DE NOVO CLASSIFICATION REQUEST FOR
Eeva™ System

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Assisted Reproduction Embryo Image Assessment System:** An assisted reproduction embryo image assessment system is a prescription device that is designed to obtain and analyze light microscopy images of developing embryos. This device provides information to aid in the selection of embryo(s) for transfer when there are multiple embryos deemed suitable for transfer or freezing.

NEW REGULATION NUMBER: 21 CFR 884.6195

CLASSIFICATION: II

PRODUCT CODE: PBH

BACKGROUND

DEVICE NAME: Eeva™ System

SUBMISSION NUMBER: K120427

DATE OF DE NOVO: AUGUST 24, 2012

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REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The Eeva System is indicated to provide adjunctive information on events occurring during the first two days of development that may predict further development to the blastocyst stage on Day 5 of development. This adjunctive information aids in the selection of embryo(s) for transfer on Day 3 when, following morphological assessment on Day 3, there are multiple embryos deemed suitable for transfer or freezing.

LIMITATIONS

The sale, distribution, and use of the device are restricted to prescription use in accordance with 21 CFR 801.109.

The Eeva™ System is limited to adjunct use on embryos graded as good or fair based on morphology on Day 3 of development.

WARNING: The Eeva System is not to be used as a substitute for traditional morphology evaluation. When using the Eeva System, always conduct traditional morphology evaluation first to identify the embryos that are suitable for transfer or freezing. The Eeva System evaluation begins only after embryos that are morphologically, good/fair have been identified. The Eeva System is then used to assist in predicting potential arrested embryos out of the selected embryos.

Precautions

Determination of good/fair embryo retention (cryopreservation) should be made according to traditional morphology only (not based on the Eeva Test Result).

The Eeva Blastocyst Prediction does not provide any information on embryo genetic quality beyond providing information about the embryo's likelihood to progress to the blastocyst stage.

The adjunctive value of the Eeva Test to predict which embryo is likely to achieve implantation and live birth has not been evaluated.

Users of the Eeva System should be trained in, and familiar with, standard *in vitro* fertilization (IVF) and incubator operating procedures. Only users trained on the use of the Eeva System should use the Eeva System. The Eeva System training is provided by an authorized Auxogyn trainer during the installation process or may be given by a trained member of the site personnel.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS AND PRECAUTIONS.

DEVICE DESCRIPTION

Device Name: Eeva™ System

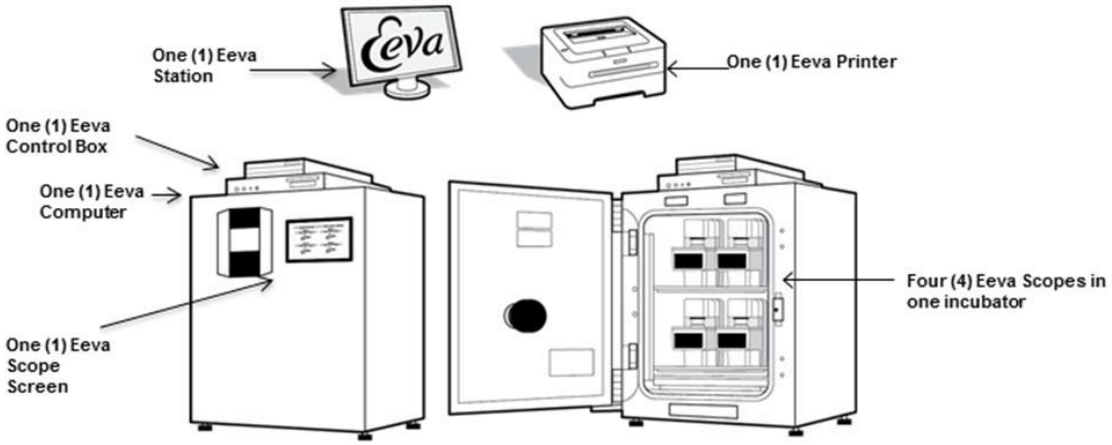
Device Model(s): EVS2000

The Eeva System provides image recording and automated analysis of cell division from high resolution time-lapse images collected until day 3 (72 hours) of development. Results of cell division timing parameters (time from first to second mitosis; and time from second to third mitosis) are provided to the user in addition to a prediction of the likelihood that an embryo will

develop to the blastocyst stage. These timing parameters are based on those published in a study by Wong, *et. al.* (2010)[1].

The Eeva System incorporates: (1) a set of up to four time-lapse image microscopes that automatically take darkfield microscopy images of embryos at regular intervals (every 5 minutes) while the embryos remain in the incubator environment, (2) Eeva Computer and other components (Control Box, Station, Scope Screen and Printer), (3) system software for image capture and recording, user interface, and patient database and (4) image analysis software that automatically identifies embryo development events, compares their times to specified timing parameters and makes a prediction of embryo development to the blastocyst stage (**Figure 1** and **Table 1**). The system is installed in an *In Vitro* Fertilization (IVF) laboratory, and is to be used as an adjunct to the traditional morphological method to identify the embryos that are more likely to develop into blastocysts.

Figure 1: Eeva and its Hardware Components



The Eeva System is designed to be used with the Eeva Dish, which is 510(k) cleared (K103028). **Figure 2** below shows the Eeva Dish on the Eeva Scope. The Eeva Dish is a standard-size petri dish with individual micro-wells arrayed in the center of the dish. Each dish accommodates a single patient's developing embryos. The Eeva Dish fits in only one position on the Eeva Scope stage, and each micro-well is identified to facilitate embryo tracking. The user aligns the orientation of the dish with help from fiducial markers. **Figure 3** shows an image of the Eeva microwell screen after imaging is complete.

[1] Wong, C. *et al.* Non-invasive imaging of human embryos before embryonic genome activation predicts development to the blastocyst stage. *Nat Biotechnol* **28**, 1115-1121 (2010)

Figure 2: Eeva Scope

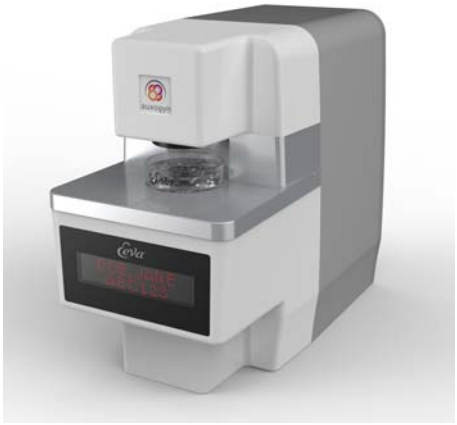
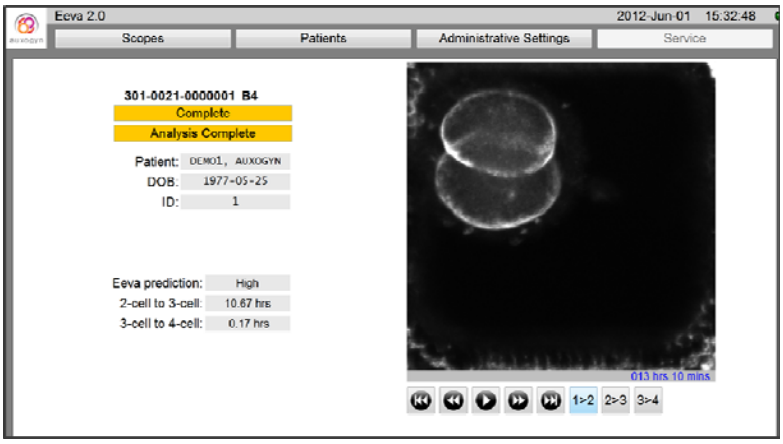


Figure 3: Eeva Microwell Screen (After Imaging Complete)



The Eeva Scope is an inverted microscope that performs darkfield microscopy at regular intervals using a low intensity LED lighting system. The microscope uses a 625nm wavelength red LED to image the embryos under darkfield illumination. Light from the illumination LED is collimated and passed through a diffuser before focusing through a dark stop and onto the Eeva dish. The microscope uses a set of objective lenses housed inside the microscope to project the image of the embryos onto an image sensor. The effective optical magnification of the Eeva System is 2.5x with a working distance of approximately 10 mm.

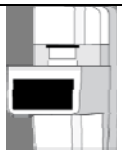
The Eeva System controls the illumination LED power to achieve a consistent average exposure level on the imaging sensor. In use, the typical optical power measured at the dish is $0.22mW/cm^2$, with a maximum of $0.7mW/cm^2$. In contrast a typical IVF microscope has an optical power of $7.6mW/cm^2$. A typical image requires 0.6 seconds of light exposure or $0.13mJ/cm^2$ of energy. Over a 3 day (72 Hour) imaging session, embryos are exposed to $114mJ/cm^2$. A worst-case analysis indicates a total exposure of $363mJ/cm^2$; equivalent to

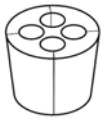
approximately 48 seconds on an IVF microscope. By comparison, in a typical IVF cycle, embryos are exposed to light for approximately 3300 seconds.

The Eeva System software runs on the Eeva Computer. The software tracks embryo features within each image frame. This information is used to generate an embryo model that includes an estimate of the number of cells in the embryo. The software quantifies the development timeline as the embryo divides. After measuring cell division times, the software compares the resulting two and three cell stage durations (parameters) to the Eeva System's predictive windows for the time from first to second mitosis and from second to third mitosis.

If all parameters measured fit within the predictive windows, then the software predicts the embryo to have a high probability of reaching the blastocyst stage. If any of the parameters measured falls outside of the predictive windows, then the software predicts that the embryo has a low probability of reaching the blastocyst stage. If incomplete imaging data is present for the embryo, a "no result" finding will be presented for that embryo.

Table 1: Eeva System Components

Component	Quantity	Image	Description
Eeva Computer	1		Operates the four **Eeva Scopes**, the **Eeva Station** and **the Eeva Scope Screen(s).** Runs the **Eeva Analysis** and computes the **Eeva Blastocyst Prediction**. Stores images and patient data for **Eeva Patient Sessions**.
Eeva Control Box	1		Receives commands from the **Eeva Computer** and operates **the Eeva Scopes** accordingly. Provides power to the **Eeva Scopes** and continuously monitors the Eeva Scope power consumption. If the power consumption exceeds normal operating limits, then a hardware error is triggered and the Eeva Control Box turns off the power to the scope. The Eeva Control Box reports errors to the Eeva Computer and the user is alerted on the Eeva Station and the Eeva Scope Screen
Eeva Scopes	4		An assisted reproductive microscope with a platform designed to hold the **Eeva Dish**. It houses the optics and provides illumination needed to create dark field image capture.
Eeva Scope Screen(s)	1 or 2		The **Eeva Scope Screen** is a touchscreen display that is used to select and operate the **Eeva Scope** for the **Eeva Patient Session**. Via the **Eeva Scope Screen**, the user can enter patient data and initiate, pause or stop the image capture and/or **Eeva Analysis** for that **Eeva Patient Session**. The **Eeva Scope Screen** can also be used to view the most recent image captured for each active **Eeva Scope**. The **Eeva Scope Screen** is mounted on the incubator door.

Eeva Station	1		A large touchscreen monitor that allows the user to manage the **Eeva Patient Session** data stored on **Eeva**. Via the **Eeva Station**, the user can view the status of each **Eeva Scope(s),** review and export images and videos, and print and export reports.
Stopper	1		Provides a thru-hole for the Eeva Scope cables to pass from the Eeva Scope inside the incubator to the Eeva Control Box outside the incubator, while maintaining the incubator environment.
Connection Cords	4		Connects the Eeva Scope to the Eeva Control Box, supplying power to the Eeva scope and communication channels.
Uninterruptable Power Supply (UPS)	1		An uninterruptible power supply to provide backup power to **Eeva**.
Eeva Printer	1		A black and white printer for printing **Eeva** reports.

Please refer to the Instructions for Use for the Eeva System for additional details on the device.

BIOCOMPATIBILITY/MATERIALS

Eeva System materials do not come in direct or indirect contact with the patient during use. Therefore, biocompatibility testing of device materials was not necessary to assess device safety.

SHELF LIFE/STERILITY

The Eeva System is a non-sterile device. Therefore, sterilization validation information was not necessary to assess device safety. The device does not have a stated shelf life, which, based upon the nature of the device components, is acceptable.

With the exception of the Eeva Dish, previously cleared through 510(k), all other components of the Eeva System are reusable, and the user manual includes validated cleaning and disinfection instructions for reusable device components. The validation testing is described in the Summary of Non-Clinical /Bench Studies.

SOFTWARE

The Eeva System's proprietary software controls the individual microscopes, coordinates image acquisition and patient data management. The Eeva System software also quantifies the development timeline as the embryo divides, and classifies the resulting two and three cell stage durations into either high or low probability of reaching a blastocyst.

All the elements of software information corresponding to moderate level of concern devices, as outlined in FDA's *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (May 11, 2005), have been provided.

The testing conducted to validate device software is described in the Summary of Non-Clinical /Bench Studies and Summary of Clinical Information.

SUMMARY OF NON-CLINICAL/BENCH STUDIES

In addition to the testing described above, the sponsor conducted a series of non-clinical performance testing to demonstrate that the Eeva System would perform as anticipated. Non-clinical testing included device effects on embryo growth and development, cleaning and disinfection, electromagnetic compatibility (EMC) and electrical safety testing, package integrity testing, simulated use testing, light output and safety evaluation, hardware and software testing. Testing is summarized in Table 2, below.

Table 2: Summary of Non-Clinical/Bench Studies

Test	Purpose	Acceptance Criteria	Results
Embryotoxicity Assessment			
Mouse Embryo Assay (MEA)	To evaluate whether the Eeva System offers appropriate conditions within the incubator for embryo culture. Testing was performed in Auxogyn's laboratory and at 4 clinical sites.	(b)(4) TS/CCI	Pass
Cleaning and Disinfection			
Cleaning	To evaluate the reprocessing procedures for the Eeva System (microscope, cable, stopper) to ensure it can be properly cleaned by manual methods (reference AAMI TIR12: 2010 & AAMI TIR30:2011).	Test samples shall be inspected with an unaided eye and determined to be visibly clean with no soil detected.	Pass
		The level of protein after cleaning shall be (b)(4) TS/CCI.	
		The carbohydrate level after cleaning shall (b)(4) TS/CCI samples.	
Disinfection	To evaluate the reprocessing procedures to ensure they are adequate to properly disinfect the Eeva System (microscope, cable, stopper) (reference AAMI TIR12: 2010 & AAMI TIR30:2011).	Test samples shall demonstrate a (b)(4) TS/CCI to the positive control samples.	Pass
		Test samples shall demonstrate a (b)(4) TS/CCI compared to the positive control sample.	
Media Spill	To evaluate the process for cleaning the Eeva Scope in case of a media spill and to ensure it is sealed from any	The Eeva Scope shall remain functional and provide usable images after media	Pass

Test	Purpose	Acceptance Criteria	Results
	ingress of fluid that would impact functionality.	spill and subsequent cleaning.	
Package Integrity and Transit Testing			
Eeva System	To evaluate if the Eeva System palletized shipping configuration can withstand simulated transit per ASTM D 4169-09.	Upon completion of the testing, the Eeva System packaging shall be intact. The Eeva System must be fully functional after testing.	Pass
EMC and Electrical Safety Testing			
EMC Testing	To evaluate whether the Eeva System meets the EMC requirements of EN/IEC 60601-1-2:2007. (Medical electrical equipment – Part 1-2: General requirements for safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests)	EMC requirements, as defined in EN/IEC 60601-1-2:2007.	Pass
Electrical Safety Testing	To evaluate whether the Eeva System meets the product safety requirements of BS EN 60601-1: 2006 + A11:2011. (Medical electrical equipment – General requirements for basic safety and essential performance)	Electrical safety requirements, as defined in BS EN 60601-1: 2006 + A11:2011.	Pass
Simulated Use			
Installation Verification	To verify that the Eeva System can be installed and functionality verified in less than 8 hours.	The Eeva System shall be installed and operational in less than 8 hours.	Pass
System Usability	To verify that the Instructions for Use can be understood by the user and that the results of each action are stated in the IFU.	The Instructions for Use can be understood by the user and the results of each action are stated in the IFU.	Pass
Simulated Use	To verify the Eeva System successfully operates in a real time simulated use procedures, and to verify that intermittent incubator door opening does not negatively impact imaging and embryo prediction.	The Eeva System shall operate successfully in a simulated use procedure and incubator door opening shall not impact image capture or embryo prediction.	Pass
Performance Testing - Bench			
Hardware			
Light Exposure and Output	To document the amount of light exposure from the Eeva microscope compared to a traditional IVF microscope.	(b)(4) TS/CCI	Pass

Test	Purpose	Acceptance Criteria	Results
		(b)(4) TS/CCI .	
Hardware Controls	To verify that the hardware controls in the Eeva System properly limit the microscope lamp LED, alignment LED and LCD, camera and motor, and turn them off if the limits are exceeded.	(b)(4) TS/CCI	Pass
Microscope, Scope Screen, Computer Hardware, Uninterruptable Power Supply, and Printer	To verify various microscope, incubator interface, scope screen, computer storage, accessory parameters and interactions.	System components conform to design specifications.	Pass
Software			
Eeva System Software Verification	To verify integrated system operation and various camera, workflow and Eeva Station component requirements.	The software conforms to all design specifications.	Pass
Software Fail-Safe Verification	To verify safety related parameters for the LED, LCD, Camera and Motor, as well as various requirements of the configuration, microscope user interface, focus motor, LCD display and Eeva Station software components. The safety-related parameters verified included: fail-safe status from the lamp LED, alignment LED and LCD, camera power monitor and motor power hardware controls; continuous on time of the lamp LED, alignment LED and LCD; camera -free run time; and control or lamp brightness and power.	The software conforms to all safety-related specifications.	Pass
Algorithm Software Validation	To validate the ability of the Eeva software to predict blastocyst formation.	(b)(4) TS/CCI	Pass

Test	Purpose	Acceptance Criteria	Results
		of embryologists.	
Algorithm Software Verification	To verify the Eeva System image analysis algorithms.	(b)(4) TS/CCI	Pass
Algorithm Reproducibility	To evaluate the reproducibility of the Eeva System algorithm software.	The software must generate repeatable outputs across multiple Eeva Systems, given the same set of input image data.	Pass

PERFORMANCE TESTING – ANIMAL

In vivo animal studies were not conducted in support of the Eeva System nor deemed necessary to support the safety and effectiveness of the Eeva System.

SUMMARY OF CLINICAL INFORMATION

The safety and effectiveness of the Eeva System was studied through the Eeva System Clinical Study. This study was a prospective, single arm, multicenter clinical study conducted at five sites in the United States. This was a non-interventional clinical study in which the Eeva output was not used in patient management. The purpose of the study was to collect data to characterize the safety and effectiveness of the Eeva System in predicting which embryos are more likely to develop to the blastocyst stage. The study design evaluated the Eeva System as an adjunct to traditional morphology grading. Imaging data was collected on embryos cultured to the cleavage stage (Day 3) or blastocyst (Day 5/6) stage. Embryologists were masked to Eeva sequential images of the developing embryos, except for the most recent image recorded. The Eeva System Clinical Study enrolled a total of 160 subjects that were allotted to different parts of the study (**Table 3**).

Table 3: Eeva System Clinical Study Enrollment

Eeva System Clinical Study Sub-Part	Number of Subjects
Training	12
Software Development	63
Software Validation	21
Pivotal Adjunct Use	54
Additional Development	10*
Total	**160**

*subjects excluded from use in the Pivotal Adjunct Use Study due to incomplete Day 5/6 embryo cohort data

The Eeva System Clinical Study had the following sub-parts:

1) Training: This group consisted of the first subjects enrolled in the study from all sites. The purpose of this part of the study was to allow the sites to become familiar with the Eeva System and the study protocol. Data from this group was not used for endpoint analysis.
2) Software Development: This part of the study was to further develop the Eeva System Software. Imaging data was collected on embryos cultured to cleavage stage (Day 3) or blastocyst stage (Day 5/6).
3) Software Validation: This part of the study was used to validate the ability of the Eeva System Software to predict blastocyst formation.
4) Pivotal Adjunct Use: This part of the study was to evaluate the use of the Eeva System, when used as an adjunct to the traditional Day 3 morphological grading compared to traditional Day 3 morphological embryo grading methods alone.

Six adverse events in six subjects (3.75%, 6/160) were determined to be related to the Eeva System, specifically to the Eeva Dish. None of these adverse events were serious. These events were embryo damage during pipetting and embryo transfer into/out of the dish (3.13%, 5/160) and embryo loss during the Day 4 dish change (0.63%, 1/160). These events were anticipated and can occur with handling of embryos in the process of IVF cycle with standard IVF equipment.

Training

Consistent with the approved protocol, these data were not used as part of the analysis that follows but rather were solely for purposes of ensuring familiarity with the protocol and the Eeva System.

Software Development

This study explored several types of blastocyst prediction models. In addition to cell division parameters, other factors were considered, but it was determined that two prediction values (termed P2 and P3) dominated the prediction. At the end of the software development phase, the results identified the parameters for P2 (time from first to second mitosis) and P3 (time from second to third mitosis) that were implemented into the Eeva System software.

Software Validation

A panel of three embryologists reviewed the image series of each embryo to identify the start/stop times of the two development parameters. The results of the embryologists' measurements were compared to the Eeva System measurements to validate the software. The study protocol required the specificity of the Eeva System software to be non-inferior to the specificity of the panel embryologist measurements and also required the lower limit of the 95% confidence interval for specificity of the Eeva System software to be greater than or equal to 65%. The specificity of the Eeva System software was 85.12%, while the specificity of the embryologists was 82.64%. The lower limit of the 95% confidence interval for the Eeva System was 77.71%. Both acceptance criteria were met and the software was deemed validated.

Pivotal Adjunct Use Study

This study utilized a panel of 5 clinical embryologists currently in practice, representing a range of geographical areas and level of experience. Each panelist provided a morphological assessment and an adjunct assessment for each subject, as follows:

Morphological assessment: Each panelist reviewed the Day 3 morphology data from a subject's cohort of embryos collected by clinical site embryologists (from Case Report Forms). The data included the number of cells, fragmentation (0%, <10%, 10-25%, >25%) and symmetry (Perfect, Moderately Asymmetric, Severely Asymmetric). Additionally, the age of subject or egg donor was provided. The panel then performed the following:

1. Assigned an embryo category (A: Good, B: Fair+, C: Fair-, D: Poor).
2. Assigned a prediction (Blastocyst; Arrested)
3. Chose the Top 2 embryos from the subject's complete cohort of embryos (Top 1, Top 2)

Adjunct assessment: For the adjunct assessment, the panelists were provided with the same information as in the traditional morphology session, with the addition of Eeva parameter values (P2 and P3), and an Eeva prediction of "High, Low." Panelists were asked to follow pre-defined recommendations in order to assign a prediction outcome (Blastocyst; Arrested). Panelists then chose the Top 2 embryos for a given subject.

In this study, the panel of embryologists did not collect the morphological data, but were instead presented with the data collected by clinical site embryologists. Therefore, this study was not designed to consider variation among embryologists in embryo data collection.

Primary Endpoint

The primary endpoint for this study was to assess the association between the adjunct prediction of blastocyst outcome and the actual blastocyst outcome. The purpose was to determine if Eeva is informative for embryos graded as an A, B, or C using Day 3 morphology category assignment). For Good/Fair embryos, the blastocyst Odds Ratio (OR) for the adjunct prediction was required to be statistically significantly greater than 1 to demonstrate that adjunctive use of Eeva led to embryologist predictions for Day 5 that were informative for outcome (i.e., Arrested; Blastocyst).

The primary endpoint for the study was met with statistical significance. For the pre-specified analysis, the overall OR for adjunct prediction was calculated by the sponsor to be 2.56 and significantly greater than 1 (95% CI: [1.75, 3.74], p<.0001). These results were based on a novel statistical procedure that the sponsor had pre-specified in an attempt to address the complex structure of the data (multiple embryos per subject, five panelists evaluating all embryos by both traditional morphology and sequential adjunctive use of Eeva).

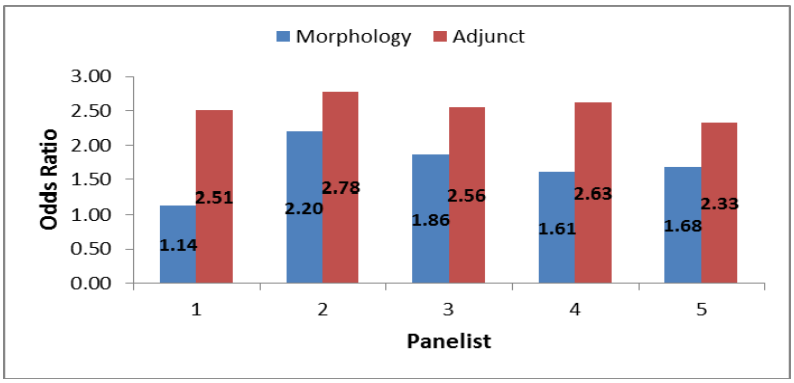
To determine if the results were robust to alternative statistical approaches that could have been used for the analysis, the data for the primary endpoint were re-analyzed with a generalized linear mixed model (GLMM) model. For the primary endpoint, the GLMM model results were comparable to the initial analysis in that the estimate of the overall OR for adjunct prediction was nearly the same (2.57) and was again significantly greater than 1 (95% CI: [1.88, 3.51]). Thus, the primary endpoint was also met with the GLMM analysis.

Embryo-Level Diagnostic Performance Measures (Secondary Endpoints)

By comparison, the overall OR for traditional morphology prediction was estimated to be 1.66 (95% CI: [0.78, 3.51]) by the pre-specified analysis. The GLMM estimate of the overall OR for traditional prediction was nearly the same (1.68) but with narrower 95% CI [1.29, 2.19].

Additionally, when the data for each panelist were considered separately, blastocyst prediction was more informative (OR greater) for adjunct use than for morphology alone for every panelist (**Figure 4)**.

Figure 4: Traditional Morphology and Adjunct Blastocyst OR by Panelist



Specificity (proportion of embryos that did not form blastocysts that were predicted to not form blastocysts) increased from 39% for morphology alone prediction to 76% for adjunct prediction, an improvement of 37%. However, sensitivity (proportion of embryos forming blastocysts that were predicted to form blastocysts) decreased from 72% for morphology alone prediction to 45% for adjunct prediction, a decline of 27%. While the increase in specificity comes with a decrease in sensitivity, this trade-off is not unexpected. As morphological selection already identified embryos deemed suitable for transfer, the sensitivity of Eeva is a less relevant performance measure, as long as Eeva predictions are informative.

The negative predictive value or NPV (proportion of embryos predicted to not form blastocysts that did not form blastocysts) was the same for adjunct and traditional prediction (68%). However, the positive predictive value or PPV (proportion of embryos predicted to form blastocysts that did so) was larger for adjunct prediction (54%) than traditional prediction (43%), an 11% improvement. The improved PPV and similar NPV indicate that adjunct use of Eeva was better than traditional morphology at predicting blastocyst status.

The negative likelihood ratio or NLR [(1 – sensitivity) ÷ specificity] was the same for adjunct and traditional predictions (0.73). However, the positive likelihood ratio or PLR [sensitivity ÷ (1 – specificity)] was higher (better) for adjunct prediction (1.86) than traditional prediction (1.21). The improved PLR and similar NLR indicate that adjunct use of Eeva was better than traditional morphology at predicting blastocyst status.

These findings demonstrate that adjunct prediction improved the selection of embryos for transfer over morphology alone. In particular, among embryos deemed suitable for transfer by morphology assessment, adjunctive use of Eeva improved specificity. This increase in specificity translated to an improved PPV, that is, an improved likelihood that selection of an embryo for transfer will go on to form a blastocyst.

Top 2 Embryo Analysis (Secondary Endpoint)

This analysis included the top 2 embryos selected by each panelist based on morphology alone. Among these embryos, the adjunct OR was estimated to be 2.26, indicating that Eeva was informative for Day 5 blastocyst status even in this selective group of embryos. The OR 2.26 among the top 2 embryos is consistent with the overall adjunct OR 2.56. However, for this odds ratio, the reported 95% confidence interval was (0.67, 7.57). Therefore, the benefit of Eeva cannot be said to be established in the subset of the two highest quality embryos available for each subject (Top 2 Analysis) as determined by traditional morphology.

Subject Level Analysis Evaluations (Secondary Endpoints)

The sponsor conducted two subject level analyses on study data (see summaries below). For the subject level performance assessment, the following definitions were used:

- True Positive (TP)
    - 1-2 embryos from the subject are predicted as “Blastocyst,” and one of these forms a blastocyst, or

    - >2 embryos are predicted as "Blastocyst," and at least one of the Top 2, as selected by the panelist, forms a blastocyst.
- False Negative (FN)
    - None of the embryos from the subject are predicted as "Blastocyst," but at least one forms a blastocyst, or
    - 1-2 embryos are predicted as "blastocyst," but none forms a blastocyst, and at least one other embryo forms a blastocyst, or
    - >2 embryos are predicted as "Blastocyst," but none in the Top 2, as selected by the panelist, forms a blastocyst, and at least one not in the Top 2 forms a blastocyst.
- False Positive (FP)
    - Some embryos from the subject are predicted as "Blastocyst," but none of the embryos from the subject forms a blastocyst.
- True Negative (TN)
    - None of the embryos from the subject are predicted as "Blastocyst," and none form a blastocyst.

Subject-Level Performance

Among 54 subjects, only one subject for panelists 2 and 4 and two subjects for panelists 1, 3, and 5 had zero blastocysts among the cohort of A, B, and C embryos for that panelist. Thus, subject level specificity was based on only one or two subjects. For this reason, the subject level analysis for specificity, and for related performance measures such as PLR, NLR, and OR that depend on specificity, is limited and not meaningful.

Subject level sensitivity is based on either 52 or 53 subjects for whom at least one embryo formed a blastocyst among the cohort of A, B, and C embryos for a panelist. Among the five panelists, subject level sensitivity ranged from 69.2% to 75.0% for traditional morphology and 71.2% to 81.1% for adjunct prediction. Although adjunct prediction is designed to rule out some embryos selected by traditional morphology, subject level sensitivity can be larger for adjunct prediction because the top 2 embryos remaining after some of the embryos are ruled out may be more likely to form a blastocyst. For four of the panelists, subject level sensitivity was larger for adjunct prediction than for traditional morphology. Differences in sensitivities were -1.9%, 3.8%, 3.9%, 5.8%, and 11.3%, for an average of 4.6% improvement in sensitivity.

LABELING

Labeling provided includes Instructions for Use, package labels, and training documents. The Eeva System Instructions for Use includes the indications for use, warnings, precautions, and instructions for the safe use of the device. The labeling satisfies the requirements of 21 CFR Part 801.109 Prescription devices.

Please see the Limitations section above for important Warnings and Precautions presented in the device labeling.

The Eeva System Training documents are consistent with the Instructions for Use.

RISKS TO HEALTH

Table 4 below identifies the risks to health that may be associated with use of an Assisted Reproduction Embryo Image Assessment System and the measures necessary to mitigate these risks.

Table 4: Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Damage or Destruction of the Embryo	Non-Clinical Performance Testing Software Verification, Validation & Hazards Analysis Clinical Testing Electromagnetic Compatibility Testing Electrical Safety Testing Labeling Training
Infection (Contamination of Device, Labware, and Incubator)	Cleaning and Disinfection Validation Labeling Training
Incorrect Embryo Development Prediction	Non-Clinical Performance Testing Software Verification, Validation & Hazards Analysis Clinical Testing Labeling Training
Electromagnetic Interference/Electrical Safety Issues	Electromagnetic Compatibility Testing Electrical Safety Testing Labeling
User Error	Labeling Training

SPECIAL CONTROLS:

In combination with the general controls of the Food, Drug &Cosmetic Act, Assisted Reproduction Embryo Image Assessment Systems are subject to the following special controls:

1. Clinical performance testing must demonstrate the safety and effectiveness of the device to predict embryo development. Classification performance (sensitivity and specificity) and predictive accuracy (Positive Predictive Value and Negative Predictive Value) must be assessed at the subject and embryo levels.

2. Software validation, verification, and hazard analysis must be provided.

3. Non-clinical performance testing data must demonstrate the performance characteristics of the device. Testing must include the following:
    a. Total light exposure and output testing
    b. A safety analysis must be performed based on maximum (worst-case) light exposure to embryos, which also includes the safety of the light wavelength(s) emitted by the device

c. Simulated-use testing
d. Mouse Embryo Assay (MEA) testing to assess whether device operation impacts growth and development of mouse embryos to the blastocyst stage
e. Cleaning and disinfection validation of reusable components
f. Package integrity and transit testing
g. Hardware fail-safe validation
h. Electrical equipment safety and electromagnetic compatibility testing
i. Prediction algorithm reproducibility

4. Labeling must include the following:
    a. A detailed summary of clinical performance testing, including any adverse events
    b. Specific instructions, warnings, precautions, and training needed for safe use of the device
    c. Appropriate electromagnetic compatibility information
    d. Validated methods and instructions for cleaning and disinfection of reusable components.
    e. Information identifying compatible cultureware and explain how they are used with the device

BENEFIT/RISK DETERMINATION

The risks of the device are based on the non-clinical laboratory studies as well as the data collected in the clinical studies described above. In the clinical studies, no device-related serious adverse events were observed, while six device-related non-serious adverse events were observed. In five of the six device-related non-serious adverse events, the subject's embryos were damaged during pipetting and embryo transfer in/out of the dish. In the remaining case, the subject's embryos were lost during the Day 4 dish change. In all cases, the IVF cycle continued with the remaining embryos for each subject. No device-related serious adverse events are anticipated with the use of the Eeva System and all non-serious adverse events are expected to be rare and are typical of those expected during IVF procedures. There are no additional procedure-related risks with the introduction of the Eeva System.

The primary clinical risks associated with the use of the Eeva System are a false positive (false Eeva = 'High') result or a false negative (false Eeva = 'Low') result. The risk of a false negative is the potential to "de-select" an embryo that would go on to form a blastocyst; however, this risk is mitigated by the likelihood that embryos with favorable morphology would be frozen for subsequent use. The risk of a false positive is that a sub-optimal embryo may be selected for transfer. However, Eeva test results are used only as an adjunct to morphology assessment, which identifies the good/fair embryos that are suitable for transfer.

The probable benefits of the device are based on the data collected in the clinical studies described above. The majority of patients studied had more embryos deemed suitable for transfer based on morphology grading than would be transferred. The Eeva test results provide a method to help narrow the selection of embryos post morphological selection. Results from the Pivotal Adjunct Study showed that the Eeva System offers a significant 37% improvement in specificity, the proportion of arrested embryos that were de-selected, when used as a sequential adjunctive tool to

morphology compared with morphology alone. This increased specificity was accompanied by an improved likelihood that an embryo will go on to form a blastocyst when the set of embryos are narrowed to those with an Eeva 'High' prediction. In sequential adjunct use of Eeva with morphology data on Day 3, the odds of an embryo forming a blastocyst on Day 5 were 2.6 times higher among embryos predicted to form a blastocyst than among embryos predicted to arrest. Because the majority of subjects in the clinical study had more embryos graded by morphology that were suitable for transfer than would be typically transferred, patients with multiple good embryos could benefit from the use of the Eeva System as an aid in identifying embryos not likely to form blastocysts, to help narrow the selection among those deemed suitable by morphologic grading. The maximum duration of benefit was not directly measured in the clinical study because observation ended with blastocyst formation. However, regardless of longer-term pregnancy outcomes, the potential duration of benefit can be approximated in terms of lost IVF cycles, if no embryos are selected for transfer that go on to form blastocysts.

In conclusion, given the information above, the data support a favorable benefit / risk profile for the Eeva System when it is used in a sequential adjunctive manner to Day 3 morphology assessment as an aid in the selection of embryo(s) for transfer, when multiple embryos are deemed suitable for transfer or freezing. The data support the conclusion that the probable benefits of using the Eeva System outweigh the probable risks. The device provides substantial benefits, and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The de novo for the Eeva System is granted and the device is classified under the following:

Product Code: PBH
Device Type: Assisted Reproduction Embryo Image Assessment System
Class: II (Special Controls)
Regulation: 21 CFR 884.6195