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

A. 510(k) Number:

K182225

B. Purpose for Submission:

New Device

C. Measurand:

Cardiac troponin I (cTnI)

D. Type of Test:

Quantitative immunoassay

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Dimension Vista® High-Sensitivity Troponin I (TNIH) Assay

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
MMI	Class II	21 CFR 862.1215 - Creatine phosphokinase/creatine kinase or isoenzymes test system	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s)

   See indication(s) for use.

2. Indication(s) for use:

   The Dimension Vista® High-Sensitivity Troponin I (TNIH) assay is for in vitro diagnostic use in the quantitative measurement of cardiac troponin I in human plasma using the Dimension Vista system. The assay can be used to aid in the diagnosis of acute myocardial infarction (AMI).

3. Special conditions for use statement(s):

   - For prescription use
   - For *in vitro* diagnostic use

4. Special instrument requirements:

   Dimension Vista 1500 Analyzer

I. Device Description:

The Dimension Vista® High-Sensitivity Troponin I TNIH assay is a homogeneous, sandwich chemiluminescent immunoassay based on LOCI technology. It is comprised of the following:

The cartridge reagent includes: two synthetic bead reagents and two biotinylated anti-cardiac troponin I monoclonal antibody fragments. The first bead reagent (Sensibeads) is coated with streptavidin and contains photosensitizer dye. The second bead reagent (Chemibeads) is coated with a third anti-cardiac troponin I monoclonal antibody and contains chemiluminescent dye.

These additional materials are required for assay measurement, but not provided:

TNIH Calibration Material (TNIH CAL)
CTNI on board sample diluent (SDIL)
LOCI Reaction Vessels
Quality Control Materials

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Elecsys Troponin T Gen 5 STAT Immunoassay

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

   K162895

3. Comparison with predicate:

Similarities		
Item	Dimension Vista® High-Sensitivity Troponin I (TNIH) Assay (Candidate Device)	Elecsys Troponin T Gen 5 STAT Immunoassay K162895 (Predicate Device)
Indications for use	The assay can be used to aid in the diagnosis of acute myocardial infarction.	Same
Type of immunoassay	Sandwich immunoassay	Same
Specimen Type	Lithium heparin plasma	Same

Differences		
Item	Dimension Vista® High-Sensitivity Troponin I (TnIH) Assay (Candidate Device)	Elecsys Troponin T Gen 5 STAT Immunoassay K162895 (Predicate Device)
Detection technology	Homogeneous chemiluminescent immunoassay	Electrochemiluminescent immunoassay
Upper 99th percentile cutoff	Lithium Heparin: Female: 53.7 pg/mL Male: 78.5 pg/mL Overall (male and female combined): 58.9 pg/mL	Lithium Heparin: Female: 14 pg/mL Male: 22 pg/mL For both: 19 pg/mL
Measuring range	3.0-25,000 pg/mL	6.0-10,000 pg/mL

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

Clinical and Laboratory Standards Institute (CLSI) EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Third Edition

CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline

CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition

L. Test Principle:

The Dimension Vista® High-Sensitivity Troponin I TNIH assay is a homogeneous, sandwich chemiluminescent immunoassay based on LOCI technology. The LOCI reagents include two synthetic bead reagents and two biotinylated anti-cardiac troponin I monoclonal antibody fragments. The first bead reagent (Sensibeads) is coated with streptavidin and contains photosensitizer dye. The second bead reagent (Chemibeads) is coated with a third anti-cardiac troponin I monoclonal antibody and contains chemiluminescent dye. The sample is incubated with Chemibeads and biotinylated antibodies to form bead-cardiac troponin I-biotinylated antibody sandwiches. Sensibeads are added and bind to the biotin to form bead-pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffuses into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is a direct function of the cardiac troponin I concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   The sponsor provided results from precision studies across multiple reagent lots. Native pooled plasma samples and one quality control sample (QC) were tested on one instrument two times a day, each with two replicates, for 20 days, for a total of 80 measurements per sample. Analysis of variance (ANOVA) was used to evaluate the data following recommendations in EP05-A3. This was repeated for 3 reagent lots using the plasma samples. Results from one representative lot of the three lots tested, are described in the table below. The within-lab precision estimate described in the table is a total of within-run variability, within-day, run-to-run variability, and day-to-day variability.

			Repeatability		Within-Lab	
Sample	N	Mean (pg/mL)	SD	%CV	SD	%CV
plasma	80	48.9	1.12	2.3	3.05	6.2
plasma	80	157.7	1.55	1.0	2.60	1.6
QC	80	8088.5	99.54	1.2	200.36	2.5

The sponsor tested additional native plasma samples as described above and the results of a representative lot are summarized below:

			Repeatability		Within-Lab	
Sample	N	Mean (pg/mL)	SD	%CV	SD	%CV
plasma	80	51.1	1.07	2.1	1.21	2.4
plasma	80	77.3	1.14	1.48	1.45	1.88

The sponsor also evaluated site to site reproducibility following the recommendations in CLSI EP05-A3. Imprecision was evaluated using seven samples spanning the measurement range of the assay and comprising of native pooled lithium heparin patient samples across three sites using one lot of reagents. Testing was performed over five days, with two samples a day and three replicates per sample. The reproducibility estimate is a total of within-run variability, within-day variability, run-to-run variability, day-to-day variability, and site to site variability. The sample at the upper end of the assay measuring range was prepared by spiking normal human plasma with human troponin complex to desired test levels, as noted in the table below.

			Repeatability		Within-Lab		Reproducibility	
Sample Composition	Concentration (pg/mL)	N	SD	% CV	SD	% CV	SD	% CV
plasma	14.2	90	0.7	5.2	0.7	5.2	0.9	6.2
plasma	53.8	90	1.1	2.1	1.5	2.8	1.5	2.8
plasma	74.4	90	1.3	1.7	1.6	2.2	1.6	2.2
plasma	249.4	90	4.2	1.7	6.2	2.5	6.7	2.7
plasma	1865.4	90	20	1.1	32.5	1.7	41.9	2.2
plasma	9078.7	90	159.5	1.8	254.8	2.8	254.8	2.8
plasma	18240	90	376.6	2.1	638.1	3.5	771.7	4.2

b. *Linearity/assay reportable range:*

Linearity was evaluated following the recommendations in the CLSI Guideline EP06-A with 16 lithium heparin plasma samples ranging in concentrations from 1.8 pg/mL to >25,000 pg/mL. The high samples and the low samples were native and the intermediate samples were prepared by mixing high and low concentration samples. At least five replicates were measured for each sample, and the mean of these replicates was used to calculate the reported results. Deviations from linearity within the claimed range were never observed to be greater than 10%.

The measuring range is 3-25000 pg/mL with the upper end of the measuring range being defined by the upper linear range of the assay. See detection limits in M. item d. below for information supporting the lower end of the measuring range.

Hook Effect
The sponsor demonstrated that there is no hook effect with the assay up to 1,223,723 pg/mL.

Dilution Recovery
The sponsor provided dilution studies which supported the measurement of samples above the measurement range diluted by up to a factor of five.

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

The sponsor's traceability scheme was reviewed and found acceptable. The assay is traceable to a commercially available troponin assay.

d. *Detection limit:*

Limit of Blank (LoB) Test Protocol

The LoB was determined as described in the CLSI Guideline EP17-A2. Testing was performed using three lots of reagents, each on one instrument. 60 determinations were obtained by testing five samples with no analyte (the zero level calibrator material) four times a day for three days across three reagent lots. LoB was calculated non-parametrically. The largest estimate across all reagent lot-instrument combinations tested was 1.0 pg/mL.

Limit of Detection (LoD) Test Protocol

The LoD was determined following the recommendations in the CLSI Guideline EP17-A2. Testing was performed using three reagent lots. For the three lots tested,

seven to ten native low analyte lithium heparin plasma samples were tested every day, respectively, with four replicates for each test, for 3 days.

The nonparametric approach described in EP17-A2 was followed to determine the LoD. The largest estimate across all reagent lot-instrument combinations tested was 1.8 pg/mL.

Limit of Quantitation (LoQ) Protocol

The Limit of Quantitation (LoQ) was determined as the analyte level with a within-lab CV of less than or equal to 20.0% following the recommendations in the CLSI EP17-A2 Guideline. Testing was completed two times a day (n=2) for at least 20 days for a total of 80 replicates with eight to 11 native lithium heparin plasma pools measured on one instrument using three reagent lots. For each reagent lot-instrument combination, the within-laboratory precision for each sample, expressed as %CV, was plotted against the mean concentration obtained for each sample. LoQ was determined by this precision profile as the concentration where the %CV was less than 20%. The largest estimate across all reagent lot-instrument combinations tested was 2.4 pg/mL.

The sponsor claims an LoB of 1.0 pg/mL, and LoD of 2.0 pg/mL, and an LoQ of 3.0 pg/mL.

e. *Analytical specificity:*

Endogenous interference studies were performed following the recommendations in CLSI EP07-A2. Two sample pools were tested. One sample pool had 20-60 pg/mL cTnI and the second sample pool had 700-2000 pg/mL cTnI. These sample pools were spiked with potential interferents. Test results from samples spiked with the potential interferent were compared to test results from the control samples lacking the potential interferent. At the tested concentrations, these compounds caused <10% interference.

Endogenous Substance	**Highest Concentration Tested Without Significant Interference**
Bilirubin (Conjugated)	40 mg/dL
Bilirubin (Unconjugated)	40 mg/dL
Biotin	300 ng/mL
Intralipid	3000 mg/dL
Cholesterol	300 mg/dL
Hemoglobin	400 mg/dL
Protein (Albumin)	6 g/dL
Protein (Gamma Globulin)	2.5 g/dL

Endogenous Substance	Highest Concentration Tested Without Significant Interference
Protein (Total)	12 g/dL
Triglycerides	1000 mg/dL
Rheumatoid factor (RF)	1500 IU/mL

Therapeutic drug interference studies were designed following the recommendations in CLSI EP07-A2. Two sample pools were tested. One sample pool had 20-60 pg/mL cTnI and the second sample pool had 700-2000 pg/mL cTnI. These sample pools were spiked with potential interferents at low and high levels. Test results from samples spiked with the potential interferent were compared to test results from the control samples lacking the potential interferent. At the tested concentrations, all drugs caused <10% interference.

Drug	Highest Concentration Tested Without Significant Interference
Abciximab	40 µg/mL
Acetaminophen	1324 µmol/L
Acetylsalicylic Acid	3.62 mmol/L
Allopurinol	294 µmol/L
Amiodarone	8.92 µmol/L
Ampicillin	152 µmol/L
Ascorbic Acid	342 µmol/L
Atenolol	37.6 µmol/L
Caffeine	308 µmol/L
Captopril	23 µmol/L
Cefoxitin	1546 µmol/L
Cinnarizine	25000 ng/mL
Clopidogrel	75 µg/mL
Cocaine	10 µg/mL
Digoxin	7.8 nmol/L
Digitoxin	60 ng/mL
Diltiazem	15 µmol/L
Disopyramide	29.5 µmol/L
Dopamine	5.87 µmol/L
Doxycycline	67.5 µmol/L
Erythromycin	81.6 µmol/L

Drug	Highest Concentration Tested Without Significant Interference
Furosemide	181 µmol/L
Ibuprofen	2425 µmol/L
Isosorbide Dinitrate	636 nmol/L
Lisinopril	0.74 µmol/L
Lovastatin	80 ng/mL
Low MW Heparin	2.0 U/mL
Methotrexate	2 mmol/mL
Methyldopa	71 µmol/L
Methylprednisolone	40 µg/mL
Mexiletine	22.3 µmol/L
Nicotine	6.2 µmol/L
Nifedipine	1156 nmol/mL
Nitroglycerine	160 ng/mL
Nitrofurantoin	16.8 µmol/L
Phenobarbital	431 µmol/L
Phenytoin	198 µmol/L
Primidone	183 µmol/L
Propranolol	7.71 µmol/L
Quinidine	37 µmol/L
Simvastatin	32 µmol/L
Theophylline	222 µmol/L
Thyroxine	6 µg/mL
Tissue Plasminogen Activator	2.3 µg/mL
Trimethoprim	138 µg/mL
Verapamil	4.4 µg/mL
Warfarin	32.5 µg/mL

Cross-Reactivity

Potential cross-reactivity was evaluated following the recommendations in the CLSI document EP07-A2.

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma patient samples at two cTnI concentrations (~ 0 and ~ 40 pg/mL). Test results from samples spiked with the cross-reactant were compared to

test results from samples without cross-reactant added. Samples were measured on three lots. The sponsor claims that at the tested concentrations, these compounds caused <0.003% cross-reactivity.

Potential Cross-Reacting Substance	Highest concentration tested (ng/mL)
Cardiac Troponin T	1000
Skeletal Troponin I	1000
Tropomyosin	1000
Actin	1000
Troponin C	1000
Myosin Light Chain	1000
Myoglobin	1000
CK-MB	1000

Biotin interference:

Biotin interference was tested up to 1200 ng/mL in plasma samples at troponin concentrations of approximately 40 pg/mL and approximately 1300 pg/mL. Test results from samples spiked with biotin were compared to test results from the control samples lacking biotin. Interference was defined as a difference >±10% of the control sample values. The results are summarized in the tables below:

Biotin Concentration	cTnI (pg/mL)	Bias
300 ng/mL	36.1	-5%
	1309.1	-1%
360 ng/mL	43.0	-13%
	1423.1	-12%
480 ng/mL	43.0	-18%
	1423.1	-18%
840 ng/mL	43.0	-49%
	1423.1	-49%
1200 ng/mL	43.0	-91%
	1423.1	-96%

The labeling states:

See limitations section for information regarding patients with either renal impairment or multiple sclerosis. Some studies have shown that serum concentrations of biotin can reach 355 ng/mL within the first hour after biotin ingestion for apparently healthy subjects consuming supplements of 20 mg biotin per day and plasma concentrations of biotin can reach up to 1160 ng/mL for apparently

healthy subjects after a single dose of 300 mg biotin.

The following limitations are included in the labeling:

Testing specimens from renal dysfunction patients taking biotin may lead to false negative results. Therefore, do not use this device in patients with renal impairment (eGFR<60), unless it is confirmed that the patient is not taking biotin.

Patients taking more than 20 mg/day of biotin may have falsely negative results, and should not use this test. There have been reports of multiple sclerosis patients taking biotin doses exceeding 20 mg/day. Therefore, do not use this device in patients with multiple sclerosis, unless it is confirmed that the patient is not taking more than 20 mg/day of biotin.

Protein gamma globulin at 6 g/dL increases the troponin result in plasma samples at approximately 40 pg/mL [ng/L] and 1000 pg/mL [ng/L] of troponin. Protein gamma globulin at 2.5 g/dL demonstrates less than 10% change in results when testing plasma samples at the concentrations stated above.

Dextran 40 at 60 g/L increases the troponin result in plasma at 35.1 pg/mL [ng/L] and 1337.4 pg/mL [ng/L] by 22% and 4% respectively. Dextran 40 at 15 g/L and 45 g/L demonstrates less than 10% change in results when testing plasma samples at the concentrations stated above.

Patient samples may contain cardiac troponin-specific autoantibodies that could react in immunoassays to give depressed results. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution.

Samples from patients receiving preparations of mouse monoclonal antibodies for therapy or diagnosis may contain human anti-mouse antibodies (HAMA). Such samples may show either falsely elevated or falsely depressed values. This assay has been designed to minimize interference from heterophilic antibodies. Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution.

f. Assay cut-off:

See Section 4: Clinical cut-off.

2. Comparison studies:

   a. *Method comparison with predicate device:*

      Not applicable.

   b. *Matrix comparison:*

      Not applicable.

3. Clinical studies:

   a. *Clinical Sensitivity:*

      A clinical study was performed to evaluate the clinical performance of the device at the different clinical cut-offs (see section 5, Expected values/Reference range, below). A multicenter prospective study evaluated 2498 patients from emergency departments presenting with chest pain or equivalent symptoms suggestive of acute coronary syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction (MI). Serial samples were collected from patients presenting to the emergency department. The number of patients adjudicated with an MI was 13% (325/2498). The sample collection times were at 0 – 1.5 hours (from time since presentation) and at the following timepoint relative to the time from presentation: 1.5 to 2.5 hours, 2.5 to 3.5 hours, 3.5 to 4.5 hours, 4.5 to 6 hours, 6 to 9 hours, 9 to 24 hours, and greater than 24 hours after presentation to the emergency department. Investigators and adjudicators were blinded to the proposed device's results. Adjudicators were also blinded to site diagnoses. All results presented below were based on the adjudicated diagnoses. Clinical performance was estimated at overall (male and female combined) and male- and female-specific 99th percentile upper reference limit (URL) cut-offs, calculated as described in Section 5, Expected values/Reference range, below. The results are summarized below.

Using the overall 99th percentile (58.9 pg/mL), the following results were obtained for males and females combined:

Interval (hr)	Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
	Result	95%CI	Result	95%CI	Result	95%CI	Result	95%CI
0-<1.5	79.0	71.4-85.0	92.5	90.6-94.0	59.9	52.6-66.7	96.9	95.5-97.8
1.5-<2.5	89.9	85.4-93.1	91.2	89.7-92.5	59.6	54.5-64.6	98.4	97.7-98.9
2.5-<3.5	90.5	85.6-93.8	90.6	89.0-92.1	58.3	52.7-63.6	98.5	97.7-99.0
3.5-<4.5	93.2	87.9-96.2	90.9	89.0-92.4	57.6	51.2-63.8	99.0	98.2-99.5
4.5-<6	94.2	86.0-97.7	88.9	85.7-91.4	55.6	46.5-64.2	99.0	97.6-99.6
6-<9	92.7	88.1-95.6	87.4	85.1-89.4	60.6	54.9-66.0	98.3	97.1-99.0
9-24	93.1	88.9-95.7	85.5	83.0-87.8	62.4	57.0-67.5	97.9	96.6-98.8
<24	93.8	85.0-97.5	85.8	81.0-89.6	62.5	52.5-71.5	98.2	95.5-99.3

Using female-specific 99th percentiles (53.7 pg/mL), the following results were obtained in females:

Interval (hr)	Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
	Result	95%CI	Result	95%CI	Result	95%CI	Result	95%CI
0-<1.5	83.3	69.4-91.7	94.4	91.7-96.2	60.3	47.5-71.9	98.2	96.4-99.1
1.5-<2.5	89.6	80.8-94.6	92.3	90.1-94.0	55.2	46.5-63.6	98.8	97.7-99.4
2.5-<3.5	94.4	86.4-97.8	92.6	90.3-94.4	59.3	50.1-67.9	99.3	98.2-99.7
3.5-<4.5	94.0	83.8-97.9	91.4	88.6-93.6	52.8	42.5-62.8	99.3	98.1-99.8
4.5-<6	96.3	81.7-99.3	86.0	81.1-89.8	43.3	31.6-55.9	99.5	97.4-99.9
6-<9	94.0	85.6-97.7	88.1	84.5-91.0	58.3	48.9-67.2	98.8	97.0-99.5
9-24	93.1	84.8-97.0	89.0	85.2-91.9	63.8	54.3-72.4	98.4	96.3-99.3
<24	96.4	82.3-99.4	83.8	75.8-89.5	60.0	45.5-73.0	98.9	94.2-99.8

Using the male-specific 99th percentiles (78.5 pg/mL), the following results were obtained in males:

Interval (hr)	Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
	Result	95%CI	Result	95%CI	Result	95%CI	Result	95%CI
0-<1.5	74.0	64.4-81.7	92.5	90.0-94.4	62.8	53.6-71.2	95.4	93.3-96.9
1.5-<2.5	84.5	78.1-89.3	91.8	89.9-93.4	64.5	57.8-70.6	97.1	95.8-98.0
2.5-<3.5	85.2	78.0-90.3	90.4	88.1-92.3	60.2	52.9-67.1	97.3	95.8-98.3
3.5-<4.5	86.5	78.2-91.9	92.4	90.1-94.3	64.3	55.8-72.1	97.7	96.2-98.7
4.5-<6	88.1	75.0-94.8	92.0	87.7-94.9	67.3	54.1-78.2	97.6	94.6-99.0
6-<9	87.9	81.0-92.5	90.6	87.9-92.8	68.6	61.0-75.3	97.0	95.1-98.2
9-24	90.3	84.3-94.1	87.2	84.0-89.9	67.4	60.5-73.6	96.8	94.8-98.1
<24	88.9	74.7-95.6	91.6	85.9-95.1	72.7	58.2-83.7	97.0	92.6-98.8

The following statements about cut-offs are included in the labeling:

Using the higher male-specific 99th percentile instead of the overall 99th percentile of 58.9 pg/mL (ng/L) may result in a higher proportion of negative test results for males that are MI. For males that are MI, data analyzed using the male-specific cut-off versus the overall cutoff increased the false-negative rate by up to 3.8%.

Using the lower female-specific 99th percentile instead of the overall 99th percentile of 58.9 pg/mL (ng/L) may result in a higher proportion of positive test results for females that are non-MI. Taking into consideration the lower bound of the 95% confidence interval, in the worst-case scenario (samples drawn at ≥4.5-<6 hours after presentation), up to 68% of positive test results for females may be non-MI.

b. Clinical specificity:

See clinical sensitivity section, M.3.a., above.

4. Clinical cut-off**:**

The cut-offs for this assay were determined based on the 99th percentile upper reference limit in apparently healthy adults. Please see section 5, Expected values/Reference range, below for the determination of the clinical cut-offs.

5. Expected values/Reference range:

The sponsor conducted a multicenter prospective study to establish the 99th percentile in a population of apparently healthy adults.

Lithium-heparin plasma specimens were collected from apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections from the United States who ranged in age from 22–91 years of age.

Plasma samples from 2021 subjects were tested in singlicate. The 99th percentile value for results in apparently healthy subjects was calculated. The 99th percentile values were determined using the non-parametric empirical univariate distribution function. The results are summarized below:

Population	N	99th percentile URL pg/mL (ng/L)	95% CI pg/mL (ng/L)
Overall	2021	58.9	42.2-82.
Females	1017	53.7	37.7-115.7
Males	1004	78.5	41.4-114.5

Two female subjects had troponin values of approximately 400 pg/mL and 5000 pg/mL and were considered to be outliers. These results were not included in the 99th percentile determination.

Overall (combination cut-off for all males and females): 58.9 pg/mL

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.