

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k093908

B. Purpose for Submission:

New device

C. Analyte:

Anti-cyclic citrullinated peptide (CCP) IgG antibodies

D. Type of Test:

Single-use, qualitative lateral flow device

E. Applicant:

Euro-Diagnostica AB

F. Proprietary and Established Names:

Euro-Diagnostica CCpoint[®]

G. Regulatory Information:

1. Regulation section:
21CFR§866.5775 – Rheumatoid factor immunological test system
2. Classification:
Class II
3. Product code:
NHX, Antibodies, Anti-Cyclic Citrullinated Peptide (CCP)
4. Panel:
Immunology (82)

H. Intended Use:

1. Intended use(s):
The Euro-Diagnostica CCPoint[®] test is a visually read, qualitative rapid lateral flow test for the detection of IgG antibodies to Cyclic Citrullinated Peptides (CCP) in human plasma or serum. The results of the test are to be used as an aid to the diagnosis of Rheumatoid Arthritis (RA), in conjunction with other laboratory and clinical findings. For use by trained laboratory professionals. For in-vitro diagnostic use
2. Indication(s) for use:
Same as intended use
3. Special conditions for use statement(s):
Prescription use only
4. Special instrument requirements:
None.

I. Device Description:

The CCPoint[®] test is a colloidal gold based lateral flow immunoassay. Reactive cyclic citrullinated peptides are immobilized as a discrete line on a porous membrane located in the test zone. The detection reagent, consisting of colloidal gold particles conjugated to anti-human IgG, is deposited within the device onto the conjugate pad.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Eurodiagnostica Immunoscan RA anti-CCP Test Kit

2. Predicate 510(k) number(s):
k052133
2. Comparison with predicate:

| Similarities | | |
|--------------------------------------|---|-----------|
| Item | Device | Predicate |
| Intended Use/ Indications for Use | The results of the test are to be used as an aid to the diagnosis of Rheumatoid Arthritis (RA), in conjunction with other laboratory and clinical findings. | Same |
| Analyte measured | Anti-CCP | Same |
| Coated antigen | Synthetic CCP | Same |
| Conjugate | Anti-human IgG | Same |

| Differences | | |
|----------------------|---|-----------------------------------|
| Item | Device | Predicate |
| Method | Lateral flow | ELISA |
| Specimen type | Serum and plasma (EDTA, lithium or heparin) | Serum |
| Type of test | Qualitative | Qualitative and semi-quantitative |
| Sample dilution | Undiluted | Diluted 1:50 |
| Measuring of results | Visually read | ELISA plate reader |

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

None

L. Test Principle:

In the assay procedure, a sample of blood is added to the sample port. A blood cell separation membrane transfers the sample fluid onto the porous membrane. After a short incubation running buffer is added to the buffer port. This buffer mobilizes the colloidal gold particles from the conjugate pad. The gold particles and the sample move by capillary force across the membrane. If the sample contains anti-CCP antibodies they will bind to the peptide-antigens and a red line will appear in the test zone (marked T). If the sample does not contain any anti-CCP antibodies no line will appear. With any sample a red control line should appear in the control zone (marked C). The control ensures that the coated colloidal gold is still active.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Inter-assay performance of the CCPoint assay was determined by testing 8 human serum samples: negative, low positive, and high positive for

antibodies against CCP. The samples were tested eight times each, by three different persons. All results obtained were in agreement with the expected results.

| | | CCPoint Results | | | | | |
|---------------|-------------------------------|-----------------|------------|------------|------------|------------|------------|
| Sample | Immunoscan RA anti-CCP result | Operator 1 | | Operator 2 | | Operator 3 | |
| | | # positive | # negative | # positive | # negative | # positive | # negative |
| QC1 | 1746 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| QC2 | 324 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| QC3 | 132 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| QC4 | 44 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| QC5 | 39 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| Low Positive | 28 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| High Negative | 16 U/mL | 0 | 8 | 0 | 8 | 0 | 8 |
| QC6 | 4 U/mL | 0 | 8 | 0 | 8 | 0 | 8 |

Batch-to-batch variation was determined by testing 8 human serum samples: negative, low positive, and high positive for antibodies against CCP, eight times each using three different batches of the CCPoint device. All results obtained were in agreement with the expected results.

| | | CCPoint Results | | | | | |
|---------------|-------------------------------|-----------------|------------|------------|------------|------------|------------|
| Sample | Immunoscan RA anti-CCP result | Batch 1 | | Batch 2 | | Batch 3 | |
| | | # positive | # negative | # positive | # negative | # positive | # negative |
| QC1 | 1746 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| QC2 | 324 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| QC3 | 132 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| QC4 | 44 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| QC5 | 39 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| Low Positive | 28 U/mL | 8 | 0 | 8 | 0 | 8 | 0 |
| High Negative | 16 U/mL | 0 | 8 | 0 | 8 | 0 | 8 |
| QC6 | 4 U/mL | 0 | 8 | 0 | 8 | 0 | 8 |

b. *Linearity/assay reportable range:*

Not applicable.

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

An international reference material for anti-CCP antibodies is not available.

The CCPoint device was shown to be stable for 25 months at 18-25°C and for at least 24 months at 2-8°C. The test can be run for up to 4 hours after opening the package, without any adverse effect on test performance. The CCPoint signals are stable for at least 60 minutes after running of the assay.

d. *Detection limit:*

Not applicable

e. *Analytical specificity:*

Four human serum samples (one moderately positive for anti-CCP, one low positive, one high negative and one strongly negative) were spiked with

interferents to the following concentrations: Bilirubin F at 18.8 mg/dL, Bilirubin C at 20 mg/dL, Haemoglobin at 453 mg/dL, Chyle at 23.6 U/dL and Rheumatoid Factor (IgM) at 55 IU/mL. No significant interference effects were observed with any of the samples.

To assess potential cross-reactivity of CCP IgG antigen with other autoantibodies, a total of 498 samples of different etiology were assayed. Samples from patients diagnosed with Crohn’s disease, Colitis ulcerosa, SLE, Sjögren’s syndrome, Osteoarthritis, Scleroderma, Multiple sclerosis, MCTD, Inflammatory bowel disease, Polymyositis/Dermatomyositis, nonRA autoimmune patients and samples reacting with MPO-ANCA, PR3-ANCA and ds-DNA. Data indicates that the assayed autoantibodies show no significant cross-reactivity.

f. Assay cut-off:

The cutoff was established by designing the CCPoint assay so that the visual cutoff correlated with the 25 U/mL cutoff established for the predicate ELISA assay (the Eurodiagnostica Immunoscan RA anti-CCP Test Kit). Two preliminary studies with patient samples were performed and the cutoff was set to minimize nonconcordant results between CCPoint and the Immunoscan RA anti-CCP Test Kit. A total of 78 samples (39 negative and 39 positive) were used for these studies, including several samples close to the cutoff.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 403 frozen retrospective sera samples that were within the reportable range of the predicate device were tested with both the predicate assay and with CCPoint. Note that very few negative samples are within the reportable range of the predicate assay (15-1600 U/mL), because the cutoff is very close to the lower limit of the reportable range at 25 U/mL. The results are shown in the table below. 95% confidence intervals (CI) were calculated using the exact method.

| | | Predicate Assay (Immunoscan RA anti-CCP) | | |
|----------|-------|---|----|-------|
| | | + | - | Total |
| CCPoint® | + | 377 | 4 | 381 |
| | - | 2 | 16 | 18 |
| | Total | 379 | 20 | 403 |

Positive Percent Agreement: $377/379 = 99.5\%$ 95% CI = 98.1 - 99.9%

Negative Percent Agreement: $16/20 = 80.0\%$ 95% CI = 56.3 - 94.3%

Overall Percent Agreement: $393/399 = 98.5\%$ 95% CI = 96.8 - 99.4%

Overall, 1052 frozen retrospective serum samples (596 from RA patients and 456 from apparently healthy donors) were tested with both the predicate assay and with CCPoint. The method comparison results with all samples included are shown in the table below.

| | | Predicate Assay (Immunoscan RA anti-CCP) | | |
|----------|-------|---|------|-------|
| | | + | - | Total |
| CCPoint® | + | 444 | 4 | 441 |
| | - | 2 | 612 | 610 |
| | Total | 596 | 1219 | 1815 |

Positive Percent Agreement: $439/441 = 99.6\%$ 95% CI = 98.4 - 99.9%
 Negative Percent Agreement: $608/611 = 99.4\%$ 95% CI = 98.3 - 99.8%
 Overall Percent Agreement: $1047/1052 = 99.4\%$ 95% CI = 98.8 - 99.8%

b. Matrix comparison:

A total of 109 samples (103 established RA patients and 6 apparently healthy blood donors) were assayed by CCPoint to determine the correlation between serum and EDTA, heparin, or citrated plasma.

Serum vs. EDTA plasma:

| Predicate device conc range (U/mL) | Number of samples | Number of serum samples testing positive by CCPoint | Number of EDTA plasma samples testing positive by CCPoint |
|------------------------------------|-------------------|---|---|
| > 100 U/mL | 14 | 14 | 14 |
| 25-100 U/mL | 10 | 10 | 10 |
| 5-25 U/mL | 4 | 0 | 0 |
| <5 U/mL | 6 | 0 | 0 |

Serum vs. Heparin plasma:

| Predicate device conc range (U/mL) | Number of samples | Number of serum samples testing positive by CCPoint | Number of heparin plasma samples testing positive by CCPoint |
|------------------------------------|-------------------|---|--|
| > 100 U/mL | 20 | 20 | 20 |
| 25-100 U/mL | 7 | 7 | 7 |
| 5-25 U/mL | 5 | 1* | 1* |
| <5 U/mL | 0 | 0 | 0 |

*The one discrepant sample was the same for serum as for heparin plasma.

Serum vs. Citrated Plasma

| Predicate device conc range (U/mL) | Number of samples | Number of serum samples testing positive by CCPoint | Number of citrated plasma samples testing positive by CCPoint |
|------------------------------------|-------------------|---|---|
| > 100 U/mL | 21 | 21 | 21 |
| 25-100 U/mL | 5 | 5 | 5 |
| 5-25 U/mL | 4 | 0 | 0 |
| <5 U/mL | 7 | 0 | 0 |

3. Clinical studies:

a. *Clinical Sensitivity and Specificity*

A total of 596 frozen retrospective sera from patients with clinically defined RA were assayed. 438 of these samples were positive using the CCPoint assay and 158 were negative. The clinical specificity of the CCPoint assay was tested using a total of 1219 retrospective sera samples from patients characterized as negative for RA, including 456 asymptomatic patients (healthy blood donors) and 763 samples from non-RA diseased patients. The results are summarized in the table below:

| | | RA Diagnosis | | |
|----------|-------|--------------|------|-------|
| | | + | - | Total |
| CCPoint® | + | 438 | 13 | 451 |
| | - | 158 | 1206 | 1364 |
| | Total | 596 | 1219 | 1815 |

Sensitivity (438/596) = 73.5% (95% CI = 69.9 – 77.0%)

Specificity (1206/1219) = 98.9% (95% CI = 98.2 – 99.4%)

Overall agreement (1644/1815) = 90.6% (95% CI = 89.2 – 91.8%)

Detailed summary table for clinical specificity:

| Disease type | # CCPoint negative samples | Total # samples | Clinical Specificity | 95% CI |
|--|----------------------------|-----------------|----------------------|--------------|
| Healthy controls (blood donors) | 452 | 456 | 99.1% | 97.8 – 99.8% |
| Non-RA arthritis | 187 | 187 | 100% | 98.0 – 100% |
| Spondylarhropathy including Ankylosing spondylitis | 21 | 21 | 100% | 83.9 – 100% |
| Systemic collagen disease | 123 | 126 | 97.6% | 93.2 – 99.5% |
| Vasculitis/Polymyalgia rheumatica | 59 | 59 | 100% | 93.9 – 100% |
| Degenerative disease | 77 | 77 | 100% | 95.3 – 100% |
| Pain syndrome/miscellaneous | 56 | 57 | 98.2% | 90.6 – 100% |
| Other non-rheumatic autoimmune diseases | 49 | 49 | 100% | 92.7 – 100% |
| Infectious diseases | 105 | 108 | 97.2% | 92.1 – 99.4% |
| Routine samples (not RA) | 77 | 79 | 97.4% | 91.2 – 99.7% |

4. Clinical cut-off:

See Assay cut-off.

5. Expected values/Reference range:

See Assay cut-off. The expected value in the normal population is negative.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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