Integrated Analysis Plan

Clinical Trial Protocol Identification No.	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
Investigational Medical Device	GERI+ incubator equipped with EEVA and GERI Assess software.
Clinical Trial Protocol Version	31 January 2018/ Version 3.0
Integrated Analysis Plan Author	**Coordinating Author** PPD, Merck PPD **Function** / **Author** PPD / PPD, Study Statistician
Integrated Analysis Plan Date and Version	14 January 2020/ Version 2.0
Integrated Analysis Plan Reviewers	**Function** / **Name** PPD, Merck / PPD PPD, Merck / PPD PPD, Merck / PPD **Function** / **Name** PPD / PPD, Study Reviewer PPD / PPD, Study Programmer PPD / PPD, Medical Writer PPD / PPD, PPD

Signature Page

Integrated Analysis Plan: MS200497_0006

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.

Merck responsible	Date	Signature
PPD	13 JAN 2020	Approved by e-mail

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADR	Adverse Drug Reaction
AE	Adverse Event
AFC	Antral Follicle Count
AMH	Anti-Mullerian Hormone
ART	Assisted Reproductive Technologies
BMI	Body Mass Index
COS	Controlled Ovarian Stimulation
CRF	Case Report Form
CSR	Clinical Study Report
EEVA	Early Embryo Viability Assessment
(FA) dataset	Full Analysis dataset
FPI	First Patient In
FSH	Follicle-Stimulating Hormone
GERI+	Genea Embryo Review Instrument Plus
GnRH	Gonadotropin Releasing Hormone
hCG	Human Chorionic Gonadotropin
IAP	Integrated Analysis Plan
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICSI	Intra cytoplasmic Sperm Injection
IHC	Internationally Harmonized Consensus
IVF	In Vitro Fertilization

LH	Luteinizing Hormone
LPI	Last Patient In
LPO	Last Patient Out
(PP) dataset	Per Protocol dataset
POR	Poor Ovarian Response
r-hFSH	Recombinant Human Follicle-Stimulating Hormone
r-hLH	Recombinant Human Luteinizing Hormone
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SmPC	Summary of Product Characteristics

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
0.1	16APR2018	PPD	Baseline Version
0.2	19JUN2018	PPD	Based on Client comments
0.3	17JAN2019	PPD	Based on Client comments
0.4	12FEB2019	PPD	Based on client comments
1.0	14FEB2019	PPD	Final Version
1.1	09DEC2019	PPD	Based on Client suggestions
2.0	14JAN2020	PPD	Final Version

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for protocol MS200497_0006. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon the trial protocol and is prepared in compliance with ICHE9. This IAP is mainly focused on the Clinical pregnancy with positive fetal heart beat in gestational week 6-8 after fresh embryo transfer on Day 3. Statistical analyses of other variables such as Utilizable Embryos, Good Quality Embryos, Non-viable Embryos and Implantation with positive fetal heart beat, Biochemical Pregnancy, Ongoing Pregnancy, Multiple Pregnancy, Ectopic Pregnancy and Spontaneous Miscarriage also added in this version of IAP.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Trial Objective	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	**Primary Endpoint** Clinical pregnancy with positive fetal heart beat in gestational week 6-8 after fresh embryo transfer on Day 3.	14.1
		Secondary Endpoints 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	14.2

6 Overview of Planned Analyses

This IAP describes final analysis of the study. No interim analyses are planned for this study.

6.1 Interim Analysis

Not applicable.

6.2 Final Analysis

Final analyses will be performed only after the database locked. In addition, no database can be locked and no randomization code should be unblinded until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The statistical methods as described in the protocol were adopted and no changes to the planned analyses. However Statistical comparison between groups and confidence intervals will not be performed. No regression models will be constructed in this study.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations

The definition of the major and minor protocol deviations are as follows.

Major protocol deviations are:

1. The number of 2PNs is less than 4 or missing
2. Subject is not randomized or not treated as randomized
3. Technical issues with GERI which are not reported as device deficiency
4. EEVA test applied to Poor Quality embryos instead of standard morphology
5. Control arm- Embryos with optimal cell number and grade were NOT transferred

All other deviations will be counted as minor deviations.

8.2 Definition of Analysis Sets and Subgroups

Full Analysis (FA) dataset:

(FA) dataset includes all randomized subjects. Subjects will be presented as randomized.

Per Protocol (PP) dataset:

(PP) dataset is defined as:

Subjects, who completed the study without major protocol deviation, and:

- For subject randomized Geri+ group:
  - embryos are cultured to Day 3, and are assessed by Eeva per Eeva IFU, or by standard morphology if this subject only has poor quality embryos;
  - embryo(s) with the highest Eeva score (for subjects with good and fair quality embryos), or best morphology grade (for subjects with poor quality embryos only, or with poor quality embryos and no more than one good/fair quality embryos) is/are transferred on Day 3 of embryo culture;
- For subjected randomized to Control group:
  - Embryos are cultured to Day 3, and the embryo(s) with the optimal cell number and grade is/are transferred.

Major protocol deviations are defined in section 8.1

The FA population is the primary analysis population.

PP population is used for sensitivity analysis. PP population will be considered only if it is less than 90% of FA population and more than 40% of total planned number of subjects.

9 General Specifications for Data Analyses

All analyses will be performed for the two treatment groups.

Descriptive statistics such as

- Number of subjects (n), number of subjects with missing values (Missing),
- mean, standard deviation (SD),
- median, first quartile (Q1), third quartile (Q3),
- minimum and maximum

will be provided for all continuous variables.

Mean, median, Q1 and Q3 will have one decimal place more than the raw data and SD will have 2 decimal places more than the raw data. The decimal place for minimum and maximum values will be same as the raw data.

The frequency (n) and percentage will be calculated for all categorical variables including missing observations and the percentages will be rounded off to one decimal place.

Unless otherwise stated the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits percentages will be based on the number of subjects still present in the trial at that visit, unless otherwise specified.

All the tables will provide for the two treatment groups (GERI+ incubator and Conventional incubator) and overall.

Handling of missing data:

Missing information will be captured for quantitative as well as qualitative variables by the category “Missing” in the summary statistics. If there are no missing values this will be indicated by „0“. Missing data will not be imputed. Missing statistics, e.g. when they cannot be calculated,

should be presented as "nd". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nd".

All analyses will be performed using SAS® Software version 9.1.3 or higher.

10 Trial Subjects

10.1 Disposition of Subjects and Discontinuations

A table with

- Number of subjects screened
- Number of subjects with screen failure
- Number of subjects enrolled in the study
- Number of subjects randomized in the study
- Number of subjects in Full Analysis (FA) dataset
- Number of subjects in Per Protocol (PP) dataset
- Number of subjects completed the study as per protocol
- Subject completed the study as per protocol and appropriate outcome (Failed to conceive/ Biochemical pregnancy/ Spontaneous Miscarriage/ Clinical pregnancy/ Ongoing pregnancy/ Subject underwent therapeutic abortion/elective abortion)
- Number of subjects who discontinued from the study
- Subject did not complete the study as per protocol and appropriate outcome (Fresh embryo transfer was cancelled/ Subject requested to be withdrawn after embryo transfer/ Investigator withdrew subject/ Imaging was discontinued prior to completion/ Subject was lost to follow-up/ Subject was non-compliant/ Other)
- Fresh embryo transfer was cancelled, appropriate reason (No cleavage/ No viable embryo for transfer/ Freeze all due to elevated risk of OHSS/ Other)

will be summarized as number and percentage for both the treatment groups and overall.

Subjects Screened are the subjects for whom "Date informed consent signed by subject/partner" is available.

Subjects enrolled in the study are the subjects who satisfy both the inclusion and exclusion criteria.

Screen failure subjects are the subjects who are screened but not satisfying any one of the inclusion or exclusion or both criteria.

Listing will be provided for details of randomized subjects from (FA) dataset.

10.2 Protocol Deviations

10.2.1 Major Protocol Deviations

The following summary table and listing of major protocol deviations will be provided for both treatment groups and overall:

- Frequency table per reason of major protocol deviations
- Listing of major protocol deviations

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

For subjects excluded from the PP, the reasons for exclusion will be summarized by treatment groups and overall and a listing also will be provided for the same.

- Frequency table per reason of exclusion from the PP population
- Listing of reasons of exclusion from the PP population

11 Demographics and Other Baseline Characteristics

11.1 Demographics

The quantitative variables

- Age (years)
- Body weight (kg)
- Height (cm)

- BMI (kg/m^2)

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset.

Age (years) = (Date informed consent signed by Subject (Female) or Partner- Date of Birth (Subject) + 1)/ 365.25.

If day is missing for either date of informed consent or date of birth, then it will be replaced by 1^{st} day of the month. Similarly, missing month will be replaced by 1^{st}July of the year.

The qualitative variable

- Current smoker (Yes/ No)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset.

11.2 Medical History

Cause of Infertility:

The quantitative variable

- Duration of infertility (Months)

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset.

The qualitative variables

- Type of infertility (Primary infertility/ Secondary infertility)
- Reasons of infertility (Male factor/ Tubal factor/ Endometriosis/ Anovulation/ Unexplained/ Other)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset.

Listing will be provided for Cause of Infertility from (FA) dataset.

Obstetrical History:

The quantitative variables

- Number of previous pregnancies
- Number of live births
- Number of spontaneous miscarriages
- Number of therapeutic/elective abortions
- Number of stillbirths
- Number of ectopic pregnancies
- Number of multiple pregnancies
- Number of babies with congenital anomalies
- Prior Gonadotropin cycles (non-ART)
- Prior fresh ART cycles
- Prior frozen ART cycles

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset.

The qualitative variable

- Subject has obstetrical history (Yes/ No)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset.

Listing will be provided for Obstetrical History from (FA) dataset.

11.3 Other Baseline Characteristics

Cycle Day 2-4 hormones:

Listing will be provided for Cycle Day 2-4 hormones from (FA) dataset.

Antral Follicle Count:

The quantitative variable

- Total AFC (Only follicles between > or = 2mm and < 11mm)

will be summarized by descriptive statistics for both treatment groups and overall from (FA) dataset.

The qualitative variable

- Day of menstrual cycle for Assay (1/ 2/ X/ X)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset.

12 Previous or Concomitant Medications/Procedures

Not Applicable.

13 Treatment Compliance and Exposure

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

COS and Ovulation triggering Visit:

Down Regulation:

The qualitative variable

- Type of Protocol (Antagonist protocol/ Long agonist protocol/ Other)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset.

Listing will be provided for Down Regulation, Controlled Ovarian Stimulation and Ovulation triggering from (FA) dataset.

Ovulation triggering and luteal phase support (LPS):

The qualitative variables

- Luteal phase support (Ovulation triggering with hCG/ Ovulation triggering with GnRH-a/ No LPS)
- LPS after Ovulation triggering with hCG
  - Vaginal micronized progesterone gel
  - Vaginal progesterone capsule/tablet/suppository
  - Intramuscular progesterone
  - Other
- LPS after Ovulation triggering with GnRH-a (hCG/ Vaginal micronized progesterone gel/ Estradiol/ Other)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset.

Listing will be provided for Luteal phase support (LPS) from (FA) dataset.

Eeva conformity:

The qualitative variables

- Eeva conformed subjects
- Eeva non-conformed subjects

will be summarized by using number and percentage for GERI+ Incubator treatment group from (FA) dataset.

Eeva conformed subjects: embryo transfer is based on Eeva result applied to good and fair quality embryos.

Eeva non-conformed subjects: embryo transfer is not based on Eeva result (when either of the boxes in the last two columns of eCRF CP6 is ticked).

14 Efficacy Analyses

14.1 Clinical Pregnancy with positive fetal heartbeat (Primary Endpoint)

The primary end point is clinical pregnancy with positive fetal heartbeat. It is defined as the pregnancy diagnosed by ultrasonographic or clinical documentation of at least one fetus with heart beat in gestational week 6 to 8. It includes ectopic pregnancy.

The qualitative variables

- Ultrasound performed (Yes/ No)
- Result of ultrasound (Biochemical pregnancy/ Ectopic pregnancy/ Intrauterine clinical pregnancy (with and without positive FHB)/ Clinical pregnancy (FHB positive or negative intrauterine pregnancy + ectopic pregnancy)/ Other)
- Number of subjects with Embryo transfer attempted (Yes/ No)
- Subjects with FHB positive clinical pregnancy

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset and (PP) dataset.

The quantitative variables

- Number of intrauterine gestational sacs
- Number of sacs with fetal heartbeats

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset and (PP) dataset.

The quantitative variable

- FHB positive Clinical pregnancy rate (%)

will be summarized by percentage for both treatment groups and overall from (FA) dataset and (PP) dataset.

No. of subjects with clinical pregnancy = Intrauterine clinical pregnancy subjects (with and without positive FHB) + Ectopic pregnancy subjects.

Subject with FHB positive clinical pregnancy = Intrauterine Clinical Pregnancy subject with at least one or more sacs with fetal heartbeats

FHB positive clinical pregnancy rate (%) = No. of subjects with FHB positive clinical pregnancy)/ No. of subjects with embryo transfer)* 100.

No. of subjects with embryo transfer = Subjects with embryo transfer attempted.

14.2 Day 3 Embryo assessment and Clinical outcome (Secondary Endpoints)

14.2.1 Utilization Rate

Individual Utilization Rate per woman (%) = (No. of Utilizable Embryos per that woman (vitrified and transferred)/ No. of 2PN zygotes per that woman)*100

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset and PP dataset.

Utilization rate (%) is calculated as the sum of individual utilization rates divided by the number of women

will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

14.2.2 Good Quality Embryo Rate

Individual Good Quality Embryo Rate per woman (%) = (No. of good quality embryos per that woman / No. of 2PN zygotes per that woman)*100

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset and PP dataset.

Good Quality Embryo Rate (%) is calculated as the sum of individual good quality embryo rates divided by the number of women

will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

14.2.3 Non-viable Embryo Rate

Individual Non-viable Embryo Rate per woman (%) = (No. of non-viable embryos per that woman / No. of 2PN zygotes per that woman)*100

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset and PP dataset.

Non-viable Embryo Rate (%) is calculated as the sum of individual non-viable embryo rates divided by the number of women

will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

14.2.4 FHB positive implantation rate

FHB positive implantation rate is calculated per embryo transferred (IR) and per subject randomized (IR*):

a) IR: the number of intrauterine gestational sacs with positive FHB under ultrasound scans at gestational weeks 6-8 divided by the total number of embryos transferred.

b) IR*: Sum of ((Number of intrauterine Gestational Sacs with positive FHB under ultrasound scans at gestational weeks 6-8 at women level/ Number of embryos transferred at women level)*100) / Number of women who had embryo(s) transfer.

will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

14.2.5 Biochemical Pregnancy Rate

Biochemical Pregnancy Rate (%) = (No. of subjects with biochemical pregnancy/ No. of subjects with embryo transfer)*100.

will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

14.2.6 Ongoing Pregnancy Rate

Ongoing Pregnancy Rate (%) = (No. of subjects with ongoing pregnancy/ No. of subjects with embryo transfer)*100.
will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

14.2.7 Multiple Pregnancy Rate

Multiple Pregnancy Rate (%) = (No. of subjects with multiple pregnancy/ No. of subjects with ongoing pregnancy)*100.
will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

(Multiple Pregnancy is defined by protocol as a pregnancy with more than one fetus identified by ultrasonography at gestational weeks 10-12).

14.2.8 Ectopic Pregnancy Rate

Ectopic Pregnancy Rate (%) = (No. of subjects with ectopic pregnancy/ No. of subjects with embryo transfer)*100.
will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

14.2.9 Spontaneous Miscarriage Rate

Spontaneous Miscarriage Rate (%) = (No. of subjects with spontaneous miscarriage/ No. of subjects with clinical pregnancy)*100
will be summarized for both treatment groups and overall from (FA) dataset and PP dataset.

14.2.10 Urine or Serum hCG Test (final assessment)

The qualitative variables

- hCG test performed (Yes/ No)
- hCG test method (Blood/ Urine)
- Conclusion of hCG test (Positive/ Negative)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset and PP dataset.

The quantitative variable

- Beta-hCG (IU/L) (from blood only)

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset and PP dataset.

The quantitative variable

- hCG positivity rate (%)

will be summarized by percentage for both treatment groups and overall from (FA) dataset and PP dataset.

hCG positivity rate (%) = (The number of subjects with positive hCG result / The number of subjects with hCG test performed)*100.

Listing will be provided for Urine or Serum hCG Test (final assessment) from (FA) dataset.

14.3 Other Analyses Variables

14.3.1 Oocyte Retrieval

The quantitative variables

- Number of Oocytes in GV
- Number of Oocytes in M1
- Number of Oocytes in M2
- Number of Oocytes in Other
- Total number of Oocytes retrieved

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset and PP dataset.

The qualitative variable

- Oocyte retrieved (Yes/ No)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset and PP dataset.

14.3.2 Insemination

The qualitative variables

- Type of insemination (IVF/ ICSI/ Both/ No)
- Raw semen sample (Fresh/ Frozen/ Both)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset and PP dataset.

14.3.3 Embryo culture condition

The quantitative variables

- CO_2 (%)
- O_2 (%)

will be summarized by using descriptive statistics for both treatment groups and overall from (FA) dataset and PP dataset.

The qualitative variables

- Culture environment (with humidification/ without humidification)
- Gas type (Premixed gas/ Internal gas mixer/ External gas mixer)
- Brand of fertilization media used on Day 0 of embryo culture (Cook/ Vitrolife/ Origio/ GeneaBiomedx/ Irvine/ Other)
- Embryo culture media used from Day 1 of embryo culture (Sequential media/ Non-sequential media)
- Brand of cleavage culture media (Cook/ Vitrolife/ Origio/ GeneaBiomedx/ Irvine/ Other)
- Brand of blastocyst media (Cook/ Vitrolife/ Origio/ GeneaBiomedx/ Irvine/ Other)
- Brand of single step media (Cook/ Vitrolife/ Origio/ GeneaBiomedx/ Irvine/ Other)
- Brand of oil (Cook/ Vitrolife/ Origio/ GeneaBiomedx/ Irvine/ Other)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset and PP dataset.

Listing will be provided for Embryo culture condition from (FA) dataset.

14.3.4 Day 3 Embryo assessment form (Conventional incubator)

Listing will be provided for Day 3 Embryo assessment form (Conventional incubator) from (FA) dataset.

14.3.5 Day 3 Embryo assessment form (GERI+ incubator)

Listing will be provided for Day 3 Embryo assessment form (GERI+ incubator) from (FA) dataset.

14.3.6 Embryo Transfer

The qualitative variables

- Transfer attempted (Yes/ No)
- Ultrasound guidance (Yes/ No)
- Grading of procedure (Easy/ Intermediate/ Difficult)
- Number of embryos transferred (1/ 2/ 3/ X/ X)

will be summarized by using number and percentage for both treatment groups and overall from (FA) dataset.
For the variable “Number of embryos transferred” Mean number of embryos transferred ±SD will be provided for both treatment groups and overall from (FA) dataset and PP dataset.

14.4 Exploratory Analysis

Not applicable.

15 Safety Analyses

Not applicable.

15.1 Adverse Events

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. However, a listing will be provided for device deficiency data, if available.

15.1.1 All Adverse Events

Not applicable.

15.1.2 Adverse Events Leading to Treatment Discontinuation

Not applicable.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

Not applicable.

15.2.2 Serious Adverse Events

Not applicable.

15.2.3 Other Significant Adverse Event

Not Applicable.

15.3 Clinical Laboratory Evaluation

Not Applicable.

15.4 Vital Signs

Not applicable.

15.5 Other Safety or Tolerability Evaluations

Not applicable.

16 Analyses of Other Endpoints

Not applicable.

16.1 Pharmacokinetics

Not applicable.

16.2 Pharmacodynamics

Not applicable.

16.3 Quality of Life

Not applicable.

17 References

1. Protocol Number: MS200497_0006, dated 31 January 2018, Version 3.0
2. CRF Version- Version 5.0 dated 14 June 2018.
3. ICH E3 - “Structure and Content of Clinical Study report” and E9 - “Statistical Principles for Clinical Trials”.
4. ISO 14155: 2011 Clinical investigation of medical devices for human subjects – Good Clinical Practice.

18 Appendices

Not applicable.