Clinical Trial Protocol

Trial Protocol Number	MS200497_0006
Title	A phase IV, single-blinded, prospective, randomized, controlled, multi-center study to compare the clinical outcomes of GERI+ time lapse system with a conventional embryo culture and assessment system Short title: TICON-Day 3, Time lapse versus conventional method in Day 3 embryo culture and assessment
Trial Phase	Phase IV
Coordinating Investigator	PPD , Address: PPD PPD E-mail address: PPD
Trial center(s) /country(ies)	Approximately 16 centers in 7 countries: Italy, Spain, Portugal, France, Denmark, Norway, Canada
Sponsor	Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany Medical Responsible: PPD and PPD
Protocol Version	Version 3.0/ Jan 31, 2018

[redacted]

SIGNATURE PAGE

Sponsor representatives responsible for the trial:

We approve the design of the trial.

PPD

PPD

PPD

PPD

PPD

Signature *Date of Signature*

PPD

Merck KGaA

Frankfurter Str. 250, 64293 Darmstadt, Germany

Mobile: PPD

E-mail: PPD

PPD

PPD

PPD

Signature *Date of Signature*

PPD

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Frankfurter Str. 250, 64293 Darmstadt, Germany

Mobile: PPD

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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

PPD PPD

Signature *Date of Signature*

PPD

Title: PPD

Address: PPD

PPD

Phone: PPD

Mobile: -

E-mail: PPD

Principal Investigator Signature

Trial Title: A phase IV, single-blinded, prospective, randomized, controlled, multi-center study to compare the clinical outcomes of GERI+ time lapse system with a conventional embryo culture and assessment system (TICON-Day 3)

Trial Number: MS200497_0006

Protocol Version/Date: Version 3.0 / Jan 31, 2018

Center Number:16

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, 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*

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
AFC	Antral Follicle Count
AMH	Anti-Müllerian Hormone
ART	Assisted Reproductive Technologies
ASADE	Anticipated Serious Adverse Device Effect
CAE	Clinical Applications Engineer
CE	European Conformity
COS	Controlled Ovarian Stimulation
CRF	Case Report Form
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EEVA	Early Embryo Viability Assessment
ET	Embryo Transfer
EU	European Union
E2	Estradiol
FA	Full Analysis
FHB	Fetal Heart Beat
FPI	First Patient In
FSH	Follicle Stimulation Hormone
GERI+	Genea Embryo Review Instrument Plus
hCG	Human Chorionic Gonadotropin
ICF	Informed Consent Form
ICSI	Intracytoplasmic Sperm Injection
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVF	In Vitro Fertilization
LPI	Last Patient In
LPO	Last Patient Off study
NCA	National Competent Authorities

PN	Pronuclear stage
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SA	Subgroup Analysis
SAP	Statistical Analysis Plan
SD	Standard Deviation
TL	Time-lapse
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

1. SYNOPSIS

Trial title	A phase IV, single-blinded, prospective, randomized, controlled, multi-center study to compare the clinical outcomes of GERI+ time lapse system with a conventional embryo culture and assessment system
Trial number	MS200497_0006
Sponsor	Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
Trial type	Phase IV company sponsored trial
Coordinating Investigator	TBC
Trial center(s)/country(ies)	16 Centers in 7 Countries: Italy, Spain, Portugal, France, Denmark, Norway, Canada
Study duration	21 months recruitment time + 3 months observation time = 24 months from FPI (First Patient In) until LPO (Last Patient Off study)
Trial objectives	The main objective of this trial is to evaluate the overall clinical value of GERI+ as an integrated embryo culture and assessment system, providing an undisturbed culture environment, continuous monitoring of embryo development and automated scoring using a predictive algorithm.
Trial design and plan	Single-blinded, prospective, randomized, controlled, multicenter trial with two treatment arms. No interim analysis is planned.
Planned number of subjects	1,386
Study population	IVF/ICSI patients
Main inclusion and exclusion criteria	Inclusion: 1. Couples with ≤ two failed fresh IVF/ICSI embryo transfer cycles.

	2. Age ≥ 18 and ≤ 40 years 3. BMI: 18-30 kg/m^2 4. Normal uterine cavity under ultrasound. 5. Subject and her husband/partner must have read and signed the Informed Consent form. 6. At least four normally fertilized oocytes (2PN) in the current cycle. <u>Exclusion:</u> 1. Male with non-ejaculated sperm 2. Subjects with abnormal, undiagnosed gynecological bleeding or with genitourinary malformations. 3. Subjects with any contraindication to COS for ART or to gonadotropins. 4. Planned "freeze all" cycle (oocytes or embryos). 5. Planned PGS or PGD cycle. 6. Concurrent participation in another clinical study.
Investigational Medicine Product	Not applicable.
Investigational Medical Device	GERI+ incubator equipped with EEVA and GERI Assess software.
Planned duration of observation for each subject	10-12 weeks.
Primary endpoint(s)	Clinical pregnancy with positive fetal heart beat in gestational week 6-8 after fresh embryo transfer on Day 3.
Secondary endpoint(s)	1. Number of utilizable embryos 2. Number of good quality embryos 3. Number of non-viable embryos 4. Implantation with positive fetal heart beat 5. Biochemical pregnancy 6. Ongoing pregnancy

	7. Multiple pregnancy 8. Ectopic pregnancy 9. Spontaneous miscarriage
Estimated Trial calendar	FPI: April 2018 LPI: December 2019 LPO: March 2020 Trial Report Date: October 2020

2. SPONSOR, INVESTIGATOR AND ADMINISTRATIVE STRUCTURE

- The Sponsor of this trial is Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany.
- It is planned to perform the trial at approximately 16 sites in about 7 countries from Europe (EU) and Canada.
- Principal Investigator: TBD
- PPD is the Contract Research Organization (CRO) appointed for trial management including monitoring activities.
- PPD 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.

3. BACKGROUND INFORMATION

Embryo incubators equipped with function of continuous time-lapse (TL) imaging have been widely used in IVF laboratories. However, there is still a lack of consolidated evidence to ascertain whether embryos cultured in an undisturbed environment and assessed by TL images in combination with predictive algorithm may yield superior clinical outcomes than those cultured in conventional incubators and evaluated by benchtop microscopes (Armstrong et al., 2015a; Armstrong et al., 2015b). In general, there are two potential benefits of TL incubators:

A. The undisturbed embryo culture conditions

When cultured in conventional incubators, the embryos of a patient are usually taken out from the incubator and examined at least twice with the bench-top microscopy for Day 3 fresh embryo transfer, the first time on Day 1 for fertilization check, and the second time on Day 3 for cleavage-stage embryo viability assessment (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011). If the embryos of more than one patients are stored in one conventional box incubator, the exposure of embryos to external environment caused by the frequent opening of incubator doors are even more. Such disturbance to the homeostatic temperature and pH conditions has been proved to be detrimental to the growth of embryos (Zhang et al., 2010).

A recent single-center RCT showed that embryos cultured in EmbryoScope (Vitrolife, Sweden), a box TL incubator, showed no benefit in clinical outcomes over those cultured in conventional box incubators (Park et al., 2015). This might be explained by the fact that culturing of embryos of multiple patients in one big chamber may inevitably lead to lid openings disturbing the culture conditions. In contrast, TL incubators such as GERI (Genea Embryo Review Instrument, Genea Biomedx, Australia) and GERI+ (Genea Biomedx, Australia) are equipped with both microscopes/cameras and independent incubation chamber for each individual patient, providing undisturbed homeostatic conditions throughout the culture period. High-level evidence is needed to confirm whether undisturbed culture conditions, as provided by GERI or GERI+ incubators, may contribute to the optimal growth of embryos.

B. The continuous monitoring of embryos

The conventional method for embryo assessment developed in 1980s is based on daily observations of embryos under regular epi-light microscopy (Fisch et al., 2001; Scott, 2003). This system relies on the static images of embryos analyzing the cell numbers, symmetry of the blastomeres, multinucleation, fragmentation, vacuoles, and etc. (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011). Due to the limited number of images examined, the predictive value of such embryo assessment system is very limited, as elaborated in detail below:

1) The status of embryo fragmentation and multinucleation are usually highly dynamic (Bromer and Seli, 2008).
2) Irregular divisions such as direct cleavage (i.e. division from one cell to three cells) (Athayde Wirka et al., 2014) and reverse cleavage (fusion of two cells) (Liu et al., 2014) are hallmarks of embryos of poor quality but cannot be captured by conventional microscopic observation.
3) Studies showed that cell number and morphology of approximately 50% of the embryos may change within 4 hours from 38 to 42 h post insemination, resulting in alternations in their assessment (Bromer and Seli, 2008; Montag et al., 2011).
4) Embryo assessment only by Day 3 morphology does not necessarily reflect the viability and developmental potential of the embryo (Milki et al., 2002; Rijnders

and Jansen, 1998).

The GERI Assess software embedded in the GERI+ system facilitates the identification of the irregular divisions and recording of the developmental timing and cell numbers at different developmental stages by continuous TL imaging. Again, evidence is needed to prove whether such objective and continuous assessment of embryos will lead to better clinical outcomes.

EEVA (Early Embryo Viability Assessment) is an automated embryo prognostic software. It analyzes the dark-field images obtained through a GERI+ incubator and assesses the embryo quality automatically based on morphokinetic parameters and morphology (VerMilyea et al., 2014; Wong et al., 2010). There is also another embryo assessment model based on morphokinetic parameters (Rubio et al., 2014). However, a well-accepted universal empirical algorithm is currently unavailable. The benefit of embryo assessment based on morphokinetics is still in debate and contradicting results have been reported in several single-center RCTs using different algorithms (Adamson et al., 2016; Armstrong et al., 2015b; Basile et al., 2015; Goodman et al., 2016).

In this multi-centric, single-blinded, randomized and controlled trial we will investigate whether embryos cultured under the undisturbed conditions and assessed with continuous monitoring of morphological and morphokinetic parameters may lead to better clinical outcomes as compared to embryos cultured in conventional incubators and assessed by bench-top microscopy. The main aim of this trial is to evaluate the overall clinical value of GERI+ as an integrated embryo culture and assessment system, providing an undisturbed culture environment, continuous monitoring of embryo development and automated scoring using a predictive algorithm.

4. BENEFIT-RISK ASSESSMENT

The GERI+ system is composed of the following two components:

1) GERI+ embryo incubator, a CE marked Class IIA medical device.
2) EEVA automated embryo prognosticsoftware, a CE marked Class IIA/B medical device.

The analysis of the risks and benefits demonstrated that, the GERI+ system met its safety and performance requirements and the device fulfilled its intended use as claimed by Genea Biomedx, the manufacturer of GERI+ incubator, in the CE certificate. In addition, Merck KGaA confirms that the GERI+ incubator and EEVA system comply with the Essential Requirements of the European directives 93/42/EEC (Medical Device Directive). Following is a description of potential risks and expected benefits that may be associated with the use of GERI+ system.

4.1 Risks Related to the GERI+ system

There is a potential risk to embryonic viability brought about by suboptimal culture conditions. The GERI+ incubator minimizes the risks that might potentially impact the embryo survival and growth as CCI

CCI

CCI

EEVA is a medical device prognostic software used adjunctively with conventional

morphological assessment, and no risk is expected for clinical use of EEVA in embryo assessment.

4.2 Benefits of the GERI+ system

The GERI+ system provides undisturbed and comparable embryo culture conditions to the conventional embryo culture system.

Adjunctive use of the EEVA prognostic test (early version with 2 EEVA categories, High and Low) has been shown to significantly improve the ability to identify embryos that would reach the usable blastocyst stage, with a specificity of 84.7% (52% for morphology alone) and a positive predictive value (PPV) of 54.7% (34.5% for morphology alone) (Conaghan et al., 2013). Specificity (or true negative rate) is the percentage of embryos that have a negative "test" result ("EEVA Low") and a negative outcome (non-usable blastocyst). The EEVA test also reduced inter-embryologist specificity variability in embryo assessment (Conaghan et al., 2013). The value of EEVA in predicting blastocyst formation and improving consistency of embryo assessment was later reconfirmed in a prospective multicenter study (Diamond et al 2015). Quite recently, Adamson et al (2016), in a prospective concurrent controlled trial comparing adjunctive use of EEVA (version 2.0, with 2 EEVA categories, High, and Low) against conventional morphology alone, showed significantly higher Day 3 implantation (30.2% vs 19.0%) and clinical pregnancy rates (46.0 vs 32.1%) in the 2 groups respectively (Adamson et al., 2016). They conclude that this non-invasive test adds valuable information to conventional morphological assessment (Adamson et al., 2016; Diamond et al., 2015).

An additional benefit is that the GERI+ system generates consistent and objective data that help embryologists to standardize embryo assessment between embryologists and IVF clinics (Adamson et al., 2016; Diamond et al., 2015). The subjects included in this trial may also benefit from the GERI+ system by getting more viable embryos with high implantation potential for transfer.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

The main aim of this trial is to evaluate the overall clinical value of GERI+ as an

integrated embryo culture and assessment system, providing an undisturbed culture environment, continuous monitoring of embryo development and automated scoring using a predictive algorithm

5.2 Endpoints

5.2.1 Primary Endpoint

The primary end point is clinical pregnancy with fetal heartbeat. It is defined as the pregnancy diagnosed by ultra-sonographic or clinical documentation of at least one fetus with heart beat in gestational week 6 to 8. It includes ectopic pregnancy (Zegers-Hochschild et al., 2009).

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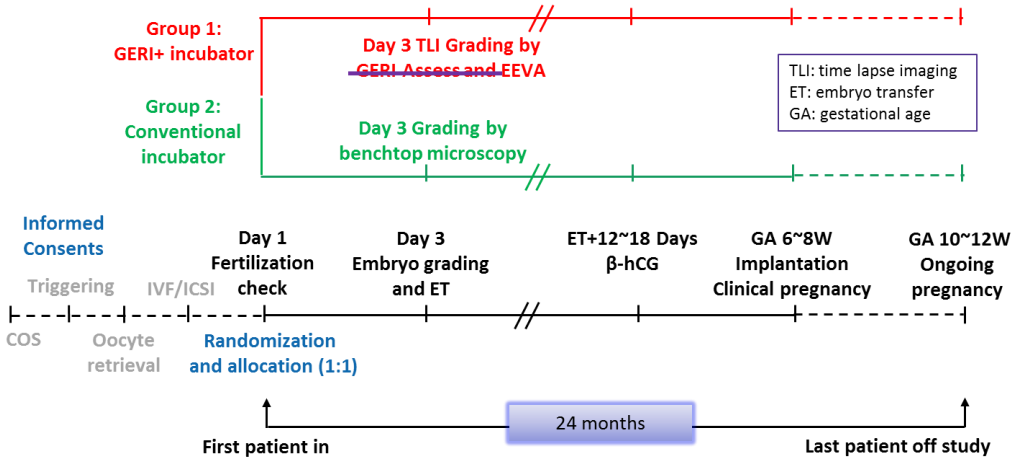
5.2.2 Secondary Endpoints

- The number of Utilizable Embryos: defined as the number of embryos that are transferred and/or cryopreserved per subject.
- The number of Good Quality Embryos: defined as the number of embryos with 7 or more blastomeres, <25% fragmentation, size and symmetry of blastomeres appropriate to the cell number, and no evidence of multinucleation, based on the morphology on Day 3 of embryo culture per subject (modified from Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011).
- The number of Non-viable Embryos: defined as the number of embryos in which development has been arrested for at least 24 h or in which all the cells have degenerated or lysed (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011).
- Implantation with positive fetal heart beat: Implantation refers to the attachment and subsequent penetration by the zona-free blastocyst (usually in the endometrium) that starts 5 to 7 days after fertilization (Zegers-Hochschild et al., 2009). A successful implantation is defined as the presence of one gestational sac with fetal heart beat under ultrasonography at gestational weeks 6-8.
- Biochemical Pregnancy: defined as a pregnancy diagnosed only by the detection of hCG in serum or urine and that does not develop into a clinical pregnancy (Zegers-Hochschild et al., 2009).
- Ongoing Pregnancy: defined as the presence of viable fetuses identified by ultrasonography at gestational weeks 10-12 (Rubio et al., 2014).

- Multiple Pregnancy: defined as a pregnancy with more than one fetus. It is identified by ultrasonography at gestational weeks 10-12 (Zegers-Hochschild et al., 2009).
- Ectopic Pregnancy: defined as a pregnancy in which implantation takes place outside the uterine cavity. It is identified by ultrasonography at weeks 6-8 (Zegers-Hochschild et al., 2009).
- Spontaneous Miscarriage: the spontaneous loss of a clinical pregnancy before 20 completed weeks of gestational age (18 weeks after fertilization) (Zegers-Hochschild et al., 2009). In this study, the spontaneous miscarriage is tracked up to 10-12 weeks of gestational age.

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan



This is an interventional, multi-center, single-blinded (the subjects are blinded while the clinicians and the embryologists are not blinded), randomized, controlled clinical trial and will include 16 investigational sites. Each site will conduct the trial using the same clinical protocol. Recruitment of subjects at each site, with subjects who voluntarily consent to participate, is expected to continue for up to 21 months. Competitive enrollment is applied to maximize subject recruitment. Additional follow-up after embryo transfer will take place up to 12-18 days to verify hCG positivity, at 6-8 gestational weeks to verify implantation and clinical pregnancy, and 10-12 gestational weeks to verify ongoing pregnancy. Total duration of the trial, including start up (First patient in, FPI) and close out activities (Last patient off study, LPO), is approximately 24 months.

6.2 Discussion of the Study Design

The design selected for this trial is defined based on the need to locally validate the value of GERI+ system to improve clinical outcomes by collecting real life clinical data. It will be the first multi-centric RCT to be implemented in Europe testing the potential benefit brought about by the GERI+ integrated embryo culture and EEVA assessment system over conventional embryo culture and microscopy-based static morphological assessment method. Considering the large sample size, it will also be a landmark for the future application of this integrated continuous monitoring and undisturbed embryo culture and assessment system worldwide.

The rate of clinical pregnancy with positive fetal heart beat (CPR with positive FHB) will be studied in this trial as the primary endpoint. CPR with positive FHB provides strong evidence for continued viability of embryos, following culture and assessment.

This trial is single-blinded for subjects and is open to embryologists who will process, culture and grade the embryos, and to clinicians/nurses who will perform the embryo transfer and pregnancy tests and scans. Considering the volume of IVF and ICSI patients in these 16 sites participating in this trial, recruitment of subjects should be completed within 21 months.

6.3 Inclusion of Special Populations

Not applicable.

6.4 Enrollment of Trial Population

All subjects must meet all the inclusion criteria and must not meet any of the exclusion criteria.

6.4.1 Inclusion Criteria

1) Couples with ≤ two failed fresh IVF/ICSI embryo transfer cycles.
2) Age ≥ 18 and ≤ 40 years.
3) BMI: 18-30 kg/m^2.
4) Normal uterine cavity under ultrasound.
5) Subject and her husband/partner must have read and signed the Informed

Consents form.

6) At least four normally fertilized oocytes (2PN) in the current cycle.

6.4.2 Exclusion Criteria

1) Male with non-ejaculated sperm.
2) Subjects with abnormal, undiagnosed gynecological bleeding or with genitourinary malformations.
3) Subjects with any contraindication to COS for ART or to gonadotropins.
4) Planned "freeze all" cycle (oocytes or embryos).
5) Planned PGS or PGD cycle.
6) Concurrent participation in another clinical study.

6.5 Recruitment of Participants

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

6.6 Method of Blinding

- Blinding: The trial is blinded to the subjects. The trial is not blinded to the embryologists handling the embryos or the clinicians/nurses conducting embryo transfer and pregnancy tests/scans.
- Emergency Un-blinding: in case of a medical emergency, the subject will be informed by her trial doctor or embryologist which incubator and embryo grading method are used for her embryos.

6.7 Randomization and Allocation of Subjects

After signing the informed consent form, all eligible subjects will be randomized and allocated to either of the two treatment groups immediately after fertilization check on Day 1 of embryo culture.

A stratified block randomization with fixed block length and allocation ratio 1:1 will be used. The stratification will be based on site and the age of subject (age group 18-35 vs. 36-40). Randomization will be accomplished using the Interactive Web Response Services (IWRS) system. An independent statistician will generate the

randomization schedule and upload to the IWRS system. All randomization codes will not be reused and subjects who discontinue the study early will not be replaced.

A subject can be considered as a drop-out during the study if she is randomized but primary endpoint data is not available for this subject, for whatever reason. Reasons for study discontinuation will be recorded in the **Trial Exit eCRF**.

6.8 Description of Treatment and Definition of Exposure to Trial Medication

Treatment is defined as the process of embryo culture and assessment, whereas no trial medication is applied in this trial.

In the experimental treatment arm:

- On Day 1 of embryo culture, all 2PN zygotes are transferred by embryologists into the GERI dishes which have been pre-equilibrated. The GERI dishes are then placed in the GERI+ incubator for both bright-field and dark-field time lapse monitoring until Day 3. Pre-mixed Gas with 6% CO_2 (or whichever CO_2 concentration is required to meet manufacturers requirements for optimal pH of their culture media) and 5% O_2 is recommended.

. If a different gas composition is used, this must be the same for both test and control arms.

- On Day 3 of embryo culture, all embryos are reviewed firstly by GERI Assess software, using bright-field imaging. Five parameters, including cell number, abnormal divisions (reverse cleavage and direct cleavage), multinucleation, fragmentation and symmetry of blastomeres are annotated in the GERI Assess system.
- It is recommended that Day 3 cell count is assessed at 68±1 hours post-insemination across all sites, for generation of final EEVA score (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011).
- The prognostic EEVA information, used adjunctively with morphology assessment will assist embryologists to further identify, for transfer, the embryo(s) with optimal potential to form a blastocyst.
- Finally, the embryo(s) with the highest EEVA grade are transferred. **Note:**

- Cell number should be entered via the EEVA system, to generate a final EEVA test result (based on the dark-field imaging). A second review of embryo videos should be carried out to confirm P2 and P3 parameters, and when required, a manual update should be carried out.
- EEVA results should be applied only to those embryos of overall good and fair quality i.e. ≥ 6 cells with ≤ 25% fragmentation and without severe asymmetry. EEVA test results are not recommended for adjunctive use with poor quality embryos i.e. ≤ 5 cells or 6 cells with > 25% fragmentation and with severe asymmetry.
- Priority should be given to transfer embryos without direct cleavage or reverse cleavage.
- If the EEVA result shows "NR" (No Result) or there are only poor-quality embryos, the embryologist will grade the embryos with morphology (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011) and apply the decision grid used in the control group.

- If two or more embryos have the same EEVA score, preference should be given to the embryos with better morphology and subject to the embryologist's decision grid used in the control group.

• National/regional regulations and procedures will be followed to manage the remaining embryos, provided that in each case the provisions of the Germany Embryo Protection Act are observed.

In the control treatment arm:

• On Day 1 of embryo culture, all 2PN zygotes are transferred by embryologists into the GERI dishes which have been pre-equilibrated with embryo culture medium routinely used in their laboratory. The GERI dishes are then placed in a conventional incubator for culture until Day 3. Gas with 6% CO_2 (or whichever CO_2 concentration is required to meet manufacturers requirements for optimal pH of their culture media) and 5% O_2 is recommended. If a different gas composition is used, this must be the same for both test and control arms.
• On Day 2 of embryo culture, the embryos may or may not be taken out of the incubators for observation using bench-top microscopy, to follow the routine protocols of the laboratory.

- On Day 3 of embryo culture, all embryos are assessed using a bench-top microscope by embryologists, at a recommended time of 68±1 hours post insemination. (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011). The embryo(s) with optimal cell stage and grade will be transferred. National/regional regulations and procedures will be followed to manage the remaining embryos, provided that in each case the provisions of the Germany Embryo Protection Act are observed.

Please be advised that there is no restriction on the number of embryos to be transferred but we recommend a single embryo transfer in this study.

6.9 Criteria for Subject Withdrawal

Subjects will be informed that they have the right to withdraw from the trial at any time between randomization and completion of the study, 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, including the reason for withdrawal.

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

6.10 Definition of Completion of the Study

Completion of the study is achieved when all subjects finish the test for ongoing pregnancy.

The subject may complete and exit from this trial at the following time points:

- Test for hCG 12-18 days post embryo transfer: a subject will exit from the trial if the blood or urinary test result for hCG is negative. Otherwise subject waits until the test for clinical pregnancy.
- Test for clinical pregnancy at gestational weeks 6-8: a subject will exit from the trial if the ultrasound test result for clinical pregnancy is negative. Otherwise the subject waits until the test for ongoing pregnancy.
- Test for ongoing pregnancy at gestational weeks 10-12: a subject will finish the

trial at this time point, regardless of whether the ultrasound result for ongoing pregnancy is positive or negative.

- Miscarriage: a subject will exit from the trial upon spontaneous or therapeutic miscarriage.

6.11 Potential Confounding Factors

Smoking status, age, gestational history, COS strategy, embryo culture media, luteal phase support, number of embryos transferred and site locations are potential confounding factors in this study. Multivariate logistic analysis will be performed with these factors in the model as covariates when testing the primary endpoint.

6.12 Estimated Trial Calendar

Trial will begin enrollment in April 2018 and will continue until 1,386 subjects are enrolled. Last patient off study is expected to be accomplished by March 2020 and close-out activities and clinical trial report will follow within 7 months after.

7. STUDY PROCEDURES, ASSESSMENTS AND DATA COLLECTION

Embryos will be observed until they are transferred and then the clinical outcome of all subjects will be recorded until the ongoing pregnancy is verified (up to 10-12 weeks of gestation).

Subjects will be followed up until lost to follow-up, meeting the withdrawal or premature discontinuation criteria (as defined in Sections 6.9 and 10.13), or exiting from the trial (as defined in Section 6.10), whichever comes first.

7.1 Baseline Data Collection

Before controlled ovarian stimulation (COS), potential subjects in the trial will undergo pre-ICSI/IVF preparations per the standard protocol currently in force at each site. Collection of trial-related information may take place only after the potential subject and her partner have given voluntary, documented, informed consents (ICFs).

The following information is recorded in the **Screening and Baseline eCRF**:

- Date of Informed Consents to be signed by potential subjects and their partners;
- Demographics, pregnancy history, cause of infertility, hormone levels (FSH, LH,

E2 and AMH) and antral follicle count (AFC) of the potential subject, as well as the date of data collection.

7.2 Data Collection on Day of Ovulation Triggering

The following data on COS and ovulation triggering is recorded in the **COS and Ovulation Triggering eCRF:**

- Downregulation and COS regimen, total dose of gonadotropin, type of gonadotropin, the date of the first dose of gonadotropin and the duration of COS;
- The date, time and method of ovulation triggering, and the pre-trigger hormonal and ultra-sonographic data.

7.3 Data Collection on Day 0-3 of Embryo Culture

Oocyte retrieval and ICSI/IVF will follow the local protocols/practice in place at each trial site. All oocytes/zygotes are cultured in routine culture dishes in conventional incubators for both treatment groups until fertilization check on Day 1 of embryo culture. Immediately after confirming the number of 2PN zygotes, the last step of subject screening is accomplished and randomization is conducted.

The following information is captured in the **OPU** (Oocyte pick-up) **and Insemination eCRF**:

- Date and time of oocyte retrieval, the number of oocytes retrieved and the maturation status: GV, MI, MII, and degenerated;
- Date, time and method(s) of insemination: (i) ICSI (ii) IVF (iii) both;
- Date and time of fertilization check and the number of 2PN zygotes.
- Randomization and allocation of subjects.

After randomization and allocation, the 2PN zygotes are transferred to GERI dishes with pre-equilibrated culture media and are relocated to either GERI+ incubators or conventional incubators. The embryo culture, assessment and transfer are described in detail in Section 6.8 Description to Treatment.

The following data is collected in the **Embryo Culture, Assessment and Transfer eCRF**:

- Embryo culture conditions (including humidification, gas phase, brand of oil and

media);

- Date and time of embryo assessment;
- Status and fate of each individual embryo;
- Date and time of embryo transfer;
- The number of embryos(s) transferred;
- The procedure of embryo transfer: with ultrasound guidance or not, and difficulty.

7.4 Data Collection on Day of hCG Test

A standard urine or blood serum hCG test is performed 12-18 days after embryo transfer, following the routine practices at the trial site. The following information is recorded in the **LPS** (Luteal Phase Support) **and Clinical Outcome eCRF:**

- Strategy of LPS;
- Date of the hCG test;
- Method of hCG test and the result;
- Quantitative β-hCG, as applicable.

If the result of the hCG test is negative, the subject will have completed the trial and be exited at that time (complete **Trial Exit eCRF**).

7.5 Data Collection for Clinical Pregnancy Ultrasound Test

The ultrasound test to verify clinical pregnancy is carried out between gestational weeks 6 and 8. The following information is recorded in the **LPS and Clinical Outcome eCRF**:

- Date of the last ultrasound test for clinical pregnancy;
- Result
  - Number of intrauterine gestational sacs
  - Number of fetal heartbeats
  - Ectopic pregnancy (Yes or No)
  - Biochemical pregnancy (Yes or No)
  - Other

If the result of the ultrasound test 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 eCRF**).

7.6 Data Collection for Ongoing Pregnancy Ultrasound Test

The ultrasound test to verify ongoing pregnancy is done between gestational weeks 10 and 12 for subjects who are confirmed as being pregnant at ultrasound scan during gestational weeks 6 to 8. The following information is recorded in the **LPS and Clinical Outcome eCRF**:

- Date of the last ultrasound test for ongoing pregnancy;
- Result
  - Number of intrauterine viable fetus;
  - Spontaneous Miscarriage (miscarriage after the initial confirmation of clinical pregnancy).

Conclusion of the clinical outcome (ongoing pregnancy or miscarriage) is recorded on the **Trial Exit eCRF** as well.

7.7 Adverse Events and Assessment of Safety

An adverse event or a serious adverse event, whether or not related to the investigational medical device, in subjects participating in the study, is not applicable. In addition, according to European Guidelines for post-marketing device studies (MEDDEV 2.12/2 rev2, dated January 2012), reporting of serious adverse events to Health Authorities is not applicable. 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 Section 7.7.1 Definitions).

Safety of GERI+ system will be evaluated by the assessment of routine embryological data collected in the eCRF (See Section 7.7.3), and by reporting of device deficiencies (See Section 7.7.4).

7.7.1 Definitions

As per the European Guidelines on medical devices (MEDDEV 2.7/3 REV 3), dated May 2015:

<u>Investigational medical device</u>

Medical device being assessed for safety or performance in a clinical investigation
NOTE: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

Adverse Event (AE)

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.
NOTE 1: This definition includes events related to the investigational device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Event (SAE)

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.
b) led to a serious deterioration in health of the subject, that either resulted in:
   - a life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function, or
   - in-patient hospitalization or prolongation of existing hospitalization, or
   - in medical or surgical intervention to prevent life threatening illness
c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

Device deficiency

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

7.7.2 Reporting period for safety surveillance

The reporting period for safety surveillance begins when the subject is included into the trial (date of randomization) and continues after embryo transfer until achievement of ongoing pregnancy. There is no live birth follow-up planned in the frame of this study.

7.7.3 Safety assessment of embryological data

To comprehensively evaluate the safety of GERI+ embryo culture system, as provided by the GERI+ incubator, we will monitor the following secondary endpoints/parameters which are closely related to the quality and viability of embryos and report to Merck Global Drug Safety after the completion of this trial:

- The number and percentage of Good Quality Embryos per subject, in both arms of study: Good Quality Embryos are embryos with 7 or more blastomeres, <25% fragmentation, size and symmetry of blastomeres appropriate to the cell number, and no evidence of multinucleation, based on the Day 3 morphology (modified from Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011)
- The number and percentage of Non-viable Embryos per subject, in both arms of

study: Non-viable Embryos are embryos in which development has been arrested for at least 24 h or in which all the cells have degenerated or lysed (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011).

7.7.4 Device Deficiency

Methods of recording Device Deficiencies

Investigators must inform, via the established customer complaint process, their local Merck KGaA contact, usually the Clinical Applications Engineer (CAE) in case of any device related complaint and/or deficiency. Feedback may consist of any alleged deficiency related to the physical characteristics, identity, quality, durability, reliability, effectiveness or performance of GERI+ system.

Genea Biomedx, the legal manufacturer of GERI+ system, will investigate device malfunctions/deficiencies and perform an evaluation to determine and document the root cause of any device deficiency. A final list of all device deficiencies occurring at the study sites during the course of the study will be attached to the clinical study report.

Reporting of Device Deficiencies

Investigators are responsible for reporting to Merck KGaA device deficiencies that may affect the culture and 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.

Genea Biomedx is responsible for reporting of device deficiencies to NCA (National Competent Authorities) according to applicable legal post-marketing reporting obligations for medical devices (e.g. Directive 93/42/EEC).

7.7.5 Reporting after defined reporting period for safety surveillance

Beyond the defined reporting period of this study, it is the responsibility of the investigators to inform any serious abnormal pregnancy outcome in subjects who participated in this study, including of any congenital anomalies in the offspring of these subjects, to spontaneously report the serious adverse events either directly to the

marketing authorization holder Genea Biomedx or to their local regulatory health authorities, if necessary, as required by the local reporting guidelines.

8. STATISTICS

8.1 Sample Size

Based on an expected clinical pregnancy rate of 30% (Adamson et al., 2016) in the control group and a 25% relative increase of clinical pregnancy rate in the experimental group, a two-sided test with an alpha level of 0.05 needs 623 subjects per group to reach a power of 80%. With a drop-out rate of 10%, 1,386 subjects (693 per group) need to be randomized. A subject can be considered as a drop-out during the study if she is randomized but primary endpoint data is not available for this subject, for whatever reason.

The calculation of sample sizes was performed using nQuery Advisor® version 7.0.

8.2 Randomization

A stratified permutated block randomization with fixed block size and allocation ratio 1:1 will be used. Randomization will be accomplished using Interactive Web Response Services (IWRS) system. The stratification will be based on site and age of the subject (18-35 versus 36-40). This guarantees, at any time, a similar number of subjects between experimental and control groups at each site.

8.3 Analysis Sets

Three analysis sets will be used: the Full Analysis dataset, the Per Protocol dataset and the Subgroup Analysis dataset.

- Full Analysis (FA-) dataset includes all randomized subjects. Subjects will be presented as randomized.
- Per Protocol (PP) dataset includes all subjects who have been treated according to the Clinical Trial Protocol and have received Day 3 fresh embryo transfer, with no major Clinical Trial Protocol violation in respect of factors likely to affect the efficacy of treatment.
- Subgroup Analysis dataset (SA):Subjects who had embryos transferred which were either good or fair (i.e. not poor quality)
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- .

The FA population is the primary analysis population. PP population is used for sensitivity analysis. SA population is used for supportive analysis.

8.4 Description of Statistical Analyses

8.4.1 General Consideration

Descriptive Statistics

For continuous variables, the following parameters will be presented: Number (N) of subjects, mean, standard deviation (SD), median, first quartile (q1), third quartile (q3), minimum, and maximum. For categorical variables, the total number ('N') of subjects and proportions will be presented. Graphical methods will be used as appropriate. Number of subjects with missing values ('Missing') will be listed for the analyses based on observed case data.

Method of handling missing data

Missing data will not be imputed.

8.4.2 Analysis of Primary Endpoint

The FHB positive clinical pregnancy rate (the number of subjects with FHB positive clinical pregnancy divided by the number of subjects with embryo transfer) for either of the two treatment groups will be computed.

Primary hypothesis will be tested between the treatment groups based on a Cochrane-Mantel-Haenzel CMH test adjusting for stratification factors providing the derived Odds Ratio and its 95% confidence interval. As sensitivity analysis, a logistic regression model with confounding factors and stratification factors as covariates will be performed. Details regarding the model and analysis will be specified in the SAP.

8.4.3 Analysis of Secondary Endpoints

- Utilization Rate: the number of transferred and cryopreserved embryos divided by the number of 2PN zygotes per subject.
- Good Quality Embryo Rate: the number of good quality embryos divided by the number of 2PN zygotes per subject.

- Non-viable Embryo Rate: the number of non-viable embryos divided by the number of 2PN zygotes per subject.
- FHB positive implantation rate is calculated per embryo transferred (IR) and per subject randomized (IR*):
  a. IR: the number of gestational sacs with positive FHB under ultrasound scan at gestational weeks 6-8 divided by the total number of embryos transferred.
  b. IR*: IR_w is calculated for each subject and not aggregated per group of patients. In the scenario where maximally two or maximally three embryos are transferred at once, the IR_w can only have two (0 and 1.0), three (0, 0.5 and 1.0) and four (0, 0.33, 0.66 and 1.0) states, respectively. As such, IR_w is an ordinally scaled categorical event. Then the overall IR* for each treatment group= $(1/n)^* \Sigma_{w=1,n} IR_w$.
- Biochemical Pregnancy Rate: the number of subjects with biochemical pregnancy divided by the number of subjects with embryo transfer.
- Ongoing Pregnancy Rate: the number of subjects with ongoing pregnancy divided by the number of subjects with embryo transfer.
- Multiple Pregnancy Rate: the number of subjects with multiple pregnancy divided by the number of subjects with ongoing pregnancy.
- Ectopic Pregnancy Rate: the number of subjects with ectopic pregnancy divided by the number of subjects with embryo transfer.
- Spontaneous Miscarriage Rate: the number of subjects with spontaneous miscarriage divided by the number of subjects with clinical pregnancy.

Descriptive statistics for all of the secondary endpoints will be provided. Detailed statistical analysis methods will be specified in the SAP.

8.4.4 Interim Analysis

Not applicable.

9. ETHICAL AND REGULATORY ASPECTS

9.1 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 as well as the provisions of German Embryo Protection Act. In particular, the Investigator must ensure that only subjects who have given their informed consent are included into the trial.

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 7.7.

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

9.2 Subject Information and Informed Consents

An unconditional prerequisite for a subject's participation in the trial is the written informed consents of the subject and her partner. Informed consents should be signed before oocyte retrieval.

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. The confidentiality provisions within all applicable laws and regulations will apply throughout. Obtaining informed consents in accordance with the policy of the EC, this clinical protocol, and applicable regulations is mandatory for subject participation. Merck KGaA 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 and her partner read and understand. All subjects and their partners must provide voluntary, written informed consents prior to the start of any trial-related activities.

Adequate information must therefore be given to the subject by the Investigator

before informed consents are 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 Merck KGaA for the purpose of obtaining informed consents. 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 partner and sign the Informed Consent Form.

The Informed Consent Form must be signed and personally dated by the subject, her partner 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 and partner prior to participation.

Whenever important new information becomes available that may be relevant to the subject and partner's consent, the written subject information sheet and any other written information provided to subjects will be revised by Merck KGaA and be submitted again to the EC for review and favorable opinion. The agreed, revised information will be forwarded to each subject and partner 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 and partners may be required to re-consent, as determined by the reviewing EC.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consents are obtained and the randomization is triggered. 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 Merck KGaA, 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 Merck KGaA, 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 Merck KGaA, 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 Merck KGaA 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 and partners consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Subject Card

Not applicable.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance covers all the subjects who are included in the study. After signing the ICF,

appropriate insurance should be conducted according to requirements of local legislation, GCP guidelines and relevant provisions of hospitals in the study. No compensation is planned for subjects participating in this trial.

9.6 Independent Ethics Committee

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 for its favorable opinion/approval. The written favorable opinion/approval of the IEC 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 Merck KGaA has obtained written confirmation of favorable opinion/approval from the concerned IEC. The IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval is 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 to Merck KGaA by the investigator. Where possible, copies of the meeting minutes should be obtained and provided to Merck KGaA by the investigator.

Amendments to the clinical trial will also be submitted to the concerned IEC, before implementation in case 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 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.

10. STUDY MANAGEMENT

The whole process of the study will be monitored remotely by the CRO. The Electronic Data Capture (EDC) system will be jointly managed by the CRO and

PPD . PPD will conduct data analysis and complete the statistical report. For eCRFs which are not completely filled or with missing data, monitors from CRO will contact Investigator for clarification.

Investigator should conduct the study according to the study protocol, ISO14155-GCP guidelines, requirements of IEC and applicable local guidelines and legislations, including, but not limited to, the provisions of the German Embryo Protection Act, and follow precautions and indications in medical practice.

10.1 Data collection and Electronic Case Report Form Handling

Merck KGaA will use an EDC system to collect subject data. The eCRFs are the primary component of EDC that the site personnel will interface with. 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 in a timely fashion. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs. 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.

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. CRO will be responsible for data processing. 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 Investigator at the completion of the trial.

In addition, embryo images (1 image every 5 minutes of culture over 3 days) and implantation data of subjects in the test group will be anonymously collected by Merck KGaA Clinical Application Engineer (CAE) twice during the duration of the study. These images will be sent to the bioanalytical department of PPD to explore the possibility of strengthening the prognostic algorithm.

10.2 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, medical and laboratory 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

10.3 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 Merck KGaA (or the CRO), 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 25 years (or per local requirements or as otherwise notified by Merck KGaA) 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 Merck KGaA.

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 local 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 Merck KGaA.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

Study monitoring, quality assurance and regulatory audits will be conducted in accordance with GCP principles, ISO14155 and site-level regulations.

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

Representatives of Merck KGaA and/or the CRO will monitor the registry. Monitoring, data management, data cleaning and auditing procedures developed by the CRO 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 onsite or remotely. The CRO 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 the CRO. Appropriate considerations for medical confidentiality and data protection will be maintained at every visit onsite or remotely.

10.5 Protocol Deviations

A protocol/GCP deviation occurs when an 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 and specific requirements of IEC.

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

10.6 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 relevant IEC 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 Merck KGaA and at the site. They will be submitted to the relevant IEC 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.

10.7 Assessment of Clinical Investigators and Sites

Investigators will be responsible for fulfilling the clinical trial requirements as specified in this clinical protocol. The site must have the necessary resources to comply with the requirements. The following criteria will be used to select investigators 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 subjects.
- Appropriate facilities, resources, and equipment.
- An expressed desire to participate in the trial.
- Willing to undergo required trial training.
- Have completed training on the GERI+ system.

10.8 Trial Training

All investigators will sign the appropriate 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. 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
- GERI+ incubator instructions for use
- Informed consent procedure
- GERI dish preparation
- EEVA software instructions for use
- GERI Assess/EEVA decision tree for embryo assessment
- GERI+ and EEVA system malfunctions
- EDC system, eCRF completion instructions and corrections
- Monitoring procedures
- EC policies and procedures
- Regulatory requirements and compliance

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

10.9 Required Trial Equipment

A GERI+ incubator and a server installed with GERI Connect & Assess and an EEVA server and monitor will have been previously installed at each site for clinical use.

10.10 Site Activation and Supply of Trial Materials

Before the first subject 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 the CRO) 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

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. GERI consumables will be supplied throughout the trial period.

10.11 Clinical Trial Report and Publication Policy

After completion of the trial, a clinical investigational report according to ISO14155 will be written by PPD in consultation with Merck KGaA responsible persons, the Coordinating Investigator and assigned Medical Writer. 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.

Institution and Investigator shall have the right to publish or present their Site Study results following from Site's own activities conducted for this trial. Any proposed publication or presentation of the Site shall be consistent with scientific standards by (i) applying the highest industry standards, including but not limited to the Good Publication Practice and the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals of the International Committee of Medical Journal Editors (ICMJE) in their current version and (ii) publishing Site Study Data first after the primary source publication of the Sponsor is made public. In addition, Institution and Investigator agree to submit any proposed publication or presentation to Sponsor's Head of Global Medical Publication, email address: medical.publication@merckgroup.com, for review at least sixty (60) days prior to submitting any such proposed publication to a publisher or proceeding with such proposed presentation. Within sixty (60) days of its receipt, Sponsor shall advise

Institution and/or Investigator, as the case may be, in writing of any information contained therein which is Confidential Information (other than Study Data) or which may impair the availability of patent protection for Inventions. Sponsor shall have the right to require Institution and/or Investigator, as applicable, to remove specifically identified Confidential Information (other than Study Data) and/or to delay the proposed publication or presentation for an additional sixty (60) days to enable Sponsor to seek patent protection for Inventions.

Institution and Investigator shall not, without the Sponsor's prior written consent, independently publish, present or otherwise disclose any results of or information pertaining to Site's own activities conducted for this trial until a multi-center publication is published. In the event the Sponsor coordinates the multi-center publication, the participation of the Investigator as a named author shall be determined in accordance with Sponsor's policies, requirements of the publisher and generally accepted standards of authorship. If a multi-center publication is not published within eighteen (18) months after completion of the Study and lock of the database at all research sites or any earlier termination or abandonment of the Study, Institution and Investigator shall have the right to publish and present the Site Study results following from Site's own activities conducted for this trial, including Study Data, solely consistent with scientific standards and the submission requirements as outlined in this section.

Institution and Investigator acknowledges and agrees that Study Data that is not published, presented or otherwise disclosed ("Unpublished Data") shall be subject to the provisions on Confidential Information according to Section 10.12 of this protocol, and Institution and Investigator shall not, and shall require their personnel not to, disclose Unpublished Data to any other site participating in this trial or any third party or disclose any Study Data to any other site participating in this trial or any third party in greater detail than the same may be disclosed in any publications, presentations or disclosures made in accordance with this section.

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

10.12 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.

10.13 Trial or Site Discontinuation

- At any time of the study, due to adverse events, or risks outweighing the benefit as determined by the investigators;
- Merck KGaA 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, Merck KGaA 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. Where required by local regulations, Merck KGaA will be responsible for informing the EC of trial or site discontinuation.

10.14 Trial Closure

Upon completion (when all subjects enrolled have completed the ongoing pregnancy ultrasound test 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 activities will be performed. The GERI+ system and any unused trial material will be collected and returned to Merck KGaA and/or the CRO. The monitors (CRO) 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.

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