

Statistical Analysis Plan

**Observational study Protocol
Identification No.** EMR 700623-545

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

**Observational study Protocol
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1 Signature Page

Statistical Analysis Plan: EMR 200623-545

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

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2 Table of Contents

1	Signature Page	2
2	Table of Contents.....	3
3	List of Abbreviations and Definition of Terms	5
4	Purpose of the Statistical Analysis Plan	6
5	Summary of Clinical Study Features	6
5.1	Primary endpoint	6
5.2	Secondary endpoints	6
5.3	Selection of Trial Population and randomization	6
5.4	Documented variables	6
5.4.1	Screening and treatment	6
5.4.2	Oocyte Retrieval	7
5.4.3	Embryo Day 3.....	7
5.4.4	Embryo Transfer.....	7
5.4.5	Embryo Day 5-6	7
5.4.6	Dates	7
5.4.7	Post Oocyte Retrieval or Post Transfer Day 12-18	7
5.4.8	Gestational Age Week 5-8 (Transfer and Treatment Outcome eCRF).....	7
5.4.9	Post-Pregnancy follow-up	8
5.4.10	Additional Ultrasound > 8 weeks (Optional).....	8
5.4.11	Assessment of Safety	8
6	Sample Size/Randomization.....	8
7	Overview of Planned Analyses.....	8
7.1	Sequence of Analysis.....	8
7.2	Interim Analysis.....	8
7.3	Final Analysis	8
8	Analysis Sets.....	8
8.1	Intention-to-treat (Full Analysis Set).....	8
8.2	Subgroups EC and ENC within the Eeva plus morphology grading group.....	8
8.3	Added selection	9
9	General Specifications for Statistical Analyses.....	9
10	Study Subjects	9
10.1	Disposition of Subjects and Discontinuations	9
10.2	Protocol Deviations	9
11	Demographics and Other Baseline Characteristics.....	9
11.1	Demographics, Medical History, Other Baseline Characteristics	9
11.2	Descriptive tables for post-baseline variables	9
12	Previous or Concomitant Medications/Procedures.....	10
13	Treatment Compliance and Exposure.....	10
14	Endpoint Evaluation	10

14.1	Primary analysis.....	10
14.2	Implantation rate in other selections.....	10
14.3	KID selection.....	10
14.4	Secondary variables selection of ITT.....	10
14.5	Secondary variables KID.....	10
14.6	Exploratory Variables.....	11
15	Safety Evaluation.....	12
16	References.....	12
17	Used Variables.....	12
18	Table description: principles of reporting.....	15
18.1	Generalities.....	15
18.1.1	Type of table.....	15
18.1.2	Format.....	15
19	List of Tables of the report.....	15
19.1	Randomization.....	15
19.2	Screening.....	16
19.2.1	Inclusion/exclusion :.....	16
19.2.2	Patient Disposition.....	16
19.2.3	Comparison at baseline.....	16
19.2.4	Treatment.....	16
19.2.5	Oocytes Retrieval.....	16
19.2.6	Transfer.....	16
19.2.7	Additional Optional Ultrasound.....	17
19.2.8	device Incident.....	17
19.2.9	Study Exit.....	17
19.2.10	Dates.....	17
19.2.11	Safety.....	17
20	Table format.....	18

3 List of Abbreviations and Definition of Terms

AE	Adverse Event
BP	Biochemical Pregnancy
CP	Clinical Pregnancy
CPR	Clinical Pregnancy Rate
EC	Eeva Conform
Eeva	Early embryo Viability Assessment
EMG	arm treated Eeva + Morphology grading
ENC	Eeva Non-conform
IR	Implantation Rate
ITT	Intent to Treat
KID	Known Implantation Data
MG	arm Morphology Grading only
MP	Multiple Pregnancy
nET	Number of Transferred Embryos
nFS	Number of Foetal Sacs
OP	On Going Pregnancy
OPR	Ongoing Pregnancy Rate
RR	Risk Ratio
SM	Spontaneous Miscarriage
SMR	Spontaneous Miscarriage Rate
TRT	Treatment Variable
UR	Utilization Rate

4 Purpose of the Statistical Analysis Plan

Eeva is a time lapse monitoring system able to picturing embryos every 5 minutes during embryo culture and embryo development. The standard technique (Morphology Grading MG) is based on multiple observations of embryos under regular light microscopes, known of limited predictive value: In a Trial, from 2 embryos chosen by MS, 39% , 38% and 23% of cycles resulted in none, one and two blastocysts, respectively. The benefits demonstrated during the first investigations of Eeva is a specificity of 85%. (Eeva should detect 85% of transferred failed embryos). The purpose of this plan is the evaluation of the Early Embryo Viability Assessment (Eeva) efficacy in predicting confidence intervals for relative embryo implantation potential over baseline outcomes

5 Summary of Clinical Study Features

5.1 Primary endpoint

The primary objective of the trial is the point and relative interval estimate of the Implantation Rate (IR) performed on day 3 or day 5 (with and without genetic analysis) in the groups Eeva plus MG (EMG) and MG alone (MG)

5.2 Secondary endpoints

- (a) Utilization Rate (UR) (number of transferred and frozen embryos divided by number of normally fertilized oocytes x 100),
- (b) Clinical Pregnancy Rate (CP) (assessed by ultrasonography at weeks 5 to 8),
- (c) Ongoing Pregnancy Rate (OP) (assessed by ultrasonography at weeks 10 to 12),
- (d) Multiple Pregnancy Rate (MP) (assessed by ultrasonography at weeks 5 to 8) and
- (e) Spontaneous Miscarriage (SM).
- (e) Drugs protocol type (GnRH agonist/GnRH antagonist) and gonadotrophin dose for Controlled Ovarian Stimulation in relation with Eeva categories and implantation outcomes.

5.3 Selection of Trial Population and randomization

See protocol section 5.3 and 5.6

5.4 Documented variables

5.4.1 Screening and treatment

Inclusion Criteria, Age, Pregnancy History , Number of attempts , Number of Spontaneous abortions, Number of Live Births , Number of Non-ART cycles, Number of Fresh ART cycles, Number of Frozen ART cycles, Follicle Stimulating Hormone Maximum, Follicle Stimulating Hormone Units, Anti Mullerian Hormone Max, Anti Mullerian Hormone Unit, Estradiol Max, Estradiol Units, Luteinizing Hormone Max, Luteinizing Hormone Units, Antral Follicle Count ,

Male Infertility, Polycystic Ovaries, Reduced Ovarian Reserve, Tubal Factor , Unexplained, Other.

Treatment variables: Protocol of Stimulation, stimulation medication, Time of hCG trigger to oocyte retrieval, Pre-trigger Endometrium (Trt Set).

5.4.2 Oocyte Retrieval

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

5.4.3 Embryo Day 3

Type of Eeva Petri Dish (number of micro-wells); Eeva micro-well identification; Cell stage and Morphology grading; Eeva results; Fate of each embryo (Transferred, Cryopreserved, Discarded or extended culture to Day 5/6); Eeva Petri Dish and Scope information; Culture conditions.

5.4.4 Embryo Transfer

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

5.4.5 Embryo Day 5-6

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

5.4.6 Dates

All date of each stage are available

5.4.7 Post Oocyte Retrieval or Post Transfer Day 12-18

Pregnancy test results, Quantitative hCG, as applicable. If the result of the pregnancy test is negative, the subject will have completed the trial and be exited at that time.

5.4.8 Gestational Age Week 5-8 (Transfer and Treatment Outcome eCRF)

Result of initial pregnancy ultrasound; Number of intrauterine gestational sacs; Number of fetal heartbeats. If the result of the ultrasound is negative (no fetal heartbeat is detected), the subject stops

5.4.9 Post-Pregnancy follow-up

Pregnancy outcome

5.4.10 Additional Ultrasound > 8 weeks (Optional)

Result of initial pregnancy ultrasound; Number of fetal sacs and number of fetal heartbeats

5.4.11 Assessment of Safety

Safety of Eeva will be evaluated by assessment of device deficiency only. Each individual occurrence will be listed.

6 Sample Size/Randomization

See protocol 5.3

7 Overview of Planned Analyses

7.1 Sequence of Analysis

One sequence

7.2 Interim Analysis

Interim analysis was planned when half of the patients completed the study in the protocol. But based on medical affairs advice it was decided not to conduct the interim analysis.

7.3 Final Analysis

See section 8 below

Changes to the Planned Analyses

No changes

8 Analysis Sets

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

8.1 Intention-to-treat (Full Analysis Set)

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

8.2 Subgroups EC and ENC within the Eeva plus morphology grading group

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

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

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

PPD will share the "Embryo Days 2, 3, 5, 6 Laboratory Data Morphological/EEVA Grading" data with Merck after the database lock.

8.3 Added selection

The KID sample (Known Implantation Data) is the subset of ITT sample such that the IR=0% or 100% (for single,double or triple) mbryo transfer, ITT=KID; for other implantations, women such that $0 < IR < 1 < 2 < 3$ will be disregarded).

9 General Specifications for Statistical Analyses

10 Study Subjects

10.1 Disposition of Subjects and Discontinuations

This table will provide the distribution of the randomized patients for each group into completers and non completers. For completers, the table will provide the distribution of the type of completion (variable cycleCST, cfr section 19), and for non completers, the distribution of the reason of non completion (variable cycleNST, cfr section 19).

10.2 Protocol Deviations

Protocol deviations will be determined before database lock.

11 Demographics and Other Baseline Characteristics

11.1 Demographics, Medical History, Other Baseline Characteristics

Table will describe each group EMG and MG on all the above described existing variables at baseline. Depending on the type of variable, two-way Crosstab or Mean tables across (EMG/MG) Groups will be provided (cfr table contents and individual description of these tables in section 19).

11.2 Descriptive tables for post-baseline variables

For all the variables after baseline, each variable (described in table 19) will be documented for each subgroup (EMG/MG) according a frequency two-way cross tabulation or a mean table, depending on the type of variable (nominal, continuous).

12 Previous or Concomitant Medications/Procedures

Does not apply

13 Treatment Compliance and Exposure

Does not apply

14 Endpoint Evaluation

14.1 Primary analysis

Implantation rate will be analyzed with two definitions

First definition: The IR (at embryo level) corresponding to a group of patients is calculated as the ratio of the total fetal sacs (nFS) identified by ultrasonography at weeks 5 to 8 divided by the number of embryos transferred (nET), thus $IR = nFS/nET$.

Alternative Definition of Implantation Rate: The previous (and usual) calculation of IR as mentioned in the protocol ($IR = nFS/nET$) has problems, in particular the implanted embryos are not independent. The international definition used by WHO in particular (see for instance <http://www.advancedfertility.com/ivf.htm>) is: The alternative definition IR^* at women level is $IR_w = nFS_w/nET_w$ and $IR^* = (1/n) \cdot \sum_{w=1,n} IR_w$.

Note: The two definitions IR and IR^* coincide in some cases, in particular for elective Single Embryo transfer eSET (where only one embryo is transferred) or when KID sample is used, but in the general case (ITT sample for instance, IR and IR^* will be different).

The point estimate and 95% CI of IR and IR^* will be calculated in both groups EMG and MG for the ITT selection. No inferential comparison will be conducted between these two groups (as this study is purely descriptive).

The following sections are considered as secondary analyses.

14.2 Implantation rate in other selections

The point estimate and 95% CI of IR and IR^* will be calculated in the subgroups EC and ENC. No tests of comparison between any subgroup will be conducted.

14.3 KID selection

The same calculations will be conducted for EMG and MG groups and EC and ENC restrained to KID selection.

14.4 Secondary variables selection of ITT

Utilization Rate (UR), Clinical Pregnancy rate (CP), Ongoing Pregnancy rate (OP), Multiple Pregnancy rate (MP), Spontaneous Miscarriage (SM). The estimate and 95% CI will be calculated in both groups EMG and MG, and in both groups EC and ENC.

14.5 Secondary variables KID

The same analysis will be conducted on KID selection for Utilization Rate (UR), Clinical Pregnancy rate (CP), Ongoing Pregnancy rate (OP), Multiple Pregnancy rate

(MP), Spontaneous Miscarriage (SM) . The estimate and 95% CI will be calculated in both groups EMG and MG, and in both groups EC and ENC.

14.6 Exploratory Variables

Multiple Linear regression analysis of IR (based on subject level) as dependent variable and treatment as independent parameter effected by the following confounding factors

Factors	Description
Stimulation protocol	Categorical variable, 3 states: Agonist Luteal phase; Antagonist; and Agonist Mirco-dose Flare and Other
Drugs used	Categorical variable, 3 states: recombinant Gn, urinary Gn, and mix-use of recombinant and urinary Gns
Day of transfer	Categorical variable, 2 states: D3 Vs D5/6
Age of patients	Continuous variable , years
Culture medium	Categorical variable, 5 states: Quinn's Advanced Fertilization, Global Medium, Vitro life G-IVF, Irvine Single Step Medium, and Other

A better estimate of implantation rate will be obtained based on subject level adjusted for confounding factors by a Multiple Linear regression.

Given the exploratory nature of the design, the model will be investigated stepwise and repeated backward. The final model will exclude backward P-values > 0.10.

The Center effect will also to be considered in the model.

The results of regression analysis will be reported with the following items

- Regression Coefficient with 95% CI
- Standard Error
- P-value
- Coefficient of Determination (R^2)

Subgroup analyses

Further subgroup analysis based on selected baseline parameter could be conducted as follows.

- 1) IR of the two treatment groups at each site (descriptive summary statistics with 95% CI,

and RR with 95% CI and P value). The Risk Ratio, 95% CI and P-value will be calculated, provided the number of subjects in a site will be at least 30, otherwise only descriptive statistics will be provided for that particular site.

- 2) IR, CPR, OPR and SMR of the two treatment groups for subgroups of patients with ET on D3 and D5/6 (descriptive summary statistics, RR with 95% CI and P value);
- 3) IR, CPR, OPR and SMR of the two treatment groups for subgroups of patients with age ≤35 and >35(descriptive summary statistics, RR with 95% CI and P value).
- 4) IR of the two treatment groups for subgroups of patients using 5 types of culture media (descriptive summary statistics, RR with 95% CI and P value).
- 5) IR of subgroups of patients using 5 types of culture media (regardless the method of embryo assessment, descriptive summary statistics and 95% CI)

15 Safety Evaluation

In conformity with protocol, device deficiency will be individually listed.

16 References

No reference at this stage

17 Used Variables

In the following table, each variable is characterized by its ID (short name), variable label, type (B=Binary, I=Numerical Integer (such as count), C=Categorical, F=Real Numeric). Format (I.J where I denotes the total number of digits, and J=number of decimals, i:j is a format with j decimals for the tables, but 0 decimal for data list, while i.j denotes j decimals for the tables and data list). The groups of binary variables highlighted in gray will be presented on the same table.

<u>Variable ID</u>	<u>Variable Label</u>	<u>Type</u>	<u>Fmt</u>	<u>Value Labels</u>
Baseline Variables				
Inc<1,13>	Inclusion Criteria	B		
Age	Age	I	6:1	
Preg1	Pregnancy History	B		
Preg2	Number of attempts	I	6:1	
Preg3	Number of Spontaneous abortions	I	6:1	

Preg4	Number of Live Births	I	6:1	
Pt1	N of Non-ART cycles	I	6:1	
Pt2	N of Fresh ART cycles	I	6:1	
Pt32	N of Frozen ART cycles	I	6:1	
FSHm	Folicle Stim Hormone Maximum	F	8:2	
FSHu	Folicle Stimulating Hormone Units	F	8:2	
AMHm	Anti Mullerian Hormone Max	F	8:2	
AMHu	Anti Mullerian Hormone Unit	F	8:2	
E2m	Estradiol Max	F	8:2	
E2u	Estradiol Units	F	8:2	
LHm	Luteinizing Hormone Max	F	8:2	
LHu	Luteinizing Hormone Units	F	8:2	
AFC	Antral Follicle count	I	6:1	
RI1	Male Infertility	B		
RI2	Polycystic Ovaries	B		
RI3	Reduced Ovarian Reserve	B		
RI4	Tubal Factor	B		
RI5	Unexplained	B		
RI6	Other	B		
Prot	Stimulation protocol	C	4	1=Agonist Luteal Phase Start 2=Agonist Micro-Dose Flare 3=Antagonists suppression 4=Other
FSHtd	rFSH (Total Dose)	F	8:2	
FSHnd	rFSH (N of Days)	F	8:2	
LHtd	rLH (Total Dose)	F	8:2	
LHnd	rLH (N of Days)	F	8:2	
FLtd	rFSH-rLH (Total Dose)	F	8:2	
FLnd	rFSH-rLH (N of Days)	F	8:2	
Hmgtd	Hmg (Total Dose)	F	8:2	
Hmgnd	Hmg (N of Days)	F	8:2	
Ufshtd	uFSH (Total Dose)	F	8:2	
Ufshnd	uFSH (N of Days)	F	8:2	
Otttrtd	Other treatments (Total Dose)	F	8:2	
otttrnd	Other treatments (N of Days)	F	8:2	
stimdur	Total number of days of stimulation	I	8:2	

E2pk	Peak estradiol	F	8.2	
E2u	Unit Estradiol	B	4	1=pmol/L 2=pg/mL
Nfol12	N of follicles > 12mm	I	5:1	
Nfol18	N of follicles > 18 mm	I	5:1	
endoth	Endometrium Thickness	F	8.2	
Post Baseline Variables				
Noo	N of oocytes	I	8:1	
Noom	N of Mature oocytes	I	8:1	
Sps	Sperm Sample	C	4	1=Fresh 2=Frozen 3=both
ltype	Insemination Type	C	4	1=ICSI 2=lvf 3= Both
Cult	Culture medium	C	4	1= Quinns Advantage Fertilization 2= Global Medium 3= Vitrolife G-IVF 4= Irvine Single Step Medium 5= Other
Incub1	Incubator Information O2	C	4	1= 5% 2=20%
Incub2	Incubator CO2	F	8.2	
Psupp	Protein Supplement	C	4	1= None used, 2 = SPS, 3 = HAS, 4 = SSS, 5 = Other
Negg	N of retrieved eggs	I	6.1	
eggGV	Egg type GV	B		
eggMI	Egg type MI	B		
eggMII	Egg type MII	B		
eggOt	Egg type Other	B		
Trf	Was a transfer attempted ?	B		
Nte	N of transferred Embryos	I	4.1	
Usg	Ultra sound guided	B		1=Yes 2=No
Cat1	Catheter Typ Mucous	B		
Cat2	Catheter Typ Blood	B		
Cat3	Catheter Typ retained embryos	B		
Cat4	Catheter Typ N/A	B		
Grading	Procedure Grading	C	4	1= Easy 2= Difficult
Pdg	Embryo assessed by PGD/PGS	C	4	1=Yes 2=No
Euploid	Euploid transferred ?	B	4	
LPS	Luteal Phase support	B		1=Yes 2=No
DelMet	Delivery Method	C		1= Crinone 2=Endometrin 3=Other Vaginal 4=Intramuscular 5=Other
Test1	Post Transfer test 1	B		1= Urine 2=Blood
Test1r	Post Transfer test 1 result	B		1= Positive 2= Negative
Test2	Post Transfer test 2	B		1= Urine 2=Blood
Test2r	Post Transfer test 2 result	B		1= Positive 2= Negative

US1	Ultra Sound result	B		1= Positive 2= Negative
Nsac	N of gestational Sacs	I	4:1	
Nhbt	N of Heartbeats	I	4:1	
Outc	Final outcome further to Ultra Sound	C		1=No pregnancy 2=Biochemical pregnancy 3=Ectopic 4=miscarriage 5= Ongoing
EndPP	Cycle completed on Per Protocol	B		1=yes 2=o
cycleCSt	IF cycle complete : Status	C		1= Ongoing pregnancy 2= Pregnancy came to term 3= Pregnancy lost 4= Failed to conceive 9= therapeutic abortion 10= Other
cycleNst	If cycle non complete : Status	C		0=Normal 1= OHSS risk 2= Embryo transfer cancelled 5= Freeze all 6= Other 7= Imaging discontinued prior to completion 8= Subject requested to be withdrawn 9= Investigator withdrew subject 10= Subject was lost to follow-up 11= Subject was noncompliant

18 Table description: principles of reporting

18.1 Generalities

Unless otherwise specified, all these tables are two-way table in subdividing the whole sample following treatment group (trt).

18.1.1 Type of table

- DataList Individual list of a subset of variables in text format for a selection of patients
- Mean Mean, SD, Count, Minimum, Maximum, quartiles (ex : Section 20, table 1)
- MeanCI Mean, SD, 95%CI, count (ex : Section 20, table 2)
- Perc Percentage, Count (ex : Section 20, table 3)
- PercCI Percentage, Count, 95% CI (ex : Section 20, table 4)
- CrossTab Two-way Cross-tabulation with count and % in columns (ex : Section 20, table 5)

18.1.2 Format

Percentage and associated CI	1 decimal
Proportion	3 decimals
Count	0 decimals
Continuous variable described by mean, quartiles, range, standard deviation and their CI	Conform to goldilocks rounding ref: Lang T, Altman D. Basic statistical reporting for articles published in clinical medical journals: the SAMPL Guidelines. (cited 19 June 2014). http://www.equator-network.org/wp-content/uploads/2013/07/SAMPL-Guidelines-6-27-13.pdf

19 List of Tables of the report

19.1 Randomization

Data List with Patient ID , randomization Date, Treatment code 0=MG, 1=EMG

19.2 Screening

19.2.1 Inclusion/exclusion :

Data List ID patients list out of exclusion/inclusion criteria

Cross-tab Inclusion/exclusion by TrT

19.2.2 Patient Disposition

crossT cycleST * trt
crossT cycleNST * trt

19.2.3 Comparison at baseline

Mean Age * trt
Mean Number of pregnancies, Abortions, Live Births * trt
Mean Number of Gonad cycles, Fresh , Frozen Art Cycles * trt
Mean FSH, AMH, E2, LH, AFC (units/ Maximum) * trt
CrossT Reason for ART * trt

19.2.4 Treatment

CrossT Stimulation Protocol * trt
Mean rFSH, rLH, rFSH+rLH,hMG, uFSH * trt
Mean Thickness of endometrium * trt

19.2.5 Oocytes Retrieval

Mean NOO, NMO * trt
Mean Sperm * trt
CrossT Type of Insemination * trt
CrossT culture Medium * trt
Mean CO2, O2 * trt (Incubator information)
Mean Total Number of Eggs * trt

19.2.6 Transfer

Percent Transfer (0/1) * trt
Percent conformity with Eeva * trt
Percent nET * trt
Percent Ultrasound guided * trt
DataList Brand of Ultrasound
crossT Catheter Type * trt
CrossT Grading of Procedure * trt

Percent embryos assessed with PDG
Percent euploid Transformed
Percent Luteal Phase provided
crossT method of delivery
crossT Urine Sample-A/B * trt
crossT Urine-A/B-Result * trt
mean Quant-HCG-A/B * trt
Percent (InitialPregnancyUS, nFS, nHeartBits) * trt

19.2.7 Additional Optional Ultrasound

Percent (InitialPregnancyUS, nFS, nHeartBits) * trt (for

19.2.8 device Incident

DataList Patient, Time, Eeva component, Description, troubleshooting, contact

19.2.9 Study Exit

CrossT Study exit Categories * trt

19.2.10 Dates

data list for each patient, the dates associated with each event (from Recruitment to Live birth)

19.2.11 Safety

Each Individual device deficiency event will be listed.

20 Table format

.	Mean	SD	Q1	Median	Q3	Min	Max	Count
MG	3.68	2.82	2.00	3.00	5.00	0.00	13.00	155
Eeva+MG	3.28	2.59	1.00	3.00	5.00	0.00	11.00	142
Total	3.49	2.72	1.00	3.00	5.00	0.00	13.00	297

Table 1. example of a Mean table

.	Mean	95% CI	Count
MG	3.57	3.12, 4.01	143
Eeva+MG	3.40	2.91, 3.88	124
Total	3.49	3.16, 3.81	267

Table 2. example of a Mean table with 95%CI

.	Percent	Count
MG	12.6	135
Eeva+MG	9.6	135
Total	11.1	270

Table 3. example of a Percent table

.	Percent	95% CI	Count
MG	13.9	8.56, 20.81	137
Eeva+MG	6.7	3.11, 12.37	134
Total	10.3	6.97, 14.59	271

Table 4. example of a Percent table with 95%CI

.	MG		Eeva+MG		Total	
	Count	Col %	Count	Col %	Count	Col %
GBR	4	2.9	8	5.9	12	4.4
HUN	7	5.1	12	8.9	19	7.0
...
LVA	7	5.1	12	8.9	19	7.0
SWE	1	0.7	0	0.0	1	0.4
Total	137	50.4	135	49.6	272	100.0

Table 5. example of a Cross table (Count, Col %).