510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K210546

B Applicant

Roche Diagnostics

C Proprietary and Established Names

Elecsys proBNP II, Elecsys proBNP II STAT

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
NBC	Class II	21 CFR 862.1117 - B-Type Natriuretic Peptide Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

Modification to previously cleared assays (K072437 and K092649) to attenuate biotin interference

B Measurand:

N-terminal pro-BRAIN natriuretic peptide (NT-proBNP)

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:

Both the Elecsys proBNP II and Elecsys proBNP II STAT have the following intended use:

Immunoassay for the in vitro quantitative determination of N terminal pro Brain natriuretic peptide in human serum and plasma. This assay is used as an aid in the diagnosis of individuals suspected of having heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure. The test may also serve as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

For in vitro Diagnostic Use Only

D Special Instrument Requirements:

Performance data for this submission were generated using the cobas e 411 immunoassay analyzer (Elecsys proBNP II) and the cobas e 601 immunoassay analyzer (Elecsys proBNP II STAT).

IV Device/System Characteristics:

A Device Description:

The Elecsys proBNP II and the Elecsys proBNP II STAT consist of three reagents in separate bottles labeled M, R1, and R2:

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

R1: Anti-NT-proBNP-Ab~biotin (gray cap), 1 bottle, 9 mL: Biotinylated monoclonal anti-NT-proBNP antibody (mouse) 1.1 µg/mL; phosphate buffer 40 mmol/L, pH 5.8; preservative.

R2: Anti-NT-proBNP-Ab~Ru(bpy) (black cap), 1 bottle, 9 mL: Monoclonal anti-NT-proBNP antibody (sheep) labeled with ruthenium complex 1.1 µg/mL; Biotin scavenger antibody 1.5 mg/mL; phosphate buffer 40 mmol/L, pH 5.8; preservative.

B Principle of Operation:

The Elecsys proBNP II assay follows the procedure below:

1st incubation: Antigen in the sample (15 µL), a biotinylated monoclonal NT-proBNP-specific antibody, and a monoclonal NT-proBNP-specific antibody labeled with a ruthenium complex (Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)) to form a sandwich complex.

2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

Results are determined via a calibration curve which is instrument specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

The Elecsys proBNP II STAT assay follows a similar procedure outlined above except that the first and second incubations are combined into a single step.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Elecsys proBNP II, Elecsys proBNP II STAT Immunoassay

B Predicate 510(k) Number(s):

K072437, K092649

C Comparison with Predicate(s):

Device & Predicate Device(s):	K210546	K072437
Device Trade Name	Elecsys proBNP II	Elecsys proBNP II
General Device Characteristic Similarities		

Device & Predicate Device(s):	K210546	K072437
Intended Use/Indications For Use	Immunoassay for the in vitro quantitative determination of N-terminal pro-Brain natriuretic peptide (NTproBNP) in human serum and plasma. This assay is used as an aid in the diagnosis of individuals suspected of having heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure. The test may also serve as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease.	Same
Principale of Operation	ECLIA	Same
Cutoffs	125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years or older.	Same
General Device Characteristic Differences		
Specimen Types	Serum, Li-heparin plasma, and K_2-EDTA plasma	Serum, Li-heparin plasma, K_2-EDTA plasma and K_3-EDTA plasma
Measuring Range	36-35,000 pg/mL	5-35,000 pg/mL
Reagents	Contains biotin scavenger antibody	Does not contain biotin scavenger antibody

Device & Predicate Device(s):	K210546	K092649
Device Trade Name	Elecsys proBNP II STAT	Elecsys proBNP II STAT
General Device Characteristic Similarities		
Intended Use/Indications For Use	Immunoassay for the in vitro quantitative determination of N-terminal pro-Brain natriuretic peptide (NTproBNP) in human serum and plasma. This assay is used as an aid in the diagnosis of individuals suspected of having heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure. The test may also serve as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease.	Same
Principale of Operation	ECLIA	Same
Cutoffs	125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years or older.	Same
General Device Characteristic Differences		
Specimen Types	Serum, Li-heparin plasma, and K_2-EDTA plasma	Serum, Li-heparin plasma, K_2-EDTA plasma and K_3-EDTA plasma
Measuring Range	36-35,000 pg/mL	5-35,000 pg/mL

Device & Predicate Device(s):	K210546	K092649
Reagents	Contains biotin scavenger antibody	Does not contain biotin scavenger antibody

VI Standards/Guidance Documents Referenced:

- Clinical and Laboratory Standards Institute (CLSI) EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition
- CLSI EP06-Ed2 Evaluation of the Linearity of Quantitative Measurement Procedures, Approved Guideline—Second Edition
- CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition
- Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications; Final Guidance for Industry and FDA Reviewers. Document issued on: November 30, 2000

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Single-site Precision Study
The precision of the Elecsys proBNP II assay was evaluated on one cobas e 411 and Elecsys proBNP II STAT assay was evaluated on one cobas e 601 analyzer at one internal site with three reagent lots over 21 days.

Testing was conducted with nine serum samples and two controls in single determinations in four separate aliquots (divided into two runs per day) for 21 operating days (n=84). Repeatability, Between-Run, Between-Day, and Within-Laboratory Precision were calculated per recommendations in the CLSI EP05-A3 guideline.

Human serum samples 1, 2, 3, 4, 5, and 8 are pooled unaltered human serum samples. Samples 6 and 7 are human serum sample pools spiked with synthetic NT-proBNP peptide. In addition, 2 control samples were tested, PreciControl Cardiac II 1 and PreciControl Cardiac II 2. The tables below present data from one representative lot of the Elecsys proBNP II and Elecsys proBNP II STAT.

Elecsys proBNP II on the cobas e 411 analyzer									
		Repeatability		Between-Run		Between-Day		Within Laboratory	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %	SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	55.9	2.62	4.7	1.19	2.1	3.26	5.8	4.35	7.8
Human serum 2	129	3.07	2.4	0.00	0.00	6.73	5.2	7.40	5.7
Human serum 3	423	8.91	2.1	8.51	2.0	13.2	3.1	18.0	4.3
Human serum 4	925	23.0	2.5	11.3	1.2	36.1	3.9	44.3	4.8
Human serum 5	1,924	43.8	2.3	39.3	2.0	66.5	3.5	88.8	4.6
Human serum 6	15,620	248	1.6	272	1.7	550	3.5	662	4.2
Human serum 7	33,526	778	2.3	446	1.3	1,314	3.9	1,591	4.7
Human serum 8	337	5.11	1.5	4.64	1.4	9.08	2.7	11.4	3.4
PreciControl Cardiac II 1	132	3.29	2.5	2.17	1.6	4.48	3.4	5.97	4.5
PreciControl Cardiac II 2	4,477	135	3.0	0.00	0.00	169	3.8	216	4.8

Elecsys proBNP II STAT on the cobas e 601 analyzer									
		Repeatability		Between-Run		Between-Day		Within-Laboratory	
Sample (Serum)	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %	SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	63.9	2.42	3.8	3.00	4.7	2.09	3.3	4.39	6.9
Human serum 2	144	3.36	2.3	3.29	2.3	3.51	2.4	5.87	4.1
Human serum 3	482	12.7	2.6	4.44	0.9	12.7	2.6	18.5	3.8
Human serum 4	1,060	24.6	2.3	12.5	1.2	20.4	1.9	34.4	3.2
Human serum 5	2,219	51.4	2.3	10.7	0.5	56.6	2.5	77.2	3.5

Elecsys proBNP II STAT on the cobas e 601 analyzer									
		Repeatability		Between-Run		Between-Day		Within-Laboratory	
Human serum 6	18,371	405	2.2	188	1.0	478	2.6	654	3.6
Human serum 7	33,967	912	2.7	450	1.3	869	2.6	1,338	3.9
Human serum 8	331	5.01	1.5	5.31	1.6	10.4	3.1	12.7	3.8
PreciControl Cardiac II 1	155	4.06	2.6	2.77	1.8	3.58	2.3	6.08	3.9
PreciControl Cardiac II 2	5,660	116	2.1	71.3	1.3	138	2.4	194	3.4

Multi-site Precision Study

Inter-instrument variability testing was performed using the Elecsys proBNP II and proBNP II STAT assays on three cobas e 411 analyzers and on three cobas e 601 analyzers, respectively, per recommendations in the CLSI EP5-A3 guideline. One reagent lot for the Elecsys proBNP II and Elecsys proBNP II STAT was used for measurements taken at three laboratory sites, over 5 days with 5 replicates of each sample tested per day.

Human serum (HS) samples 1, 2, 3, 4, 5, and 8 are pooled unaltered human serum samples. Samples 6 and 7 are human serum sample pools spiked with synthetic NT-proBNP peptide. In addition, 2 control samples were tested, PreciControl Cardiac II 1 and PreciControl Cardiac II 2 (referred to as PC 1 and PC 2, respectively, in the tables below).

cobas e 411 analyzer, Elecsys proBNP II										
			Repeatability		Between-Day		Between-Site		Reproducibility	
Sample	Mean pg/mL	N	SD pg/mL	CV %	SD pg/mL	CV %	SD pg/mL	CV %	SD pg/mL	CV %
HS 1	55.2	75	1.88	3.4	1.92	3.5	1.02	1.8	2.87	5.2
HS 2	131	75	2.56	1.9	2.49	1.9	3.46	2.6	4.97	3.8
HS 3	332	75	7.41	2.2	8.15	2.5	5.5	1.7	12.3	3.7
HS 4	471	75	8.14	1.7	10.3	2.2	10.3	2.2	16.7	3.5
HS 5	963	75	20.7	2.1	26.8	2.8	13.2	1.4	36.3	3.8
HS 6	1,773	75	38.0	2.1	39.8	2.2	20.0	1.1	58.5	3.3
HS 7	18,719	75	311	1.7	440	2.4	0.00	0.00	539	2.9
HS 8	31,425	75	735	2.3	815	2.6	0.00	0.00	1,097	3.5
PC 1	144	75	2.57	1.8	3.62	2.5	1.89	1.3	4.82	3.3
PC 2	4,799	75	97.0	2.0	79.1	1.6	0.00	0.00	125	2.6

cobas e 601 analyzer, Elecsys proBNP II STAT										
			Repeatability		Between-Day		Between-Site		Reproducibility	
Sample	Mean pg/mL	N	SD pg/mL	CV %	SD pg/mL	CV %	SD pg/mL	CV %	SD pg/mL	CV %
HS 1	52.1	75	1.25	2.4	1.74	3.3	3.91	7.5	4.46	8.6
HS 2	128	75	2.33	1.8	3.89	3.0	9.22	7.2	10.3	8.0
HS 3	317	75	6.76	2.1	5.63	1.8	23.8	7.5	25.4	8.0
HS 4	465	75	8.50	1.8	9.74	2.1	34.6	7.4	36.9	7.9
HS 5	961	75	16.1	1.7	23.9	2.5	74.3	7.7	79.7	8.3
HS 6	1,845	75	33.7	1.8	43.0	2.3	134	7.3	145	7.8
HS 7	18,477	75	313	1.7	384	2.1	1,466	7.9	1,548	8.4
HS 8	30,089	75	539	1.8	648	2.2	2,394	8.0	2,538	8.4
PC 1	145	75	2.65	1.8	4.29	3.0	10.9	7.5	12.0	8.2
PC 2	5,328	75	91.9	1.7	114	2.1	399	7.5	425	8.0

2. Linearity:

One high analyte human, native serum sample with a NT-proBNP concentration above the measuring rage was diluted with analyte free serum. A total of 11 concentrations were prepared that spanned the measuring range. Samples were assayed in 3-fold determination within a single run. Samples were tested using the Elecsys proBNP II on the cobas e 411 and the Elecsys proBNP II STAT on the cobas e 601. The linearity data were analyzed per the recommendations in CLSI EP06-Ed2.

The maximum deviation from linearity observed within the claimed measuring range for the Elecsys proBNP II was -10.5%.

The maximum deviation from linearity observed within the claimed measuring range for the Elecsys proBNP II STAT was -16.9%.

The results of the linearity study support that the Elecsys proBNP II and the Elecsys proBNP II STAT are linear across the claimed measuring range of 36 pg/mL to 35000 pg/mL.

3. Analytical Specificity/Interference:

Endogenous Compounds, Biotin, and Intralipid

The Elecsys proBNP II and Elecys proBNP II STAT were evaluated for potential interference from endogenous compounds, intralipid, and biotin. Testing was conducted with three levels of NT-proBNP: low (~125-140 pg/mL), medium (~800-1000 pg/mL), and high (~18000-23000 pg/mL). Samples were measured using the Elecsys proBNP II on the cobas e 411 analyzer and using the Elecsys proBNP II STAT on the cobas e 601 analyzer. Interference was defined as a mean percent recovery of samples containing potential

interferent that exceeds 100±10% of the control sample.

No interference was observed for the following substances up the concentrations listed below.

Compound	Concentration
Conjugated Bilirubin	66 mg/dL
Unconjugated Bilirubin	66 mg/dL
Hemoglobin	1000 mg/dL
Intralipid	1500 mg/dL
Biotin	5000 ng/mL
Rheumatoid factors	1500 IU/mL
Albumin	7 g/dL

The sponsor's study supports the claims in the labeling that there is no significant interference in the presence of, ≤1000 mg/dL hemoglobin, ≤1500 mg/dL Intralipid, , ≤1500 IU/mL rheumatoid factors, and ≤7 g/dL albumin. Although no significant interference was observed in the presence of unconjugated bilirubin, conjugated bilirubin, and biotin at the concentrations listed in the table above, the sponsor is claiming that there is no significant interference at lower concentrations of these compounds; the sponsor is claiming that there is no significant interference in the presence of ≤25 mg/dL bilirubin and ≤3500 ng/mL biotin.

Cross-Reactivity

The cross-reactivity of the Elecsys proBNP II and Elecsys proBNP II STAT was evaluated with two human native serum samples with low (about 150 pg/mL) and high (about 2500-3000 pg/mL) NT-proBNP levels. The cross-reactant concentrations tested are the highest concentration that may be expected in the intended use population. Samples were measured using the Elecsys proBNP II on the cobas e 411 analyzer and using the Elecsys proBNP II STAT on the cobas e 601 analyzer. Significant cross-reactivity was defined as a mean percent recovery of samples containing potential cross-reactant that exceeds 100±10% of the control sample.

Elecsys proBNP II Cross-Reactivity

Cross-reactant	Concentration of cross-reactant tested	Low NT-proBNP	High NT-proBNP
		Recovery with cross- reactant [%]	Recovery with cross-reactant [%]
Adrenomedullin	1.0 ng/mL	91	97
Angiotensin I	0.6 ng/mL	99	99
Angiotensin II	0.6 ng/mL	100	98
Angiotensin III	1.0 ng/mL	100	97

Cross-reactant	Concentration of cross-reactant tested	Low NT-proBNP	High NT-proBNP
		Recovery with cross- reactant [%]	Recovery with cross-reactant [%]
Arg-Vasopressin	1.0 ng/mL	100	100
Endothelin	20 pg/mL	100	97
Aldosterone	0.6 ng/mL	97	96
Renin	50 ng/mL	94	94
BNP32	3.5 µg/mL	100	100
CNP22	2.2 µg/mL	91	96
Urodilatin	3.5 µg/mL	100	99
ANP 1-28	3.1 µg/mL	101	99
NT-proANP (1-30) [preproANP (26-55)]	3.5 µg/mL	99	96
NT-proANP (31-67) [preproANP 56-92]	1.0 ng/mL	97	97
NT-proANP (79-98) [preproANP 104-123]	1.0 ng/mL	100	103

Elecsys proBNP II STAT Cross-Reactivity

Cross-reactant	Concentration of cross-reactant tested	Low NT-proBNP	High NT-proBNP
		Recovery with cross- reactant [%]	Recovery with cross-reactant [%]
Adrenomedullin	1.0 ng/mL	99	101
Angiotensin I	0.6 ng/mL	99	99
Angiotensin II	0.6 ng/mL	100	100
Angiotensin III	1.0 ng/mL	98	96
Arg-Vasopressin	1.0 ng/mL	98	98
Endothelin	20 pg/mL	100	99
Aldosterone	0.6 ng/mL	98	97
Renin	50 ng/mL	96	94
BNP32	3.5 µg/mL	100	98
CNP22	2.2 µg/mL	97	96
Urodilatin	3.5 µg/mL	99	99
ANP 1-28	3.1 µg/mL	100	99
NT-proANP(1-30) [preproANP (26-55)]	3.5 µg/mL	96	95

Cross-reactant	Concentration of cross-reactant tested	Low NT-proBNP	High NT-proBNP
		Recovery with cross- reactant [%]	Recovery with cross-reactant [%]
NT-proANP(31-67) [preproANP 56-92]	1.0 ng/mL	100	99
NT-proANP(79-98) [preproANP 104-123]	1.0 ng/mL	99	106

No significant cross-reactivity to the substances listed in the tables above was observed for the Elecsys proBNP II and the Elecsys proBNP II STAT.

Exogenous Substances

The Elecsys proBNP II and Elecys proBNP II STAT were evaluated for potential interference from pharmaceutical compounds. Testing was conducted with two levels of native human samples with ~125 pg/mL and ~2000 pg/mL NT-proBNP. The drugs and drug levels tested were determined per recommendations in CLSI EP07 and CLSI EP37. Samples were measured using the Elecsys proBNP II on the cobas e 411 analyzer and using the Elecsys proBNP II STAT on the cobas e 601 analyzer. Interference was defined as a mean percent recovery of samples containing potential interferent that exceeds 100±10% of the control sample.

No significant interference was observed with the 50 pharmaceutical compounds listed in the table below:

Common therapeutic drugs	Drug concentration [mg/dL]	Special therapeutic drugs	Drug concentration [mg/dL]
Acetylcysteine	15.0	Carvedilol	15.0
Ampicillin-Na	100.0	Clopidogrel	7.5
Ascorbic acid	30.0	Digoxin	0.05
Cefoxitin	250.0	Epinephrine	0.037
Heparin	5000 IU/L	Insulin	0.084
Levodopa	2.0	Lidocaine	10.0
Methyldopa	2.0	Lisinopril	4.0
Metronidazole	20.0	Methylprednisolone	8.0
Doxycycline	5.0	Metoprolol	1.5
Acetylsalicylic Acid	100.0	Nifedipine	6.0
Rifampicin	6.0	Marcumar	0.6
Cyclosporine	0.5	Propafenone	90.0
Phenylbutazone	40.0	Reteplase	0.112
Acetaminophen	20.0	Simvastin	4.0
Ibuprofen	50.0	Spirinolactone	40.0

Common therapeutic drugs	Drug concentration [mg/dL]
Theophylline	10.0
Ca-Dobesilate	20.0

Special therapeutic drugs	Drug concentration [mg/dL]
Tolbutamide	300.0
Torasemide	20.0
Verapamil	12.0
Propranolol	0.032
Enalapril	4.0
Captopril	5.0
Gentamycin	50.0
Lovastatin	8.0
Pravastatin	4.0
Bisoprolol	1.0
Glycerol nitrate	19.2
Molsidomin	2.4
Nicardipine	9.0
Streptokinase	300 IE/mL
Urokinase	600 IE/mL
Digitoxin	0.03
Sotalol	32.0
Low molecular weight heparin	1.8

4. Assay Reportable Range:

   36-35,000 pg/mL

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

   The assays are traceable gravimetrically to an in-house reference material. The reference material has not changed compared with clearances of previous generations of these devices.

6. Detection Limit:

   Limit of Blank (LoB):
   The LoB of the Elecsys proBNP II on the cobas e 411 analyzer and of the Elecsys proBNP II STAT on the cobas e 601 analyzer was determined per recommendations in CLSI EP17-A2. In total, 60 determinations of an analyte-free sample were obtained on one instrument in 6 runs with 10-fold determination per run. Three lots of reagent were used in the experimental design. The LoB was determined as the 95th percentile of measurements of blank samples.

   The sponsor's study supports that the LoB for the Elecsys proBNP II and the Elecsys proBNP II STAT is ≤ 8 pg/mL.

Limit of Detection (LoD):
The LoD of the Elecsys proBNP II on the cobas e 411 analyzer and of Elecsys proBNP II STAT (updated assay) on the cobas e 601 analyzer was determined per recommendations in CLSI EP17-A2. Five low-level human serum samples were measured on one instrument in 60 total determinations per sample per reagent lot. The study was conducted using three reagent lots. The LoD was determined by parametric analysis.

The sponsor's study supports the claimed LoD of 10 pg/mL for the Elecsys proBNP II and the Elecsys proBNP II STAT.

Limit of Quantitation (LoQ):
The LoQ of the Elecsys proBNP II on the cobas e 411 analyzer and of the Elecsys proBNP II STAT on the cobas e 601 analyzer was determined per recommendations in CLSI EP17-A2. Nine native, unaltered serum samples were tested with the Elecsys proBNP II and 10 native, unaltered serum samples were tested with the Elecsys proBNP II STAT. Each sample was tested in 5 replicates on one instrument in singleton per day, over 5 days with 1 run per day. Three lots of reagent were used in the study. A total of n=25 measured values were obtained for each sample. The LoQ was determined as the lowest concentration of analyte which can be measured with an intermediate precision of 20% CV.

The sponsor's study supports the claimed LoQ of 36 pg/mL for the Elecsys proBNP II and the Elecsys proBNP II STAT.

7. Assay Cut-Off:

Previously established in K022516

B Comparison Studies:

1. Method Comparison with Predicate Device:

a) Elecsys proBNP II

The sponsor obtained 2414 native serum samples each collected from independent subjects in the sponsor's intended use population from the US and Europe. The sponsor conducted a Passing-Bablok regression analysis on 1940 native serum samples comparing the measurements made using the biotin-remediated Elecsys proBNP II (subject device, y) with measurements made using the non-biotin remediated Elecsys proBNP II (predicate device, x). A total of 474 samples were not included in the regression analysis because the NT-proBNP values fell outside the common measuring range of the predicate and subject devices. The following Passing-Bablok regression fit was determined from the comparison study:

$y = 0.98x - 2.88$

The 95% confidence interval (CI) for the estimate of the slope was between 0.98 and 0.98 and the 95% CI for the estimate of the intercept was between -3.20 and -2.46.

Based on the regression analysis above, the sponsor will include in the labeling the following information concerning the predicted systematic differences between the biotin-remediated Elecsys proBNP II and non-biotin-remediated Elecsys proBNP II assays at different NT-proBNP concentrations:

		(-4.4,-3.9)	(-3.0,-2.7)	(-2.6,-2.4)	(-2.3,-2.1)	(-2.2,-1.9)

The sponsor also conducted a concordance analysis with the 2414 native serum samples collected from subjects in the US and Europe comparing the agreement between the subject and predicate devices at the two age-dependent cutoffs (125 pg/mL for patients <75 years of age and 450 pg/mL for patients ≥75 years of age). Of these subjects with a confirmed diagnosis of heart failure (N = 1015), the total agreement between the subject and predicate devices was 98.6% (1001/1015). Of the subjects without a confirmed heart failure diagnosis (N =1399) the total agreement between the subject and predicate devices was 98.7% (1381/1399). In a subset of US subjects, heart failure severity was classified per the New York Heart Association Functional Classification for heart failure (NYHA Class I-IV). The total agreement between the subject and predicate devices for subjects classified in NYHA Classes I, II, II, and IV were 98% (193/197), 98.7% (224/227), 98.4% (254/258), and 98.2% (166/169), respectively.

b) Elecsys proBNP II STAT

The sponsor obtained 2414 native serum samples each collected independent subjects in the sponsor's intended use population from the US and Europe. The sponsor conducted a Passing-Bablok regression analysis on 1928 native serum samples comparing the measurements made using the biotin-remediated Elecsys proBNP II STAT (subject device, y) with measurements made using the non-biotin remediated Elecsys proBNP II STAT (predicate device, x). A total of 486 samples were not included in the regression analysis because the NT-proBNP values fell outside the common measuring range of the predicate and subject devices. The following Passing-Bablok regression fit was determined from the comparison study:

$y = 1.01x – 1.60$

The 95% confidence interval (CI) for the estimate of the slope was between 1.00 and 1.01 and the 95% CI for the estimate of the intercept was between -2.09 and -1.16.

Based on the regression analysis above, the sponsor will include the following information concerning the predicted systematic differences between the biotin-remediated Elecsys proBNP II STAT and non-biotin-remediated Elecsys proBNP II

STAT assays at different NT-proBNP concentrations in the labeling,

		Predicted Relative Bias (%)				
Test Method	Comparison Method	125 pg/mL (95% CI)	300 pg/mL (95% CI)	450 pg/mL (95% CI)	900 pg/mL (95% CI)	1800 pg/mL (95% CI)
Biotin-remediated Elecsys proBNP II STAT	Elecsys proBNP II STAT	-0.8 (-1.0,-0.5)	0 (-0.2,0.2)	0.2 (-0.1,0.4)	0.3 (0.1,0.6)	0.4 (0.2,0.7)

The sponsor also conducted a concordance analysis with the 2414 native serum samples collected from subjects in the US and Europe comparing the agreement between the subject and predicate devices at the two age-dependent cutoffs (125 pg/mL for patients <75 years of age and 450 pg/mL for patients ≥75 years of age). Of these subjects with a confirmed diagnosis of heart failure (N = 1015), the total agreement between the subject and predicate devices was 99.7% (1012/1015). Of the subjects without a confirmed heart failure diagnosis (N =1399) the total agreement between the subject and predicate devices was 99.2% (1388/1399). In a subset of US subjects, heart failure severity was classified per the New York Heart Association Functional Classification for heart failure (NYHA Class I-IV). The total agreement between the subject and predicate devices for subjects classified in NYHA Classes I, II, II, and IV were 100% (197/197), 99.6% (226/227), 99.6% (257/258), and 99.4% (168/169), respectively.

The sponsor provided information on the potential impact the performance characteristics of the Elecsys proBNP II and the Elecsys proBNP II STAT may have on the labeled clinical performance of the device. This information was reviewed and determined to support that the clinical performance claims are applicable to the Elecsys proBNP II and Elecsys proBNP II STAT.

The sponsor also provided information to support the use of the frozen samples used in the method comparison and concordance studies.

2. Matrix Comparison:

The sponsor conducted a matrix comparison study with the Elecsys proBNP II on the cobas e 411 and with the Elecsys proBNP II STAT on the cobas e 601 by comparing values obtained from testing matched native (single donors) serum, lithium heparin (Li-Heparin) plasma, and K2-EDTA plasma samples. The following tables summarize the Passing-Bablok regression analysis comparing the results from serum to those from lithium heparin plasma and K2-EDTA plasma samples.

Sample Matrix Comparison for Elecsys proBNP II

Elecsys proBNP II	Li-Heparin	K2-EDTA
Slope [95% LCL/UCL]	0.990 [0.981/0.997]	1.01 [0.994/1.01]

Elecsys proBNP II	Li-Heparin	K2-EDTA
Intercept (pg/mL) [95% LCL/UCL]	0.898 [-0.981/3.45]	-0.985 [-4.23/2.21]
Correlation coefficient Pearson's r	0.998	0.999
Serum/plasma pairs	98	111

Sample Matrix Comparison for Elecsys proBNP II STAT

Elecsys proBNP II STAT	Li-Heparin	K2-EDTA
Slope [95% LCL/UCL]	0.983 [0.974/0.988]	1.00 [0.991/1.01]
Intercept (pg/mL) [95% LCL/UCL]	0.803 [-1.09/3.25]	-2.41 [-7.75/0.275]
Correlation coefficient Pearson's r	0.998	0.999
Serum/plasma pairs	98	112

The sponsor's study results support claims for testing serum, lithium heparin, and K2-EDTA plasma with the Elecsys proBNP II on the cobas e 411 and the Elecsys proBNP II STAT on the cobas e 601.

C Clinical Studies:

1. Clinical Sensitivity:

   Previously established in K022516

2. Clinical Specificity:

   Previously established in K022516

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   See section B Comparison Studies, above.

D Clinical Cut-Off:

Previously established in K022516

E Expected Values/Reference Range:

Previously established for K022516

VIII Proposed Labeling:

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

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.