510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K201441

B Applicant

Roche Diagnostics

C Proprietary and Established Names

Elecsys Troponin T Gen 5

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
MMI	Class II	21 CFR 862.1215 - Creatine Phosphokinase/Creatine Kinase Or Isoenzymes Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

Modification of a previously cleared assay (k162895) to decrease interference to biotin.

B Measurand:

Cardiac troponin T (cTnT)

C Type of Test:

Quantitative immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

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 electrochemluminescence immunoassay "ECLIA" is intended for use on the cobas e immunoassay analyzers.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

For in vitro diagnostic use.

D Special Instrument Requirements:

Performance data for this submission were generated using the previously cleared cobas e 801 analyzer.

IV Device/System Characteristics:

A Device Description:

The Elecsys Troponin T Gen 5 is a one-step sandwich immunoassay. The assay uses streptavidin-coated microparticles, a biotinylated monoclonal anti-cardiac Troponin T-specific antibody, a monoclonal anti-cardiac Troponin T-specific antibody labeled with a ruthenium complex and electrochemiluminescence detection. Results are determined using a calibration curve that is generated specifically on each instrument by a 2-point calibration and a master curve (6-point calibration) provided with the reagent bar code.

The Elecsys Troponin T Gen 5 reagent kit includes:

- 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) (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.

For the neutralization of free biotin in Li-Heparin plasma patient samples, the sponsor developed a monoclonal biotin scavenging antibody which binds to free biotin. The scavenger antibody is specific for free biotin in the Li-Heparin plasma patient samples and blocks potential interference from free biotin. The scavenger antibody does not bind to or interact with the biotin-linker conjugates.

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."

B Principle of Operation:

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. The sample is mixed with biotinylated monoclonal cTnT-specific antibody and a ruthenium labeled-monoclonal cTnT antibody that reacts 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. 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.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Elecsys Troponin T Gen 5 STAT Assay

B Predicate 510(k) Number(s):
k162895

C Comparison with Predicate(s):

Device & Predicate Device(s):	K201441	K162895
Device Trade Name	Elecsys Troponin T Gen 5	Elecsys Troponin T Gen 5 STAT Assay
General Device Characteristic Similarities		
Intended Use/Indications For Use	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	Same

Device & Predicate Device(s):	K201441	K162895
	system analyzers.	
Immunoassay Protocol	Sandwich immunoassay	Same
Detection Protocol	Electro-chemiluminescence immunoassay (ECLIA)	Same
Assay Reaction Time	9 minutes	Same
Traceability	This method has been standardized against the Elecsys Troponin T STAT assay (4th generation). This in turn was originally standardized against the Enzymun-Test Troponin T (CARDIAC T) Test method.	Same
Epitopes	MAK-Biotinylated: aa 125-131 MAK-Ruthenium: aa 136-147	Same
General Device Characteristic Differences		
Reagent Update	1. Addition of a monoclonal biotin scavenging antibody to the reaction mix. 2. Increase in the length of the linker on the biotinylated capture antibody.	Not present
Biotin Tolerance	No interference up to 1500 ng/mL.	No interference up to 20 ng/mL.

VI Standards/Guidance Documents Referenced:

Assay Migration Studies for In Vitro Diagnostic Devices. Guidance for Industry and FDA Staff. Document issued on April 25, 2013.

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

CLSI EP06-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 - Second Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Repeatability and Intermediate Precision
Repeatability (within-run precision) and intermediate precision (within-laboratory precision) studies were conducted according the CLSI EP05-A3 guideline. Six lithium-heparin plasma samples (samples ≤100 ng/L cTNT were native and samples >100 ng/L were spiked with cTNT to achieve the targeted concentration) and two PreciControl Troponin controls were assayed in two runs per day over 21 days using three reagent lots on a single cobas e 801 analyzer. For each lithium-heparin plasma sample and PreciControl Troponin control, 2 replicates were measured in each run. The analysis did not differentiate between runs conducted on the same day, therefore, the precision estimates reported below are for 21 days, 1 run/day, and 4 replicates. Results from one representative lot of the three lots tested are described in the table below. Within laboratory precision includes within-run and between-day variability.

Sample Material	n	Mean (ng/ L)	Within Run		Between Day		Within Laboratory	
			SD	%CV	SD	%CV	SD	%CV
Native 1	84	9.01	0.4	4.9	0.3	3.4	0.5	6.0
Native 2	84	15.2	0.5	3.1	0.5	3.1	0.6	4.3
Native 3	84	21.9	0.5	2.4	0.6	2.9	0.8	3.7
Contrived 1	84	164	3.4	2.1	4.4	2.7	5.6	3.4
Contrived 2	84	4705	77.6	1.6	130	2.8	151	3.2
Contrived 3	84	9267	155	1.7	252	2.7	296	3.2
Control 1	84	26.2	0.5	1.8	0.8	3.0	0.9	3.5
Control 2	84	1924	25.6	1.3	42.5	2.2	49.6	2.6

A separate study was conducted according to the CLSI EP05-A3 guideline to evaluate between run and between lot imprecision. Six pooled lithium-heparin plasma samples (samples ≤100 ng/L cTNT were native and samples >100 ng/L were spiked with cTNT to achieve the targeted concentration) and two PreciControl Troponin controls were assayed in two runs per day over 21 days using three reagent lots on a single cobas e 801 analyzer. For each lithium-heparin plasma sample and PreciControl Troponin control, 2 replicates were measured in each run. Between run and between lot precision were calculated and are presented below.

Sample Material	n	Mean (ng/ L)	Between Run		Between Lot	
			SD	%CV	SD	%CV
Native 1	84	9.15	0.2	1.8	0.4	4.4
Native 2	84	15.4	0.1	0.6	0.3	2.2
Native 3	84	22.0	0.1	0.5	0.2	0.8
Contrived 1	84	164	0.5	0.3	0.1	0.1
Contrived 2	84	4749	48.3	1.0	112	2.4
Contrived 3	84	9416	58.9	0.6	342	3.6
Control 1	84	26.2	0.2	0.6	0.4	1.5
Control 2	84	1930	14.3	0.7	29.5	1.5

Reproducibility

A reproducibility study was conducted according to the CLSI EP05-A3 guideline. Five lithium-heparin plasma samples (samples ≤100 ng/L cTNT were native and samples >100 ng/L were contrived) and two PreciControl Troponin controls were assayed at three different sites (one internal and two external sites) on three cobas e 801 analyzers over 5 days. Each sample was measured in five replicates. A single reagent lot was used at each site. Repeatability, between day, between site, and reproducibility were calculated and are presented below. Reproducibility includes repeatability, between day, and between site variance components.

Sample Material	n	Mean (ng/L)	Repeatability		Between Day		Between Site/ Instrument/ Lot		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Native 1	75	8.7	0.3	3.0	0.2	2.6	0.7	7.9	0.8	8.9
Native 2	75	21.6	0.4	1.7	0.4	2.0	0.6	2.7	0.8	3.8
Contrived 1	75	171	4.5	2.6	3.8	2.2	1.1	0.7	6.0	3.5
Contrived 2	75	4806	71.8	1.5	114.1	2.4	109.7	2.3	173.8	3.6
Contrived 3	75	9494	157.7	1.7	193.2	2.0	132.2	1.4	282.3	3.0
PreciControl 1	75	25.4	0.5	1.9	0.6	2.3	0.9	3.6	1.2	4.7
PreciControl 2	75	1922	30.5	1.6	42.4	2.2	49.3	2.6	71.8	3.7

2. Linearity:

A linearity study was conducted according to the CLSI EP06-A guideline. A 15-step dilution series was prepared using a mixing scheme by mixing one native Li-heparin plasma sample with cTnT concentration >10,000 ng/L (single donor) with low troponin T (~5 ng/L) native patient samples (pooled single samples). The dilution series was measured on a single cobas e 801 analyzer using five replicate measurements. The mean of these replicates was used to calculate the reported results. Data were analyzed using weighted linear regression analyses.

Deviation from linearity within the claimed measuring range of the candidate test was up to 14.6%. The results confirm that the assay is linear across the measuring range of 6 to 10,000 ng/L.

3. Hook Effect
   A study was performed to support the claim that there was no hook effect up to 100,000 ng/L cTnT.

4. Analytical Specificity/Interference:

   Endogenous Interference
   The effect of endogenous interfering substances on the Elecsys Troponin T Gen 5 assay was determined on the cobas e 801 analyzer for the following seven interfering substances: intralipid, biotin, bilirubin, hemoglobin, rheumatoid factors, cholesterol and human serum albumin (HSA).

   Three native Li-Heparin plasma samples spiked with low (20 ng/L), medium (100 ng/L), and high (900 ng/L) concentrations of Troponin T were used to prepare dilution series. The series were tested with one lot of the reagent for intralipid, hemoglobin, rheumatoid factors, cholesterol and HSA and three reagent lots were used to evaluate interference from biotin. For each dilution series, the sample pool spiked with troponin was divided into two parts. One part of each sample pool was spiked with the interfering endogenous substance and the other part of the same sample pool was spiked with the same volume of the solvent of the interfering endogenous substance (without interfering substance). Three replicate measurements were performed on each sample. For each interferent concentration level, the recovery was calculated based on the mean value of the three replicates. Interference was determined to be recovery > 100 ± 10%.

Interferent	Highest concentration tested without interference
Biotin	1,500 ng/mL
Intralipid (lipemia)	2,000 mg/dL
Hemoglobin	200 mg/dL
Rheumatic Factor	1,200 IU/mL
HSA	7 g/dL
Cholesterol	310 mg/dL

   The labeling contains the following limitations:
   It is recommended to run serum indices on samples for troponin T measurement.

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

   To evaluate potential interference from bilirubin, three native Li-Heparin plasma samples spiked with low (20 ng/L), medium (100 ng/L), and high (1000 ng/L) concentrations of Troponin T were used to prepare a dilution series. The series was tested with one lot of the reagent. For each dilution series, the sample pool spiked with troponin was divided into two

parts. One part of each sample pool was spiked with the interfering endogenous substance (conjugated or unconjugated bilirubin) and the other part of the same sample pool was spiked with the same volume of the solvent of the interfering endogenous substance (without interfering substance). Five replicates measurements were performed on each sample. For each interferent concentration level, the recovery was calculated is based on the mean value of the five replicates. Interference was determined to be recovery > 100 ± 10%.

Interferent	Highest concentration tested without interference
Bilirubin (conjugated)	66 mg/dL
Bilirubin (unconjugated)	66 mg/dL

The labeling contains the following limitation:

There are reports of autoantibodies to troponin T in the medical literature. Use caution when interpreting a troponin T test result that does not appear to reflect the clinical picture. The Elecsys Troponin T Gen 5 assay may be interfered with by these autoantibodies causing a falsely elevated or depressed result.

Exogenous Interference

The effect of exogenous interfering substances on the Elecsys Troponin T Gen 5 assay was determined on the cobas e 801 analyzer for 22 cardiac drugs. Native Li-Heparin plasma samples with low Troponin T (~20 ng/L) and Li-heparin plasma samples spiked with Troponin T (9,000 ng/L) were used to prepare dilution series. For each dilution series, the samples were divided into two parts. One part of each sample pool was spiked with the interfering endogenous substance and the other part of the same sample pool was spiked with the same volume of the solvent of the interfering endogenous substance (without interfering substance). Three replicate measurements were performed on each sample (except for ascorbic acid, which was measured in five replicate measurements). The series were tested with one lot of the reagent in one run on two different cobas e 801 analyzers. For each interferent concentration level, the recovery was calculated based on the mean value of the replicates tested. Interference was determined to be recovery > 100 ± 10%. At the tested concentrations, all drugs caused <10% interference.

Interferent	Highest concentration tested without interference (mg/L)	
	Low Troponin (~20 ng/L)	High Troponin (~9,000 ng/L)
N-Acetylcysteine	1,660	553
Ampicillin - Na	1,000	1,000
Ascorbic Acid	300	300
Cyclosporine	5	5
Cefoxitin	2,500	250
Heparin	5,000 (IU/L)	5,000 (IU/L)
Levodopa	20	20
Methyldopa	20	20
Metronidazole	200	200
Phenylbutazone	400	400

Interferent	Highest concentration tested without interference (mg/L)	
	Low Troponin (~20 ng/L)	High Troponin (~9,000 ng/L)
Doxycycline	50	50
Acetylsalicylic Acid	1,000	1,000
Rifampicin	60	60
Acetaminophen	200	200
Ibuprofen	500	500
Theophylline	100	100
Itraconazole	50	50
Carvedilol	37.5	37.5
Clopidogrel	75	75
Dabigatran	300	300
Digoxin	0.25	0.25
Epinephrine (Adrenaline)	0.50	0.50
Insulin	2	2
Lidocaine	80	80
Lisinopril	10	10
Methylprednisolone	7.5	7.5
Metoprolol	150	150
Nifedipine	30	30
Phenprocoumon (Marcumar)	3	3
Propafenone	300	300
Reteplase	33.3	33.3
Rivaroxaban	40	40
Sacubitril	194	194
Simvastatin	30	30
Spironolactone	75	75
Tolbutamide	1,500	1,500
Torsemide	15	15
Valsartan	206	206
Verapamil	240	240

Cross-Reactivity

To evaluate potential interference due to 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 (19-19.8 ng/L, 4,934-5,109 ng/L, and 6,762-7,501 ng/L). The low samples were native samples, and the medium range and high range samples were samples spiked with recombinant troponin. Three replicate measurements on a single cobas e 801 analyzer were recorded for each sample. 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%).

Interferent	Highest concentration tested without interference (ng/L)
Skeletal muscle TnT	30,000
Skeletal muscle TnI	100,000
Cardiac TnI	12,500
Human TnC	100,000

HAMA
The effect of human anti-mouse-antibodies (HAMA) on the Troponin T Gen 5 assay was assessed on the cobas e 801 analyzer using Li-heparin plasma samples with Troponin T at ~20 ng/L and ~1,000 ng/L that were spiked with up to 805 µg/L HAMA. No interference (bias < 10%) was observed at concentrations up to 644 µg/L HAMA.

5. Assay Reportable Range:

6-10,000 ng/L. See linearity section above.

6. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Traceability
The assay is traceable to the Elecsys Troponin T STAT assay (4th generation).

Calibration
Data was provided to support the recommended calibration schedule.

7. Detection Limit:

Limit of Blank (LoB)
The LoB of the Elecsys Troponin T Gen 5 assay on the cobas e 801 was determined according to the CLSI EP17-A2 guideline. The sample used was an analyte-free native Li-Heparin sample. The distribution of values for the analyte-free Li-Heparin plasma sample was determined with three reagent lots on one cobas e 801 analyzer and one reagent lot on two cobas e 801 analyzers. Each sample was measured in six runs performed over at least three days with 10 replicates in each run (N=60 per reagent lot). The LoB was calculated using the nonparametric option described in the CLSI EP17-A2 guideline. The LoB was determined as the 95th percentile of measurements of the blank sample for each lot. The highest observed LoB across all lots and instruments was 1.87 ng/L.

Limit of Detection (LoD)
The LoD of the Elecsys Troponin T Gen 5 assay on the cobas e 801 was determined as the lowest amount of analyte in a sample that can be detected with a 95% probability according to CLSI EP17-A2 guideline. The distribution of values for five low-analyte Li-Heparin plasma samples was determined using three reagent lots on one cobas e 801 instrument and using a single reagent lot on two cobas e 801 instruments. Each sample was measured in six runs over at least three days and with duplicate measurements per run (N=60 per reagent lot). A pooled estimate of the precision (SD total) of the five samples was calculated. The LoD

was calculated using the formula, LoD = highest LoB + 1.653 x SD total. The highest LoD observed across all lots and instruments was 2.99 ng/L.

Limit of Quantitation (LoQ)
The LoQ of the Elecsys Troponin T Gen 5 assay was determined on the cobas e 801 analyzer according to the CLSI EP17-A2 guideline as the lowest concentration of analyte which can be quantified with a CV (intermediate precision) of no more than 20%. The LoQ was determined using ten native Li-Heparin plasma pools at cTnT concentrations spanning the low-end of the measuring range of the candidate assay. Data were collected for each sample using three reagent lots on one cobas e 801 instrument over 21 days with 2 runs per day and duplicate measurements per run (N=84). Estimates of the mean and within-lab precision were calculated for each sample for each reagent lot. Total CV is based on the total variance, calculated as the sum of the variance components from day, run and within run (N = 21 x 2 x 2 = 84 measurements). The results are summarized below:

LoQ

Lot	Lowest Mean Troponin (ng/L) Tested	Intermediate Precision	
		SD (ng/L)	CV (%)
Lot 1	5.31	0.299	5.6
Lot 2	4.48	0.551	12.3
Lot 3	4.40	0.499	11.3

The above studies support the following detection limits for the Elecsys Troponin T Gen 5 assay on the cobas e 801 analyzer:

Parameter	Value (ng/L)
LoB	2.5
LoD	3.0
LoQ	6.0

8. Assay Cut-Off:

See section D "Clinical cut-off."

Comparison Studies:

9. Method Comparison with Predicate Device:

The sponsor followed the recommendations in the "Assay Migration Studies for In Vitro Diagnostic Devices. Guidance for Industry and FDA Staff" to demonstrate equivalence between the unmodified assay (k162085) on the cobas e601 and the candidate assay on the cobas e801. The sponsor conducted the studies recommended in the guidance including a method comparison study using the predicate device reagent on the cobas e601 and the candidate assay reagents on the cobas e 801.

One set of 299 lithium-heparin plasma samples collected from individual donors were tested with one lot of the predicate device and three different lots of the candidate device. Of those 299 samples, 267 were within the measuring range of the device. Four of the samples were pooled native lithium-heparin plasma samples spiked with recombinant human cardiac troponin T. Passing-Bablok and weighted Deming regression analyses were performed comparing the concentrations from the three different lots of the candidate assay on the cobas e 801 to the predicate device. Results for a representative lot are shown below:

Sample Range	N	Passing-Bablok			Weighted Deming		
		Slope	Intercept	T	Slope	Intercept	R
6-8,604	267	0.993	1.34	0.976	0.995	1.26	1.00

The sponsor also provided information to show no significant systematic differences between the test systems.

10. Matrix Comparison:

To support the use of lithium heparin tubes containing separator gel for specimen collection, 174 paired native samples were tested using the candidate assay. Agreement rates were calculated at each cutoff.

Clinical Cutoff	Positive Percent Agreement (LCI-UCI)	Negative Percent Agreement (LCI-UCI)
19 ng/L	99.2 (95.7-99.9)	100 (92.3-100.0)
14 ng/L	98.6 (95.1-99.6)	100 (87.9-100.0)
22 ng/L	100 (96.8-100)	100 (93.8-100.0)

Passing-Bablok and Weighted Deming regression analyses were performed. Minimal systematic differences and proportional differences were observed when comparing the lithium-heparin plasma tubes containing a separating gel to tubes without the gel.

Regression Coefficient	Passing-Bablok	Weighted Deming
Intercept	-0.004	-0.002
Slope	0.995	0.993
Correlation	r = 1.000	r = 1.000

The results support that lithium heparin tubes containing separator gel may be used for specimen collection.

B Clinical Studies:

1. Clinical Sensitivity:

Data from the "The Advantageous Predictors of Acute Coronary Syndromes Evaluation" (APACE) study, a multi-center prospective study were provided in support of the diagnostic accuracy of the Elecsys Troponin T Gen 5. Lithium heparin plasma specimens were collected at 5 emergency departments (ED) from 1074 patients presenting to the ED with chest pain,

with onset or peak of symptoms within 12 hours of presentation to the ED. The only exclusion criterion was kidney failure that required dialysis. Serial samples were collected from patients beginning 0-1.5 hours from presentation to the ED and at the following time-points relative to time of presentation to ED: 1.5-2.5 hours, 2.5-3.5 hours, and greater than 3.5 hours. After collection, samples were stored frozen until testing (the sponsor provided data to support using frozen samples). Diagnosis of acute myocardial infarction (AMI) was performed by an independent adjudication committee, which included cardiologists, who reviewed the clinical data and locally measured troponin test and applied the universal definition of AMI. Investigators and adjudicators were blinded to the candidate device's results. Adjudicators were also blinded to site diagnoses. Frozen samples measured by the candidate device were compared to the adjudication committee's diagnosis of AMI. The clinical performance (clinical sensitivity, clinical specificity, positive predictive value (PPV) and negative predictive value (NPV)) of the Elecsys Troponin T Gen 5 STAT assay in the diagnosis of MI in this trial is shown below. The results are summarized in the following tables.

An analysis of device performance was performed separately for males and females using the overall 99th percentile cutoff (19 ng/L). For those subjects who had more than one draw in a single time window, the data below reflect the first measurement only, but information was provided to show that the performance was equivalent using the other measurements.

Cutoff: 19 ng/L (Males)									
Time Elapsed Since Presentation to ED (hours)	**N**	**Sensitivity**		**Specificity**		**PPV**		**NPV**	
		%	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
≤1.5	660	81.5	73.9-87.6	85.7	82.4-88.6	59.5	52.0-66.6	94.7	92.3-96.6
>1.5 - ≤ 2.5	541	93.5	86.3-97.6	86.2	82.7-89.2	58.1	49.7-66.2	98.5	96.7-99.4
>2.5 - ≤ 3.5	415	98.5	92.1-100.0	84.1	79.9-87.8	54.9	45.7-63.9	99.7	98.1-100.0
>3.5	238	93.5	82.1-98.6	80.2	73.9-85.6	53.1	41.7-64.3	98.1	94.5-99.6

Cutoff: 19 ng/L (Females)									
Time Elapsed Since Presentation to ED (hours)	**N**	**Sensitivity**		**Specificity**		**PPV**		**NPV**	
		%	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
≤1.5	308	74.3	56.7-87.5	86.4	81.8-90.3	41.3	29.0-54.4	96.3	93.1-98.3
>1.5 - ≤ 2.5	255	82.6	61.2-95.0	87.5	82.5-91.5	39.6	25.8-54.7	98.1	95.1-99.5
>2.5 - ≤ 3.5	181	88.9	65.3-98.6	89.6	83.8-93.8	48.5	30.8-66.5	98.6	95.2-99.8
>3.5	113	86.7	59.5-98.3	86.7	78.4-92.7	50.0	29.9-70.1	97.7	91.9-99.7

The results using the sex-specific 99th percentile cutoffs (female 14 ng/L, male 22 ng/L) are summarized in the following tables.

Cutoff: 14 ng/L (Females)									
Time Elapsed Since Presentation to ED (hours)	N	Sensitivity		Specificity		PPV		NPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
≤1.5	308	80.0	63.1-91.6	76.9	71.5-81.8	30.8	21.5-41.3	96.8	93.5-98.7
>1.5 - ≤ 2.5	255	95.7	78.1-99.9	76.3	70.3-81.6	28.6	18.8-40.0	99.4	96.9-100.0
>2.5 - ≤ 3.5	181	94.4	72.7-99.9	81.6	74.8-87.2	36.2	22.7-51.5	99.3	95.9-100.0
>3.5	113	93.3	68.1-99.8	74.5	64.7-82.8	35.9	21.2-52.8	98.6	92.7-100.01

Cutoff: 22 ng/L (Males)									
Time Elapsed Since Presentation to ED (hours)	N	Sensitivity		Specificity		PPV		NPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
≤1.5	660	80.7	73.1-87.0	89.0	86.0-91.5	65.3	57.5-72.5	94.7	92.4-96.5
>1.5 - ≤ 2.5	541	88.0	79.6-93.9	88.9	85.6-91.6	61.8	52.9-70.2	97.3	95.3-98.7
>2.5 - ≤ 3.5	415	95.6	87.6-99.1	88.5	84.6-91.6	61.9	51.9-71.2	99.0	97.2-99.8
>3.5	238	93.5	82.1-98.6	83.3	77.3-88.3	57.3	45.4-68.7	98.2	94.7-99.6

False negative results observed in the APACE study are summarized below:

Sex	Clinical Cutoff	False Negative Count	False Negative Estimate
both sexes	19	17 / 188	9.0 %
females	19	3 / 38	7.9 %
	14	2 / 38	5.3 %
males	19	14 / 150	9.3 %
	22	14 / 150	9.3 %

The sponsor includes the following information in the package insert to describe the false negatives observed in this study:

> In this study, there were 17 false negative subjects (out of 188 subjects adjudicated with AMI). In these subjects, no result above the cutoff was obtained with the Elecsys Troponin T Gen 5. Ten of these 17 subjects had presented within 3 hours of onset of chest pain (early presenters) and for 8 of these subjects, no blood draw was tested with the Elecsys Troponin T Gen 5 when the standard of care (SOC) troponin test detected troponin concentrations above the SOC cutoff. For some subjects, this occurred more

than 7 hours after presentation to the emergency room. Two of these 8 early presenters had an adjudicated diagnosis of ST-segment elevation myocardial infarction (STEMI). Two of the 7 subjects that were not early presenters had an adjudicated diagnosis of STEMI and had no blood draw tested with the Elecsys Troponin T Gen 5 when the SOC troponin test detected troponin concentrations above the SOC cutoff (up to more than 7 hours after presentation to the emergency room). Serial sampling is required to determine a rise or fall in troponin over time.

The following limitations are included in the labeling:

Use caution in interpreting troponin values in patients who have presented within 3 hours of onset of chest pain due to the potential for false negative results. In our studies, troponin concentrations above the cutoff were sometimes only detected in these patients more than 7 hours after presentation to the emergency department. Serial sampling is required to determine a rise or fall in troponin over time. Troponin results should always be used in conjunction with clinical signs and symptoms.

At certain timepoints, the PPV of this device is low. Troponin results should always be used in conjunction with clinical signs and symptoms. Please see PPV reported in Diagnostic sensitivity and specificity for more information.

The sponsor also included the following information in the labeling:

Using the established sex-specific 99th percentile (14 ng/L for females and 22 ng/L for males), the lower end of the confidence interval (CI) for the PPV at all timepoints for female subjects was as low as 18.8 %, and for male subjects it was as low as 45.4 %. Up to 81.2 % and 54.6 % of positive troponin results in females and males, respectively, were not myocardial infarctions. Troponin results should always be used in conjunction with clinical signs and symptoms.

Using the established 99th percentile (19 ng/L), the lower end of the confidence interval (CI) for the PPV at all timepoints for female subjects was as low as 25.8 %, and for male subjects it was as low as 41.7 %. Up to 74.2 % and 58.3 % of positive troponin results in females and males, respectively, were not myocardial infarctions. Troponin results should always be used in conjunction with clinical signs and symptoms.

In addition, clinical performance estimates were provided from a second multicenter study performed using the Elecsys Troponin T Gen 5 STAT (k162895) in the United States. Serial samples were collected from patients upon presentation to the ED and at the following time-points relative to time of presentation to ED: 3 hours, 6-9 hours, and 12-24 hours. 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, 1675 subjects were evaluated on the cobas e 601 analyzer and there were 173 adjudicated MIs. 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 601 analyzer are provided below.

Cutoff: 19 ng/L (Females)									
Time Elapsed Since Presentation to ED (hours)	**N**	**Sensitivity**		**Specificity**		**PPV**		**NPV**	
		%	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
Baseline	771	82.5	70.9-90.9	91.9	89.7-93.8	47.7	38.1-57.5	98.3	97.0-99.2
3	682	91.8	80.4-97.7	90.2	87.6-92.4	42.1	32.6-52.0	99.3	98.2-99.8
6-9	536	91.3	79.2-97.6	90.8	87.9-93.2	48.3	37.4-59.2	99.1	97.7-99.8
12-24	399	87.2	72.6-95.7	85.3	81.2-88.8	39.1	28.8-50.1	98.4	96.3-99.5

Cutoff: 19 ng/L (Males)									
Time Elapsed Since Presentation to ED (hours)	**N**	**Sensitivity**		**Specificity**		**PPV**		**NPV**	
		%	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
Baseline	829	88.1	80.2-93.7	84.1	81.2-86.7	43.4	36.5-50.5	98.1	96.7-99.0
3	733	95.6	89.1-98.8	83.0	79.9-85.8	44.4	37.3-51.6	99.3	98.1-99.8
6-9	622	96.7	90.8-99.3	80.2	76.5-83.5	45.9	38.7-53.2	99.3	98.0-99.9
12-24	473	94.4	86.4-98.5	76.3	71.8-80.4	41.7	34.1-49.7	98.7	96.7-99.6

Cutoff: 14 ng/L (Females)									
Time Elapsed Since Presentation to ED (hours)	**N**	**Sensitivity**		**Specificity**		**PPV**		**NPV**	
		%	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
Baseline	771	85.7	74.6-93.3	88.1	85.5-90.4	39.1	30.9-47.8	98.6	97.3-99.3
3	682	91.8	80.4-97.7	86.9	84.0-89.4	35.2	26.9-44.1	99.3	98.2-99.8
6-9	536	91.3	79.2-97.6	86.5	83.2-89.4	38.9	29.7-48.7	99.1	97.6-99.7
12-24	399	92.3	79.1-98.4	81.4	77.0-85.3	35.0	25.8-45.0	99.0	97.1-99.8

Cutoff: 22 ng/L (Males)									
Time Elapsed Since Presentation to ED (hours)	N	Sensitivity		Specificity		PPV		NPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
Baseline	829	85.1	76.7-91.4	87.2	84.6-89.6	48.0	40.5-55.6	97.7	96.2-98.7
3	733	95.6	89.1-98.8	86.3	83.4-88.9	49.7	42.1-57.4	99.3	98.2-99.8
6-9	622	93.5	86.3-97.6	82.3	78.7-85.4	47.8	40.3-55.3	98.6	97.1-99.5
12-24	473	94.4	86.4-98.5	80.0	75.8-83.9	45.9	37.7-54.3	98.8	96.9-99.7

False negative results observed in the US study are summarized below:

Sex	Clinical Cutoff	False Negative Count	False Negative Estimate
both sexes	19	11/173	6.4 %
Females	19	7/66	10.6 %
	14	6/66	9.1 %
males	19	4/107	3.7 %
	22	4/107	3.7 %

The sponsor includes the following information in the package insert to describe the false negatives observed in this study:

> In this study, we observed 11 false negatives (out of 173 subjects adjudicated with AMI). In these subjects, no result above the cutoff was obtained with the Elecsys Troponin T Gen 5. Six of these 11 subjects had presented within 3 hours of onset of chest pain (early presenters), and for 4 of these subjects no blood draw was tested with the Elecsys Troponin T Gen 5 when the SOC troponin test detected troponin concentrations above the SOC cutoff. For some subjects this occurred more than 6 hours after presentation to the emergency room. Four of these 6 early presenters had an adjudicated diagnosis of STEMI.

The following information is included in the labeling:

> Using the established sex-specific 99th percentile (14 ng/L for females and 22 ng/L for males), the lower end of the confidence interval (CI) for the PPV at all timepoints for female subjects was as low as 25.8 %, and for male subjects it was as low as 37.7 %. Up to 74.2 % and 62.3 % of positive troponin results in females and males, respectively, were not myocardial infarctions. Troponin results should always be used in conjunction with clinical signs and symptoms.
>
> Using the established 99th percentile (19 ng/L), the lower end of the confidence interval (CI) for the PPV at all timepoints for female subjects was as low as 28.8 %, and for male subjects it was as low as 34.1 %. Up to 71.2 % and 65.9 % of positive troponin results in

females and males, respectively, were not myocardial infarctions. Troponin results should always be used in conjunction with clinical signs and symptoms.

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

> Troponins are released during the process of myocyte injury. 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). In these disease states, serial sampling of troponin can help distinguish between acute and chronic myocyte necrosis. The 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..

2. Clinical Specificity:

See clinical sensitivity above.

C Clinical Cut-Off:

This assay has three claimed clinical cut-offs. These are an overall cutoff for all patients (19 ng/L), a cut-off for females (14 ng/L), and a cut-off for males (22 ng/L). These three clinical cut-offs all were determined using the 99th percentile upper reference limit.

D Expected Values/Reference Range:

Data establishing the reference range for the Elecsys Troponin T Gen 5 STAT Assay was previously reviewed in k162895. 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.

VIII Proposed Labeling:

The labeling supports a finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification supports substantial equivalence to the predicate.