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

A. 510(k) Number:

K171274

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:

ADVIA Centaur High-Sensitivity Troponin I (TNIH)

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 ADVIA Centaur High-Sensitivity Troponin I (TNIH) assay is for in vitro diagnostic

use in the quantitative measurement of cardiac troponin I in human serum or plasma (lithium heparin) using the ADVIA Centaur XP 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:

    ADVIA Centaur XP

I. Device Description:

ADVIA Centaur TNIH ReadyPack primary reagent pack; Lite Reagent consists of 8.0 mL/reagent pack with bovine serum albumin (BSA) conjugated to a recombinant monoclonal Fab anti-human cTnI (~0.2–0.4 µg/mL) labeled with acridinium ester in HEPES buffer with stabilizers and preservatives

ADVIA Centaur TNIH ReadyPack primary reagent pack; Solid Phase Reagent 13.0 mL/reagent pack with 0.45 mg/mL streptavidin-coated magnetic latex particles with 2 biotinylated (mouse and sheep) monoclonal anti-troponin I antibodies in buffer with stabilizers and preservatives

ADVIA Centaur TNIH High Calibrator 1.0 mL/vial after reconstitution human serum with human cTnI and preservatives (lyophilized)

ADVIA Centaur TNIH Low Calibrator 1.0 mL/vial HEPES buffer with bovine serum albumin (BSA), surfactants, and preservatives (liquid)

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	**ADVIA Centaur TNIH (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 (AMI).	Same
Type of immunoassay	Sandwich immunoassay	Same
Calibration	2-point calibration	Same

Differences		
Item	**ADVIA Centaur TNIH (Candidate Device)**	**Elecsys Troponin T Gen 5 STAT Immunoassay K162895 (Predicate Device)**
Analyte	Cardiac troponin I	Cardiac troponin T
Detection technology	Chemiluminescence	Electrochemiluminescence
Specimen Type	Serum and lithium heparin plasma	Lithium heparin plasma
Upper 99th percentile cutoff	Lithium Heparin: Female: 36.99 pg/mL Male: 57.27 pg/mL Combined: 47.34 pg/mL Serum: Female: 39.59 pg/mL Male: 58.05 pg/mL Combined: 46.47 pg/mL Overall (for serum and plasma males and females): 47.34 pg/mL	Lithium Heparin: Female: 14 pg/mL Male: 22 pg/mL Combined: 19 pg/mL
Measuring range	2.50-25,000 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—Second Edition

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

L. Test Principle:

The ADVIA Centaur TNIH is a 3-site sandwich immunoassay using direct chemiluminometric technology. The Solid Phase reagent is magnetic latex particles conjugated with streptavidin with two bound biotinylated capture monoclonal antibodies each recognizing a unique cardiac troponin I (cTnI) epitope.

The Lite Reagent comprises a conjugate whose architecture consists of a proprietary acridinium ester and a recombinant anti-human cTnI sheep Fab covalently attached to BSA for chemiluminescent detection. The accumulated light signal is directly related to the sample cTnI concentration.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:
The sponsor evaluated precision in several studies following the recommendations in CLSI EP05-A3. The ADVIA Centaur TNIH precision study was performed in a single-site for 20 days using two instruments, one reagent lot with two readings a day with native patient samples and samples from AMI patients that were diluted with native serum or lithium heparin plasma from healthy subjects for a total of 80 replicates per troponin level. Within-lab precision estimate is a total of within-run variability, within-day run-to-run variability, and day-to-day variability.

Within-laboratory precision studies:

		Concentration pg/mL	**Repeatability (Within-Run)**		**Within-Lab**	
			SD	**%CV**	**SD**	**%CV**
Instrument 1	Serum	12.68	0.45	3.6	0.62	4.9
		145.93	1.84	1.3	2.28	1.6
		1522.05	13.56	0.9	21.32	1.4
		13436.79	104.88	0.8	148.73	1.1

		Concentration pg/mL	Repeatability (Within-Run)		Within-Lab	
			SD	%CV	SD	%CV
	Plasma	13.11	0.63	4.8	0.70	5.4
		138.62	1.81	1.3	2.68	1.9
		1461.93	12.47	0.9	17.52	1.2
		14099.79	102.77	0.7	133.95	0.9
Instrument 2	Serum	11.94	0.32	2.7	0.45	3.8
		143.33	1.52	1.1	1.96	1.4
		1497.26	16.44	1.1	21.28	1.4
		13376.58	112.43	0.8	126.94	0.9
	Plasma	12.33	0.36	2.9	0.42	3.4
		136.56	1.44	1.1	2.04	1.5
		1430.42	14.12	1.0	20.28	1.4
		13981.63	115.66	0.8	164.50	1.2

Additional precision studies evaluated lot-to-lot imprecision using 3 reagent lots for 6 serum and 4 plasma samples over 20 days on two instruments and provided similar results to those reported above.

Site-to-site reproducibility was evaluated on the ADVIA Centaur TNIH across 3 sites, 1 lot of reagents, for 5 days with 2 samples a day and 3 replicates a day in accordance with CLSI EP05-A3. The precision reported in the site-to-site variability study was similar to the results reported above in the instrument-to-instrument study.

b. Linearity/assay reportable range:

Two linearity studies were performed according to CLSI EP06-A ranging from 0 to 150 pg/mL and 2 to 25,000 pg/mL. High serum and lithium heparin plasma pools were prepared by diluting native cTnI samples from AMI patients with negative samples from healthy subjects. Low pools were prepared from negative samples from healthy subjects. Each dilution series comprised of 9 levels that were prepared by mixing the high and low pools. The mean was taken from each sample tested in duplicate. Test results did not deviate from linearity by more than 10%.

Representative results for weighted linear regression are shown below:

Li Hep Plasma
y = 1.016x - 0.028 pg/mL

Serum
y = 0.943x + 0.339 pg/mL

The measuring range is 2.5-25000 pg/mL with the upper end of the measuring range being defined by the 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:
A study was performed to evaluate hook effect. There was no hook effect with the ADVIA Centaur TNIH assay up to 611,899 pg/mL in lithium heparin plasma and up to 578,452 pg/mL in serum.

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

Traceability
The sponsor's traceability scheme was reviewed and found acceptable. The Centaur hs-TnI primary standards are traceable to a commercially available troponin assay.

d. *Detection limit:*

Limit of Blank (LoB) Test Protocol

Limit of Blank was determined for the ADVIA Centaur TNIH assay as described in CLSI Guideline EP17-A2. Testing was performed using three lots of ADVIA Centaur TNIH reagents, each on one ADVIA Centaur XP instrument. 240 determinations per matrix per lot were obtained by testing four serum negative basepools or four lithium heparin plasma negative basepools in twenty replicates a day for three days. LoB was calculated non-parametrically. The largest estimate across all reagent lot-matrix-instrument combinations tested was taken as the LoB estimate for the measurement procedure

Limit of Detection (LoD) Test Protocol

Limit of Detection studies were performed using 3 lots of ADVIA Centaur TNIH reagents, each on two ADVIA Centaur XP instruments. 640 determinations per matrix per lot were obtained by testing four low analyte serum samples or four low analyte lithium heparin plasma samples on two instruments in two replicates in two runs each day for twenty days.

The Limit of Detection was determined as the dose at which 95% of the measurements would be greater than the LoB. The largest estimate across all reagent

lot-matrix-instrument combinations tested was taken as the LoD estimate for the measurement procedure.

Limit of Quantitation (LoQ) Protocol
Six low troponin lithium heparin plasma pools and seven low troponin serum pools across three lots and two instruments were used in these studies.

For each reagent lot, the within-laboratory precision over twenty consecutive working days 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-matrix-instrument combinations tested was taken as the LoQ estimate for the measurement procedure.

The sponsor claims an LoB of 0.50 pg/mL, an LoD of 1.60 pg/mL, and an LoQ of 2.50 pg/mL.

e. *Analytical specificity:*

Endogenous interference studies were performed according to CLSI EP07-A2. Two sample pools per matrix were tested. One sample pool had 20-60 pg/mL cTnI. The second sample pool had 1000-2000 pg/mL cTnI. These sample pools were spiked with potential interferents. Control samples were prepared by spiking sample pools with the appropriate diluent at the same volume as the interfering substance stock. Test results from samples spiked with the potential interferent were compared to test results from the control samples. At the tested concentrations, these compounds caused <10% interference on the ADVIA Centaur TNIH assay.

Endogenous Substance	Highest Concentration Tested without Significant Interference
Bilirubin (Conjugated)	40 mg/dL
Bilirubin (Unconjugated)	60 mg/dL
Biotin	3500 ng/mL
Cholesterol	500 mg/dL
Hemoglobin	500 mg/dL
Protein (Albumin)	6 g/dL
Protein (Gamma Globulin)	2.5 g/dL
Protein (Total)	12 g/dL
Triglycerides	2000 mg/dL

There is no significant interference from endogenous substances listed above.

Human anti-mouse antibodies (HAMA) and rheumatoid factor (RF) Interference:
The interference study was designed in accordance with CLSI EP7-A2 to evaluate the performance of the ADVIA Centaur TNIH assay in samples containing high levels of HAMA and RF. Interference was tested at a troponin concentration near the 99th

percentile (i.e. 30-100 pg/mL). A total of three serum and three lithium heparin plasma samples were used in this study. The high RF (1100 IU/mL) sample and the high HAMA (~200 ng/mL) sample were spiked into serum and lithium heparin plasma samples. Interference was <10% using the ADVIA Centaur TNIH assay at all combinations of HAMA/RF and troponin tested.

Therapeutic drug interference studies were performed according to CLSI EP07-A2. Two sample pools per matrix were tested. One sample pool had 20-60 pg/mL cTnI. The second sample pool had 1000-2000 pg/mL cTnI. These sample pools were spiked with potential interferents at low and high levels. Control samples were prepared by spiking sample pools with the appropriate diluent at the same volume as the interfering substance stock. At the tested concentrations, all drugs caused <10% interference on the ADVIA Centaur TNIH assay.

Drug	**Highest Concentration Tested without Significant Interference**
Abciximab	40 µg/mL
Acetominophen	1324 µmol/L
Acetylsalicylic Acid	3.62 mmol/L
Allopurinol	294 µmol/L
Amiodarone	8.92 µmol/L
Ampicilin	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	400 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
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	30 U/mL
Methotrexate	2 mmol/mL
Methyldopa	71 µmol/L

Drug	Highest Concentration Tested without Significant Interference
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
Propanolol	7.71 µmol/L
Quinidine	37 µmol/L
Simvastatin	32 µmol/L
Theophylline	222 µmol/L
Thyroxine	1.01 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:
To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma and serum patient samples at two TnI concentrations (~ 0 and 20 - 60 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 0.0% 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

The following limitations are included in the labeling:

Specimens from some individuals with pathologically high gamma globulin levels may demonstrate depressed troponin values. Additional information may be required for diagnosis.

Heterophilic antibodies and rheumatoid factor in human serum can react with reagent immunoglobulins, interfering with in vitro immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed. Additional information may be required for diagnosis.

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 when tested with this method.

An unknown interference was observed in analytical spiking and dilution studies causing negative bias that may affect interpretation of patient results. The unknown interference may be due to the presence of troponin autoantibodies, which have been reported in up to 10% of patients with or without AMI and up to 20% of patients positive for rheumatoid factor. If the cTnI result is below the 99th percentile value at the first blood draw, at least two additional blood samples should be drawn before results are interpreted as negative for AMI.

f. Assay cut-off:

Not applicable. See section 4, Clinical cut-off, below.

2. Comparison studies:

a. Method comparison with predicate device:

Not applicable.

b. Matrix comparison:

Not applicable. All performance studies were performed in all applicable matrices (lithium heparin plasma and serum).

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 enrolled 2495 patients from Emergency

Departments presenting with chest pain or equivalent ischemic 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 within 24 hours of presentation to the Emergency Department. The number of patients adjudicated with an MI was 13% (329/2495). 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 across both matrices) and male- and female-specific 99th percentile upper reference limit (URL) cut-offs for each matrix type, calculated as described in Section 5, Expected values/reference Range, below. The results are summarized below.

Lithium Heparin Plasma:

Overall 99th percentile = 47.34 pg/mL for overall (both lithium heparin and serum samples for males and females combined)

	Sensitivity		**Specificity**	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	78.0%	70.5–84.1	92.8%	91.0–94.3
≥ 1.5 – < 2.5	89.5%	85.0–92.8	90.7%	89.2–92.0
≥ 2.5 – < 3.5	92.9%	88.5–95.7	90.4%	88.7–91.9
≥ 3.5 – < 4.5	91.3%	85.6–94.8	90.9%	89.0–92.5
≥ 4.5 – < 6	95.2%	86.9–98.4	89.5%	86.3–92.0
≥ 6 – < 9	92.8%	88.3–95.7	88.1%	85.8–90.1
≥ 9 – < 24	92.9%	88.7–95.7	85.9%	83.4–88.1
≥ 24	93.5%	84.6–97.5	86.2%	81.3–89.9

	Positive Predictive value (PPV)		**Negative Predictive Value (NPV)**	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	61.5%	54.2–68.3	96.6%	95.3–97.6
≥ 1.5 – < 2.5	58.5%	53.4–63.5	98.3%	97.5–98.9
≥ 2.5 – < 3.5	58.8%	53.3–64.1	98.9%	98.1–99.3
≥ 3.5 – < 4.5	58.1%	51.7–64.3	98.7%	97.8–99.2
≥ 4.5 – < 6	55.6%	46.2–64.6	99.3%	97.9–99.8
≥ 6 – < 9	62.9%	57.2–68.3	98.2%	97.1–99.0
≥ 9 – < 24	62.5%	57.1–67.7	98.0%	96.7–98.8
≥ 24	63.0%	52.8–72.2	98.1%	95.3–99.3

Females (99th percentile = 36.99 pg/mL for lithium heparin plasma)

	Sensitivity		Specificity	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	82.9%	68.7- 91.5	93.9%	91.1- 95.9
≥ 1.5 – < 2.5	89.5%	80.6- 94.6	91.8%	89.6- 93.6
≥ 2.5 – < 3.5	95.8%	88.5- 98.6	91.9%	89.5- 93.8
≥ 3.5 – < 4.5	94.2%	84.4- 98.0	89.4%	86.3- 91.8
≥ 4.5 – < 6	95.8%	79.8- 99.3	86.2%	81.2- 90.0
≥ 6 – < 9	95.7%	88.1- 98.5	87.8%	84.1- 90.8
≥ 9 – < 24	94.4%	86.4- 97.8	88.8%	85.0- 91.7
≥ 24	100.0%	86.7- 100	82.1%	73.7- 88.2

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	58.6%	45.8- 70.4	98.2%	96.2- 99.1
≥ 1.5 – < 2.5	54.0%	45.3- 62.4	98.8%	97.6- 99.4
≥ 2.5 – < 3.5	58.5%	49.5- 67.0	99.5%	98.4- 99.8
≥ 3.5 – < 4.5	49.0%	39.4- 58.7	99.3%	98.0- 99.8
≥ 4.5 – < 6	41.1%	29.2- 54.1	99.5%	97.3- 99.9
≥ 6 – < 9	59.8%	50.6- 68.4	99.1%	97.3- 99.7
≥ 9 – < 24	63.2%	53.7- 71.8	98.7%	96.8- 99.5
≥ 24	56.8%	42.2- 70.3	100.0%	95.8- 100

Males (99th percentile URL = 57.27 pg/mL for lithium heparin plasma)

	Sensitivity		Specificity	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	74.0%	64.6–81.6	92.0%	89.4- 94.0
≥ 1.5 – < 2.5	87.7%	81.7–91.9	90.7%	88.6- 92.4
≥ 2.5 – < 3.5	89.7%	83.1–93.9	90.1%	87.8- 92.1
≥ 3.5 – < 4.5	86.6%	78.4–92.0	92.5%	90.1–94.3
≥ 4.5 – < 6	92.3%	79.7–97.3	92.2%	87.9–95.1
≥ 6 – < 9	87.9%	81.0–92.5	88.8%	85.9–91.3
≥ 9 – < 24	91.5%	85.7–95.1	84.7%	81.3–87.6
≥ 24	86.5%	72.0–94.1	89.3%	83.1–93.4

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	62.2%	53.2- 70.4	95.2%	93.1- 96.7
≥ 1.5 – < 2.5	62.6%	56.1- 68.6	97.6%	96.4- 98.5
≥ 2.5 – < 3.5	60.8%	53.6- 67.5	98.1%	96.8- 98.9
≥ 3.5 – < 4.5	65.1%	56.6–72.8	97.7%	96.1–98.7
≥ 4.5 – < 6	67.9%	54.5–78.9	98.5%	95.8–99.5
≥ 6 – < 9	65.3%	57.8–72.1	96.9%	94.9–98.1
≥ 9 – < 24	63.2%	56.4–69.6	97.2%	95.2–98.4
≥ 24	68.1%	53.8–79.6	96.2%	91.3–98.3

Serum:
Overall 99th percentile = 47.34 pg/mL for overall (both lithium heparin and serum samples for males and females combined)

	Sensitivity		Specificity	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	78.9%	71.4–84.8	93.1%	91.4–94.6
≥ 1.5 – < 2.5	88.6%	83.9–92.0	91.4%	90.0–92.7
≥ 2.5 – < 3.5	92.1%	87.4–95.2	91.2%	89.6–92.6
≥ 3.5 – < 4.5	90.3%	84.4–94.2	91.5%	89.7–93.0
≥ 4.5 – < 6	96.8%	89.0–99.1	89.1%	85.9–91.6
≥ 6 – < 9	91.6%	86.8–94.8	88.5%	86.3–90.4
≥ 9 – < 24	93.0%	88.8–95.7	86.7%	84.2–88.8
≥ 24	92.3%	83.2–96.7	86.3%	81.5–90.0

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	62.6%	55.3–69.3	96.8%	95.5–97.8
≥ 1.5 – < 2.5	59.9%	54.7–64.9	98.2%	97.4–98.8
≥ 2.5 – < 3.5	59.1%	53.4–64.6	98.8%	98.1–99.3
≥ 3.5 – < 4.5	58.5%	51.9–64.7	98.6%	97.7–99.2
≥ 4.5 – < 6	54.5%	45.2–63.5	99.5%	98.2–99.9
≥ 6 – < 9	62.6%	56.8–68.1	98.0%	96.8–98.8
≥ 9 – < 24	63.8%	58.3–68.9	98.0%	96.7–98.8
≥ 24	63.2%	53.1–72.2	97.8%	94.9–99.0

Females (99th percentile = 39.59 pg/mL for serum)

	Sensitivity		Specificity	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	80.5%	66.0- 89.8	94.8%	92.2- 96.6
≥ 1.5 – < 2.5	88.3%	79.3- 93.7	91.9%	89.7- 93.7
≥ 2.5 – < 3.5	95.5%	87.6- 98.5	92.8%	90.5- 94.6
≥ 3.5 – < 4.5	93.6%	82.8- 97.8	90.3%	87.3- 92.6
≥ 4.5 – < 6	95.8%	79.8- 99.3	87.0%	82.2- 90.7
≥ 6 – < 9	95.6%	87.8- 98.5	88.7%	85.1- 91.5
≥ 9 – < 24	94.4%	86.4- 97.8	89.8%	86.2- 92.5
≥ 24	96.4%	82.3- 99.4	84.1%	76.0- 89.8

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	61.1%	47.8- 73.0	98.0%	96.0- 99.0
≥ 1.5 – < 2.5	54.4%	45.7- 62.9	98.6%	97.4- 99.3
≥ 2.5 – < 3.5	59.3%	49.8- 68.1	99.5%	98.5- 99.8
≥ 3.5 – < 4.5	48.4%	38.4- 58.5	99.3%	98.0- 99.8
≥ 4.5 – < 6	42.6%	30.3- 55.8	99.5%	97.3- 99.9
≥ 6 – < 9	60.2%	50.8- 68.9	99.1%	97.4- 99.7
≥ 9 – < 24	65.0%	55.5- 73.6	98.8%	96.8- 99.5
≥ 24	61.4%	46.6- 74.3	98.9%	94.0- 99.8

Males (99th percentile = 58.05 pg/mL for serum)

	Sensitivity		Specificity	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	75.2%	66.0- 82.6	92.8%	90.4- 94.7
≥ 1.5 – < 2.5	85.5%	79.2- 90.2	91.5%	89.6- 93.2
≥ 2.5 – < 3.5	86.2%	79.0- 91.2	91.1%	88.9- 93.0
≥ 3.5 – < 4.5	84.7%	76.3- 90.5	93.1%	90.7- 94.8
≥ 4.5 – < 6	94.7%	82.7- 98.5	90.9%	86.4- 94.0
≥ 6 – < 9	87.7%	80.7- 92.4	90.5%	87.7- 92.7
≥ 9 – < 24	91.6%	85.9- 95.1	86.1%	82.8- 88.9
≥ 24	89.2%	75.3- 95.7	89.9%	84.0- 93.8

	Positive Predictive value		Negative Predictive	
Interval (hr)	**Estimate (%)**	**95% CI**	**Estimate (%)**	**95% CI**
0 – < 1.5	65.0%	56.0- 73.0	95.5%	93.5- 96.9
≥ 1.5 – < 2.5	63.6%	56.9- 69.7	97.3%	96.1- 98.2
≥ 2.5 – < 3.5	61.3%	53.8- 68.2	97.6%	96.2- 98.5
≥ 3.5 – < 4.5	66.4%	57.7- 74.1	97.4%	95.8- 98.4
≥ 4.5 – < 6	64.3%	51.2- 75.5	99.0%	96.5- 99.7
≥ 6 – < 9	68.2%	60.5- 74.9	96.9%	95.0- 98.1
≥ 9 – < 24	65.5%	58.7- 71.7	97.3%	95.3- 98.4
≥ 24	68.8%	54.7- 80.1	97.1%	92.7- 98.9

The following statements about cutoffs are included in the labeling:

"Using the higher male-specific 99th percentiles instead of the overall 99th percentile of 47.34 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 cutoff versus the overall cutoff increased the false-negative rate by up to 2.9%."

"Using the lower female-specific 99th percentiles instead of the overall 99th percentile of 47.34 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 (lithium-heparin plasma drawn at ≥4.5-<6 hours after presentation) up to 71% of positive test results for females may be non-MI."

b. Clinical specificity:

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

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

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 health adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Serum and lithium-heparin plasma specimens were collected from 1990 apparently health 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.

Both male and female subjects were included in the reference range study to determine the 99th percentile URL using a non-parametric empirical univariate distribution function. Results are as follows:

Population	N	99th Percentile Upper Reference Limit in pg/mL	
		Lithium Heparin Plasma	Serum
Females	1006	36.99 pg/mL	39.59 pg/mL
Males	984	57.27 pg/mL	58.05 pg/mL
Overall (males and females combined)	1990	47.34 pg/mL	46.47 pg/mL

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. The sponsor demonstrated that the change in the cut-off values (either for women or overall) were not impacted by this exclusion.

Overall (combination of all cut-offs for both serum and plasma): 47.34 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.