510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K233242

B Applicant

Siemens HealthCare Diagnostics Inc.

C Proprietary and Established Names

Atellica® CH High Sensitivity C-Reactive Protein 2 (hCRP2)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
NQD	Class II	21 CFR 866.5270 - C-Reactive Protein Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

C-Reactive Protein (high sensitivity)

C Type of Test:

Quantitative Immunonephelometry

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Atellica® CH High Sensitivity C-Reactive Protein 2 (hCRP2) assay is for in vitro diagnostic use in the quantitative determination of the concentration of C-Reactive Protein (CRP) in human serum and plasma (lithium heparin, sodium heparin or K2 EDTA) on the Atellica® CH Analyzer.

Measurements from Atellica® High Sensitivity C-Reactive Protein 2 (hCRP2) may be used as an aid in identification of individuals at risk for future cardiovascular disease. Measurement of hCRP2, when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, may be useful as an independent marker of prognosis for recurrent events in patients with stable coronary disease or acute coronary syndromes.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Atellica® CH Analyzer, K151767

IV Device/System Characteristics:

A Device Description:

The Atellica® CH High Sensitivity C-Reactive Protein 2 (hCRP2) assay includes two ready-to-use reagent packs consisting of 23.1mL Phosphate buffer, polidocanol (1.9g/L), and sodium azide (0.1%) in Pack 1 and 12.3mL Mouse anti-CRP monoclonal antibodies (13mg/L), polystyrene particles (1g/L), human albumin (0.05%) and sodium azide (<0.1%) in Pack 2. This product consists of two (2) kits consisting of 360 tests each for a total of 720 tests.

Kit Contents:

- Pack1 (P1)
  Well 1 (W1) 23.1 mL of Reagent 1
  Well 2 (W2) 23.1 mL of Reagent 1
- Pack 2 (P2)
  Well 1 (W1) 12.3 mL of Reagent 2
  Well 2 (W2) 12.3 mL of Reagent 2

Materials required but not provided:

- Atellica CH Analyzer
- Atellica CH PROT2 CAL
- Commercially available quality control materials

- Additional system fluids are required to operate the system: Atellica CH Diluent, Atellica CH Wash, Atellica CH Conditioner, Atellica CH Cleaner, Atellica CH Reagent Probe Cleaner 1, Atellica CH Reagent Probe Cleaner 2, Atellica CH Reagent Probe Cleaner 4, Atellica CH Lamp Coolant, and Atellica CH Water Bath Additive.

B Principle of Operation:

Polystyrene particles coated with monoclonal antibodies specific to human CRP are aggregated when mixed with samples containing CRP. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the respective protein in the sample. The result is evaluated by comparison with a standard of known concentration.

V Substantial Equivalence Information:

A Predicate Device Name(s):
CardioPhase® hsCRP

B Predicate 510(k) Number(s):
K212559

C Comparison with Predicate(s):

Device & Predicate Device(s):	K233242	K212559
Device Trade Name	Atellica® CH High Sensitivity C-Reactive Protein 2 (hCRP2)	CardioPhase® hsCRP
General Device Characteristic Similarities		
Intended Use/Indications For Use	For quantitative determination of C-reactive protein (CRP) in human serum and plasma	Same
Assay Principle	Particle enhanced immunonephelometry	Same
Traceability/ Standardization	ERM-DA474/IFCC	Same
Calibration	Multi-Level calibration	Same
General Device Characteristic Differences		
Assay Range / Measuring Interval	0.16 mg/L - 9.50 mg/L	0.155 – 9.95 mg/L (calibrator lot dependent)
Calibrators	Atellica® CH Protein 2 Calibrator (PROT2	N Rheumatology Standard SL

	CAL)	
Reagent Formulation	Pack 1: 23.1 mL Phosphate buffer; polidocanol (1.9 g/L); sodium azide (0.1%) Pack 2: 12.3 mL Mouse anti-CRP monoclonal antibodies (13 mg/L); polystyrene particles (1 g/L); human albumin (0.05%); sodium azide (<0.1%)	Polystyrene particles coated with mouse monoclonal antibodies (< 0.016 g/L) to CRP and preservatives (Gentamicin 6.25 mg/L, Amphotericin 0.625 mg/L).
Sample stability	Room temperature: Up to 26 hours 2–8°C: Up to 188 hours Frozen at -20°C: 2 years	2–8°C: eight days Frozen ≤ -20°C: up to eight months if frozen within 24 hours after collection and if repeated freeze-thaw cycles are avoided

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition.

CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-2nd Edition.

CLSI EP06 -ED2:2020, Evaluation of Linearity of Quantitative Measurement Procedures, 2nd Edition.

CLSI EP07, Interference Testing in Clinical Chemistry, 3rd Edition.

CLSI EP37, Supplemental Tables for Interference Testing in Clinical Chemistry, 1st Edition.

Guidance for Industry and FDA Staff: Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays. Issued on September 22, 2005.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision studies were performed according to CLSI EP05-A3. Repeatability and within-lab precision were evaluated by testing five native serum samples and one quality control sample in duplicate twice per day for twenty days using three lots of the candidate device. Results from multiple lots were similar with results from one representative lot provided in the table below:

Sample	N	Mean mg/L	Repeatability		Within-Lab	
			SD mg/L	CV (%)	SD mg/L	CV (%)
QC1	80	0.81	0.017	2.1	0.020	2.5
Serum 1	80	1.06	0.015	1.4	0.017	1.6
Serum 2	80	2.55	0.021	0.8	0.048	1.9
Serum 3	80	2.90	0.015	0.5	0.023	0.8
Serum 4	80	4.12	0.030	0.7	0.084	2.0
Serum 5	80	8.74	0.065	0.7	0.110	1.3

Reproducibility was evaluated using three pooled serum samples and three quality control samples assayed with five replicates per run for five days using three instruments and three reagent lots. The data was analyzed to calculate the following components of precision: repeatability, between-day, between-lot, between-instrument, and reproducibility (total). The results are shown below.

Sample	N	Mean mg/L	Reproducibility									
			Repeatability		Between Day		Between Lot		Between Instrument		Total Reproducibility	
			SD mg/L	CV %	SD mg/L	CV %	SD mg/L	CV %	SD mg/L	CV %	SD mg/L	CV %
QC1	225	0.72	0.012	1.6	0.001	0.2	0.005	0.6	0.013	1.8	0.018	2.5
QC2	225	1.86	0.012	0.6	0.008	0.4	0.007	0.4	0.017	0.9	0.023	1.2
QC3	225	5.63	0.030	0.5	0.018	0.3	0.026	0.5	0.029	0.5	0.052	0.9
Serum 1	225	1.06	0.017	1.6	0.008	0.8	0.000	0.0	0.014	1.3	0.023	2.2
Serum 2	225	2.91	0.023	0.8	0.014	0.5	0.000	0.0	0.016	0.5	0.032	1.1
Serum 3	225	3.98	0.021	0.5	0.018	0.4	0.023	0.6	0.030	0.7	0.047	1.2
Serum 4	225	7.12	0.045	0.6	0.031	0.4	0.017	0.2	0.064	0.9	0.086	1.2
Serum 5	225	8.56	0.059	0.7	0.062	0.7	0.002	0.0	0.047	0.5	0.098	1.1

2. Linearity:

Linearity studies were performed according to CLSI EP06-A. A native high and low serum sample were used as the high and low samples. A dilution series composed of nine levels

distributed across the analytical measuring range was prepared by mixing the high and low samples. Measurements were made in replicates of five per level using three reagent lots. The linearity study results support that the assay is linear across the claimed reportable range from 0.16 to 9.50 mg/L.

3. Analytical Specificity/Interference:

Interference testing was performed in accordance with CLSI EP07-ED3. Testing of hemolysis, icterus, and lipemia was conducted comparing a sample spiked with interferent to a sample spiked with control material. Three replicates were tested. Percent interference was calculated. Interference is defined as a bias >10% when compared to the control sample. The results are summarized in the table below:

Substance	Highest concentration tested that did not show significant interference
Hemoglobin	1000 mg/dL
Conjugated Bilirubin	40 mg/dL
Unconjugated Bilirubin	40 mg/dL
Lipemia (from Intralipid®)	3000 mg/dL
Rheumatoid Factor	500 IU/mL

CRP (high sensitivity) prozone study:

A study was performed to verify the CRP prozone performance. Samples were created using saline-diluted spiking material and tested in singlicate using one reagent lot. Results support that levels as high as 1300.00 mg/L will report > 9.50 mg/L. The labeling states: "High C-reactive protein levels can cause a paradoxical decrease in signal as a result of the high-dose hook effect. In the Atellica® CH hCRP2 assay, C-reactive protein levels as high as 1300.00 mg/L will read > 9.50 mg/L."

4. Assay Reportable Range:

The assay's reportable range is 0.16 mg/L to 9.50 mg/L.

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

Traceability
The assay is traceable to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference material ERM-DA474/IFCC.

Sample stability
A study was conducted to verify sample stability with the candidate device. The results support the sponsor's sample stability claims that serum, sodium heparin plasma, lithium heparin plasma, and potassium EDTA plasma can be stored at Room Temperature (18-26 °C) for up to 26 hours, refrigerated (2-8 °C) for up to 188 hours and Frozen (-20 °C) for up to 2 years.

6. Detection Limit:

Detection capability was determined in accordance with CLSI EP17-A2.

The Limit of Blank (LoB) corresponds to the highest value expected in a series of results on a sample that contains no analyte. LoB was determined using six blank samples, 5 lots of Atellica CH diluent (saline) and 1 lot of 6% BSA, tested using three reagent lots on one instrument in replicates of five for three days, for 90 measurements per reagent lot and a total of 270 blank measurements.

The Limit of Detection (LoD) is the lowest concentration of c-reactive protein that can be detected with a probability of 95%. LoD was determined using five separate human serum samples, diluted with Atellica CH diluent targeted to 0.05 mg/L, tested using three reagent lots on one instrument in replicates of five for three days, for 75 measurements per reagent lot and a total of 225 low level measurements.

The Limit of Quantitation (LoQ) is the lowest concentration of c-reactive protein that met the required analyte level but did not reach 20% CV. LoQ was determined using five separate human serum samples, diluted with Atellica CH diluent targeted to approximately 0.16 mg/L, tested using three reagent lots on one instrument in replicates of five for five days.

Detection Limit Summary

Analyte	LoB	LoD	LoQ
Atellica® CH hCRP2	0.06 mg/L	0.11 mg/L	0.16 mg/L

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Method comparison studies were conducted based on CLSI EP09c. One-hundred native serum samples that ranged from 0.26 - 9.41 mg/L CRP were tested with the candidate device and the predicate device. A single replicate was tested and processed for each sample on both systems. The method comparison study was evaluated by weighted Deming regression analysis. The regression analysis is summarized below:

N	Slope	Intercept	r	Test Range (mg/L)	Claimed Measuring Range (mg/L)
100	0.96	0.03	0.999	0.26 – 9.41	0.16 - 9.50

2. Matrix Comparison:

A matrix comparison study was performed to demonstrate the equivalence between serum and plasma samples when measuring CRP using the candidate device. Matched native human serum and plasma (Sodium Heparin, K2 EDTA and Lithium Heparin) samples were tested in singlicate on the Atellica® CH Analyzer. Sixty samples were tested across the assay range. Five samples fell outside the measuring range (three below, two above) with fifty-five total samples remaining. The results were analyzed using Deming regression with the following results.

Specimen Type	N	Slope	Intercept	r	Test Range (mg/L)
Sodium Heparin	55	1.070	-0.020	0.998	0.22 - 7.40
K2 EDTA	55	0.970	-0.030	0.997	
Lithium Heparin	55	1.070	-0.030	0.998	

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

Group	Specimen Type	Reference Interval mg/L
Low risk for cardiovascular disease prediction	Serum/plasma	< 1.00
Average risk for cardiovascular disease prediction	Serum/plasma	1.00-3.00
High risk for cardiovascular disease prediction	Serum/plasma	> 3.00

Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003 Jan 28;107(3):499-511

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.