SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Parvovirus B19 IgG

Device Trade Name: LIAISON Biotrin Parvovirus B19 IgG Plus
LIAISON Biotrin Control Parvovirus B19 IgG Plus

Device Procode: MYL

Applicant's Name and Address: DiaSorin Inc.
1951 Northwestern Avenue
Stillwater, MN 55082

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P220034

Date of FDA Notice of Approval: March 29, 2024

II. INDICATIONS FOR USE

LIAISON Biotrin Parvovirus B19 IgG Plus

The LIAISON Biotrin Parvovirus B19 IgG Plus, a chemiluminescent immunoassay (CLIA), is intended for the qualitative detection of IgG antibodies to B19 virus (B19V, previously known as human parvovirus B19) in human serum, lithium heparin, dipotassium EDTA (K_2-EDTA), and sodium citrated plasma. The test may be used for testing women of childbearing age where there is a suspicion of exposure to human B19V. The test may also be used for all patients as an aid in the diagnosis of fifth disease (erythema infectiosum). The test must be performed on the LIAISON XL Analyzer.

LIAISON Biotrin Control Parvovirus B19 IgG Plus

The LIAISON Biotrin Control Parvovirus B19 IgG Plus (negative and positive) is intended for use as assayed quality control samples to monitor the performance and reliability of LIAISON Biotrin Parvovirus B19 IgG Plus assay. The performance characteristics of LIAISON Biotrin Control Parvovirus B19 IgG Plus have not been established for any other assays or instrument platforms different from the automated LIAISON XL Analyzer.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the LIAISON Biotrin Parvovirus B19 IgG Plus and LIAISON Biotrin Control Parvovirus B19 IgG Plus labeling.

V. DEVICE DESCRIPTION

Kit Components

The assay configuration allows performance of 100 tests. All reagents are supplied ready to use.

Reagent Integral: The Reagent Integral is comprised of the following five (5) components:

- 1 vial of Magnetic particles coated with recombinant parvovirus B19 VP2 antigen (obtained in baculovirus), BSA, phosphate buffer, < 0.1% sodium azide.
- 1 vial Calibrator 1 containing low parvovirus B19 IgG levels, BSA, phosphate buffer, detergents, ProClin 300, an inert yellow dye.
- 1 vial Calibrator 2 containing high parvovirus B19 IgG levels, BSA, phosphate buffer, detergents, ProClin300, an inert blue dye.
- 1 vial Specimen Diluent containing Casein, BSA, phosphate buffer, detergents, ProCli 300, an inert blue dye.
- 1 vial Conjugate containing Mouse monoclonal IgG antibodies to human IgG conjugated to an isoluminol derivative, BSA, phosphate buffer, ProClin 300, preservatives.

Controls: The LIAISON Biotrin Control Parvovirus B19 IgG Plus set consists of 2 levels (positive and negative) ready to use controls. Each control solution allows at least 15 tests to be performed. The control set is an additional material required to perform the test.

The controls are comprised of the following components:

- 2 vials Negative Control containing human serum non-reactive for parvovirus B19 IgG antibodies, ProCli 300 and preservatives.
- 2 vials Positive Control containing human serum / plasma reactive for parvovirus B19 IgG antibodies, ProClin 300 and preservatives.

In addition, the following Analyzer and accessories are required for performing the LIAISON Biotrin Parvovirus B19 IgG Plus assay and the LIAISON Biotrin Control Parvovirus B19 IgG Plus set.

- LIAISON XL Analyzer is a fully automated chemiluminescent analyzer, performing the complete sample processing steps of the chemiluminescent assay.
- LIAISON Wash/System Liquid (10x)
- LIAISON XL Starter Kit

Assay Principle

The LIAISON Biotrin Parvovirus B19 IgG Plus is an indirect sandwich chemiluminescence immunoassay (CLIA) for the qualitative detection of IgG antibodies to Parvovirus B19. Recombinant parvovirus B19 VP2 antigen is used for coating magnetic particles (solid phase) and mouse monoclonal antibody directed against human IgG is linked to an isoluminol derivative (isoluminol-antibody conjugate). During the first incubation, parvovirus B19 antibodies, if present in calibrators, samples or controls, bind to the solid phase. During the second incubation, the antibody conjugate reacts with any human anti-parvovirus B19 IgG already bound to the solid phase. After each incubation, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescence reaction is thus induced. The light signal, and hence the amount of isoluminol-antibody conjugate, is measured by a photomultiplier as relative light units (RLU) and indicates the presence or absence of IgG to parvovirus B19 in calibrators, samples or controls.

Interpretation of Results

The analyzer automatically calculates the LIAISON Biotrin Parvovirus B19 IgG Plus AU test output and grades the results as indicated in the interpretation table below.

Table 1: LIAISON Biotrin Parvovirus B19 IgG Plus - Interpretation of Results

LIAISON Biotrin Parvovirus B19 IgG Plus		
AU	**Results**	**Interpretation**
< 1.00	Negative	A result below 1.00 AU may indicate the absence, or a level of IgG antibodies to Parvovirus B19 below the assay threshold.
≥ 1.00	Positive	A result above or equal to 1.00 AU indicates detection of IgG antibodies to parvovirus B19.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other alternatives for the detection of antibodies to parvovirus B19. There are currenty FDA approved *in vitro* diagnostic tests commercially available for the qualitative detection of specific IgG to parvovirus B19. For childhood infections, diagnosis can be largely made based upon the clinical presentation. For pregnant women, serology tests such as ELISA, indirect fluorescent assays (IFA) or western blot are the primary means of determining the mother's serological status. In the case of fetal infections, ultrasound; more specifically, Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) is a non-invasive means for determining the degree of fetal anemia.

VII. MARKETING HISTORY

The LIAISON Biotrin Parvovirus B19 IgG Plus (311550) and LIAISON Biotrin Control Parvovirus B19 IgG Plus (311551) are new kits for the United States and have not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the product to perform as intended or errors in the use of the product may lead to a false result and improper patient management. A false negative result may cause spreading of the virus to other individuals through contact and thus present a public health risk. Parvovirus B19 infection is generally self-limiting and benign for most healthy children but may pose a threat for high-risk populations such as immunocompromised patients or those with hemolytic anemia. The impact of missed or delayed recognition of infection may be substantial in specific high-risk populations, such as immunocompromised hosts, those with chronic hemolytic anemia, and pregnant women and their fetus(es), due to delays in treatment or coordination of care that could reduce morbidity or mortality. The virus can spread through blood and, therefore, a pregnant woman is at risk of passing the virus to the fetus causing serious complications. A false negative result may falsely reassure a clinician and a pregnant woman about potential risks to their fetus and lead them to be unprepared for potentially clinically significant sequelae such as spontaneous abortion, fetal anemia, neurological anomalies or fetal death.

A false positive sresult is not considered a public health risk except that the person may be isolated and monitored for a short period of time. A false positive result could lead to additional unnecessary monitoring for possible sequelae of acute B19V infection on infected individuals and/or fetus(es) of infected pregnant women, unnecessary anxiety in pregnant women about fetal risks of infection, and premature discontinuation of diagnostic evaluation due to clinicians being falsely reassured about the etiology of an individuals symptoms. False attribution of an individual's symptoms/signs to acute B19V infection may lead to delay in diagnosis and management of the true etiology for symptom

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

1. Cut-off Determination

   The cut-off for the LIAISON Biotrin Parvovirus B19 IgG Plus assay was established by testing a total of 384 serum samples (249 known positive and 130 known negative) from a Parvovirus serology routine population from the U.S.

   A Receiver Operating Characteristic (ROC) curve analysis was performed on the results of the specimens tested. The assay’s cut-off was evaluated with the observed results to demonstrate that its selection represents the best level of specificity, without compromising the sensitivity.

The cut-off value at 1.00 AU is within the optimal range determined by the ROC curve to discriminate between negative and positive results.

2. Cut-Off in International Standard Units

   The purpose of this study was to evaluate analytical sensitivity at the assay cut-off. The analytical sensitivity at the cut-off of the LIAISON Biotrin Parvovirus B19 IgG Plus assay was evaluated using serial dilutions of the WHO Second International Standard for Anti-Parvovirus B19 plasma, National Institute for Biological Standards and Control (NIBSC) code: 01/602 in negative human serum. Dilutions were tested in five (5) replicates, using three (3) reagent lots.

   The analytical sensitivity at the cut-off for the LIAISON Biotrin Parvovirus B19 IgG Plus assay is 1.00 IU/mL.

3. Sensitivity/ Seroconversion Panels

   The seroconversion sensitivity of the LIAISON Biotrin Parvovirus B19 IgG Plus assay has been demonstrated by testing 8 commercial seroconversion panels in comparison to a reference Parvovirus B19 test in terms of number of days and number of blood draws from initial draw to first positive sample, as well as the difference between the last negative results and the first positive results.

   The sensitivity of the LIAISON Biotrin Parvovirus B19 IgG Plus assay was similar to the reference assay. One (1) out of the 8 panels evaluated yielded a positive result sooner by one blood draw (3 days) than the reference assay.

4. Analytical Specificity - Potential Cross-Reactivity

   The potential cross-reactivity of the LIAISON Biotrin Parvovirus B19 IgG Plus assay was evaluated by testing samples containing antibodies to other infectious agents or associated with other disease states unrelated to Parvovirus B19. A total of 220 samples from 22 unrelated medical conditions were evaluated. Out of the 220 samples, only one false positive result was observed out of the 14 samples containing parainfluenza antibodies evaluated. The potential cross-reactant and number of samples evaluated are listed in the table below.

Table 2: LIAISON Biotrin Parvovirus B19 IgG Plus assay Potential Cross-Reactivity study

ID	Potential Cross reactants	Number of tested samples
1	CMV (anti-CMV positive)	10
2	Epstein-Bar Virus (anti-EBV positive)	10
3	Herpes Simplex Virus (anti-HSV1/2 positive)	11
4	Rubella (anti-Rubella positive)	10
5	Hepatitis C Virus (anti-HCV positive)	8
6	Human Immunodeficiency Virus (anti-HIV antibodies)	7
7	Hepatitis A Virus (anti-HAV positive)	11
8	*Borrelia burgdorferi* (anti-*B. burgorferi* antibodies)	10
9	*Toxoplasma. gondii* (anti-*T. gondii* antibodies)	7
10	Varicella Zoster Virus (anti-VZV positive)	14
11	Measles virus (anti-Measles antibodies)	12
12	Mumps virus (anti-Mumps antibodies)	10
13	Adenovirus (anti-Adenovirus antibodies)	10
14	Anti-Influenza A antibodies	8
15	Anti-Influenza B antibodies	7
16	*Mycoplasma pneumonia* (anti-*M. pneumonia* antibodies)	13
17	Respiratory syncytial virus (RSV) antibodies	8
18	*Treponema Pallidum* (anti-*T. pallidum* antibodies)	9
19	Rheumatoid Factor (anti-Fc Immunoglobulin)	7
20	Human anti-mouse antibodies (HAMA)	8
21	Anti-nuclear antibodies (ANA)	16
22	Parainfluenza antibodies	14*
	TOTAL	**220**

* A false positive result was observed in one out of fifteen (15) parainfluenza antibodies samples .

5. Analytical Specificity - Potential Interference

The LIAISON Biotrin Parvovirus B19 IgG Plus assay was evaluated for potential interference caused by endogenous and exogenous substances. Three samples high negative, around cut-off and low positive for parvovirus B19 IgG antibodies were spiked with the potential interferents as shown below. No significant interference was observed at the concentration for each substance listed below.

Table 3: Endogenous and Exogenous Interfering Substances Evaluated

Substance	Tested Concentrations
Endogenous Substances	
Unconjugated bilirubin	40 mg/dL
Conjugated bilirubin	40 mg/dL
Hemoglobin	1000 mg/dL
Triglycerides	1500 mg/dL
Total protein (high)	≥ 120 g/L
Total protein (low)	≤ 60 g/L
Cholesterol	400 mg/dL
Human Albumin	6000 mg/dL
Total IgG	2000 mg/dL
Total IgM	400 mg/dL
Human anti-mouse antibody (HAMA)	820 ng/mL
Rheumatoid Factor (RF)	2000 IU/mL
Exogenous Substances	
Biotin	3500 ng/mL
Vitamin A	800 µg/dL
Vitamin B12	2850 pg/mL
Vitamin C	20 mg/dL
Vitamin D	450 ng/mL
Vitamin E	120 mg/L
Folic Acid	160 ng/mL
Acetaminophen	15.6 mg/dL
Ibuprofen	21.9 mg/dL
Naproxen	36.0 mg/dL
Penicillin	110 mg/dL
Streptomycin (sulphate)	25.8 mg/dL
Erythromycin	13.8 mg/dL

6. Antibody Class Specificity

IgG class antibody specificity study was designed to evaluate LIAISON Biotrin Parvovirus B19 IgG Plus assay specific reactivity to Parvovirus B19 IgG antibodies in the presence or absence of Parvovirus B19 IgM antibodies. Anti-Parvovirus B19 IgM antibodies may interfere by competing with human anti-Parvovirus B19 IgG to then elicit false negative results, or alternatively, by cross reacting to produce false positive results.

Class specificity of the LIAISON Biotrin Parvovirus B19 IgG Plus assay was evaluated by testing 10 samples containing Parvovirus B19 IgM as well as IgG antibodies (including samples with Parvovirus B19 IgG antibody levels around the assay cut-off) in the presence and absence of IgM antibodies i.e., tested before and after IgM antibodies depletion using Dithiothreitol (DTT), treatment.

For data analysis the Percent Interference of IgM present in the samples was calculated as:

$$\%\ Interference = \frac{(Mean\ DTT\ Treated - Mean\ untreated)x\ 100}{(Mean\ untreated)}$$

Table 4: Results of IgG class antibody specificity study

ID SAMPLE	Untreated				Treated with 10 mM DTT				% Interference
	Candidate Test LIAISON Biotrin Parvovirus B19 IgG Plus Results		Parvovirus B19 IgM Test Results		Candidate Test LIAISON Biotrin Parvovirus B19 IgG Plus Results		Parvovirus B19 IgM Test Results		
	AU	Class	Index	Class	AU	Class	Index	Class	
Sample0l	1.73	POS	4.52	POS	1.86	POS	0.192	NEG	7.5%
Sample02	2.16	POS	4.63	POS	2.28	POS	0.0625	NEG	5.6%
Sample03	2.52	POS	8.30	POS	2.37	POS	0.162	NEG	-6.0%
Sample04	2.38	POS	1.30	POS	2.37	POS	0	NEG	-0.4%
Sample05	1.68	POS	3.29	POS	1.64	POS	0	NEG	-2.4%
Sample06	2.34	POS	3.11	POS	2.17	POS	0	NEG	-7.3%
Sample07	2.51	POS	4.59	POS	2.70	POS	0	NEG	7.6%
Sample08	1.70	POS	2.99	POS	1.65	POS	0	NEG	-2.9%
Sample09	1.68	POS	3.09	POS	1.56	POS	0	NEG	-7.1%
Sample10	2.72	POS	4.33	POS	2.53	POS	0	NEG	-7.0%

Results before and after depletion of IgM signal demonstrated that the LIAISON Biotrin Parvovirus B19 IgG Plus assay is specific to Parvovirus B19 IgG class antibody (percent interference measured was lower than 10%).

7. Matrix Equivalency/Tube Type Equivalency

A study was conducted to confirm that the claimed blood collection tube types are suitable for use with the LIAISON Biotrin Parvovirus B19 IgG Plus assay.
Matched serum and plasma (potassium EDTA (K2EDTA, lithium heparin and sodium citrate) samples consisted of twenty (20) Anti-Parvovirus B19 IgG negative samples and thirty-five (35) Anti-Parvovirus B19 IgG positive samples, including samples around the cutoff, were tested with the LIAISON Biotrin Parvovirus B19 IgG assay to determine if these sample types provide equivalent results.

The results of the regression analysis (slope, intercept and correlation coefficient) are reported in the following tables.

Table 5: Matrix Comparison Study Results

Test Speciment (y)	Reference Specimen (x)	Estimated Intercept	Intercept: 95% CI	Estimated Slope	Slope: 95% CI
K2 EDTA plasma	Serum	-0.02000	-0.06070 to 0.01566	1.0000	0.9845 to 1.008
Lithium Heparin plasma	Serum	-0.01696	-005634 to 0.000 15	0.9955	0.9854 to 1.006
Sodium Citrate plasma	Serum	0.004190	-0.04598 to 0.06242	0.9498	0.9156 to 0.9701

The results support the use of serum, K2 EDTA, lithium heparin, and sodium citrate plasma matrices with the LIAISON Biotrin Parvovirus B19 IgG Plus assay.

8. Sample Carry Over Study

A study was performed to evaluate the susceptibility of the LIAISON Biotrin Parvovirus B19 IgG Plus assay to sample carryover. The LIAISON XL Analyzer uses disposable tips for sample pipetting. A carry-over study was performed to evaluate whether any significant amount of analyte is carried over from one (1) sample reaction cuvette into the subsequent sample reaction cuvettes. The study included one (1) Anti-Parvovirus B19 IgG high positive sample and one (1) Anti-Parvovirus B19 IgG negative sample. The samples were divided in five (5) aliquots.

This test study was performed in 2 stages (Stage A and Stage B) as described below.

- Stage A with negative sample alone was performed in duplicate, in two separate runs using 5 aliquots per run.

- Stage B was performed 5 times, testing one replicate in 5 separate runs with five aliquots of the negative sample and the high positive sample, in the following sequence: Pos, Neg Aliquot 1, Pos, Neg Aliquot 2, Pos, Neg Aliquot 3, Pos, Neg Aliquot 4, Pos, Neg Aliquot 5.

The mean signal obtained for the negative sample alone (Stage A) was compared to the mean signal of the negative samples when alternated with high Parvovirus B19 IgG positive sample (Stage B).

All acceptance criteria were fulfilled, demonstrating that no significant amount of analyte is carried over from one sample reaction into the subsequent sample reactions.

9. Hook Effect

A high dose hook study was conducted to demonstrate that LIAISON Biotrin Parvovirus B19 IgG Plus assay is not sensitive to high dose hook effect, where saturation effect may appear when testing samples containing very high levels of Parvovirus B19 IgG antibodies, resulting in a reported lower than the expected AU output result.

Three (3) high titer positive anti-Parvovirus B19 IgG samples, with high levels of antibodies were serially diluted in negative serum in 9 dilutions steps to generate a dilution series that covers from high positive to negative. The dilutions were tested in triplicate. The data showed that the sample dilutions with high levels of Parvovirus B19 IgG antibodies were still detected. The study demonstrates that the LIAISON Biotrin Parvovirus B19 IgG Plus assay is not susceptible to high-dose hook effect .

10. Stability Studies

Sample stability

Studies were performed to determine the sample storage stability of human serum, and K2 EDTA, lithium heparin and sodium citrate plasma samples at 2-8°C, room temperature (RT), -20 °C and after multiple freeze/thaw (F/T) cycles.

The serum and plasma samples evaluated contained anti-parvovirus B19 IgG levels of high negative, low positive and moderate/positive were evaluated in 2 replicates using the LIAISON Biotrin Parvovirus B19 IgG Plus assay. Data analysis was performed for each sample and storage condition. For positive samples, the percent difference for results with respect to the baseline (time zero) was calculated. In addition, regression analysis was conducted for each positive sample to determine the time point at which the regression line crosses the proposed maximum 20% deviation from the regression intercept. The sample storage stability claim is the next to the last time point tested that was within defined acceptance criteria. For negative samples, sample stability was adequate if samples stay negative during storage.

- 2-8°C study – samples were tested unstressed (T=0), and again after 1, 2, 3, 4, 7, 8 and 9 days of storage at 2-8°C for at least 24 hours per day.
- room temperaturestudy (RT) – samples were tested immediately after preparation and again after 1, 2, 3 and 4 days of storage at RT (30±1°C) for 24 hours each day.
- -20 °C study –samples were tested unstressed (T=0) and stored at -20°C or lower for 1, 2, 3, 4, and 6 months.
- Freeze/Thaw (F/T) study–samples were tested unstressed (T=0) and after 1, 2, 3, 4, 5, 6, and 7 F/T cycles. Samples were frozen for at least 8 hours at -20°C or lower and thawed at room temperature.

The studies indicate serum and plasma (K2-EDTA, lithium heparin and sodium citrate) samples are stable for:
- 15°-30°C for one (1) day;
- 2°-8°C for three (3) days;
- Up to three (3) freeze-thaw cycles;
- Up to six (6) months at -20°C or below.

Reagent stability

Real-Time (Shelf-Life)

Real-Time studies were performed to establish the shelf-life for the LIAISON Biotrin Parvovirus B19 IgG Plus assay. Three (3) lots of LIAISON Biotrin Parvovirus B19 IgG Plus assay were stored at the recommended storage temperature of 2-8°C throughout the study. Performance was assessed against clinically relevant acceptance criteria using three (3) lots LIAISON Biotrin Control Parvovirus B19 IgG Plus along with an internal stability panel consisting of three (3) serum samples. Study results demonstrate that reagents are stable and continue to meet acceptance criteria twenty four (24) months after the date of manufacture for the LIAISON Biotrin Parvovirus B19 IgG Plus.

Reagent On-Board

The aim of this study was to determine the length of time the LIAISON Biotrin Parvovirus B19 IgG Plus assay can be stored on-board the LIAISON XL Analyzer in the refrigerated area).

One (1) lot of the LIAISON Biotrin Parvovirus B19 IgG Plus assay was stored on-board the LIAISON XL Analyzer throughout the 13 weeks of the study. The LIAISON Biotrin Control Parvovirus B19 IgG Plus along with the internal stability panel was tested in triplicate at one (1) week intervals up to the 13 weeks.

The LIAISON Biotrin Parvovirus B19 IgG Plus assay is stable on-board the LIAISON XL Analyzer for 11 weeks.

Reagent Open Use

The aim of this study was to assess the open use stability of the LIAISON Biotrin Parvovirus B19 IgG Plus assay reagents by simulating normal conditions of use as specified in the Instructions for Use. After testing the opened Reagent Integral was removed from the XL Analyzer and stored at 2-8 °C until the next testing time point. Kit performance using the opened Reagent Integral was evaluated weekly up to 13 weeks.

Testing of samples was performed in triplicate, on one (1) lot of the LIAISON Biotrin Parvovirus B19 IgG Plus assay and one (1) lot of the LIAISON Biotrin Control Parvovirus B19 IgG Plus. Results were calculated using the initial (time zero) assay calibration.
The Reagent Integral is stable after opening for 11 weeks when stored at 2-8 °C.

Temperature Stress/Reagent Transport Study

The transport simulation tests were performed in order to ensure that kit reagents maintains its properties during the shipment and delivery conditions to the customer. After being subjected to simulates stress conditions, testing was performed on one (1) lot of kit reagents and one (1) lot of kit controls, with a fresh calibration at each test time point. All testing performed met acceptance criteria under various simulated transport conditions.

Calibrator Stability

The LIAISON Biotrin Parvovirus B19 IgG Plus calibrators are included on the Reagent Integral. All studies for the Reagent Integral are applicable to the calibrators provided.

Calibration Interval Stability

The aim of this study was to assess stability of the product calibration interval by simulating normal condition of use as specified in the Instruction for use.

A calibration was performed at time 0 and the Reagent Integral was stored on board the analyzer, in the refrigerated reagent bay for the duration of the study. Kit performance, using the opened Reagent Integrals, was evaluated weekly up to 9 weeks by testing the stability panel and one (1) lot of LIAISON Biotrin Control Parvovirus B19 IgG Plus, on one (1) lot of LIAISON Biotrin Parvovirus B19 IgG Plus reagents.

Results demonstrate that the LIAISON Biotrin Parvovirus B19 IgG Plus calibration is stable for eight (8) weeks.

Control stability

Real-time (Shelf-Life)

Studies were performed to establish the shelf-life for the LIAISON Biotrin Control Parvovirus B19 IgG Plus. Three (3) lots of LIAISON Biotrin Control Parvovirus B19 IgG Plus were stored at the recommended storage temperature of 2-8°C throughout the study. Study results demonstrate that positive and negative controls are stable and continue to meet acceptance criteria twenty four (24) months after the date of manufacture for the LIAISON Biotrin Control Parvovirus B19 IgG Plus.

Open Use

The aim of this study was to assess stability of the opened Control vials by simulating normal conditions of use, as specified in the Instruction for Use. Once opened the controls were stored for at least 4 hours on the LIAISON XL Analyzer, then returned to 2-8°C until the next testing time point. One (1) lot of LIAISON Biotrin Control Parvovirus B19 IgG Plus was tested in triplicate, on one (1) lots of LIAISON Biotrin Parvovirus B19 IgG Plus assay. The LIAISON Biotrin Control Parvovirus B19 IgG Plus (positive and negative) is stable for 12 weeks after opening when stored at 2-8 °C between uses.

Temperature Stress/Control Transport Study

The transport simulation tests were performed in order to ensure that controls maintain its properties during the shipment and delivery conditions to the customer. After being subjected to simulates stress conditions, testing of samples was performed in triplicate, on one (1) lot of LIAISON Biotrin Parvovirus B19 IgG Plus assay and one (1) lot of LIAISON Biotrin Control Parvovirus B19 IgG Plus with a fresh calibration at each testing point.

All testing performed met acceptance criteria under various simulated transport conditions.

11. Precision

Within-Laboratory Precision Study

A within laboratory precision study was carried out over a period of twelve (12) days on the LIAISON Biotrin Parvovirus B19 IgG Plus assay using the LIAISON XL Analyzer. The Clinical and Laboratory Standards Institute (CLSI) document EP05-A3 was consulted in the preparation of the testing protocol. The testing was performed internally at DiaSorin S.p.A.

A coded panel of six (6) serum samples and controls were tested in 2 replicates per run, 2 runs per day for 12 days using 3 different LIAISON Biotrin Parvovirus B19 IgG Plus

assay reagent kit lots. The testing days were within one calibration cycle. The results are shown below.

Table 6: LIAISON Biotrin Parvovirus B19 IgG Plus Within-Laboratory Precision

Sample ID	N	Mean (AU)	Within Run		Between Run		Between Day		Between-Lot		Total	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Neg Ctrl RS1117	144	499 (*)	55.5	11.1%	50.7	10.2%	49.3	9.9%	52.0	10.4%	103.8	20.8%
Neg Ctrl RS1118	144	661 (*)	41.1	6.2%	19.4	2.9%	54.1	8.2%	38.9	5.9%	80.6	12.2%
Pos Ctrl RS1119	144	4.36	0.112	2.6%	0.215	4.9%	0.239	5.5%	0.101	2.3%	0.355	8.1%
Pos Ctrl RS1120	144	5.38	0.137	2.5%	0.274	5.1%	0.340	6.3%	0.000	0.0%	0.458	8.5%
Pos Ctrl RS1121	144	5.16	0.111	2.2%	0.244	4.7%	0.462	9.0%	0.000	0.0%	0.534	10.4%
PARVOG-1-Ul	144	0.605	0.023	3.9%	0.025	4.1%	0.030	5.0%	0.059	9.7%	0.074	12.3%
PARVOG-l-U2	144	0.595	0.024	4.0%	0.028	4.8%	0.026	4.4%	0.048	8.1%	0.066	11.1%
PARVOG-1-U3	144	1.72	0.048	2.8%	0.026	1.5%	0.058	3.4%	0.077	4.4%	0.111	6.4%
PARVOG-1-U4	144	2.57	0.048	1.9%	0.055	2.1%	0.101	3.9%	0.171	6.7%	0.212	8.2%
PARVOG-1-U5	144	7.03	0.184	2.6%	0.196	2.8%	0.290	4.1%	0.069	1.0%	0.401	5.7%
PARVOG-1-U6	144	8.10	0.146	1.8%	0.127	1.6%	0.432	5.3%	0.120	1.5%	0.488	6.0%

(*) Data analysis in RLU values

Reproducibility (External Precision 5-day Study)

A five (5) day reproducibility study was conducted at two (2) external laboratories and at DiaSorin Inc. to verify the precision of the LIAISON Biotrin Parvovirus B19 IgG Plus assay. The coded panel, comprised of six (6) frozen serum samples was the same panel used in the 12-day precision study.

The precision panel was tested using the LIAISON Biotrin Parvovirus B19 IgG Plus assay at all three (3) sites on the LIAISON XL Analyzer using three (3) replicates per run in two (2) runs per day for five (5) operating days with multiple technicians performing the testing.

Table 7: LIAISON Biotrin Parvovirus B19 IgG Plus assay Reproducibility

Sample	N	Mean AU	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Neg Ctrol RS1117	90	565*	38.8	6.9%	26.7	4.7%	35.6	6.3%	67.1	11.9%	89.4	15.8%
Pos Ctrol RS1119	90	4.35	0.151	3.5%	0.174	4.0%	0.329	7.6%	0.201	4.6%	0.449	10.3%
PARVOG-1- U1	90	0.666	0.035	5.2%	0.032	4.9%	0.046	6.9%	0.048	7.1%	0.081	12.2%
PARVOG-1- U2	90	0.811	0.030	3.7%	0.018	2.2%	0.028	3.4%	0.097	11.9%	0.106	13.1%
PARVOG-1- U3	90	1.83	0.054	3.0%	0.037	2.0%	0.057	3.1%	0.113	6.2%	0.143	7.8%
PARVOG-1- U4	90	2.76	0.078	2.8%	0.059	2.2%	0.115	4.2%	0.230	8.3%	0.275	10.0%
PARVOG-1- U5	90	6.83	0.251	3.7%	0.211	3.1%	0.395	5.8%	0.646	9.5%	0.825	12.1%
PARVOG-1- U6	90	8.28	0.191	2.3%	0.190	2.3%	0.508	6.1%	0.811	9.8%	0.994	12.0%

*The low control was analyzed in RLU values

B. Animal Studies

Not Applicable

C. Additional Studies

Not Applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for the detection of IgG antibodies to Parvovirus B19 antigen with the Biotrin Parvovirus B19 IgG Plus assay using samples that would routinely be tested for anti-parvovirus B19 IgG in the US. 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

A multi-site clinical agreement study was conducted to determine the clinical performance of the LIAISON Biotrin Parvovirus B19 IgG Plus assay on specimens that would routinely be tested for anti-parvovirus B19 IgG including pregnant women, females of child-bearing age and suspected of exposure to parvovirus B19 or are fifth disease.

The prospective population of subjects which were suspected of parvovirus was collected from three (3) geographical regions within the United States – California

(n=167), North Carolina (n=167) and Texas (n=166) – and included 500 total specimens. In addition, a population of 250 pregnant women, were also prospectively collected. Approximately, the same number of samples were collected at each trimester: 1st trimester (n=83), 2nd trimester (n=84) and 3rd trimester (n=83).

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the LIAISON Biotrin Parvovirus B19 IgG Plus Clinical Testing study was limited to patients who met the following inclusion criteria:

   i. Leftover de-identified pregnant subjects, or leftover de-identified prospective subjects with signs and symptoms of parvovirus.
   ii. Sample types: serum, K2 EDTA plasma, Na Citrate plasma, or Li Heparin plasma.
   iii. Specimens stored within 8 hours at RT, 48 hours at 2-8°C, or 12 months at -20°C.
   iv. Availability of gender, age, collection date, pregnancy trimester, and signs/symptoms/reasons for suspicion for each subject.
   v. Minimum volume 1 mL.
   vi. Only one (1) specimen per patient.

   Patients were not permitted to enroll in the LIAISON Biotrin Parvovirus B19 IgG Plus clinical agreement study if they met any of the following exclusion criteria:

   i. Collection and/or samples not meeting inclusion criteria.
   ii. Specimens having undergone multiple freeze/thaw cycles.
   iii. Grossly hemolyzed, lipemic or containing gross particulate matter.

2. Follow-up Schedule

   Patient follow up was not applicable.

3. Clinical Endpoints

   Safety and effectiveness were evaluated in the clinical validation study with estimates of specificity and sensitivity. Specificity and sensitivity were estimated by negative percent agreement and positive percent agreement with an FDA-approved comparator assay.

B. Accountability of PMA Cohort

The clinical agreement study involved the testing of 750 samples on one FDA approved reference assay. All 750 samples were collected in United States.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for anti-Parvovirus B19 IgG detection study performed in the US.

The majority of the prospectively collected specimens were from women (n=661 out of 750; 88.1%). Of the 750 prospective specimens, 631 were collected from adult subjects ranging in ages from 22 to 87 years and 119 pediatric subjects ranging in ages from 0 to 21 years. Two hundred fifty (250) of the specimens were from pregnant women. The specimens were routine submits for parvovirus B19 serology consisting of approximately 88% female and 12% male with an age range of <1-89 years.

Table 8: Demographics of Collected Clinical Study Specimens by Age and Gender

Age Range	Gender	n	%	Total
0-9	**Female**	17	61%	28
	Male	11	39%	
10-19	**Female**	43	74%	58
	Male	15	26%	
20-29	**Female**	232	97%	239
	Male	6	3%	
	Unknown	1	0.4%	
30-39	**Female**	265	97%	272
	Male	7	3%	
40-49	**Female**	34	72%	47
	Male	13	28%	
50-59	**Female**	18	58%	31
	Male	13	42%	
60-69	**Female**	29	74%	39
	Male	10	26%	
70-79	**Female**	19	63%	30
	Male	11	37%	
80-89	**Female**	4	67%	6
	Male	2	33%	
Total	**Female**	**661**	**88%**	**750**
	Male	**88**	**12%**	
	Unknown	**1**	**0.1%**	

D. Safety and Effectiveness Results

1. Safety Results

The results of the Clinical Agreement study show the LIAISON Biotrin Parvovirus B19 IgG Plus assay and the LIAISON Biotrin Control Parvovirus B19 IgG Plus pose no safety hazards to the patient as results from this *in vitro* diagnostic device are to be used in conjunction with other clinical and laboratory data to assist the clinician in making individual patient management decisions.

There were no adverse effects that occurred in the PMA clinical study.

2. Effectiveness Results

The analysis of effectiveness was based on the 750 evaluable patient specimens. Key effectiveness outcomes are presented in Tables 8 and 9 below.

Table 9: LIAISON Biotrin Parvovirus B19 IgG Plus Agreement for Pregnant Cohort

LIAISON Biotrin Parvovirus B19 IgG Plus	Comparator			Total
	Positive	Equivocal	Negative	
Positive	154	0	3	157
Negative	13	0	80[a]	93
Total	167	0	83	250
Positive Percent Agreement (PPA)	154/167	92.22%	95% CI = 87.14% - 95.40%	
Negative Percent Agreement (NPA)	80/83	96.39%	95% CI = 89.90% - 98.76%	

[a]One (1) specimen repeatedly equivocal by the comparator test was further tested following the comparator package insert and resulted negative

Table 10: LIAISON Biotrin Parvovirus B19 IgG Plus Agreement for Routine Laboratory Specimens

LIAISON Biotrin Parvovirus B19 IgG Plus	Comparator			Total
	Positive	Equivocal	Negative	
Positive	328[c]	0	6	334
Negative	20	1[b]	145[a]	166
Total	348	1	151	500
Positive Percent Agreement (PPA)	328/349	93.98%	95% CI = 90.98% - 96.03%	
Negative Percent Agreement (NPA)	145/151	96.03%	95% CI = 91.60% - 98.17%	

[a]One (1) specimen repeatedly equivocal by the comparator was further tested following the comparator package insert and resulted negative

[b]One (1) specimen repeatedly equivocal by the comparator was further tested following the

comparator package insert and remained equivocal
[c]Four (4) specimens repeatedly equivocal by the comparator were further tested following the comparator package insert and resulted positive

3. Subgroup Analyses
   The study design enabled an assessment of assay performance as depicted in tables above which show subjects stratified by risk of Parvovirus B19 infection. No analyses were performed for [gender-, age-, or ethnicity- specific] subgroups.

4. Pediatric Extrapolation

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

XI. 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 3 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.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

There were no deviations made to the clinical protocol PROT.648.00027 as part of method agreement testing.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Microbiology Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the LIAISON Biotrin Parvovirus B19 IgG Plus assay for detecting antibodies to Parvovirus B19 antigen in human serum and plasma (dipotassium EDTA, lithium heparin and sodium citrate) samples, on the LIAISON XL Analyzer has been demonstrated in pregnant women. The results of this test may be used for testing women of childbearing age where there is a suspicion of exposure to human B19V. The test may also be used for all patients as an aid in the diagnosis of fifth disease

(erythema infectiosum). The positive percent agreement of the assay in pregnant cohort is 92.22% with a two-sided 95% confidence interval (CI) of 87.14% - 95.40% and the negative percent agreement is 96.39% with a two-sided 95% CI of 89.90 - 98.76%. The positive percent agreement of the assay in routine laboratory specimens is 93.98% with a two-sided 95% confidence interval (CI) of 90.98% - 96.03% and the negative percent agreement is 96.03% with a two-sided 95% CI of 91.60 - 98.17%.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study conducted to support PMA approval as described above. Based on the results of these studies the LIAISON Biotrin Parvovirus B19 IgG Plus assay when used according to the manufacturer's instructions can aid the physician in the diagnosis of fifth disease (erythema infectiosum).

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of this assay are: 1) to diagnose, in conjunction with other serological tests and clinical information, acute parvovirus B19 infection in individuals with symptoms concerning for parvovirus B19 (B19V) infection; 2) to rule out, in conjunction with other serological tests, acute B19V infection in individuals displaying symptoms or signs consistent with B19V infection; and 3) to determine serological status of B19V infection in pregnant women after possible exposure to parvovirus B19. Test results can facilitate initiation of appropriate monitoring of patients with active B19V infection to ensure early identification and management of possible sequelae of B19V infection in infected individuals. Specifically in pregnant women, test results may facilitate appropriate monitoring for possible sequelae of infection in the fetus and timely intervention to mitigate morbidity/mortality in mother and fetus. Test results may also help pregnant women and their families have knowledge of and prepare for possible fetal abnormalities, as well as provide reassurance against likelihood of potential fetal abnormalities. Test results may also reassure patients and providers as to the etiology of a new rash, arthralgias or other symptoms/signs of B19V diagnosis and reduce the need for additional diagnostic testing or evaluation..

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Risks of a false positive test include improper patient management, such as leading to additional unnecessary monitoring for possible sequelae of acute B19V infection on infected individuals and/or fetus(es) of infected pregnant women, unnecessary strain/worry in pregnant women about fetal risks of infection, and premature discontinuation of diagnostic evaluation due to clinicians being falsely reassured about the etiology of an individuals symptoms. False attribution of an individual's symptoms/signs to acute B19V infection may lead to delay in diagnosis and management of the true etiology for symptoms.

Risks of a false negative test include improper patient management, including missed/delayed recognition of potential sequelae of B19V infection in infected individuals. The impact of missed/delayed recognition may be substantial in specific high-risk populations, such as immunocompromised hosts, those with chronic hemolytic anemia, and pregnant women and their fetus(es), due to delays in treatment/coordination of care that could reduce morbidity/mortality. False negative results may also falsely reassure clinicians and pregnant women about potential risks to their fetuses and lead them to be unprepared for potentially clinically significant sequelae such as spontaneous abortion, fetal anemia, neurological anomalies or fetal death. The risk of false-negative tests is likely mitigated by the fact that clinicians who have a high degree of clinical suspicion for acute B19V infection may not be reassured by a negative result due to the variability in IgG development in the disease course and may treat patients conservatively as still being at risk despite negative result.

1. Patient Perspective

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the claimed intended use of the device, the probable benefits outweigh the probable risks.

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 clinical benefits outweigh the risks for the LIAISON Biotrin Parvovirus B19 IgG Plus assay considering the performance of the device in the clinical study and the risk mitigations afforded by the premarket application. The proposed assay labeling will facilitate accurate assay implementation and interpretation of results. The clinical performance observed in the analytical and clinical studies suggests that errors will be uncommon and that the assay may provide substantial benefits to patients when used with other laboratory results and clinical information as an aid to the diagnosis of parvovirus infection in patients with signs and symptoms of parvovirus infection.

XV. CDRH DECISION

CDRH issued an approval order on March 29, 2024.

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

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

Not Applicable