SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Placental Alpha Microglobulin-1 Immunoassay

Device Trade Name: PartoSure test

Device Procode: QBB

Applicant's Name and Address: Parsagen Diagnostics, Inc.
Harvard Innovation Launch Lab
114 Western Avenue
Boston, MA 02134

Date(s) of Panel Recommendation: Not Applicable

Premarket Approval Application (PMA) Number: P160052

Date of FDA Notice of Approval: 04/11/2018

II. INDICATIONS FOR USE

The PartoSure test is a rapid, qualitative test for detecting the presence of placental alpha microglobulin 1 (PAMG-1) in cervicovaginal secretions. The device is indicated as an aid to rapidly assess the risk of spontaneous preterm delivery in ≤ 7 days from the time of cervicovaginal sample collection in pregnant women with signs and symptoms of early preterm labor, intact amniotic membranes and minimal cervical dilatation (<3 cm), sampled between 24 weeks, 0 days and 34 weeks, 6 days gestation in women with a singleton gestation.

III. CONTRAINDICATIONS

There are no known contraindications.

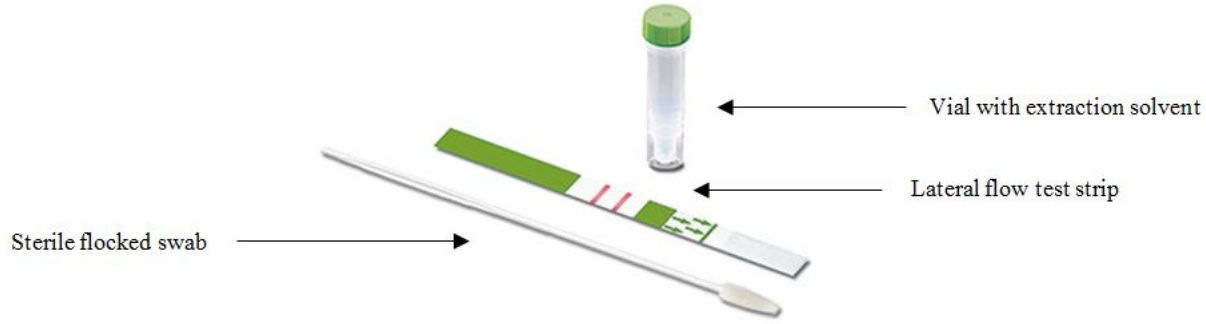
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PartoSure test labeling.

V. DEVICE DESCRIPTION

The PartoSure test is a rapid qualitative immunochromatographic test for the in vitro detection of placental alpha microglobulin-1 (PAMG-1) in vaginal secretions of pregnant women. PAMG-1 is a protein released from decidual cells into the amniotic cavity throughout pregnancy. The presence of PAMG-1 when labor and delivery are imminent is likely due to the transudation of the protein through preexisting pores in the chorioamniotic membranes during uterine contractions and, potentially, degradation of the extracellular matrix of fetal membranes due to an inflammatory process of labor. The self-contained PartoSure test is comprised of a sterile flocked swab, a vial with an extraction solvent, and a lateral flow test strip (see Figure 1). The device relies on the principles of immunochromatography to produce a qualitative test result. A sample of cervicovaginal secretions is taken with a sterile vaginal swab, diluted in the solvent vial, and tested with a lateral flow strip. The result is negative if only the control line is visible in the test region. The result is to be interpreted as positive if there are both control and test lines visible in the test region. The result is to be interpreted as invalid if there are no visible lines in the test region or if there is only a visible test line in the test region, without a visible control line.

Figure 1: PartoSure test kit



The three parts of the PartoSure test are described below.

1. Sterile, Vaginal Swab: The sterile, vaginal swab is a cone-shaped, single wrapped flocked swab with a nylon applicator on a plastic shaft. It is sterilized using ethylene oxide. The brush tip of the swab is made of nylon whereas the plastic shaft is made of polystyrene. The swab is provided in its own package. The swab is used for taking a vaginal secretion sample from the vagina.

2. Vial with Extraction Solvent: The plastic (polypropylene) vial with cap and solvent solution is 44 mm high; with a diameter of 10.8 mm; and max volume of 2.0 ml. The vial is transparent and contains 0.55 ml of solvent solution. The solvent is a saline solution with solubilizer and dispersant (Triton X100) and preservative (sodium azide). The solvent extracts the sample of vaginal secretions from the swab that is dipped into the vial as part of the test procedure.

3. Lateral Flow Test Strip: The PartoSure test is a lateral flow, immunochromatographic assay designed to identify the presence of human placental-alpha-microglobulin-1 (PAMG-1). The test employs goat anti-mouse monoclonal antibodies at the test region to detect PAMG-1 and goat anti-mouse anti-immunoglobulin antibodies at the control region to detect IgG.

To perform the PartoSure test, a sample of vaginal secretions taken by the provided vaginal swab is placed into the provided vial with extraction solvent. The solvent then extracts the sample from the swab for 30 seconds, after which the swab is disposed. The PartoSure test strip is then dipped into the vial. The sample then flows by capillary action from the pad region through the test region of the test strip. The test result is to be visually read between 5 and 10 minutes after sample application.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

A variety of clinical methods are used to assess the risk of preterm delivery in symptomatic women. Clinically, the risk assessment of preterm delivery includes suggestive symptoms of preterm labor, such as suspected amniorrhexis (or rupture of the fetal membranes [ROM]), uterine activity, abdominal discomfort, change in vaginal discharge, bleeding, or cramping. Biophysical markers that are also relied upon include: changes in cervical length, cervical dilatation, and contractions, all of which may be precursors of labor. In addition, there is a commercially-available biochemical marker test for the prediction of preterm delivery in patients presenting with signs, symptoms or complaints suggestive of preterm labor: the fetal fibronectin (fFN) Test.

VII. MARKETING HISTORY

The PartoSure test has not been marketed in the United States.
The PartoSure test has been marketed in the European Union since January 2013. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse effects of the device are indirect and consist of false positive or false negative results. A false negative result could contribute to a missed opportunity to administer antenatal interventions, primarily corticosteroids, which significantly reduce neonatal morbidity and mortality. A false positive result could contribute to pregnant women undergoing an admission to an acute care facility and possible unnecessary interventions for preterm labor.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Limit of Detection (LoD)/Reproducibility
   To establish the analytical LoD, seven levels of PAMG-1 samples (0.0, 0.2, 0.5, 0.7, 0.9, 1.0 and 2.0 ng/ml) were tested in 5 replicates per lot using 3 lots of devices by 9 test operators at 3 intended-use sites (i.e., 3 operators per site). The study results are summarized in Table 1 below. The sponsor claimed that the Limit of Detection for PartoSure test is 1.0 ng/mL.

Table 1 Reproducibility, by lot

PAMG-1 (ng/mL)	Lot 1		Lot 2		Lot 3		Total
	Negative	Positive	Negative	Positive	Negative	Positive	%
0	45	0	45	0	45	0	0%
0.2	45	0	45	0	45	0	0%
0.5	45	0	45	0	45	0	0%
0.7	10	35	12	33	13	32	74%
0.9	3	42	8	37	8	37	86%
1.0	0	45	0	45	0	45	100%
2.0	0	45	0	45	0	45	100%

The reproducibility performance by study site is summarized in Table 2 below:

Table 2 Reproducibility, by site

PAMG-1 (ng/mL)	Site 1		Site 2		Site 3	
	Negative	Positive	Negative	Positive	Negative	Positive
0	45	0	45	0	45	0
0.2	45	0	45	0	45	0
0.5	45	0	45	0	45	0
0.7	14	31	13	32	8	37
0.9	13	32	2	43	4	41
1.0	0	45	0	45	0	45
2.0	0	45	0	45	0	45

2. Interference

   Pharmacological Agents
   To evaluate potential interference from pharmacological substances, 4 replicates of a negative sample (0.2 ng/mL PAMG-1) and a positive sample (2.0 ng/mL PAMG-1) were tested after being individually spiked with potential interfering pharmacological substances. No interference was observed for any of the following substances in Table 3 below, at the testing levels indicated:

Table 3 Interference Evaluation of Pharmacological Substances

Substance	Testing Level (concentrations)
17-OH progesterone	50 µg/ml
Ampicillin	152 µmol/L
Cephalexin	337 µmol/L
Erythromycin	81.6 µmol/L
Gentamycin	21 µmol/L
Dexamethasone	1.53 µmol/L
Magnesium Sulfate	50 µg/mL
Oxytocin	10 mU/mL
Terbutaline	1 mg/mL
Ritodrine	100 µg/mL

Semen and Urine

To evaluate potential interference from semen and maternal urine, a negative sample (0.2 ng/mL PAMG-1) and a positive sample (2.0 ng/mL PAMG-1) were tested after being spiked with 10 independent samples of maternal urine and 10 independent samples of semen, for a total of 20 samples spiked with maternal urine and 20 samples spiked with semen. No interference was observed from maternal urine or semen at the testing levels summarized in Table 4 below:

Table 4 Interference Evaluation of Semen and Urine

Substance	Testing Level (% sample volume)
maternal urine	12.5%
Semen	12.5%

Maternal Blood

To evaluate potential interference from maternal bleeding, 4 replicates of a negative sample (0.2 ng/mL PAMG-1) and a positive sample (2.0 ng/mL PAMG-1) were tested against 10 independent maternal blood samples at 3 admixture levels ("trace", "moderate", or "gross" levels of maternal bleeding) on the vaginal collection swab. False positive results were observed at moderate and gross vaginal bleeding conditions, as summarized in Table 5 below.

Table 5 Interference Evaluation of Maternal Bleeding

Maternal Blood Admixture Category	PAMG-1 Concentration	
	0.2 ng/mL	2.0 ng/mL
Trace	10- / 0+	10+ / 0-
Moderate	8- / 2+	10+ / 0-
Gross	5- / 5+	10+ / 0-

The sponsor includes the following limitation in the labeling:

"The PartoSure test is not intended for use in women with moderate or gross vaginal bleeding. The presence of vaginal bleeding may contribute to difficulty in interpreting the PartoSure test result. Testing a moderately to grossly bloody sample may lead to false positive results. If upon visual examination you are concerned about the presence of moderate or gross vaginal blood, it is recommended that the sample is collected following cessation of active vaginal bleeding."

Lubricants, Disinfectants, Soaps & Creams

To evaluate potential interference from lubricants, disinfectants, soaps, and creams, 4 replicates of a negative sample (0.2 ng/mL PAMG-1) and a positive sample (2.0 ng/mL PAMG-1) were tested after being individually spiked with potentially interfering Miconazole Nitrate disinfectant cream, Lubricant Jelly, antiseptic cleanser, body wash soap, and vaginal cream. False negative results were observed at 12.5% Miconazole Nitrate level, and invalid results were observed at 12.5% Lubricant Jelly and 12.5% Betadine® Cleanser, as summarized in Table 6 below.

Table 6 Interference Evaluation of Lubricant, Disinfectant, Soap and Cream

Substance	Testing Level (% sample volume)	PAMG-1 Concentration	
		0.2 ng/mL	2.0 ng/mL
Miconazole Nitrate	12.5%	4- / 0+	4- / 0+
Lubricant Jelly	12.5%	1- / 0+*	0- / 2+**
Betadine® Cleanser	12.5%	Invalid***	Invalid***
Vagisil® Anti-Itch Cream	12.5%	4- / 0+	0-/4+
Dove® Body Wash Soap	12.5%	4- / 0+	0-/4+

**a total of 3 out of 4 replicates showed invalid results*
***a total of 2 out of 4 replicates showed invalid results*
****a total of 4 out of 4 replicates showed invalid results*

The sponsor includes the following limitation in the labeling:

"Invalid test results may occur if lubricants or antiseptics (e.g. K-Y® or Surgilube® lubricating jelly, Betadine® Cleanser) have been used by the patient.

Care must be taken not to contaminate the swab or cervicovaginal secretions with lubricants or antiseptics (e.g. K-Y® or Surgilube® lubricating jelly, Betadine® Cleanser). These substances may interfere with absorption of the specimen by the swab or with the antibody-antigen reaction of the PartoSure test and lead to invalid test results.

If it is suspected that the patient has applied a topical disinfectant (e.g. Monistat®, miconazole nitrate cream) to the vaginal area within 24 hours, delay specimen

collection until 24 hours from application have passed as these products can lead to false negative test results."

Vaginal Bacterial Pathogens

To evaluate potential interference from vaginal bacterial pathogens, 4 replicates of a negative sample (0.2 ng/mL PAMG-1) and a positive sample (2.0 ng/mL PAMG-1) were tested after being independently spiked with 3 vaginal bacterial pathogens including Gardnerella vaginalis, Candida albicans, and Trichomonas vaginalis. None of these vaginal infection pathogens interfered with the PartoSure test at the testing levels summarized in Table 7 below:

Table 7 Interference Evaluation of Vaginal Bacterial Pathogens

Interfering Substance	Testing Level (concentration)
Gardnerella vaginalis	$> 10^7$ cfu/mL
Candida albicans	$> 10^7$ cfu/mL
Trichomonas vaginalis	$> 10^7$ cfu/mL

3. Cross-Reactivity

A cross-reactivity study was conducted by independently spiking negative (0.2 ng/mL) and positive (2 ng/mL) PAMG-1 samples with potentially cross-reacting proteins likely to be found in vaginal specimens, at clinically relevant concentrations. Four replicates were tested for each potential cross-reacting substance at each PAMG-1 level. No cross reactivity was observed for the following substances at the testing levels summarized in Table 8 below:

Table 8 Cross-Reactivity Evaluation

Cross–Reactive Substance	Testing Level
Human chorionic gonadotropin	444 mIU/mL
Trophoblastic beta-2 glycoprotein	59 µg/mL
Human placental lactogen	275 ng/mL
Alphafetoprotein	325 ng/mL (393 IU/mL)
IGFBP-3	991 ng/mL
Human Serum Albumin	13 g/L

4. High Dose Hook Effect

To evaluate potential high dose hook effect, a high-level sample containing 40,000 ng/mL of PAMG-1 was tested in 2 replicates per lot using 8 lots of devices. All results were positive for PAMG-1, which demonstrated no hook effect from PAMG-1 up to 40,000 ng/mL.

5. Stability

Shelf-Life Stability Study:

A real-time shelf-life stability study was conducted with 4 lots of test strips and 3 lots of solvent reagents that have been stored for ≥ 28 months per the manufacturer's recommended storage conditions. Four levels of samples (0, 0.5, 1.0, and 5.0 ng/mL PAMG-1) were tested in the test strip and solvent reagent stability study with 10 replicates of measurements at each concentration across each lot. The sponsor concluded that the shelf life of the PartoSure test kit is 27 months when stored between 15 and 25°C.

Sample Stability Study:
Sample stability study was conducted by testing two levels of samples (0.2 and 2.0 ng/mL PAMG-1) in 4 replicates per level using 3 lots of device at both refrigerated temperature (2-8°C) and room temperature (15-30°C). The sample stability study results are shown in Table 9 below:

Table 9 Sample Stability

2-8°C Storage Condition							
Lot #	**Concentration**	**0 h**	**12 h**	**24 h**	**48 h**	**72 h**	**120 h**
Lot 1	0.2 ng/mL	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+
Lot 2		4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+
Lot 3		4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+
Lot 1	2.0 ng/mL	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+
Lot 2		0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+
Lot 3		0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+

15-30°C Storage Condition								
Lot #	**Concentration**	**0 h**	**4 h**	**6 h**	**8 h**	**10 h**	**12 h**	**24 h**
Lot 1	0.2 ng/mL	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+
Lot 2		4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+
Lot 3		4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+	4- / 0+
Lot 1	2.0 ng/mL	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+
Lot 2		0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+
Lot 3		0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+	0- / 4+

The sponsor concluded that PAMG-1 samples are stable for up to 120 hours when stored at 2-8°C and up to 24 hours when stored at 15-30°C.

6. Device Read-Time and Lighting Condition

The read-time conditions were evaluated by reading test results at 2, 3, 4, 5, 10 and 15 mins after test strips were inserted into solvent solution vials containing PAMG-1 at concentrations of 0.2 ng/ml, or 2.0 ng/ml. Three lots of devices were tested in 5 or 10

replicates at each concentration level. The read-time study results are summarized in Table 10 below.

Table 10 Read-Time Evaluation

	0.2 ng/ml PAMG-1					
Lot #	**2 mins**	**3 mins**	**4 mins**	**5 mins**	**10 mins**	**15 mins**
Lot 1	10- / 0+	10- / 0+	10- / 0+	10- / 0+	5- / 0+	5- / 0+
Lot 2	9- / 0+*	9- / 0+*	9- / 0+*	9- / 0+*	5- / 0+	5- / 0+
Lot 3	10- / 0+	10- / 0+	10- / 0+	10- / 0+	5- / 0+	5- / 0+
	2.0 ng/ml PAMG-1					
Lot #	**2 mins**	**3 mins**	**4 mins**	**5 mins**	**10 mins**	**15 mins**
Lot 1	5- / 5+	0- / 10+	0- /10+	0- / 10+	0- / 5+	0- / 5+
Lot 2	8- / 2+	5- / 5+	0- / 10+	0- / 10+	0- / 5+	0- / 5+
Lot 3	8- / 2+	1- / 9+	0- / 10+	0- / 10+	0- / 5+	0- / 5+

** only 9 test strips were tested.*

Lighting conditions were evaluated by reading test results under natural, fluorescent, incandescent, LED or halogen lighting conditions for samples containing PAMG-1 at concentrations of 0.2 ng/ml, or 2.0 ng/ml. Three lots of devices were tested in 5 replicates at each concentration level. All test strips gave negative results for 0.2 ng/ml sample, and positive results for 2.0 ng/ml samples.

The sponsor states the following instructions regarding reading results in the package insert:

"Remove the test strip from the vial if two lines are clearly visible in the test region or after 5 minutes sharp. Read the results by placing the test strip on a clean, dry flat surface in a well-lit environment via either natural or fluorescent lighting. A positive result is indicated by two lines in the test region, while a negative result is indicated by a single line in the test region. Do not read or interpret the results after 10 minutes have passed since inserting the test strip into the vial."

7. Sterilization

Sterilization testing of the sterile flocked swab included in the PartoSure test kit was performed referencing ISO 11135-1:2007, "Sterilization of health care products -- Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices". Product Bioburden was tested according to the requirements outlined in ISO 11737-1:2006. Product Sterility was tested according to the requirements outlined in ISO 11737-2:2009. Product Ethylene Oxide (EO) and Chloridine (ECH) Residuals was tested according to the requirements outlined in ISO 10993-7:2008. The recommended sterility studies were performed with the sterile flocked swab or extracts thereof with passing results as summarized in Table 11 below:

Table 11 Summary of the Sterility Tests and Results for the Sterile Vaginal Swab

Sterilization Test	Applicable ISO 10993 Standard	Test Method	Results
Product Bioburden	ISO 11737-1:2006 Determination of a population of microorganisms on products	Bioburden Test	1 UFC/pieces of viable bioburden
Product Sterility	ISO 11737-2:2009 Tests of sterility performed in the definition, validation and maintenance of a sterilization process	Sterility Test; Growth Promotion Test	Culture medium for bacteria (TSB) negative; Culture medium for molds and yeasts (FTM) negative
EO and ECH Residuals	ISO 10993-7:2008 Ethylene oxide sterilization residuals	Exhaustive Extractions; Exhaustive Thermal Extraction	EO - 0.1 mg/device; ECH - < LOQ (1 mg/device)

8. Biocompatibility

Biocompatibility testing of the sterile flocked swab included in the PartoSure test kit was performed referencing ISO 10993-1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing, and following the FDA guidance entitled "Use of International standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process," dated June 16, 2016.

The sterile vaginal swab, which is used to collect a vaginal secretion sample from the vagina and which has transient (less than a minute) contact with the patient's mucosal vaginal tissue, is a Surface Device with Mucosal Membrane Contact (Category and Contact) with a duration of contact of ≤ 24 hours (Contact Duration – A, Limited).

The recommended biocompatibility studies were performed with the sterile flocked swab or extracts thereof with passing results as summarized in Table 12 below:

Table 12 Summary of the Biocompatibility Tests and Results for the Sterile Flocked Swab

Biocompatibility Test	Applicable ISO 10993 Standard	Test Method	Results
Cytotoxicity	ISO 10993-5: Tests for Cytotoxicity – In Vitro methods	MEM Elution	Non-cytotoxic

Biocompatibility Test	Applicable ISO 10993 Standard	Test Method	Results
Sensitization	ISO 10993-10: Tests for Sensitization and Irritation	Maximization Sensitization	No delayed dermal contact sensitization
Irritation	ISO 10993-10: Tests for Sensitization and Irritation	Intracutaneous Reactivity	No irritation
Acute Systemic Toxicity	ISO 10993-11: Tests for Acute Systemic Toxicity	Systemic Toxicity Test	No toxic signs or symptoms

B. Animal Studies

None

C. Additional Studies

1. Traceability

   The PAMG-1 tractability is maintained through manufacturer's internal reference standards and procedures.

2. Quality Control

   The PartoSure test strip contains an internal procedural control line in the test region that verifies analytical functionality during sample analysis. The appearance of the control line, alone, or both the control and test lines in the test region of the test strip verifies the integrity of the test procedure and components.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of PartoSure test as an aid to rapidly assess the risk of spontaneous preterm delivery in ≤7 days from the time of cervicovaginal sample collection in pregnant women with singleton gestation, signs and symptoms of early preterm labor, intact amniotic membranes and minimal cervical dilatation (<3 cm), sampled between 24 weeks, 0 days and 34 weeks, 6 days gestation in the United States (U.S.). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The study followed a prospective observational design across 15 different sites in the U.S. to evaluate the safety and effectiveness of the PartoSure test in a symptomatic pregnant population when used by the intended users (i.e., healthcare professionals without formal laboratory training). The data were collected between April 2015 and July 2016, and included 839 patients, as shown in Table 13 below:

Table 13 Study Site Enrollment Information – US Study

Site Number	Number of Subjects Enrolled
1	196
2	90
3	97
4	41
5	68
6	119
7	105
8	37
9	31
10	14
11	21
12	6
13	1
14	1
15	12

In this study, healthcare professionals remained blinded to the results of the PartoSure test throughout the course of patient management.

Subjects were enrolled at the time they presented to each study site with complaints that were suggestive of preterm labor, after providing written, informed consent. Once each subject was enrolled, the intended users collected a sample from the study subject and performed the PartoSure test. A physical examination with the aid of a sterile speculum was then performed to assess vaginal and cervical conditions.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the U.S. clinical study was limited to patients who met the following inclusion criteria:

   1) Subjects must be pregnant.
   2) Subjects must be between 24 weeks, 0 days and 34 weeks, 6 days gestation
   3) Subjects must present with suspicion, signs, or symptoms suggestive of pre-term labor:
      - Uterine contractions, with or without pain
      - Intermittent lower abdominal pain

- Dull backache
- Pelvic pressure
- Bleeding during the second or third trimester
- Menstrual-like or intestinal cramping, with or without diarrhea
- Patient not feeling "right", which may include such symptoms as general malaise, aches, and/or discomfort that are suggestive of possible preterm labor

4) Subjects must provide informed consent in accordance with the IRB at each institution.
5) Subjects must be at least 18 years old or emancipated consenting minors.

Patients were <u>not</u> permitted to enroll in the clinical study if they met any of the following exclusion criteria:

1) Subjects who have received tocolytic medications for treatment of threatened preterm delivery prior to collection of the cervicovaginal specimens or cervical length measurements.
2) Subjects who have cervical dilatation ≥ 3 centimeters.
3) Subjects who have suspected placenta previa.
4) Subjects who have had intercourse within past 24 hours.
5) Subjects who are <24 weeks, 0 days of gestation or ≥ 35 weeks of gestation.
6) Subjects who have overt rupture of the fetal membranes (ROM) as indicated by visualized leakage of fluid from the cervical os.
7) Subjects who have cervical cerclage in place.
8) Subjects who have a symptom not associated with idiopathic threatened preterm delivery (e.g. trauma).
9) Subjects who have had a digital vaginal exam prior to specimen collection.
10) Subjects who are enrolled in a tocolytic study.
11) Subjects who are less than 18 years old in jurisdictions where individuals less than 18 years old are not considered as emancipated minors.

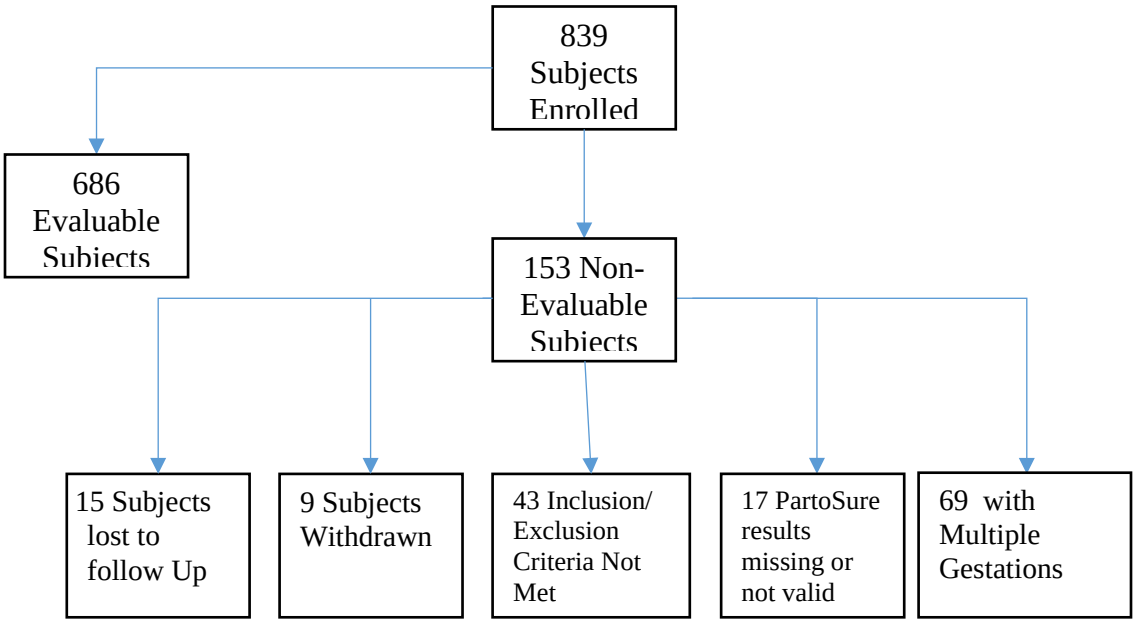
2. <u>Follow-up Schedule</u>
Information about the subject's labor and delivery, as well as maternal and neonatal outcomes, was documented by review of the subject's (and her infant's) medical records. Follow-up telephone calls using a scripted text initiated by the study sites to the subjects were also used to confirm on-going pregnancy or delivery. Adverse events were recorded in compliance with federal regulations and IRB requirements.

3. <u>Clinical Endpoints</u>
With regard to safety, the number of subjects experiencing adverse events during either the testing period or the follow-up period was monitored and reported.

With regard to effectiveness, analyses for Positive Predictive Value (PPV), Negative Predictive Value (NPV), Sensitivity and Specificity were provided. See section D below for discussion of effectiveness outcomes.

B. Accountability of PMA Cohort

At the time of database lock, of the 839 subjects enrolled, 686 (81.8%) were evaluable and 153 (18.2%) were not. The detailed reasons describing the 153 subjects that were not evaluable are listed in the figure below:



C. Study Population Demographics and Baseline Parameters

A description of subject demographic and obstetric characteristics at presentation for enrolled subjects (N=839) and the evaluable subjects (N=686) are shown in Table 14 below:

Table 14 Study Population Demographics and Baseline Parameters – US Study*

Characteristic	Enrolled Subjects (N=839)	Evaluable Subjects (N=686)
Previous term delivery	58.4% (479/820)	59.2% (405/684)
Prior preterm delivery	21.7% (178/820)	22.7% (155/684)
Previous abortion	38.9% (319/821)	39.1% (268/685)
Maternal age		
Mean ± SD	27.99 ± 5.78	28.0 ± 5.80
Median	27.00	27.00
Range (Min, Max)	(14.00, 44.00)	(17.00, 44.00)

Characteristic	Enrolled Subjects (N=839)	Evaluable Subjects (N=686)
Ethnicity		
Hispanic or Latino	20.4% (164/805)	20.8% (139/667)
Not Hispanic or Latino	79.6% (641/805)	79.2% (528/667)
Race		
White	66.4% (553/833)	66.3% (455/686)
Black of African American	24.4% (203/833)	25.1% (172/686)
Native American or Alaska Native	0.5% (4/833)	0.6% (4/686)
Native Hawaiian or other Pacific Islander	0.1% (1/833)	0.0% (0/686)
Asian	1.6% (13/833)	0.9% (6/686)
Other	1.9% (16/833)	2.0% (14/686)
Gestational age at sampling (wk)		
Mean ± SD	29.74 ± 2.99	29.85 ± 2.96
Median	30.00	30.14
Range (Min, Max)	(22.29, 34.86)	(24.00, 34.86)
Cervical dilatation ≤1 cm	94.4% (764/809)	96.9% (665/686)
Uterine contractions < 4/hr	16.7% (37/222)	17.7% (35/198)
PAMG-1 detected	2.8% (23/816)	2.0% (14/686)

*Denominators vary as a result of data availability for the given parameter.

D. Safety and Effectiveness Results

Pregnancy Outcomes: Study endpoints (positive and negative predictive values) are based upon the presence or absence of imminent spontaneous preterm delivery in women with a singleton gestation. Of the 686 evaluable subjects, 0.9% delivered ≤ 7 days. Table 15 below shows the prevalence of preterm delivery ≤ 7 days.

Table 15 Prevalence of Spontaneous Preterm Delivery ≤ 7 Days – US Study

Days from Testing	Prevalence
≤ 7 Days	0.9% (6/686)

*A Clinical Consensus Panel (CCP) was responsible for the evaluation and categorization of all preterm deliveries within 7 days of sample collection as either a "spontaneous preterm birth" or a "medically-indicated preterm birth", using the following standard definitions, and CCP members were blind to the results of the PartoSure test when making their classifications:

Spontaneous preterm birth was defined as delivery occurring subsequent to spontaneous onset of preterm labor or preterm premature rupture of the membranes or fetal membrane prolapse, regardless of subsequent labor augmentation or cesarean delivery.

A medically-indicated preterm birth was defined as delivery occurring as the result of one or more obstetrical conditions (e.g. placenta previa or multiple gestation), or maternal medical conditions (e.g. preeclampsia) that does/do not coincide with spontaneous onset of preterm labor or preterm premature rupture of the membranes or fetal membrane prolapse.

Table 16 below summarizes spontaneous vs. medically indicated preterm births observed in this clinical study:

Table 16 Delivery Characteristics for Subjects Who Delivered ≤ 7 Days of Specimen Collection – US Study

Characteristic	N
Evaluable Subjects	686
Delivery ≤ 7 Days of Testing	14
Nature of Preterm Delivery	
Spontaneous	6
Medically Indicated	8

The eight (8) subjects with medically-indicated preterm deliveries within 7 days of testing were treated as "negative" for spontaneous preterm delivery in the final analysis of the ability of the PartoSure test to predict spontaneous preterm delivery.

1. Effectiveness Results

   The analysis of effectiveness was based on the 686 evaluable results. Key effectiveness outcomes are summarized in primary and secondary study endpoints.

   Primary Study Endpoints: The performance statistics, including positive and negative predictive values, 95% confidence intervals are summarized in Table 17 below for delivery ≤ 7 days of specimen collection among women with a singleton gestation.

Table 17 PartoSure Performance (PPV/NPV) – US Study

	Delivery ≤7 Days of Specimen Collection	
Statistic	**Proportion**	**% (95% CI)**
Positive Predictive Value (PPV)	3/14	21.43 (4.66, 50.80)
Negative Predictive Value (NPV)	669/672	99.55 (98.70, 99.91)

Secondary Endpoints: The sensitivity and specificity of the PartoSure test, along with the 95% confidence intervals are summarized in Table 18 below for delivery ≤ 7 days of specimen collection among women with a singleton gestation.

Table 18 PartoSure Performance (SN/SP) – US Study

	Delivery ≤ 7 Days of Specimen Collection	
Statistic	**Proportion**	**% (95% CI)**
Sensitivity (SN)	3/6	50.00 (11.81, 88.19)
Specificity (SP)	669/680	98.38 (97.12, 99.19)

2. Safety Results

The analysis of safety was based on the severity and frequency of adverse events and device failures observed in the clinical study. The key safety outcomes for this study are presented below.

This clinical study enrolled 839 subjects and there were no adverse events (AEs), deaths, or unanticipated adverse device defects (UADEs) reported during the course of the study. Subjects enrolled in the study were subject to minimal health risk due to simple sample collection procedure.

The PartoSure test kit includes three components: a sterile flocked swab, a solvent vial, and a lateral flow test strip. In this study of 839 enrolled subjects, there were two reported device deficiencies (one for an empty solvent vial, and the other for a missing test strip).

3. Pediatric Extrapolation

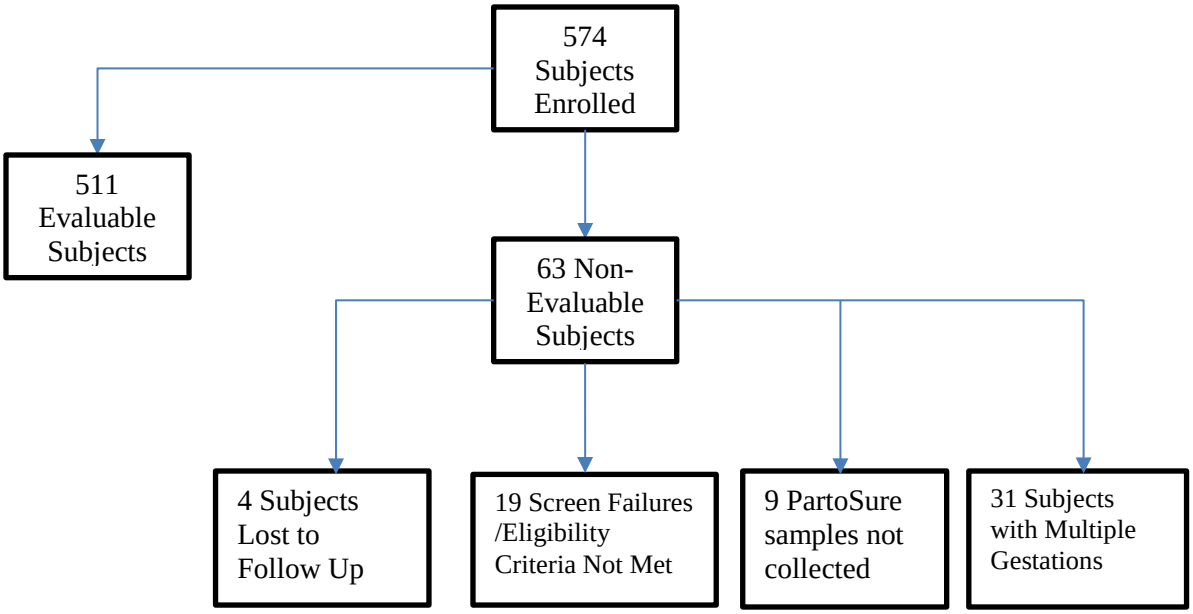
In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 21 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The applicant provided a prospectively conducted, retrospective cohort study evaluating the performance of the PartoSure test at a hospital site in Spain between January 2016 and June 2017 to support the safety and effectiveness of the PartoSure test. A total of 511 subjects (out of 574 enrolled), who upon review of each patients' medical records, met the same inclusion criteria as those in the U.S. clinical study (section X.A., above), were considered evaluable, as shown in the chart below:



A description of subject demographic and obstetric characteristics at presentation for enrolled subjects (N=574) and the evaluable subjects (N=511) are shown in Table 19 below:

Table 19 Enrolled Subject Demographic and Obstetric Characteristics – Spain Study

Characteristic	Enrolled Subjects (N=574)	Evaluable Subjects (N=511)
Maternal age		
Mean ± SD	32.40 ± 5.90	32.20 ± 5.95
Median	33.00	33.00
Range (Min, Max)	(15.00, 46.00)	(15.00, 46.00)
Gestational age at sampling (wk)		
Mean ± SD	30.40 ± 3.00	30.36 ± 3.06
Median	30.93	30.86
Range (Min, Max)	(24.00, 34.86)	(24.00, 34.86)
Cervical dilatation ≤1 cm	92.3% (524/568)	93.7% (479/511)
PAMG-1 detected	6.4% (36/564)	5.7% (29/511)

Pregnancy Outcomes: Study endpoints (positive and negative predictive values) are based upon the presence or absence of imminent spontaneous preterm delivery in women with a singleton gestation. Of the 511 evaluable subjects, 3.5% delivered spontaneously ≤ 7 days. Table 15 below shows the prevalence of preterm delivery ≤ 7 days in this study

Table 20 Prevalence of Spontaneous Pre-Term Delivery ≤ 7 Days– Spain Study

Days from Testing	Prevalence
≤ 7 Days	3.5% (18/511)

Table 21 shows the number of preterm deliveries within 7 days of testing classified as either spontaneous or medically-indicated.

Table 21 Delivery Characteristics for Subjects Who Delivered ≤ 7 Days of Specimen Collection – Spain Study

Characteristic	N
Evaluable Subjects	511
Delivery ≤ 7 Days of Testing	19
Nature of Preterm Delivery	
Spontaneous	18
Medically Indicated	1

The one subject with medically-indicated preterm deliveries within 7 days of testing was treated as "negative" for spontaneous preterm delivery in the final analysis of the ability of the PartoSure test to predict spontaneous preterm delivery.

The analysis of effectiveness was based on the 511 evaluable results. Key effectiveness outcomes are summarized in Table 22 below:

Table 22 Prediction of Spontaneous Preterm Delivery ≤ 7 Days

	PPV		NPV		Sensitivity		Specificity	
Statistic	Proportion	% (95% CI)	Proportion	% (95% CI)	Proportion	% (95% CI)	Proportion	% (95% CI)
PartoSure	9/29	31.03 (15.28, 50.83)	473/482	98.13 (96.49, 99.14)	9/18	50.00 (26.02, 73.98)	473/493	95.94 (93.80, 97.50)

There were no adverse events, deaths, or unanticipated adverse device defects reported among the 574 enrolled subjects.

Post-Approval Study

As a condition of approval, Parsagen must perform a confirmatory (post-market) study for the PartoSure test. The purpose of this prospective study will be to collect additional data on the safety and effectiveness of the PartoSure test in the intended use setting. A diverse U.S. population of singleton pregnancy patients between 24 weeks, 0 days and 34 weeks, 6 days gestation with signs and symptoms of early preterm labor, intact amniotic membranes and minimal cervical dilatation (<3 cm), will be included. A PMA supplement that includes complete protocol of the post-approval study should be submitted within 30-days of approval.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provision of Section 515(c)(2) of the Act as amended by the Safety Medical Devices Act of 1990, this PMA was not referred to the Clinical Chemistry and Clinical Toxicology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical accuracy and precision of prediction for spontaneous preterm delivery in ≤ 7 days from the time of cervicovaginal sample collection in singleton pregnant women with signs and symptoms of early preterm labor, intact amniotic membranes and minimal cervical dilation (<3 cm), sampled between 24 weeks, 0 days and 34 weeks, 6 days gestation was assessed. The endpoints evaluated include positive predictive value, negative predictive value, sensitivity, and specificity for the test.

In the U.S. study to assess PartoSure performance for spontaneous preterm delivery ≤ 7 days in women with a singleton gestation, there were a total of 6 preterm deliveries within 7 days from the time of cervicovaginal sample collection. Of the 6 spontaneous preterm deliveries, 3 were predicted by the PartoSure test (i.e., true positives) and 3 were missed by the PartoSure test (i.e., false negatives). The sensitivity of the test was calculated as 50% (CI: 11.8% - 88.2%) and specificity was 98.4% (CI: 97.1% - 99.2%). Given a prevalence of 0.9% for spontaneous preterm delivery ≤7 days among singleton pregnancies, the NPV was 99.6% (CI: 98.7% - 99.9%) and the PPV was 21.4% (CI: 4.7% - 50.8%). In the retrospective Spain study, for spontaneous preterm delivery ≤ 7 days in women with a singleton gestation, there were a total of 18 preterm deliveries ≤7 days from the time of cervicovaginal sample collection. Of the 18 spontaneous preterm deliveries ≤7 days, 9 were predicted by the PartoSure test (i.e., true positives) and 9 were missed by the PartoSure test (i.e., false negatives). The sensitivity of the test was calculated as 50% (CI: 26.0% - 74.0%) and specificity was 95.9% (CI: 93.8% - 97.5%). Given a prevalence of 3.5% for spontaneous preterm delivery within 7 days among singleton pregnancies, the NPV was 98.1% (CI: 96.5% - 99.1%) and the PPV was 31.0% (CI: 15.3% - 50.8%).

The data from both the US pivotal study and the Spain retrospective study have demonstrated the performance characteristics of the PartoSure test in the intended patient population when performed by the intended users. The results of the clinical studies performed to support approval establish a reasonable assurance that the PartoSure test is effective for its intended use, and this performance will be assessed for confirmation through post-approval studies.

B. Safety Conclusions

The results of the nonclinical laboratory studies as well as the clinical studies performed and described in section IX, X and XI above to support the PMA approval establish a reasonable assurance that the PartoSure test is safe for its intended use.

The risk from a false negative result would be that the mother could progress to have an unanticipated spontaneous preterm delivery and risk missing an opportunity to take corticosteroids. Neonates whose mothers do not receive antenatal corticosteroids may have increased risk or increased severity of respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, and death compared with neonates whose mothers do receive antenatal corticosteroids.

C. Benefit-Risk Determination

1. Summary of Benefits

   The PartoSure test, used in conjunction with other clinical parameters, can provide additional information to aid in the risk assessment of spontaneous preterm delivery. Spontaneous preterm delivery is difficult to reliably predict based on risk factors or medical history. Causality is difficult to prove and identifying women with preterm labor who ultimately will give birth preterm is difficult. According to the American College of Obstetricians and Gynecologists (ACOG) 2016 practice bulletin on management of preterm labor, approximately 30% of preterm labor spontaneously resolves and 50% of patients hospitalized for preterm labor actually give birth at term. The PartoSure test likely improves upon the pre-test probability based on clinical risk factors of not having spontaneous preterm delivery within 7 days from the time of cervicovaginal sample collection in symptomatic singleton gestation women who are tested between 24 weeks (0 days) and 34 weeks (6 days) gestation, with intact amniotic membranes and minimal cervical dilatation. Use of the PartoSure test in conjunction with clinical evaluation and diagnostic procedures/tests is expected to further improve upon the prediction of not undergoing preterm delivery.

   While clinicians are highly likely to admit, treat, or transfer a patient with clinical risk factors even if a biomarker test result is negative, at the time of testing only 25% present with non-sporadic contractions, 6% present with bleeding, 3% present with cervical dilation between 2-3cm, according to data from the U.S. Study. Thus, in the 67% of patients presenting without these clinical risk factors – for whom the prognosis of spontaneous preterm delivery is uncertain – the addition of a biomarker test with a high negative predictive value may be effective in helping clinicians rule out imminent spontaneous preterm delivery.

   Given a prevalence of 0.9% for spontaneous preterm delivery within 7 days, the NPV was 99.6% (98.7%, 99.9%). This high NPV, when interpreted along with other clinical signs and symptoms, will likely reduce unnecessary hospitalization and exposure to tocolytics and corticosteroids.

Additionally, the PartoSure test is a point of care device that does not require a speculum examination (however a speculum exam is routine in preterm birth assessments), and may have faster turnaround time (5-10 minutes) than the state of the art test for the indication, and sperm does not interfere with PartoSure test. The point of care feature of the test can be an added benefit as far as availability in communities where a laboratory is not readily accessible.

2. Summary of Risks
   The risk from a false negative result would be that the mother could progress to have an unanticipated spontaneous preterm delivery and risk missing an opportunity to take corticosteroids. According to the ACOG 2016 Practice Bulletin on the management of preterm labor, neonates whose mothers receive antenatal corticosteroids have significantly lower severity, frequency, or both of respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, and death compared with neonates whose mothers did not receive antenatal corticosteroids.

   Labeling that specifies the performance and the potential for false negative tests in addition to labeling to use the test in the context of all other clinical assessments and diagnostic procedures can help mitigate the risks of false negative results. Though there is still some residual risk to the patient following these mitigations, the benefits described above are sufficient to outweigh these residual risks.

3. Summary of Other Factors
   PartoSure test results should always be considered in conjunction with all other information provided by the patient's clinical evaluation and diagnostic procedure results such as cervical examination, assessment of uterine activity, and evaluation of other risk factors.

   In addition, post-approval studies are required as a condition of approval to obtain additional data to verify the safety and effectiveness of the device.

4. Patient Perspectives
   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support the PartoSure test to be used as an aid to rapidly assess the risk of spontaneous preterm delivery in ≤7 days from the time of cervicovaginal sample collection in pregnant women with signs and symptoms of early preterm labor, intact amniotic membranes and minimal cervical dilatation (<3 cm), sampled between 24 weeks, 0 days and 34 weeks, 6 days gestation in women with a singleton gestation.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The benefits of using the PartoSure test, as discussed above, outweigh the risks.

XIV. CDRH DECISION

CDRH issued an approval order on April 11, 2018. The final conditions of approval cited in the approval order are described below.

See Section XI above regarding the post approval study.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Intended Use, Precautions and Warnings, , and Limitations of the Test in the device labeling.

Post-approval Requirements and Restrictions: See approval order.