# 510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
# DECISION SUMMARY
ASSAY ONLY

## I Background Information:

### A 510(k) Number

K253528

### B Applicant

Siemens Healthcare Diagnostics, Inc.

### C Proprietary and Established Names

Atellica IM CA 19-9 II

### D Regulatory Information

| Product Code(s) | Classification | Regulation Section | Panel |
|---|---|---|---|
| NIG | Class II | 866.6010 Tumor-Associated Antigen Immunological Test System | IM - Immunology |

## II Submission/Device Overview:

### A Purpose for Submission:

- Migration of the cleared assay on the previously cleared instrument, Atellica IM Analyzer;
- Addition of plasma matrix

### B Measurand:

Carbohydrate Antigen (CA 19-9)

### C Type of Test:

Quantitative, Chemiluminescent Immunoassay

## III Intended Use/Indications for Use:

### A Intended Use(s):

See Indications for Use below.

### B Indication(s) for Use:

The Atellica IM CA 19-9 II (CA 19-9 II) assay is an in vitro diagnostic immunoassay for the quantitative measurement of the CA 19-9 tumor-associated antigen in human serum and plasma (EDTA and lithium heparin) using the Atellica IM Analyzer. This assay is indicated for the serial measurement of CA 19-9 to aid in the management of patients diagnosed with cancers of the exocrine pancreas. The test is useful as an aid in monitoring of disease status in those patients having confirmed pancreatic cancer who have levels of serum or plasma CA 19-9 at some point in their disease process exceeding the upper limit of normal determined for the apparently healthy cohort. CA 19-9 values must be interpreted in conjunction with all other clinical and laboratory data before a medical decision is determined.

### C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The Instruction for Use (Package Insert) of the device contains the following warning statement:

"The concentration of CA 19-9 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 19-9 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 19-9 is changed, the laboratory must perform additional serial testing to confirm baseline values. The Atellica IM CA 19-9 II assay is based on the 1116-NS-19-9 antibody available through agreement with Fujirebio Diagnostics, Inc. Assays using antibodies other than 1116-NS-19-9 may give different results.

Patients must possess the ability to express the Lewis blood group antigen, or they will be unable to produce the CA 19-9 antigen even in the presence of proven malignancy. A patient with a positive genotype for the Lewis antigen may produce varying levels of CA 19-9. Phenotyping for the presence of the Lewis blood group antigen may be insufficient to detect true Lewis antigen negative individuals."

### D Special Instrument Requirements:

Atellica IM Analyzer (cleared under K151792)

## IV Device/System Characteristics:

### A Device Description:

The following materials are included in the Atellica IM CA 19-9 II:

- Atellica IM CA 19-9 II ReadyPack:

  Solid Phase (19.7 mL/pack): Mouse monoclonal anti-CA 19-9 (~ 0.02 µg/mL) bound to paramagnetic particles; protein stabilizers and preservatives

  Lite Reagent (5.8 mL/pack): Mouse monoclonal anti-CA 19-9 (~ 0.4 µg/mL) labeled with acridinium ester; protein stabilizers and preservatives

- Atellica IM CA 19-9 II CAL (2.0 mL/vial): After reconstitution, various levels of CA 19-9 (human), bovine serum albumin and preservatives

The following materials are needed but not supplied:

- Atellica IM Multi-Diluent 10 (5.0 mL/pack): Tris buffer, bovine serum albumin; goat serum, mouse serum and preservatives
- Atellica IM APW3 ReadyPack (25.0 mL/pack): Phosphate-buffered saline, preservatives and surfactant
- Atellica IM CA 19-9 II MCM (Master Curve Material)

### B Principle of Operation:

This assay is an automated sandwich immunoassay using acridinium ester chemiluminescent technology. The antibody on the surface of the solid phase binds to CA 19-9 from the patient sample. Bound antigen remains in the reaction vessel following magnetic separation and washing. Antibody on the lite reagent binds to a second CA 19-9 moiety to form a sandwich, which goes through a second magnetic separation and washing. Retained acridinium ester gives off light when activated by the addition of acid and base solutions. Increase in light emittance is a direct function of the amount of CA 19-9 antigen in the sample when measured against a calibration curve.

## V Substantial Equivalence Information:

### A Predicate Device Name(s):

ADVIA Centaur CA 19-9 Assay

**B Predicate 510(k) Number(s):**

K031393

**C Comparison with Predicate(s):**

| Device & Predicate | K251440 (Candidate) | K031393 (Predicate) |
|---|---|---|
| Device Trade | Atellica IM CA 19-9 II | ADVIA Centaur CA 19-9 assay |
| **General Device Characteristic Similarities** | | |
| Intended Use/ Indications For Use | The Atellica IM CA 19-9 II (CA 19-9 II) assay is an in vitro diagnostic immunoassay for the quantitative measurement of the CA 19-9 tumor-associated antigen in human serum and plasma (EDTA and lithium heparin) using the Atellica IM Analyzer. This assay is indicated for the serial measurement of CA 19-9 to aid in the management of patients diagnosed with cancers of the exocrine pancreas. The test is useful as an aid in monitoring of disease status in those patients having confirmed pancreatic cancer who have levels of serum or plasma CA 19-9 at some point in their disease process exceeding the upper limit of normal determined for the apparently healthy cohort. CA 19-9 values must be interpreted in conjunction with all other clinical and laboratory data before a medical decision is determined. | The ADVIA Centaur CA 19-9 Assay is an in vitro immunoassay for the quantitative measurement of the CA 19-9 tumor-associated antigen, in human serum, using the ADVIA Centaur System. This assay is indicated for the serial measurement of CA 19-9 to aid in the management of patients diagnosed with cancers of the exocrine pancreas. The test is useful as an aid in monitoring of disease status in those patients having confirmed pancreatic cancer who have levels of serum CA 19-9 at some point in their disease process exceeding the median concentration determined for the apparently healthy cohort. CA 19-9 values must be interpreted in conjunction with all other clinical and laboratory data before a medical decision is determined. This assay is not intended for use on any other system. |
| Technology | Chemiluminescent | Same |
| Sample Handling | Automated | Same |
| Operating | Automated Sandwich immunoassay | Same |
| Analyte | Carbohydrate Antigen (CA 19-9) | Same |
| Measurement | Quantitative | Same |
| Capture Antibody | Monoclonal mouse anti-CA 19-9 antibody covalently coupled to paramagnetic particles | Same |
| Detection Antibody | Monoclonal mouse anti-CA 19-9 antibody labeled with acridinium | Same |
| Sample volume | 75 µL | Same |

| Device & Predicate | K251440 (Candidate) | K031393 (Predicate) |
|---|---|---|
| Calibrators | Two Levels | Same |
| Units of Measure | U/mL | Same |
| **General Device Characteristic Differences** | | |
| Instrument | Atellica IM Analyzer | ADVIA Centaur System |
| Sample Matrix | Serum and Plasma (EDTA and Lithium heparin) | Serum |
| Measuring | 2.0 – 700.0 U/mL | 1.20 – 700.00 U/mL |
| Detection Limits | LoB: 1.20 U/mL<br>LoD: 1.50 U/mL<br>LoQ: 2.00 U/mL | Analytical Sensitivity: 1.20 U/mL |

## VI Standards/Guidance Documents Referenced:

The following Clinical and Laboratory Standards Institute (CLSI) guidelines and International Organization for Standardization (ISO) were used:

- CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition
- CLSI EP06 2nd Edition, Evaluation of Linearity of Quantitative, Measurement Procedures
- CLSI EP07 3rd Edition, Interference Testing in Clinical Chemistry
- CLSI EP09c 3rd Edition, Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition
- CLSI EP25 2nd Edition, Evaluation of Stability of In Vitro Medical Laboratory Test Reagents
- CLSI EP28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition
- CLSI EP34 1st Edition, Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking
- CLSI EP37 1st Edition, Supplemental Tables for Interference Testing in Clinical Chemistry
- ISO 17511:2020, In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples

## VII Performance Characteristics (if/when applicable):

### A Analytical Performance:

1. Precision/Reproducibility:

The studies were performed in accordance with CLSI guideline EP05-A3.

*Within Laboratory precision:*

The study was performed at a single site using one lot of the Atellica IM CA 19-9 II reagent on one Atellica IM Analyzer. Five levels of human serum samples were run in two replicates per run, two runs daily over the course of 20 days, resulting in a total of 80 datapoints for each sample. The data were analyzed for repeatability (within-run), between-run, between-day, and within-laboratory precision. The mean (U/mL), standard deviation (SD) (U/mL) and percent coefficient of variation (%CV) are summarized in table below.

| Sample | N | Mean (U/mL) | Within-Run (Repeatability) | | Between-Run | | Between-Day | | Within-Laboratory | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| 1 | 80 | 10.0 | 0.15 | 1.5 | 0.62 | 6.2 | 0.52 | 5.2 | 0.82 | 8.2 |
| 2 | 80 | 37.1 | 0.77 | 2.1 | 0.88 | 2.4 | 0.59 | 1.6 | 1.31 | 3.5 |
| 3 | 80 | 121.1 | 2.88 | 2.4 | 1.39 | 1.1 | 2.85 | 2.4 | 4.28 | 3.5 |
| 4 | 80 | 298.1 | 9.67 | 3.2 | 2.35 | 0.8 | 8.13 | 2.7 | 12.85 | 4.3 |
| 5 | 80 | 529.0 | 16.47 | 3.1 | 10.29 | 1.9 | 14.67 | 2.8 | 24.34 | 4.6 |

*Instrument-to-Instrument Reproducibility:*

The study was performed using three Atellica IM Analyzers with a single lot of the Atellica IM CA 19-9 II reagent. Five levels of human serum samples were run in five replicates per run, one run per day over the course of a minimum five days, resulting in a total of 75 datapoints for each sample. The data was analyzed for repeatability (within-run), between-day, between-instrument, and reproducibility. The mean (U/mL), standard deviation (SD) (U/mL) and percent coefficient of variation (%CV) are summarized in the table below:

| Sample | N | Mean (U/mL) | Within-Run (Repeatability) | | Between-Day | | Between-Instrument | | Reproducibility | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| 1 | 75 | 10.4 | 0.17 | 1.6 | 0.21 | 2.0 | 1.24 | 11.9 | 1.27 | 12.2 |
| 2 | 75 | 35.4 | 0.84 | 2.4 | 0.39 | 1.1 | 1.08 | 3.1 | 1.42 | 4.0 |
| 3 | 75 | 116.7 | 2.75 | 2.4 | 2.69 | 2.3 | 0.00 | 0.0 | 3.85 | 3.3 |
| 4 | 75 | 281.5 | 6.36 | 2.3 | 5.32 | 1.9 | 5.49 | 2.0 | 9.94 | 3.5 |
| 5 | 75 | 497.7 | 13.53 | 2.7 | 13.56 | 2.7 | 3.46 | 0.7 | 19.46 | 3.9 |

2. Linearity:

*Linearity:*

The linearity of the Atellica IM CA 19-9 II assay was performed in accordance with CLSI guideline EP06 2nd Edition. A thirteen level dilution series was prepared by mixing the high serum samples and low levels serum samples in known ratios. The dilution levels were run in replicates of six on one Atellica IM Analyzer using one Atellica IM CA 19-9 II reagent lot. The 'measured value' (mean CA 19-9 II U/mL) was compared to its predicted value for deviation percentage using a linear regression analysis. This deviation was then compared to the allowable deviation from linearity (ADL). The results are summarized in the table below.

| Range* | Slope (95% CI) | Intercept* (95% CI) | $R^2$ |
|---|---|---|---|
| 1.2 – 732.0 | 0.98 (0.94 to 1.02) | -0.2 (-0.4 to 0.0) | 0.999 |

*U/mL

The study results support the linearity of the claimed analytical measuring interval (AMI): 2.0 to 700.0 U/mL.

*Auto Dilution Recovery*

Dilutional recovery testing of the Atellica IM CA 19-9 II assay was performed in accordance with CLSI guideline EP34 1st Edition. Auto dilution recovery studies were conducted using a minimum of five human serum samples with different CA 19-9 II concentrations. The samples above the analytical measuring interval (AMI) were diluted onboard the instrument with Atellica IM Multi-Diluent 10 using the 'Instructions for Use' specified dilution factors of 10, 100, and 200. The samples were measured in four replicates per sample per instrument, using one Atellica IM CA 19-9 II reagent lot, one calibration, one test day, two Atellica IM analyzers. The mean recoveries were between 94% and 106%.

*Hook effect*

Hook effect of the Atellica IM CA 19-9 II assay was determined by using high human serum patient sample. Seven dilutions at 1:2, 1:625, 1:1,250, 1:2,500, 1:5,000, 1:10,000, and 1:20,000 were prepared by diluting a high sample (3,845,000 U/mL CA 19-9) with Atellica IM Multi-Diluent 10. The study was completed by testing each sample level in three replicates, using one Atellica IM CA 19-9 II reagent lot, one Atellica IM Analyzer. No hook effect was observed with the Atellica IM CA 19-9 II assay in samples with concentrations as high as 3,845,000 U/mL.

3. Analytical Specificity/Interference:

Interference study was performed according to CLSI guidelines EP07 (3rd Edition) and EP37 (1st Edition) to determine the effect of various endogenous and exogenous substances on the Atellica IM CA 19-9 II assay. Two human serum pool levels with a target concentration of approximately 8.1–12.0 U/mL and 40.8–60.0 U/mL were processed by paired-difference testing; samples with and without the interferent were measured, and the measurand concentration difference was determined. Test and control samples were each processed in

five replicates, using one Atellica IM CA 19-9 II reagent lot on a single Atellica IM Analyze. The percent bias was determined by comparing the result of sample with interferent or cross-reactant to a control sample without the interferent or cross-reactant. The percent difference was calculated [100* (test mean – control mean) / control mean] and an interference or cross-reactivity within ≤ 10% bias between the mean spiked sample value and the mean control value was considered non-significant.

*Endogenous Substance Interference:*

The following endogenous substances were tested using Atellica IM CA 19-9 II assay. No significant interference was found for each substance at the concentrations listed below.

| Endogenous Substance | Concentration |
|---|---|
| Albumin | 6 g/dL |
| Bilirubin (conjugated) | 40 mg/dL |
| Bilirubin (unconjugated) | 40 mg/dL |
| Triglycerides | 1,500 mg/dL |
| Hemoglobin | 1,000 mg/dL |
| Human IgG | 40 mg/mL |

The interference of heterophile, including human anti-mouse antibodies (HAMA) and rheumatoid factor (RF) on the Atellica IM CA 19-9 II assay was assessed. High patient samples containing the interferent (serum containing 1000 µg/L HAMA, plasma containing 1000 IU/mL RF) were spiked with the purified CA 19-9 analyte (made from native serum). A control sample was also spiked to the target concentration with the purified CA 19-9 analyte. No significant interference was found for HAMA at 1,000 µg/L and for RF at 1,000 IU/mL.

*Exogenous Substance Interference*

The potential interference of 39 commonly used drugs (including those used for cancer treatment) and dietary supplements, was evaluated using Atellica IM CA 19-9 II assay. No significant interference was found for each substance at the concentrations listed below.

| Exogenous Substance | Concentration | Exogenous Substance | Concentration |
|---|---|---|---|
| Acetaminophen | 15.6 mg/dL | Heparin | 330 U/dL |
| Acetylsalicylic acid | 3 mg/dL | Ibuprofen | 21.9 mg/dL |
| Amikacin | 14.4 mg/dL | Intralipid | 2,000 mg/dL |
| Biotin | 3,500 ng/mL | Irinotecan hydrochloride | 12.9 mg/mL |
| Caffeine | 108 mg/L | Leucovorin | 114 mg/L |
| Capecitabine | 22.5 mg/L | Levamisole | 40.5 mg/mL |
| Cisplatin | 225 mg/L | Lithium carbonate | 0.035 mg/mL |
| Cortisol/hydrocortisone | 100 mg/L | Mitomycin | 25 mg/L |
| Coumarin | 140 mg/L | Mitoxantrone | 100 mg/L |
| Cyclophosphamide | 1000 mg/L | Nab-paclitaxel | 2.16 mg/L |
| Cyclosporine | 0.18 mg/dL | Olaparib | 10.8 mg/L |
| Digoxin | 0.039 mg/L | Oxaliplatin | 250 mg/L |
| Doxorubicin | 75 mg/L | Phenytoin | 6 mg/dL |

| Exogenous Substance | Concentration | Exogenous Substance | Concentration |
|---|---|---|---|
| EDTA | 0.099 mg/dL | Propranolol | 0.101 mg/dL |
| Erlotinib hydrochloride | 17.6 mg/L | Salicylate | 2.86 mg/dL |
| Etoposide | 400 mg/L | Silwet L720 | 30 mg/L |
| Everolimus | 0.183 mg/L | Streptozotocin | 39.6 mg/L |
| 5-Fluorouracil | 90 mg/L | Sunitinib malate | 0.303 mg/L |
| Gemcitabine | 383 mg/L | Theophylline | 6 mg/dL |
| Gentamicin | 3 mg/dL | | |

*Cross-Reactivity*

The potential cross-reactivity of the Atellica IM CA 19-9 II with the AFP, CA 125, CA 15-3, CA 27.29, CEA, and PSA was evaluated following the same protocol as described above. No significant interference was found for each substance at the concentrations listed below.

| Cross-Reactive Substance | Concentration |
|---|---|
| AFP | 300 ng/mL |
| CA 125 | 1000 U/mL |
| CA 15-3 | 500 U/mL |
| CA 27.29 | 230 U/mL |
| CEA | 1 µg/mL |
| PSA | 100 ng/mL |

4. Detection Capability:

CLSI guideline EP17-A2 was followed to determine the Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) for the Atellica IM CA 19-9 II assay.

The LoB was determined by testing four samples over five days, two runs per day, five replicates per run using three Atellica IM CA 19-9 II reagent lots on one Atellica IM Analyzer for a total of 50 replicates per low sample per reagent lot. The LoB for each reagent lot was calculated using the non-parametrically at the 95th percentile of all measurements of the blank samples, and the highest value was taken as the LoB value. The LoB for each of the three reagent lots was 1.2 U/mL, 0.0 U/mL and 0.0 U/mL. The claimed LoB for the Atellica IM CA 19-9 II is 1.2 U/mL.

The LoD was determined by testing five serum samples containing low levels of CA 19-9 over five days, two runs per day, five replicates per run using three Atellica IM CA 19-9 II reagent lots on one Atellica IM Analyzer for a total of 50 replicates per low sample per reagent lot. The LoD was analyzed by using a precision profile approach for each reagent lot and the highest value was taken as the LoD value. The claimed LoD for the Atellica IM CA 19-9 II is 1.5 U/mL.

The LoQ was determined by testing five serum samples containing low levels of CA 19-9 over five days, two runs per day, five replicates per run using three Atellica IM CA 19-9 II reagent lots on one Atellica IM Analyzer for a total of 50 replicates per low sample per

reagent lot. For each reagent lot, within laboratory precision over five days, expressed as %CV, was plotted against the mean measurand concentration for each sample. The datasets were fitted as appropriate with power regressions. The LoQ was defined as the level at which the %CV if the within-laboratory imprecision ≤ 20%. The claimed LoQ for the Atellica IM CA 19-9 II is 2.0 U/mL.

5. Assay Reportable Range

The analytical measuring interval (AMI) for the Atellica IM CA 19-9 II assay is 2.0 U/mL – 700.0 U/mL.

Per instruction for use, the samples at > 700.0 U/mL have automatic dilution at 1:10, 1:00 and 1:200 fold. When the samples are diluted (1:200), the claimed reportable range of the Atellica IM CA 19-9 II is 2.0 U/mL – 140,000 U/mL.

6. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

*Traceability*

There is no internationally recognized reference method or material for CA 19-9. Calibration of the CA 19-9 is traceable to in-house reference calibrators, whose CA 19-9 values have been assigned in accordance with ISO 17511:2020.

*Kit Stability*

The stability of the Atellica IM CA 19-9 II assay reagent kit was determined according to CLSI guideline EP25 2nd Edition.

a) Reagent kit stability (shelf-life):

The shelf-life of the Atellica IM CA 19-9 II stored at 2–8°C was established by testing four serum samples (at 18.4, 28.8, 326.2 and 508.8 U/mL) in five replicates per sample using three Atellica IM CA 19-9 II assay reagent kit lots on one Atellica IM Analyzer at seven timepoints. The testing was done at intervals for a minimum of 45 weeks. Each individual sample was plotted in a linear regression of the mean observed analyte values (Y-axis) versus time (X-axis). The current data support the stability of the Atellica IM CA 19-9 II kit for 10 months at 2–8°C.

b) Onboard stability

The onboard stability of the Atellica IM CA 19-9 II reagent was established by testing four serum samples (at about 20, 30, 310 and 490 U/mL) using packs which were first pierced on-board the analyzer and remained on-board of the Atellica IM analyzer for at least 28 days. At each timepoint (days 0, 7, 14, 21, 23, 28), samples were tested with both pierced (in-use) and fresh packs in three replicates per sample. Each individual sample was plotted in a linear regression of the mean observed analyte

values (Y-axis) versus time (X-axis). The results support on-board stability of the Atellica IM CA 19-9 II reagents for 23 days.

7. Assay Cut-Off:

   Not applicable

## B Comparison Studies:

1. Method Comparison with Predicate Device:

   Refer to Section C. Clinical Studies

2. Matrix Comparison:

   CLSI guideline EP09c 3rd Edition was followed to demonstrate that serum, Heparin plasma and K2-EDTA plasma serum, K2 EDTA plasma, K3 EDTA plasma, and lithium heparin plasma matrices yield comparable values as serum with the Atellica IM CA 19-9 II assay. The study included 62 matched single samples with CA 19-9 concentration covering the analytical measuring interval of the assay. Samples were tested in singlicate over five days, using one Atellica IM CA 19-9 II reagent lot on one Atellica IM Analyzer. Weighted-Deming regression analyses were performed by comparing the results of samples from different plasma samples (y) to the results of corresponding serum samples (x). The results are summarized in the tables below.

| Specimen type vs Comparison | N | Sample Range (U/mL) | Slope | Intercept (U/mL) | r |
|---|---|---|---|---|---|
| Serum vs K2 EDTA Plasma | 62 | 4.0 – 674.7 | 1.03 (1.00 to 1.06) | 0.4 (0.0 to 0.8) | 0.995 |
| Serum vs K3 EDTA Plasma | 62 | 4.0 – 674.7 | 0.99 (0.96 to 1.02) | 0.4 (0.1 to 0.7) | 0.991 |
| Serum vs Lithium Heparin | 62 | 4.0 – 674.7 | 1.04 (1.00 to 1.08) | 0.2 (-0.2 to 0.7) | 0.992 |

## C Clinical Studies:

The clinical performance of the Atellica IM CA 19-9 II assay was determined on the Atellica IM Analyzer by assessing changes in CA 19-9 levels in serial serum samples from patients with exocrine pancreatic cancer and comparing the results to changes in the disease status. The patients were females and males with a confirmed diagnosis of exocrine pancreatic cancers at any stage (Stage IA to O). The sample cohort included 435 samples drawn serially from approximately 79 enrolled participants meeting the eligibility criteria outlined below.

Inclusion criteria:

- Female or Male
- 22 years of age or older

- Diagnosed with exocrine pancreatic cancer
- Appropriate informed consent or remnant sample documentation

Exclusion criteria:
- Less than 22 years old
- No diagnosis of exocrine pancreatic cancer
- Invalid informed consent or remnant sample documentation

Of the 79 enrolled subjects (435 samples), five subjects were excluded for reason of single visit, and 17 samples were excluded for insufficient sample volume and for below AMI results. Of the 71 participants (413 samples including 342 follow-up samples) included in the Atellica CA 19-9 II clinical performance evaluation, participant age ranged from 47 to 87 years with a mean (SD) of 65.3 (10.3) and median of 65 years. The clinical data collected for each subject included the following: subject ID, age, gender, race/ethnicity, date of cancer diagnosis, histology, grade, and stage. The demographic and clinical characteristics of the evaluated 71 subjects is provided below.

| Variable | Class | N=71 | |
|---|---|---|---|
| | | # | % |
| Gender | Female | 34 | 47.9% |
| | Male | 37 | 52.1% |
| Ethnicity | Hispanic | 6 | 8.5% |
| | Non-Hispanic | 65 | 91.5% |
| Race | White | 66 | 93.0% |
| | Black/African American | 3 | 4.2% |
| | Asian/Pacific Islander | 1 | 1.4% |
| | Other | 1 | 1.4% |
| Tobacco Use | Current | 9 | 12.7% |
| | Never | 27 | 38.0% |
| | Previous | 35 | 49.3% |
| Tumor Grade | G1 | 4 | 5.6% |
| | G2 | 20 | 28.2% |
| | G3 | 11 | 15.5% |
| | GX | 36 | 50.7% |
| Tumor Stage | Stage IA | 1 | 1.4% |
| | Stage IB | 5 | 7.0% |
| | Stage IIA | 1 | 1.4% |
| | Stage IIB | 23 | 32.4% |
| | Stage III | 6 | 8.5% |
| | Stage IV | 24 | 33.8% |
| | Stage O | 1 | 1.4% |
| | Unknown | 10 | 14.1% |

Each participant's clinical disease status was categorized as NED (no evidence of disease), SD (stable disease), RD (responding disease), PD (progressive disease) or RC (recurrent cancer), based on changes in clinical evidence at the follow-up visit compared to the previous visit; clinical evidence included, but was not limited to, imaging across various modalities,

physical examination findings, physician transcription notes, and other relevant laboratory data. Table below summarizes the distribution of CA 19-9 change by clinical status.

| Clinical Disease Status | n | Minimum | 1st Quartile | Median | 3rd Quartile | Maximum |
|---|---|---|---|---|---|---|
| NED | 29 | 0.35 | 0.84 | 0.92 | 1.49 | 3.42 |
| SD | 235 | 0.04 | 0.74 | 1.06 | 1.55 | 116.79 |
| RD | 15 | 0.23 | 0.50 | 0.71 | 0.78 | 2.33 |
| PD/RC | 63 | 0.25 | 1.03 | 1.48 | 2.91 | 32.30 |
| Total | 342 | | | | | |

For purposes of the analysis, Progression included all monitoring visits where a patient's clinical disease status was categorized as Progressive Disease. No Progression included all monitoring visits where a patient's clinical disease status was categorized as No Evidence of Disease, Stable Disease, or Responding Disease. Based on quantitative CA 19-9 measurements obtained using the Atellica IM CA 19-9 II assay, a positive change was defined as an increase greater than 15% at the follow-up visit relative to the previous visit. The estimates of sensitivity, specificity, PPV (positive predictive value), and NPV (negative predictive value) along with 95% confidence intervals were calculated. The results are summarized in the following tables.

| Change in CA 19-9 Concentration | Change in Disease Status | | Total |
|---|---|---|---|
| | Progression | No Progression | |
| > 15% | 43 | 111 | 154 |
| ≤ 15% | 20 | 168 | 188 |
| Total | 63 | 279 | 342* |

*Excluding 71 baseline visits.

| Performance Measurement | Performance Measure % (n/N) (95% CI) |
|---|---|
| Sensitivity | 68.3% (43/63) (59.5%–78.4%) |
| Specificity | 60.2% (168/279) (54.7%–65.2%) |
| PPV | 27.9% (43/154) (21.7%–34.4%) |
| NPV | 89.4% (168/188) (85.6%–93.4%) |

Other Clinical Supportive Data:

The clinical performance of Atellica IM CA 19-9 II assay on Atellica IM Analyzer was evaluated against the predicate device (K031393), the ADVIA Centaur CA 19-9 assay on the ADVIA Centaur XPT analyzer using the subset of 321 observations with reportable results. The clinical performance was evaluated for both devices and shown below.

| N=321 | ADVIA Centaur CA 19-9 | Atellica IM CA 19-9 II |
|---|---|---|
| Sensitivity | 66.7% (40/60) (57.1–77.4%) | 68.4% (41/60) (60.0–77.5%) |
| Specificity | 60.9% (159/261) (55.8–65.7%) | 61.2% (160/261) (55.7–66.4%) |
| PPV | 28.2% (40/142) (22.6–33.7%) | 28.9% (41/142) (22.8–35.0%) |
| NPV | 88.8% (159/179) (84.6–93.1%) | 89.4% (160/179) (85.7–93.2%) |

Based upon a performance in assessing longitudinal changes in CA 19-9 concentrations relative to clinically determined disease status comparable performance between the candidate device, the Atellica IM CA 19-9 II, and the predicate device, ADVIA Centaur CA 19-9.

### D Expected Values/Reference Range:

The Upper Limit of Normal (ULN) for the apparently healthy subjects was previously established as 35 U/mL using the ADVIA Centaur system.

The reference range of the Atellica IM CA 19-9 II assay was verified in accordance with CLSI guidelines EP28-A3c. Serum samples from a total of 40 apparently healthy individuals including 20 males and 20 females were assayed in replicates of five using one reagent lot on one test day on one Atellica IM analyzer. The results show that 95.0% of samples [38/40 (19/20 males, 19/20 females)] recovered within the range for the normal patient population.

## VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

## IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.