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

A. 510(k) Number: K162895

B. Purpose for Submission:
New device

C. Measurand:
Cardiac troponin T (cTnT)

D. Type of Test:
Quantitative immunoassay

E. Applicant:
Roche Diagnostics

F. Proprietary and Established Names:
Elecsys Troponin T Gen 5 STAT Immunoassay
Elecsys Troponin T Gen 5 STAT CalSet
Elecsys PreciControl Troponin
Elecsys Troponin T Gen 5 CalCheck 5

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
MMI	Class II	21 CFR 862.1215 - Creatine phosphokinase/creatine kinase or isoenzymes test system	Chemistry
JIT	Class II	21 CFR 862.1150 - Calibrator	
JJX	Class I, Reserved	21 CFR 862.1660 - Quality control material (assayed and unassayed)	
JJY			

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use.

2. Indication(s) for use:
   Elecsys Troponin T Gen 5 STAT Immunoassay
   Immunoassay for the in vitro quantitative determination of cardiac troponin T (cTnT) in lithium heparin plasma. The immunoassay is intended to aid in the diagnosis of myocardial infarction. The electrochemiluminescence immunoassay "ECLIA" is intended for use on the cobas system analyzers.

Elecsys Troponin T Gen 5 STAT CalSet
The Troponin T Gen 5 STAT CalSet is used for calibrating the quantitative Elecsys Troponin T Gen 5 STAT immunoassay on the cobas system analyzers.

Elecsys PreciControl Troponin
PreciControl Troponin is used for quality control of the Elecsys Troponin I and Elecsys Troponin I STAT immunoassays on the Elecsys and cobas e immunoassay analyzers. PreciControl Troponin is also used for quality control of the Elecsys Troponin T Gen 5 STAT Immunoassay on the cobas system analyzers.

Elecsys Troponin T Gen 5 CalCheck 5
The Elecsys Troponin T Gen 5 CalCheck 5 is an assayed control for use in the calibration verification and for use in the verification of the assay range established by the Elecsys Troponin T Gen 5 reagent on the cobas system analyzers.

3. Special conditions for use statement(s):
    - For prescription use
    - For *in vitro* diagnostic use
    - The positive predictive value for females using the lower sex-specific cut-off (14 ng/L) is lower when compared to the higher cut-off of 19 ng/L. When looking at the lower bound of the 95% CI, up to 69%, 82% and 78% of positive test results for females are non-MI. Troponin results should always be used in conjunction with clinical signs and symptoms.

    Please refer to the Analytical specificity section in M.1.e. below for additional limitations.

4. Special instrument requirements:
    Performance data for this submission were generated using the cobas e 411 and cobas e 601 analyzers.

I. Device Description:

Elecsys Troponin T Gen 5 STAT Immunoassay: The reagents are:

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-troponin T-Ab~biotin (gray cap), 1 bottle, 8 mL: Biotinylated monoclonal anti-cardiac troponin T‑antibody (mouse) 2.5 mg/L; phosphate buffer 100 mmol/L, pH 6.0; preservative; inhibitors.

R2 Anti-troponin T-Ab~Ru(bpy)$_3^{2+}$ (black cap), 1 bottle, 8 mL: Monoclonal chimeric anti‑cardiac troponin T‑antibody (mouse/human) labeled with ruthenium complex 2.5 mg/L; phosphate buffer 100 mmol/L, pH 6.0; preservative.

The Elecsys Troponin T Gen 5 STAT CalSet is a lyophilized product consisting of human serum with cardiac troponin T at two concentrations (approximately 18 ng/L or pg/mL and approximately 4200 ng/L or pg/mL).

The Elecsys PreciControl Troponin is a lyophilized product consisting of human serum with added troponin T (recombinant, human) and Troponin I (recombinant, human) at two concentrations. The concentrations of cardiac Troponin T are approximately 30 ng/L or pg/mL and approximately 2500 ng/L or pg/mL. This control material was initially cleared in k082699 as assayed quality control material for other analytes.

The Elecsys Troponin T Gen 5 CalCheck 5 contains 5 lyophilized levels of human recombinant cardiac troponin T in human serum in the following concentrations:

Level	Approximate Target Range (ng/L)
Check 1	≤ 5.0
Check 2	10.5 – 19.5
Check 3	1460 - 2540
Check 4	5840 - >10000
Check 5	7300 - >10000

The labeling states "All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A."

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Elecsys Troponin T STAT Assay, Elecsys Troponin T CalSet, Elecsys PreciControl Troponin, Elecsys CA 15-3 CalCheck 5

2. Predicate 510(k) number(s):
   K051752, K961500, K082699, K122242

3. Comparison with predicate:

Item	Elecsys Troponin T Gen 5 STAT Immunoassay	Elecsys Troponin T STAT Assay (K051752)
Similarities		
Indications for use	Immunoassay for the in vitro quantitative determination of cardiac troponin T in lithium heparin plasma. The immunoassay is intended to aid in the diagnosis of myocardial infarction.	Same
Analyte	Cardiac troponin T	Same
Type of immunoassay	Sandwich immunoassay	Same
Detection technology	Electrochemiluminescence	Same

Item	Elecsys Troponin T Gen 5 STAT Immunoassay	Elecsys Troponin T STAT Assay (K051752)
Differences		
Indications for use	Not indicated for these uses	Indicated for the risk stratification of patients presenting with acute coronary syndrome and for cardiac risk in patients with chronic renal failure. The test may also be useful for the selection of more intensive therapy and intervention in patients with elevated levels of cardiac Troponin T.
Cut-off for the aid in the diagnosis of myocardial infarction	19 ng/L for both sexes based on the 99th percentile upper reference limit of apparently healthy males and females. 14 ng/L for females based on the 99th percentile upper reference limit of apparently healthy females and 22 ng/L for males based on the 99th percentile upper reference limit of apparently healthy males.	0.1 ng/mL based on ROC analysis

Item	Elecsys Troponin T Gen 5 STAT Immunoassay	Elecsys Troponin T STAT Assay (K051752)
Differences		
Type of specimen	Lithium heparin plasma	Plasma and serum
Assay range	6.0 -10000 ng/L	0.01 – 25.0 ng/mL

Item	Elecsys Troponin T Gen 5 STAT CalSet	Elecsys Troponin T CalSet (K961500)
Similarities		
Intended use	Intended for use in the calibration of a troponin assay	Same
Differences		
Troponin T concentrations	2 levels (18 and 4200 ng/L)	2 Levels (0.075 and 10 ng/mL)

Item	Elecsys PreciControl Troponin	Elecsys PreciControl Troponin (K082699)
Similarities		
Intended use	Intended for use in the quality control of a troponin assay	Same
Differences		
Analyte	Troponin T and Troponin I	Troponin I

Item	Elecsys Troponin T Gen 5 CalCheck 5	Elecsys CA 15-3 CalCheck 5 (K122242)
Similarities		
Intended use	Intended for calibration verification and for verification of the assay range	Same
Differences		
Analyte	5 levels of troponin T (< 5 ng/L – 10000 ng/L)	5 Levels of CA 15-3 (1.58 – 300 U/mL)

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

Clinical and Laboratory Standards Institute (CLSI) EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline

CLSI EP6-A: Evaluation of Linearity of Quantitative Measurement Procedures, A Statistical Approach: Approved Guideline

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

L. Test Principle:

The test uses both ruthenium-labeled and biotin-labeled antibodies to form a sandwich complex with cardiac troponin T (cTnT). The formed immune complexes are immobilized onto the surface of magnetic microparticles via biotin-streptavidin binding.

cobas e 411: The sample is mixed with biotinylated monoclonal cTnT-specific antibody and a ruthenium labeled-monoclonal cTnT antibody that react with TnT in the sample to form a sandwich complex. Capture of the sandwich complex occurs during a second incubation.

cobas e 601: The sample is mixed with biotinylated monoclonal cTnT-specific antibody and a ruthenium labeled-monoclonal cTnT antibody that react with TnT in the sample to form a sandwich complex. During this incubation to form the sandwich complex, the complex is also captured to the solid phase.

All analyzers: Microparticles are magnetically captured onto the measurement electrode. Current is applied to the electrode to stimulate chemiluminescent emission that is measured by a photomultiplier. Test results are determined via a calibration curve. The measured electrochemiluminescence signal is proportional to the amount of troponin T in the sample. The STAT assay has a turnaround time of 9 minutes.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision of the Elecsys Troponin T STAT Gen 5 was evaluated in a 21 day precision study performed in-house according to CLSI EP5-A2. The study used a panel of pooled lithium heparin plasma samples: 1 low native sample (close to the Limit of Quantitation), 1 native sample close to the cut-offs, 1 sample at 4000-6000 ng/L spiked with recombinant TnT, and 1 sample at 8000-9000 ng/L spiked with recombinant TnT. The Elecsys PreciControl Troponin controls were also included in this study. Samples were split into aliquots of 4 then 2 aliquots were tested in singlicate for each of 2 runs per day for a total of 4 runs per day. Samples were tested using 3 reagent lots on each a cobas e 411 and cobas e 601, each sample tested 4 times per day for 21 days for a total of 84 measurements per lot. The study results from a representative lot are presented in the following tables for the cobas e 411 and cobas e 601 analyzers.

cobas e 411

Sample	Mean (ng/L)	Repeatability		Within Lab precision	
		SD (ng/L)	CV%	SD (ng/L)	CV%
Control 1	20.01	0.4523	2.3	0.7396	3.7
Control 2	1739	15.45	0.9	36.26	2.1
Sample 1	7.269	0.4084	5.6	0.7459	10.3

Sample	Mean (ng/L)	Repeatability		Within Lab precision	
		SD (ng/L)	CV%	SD (ng/L)	CV%
Sample 2	12.18	0.3733	3.1	0.7171	5.9
Sample 3	4673	38.19	0.8	116.5	2.5
Sample 4	9341	64.48	0.7	261.8	2.8

cobas e 601

Sample	Mean (ng/L)	Repeatability		Within Lab precision	
		SD (ng/L)	CV%	SD (ng/L)	CV%
Control 1	24.15	0.2699	1.1	0.7737	3.2
Control 2	1971	13.26	0.7	44.96	2.3
Sample 1	7.415	0.2243	3.0	0.4731	6.4
Sample 2	13.45	0.2522	1.9	0.5579	4.1
Sample 3	4831	38.04	0.8	123.8	2.6
Sample 4	9455	62.68	0.7	255.5	2.7

An additional precision study was performed with a lithium heparin plasma sample at ≈ 150 ng/L spiked with recombinant TnT using the same testing protocol described above using one reagent lot. The study results are presented in the following tables for the cobas e 411 and cobas e 601 analyzers.

Instrument	Mean (ng/L)	Repeatability		Within Lab precision	
		SD (ng/L)	CV%	SD (ng/L)	CV%
cobas e 411	152	1.43	0.9	2.20	1.4
cobas e 601	154	1.23	0.8	2.24	1.5

Data was also provided using lithium heparin samples to demonstrate that the %CV of the assay at 11 ng/L is 10%.

b. Linearity/assay reportable range:

Linearity of the Troponin T Gen 5 STAT assay for lithium heparin plasma samples was evaluated in accordance with the CLSI EP-6A guideline using 1 reagent lot for both the cobas e 411 and the cobas e 601. One lithium heparin plasma sample with a high concentration of TnT was prepared by spiking a plasma sample with recombinant TnT. Samples spanning the linear range of the assay were prepared by intermixing with a native lithium heparin plasma sample with low concentration of cTnT to generate a total of 21 samples. The samples were measured in triplicate in a single run using a single lot on each the cobas e 411 and cobas e 601.

The quadratic model was significant for the cobas e 411 and the cubic model was

significant for the cobas e 601 based on unweighted regression models. For cobas e 411, the test results did not deviate from linearity by more than 6.3%. For cobas e 601, the test results did not deviate from linearity by more than 12.4%.

The measuring range of the assay is 6 – 10000 ng/L 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 more information.)

Hook Effect: A study was performed to support the claim that there was no hook effect up to 100,000 ng/L cTnT on both the cobas e 411 and cobas e 601.

Dilution: A dilution study was performed to support the statement that the cobas e 411 and cobas e 601 can perform a dilution of 1:10 for samples that are out of range.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):
The Elecsys Troponin T STAT Gen 5 Immunoassay is traceable to the Elecsys Troponin T STAT assay.

The master calibrators (6 master calibrators) are value assigned using multiple instruments (including multiple instrument platforms) and multiple runs. The results from the testing are evaluated and specifications must be met. The protocols were reviewed and found acceptable.

The CalSets are value assigned using multiple instruments (including multiple instrument platforms) and multiple runs. The results are evaluated and specifications must be met. The protocols were reviewed and found acceptable.

The PreciControls are value assigned using multiple instruments (including multiple instrument platforms) and multiple runs. The results are evaluated and specifications must be met. The protocols for value assignment and stability for troponin T were reviewed and found acceptable. These controls were cleared in k082699 but troponin T was not included in the list of assayed analytes. In addition, the target value for the low troponin I control has changed from 0.4 ng/mL to 0.75 ng/mL. The value assignment procedure and stability protocols are unchanged since the clearance of k082699.

The CalCheck 5 are value assigned using multiple instruments (including multiple instrument platforms) and multiple runs. The results are evaluated and specifications must be met. The protocols were reviewed and found acceptable.

Calibration stability: The sponsor provided data to support the claim that the calibration is stable for 7 days when using the same reagent kit onboard the analyzer or for 12 weeks when using the same reagent lot.

Calset stability: Real time stability studies were performed and support the following claims:

- The lyophilized calibrators are stable for 18 months when stored at 2-8°C.
- Once reconstituted the calibrators are stable for 3 months when stored at -20°C but should only be frozen once.
- Once reconstituted the calibrators are stable for 2 weeks when stored at 2-8°C.
- Once reconstituted the calibrators are stable for 5 hours onboard the instruments at 20-25°C.

PreciControl stability: Real time stability studies were performed and support the following claims:

- The lyophilized controls are stable for 18 months when stored at 2-8°C.
- Once reconstituted the calibrators are stable for 3 months when stored at -20°C but should only be frozen once.
- Once reconstituted the controls are stable for 4 days when stored at 2-8°C.
- Once reconstituted the calibrators are stable for 5 hours when stored onboard the instrument at 20-25°C.

CalCheck 5 stability: Real time stability studies were performed and support the following claims:

- The lyophilized CalCheck 5 are stable for 18 months when stored at 2-8°C.
- Once reconstituted the CalCheck 5 are stable for 4 hours when stored at 20-25°C.

Lithium heparin sample stability: Sample stability studies were provided for stability at 2-8°C, -20°C, and Freeze-Thaw.

2-8°C Stability: Studies were performed and support the following lithium heparin plasma sample stability claims:
For 24 hours when stored at 2-8°C.
For 12 months when stored at -20°C.
Samples can only be frozen once.

d. Detection limit:

Limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were performed based on CLSI EP-17A and analyzed as described below.

LoB Test Protocol

To estimate LoB, a blank sample was measured in replicates of 5 for 6 runs over ≥3 days on 2 cobas e 411 and 2 cobas e 601 analyzers for each of 2 lots yielding 60 measurements for each reagent lot on both the cobas e 411 and the cobas e 601.

LoB was defined as the highest observed measured concentration for samples free of cTnT and was determined as the 95^{th} percentile of test results for the blank samples for each lot. The claim is based on the lot with the highest determined LoB for each instrument.

LoD Test Protocol

To estimate LoD, 5 low level lithium heparin plasma samples were measured in singlicate on 6 runs over multiple days using 2 cobas e 411 and 2 cobas e 601 analyzers for each of 2 lots for a total of 60 measurements per lot.

LoD was established using a parametric analysis for each lot. The claim is based on the lot with the highest determined LoD for each instrument.

LoQ Test Protocol

To estimate LoQ, 10 pooled lithium heparin plasma samples targeting the low end of the measuring range were used. The samples were measured 2 times per run for 2 runs per day for 21 days using 2 cobas e 411 and 2 cobas e 601 analyzers for each of 2 lots of reagents for a total of 84 measurements per sample for each lot. The LoQ was defined as the lowest concentration of cTnt with a %CV of ≤20%. The data were evaluated using the precision profile approach described in EP17-A2. The claim is based on the lot with the highest determined LoQ for each instrument.

The above studies support the following detection limits for each instrument:

Instrument	LoB	LoD	LoQ
cobas e 411	3 ng/L	5 ng/L	6.0 ng/L
cobas e 601	2.5 ng/L	3 ng/L	6.0 ng/L

The measuring range of the assay is 6 – 10000 ng/L and is defined by the LoQ at the low end and the linearity at the high end.

e. Analytical specificity:

To evaluate potential interference due to endogenous substances (listed in the following table), the interferents were added to pooled lithium heparin plasma samples targeting cTnT at low, medium and high concentrations of cTnT (13-18 ng/L, 93 - 4500 ng/L, and 1100 - 8500 ng/L). The low samples were native samples, the medium range and high range samples were either native samples or samples spiked with recombinant troponin. The samples were tested either in singlicate or in triplicate on each a cobas e 411 and a cobas e 601. When tested in triplicate, the means were calculated and evaluated. For each substance tested, interference was analyzed by comparing the true value sample (no interferent added) to the test sample (interferent added) and calculated according to the following formula: % recovery = test sample/true sample X 100. The potentially interfering compounds, at the following concentrations, did not interfere with the performance of the device (i.e., did not result in bias >10%).

Potentially Interfering Substance	Interferent Concentration
Bilirubin	25mg/dL
Hemoglobin	100 mg/dL

Potentially Interfering Substance	Interferent Concentration
Lipemia (Intralipid)	1500 mg/dL
Human Serum Albumin	7 g/dL
Cholesterol	310 mg/dL
Biotin	20 ng/mL
Rheumatoid Factor	900 IU/mL
Human Anti-Mouse Antibodies	322 µg/L

The following are included as limitations:

Samples showing visible signs of hemolysis may cause interference. Falsely depressed results are obtained when using samples with hemoglobin concentrations > 0.1 g/dL.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

For assays using antibodies, the possibility exists for interference by heterophile antibodies in the patient's sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures using immunoglobulin or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Carefully evaluate the results of patients suspected of having these antibodies.

In rare cases, interference due to extremely high titers of antibodies to analyte‑specific antibodies, streptavidin or ruthenium can occur. The reagent has been formulated to minimize these effects.

Cross-reactivity: To evaluate potential interference due to potentially cross reacting substances (listed in the following table), the interferents were added to pooled lithium heparin plasma samples targeting cTnT at low, medium and high concentrations of cTnT (13-22 ng/L, 93 - 4500 ng/L, and 1100 - 8500 ng/L). The low samples were native samples, the medium range and high range samples were samples spiked with recombinant troponin. The samples were tested in singlicate on each a cobas e 411 and a cobas e 601. For each substance tested, interference was analyzed by comparing the true value sample (no interferent added) to the test sample (interferent added) and calculated according to the following formula: % recovery = test sample/true sample X 100. The potentially cross-reacting compounds, at the following concentrations, did not interfere with the performance of the device (i.e., did not result in bias >10%).

Potentially Interfering Cross Reactant	Interferent Concentration	Claim in package insert
Skeletal Muscle TnT	60,000 ng/L	10,000 ng/L
Skeletal Muscle TnI	100,000 ng/L	100,000 ng/L
Cardiac TnI	100,000 ng/L	10,000 ng/L
Human TnC	80,000 ng/L	80,000 ng/L

Exogenous interference: To evaluate potential interference due to exogenous substances including common drugs and cardiac-specific drugs (listed in the following table), the interferents were added to 2 pooled lithium heparin plasma samples targeting cTnT at concentrations near the cut-off and well above the cut-off. The low samples were native samples, the high range samples were samples spiked with recombinant troponin. For common drugs, pooled samples with TnT concentrations of 15 and 9800 ng/L were used. For cardiac specific drugs, pooled samples with TnT concentrations of 15 and 1900 ng/L were used. Control and test samples were tested in triplicate on each a cobas e 411 and a cobas e 601 and the means were calculated and evaluated. For each substance tested, interference was analyzed by comparing the true value sample (no interferent added) to the test sample (interferent added) and calculated according to the following formula: % recovery = test sample/true sample X 100. The highest concentrations of interferents used in testing are included below. At the testing concentrations, test results exhibited a bias of <±10% on each the cobas e 411 and the cobas e 601.

Drug	Concentration (mg/L)
Acetylcysteine	1660
Ampicillin-Na	1000
Ascorbic acid	300
Cyclosporine	5
Cefoxitin	2500
Heparin	5000 U
Levodopa	20
Methyldopa	20
Metronidazole	200
Phenylbutazone	400
Doxycycline	50
Acetylsalicylic Acid	1000
Rifampicin	60
Acetaminophen	200
Ibuprofen	500
Theophyline	100
Carvedilol	37.5
Clopidogrel	75

Drug	Concentration (mg/L)
Digoxin	0.25
Epinephrine	0.5
Insulin	1.6
Lidocaine	80
Lisinopril	10
Methylprednisolone	7.5
Metoprolol	150
Nifedipine	30
Phenprocoumon	3
Propafenone	300
Reteplase	33.3
Simvastatin	30
Spirolactone	75
Tolbutamide	1500
Torasemide	15
Verapamil	240

f. Assay cut-off:
Not applicable.
See section 4 "Clinical cut-off".

2. Comparison studies:
   a. Method comparison with predicate device:
   Not applicable.

   b. Matrix comparison:
   Not applicable. This device is intended for use with lithium heparin samples only.

3. Clinical studies:
   a. Clinical sensitivity:
   Data from the "The Advantageous Predictors of Acute Coronary Syndromes Evaluation" (APACE) study, an international, multi-center prospective trial of acute chest pain patients that is currently continuing enrollment, was provided in support of this device. In this study, the sites enrolled all patients who presented to the emergency department with symptoms of chest pain and angina pectoris. Peak symptoms had to have occurred within the last 12 hours (onset of symptoms reported ranged from 0 to 72 hours). The only exclusion criterion was kidney failure that required dialysis. Diagnosis of myocardial infarction (MI) was done through an independent adjudication committee which included cardiologists. This included 60 day follow-up information on each subject. The subjects were diagnosed with acute MI by using the diagnostic criteria described in the ACC/ESC/AHA guidelines[1]

[1] Thygesen K, Alpert JS, White HD, et al., Universal definition ofmyocardial infarction. Circ 2007;116:2634-2653.

including ECG changes, symptoms characteristic for ischemia and elevations of cardiac troponin. The clinical information was provided for 718 subjects consecutively enrolled. All 718 subjects had a baseline test result. Five hundred fifteen (515) of the 718 subjects had a second test result at the three hour time point and 310 (of the 718) subjects had a test result at the 6 hour time point.

The clinical performance (clinical sensitivity, clinical specificity, positive predictive value and negative predictive value) of the Elecsys Troponin T Gen 5 STAT assay in the diagnosis of MI in this trial is shown below using the 99th percentile cut-off of 19 ng/L for all patients. In all tables, PPV is the positive predictive value and NPV is the negative predictive value.

All patients using 19 ng/L cut-off

	Sensitivity		Specificity		PPV		NPV	
Time-point	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Baseline	93.5 (115/123)	87.6-97.2	86.4 (514/595)	83.4-89	58.7 (115/196)	51.4-65.6	98.5 (514/522)	97-99.3
3 hours	98.3 (59/60)	91.1-100	85.1 (387/455)	81.4-88.2	46.5 (59/127)	37.6-55.5	99.7 (387/388)	98.6-100
6 hours	100 (37/37)	90.5-100	82.4 (225/273)	77.4-86.7	43.5 (37/85)	32.8-54.7	100 (225/225)	98.4-100

The clinical performance using sex specific cut-offs i.e., 14 ng/L for women and 22 ng/L for males, is provided below:

Females using the 14 ng/L cut-off

	Sensitivity		Specificity		PPV		NPV	
Time-point	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Baseline	97.1 (34/35)	85.1-99.9	77.4 (164/212)	71.1-82.8	41.5 (34/82)	30.7-52.9	99.4 (164/165)	96.7-100
3 hours	100 (17/17)	80.5-100	75.2 (124/165)	67.8-81.5	29.3 (17/58)	18.1-42.7	100 (124/124)	97.1-100
6 hours	100 (15/15)	78.2-100	72.3 (68/94)	62.2-81.1	36.6 (15/41)	22.1-53.1	100 (68/68)	94.7-100

The following limitation is included in the labeling:

The positive predictive value for females using the lower sex-specific cut-off (14 ng/L) is lower when compared to the higher cut-off of 19 ng/L. When looking at the lower bound of the 95% CI, up to 69%, 82% and 78% of positive test results for females are non-MI. Troponin results should always be used in conjunction with clinical signs and symptoms.

Males using the 22 ng/L cut-off

	Sensitivity		Specificity		PPV		NPV	
Time-point	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Baseline	90.9 (80/88)	82.9-96	89.3 (342/383)	85.8/92.2	66.1 (80/121)	57-74.5	97.7 (342/350)	95.5-99
3 hours	97.7 (42/43)	87.7-99.9	86.9 (252/290)	82.5-90.6	52.5 (42/80)	41-63.8	99.6 (252/253)	97.8-100
6 hours	100 (22/22)	84.6-100	86 (154/179)	80.1-90.8	46.8 (22/47)	32.1-61.9	100 (154/154)	97.6-100

In addition, clinical performance estimates were provided from a second multicenter study performed in the United States were a total of 1679 subjects presenting emergently with chest pain were enrolled. The trial excluded chest pain subjects with an MI within the last 3 months, subjects with surgery or hospitalization within the last 3 months, subjects with revascularization or percutaneous coronary intervention (PCI) within the last 3 months, subjects with an established acute non-cardiac primary illness and subjects transferred from another hospital or facility. These excluded subjects could be expected to have elevated troponin concentrations that would likely reflect cardiac comorbidities besides MI, and yield positive results; therefore, the estimate of specificity and the positive predictive values of this trial may be overestimated.

Within this population, there were 173 adjudicated MIs. 1679 of these subjects were evaluated on the cobas e 411 analyzer and 1675 subjects were evaluated on the cobas e 601 analyzer. Final diagnoses were determined by an independent adjudication committee which included cardiologists and emergency medicine physicians using the universal guidelines.

The clinical performance estimates for the cobas e 411 analyzer are provided below:

All patients using 19 ng/L cut-off

Time-point	n	Sensitivity		Specificity		PPV		NPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
Baseline	1628	86.7 (143/165)	80.5-91.5	87.8 (1285/1463)	86-89.5	44.5 (143/321)	39-50.2	98.3 (1285/1307)	97.5-98.9
3 hours	1429	94.4 (134/142)	89.2-97.5	87.4 (1125/1287)	85.5-89.2	45.3 (134/296)	39.5-51.1	99.3 (1125/1133)	98.6-99.7
6 -9 hours	1178	94.2 (130/138)	88.9-97.5	85.3 (887/1040)	83-87.4	45.9 (130/283)	40-51.9	99.1 (887/895)	98.2-99.6
12-24 hours	887	92.9 (104/112)	86.4-96.9	81.7 (633/775)	78.8-84.3	42.3 (104/246)	36-48.7	98.8 (633/641)	97.6-99.5

The clinical performance using sex specific cut-offs, 14 ng/L for women and 22 ng/L for males, is provided below:

Females using the 14 ng/L cut-off

Time-point	n	Sensitivity		Specificity		PPV		NPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
Baseline	787	87.3 (55/63)	76.5-94.4	87.6 (634/724)	84.9-89.9	37.9 (55/145)	30-46.4	98.8 (634/642)	97.6-99.5
3 hours	687	92.0 (45/50)	80-97.8	86.2 (549/637)	83.3-88.8	34.3 (46/134)	26.3-43	99.3 (549/553)	98.2-99.8
6 -9 hours	553	91.7 (44/48)	80-97.7	85.1 (430/505)	81.7-88.1	37 (44/119)	28.3-46.3	99.1 (430/434)	97.7-99.7
12-24 hours	410	92.3 (36/39)	79.1-98.1	79.8 (296/371)	75.3-83.8	32.4 (36/111)	23.9-42	99 (296/299)	97.1-99.8

The following limitation is included in the labeling:
The positive predictive value for females using the lower sex-specific cut-off (14 ng/L) is lower when compared to the higher cut-off of 19 ng/L. When looking at the lower bound of the 95% CI, up to 69%, 82% and 78% of positive test results for females are non-MI. Troponin results should always be used in conjunction with clinical signs and symptoms.

Males using the 22 ng/L cut-off

Time-point	n	Sensitivity		Specificity		PPV		NPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
Baseline	841	86.3 (88/102)	78-92.3	87.3 (645/739)	84.7-89.6	48.4 (88/182)	40.9-55.9	97.9 (645/659)	96.5-98.8
3 hours	742	95.7 (88/92)	89.2-98.8	85.7 (557/650)	82.8-88.3	48.6 (88/181)	41.1-56.1	99.3 (557/561)	98.2-99.8
6 -9 hours	625	93.3 (84/90)	86.1-97.5	82.1 (439/535)	78.5-85.2	46.7 (84/180)	39.2-54.2	98.7 (439/445)	97.1-99.5
12-24 hours	477	94.5 (69/73)	86.6-98.5	80.2 (324/404)	76-84	46.3 (69/149)	38.1-54.7	98.8 (324/328)	96.9-99.7

The sponsor includes the following information in the package insert about troponin in other disease states:

Troponins are released during the process of myocyte necrosis. While they are cardiac specific, they are not specific for MI and detectable levels may be seen in other disease states that involve the heart muscle (e.g. arrhythmia, acute aortic syndrome, acute heart failure, hypertensive crisis, myocarditis, pericarditis, pulmonary embolism and Takotsubo cardiomyopathy), so that ACC/ESC/AHA guidelines and the Universal Definition of MI recommend serial sampling with a rise or fall in troponin to distinguish between acute and chronic cTn elevations. Results should be interpreted in conjunction with clinical presentation including medical history, signs and symptoms, ECG data and biomarker concentrations.

*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**:**
This assay has 3 claimed cut-offs. These are overall (19 ng/L), a cut-off for females (14 ng/L), and a cut-off for males (22 ng/L) all of which were determined using the 99th percentile upper reference limit.

5. Expected values/Reference range:
To establish the 99th percentile upper reference limit in lithium heparin plasma samples, a reference range study was conducted at 4 external collection sites in a population of apparently healthy adults. In order to capture an apparently healthy population, subjects were excluded if they had a diagnosis of cancer, or any chronic disease, were taking prescriptions for a chronic diseases, had high blood pressure, had a history of acute coronary syndrome, had been hospitalized within the last 3 months, and was pregnant or had delivered a baby within the last 6 weeks. The study population of 1301 included 645 males and 656 females.

The 99th percentile upper reference limit was demonstrated to be 19 ng/L overall, 14 ng/L for females, and 22 ng/L for males.

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.