September 4, 2020

Fujirebio Diagnostics, Inc.
Kristin Maddaloni
Regulatory Affairs Specialist
201 Great Valley Parkway
Malvern, Pennsylvania 19355

Re: K192524
Trade/Device Name: Lumipulse G CA15-3
Regulation Number: 21 CFR 866.6010
Regulation Name: Tumor-Associated Antigen Immunological Test System
Regulatory Class: Class II
Product Code: MOI
Dated: August 5, 2020
Received: August 6, 2020

Dear Kristin Maddaloni:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Ying (Katelin) Mao, Ph.D.
Acting Chief
Division of Immunology
and Hematology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K192524

Device Name
Lumipulse***G*** CA15-3

Indications for Use *(Describe)*
Lumipulse ***G*** CA15-3 is a Chemiluminescent Enzyme Immunoassay (CLEIA) for the quantitative determination of CA 15-3 in human serum or plasma (sodium heparin, lithium heparin, or dipotassium EDTA) on the LUMIPULSE ***G*** System.

The assay is to be used as an aid in the management of patients previously diagnosed with stage II and III breast cancer. Serial testing for patient CA15-3 assay values should be used in conjunction with other clinical methods used for monitoring breast cancer.

WARNING: The concentration of CA 15-3 in a given specimen, as determined by assays from different manufacturers, can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay for CA 15-3 used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining serial levels of CA 15-3 is changed, the laboratory must perform additional serial testing to confirm baseline values. Prior to changing assays, the laboratory MUST confirm baseline values for patients being serially monitored. **Lumipulse *G* CA 15-3 should not be used for cancer screening or diagnosis**.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Section 5 510(k) SUMMARY

Lumipulse® ***G*** CA15-3

A. General Information

Submission Date: 12 Sep 2019

510(k) Number:

Submitter Information:

Submitter: Fujirebio Diagnostics, Inc.
201 Great Valley Parkway
Malvern, PA 19355

Contact Person: Kristin Maddaloni
Specialist, Regulatory Affairs
Phone: (610) 395-2126
Fax: (610) 240-3803
Email: maddalonik@fdi.com

B. Purpose of Submission:
New device

C. Measurand:
Cancer antigen 15-3

D. Type of Test:
Quantitative assay, automated chemiluminescent enzyme immunoassay (CLEIA)

E. Applicant:
Fujirebio Diagnostics, Inc.

F. Proprietary and Established Names:
Lumipulse ***G*** CA15-3

G. Regulatory Information:
1. Regulation section:
   21 CFR § 866.6010

2. Classification:
   Class II

3. Product codes:
   MOI - system, test, immunological, antigen, tumor

4. Panel:
   82, Immunology

H. Intended Use:

1. Intended Use:
   Lumipulse ***G*** CA15-3 Immunoreaction Cartridges

   Lumipulse G CA15-3 is a Chemiluminescent Enzyme Immunoassay (CLEIA) for the quantitative determination of CA15-3 in human serum or plasma (sodium heparin, lithium heparin, or dipotassium EDTA) on the LUMIPULSE G System.

   The assay is to be used as an aid in the management of patients previously diagnosed with stage II and III breast cancer. Serial testing for patient CA15-3 assay values should be used in conjunction with other clinical methods used for monitoring breast cancer.

   WARNING: The concentration of CA 15-3 in a given specimen, as determined by assays from different manufacturers, can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay for CA 15-3 used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining serial levels of CA 15-3 is changed, the laboratory must perform additional serial testing to confirm baseline values. Prior to changing assays, the laboratory MUST confirm baseline values for patients being serially monitored.
   Lumipulse *G* CA15-3 should not be used for cancer screening or diagnosis.

2. Indications for use:
   Same as Intended Use.

3. Special conditions for use statement(s):
   Prescription use only.

4. Special instrument requirements:
   LUMIPULSE ***G***1200 System

I. Device Description:

Lumipulse ***G*** CA15-3 is an assay system, including a set of immunoassay reagents, for the quantitative measurement of CA 15-3 in specimens based on CLEIA technology by a two-step sandwich immunoassay method on the LUMIPULSE ***G*** System.

Lumipulse ***G*** CA15-3 Immunoreaction Cartridges: REF 235102
The Lumipulse ***G*** CA15-3 Immunoreaction Cartridges consists of 3 × 14 tests.
Each kit contains the following:

1.) Antibody-Coated Particle Solution
(Liquid when used, 250 µL/Immunoreaction Cartridge) Contains 150 µg/mL anti-CA 15-3 monoclonal antibody (mouse)-coated particles, protein stabilizers (bovine and mouse) and

chemical stabilizers in 0.15 M sodium chloride/Tris buffer. This solution contains gelatin and turns into gel at 15°C or lower. Preservative: sodium azide.

2.) Enzyme-Labeled Antibody Solution
(Liquid, 350 µL/Immunoreaction Cartridge) Contains 0.2 µg/mL alkaline phosphatase (ALP: calf)-labeled anti-CA 15-3 monoclonal antibody (mouse), protein stabilizers (bovine and calf) and chemical stabilizers in 0.1 M sodium chloride/MES buffer. Preservative: sodium azide.

J. Substantial Equivalence:

1. Predicate device name(s):
   ARCHITECT CA 15-3

2. Predicate 510(k) number(s):
   K042732

3. Comparison with predicate:

Comparison between the Lumipulse® *G* CA15-3 and ARCHITECT CA15-3

Similarities and Differences		
	Lumipulse® *G* CA15-3 (Proposed Device)	**ARCHITECT CA15-3 (Predicate Device) K042732**
Device Type	*In vitro* diagnostic	Same
Classification	Class II	Same
Product Code	MOI	Same
Analyte	Cancer Antigen 15-3	Same
Regulation Number	21CFR § 866.6010	Same
Product Usage	Clinical and Hospital laboratories	Same
Principle of Operation	Automated Quantitative Chemiluminscent Enzyme Immunoassay (CLEIA)	Chemiluminscent Microparticle Immunoassay (CMEIA)
Specimen Collection Method	Routine Phlebotomy Techniques	Same
Intended Use	Lumipulse ***G*** CA15-3 is a Chemiluminescent Enzyme Immunoassay (CLEIA) for the quantitative determination of CA 15-3 in human serum or plasma (sodium heparin, lithium heparin, or dipotassium EDTA) on the LUMIPULSE G System. The assay is to be used as an aid in the management of patients previously diagnosed with stage II and III breast cancer. Serial testing for patient CA15-3 assay values	The ARCHITECT CA 15-3 assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of DF3 defined antigen in human serum and plasma on the ARCHITECT iSystem. The ARCHITECT CA 15-3 assay is to be used as an aid in the management of Stage II and III breast cancer patients. Serial testing for patient CA 15-3 assay values should be used in conjunction with other clinical

Similarities and Differences		
	Lumipulse® *G* CA15-3 (Proposed Device)	**ARCHITECT CA15-3 (Predicate Device) K042732**
	should be used in conjunction with other clinical methods used for monitoring breast cancer.	methods for monitoring breast cancer
Instrument System	LUMIPULSE ***G*** System	ARCHITECT iSystem
Assay Type	Two-step sandwich immunoassay based on chemiluminescent technology	Two-step immunoassay based on CMIA technology
Type of Specimen	Human serum and plasma (sodium heparin, lithium heparin, or dipotassium EDTA)	Human serum and plasma (sodium heparin, lithium heparin, or tripotassium EDTA)
Assay Range	1.7 U/mL - 400 U/mL	0.5 U/mL – 800 U/mL

K. Standard/Guidance Document Referenced (if applicable):

- CLSI EP05-A3 - Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition
- CLSI EP06-A - Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP07 – Interference Testing in Clinical Chemistry; Approved Guideline – Third Edition
- CLSI EP09c – Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Third Edition
- CLSI EP14-A2 - Evaluation of Matrix Effects; Approved Guideline – Second Edition
- CLSI EP17-A2 - Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition
- CLSI EP25-A – Evaluation of Stability of *In Vitro* Diagnostic Reagents: Approved Guideline
- CLSI EP28-A3c - Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition
- CLSI EP34 - Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking; Approved Guideline – First Edition
- CLSI EP37 – Supplemental Tables for Interference Testing in Clinical Chemistry; Approved Guideline – First Edition

L. Test Principle:

CA 15-3 in specimens specifically binds to anti-CA 15-3 monoclonal antibody (mouse) on the particles, and antigen-antibody immunocomplexes are formed. The particles are then washed and rinsed to remove unbound materials. Alkaline phosphatase (ALP; calf)-labeled anti-CA 15-3 monoclonal antibody (mouse) specifically binds to CA 15-3 of the immunocomplexes on the particles and additional immunocomplexes are formed. The particles are washed and rinsed to

remove unbound materials. Substrate Solution is added and mixed with the particles. AMPPD contained in the Substrate Solution is dephosphorylated by the catalysis of ALP indirectly conjugated to particles. Luminescence (at a maximum wavelength of 477 nm) is generated by the cleavage reaction of dephosphorylated AMPPD. The luminescent signal reflects the amount of CA 15-3.

M. Performance Characteristics

Data were generated using the LUMIPULSE ***G***1200 System.

1. Analytical performance:

   a. *Precision/Reproducibility:*

   The results of the 20-day precision calculations for Lumipulse ***G*** CA15-3 performed at Associated Regional and University Pathologists (ARUP) are shown below:

   - Lot A ICs/Lot A Calibrators for Panels 1-6

   The analyses determined the total precision for the Lumipulse ***G*** CA15-3 assay to be ≤ 3.3%. The total precision of the Lumipulse ***G*** CA15-3 for the six (6) panels ranged from 2.4% to 3.3%. The precision of all controls and panels for the 20-day Precision Study met the acceptance criteria of a CV ≤ 10%.

Summary for ARUP 20-day Precision (n=80 for each panel)

		Within-Run (Repeatability)		Between Run		Between-Day		Within-Laboratory (Total)	
Sample	**Mean (U/mL)**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Panel 1	2.5	0.1	2.7%	0.0	0.0%	0.0	2.0%	0.1	3.3%
Panel 2	21.0	0.4	2.0%	0.3	1.6%	0.4	1.7%	0.6	3.1%
Panel 3	35.9	0.7	2.0%	0.3	0.9%	0.4	1.2%	0.9	2.5%
Panel 4	101.8	1.8	1.8%	1.2	1.2%	1.1	1.1%	2.4	2.4%
Panel 5	232.7	4.2	1.8%	4.2	1.8%	0.9	0.4%	6.0	2.6%
Panel 6	369.3	7.2	1.9%	6.0	1.6%	2.5	0.7%	9.7	2.6%

Lot-To-Lot Reproducibility for Combined Data

The precision analyses for the combined lot-to-lot analysis for Lots A, B and C determined the total precision for Lumipulse ***G*** PCT to be ≤ 3.7% in this study. The total precision for Lumipulse ***G*** CA15-3 to be ≤ 3.3% for the six (6) panels. The total precision of Lumipulse ***G*** CA15-3 ranged from 2.2% to 3.7%. The between-lot precision for Lumipulse ***G*** CA15-3 was ≤ 4.8%.

The precision of controls and panels for the lot-to-lot reproducibility met the targeted acceptance criteria of a CV ≤ 10%.

Summary of the Lot-to-Lot Reproducibility for the Combined Data for Lots A, B and C (n=90 for each sample)

		Between-Lot		Between Day		Between Run		Within-Run (Repeatability)		Within-Laboratory (Total)	
Sample	Mean (U/mL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Panel 1	2.5	0.1	4.8%	0.0	0.3%	0.1	2.2%	0.1	2.5%	0.1	5.8%
Panel 2	20.0	0.6	3.2%	0.2	1.1%	0.2	1.0%	0.4	1.9%	0.8	4.0%
Panel 3	34.2	1.1	3.2%	0.4	1.1%	0.3	0.9%	0.5	1.6%	1.3	3.9%
Panel 4	96.7	2.9	3.0%	0.3	0.3%	0.6	0.6%	1.7	1.8%	3.5	3.6%
Panel 5	224.4	4.4	1.9%	0.0	0.0%	3.4	1.5%	4.6	2.0%	7.2	3.2%
Panel 6	360.1	6.9	1.9%	0.0	0.0%	5.7	1.6%	6.1	1.7%	10.8	3.0%

Site to Site Reproducibility for Combined Data

The precision analyses for the combined site-to-site analysis determined the total precision for Lumipulse ***G*** CA15-3 to be ≤ 6.7% for the 6 panels in this study. The total precision of Lumipulse ***G*** CA15-3 in the study ranged from 2.9% to 6.7%. The between-site precision for Lumipulse ***G*** CA15-3 was ≤ 4.9%.

The precision of the controls and panels for the site-to-site reproducibility met the targeted acceptance criteria of a CV ≤10%.

Summary of the Site-to-Site Reproducibility for the Combined Data for Lot A (n=102 for each panel)

		Between Site		Between Day		Between Run		Within-Run (Repeatability)		Reproducibility (Total)	
Sample	Mean (U/mL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Panel 1	2.4	0.1	4.9%	0.0	0.0%	0.1	4.1%	0.1	2.2%	0.2	6.7%
Panel 2	19.9	0.4	2.0%	0.2	1.1%	0.5	2.7%	0.3	1.7%	0.8	3.9%
Panel 3	33.7	0.6	1.8%	0.0	0.0%	1.0	2.8%	0.5	1.5%	1.3	3.7%
Panel 4	96.0	0.9	1.0%	1.0	1.1%	1.8	1.8%	1.7	1.7%	2.8	2.9%
Panel 5	219.2	4.2	1.9%	3.2	1.4%	4.4	2.0%	4.2	1.9%	8.0	3.7%
Panel 6	348.1	3.1	0.9%	7.0	2.0%	6.8	2.0%	5.1	1.5%	11.5	3.3%

b. Linearity/assay reportable range:

Lumipulse ***G*** CA15-3 the LUMIPULSE G1200 System demonstrated linearity in a study consistent with the guidelines in the CLSI Guideline EP6-A. High pools were created using patient serum samples that contained naturally expressed CA15-3 and diluted with a low patient serum sample pool. The linearity was found in the range of 1.7 U/mL to 434.8 U/mL. Lumipulse ***G*** CA15-3 correlated with expected concentrations according to the linear regression formula:

Range (U/mL)	Slope (95% CI)	Intercept (95% CI)	R2
1.7-400	0.965 (0.956, 0.974)	-0.226 (-0.316, -0.136)	*0.9985*

High dose effect is a phenomenon whereby very high level specimens may read within the dynamic range of the assay. For Lumipulse ***G*** CA15-3 on the LUMIPULSE ***G***1200 System, no high dose effect was observed for samples containing approximately 9,000 U/mL of CA 15-3.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Calibration of the Lumipulse ***G*** CA15-3 is traceable to in-house reference calibrators, whose values have been assigned to correlate to Fujirebio Diagnostics' CA 15-3 Radioimmunoassay.

Shelf life

The shelf life for Lumipulse ***G*** CA15-3 Immunoreaction Cartridges and the Lumipulse ***G*** CA15-3 Calibrators is 12 months at 2–10°C.

On board the LUMIPULSE ***G***1200

The Lumipulse ***G*** CA15-3 Immunoreaction Cartridges are sealed and stored at 4-12°C. To reduce risk for any misuse, the package insert states *The Lumipulse **G** CA15-3 Cartridges can be stored on-board the LUMIPULSE **G** System for a maximum of 30 days.*

The package insert recommends calibrator curve storage on the LUMIPULSE ***G***1200 for a maximum of 30 days.

Transport Conditions

Lumipulse ***G*** CA15-3 Immunoreaction Cartridges and the Lumipulse ***G*** CA15-3 Calibrators are shipped at 2-10°C.

d. Detection limit:

The Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) of Lumipulse ***G*** CA15-3 on the LUMIPULSE ***G***1200 System is ≤0.138 U/mL.

1) LoB and LoD
   The LoB for Lumipulse ***G*** CA15-3 was 0.022 U/mL. The LoD for Lumipulse ***G*** CA15-3 on the LUMIPULSE ***G***1200 System was 0.053 U/mL, determined consistent with the guidelines in the CLSI Guideline EP17-A2.

2) Limit of Quantitation (LoQ)
   The LoQ for Lumipulse ***G*** CA15-3 on the LUMIPULSE ***G***1200 System was determined to be 0.138 U/mL, when analyzed in accordance to the guidelines in the CLSI EP17-A2. The LoQ is defined as the concentration of CA 15-3 at which the standard deviation is no more than 15% of the mean.

e. Interfering Substances

Lumipulse ***G*** CA15-3 on the LUMIPULSE ***G***1200 System demonstrated an average interference of ±10% for each compound shown in the table below, in a study consistent with the guidelines in the CLSI EP07 and EP37. Human serum specimen pools with CA 15-3 concentrations ranging from approximately 30-35 U/mL, 80-100 U/mL, and 300-350 U/mL were supplemented with potentially interfering compounds. The following compounds were tested using Lumipulse ***G*** CA15-3 and found not to interfere with the assay.

Endogenous Interferences	Test Concentration
Free Bilirubin (unconjugated)	60 mg/dL
Conjugated Bilirubin	60 mg/dL
Triglycerides (Intralipid 20% Emulsion)	3,000 mg/dL
Hemoglobin	500 mg/dL
	1,000 mg/dL
Total Protein (Human Serum Albumin)	12 g/dL
	15 g/dL
	5 g/dL
Immunoglobulin G (IgG)	19.7 mg/dL
Biotin	
Human Anti-Mouse Antibodies (HAMA IgG)	1,000 ng/mL
Rheumatoid Factor (RF) IgM	1,000 IU/mL

Therapeutic Drug Interferences	Test Concentration
Abemaciclib	24 mg/dL
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	100 mg/dL
Acetylcysteine	166 mg/dL
Albumin-bound paclitaxel	27 mg/dL
Alpelisib	18 mg/dL
Ampicillin-Na	100 mg/dL
Ascorbic Acid	30 mg/dL
Atezolizumab	72 mg/dL
β-Estradiol	0.67 mg/dL
Capecitabine	128 mg/dL
Carboplatin	100 mg/dL
Cefoxitin	660 mg/dL
Cisplatin	17.5 mg/dL
Cyclophosphamide	80.0 mg/dL
Cyclosporine	0.5 mg/dL
Diethylstilbestrol	2.5 mg/dL
Docetaxel	10 mg/dL
Doxorubicin HCl	5.0 mg/dL
Doxycycline	3mg/dL

Epirubicin	12 mg/dL
Eribulin	0.14 mg/dL
Etoposide	1.0 mg/dL
Everolimus	1.2 mg/dL
Exemestane	12 mg/dL
5-Fluorouracil	28.0 mg/dL
Flutamide	1.0 mg/dL
Fulvestrant	51 mg/dL
Gemcitabine	128 mg/dL
Heparin	5000 U/L
Ibuprofen	50 mg/dL
Lapatinib	90 mg/dL
Levodopa	2 mg/dL
Liposomal doxorubicin	5 mg/dL
Megestrol acetate	3.96 mg/dL
Methotrexate	45.0 mg/dL
Methyldopa	2.25 mg/dL
Metronidazole	12.3 mg/dL
Mitomycin	7.5 mg/dL
Olaparib	18 mg/dL
Paclitaxel	0.35 mg/dL
Palbociclib	8 mg/dL
Pertuzumab	50 mg/dL
Phenylbutazone	40 mg/dL
Ribociclib	36 mg/dL
Rifampicin	6 mg/dL
Talazoparib	0.06 mg/dL
Tamoxifen	6.0 mg/dL
Testosterone	3.3 mg/dL
Theophylline	10 mg/dL
Vinblastine sulfate	0.13 mg/dL
Vincristine	0.15 mg/dL
Vinorelbine	3 mg/dL
Herceptin©	40.0 mg/dL

f. Cross Reactivity

Interferent	Test Concentration	Highest Observed % Cross Reactivity
CA19-9	11,000 U/mL	0.003
CA125	11,000 U/mL	0.024
AFP	500 ng/mL	-0.063
CEA	5,000 ng/mL	8.246

g. Assay cut-off:
See Clinical Cutoff in 4 below.

2. Comparison studies:

a. Method Comparison

System in a study consistent with the guidelines in CLSI EP09-A3.

Lumipulse ***G*** CA15-3 method comparison was performed on the LUMIPULSE ***G***1200 System in a study consistent with the guidelines in CLSI EP09-A3. The weighted Deming regression method was used to compare the performance of Lumipulse ***G*** CA15-3 to the ARCHITECT CA 15-3. The samples tested ranged from 5.3 to 375.6 U/mL for Lumipulse ***G*** CA15-3 and 5.1 to 1004.4 U/mL for ARCHITECT CA 15-3. The data are summarized in the following table.

Lumipulse *G* CA15-3 vs. ARCHITECT CA 15-3				
n	**Correlation Coefficient (r)**	**Intercept (95% CI)**	**Slope (95% CI)**	**Mean Difference (U/mL)**
117	0.8537	0.4628 (-0.3189 to 1.2445)	1.0512 (0.9674 to 1.1350)	-3.427

b. Matrix Comparison

The Lumipulse ***G*** CA15-3 matrix comparison study was performed to evaluate the difference across tube types (SST, K2EDTA, Lithium Heparin, and Sodium Heparin) versus the means of the control samples (Red top serum) analyzed per CLSI guideline EP09c. The slope for each tube type when compared to the control had 95% confidence intervals that lay entirely within the range 0.9 to 1.1 and the correlation coefficients were ≥ 0.9.

3. Clinical studies:

a. Clinical sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. *Other clinical supportive data*

Monitoring of Disease State in Patients Diagnosed with Breast Cancer

The effectiveness of Lumipulse ***G*** CA15-3 as an aid in monitoring recurrence or progressive disease in patients with breast cancer who have detectable levels of CA15-3 at some point in their disease process was determined by assessing changes in CA15-3 levels in serial serum samples from 112 patients compared to changes in disease status. The staging of the patients was done according to AJCC 7th edition. A study involving a total of 566 pairs of observations was undertaken with an average number of 6.1 observations per patient. A positive change in CA15-3 was defined as an increase in the value that was at least 21% greater than the previous value of the test. This level of change takes into account the biological and analytical variability of the assay. Twenty-five percent (25%) or 14/57 of the patient samples with a positive change correlated with the disease progression, indicating a change in CA15-3 value of <21% is associated with decreased likelihood of progression.

Lumipulse *G* CA15-3 Primary Progression Performance Measurements

Performance Measurement	Value	SE	Lower CI	Upper CI
Sensitivity	51.85 (14/27)	15.71	20.5	83.2
Specificity	86.77 (282/325)	2.02	82.73	90.8
PPV	24.56 (14/57)	7.38	9.85	39.28
NPV	95.59 (282/295)	1.97	91.67	99.52
1-NPV	4.41%	1.97	8.33	0.48
PLR	3.92	0.33	2.03	7.57
NLR	0.55	0.34	0.28	1.08
Prevalence (%)	7.7% (27/352)			

Change in Disease Status Per Sequential Pair In Stages II and III Patients

Change in CA15-3 Concentration	Progression	No Progression	Total
Suspect ≥21%	14	43	**57**
No <21%	13	282	**295**
Total	**27**	**325**	**352**

Lumipulse *G* CA15-3 Full Progression Performance Measurements

Performance Measurement	Value	SE	Lower CI	Upper CI
Sensitivity	48.89 (22/45)	10.75	27.59	70.19
Specificity	88.29 (460/521)	1.47	85.38	91.2
PPV	26.51 (22/83)	6.16	14.31	38.7
NPV	95.24(460/483)	1.48	92.31	98.16
PLR	4.18	0.25	2.52	6.91
NLR	0.58	0.21	0.38	0.88

Change in Disease Status Per Sequential Pair for All Progression Events

Change in CA15-3 Concentration	Progression	No Progression	Total
Suspect ≥21%	22	61	**83**
No <21%	23	460	**483**
Total	**45**	**521**	**566**

Lower prevalence of progression events was observed during the course of this study in all different stages of disease, demonstrating similar test performance throughout the testing. This can be primarily explained by significant improvement in breast cancer treatment.
Based on this information, an interpretation of results section will be added to the labeling according to the table below.

Change in CA15-3 Value and Associated Interpretation

Change in CA15-3 Concentration	Interpretation
<21%	Likelihood of progression is approximately 4%
≥21%	Likelihood of progression is approximately 25%

Based on the results observed in this study, the likelihood of having progression when a positive result is present (change in CA15-3 value ≥21%) is approximately 25%, while the likelihood of progression when a change in CA15-3 value <21% is approximately 4%. However, the likelihood of having progression when a positive result is present (a change in CA15-3 value ≥21%) is only 25%, indicating that 75% of women with CA15-3 value change ≥21% do not have progression.

4. Clinical cut-off**:**

   See Expected Values below.

5. Expected values/Reference range:

   Serum specimens obtained from apparently healthy males and females were tested using Lumipulse ***G*** CA15-3 per CLSI EP28-A3c.

The observed ranges are as follows:

	Apparently Healthy Males and Females (Combined)	Apparently Healthy Males	Apparently Healthy Females
N	356	120	236
Mean (SD)	16.3 (6.8)	16.2 (6.1)	16.4 (7.1)
Median	15.1	15.3	15.1
Range (min, max)	4.3, 41.4	4.3, 40.0	5.6, 41.4
Reference Interval (2.5^{th} Percentile, 97.5^{th} Percentile)	6.5, 32.5	6.2, 30.3	6.5, 33.9
N (%) with CA 15-3 ≤ 15.0	49.7%	50.0%	49.6%
N (%) with CA 15-3 ≤ 30.0	95.8%	96.7%	95.3%
N (%) with CA 15-3 ≤ 35.0	99.2%	99.2%	99.2%

All Lumipulse ***G*** CA15-3 concentrations are presented in U/mL.

In addition to the normal cohort, serum specimens obtained from subjects with benign conditions and subjects with malignant diseases were tested using Lumipulse ***G*** CA15-3 per Clinical and Laboratory Standards Institute (CLSI) EP28-A3c. All Lumipulse ***G*** CA15-3 concentrations are presented in U/mL.

The observed ranges are as follows:

Reference Intervals per Group (Apparently Healthy and Benign Subjects)

	Apparently Healthy and Benign (All)	Apparently Healthy Males and Females (Combined)	Apparently Healthy Females			Apparently Healthy Males	Benign Breast	Benign Ovarian	Urogenital	Pregnant	Hypertension
			All	Pre-menopausal	Post-menopausal						
N	591	356	236	90	119	120	75	40	40	40	40
Mean (SD)	17.0 (7.4)	16.3 (6.8)	16.4 (7.1)	14.6 (6.8)	16.9 (6.5)	16.2 (6.1)	18.4 (8.7)	16.1 (7.6)	20.1 (9.1)	16.0 (6.4)	18.6 (7.4)
Median	15.7	15.1	15.1	13.3	15.9	15.3	18.2	14.8	18.3	15.3	17.0
Range (min, max)	4.3 , 55.2	4.3, 41.4	5.6, 41.4	5.6, 34.2	6.4, 34.2	4.3, 40.0	6.1, 55.2	6.0, 33.1	8.0, 39.5	6.3,28.9	7.4, 38.9
Reference Interval (2.5th Percentile, 97.5th Percentile)	6.6, 34.2	6.5, 32.5	6.5, 33.9	60, 33.5	7.2, 31.0	6.2, 30.3	6.6, 44.5	6.0, 33.1	8.0, 39.5	6.3, 28.9	7.4, 38.7
N (%) with CA15-3 ≤ 15.0	46.9%	49.7%	49.6%	63.3%	42.0%	50.0%	37.3%	52.5%	42.5%	50.0%	35.0%
N (%) with CA15-3 ≤ 30.0	94.8%	95.8%	95.3%	95.6%	97.5%	96.7%	93.3%	92.5%	87.5%	100.0%	92.5%
N (%) with CA15-3 ≤ 35.0	98.3%	99.2%	99.2%	100.0%	100.0%	99.2%	97.3%	100.0%	90.0%	100.0%	97.5%

All Lumipulse ***G*** CA15-3 concentrations are presented in U/mL

Reference Intervals per Group (Subjects with Cancer)

	Cancers (All)	Treatment Naïve Breast (All Stages)	Uterine/ Endometrial	Ovarian	Lung	Colorectal	Pancreatic	Liver
N	368	130	40	40	40	38	40	40
Mean (SD)	31.1 (52.4)	24.4 (31.0)	28.0 (32.9)	59.0 (123.9)	44.6 (55.1)	22.5 (30.6)	28.0 (20.0)	25.3 (25.2)
Median	20.1	19.7	16.1	25.8	26.2	16.6	22.9	18.1
Range (min, max)	3.8, 749.0	3.8, 350.2	5.6, 190.0	6.0, 749.0	8.7, 283.1	4.5, 200.2	9.2, 124.7	8.3, 143.0
Reference Interval (2.5th Percentile, 97.5th Percentile)	7.0, 136.7	6.9, 58.3	5.6, 187.6	6.0, 738.4	8.7, 280.0	6.5, 47.9	9.3, 123.4	8.3, 141.9
N (%) with CA15-3 ≤ 15.0	28.8%	29.2%	47.5%	15.0%	17.5%	42.1%	10.0%	40.0%
N (%) with CA15-3 ≤ 30.0	75.5%	80.0%	75.0%	60.0%	57.5%	89.5%	75.0%	82.5%
N (%) with CA15-3 ≤ 35.0	81.0%	86.2%	80.0%	65.0%	70.0%	94.7%	77.5%	82.5%

All Lumipulse ***G*** CA15-3 concentrations are presented in U/mL

It is recommended that each laboratory establishes its own range, which may be unique to the population it serves depending upon geographical, patient, and environmental factors.

N. Proposed Labeling

The labeling satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion

The results of these analytical (nonclinical) and clinical studies demonstrate that the Lumipulse ***G*** CA15-3 assay is substantially equivalent to the performance of the ARCHITECT CA 15-3 assay.