

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

A. 510(k) Number:

K171566

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:

Atellica IM High-Sensitivity Troponin I (TnIH)

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
MMI	Class II	21 CFR 862.1215 - Creatine phosphokinase/creatinine 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 Atellica IM 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 Atellica IM Analyzer. 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:

Atellica IM Analyzer

I. Device Description:

Atellica IM 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

Atellica IM 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

Atellica IM TnIH High Calibrator 1.0 mL/vial after reconstitution in human serum with human cTnI and preservatives (lyophilized)

Atellica IM 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	Atellica IM 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	Atellica IM 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 99 th percentile cutoff	Lithium Heparin: Female: 34.11 pg/mL Male: 53.48 pg/mL Combined: 45.20 pg/mL Serum: Female: 38.64 pg/mL Male: 53.53 pg/mL Combined: 45.43 pg/mL	Lithium Heparin: Female: 14 pg/mL Male: 22 pg/mL Combined: 19 pg/mL

Differences		
Item	Atellica IM TnIH (Candidate Device)	Elecsys Troponin T Gen 5 STAT Immunoassay K162895 (Predicate Device)
	Overall: 45.20 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:

Atellica IM 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 bovine serum albumin (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 Atellica 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. The 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:

			Repeatability (Within-Run)		Within-Lab	
Instrument	Matrix	Mean (pg/mL)	SD (pg/ml)	%CV	SD (pg/ml)	%CV
Atellica IM 1	Plasma	12.09	0.52	4.3	0.56	4.7
		132.87	1.87	1.4	2.67	2.0
		1389.67	19.64	1.4	25.20	1.8
		13137.37	123.44	0.9	218.82	1.7
	Serum	12.84	0.60	4.6	0.64	5.0
		130.24	2.02	1.6	2.89	2.2
		1356.95	12.43	0.9	23.13	1.7
		14115.55	128.84	0.9	207.91	1.5
Atellica IM 2	Plasma	12.03	0.49	4.1	0.64	5.3
		131.21	2.23	1.7	2.75	2.1
		1363.38	27.11	2.0	32.00	2.3
		12862.97	212.91	1.7	291.00	2.3
	Serum	12.72	0.55	4.3	0.59	4.7
		127.93	2.30	1.8	3.09	2.4
		1334.97	22.28	1.7	27.48	2.1
		13815.89	192.05	1.4	266.91	1.9

Additional precision studies evaluated lot-to-lot imprecision using three reagent lots

for six serum and four plasma samples over 20 days on two instruments and provided similar results to those reported above. Site-to-site reproducibility was evaluated on the Atellica IM TnIH across three sites, one lot of reagents, for five days with two samples a day and three 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 with samples ranging from 0.28 to 150 pg/mL and 2.34 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 nine 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

$$y = 1.016x - 0.028 \text{ pg/mL}$$

Serum

$$y = 0.943x + 0.339 \text{ pg/mL}$$

The measuring range is 2.5-25000 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 Atellica IM TnIH assay up to 530,976 pg/mL in lithium heparin plasma and up to 603,244 pg/mL in serum.

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

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

d. Detection limit:

Limit of Blank (LoB) Test Protocol

The LoB was determined for the Atellica IM TnIH assay as described in CLSI Guideline EP17-A2. Testing was performed using three lots of the Atellica IM TnIH reagents, each on one Atellica IM analyzer. 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 of all reagent lot-matrix-instrument combinations tested was taken as the LoB estimate for the measurement procedure.

Limit of Detection (LoD) Test Protocol

The LoD was determined for the Atellica IM TnIH assay in accordance with CLSI Guideline EP17-A2. Testing was performed using three lots of Atellica IM TnIH, each on two Atellica IM TnIH instruments. For lithium heparin plasma, 960 determinations per lot were obtained by testing six low analyte lithium heparin plasma samples on two instruments in two replicates during two runs each day for twenty days. For serum, 1120 determinations per lot were obtained by testing seven low analyte serum samples on two instruments in two replicates during two runs each day for twenty days.

The LoD 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 were utilized for the study. Testing was performed using three lots of Atellica IM TnIH, each on two Atellica IM TnIH instruments.

For each reagent lot and matrix combination, 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 highest value calculated of all reagent lot-matrix combinations tested was taken as the LoQ estimate for the measurement procedure.

The sponsor claims an LoB of 0.50 pg/mL, and LoD of 1.7 pg/mL, and an LoQ of 2.5 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 Atellica IM TnIH assay.

Endogenous Substance	Highest Concentration Tested Without Significant Interference
Bilirubin (Conjugated)	40 mg/dL
Bilirubin (Unconjugated)	60 mg/dL
Biotin	3,500 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

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 Atellica IM 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 Atellica IM 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 Atellica IM TnIH assay.

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	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
Methylprednisolone	40 µg/mL
Mexiletine	22.3 µmol/L
Nicotine	6.2 µmol/L

Drug	Highest Concentration Tested without Significant Interference
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	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

Potential cross-reactivity of drugs and metabolites on the Atellica IM TnIH assay was evaluated in accordance with CLSI document EP07-A2.

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:

See Section 4: Clinical cut-off.

2. Comparison studies:

a. Method comparison with predicate device:

Not applicable.

b. Matrix comparison:

Not applicable. All 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 2494 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% (326/2494). 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. The results are summarized below.

Lithium Heparin Plasma:

Overall 99th percentile = 45.20 pg/mL for overall (both lithium heparin and serum samples for males and females combined)

Interval (hr)	Sensitivity		Specificity	
	Estimate (%)	95%CI	Estimate (%)	95%CI
0 – < 1.5	77.2	69.8-83.3	91.8	89.9-93.4
≥ 1.5 – < 2.5	90	85.6-93.2	90.6	89.1-91.9
≥ 2.5 – < 3.5	92	87.5-95.0	90.6	88.9-92.0
≥ 3.5 – < 4.5	92.6	87.3-95.8	90.9	89.1-92.5
≥ 4.5 – < 6	97	89.6-99.2	89.2	86.0-91.7
≥ 6 – < 9	92.7	88.2-95.6	87.6	85.3-89.6
≥ 9 – < 24	94	89.9-96.4	86.6	84.1-88.7
≥ 24	93.5	84.6-97.5	83.4	78.3-87.5

Interval (hr)	Positive Predictive Value (PPV)		Negative Predictive Value (NPV)	
	Estimate (%)	95%CI	Estimate (%)	95%CI
0 – < 1.5	58.6	51.6-65.4	96.4	95.0-97.4
≥ 1.5 – < 2.5	58.5	53.4-63.5	98.4	97.6-98.9
≥ 2.5 – < 3.5	58.9	53.4-64.2	98.7	97.9-99.2
≥ 3.5 – < 4.5	58.5	52.1-64.6	98.9	98.0-99.4
≥ 4.5 – < 6	56.1	47.0-64.9	99.5	98.3-99.9
≥ 6 – < 9	61.5	55.8-66.9	98.3	97.1-99.0
≥ 9 – < 24	64.3	58.9-69.4	98.2	97.0-99.0
≥ 24	58	48.2-67.2	98.1	95.3-99.3

Females (99th percentile = 34.11 pg/mL for lithium heparin plasma)

Interval (hr)	Sensitivity		Specificity	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	84.4	71.2-92.3	93.3	90.4-95.3
≥ 1.5 – < 2.5	89.9	81.3-94.8	91.7	89.4-93.5
≥ 2.5 – < 3.5	94.5	86.7-97.8	91.6	89.2-93.6
≥ 3.5 – < 4.5	94	83.8-97.9	89.5	86.5-91.9
≥ 4.5 – < 6	96.2	81.1-99.3	87	82.1-90.7
≥ 6 – < 9	94.2	86.0-97.7	88	84.3-90.9
≥ 9 – < 24	94.6	86.9-97.9	87.4	83.5-90.5
≥ 24	96.3	81.7-99.3	80.9	72.6-87.2

Interval (hr)	Positive Predictive Value (PPV)		Negative Predictive Value (NPV)	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	58.5	46.3-69.6	98.2	96.3-99.1
≥ 1.5 – < 2.5	54.2	45.7-62.5	98.8	97.7-99.4
≥ 2.5 – < 3.5	57	48.1-65.5	99.3	98.2-99.7
≥ 3.5 – < 4.5	48	38.3-57.7	99.3	98.0-99.8
≥ 4.5 – < 6	44.6	32.4-57.6	99.5	97.3-99.9
≥ 6 – < 9	59.1	49.7-67.8	98.8	97.0-99.5
≥ 9 – < 24	61.9	52.7-70.4	98.7	96.7-99.5
≥ 24	55.3	41.2-68.6	98.9	94.0-99.8

Males (99th percentile URL = 53.48 pg/mL for lithium heparin plasma)

Interval (hr)	Sensitivity		Specificity	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	75	65.7-82.5	91.5	88.9-93.5
≥ 1.5 – < 2.5	87.6	81.6-91.8	91.2	89.1-92.8
≥ 2.5 – < 3.5	89.8	83.4-94.0	90	87.6-91.9
≥ 3.5 – < 4.5	90.9	83.6-95.1	92.4	90.0-94.3
≥ 4.5 – < 6	92.5	80.1-97.4	90.6	86.0-93.8
≥ 6 – < 9	91.1	84.8-95.0	88.5	85.5-91.0
≥ 9 – < 24	93.6	88.3-96.6	85.6	82.2-88.4
≥ 24	91.4	77.6-97.0	88.1	81.8-92.4

Interval (hr)	Positive Predictive Value (PPV)		Negative Predictive Value (NPV)	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	61	52.1-69.1	95.4	93.3-96.8
≥ 1.5 – < 2.5	63.8	57.3-69.9	97.6	96.4-98.5
≥ 2.5 – < 3.5	60.5	53.4-67.2	98.1	96.8-98.9
≥ 3.5 – < 4.5	66.7	58.4-74.1	98.4	97.0-99.1
≥ 4.5 – < 6	63.8	50.9-74.9	98.5	95.8-99.5
≥ 6 – < 9	64.9	57.6-71.6	97.7	96.0-98.7
≥ 9 – < 24	65	58.2-71.3	97.9	96.1-98.9
≥ 24	65.3	51.3-77.1	97.7	93.4-99.2

Serum:

Overall 99th percentile = 45.20 pg/mL for overall (both lithium heparin and serum samples for males and females combined)

Interval (hr)	Sensitivity		Specificity	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	78.6	71.1-84.6	92.1	90.3-93.7
≥ 1.5 – < 2.5	87.9	83.1-91.4	90.9	89.5-92.2
≥ 2.5 – < 3.5	90.8	85.9-94.1	90.8	89.1-92.2
≥ 3.5 – < 4.5	91.2	85.5-94.8	91	89.2-92.6
≥ 4.5 – < 6	96.9	89.3-99.1	89.6	86.5-92.1
≥ 6 – < 9	93.5	89.0-96.3	88.7	86.5-90.6
≥ 9 – < 24	93.9	89.8-96.4	86.7	84.2-88.8
≥ 24	90.5	80.7-95.6	85.5	80.6-89.3

Interval (hr)	Positive Predictive Value (PPV)		Negative Predictive Value (NPV)	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	58.8	51.7-65.6	96.8	95.4-97.7
≥ 1.5 – < 2.5	58.5	53.3-63.5	98.1	97.3-98.7
≥ 2.5 – < 3.5	58	52.4-63.4	98.6	97.8-99.1
≥ 3.5 – < 4.5	58	51.6-64.2	98.7	97.8-99.2
≥ 4.5 – < 6	56.9	47.5-65.8	99.5	98.2-99.9
≥ 6 – < 9	62.9	57.1-68.4	98.5	97.4-99.2
≥ 9 – < 24	64.1	58.6-69.2	98.2	97.0-99.0
≥ 24	60.6	50.5-69.9	97.3	94.3-98.8

Females (99th percentile = 38.64 pg/mL for serum)

Interval (hr)	Sensitivity		Specificity	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	81	66.7-90.0	93.4	90.5-95.4
≥ 1.5 – < 2.5	89.6	80.8-94.6	91.8	89.6-93.6
≥ 2.5 – < 3.5	92.5	83.7-96.8	92.4	90.0-94.2
≥ 3.5 – < 4.5	93.8	83.2-97.9	90.3	87.3-92.6
≥ 4.5 – < 6	96.2	81.1-99.3	87.7	82.9-91.3
≥ 6 – < 9	95.2	86.9-98.4	88.6	85.0-91.4
≥ 9 – < 24	94.5	86.7-97.8	89.5	85.8-92.3
≥ 24	96.2	81.1-99.3	82.9	74.8-88.8

Interval (hr)	Positive Predictive Value (PPV)		Negative Predictive Value (NPV)	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	55.7	43.3-67.5	97.9	96.0-99.0
≥ 1.5 – < 2.5	53.9	45.3-62.3	98.8	97.7-99.4
≥ 2.5 – < 3.5	56.9	47.5-65.8	99.1	98.0-99.6
≥ 3.5 – < 4.5	48.9	38.9-59.0	99.3	98.0-99.8
≥ 4.5 – < 6	46.3	33.7-59.4	99.5	97.3-99.9
≥ 6 – < 9	58.3	48.6-67.3	99.1	97.4-99.7
≥ 9 – < 24	65.7	56.2-74.1	98.7	96.7-99.5
≥ 24	56.8	42.2-70.3	98.9	94.2-99.8

Males (99th percentile = 53.53 pg/mL for serum)

Interval (hr)	Sensitivity		Specificity	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	77.6	68.3-84.7	91.6	89.1-93.6
≥ 1.5 – < 2.5	86.4	80.3-90.9	91.5	89.5-93.1
≥ 2.5 – < 3.5	87.5	80.7-92.2	89.9	87.6-91.9
≥ 3.5 – < 4.5	88.9	81.2-93.7	92.7	90.3-94.5
≥ 4.5 – < 6	94.7	82.7-98.5	90.8	86.3-94.0
≥ 6 – < 9	91	84.6-94.9	89.9	87.1-92.2
≥ 9 – < 24	93.6	88.2-96.6	85.6	82.2-88.4
≥ 24	86.5	72.0-94.1	88.9	82.7-93.0

Interval (hr)	Positive Predictive Value (PPV)		Negative Predictive Value (NPV)	
	Estimate(%)	95%CI	Estimate(%)	95%CI
0 – < 1.5	61.3	52.5-69.4	96	94.0-97.3
≥ 1.5 – < 2.5	63.9	57.4-70.0	97.5	96.2-98.3
≥ 2.5 – < 3.5	59.3	52.1-66.0	97.7	96.3-98.6
≥ 3.5 – < 4.5	66.7	58.3-74.1	98.1	96.6-98.9
≥ 4.5 – < 6	64.3	51.2-75.5	99	96.4-99.7
≥ 6 – < 9	67.7	60.2-74.4	97.7	96.0-98.7
≥ 9 – < 24	64.5	57.7-70.8	97.9	96.1-98.9
≥ 24	66.7	52.5-78.3	96.2	91.5-98.4

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

Using the higher male-specific 99th percentiles instead of the overall 99th percentile of 45.20 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 0.9%.

Using the lower female-specific 99th percentiles instead of the overall 99th percentile of 45.20 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 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. Serum and 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 2007 subjects and serum samples from 2001 subjects were tested in singlicate using the Atellica IM TnIH assay. The 99th percentile value for results in apparently healthy subjects was calculated for lithium heparin plasma and serum. The 99th percentile was calculated using a non-parametric empirical univariate distribution function. The results are summarized below:

Sample Matrix	Population	N	99th percentile URL pg/mL (ng/L)	95% CI pg/mL (ng/L)
Lithium	Overall	2007	45.20	33.21–64.30
	Females	1007	34.11	27.36–66.23
	Males	1000	53.48	38.73–80.22
Serum	Overall	2001	45.43	35.47–63.63
	Females	1007	38.64	28.58–72.36
	Males	994	53.53	33.77–78.03

Two female subjects had troponin values of approximately 300 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): 45.43 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.