the countries involved in the trial.

9 Trial Management

9.1 Electronic Case Report Form Handling

The main purpose of the eCRF is to obtain those data required by the clinical trial protocol in a complete, accurate, legible and timely fashion. The data in the eCRF should be consistent with the relevant source documents. .

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. Merck KGaA will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

9.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible.

Additionally, any other documents containing source data must be filed. This includes ICF, Protocol, and Investigators reports. Such documents must bear at least the subject number and the date when the procedure was performed

9.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Sponsor (or designee), and must be ready for audit as well as for inspection by Health Authorities during and after the trial and must be safely archived for at least 5 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial, final trial report or first publication, whichever comes later. The documents to be thus archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

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, and/or as per applicable GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

9.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the International Standard ISO14155.

Representatives of Merck KGaA and/or its designee (PPD) will monitor the registry. Monitoring, data management, data cleaning and auditing procedures developed by Merck KGaA or designee will be followed. These procedures are in compliance with ISO 14155 GCP guidelines and ensure the acceptability of the data. The Investigator must make available all medical records and regulatory documentation at every monitoring visit. The Merck KGaA representative or designee will evaluate the EDC data for completeness and clarity, and for verification of the data with source documents in accordance with an agreed Data Management Plan and Monitoring Plan. Any discrepancies found are to be clarified by the Investigator or designee. Appropriate considerations for medical confidentiality and data protection will be maintained at every visit.

9.5 Assessment of Clinical Investigators and Sites

Investigators will be responsible for fulfilling the clinical trial requirements as specified in this clinical protocol. The trial center must have the necessary resources to comply with the requirements. The following criteria will be used to select investigators for participation in the clinical trial.

- Investigator is qualified by training and expertise in IVF/ICSI science and methods use.

- Investigator and clinical research staff have experience with IVF/ICSI clinical studies and have the time to conduct the trial in accordance with the clinical protocol.
- Agreement to comply with clinical protocol and regulatory requirements.
- Adequate volume of potential patients.
- Appropriate facilities, resources, and equipment.
- An expressed desire to participate in the trial.
- Willing to undergo required trial training.
- Have completed training on the Eeva system.

9.6 Trial Training

All investigators will sign the appropriate Eeva trial-related agreements before they are added to the clinical trial.

Training of trial personnel will be documented on the appropriate training record form and maintained with the site and Merck KGaA trial files which are centrally maintained by the CRO PPD. Clinical research staff will be supplied with the clinical protocol, instructions for use, case report form instructions, and other supporting materials.

Topics to be covered at the training may include the following, as appropriate.

- Clinical protocol overview and trial timeframes
- Subject screening and eligibility criteria
- Informed consent procedure
- Eeva instructions for use
- Eeva system malfunctions
- Electronic data capture system, eCRF completion instructions and corrections
- Monitoring procedures
- EC policies and procedures
- Regulatory requirements and compliance

Merck KGaA technical personnel and Monitors (PPD) may be present during this trial to provide technical support. Also, an investigators' meeting may be considered prior to the start of the trial for the purpose of trial-related training.

9.7 Required Trial Equipment

The Eeva system will have been previously installed on site for clinical use.

9.8 Site Activation and Supply of Trial Materials

Before a patient is enrolled at a trial site, the investigator must have been initiated and be in receipt of written confirmation (email or letter) from Merck KGaA (or designee) that the site can start. In addition, the following documentation must be on file at Merck KGaA:

- EC favorable opinion/approval letter for the clinical protocol and informed consent documentation (including any subject recruitment materials)
- EC membership list or voting list
- Fully executed Clinical Research Agreement
- Executed Non-Disclosure Agreement (or Clinical Research Agreement)
- Curriculum Vitae (investigator, sub-investigators, research coordinator) – current within 2 years, signed and dated
- Current laboratory certifications, if applicable

Merck KGaA will provide the electronic data capture system. Investigators will be provided with the clinical protocol, training, informed consent information and templates, electronic case report form instructions, and other supportive documents required for the trial.

9.9 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable 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/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation Clinical Trial Report and Publication Policy

9.9.1 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH Topic E3 will be written by the Sponsor in consultation with Merck KGaA responsible, the Coordinating Investigator and assigned Medical Writer. An initial report will be generated based on the data that is accumulated when 50% of the subjects have completed the trial with implantation results. Additionally, an interim report will be generated based on the accumulated trial data. The data cutoff date for each report will be pre-specified in its SAP.

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

9.10 Publication

If the institution or investigator prepares any presentation or publication relating to the trial, the institution or investigator will provide Merck KGaA with a draft of the same for Merck KGaA's review and comment, of which comments the institution or investigator will give due consideration. Merck KGaA will return comments to the institution or investigator within thirty (30) days after receipt of the draft from the institution or investigator. In the event that the institution or the investigator and Merck KGaA differ in their opinion or interpretation of data in the publication, the parties will resolve such differences in good faith through appropriate scientific debate. In addition, the institution or investigator will delay any proposed publication/presentation an additional sixty (60) days, in the event Merck KGaA so requests, to enable Merck KGaA to secure patent or other proprietary protection.

The first publication will be a publication of the results of the analysis of the primary endpoint(s) that will include data from all trial sites.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole 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.

10 Intellectual Property

During the term of this trial and thereafter, Institution, its employees, agents, subcontractors or affiliates will not disclose confidential information (other than to Merck KGaA or Merck KGaA-designated parties) without Merck KGaA's prior written consent. "Confidential information" will include the protocol, eCRFs, and all materials and information concerning Merck KGaA and the trial disclosed to the Institution or Investigator by Merck KGaA or developed as a result of conducting the trial, except any portion thereof which:

- Is known to Institution, its employees, agents, subcontractors or affiliates before receipt thereof under this protocol, as evidenced by its written records;
- Is disclosed to Institution, its employees, agents, subcontractors or affiliates after acceptance of this protocol by a third party who has a right to make such disclosure in a non-confidential manner; or
- Is or becomes part of the public domain through no fault of the Institution, its employees, agents, subcontractors or affiliates.
- Nothing in this trial will be construed to restrict the Institution or Investigator from disclosing confidential information as required by law or court order or other regulatory order or request,

provided in each case the party requested to make such disclosure will timely inform Merck KGaA and use all reasonable efforts to limit the disclosure and maintain the confidentiality of such confidential information to the extent possible. In addition, the disclosing party will permit Merck KGaA to attempt to limit such disclosure by appropriate legal means.

- Further, during the term of this protocol and thereafter, the Institution, its employees, agents, subcontractors or affiliates will not use the confidential information for any purpose other than that indicated in this protocol and the clinical research agreement without Merck KGaA's prior written approval.
- Institution, its employees, agents, subcontractors or affiliates will not disclose to Merck KGaA any information which is confidential or proprietary to a third party unless Institution has first obtained the prior written approval of both such third party and Merck KGaA.

11 Trial or site Discontinuation

The Sponsor may temporarily or permanently discontinue the trial at a single site or at all sites for ethical, compliance or other reasons. If this is necessary, the Sponsor will endeavor to provide advance notification to the site. If the site or trial is suspended or discontinued, the Investigator will be responsible for ensuring prompt notification to the EC/IRB. Where required by local regulations, the Sponsor will be responsible for informing the EC/IRB of trial or site discontinuation.

12 Trial Closure

Upon completion (when all subjects enrolled have completed the 5-8 weeks Ultrasound or Clinical Pregnancy data collection requirements or have previously exited the trial, and the eCRFs and queries have been completed) or termination of the trial, Merck KGaA will notify the sites.

Close-out activites will be performed. Any unused trial materials will be collected and returned to Merck KGaA and/or its designees. The monitors (PPD) will ensure that the investigator's regulatory files are up to date and complete, that printed CRFs are provided as pdf files to the sites, and that any outstanding issues from previous visits have been resolved. Other issues that may be reviewed with the investigator include: discussing record retention requirements (refer to the Section on Investigator Records), publication policy, and notifying the EC of trial closure, etc.

13 References

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