510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number
K192072

B Applicant
Roche Diagnostics Operations (RDO)

C Proprietary and Established Names
Tina-quant C-Reactive Protein IV

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DCN	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 (CRP)

C Type of Test:
Quantitative, immunoturbidimetric assay

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:

Tina-quant® C-Reactive Protein IV is an immunoturbidimetric assay for the in vitro quantitative determination of CRP in human serum and plasma on cobas c systems.

A C-reactive protein immunological test system is a device that consists of the reagents used to measure by immunochemical techniques the C-reactive protein in serum and plasma. Measurement of C-reactive protein aids in evaluation of the amount of injury to body tissues.

C Special Conditions for Use Statement(s):
Rx – For Prescription Use Only

D Special Instrument Requirements:
Cobas c 501 Analyzer

IV Device/System Characteristics:

A Device Description:
The Tina-quant C-Reactive Protein IV is a latex particle enhanced immunoturbidimetric assay consisting of two working reagents:

R1: TRIS buffer with bovine serum albumin (BSA) with preservatives
R2: Latex particles coated with mouse anti-CRP in glycine buffer, mouse immunoglobulins with preservative.

B Principle of Operation:
Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically. The assay is meant to be run on the cobas c 501.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Tina-quant C-Reactive Protein Gen. 3

B Predicate 510(k) Number(s):
K083444

C Comparison with Predicate(s):

Device & Predicate Device(s):	New Device K192072	Predicate K083444
Device Trade Name	**Tina-quant C-Reactive Protein IV**	**Tina-quant C-Reactive Protein Gen. 3**
General Device Characteristic Similarities	New Device K192072	Predicate Device K083444
Intended Use/ Indications For Use	Tina-quant® C-Reactive Protein IV is an immunoturbidimetric assay for the in vitro quantitative	Immunoturbidometric assay for the in vitro quantitative determination of CRP in human

	determination of CRP in human serum and plasma on cobas c systems. A C-reactive protein immunological test system is a device that consists of the reagents used to measure by immunochemical techniques the C-reactive protein in serum and plasma. Measurement of C-reactive protein aids in evaluation of the amount of injury to body tissues.	serum and plasma on Roche automated clinical chemistry analyzers. Measurement of C-Reactive protein aids in the evaluation of the amount of injury to body tissues.
Assay Method	Particle enhanced immunoturbidimetric assay	Same
Detection Method	Turbidimetric	Same
Sample Type	Serum and Plasma (Li-heparin, K2- and K3-EDTA)	Same
Calibrator	Calibrator f.a.s. Proteins	Same
Expected Value	<5 mg/L	Same
Reagent Stability	• Shelf-life at 2–8 °C: expiration date on cobas c pack label • On‑board in use and refrigerated on the analyzer: 12 weeks	Same
General Device Characteristic Differences	New Device K192072	Predicate Device K083444
Traceability/ Standardization	Standardized against the ERM-DA474/IFCC	Standardized against CRM 470
Instrument Platform	cobas c 501 analyzer	Roche automated clinical chemistry analyzers
Calibration Method	6-point spline	Same
Calibration Interval	• After reagent lot change • After 3 weeks on-board the analyzer • After 6 months when using a single reagent lot • As required following quality control procedures	• After reagent lot change • As required following quality control procedures
Controls	• CRP T Control N • Precinorm Protein	• Precinorm Protein • Precipath Protein

	• Precipath Protein • PreciControl ClinChem Multi 1 • PreciControl ClinChem Multi 2	• PreciControl ClinChem Multi 1 • PreciControl ClinChem Multi 2
Measuring Range	3.0 – 350 mg/L	0.3 – 350 mg/L

VI Standards/Guidance Documents Referenced:

- CLSI EP05-A3, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Third Edition
- CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach: Approved Guideline
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second 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

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

i) Precision of the Tina-quant CRP IV evaluated by testing five human serum samples and three controls with concentrations that cover the assay range. The samples were tested in two replicates per run, two runs per day for 21 days using three reagent lot on one cobas c 501 Analyzer for a total of 84 replicates per sample. The SD and %CV of the within-run, between-run, between-day, and total imprecision were calculated for each sample and results are summarized in the following table:

Sample	Mean (mg/L)	Within-Run		Between-Run		Between-Day		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
2	4.55	0.07	1.5	0.00	0.0	0.02	0.5	0.07	1.6
3	10.6	0.17	1.6	0	0.0	0.12	1.1	0.21	1.9
4	82.4	1.82	2.2	0.00	0.0	0.76	0.9	1.97	2.4
5	186	3.76	2.0	1.91	1.0	1.24	0.7	4.39	2.4
6	331	4.4	1.3	2.65	0.8	2.69	0.8	5.8	1.8
CRPTN*	3.6	0.05	1.4	0.03	0.9	0.0	0.0	0.06	1.6
PNP**	9.7	0.13	1.3	0.0	0.0	0.06	0.6	0.14	1.5
PPP***	55.2	0.86	1.6	0.57	1.0	0.17	0.3	1.04	1.9

* CRPTN: CRP T Control N

** PNP: Precinorm Protein control

*** PPP: Precipath Protein control

ii) Lot-to-lot imprecision:
The panel of four serum samples was tested with three different assay reagent lots. Each sample was tested in two replicates per run, two runs per day for 21 days. The lot-to-lot imprecision was evaluated based on a total of 252 measurements per sample. The results are summarized in the following table:

Sample	Mean (mg/L)	Within-Run		Between-Day		Between-Lot		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Serum 2	4.57	0.07	1.4	0.00	0.1	0.05	1.0	0.08	1.8
Serum 3	85.9	1.85	2.2	0.84	1.0	3.11	3.6	3.71	4.3
Serum 4	187	3.46	1.8	0.73	0.4	3.92	2.1	5.63	3.0
Serum 5	336	4.92	1.5	2.17	0.6	4.69	1.4	7.74	2.3
CRPTN*	3.61	0.05	1.5	0.00	0.0	0.02	0.5	0.06	1.7
PNP**	9.7	0.12	1.2	0.07	0.7	0.05	0.5	0.16	1.7
PPP***	55.9	0.94	1.7	0.27	0.5	0.75	1.3	1.33	2.4

* CRPTN: CRP T Control N
** PNP: Precinorm Protein control
*** PPP: Precipath Protein control

2. Linearity:
Linearity of the assay was evaluated following CLSI guideline EP6-A by preparing native unmodified high- and low-level human serum pools for the dilution series. The dilution series resulted in 15 levels (including the high and low concentration pools). Each diluted sample was tested in replicates of three and tested on a cobas c 501 analyzer. Regression statistics comparing the observed results (y) to expected results (x) of all samples are presented in the table below.

Dilution Range (mg/L)	Regression Equation	Slope (95% CI)	Intercept (95% CI)	R^2	% Bias
1.03−351	y=1.002x-0.0169	0.99−1.01	-0.06−0.03	0.9976	-5.2%−4%

The data summarized in the table above support linearity throughout the claimed measuring range from 3 mg/L to 350 mg/L.

3. Analytical Specificity/Interference:

a) Endogenous Substance Interference:
The effect of the presence of hemoglobin, triglyceride, conjugated bilirubin, unconjugated bilirubin, albumin, immunoglobulin, and rheumatoid factor in serum samples was evaluated by testing native unmodified serum pools at two levels with CRP concertation between 5−10 mg/L and 35−100 mg/L spiked with varying levels of each interferent and analyzed in triplicate in one assay run. The percent recovery for each sample spiked with the interference substance was calculated by comparing its result to that of the corresponding reference sample spiked with an equal volume of the solvent without the interference substance. No interference was noted for samples containing up to 1000 H index (hemoglobin), 1000 L index (lipemia), 60 I index (conjugated bilirubin,

unconjugated bilirubin), 60 g/L albumin, 50 g/L Immunoglobulin, and rheumatoid factor up to 1200 IU/mL.

b) Exogenous Substance Interference:
The same protocol used in the endogenous substance interference study was used to evaluate potentially interfering exogenous substances. No interference was noted for samples containing N-Acetylcysteine at 1660 mg/L, Ampicillin-Na at 1000 mg/L, Ascorbic acid at 300 mg/L, Cefoxitin at 6600 mg/L, Heparin at 5000 IU/L, Levodopa at 20 mg/L, Methyldopa + 1.5 at 22.5 mg/L, Metronidazole at 200 mg/L, Doxycyclin at 50 mg/L, Acetylsalicylic acid at 1000 mg/L, Rifampicin at 60 mg/L, Penicillamin at 24 mg/L, Phenylbutazone at 400 mg/L, Cyclosporine at 5 mg/L, Acetaminophen at 200mg/L, Ibuprofen at 500 mg/L, and Theophylline at 100 mg/L.

Ticarcillin did not show interference up to 225 mg/L; however, ticarcillin did show significant interference from 300 mg/L−750mg/L.

c) HAMA Interference:
The effect of the presence of elevated level of Human anti-mouse antibody (HAMA) in serum samples was evaluated by testing native unmodified serum pools at two levels with CRP concertation between 5−10 mg/L and 35−100 mg/L. Each C-reactive protein sample was spiked with a serum sample containing HAMA. Samples were run in triplicate, on three lots of reagent, on one cobas c 501 analyzer. The mean concentration of the three replicates was used to calculate recovery to the known C-reactive protein concentration. No cross reactivity was noted up to 2000 ng/mL for HAMA.

4. Assay Reportable Range:
The claimed measuring range is from 3.0 mg/L to 350 mg/L.

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

a) Traceability:
The CRP calibrators are traceable to the reference material, ERM-DA474/IFCC.

b) Kit Stability:

Shelf-life stability: A real-time stability study were performed in accordance with CLSI EP25-A using three lots of reagent. The study was performed at each time point with five human serum samples and three controls. The real-time stability study supports 13 months unopened shelf-life stability for Tina-quant C-Reactive Protein IV Assay when stored at 2–8 °C per the manufacturer's instruction for use.

On-board stability: A real-time stability study using three lots of reagent tested at each time point with five human serum samples and three controls. The study supports the on-board stability claim of 12 weeks.

6. Detection Limit:
The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) of the Tina-quant CRP IV assay on the cobas c 501 were determined according to CLSI guideline EP17-A2.

LoB was determined by testing 10 analyte free samples in singlicate per run, two runs per day, for three days on one cobas c 501 analyzer using three lots of reagents. The LoB was estimated as the 95th percentile of 60 measurements for each of the lots tested.

LoD was determined using five serum samples with low CRP concentrations. Each sample was tested in duplicates per run, two runs per day, for three days on one cobas c 501 analyzer using three lots of reagents. The LoD was determined for each lot based on 60 measurements as the lowest amount of analyte in a concentration level that can be detected with a 95% probability.

LoQ was determined using a set of nine samples with low CRP concentrations. Each sample was tested in replicates of five per run, one run per day, for five days with three reagent lots on one cobas c 501 analyzer for a total of 25 data points per sample per reagent lot. The LoQ is defined as the mean value of the sample which fulfills the specification for the total within-laboratory imprecision <20% CV.

The claimed LoB, LoD and LoQ for the Tina-Quant are summarized in the table below:

	LoB	LoD	LoQ
Tina-Quant CRP IV	0.2 mg/L	0.3 mg/L	3.0 mg/L

The claimed lower limit of the analytical reportable range for Tina-Quant CRP IV is set to be 3 mg/L.

7. Assay Cut-Off:
Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
A total of 110 native serum samples spanning the measuring range were tested with the Tina-quant C-Reactive Protein IV and the predicate device, Tina-quant C-Reactive Protein Gen 3 on cobas c 501. Analytical equivalence of the test device (y) and the predicate device (x) was evaluated using Passing/Bablok regression analysis. The results are summarized in the following table:

N	Range (mg/L)	Equation	Slope (95% CI)	Intercept (95% CI)	Pearson r
110	3.06–347	y = 0.985x + 0.278	0.985 (0.97–1.00)	0.278 (0.18–0.40)	0.999

2. Matrix Comparison:
The effect on quantitation of analyte in the presence of anticoagulants with the Tina-quant C-Reactive Protein IV assay was determined by comparing values obtained from samples drawn into serum, serum separation gel, Li-heparin plasma, K2- and K3-EDTA plasma primary tubes. At least 42 serum/plasma pairs per sample type were tested on one cobas c 501 analyzer. Analytical comparison between the results obtained from serum separation gel

and each plasma sample type (y) and the results from serum (x) was evaluated using the Passing/Bablok regression analyses. The results are summarized in the following table:

	N	Range (mg/L)	Slope (95% CI)	Intercept (95% CI)	Pearson r
Serum Separation Gel vs. Serum	42	3.34–344	0.985 (0.98–1.00)	0. 134 (-0.07–0.47)	0.999
Li-heparin vs. Serum	42	3.34–344	1.029 (1.02–1.04)	-0.192 (-0.36– -0.01)	0.999
K_2-EDTA vs. Serum	42	3.34–344	1.024 (1.01–1.04)	-0.201 (-0.48–0.21)	0.999
K_3-EDTA vs. Serum	42	3.34–344	1.024 (1.01–1.04)	−0.258 (-0.49– -0.10)	0.999

C Clinical Studies:

1. Clinical Sensitivity and Clinical Specificity:
   Not applicable

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

D Clinical Cut-Off

See expected values/reference range.

E Expected Values/Reference Range:

The reference interval was verified by testing samples from 500 healthy adult donors. 467 of 500 samples tested had concentrations <5 mg/L.

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.