510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K223637

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:

Expansion of the intended use

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 indications for use:

Immunoassay for the in vitro quantitative determination of N-terminal pro-Brain natriuretic peptide (NT-proBNP) in human serum and plasma. This assay is used as an aid in the diagnosis of individuals suspected of having heart failure (HF). It can be used as an aid in the diagnosis of acute decompensated heart failure (ADHF) in patients presenting with signs and symptoms of ADHF to the emergency department (ED). The assay is further indicated for the risk stratification of patients with acute coronary syndrome and HF. The test may also serve as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for HF who have stable coronary artery disease.

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

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Performance data for this submission was generated using the cobas e 601 immunoassay analyzer

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 ($Ru(bpy)_3^{2+}$)) 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 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. The total assay run time for the Elecsys proBNP II is 18 min and for the Elecsys proBNP II STAT is 9 min.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Elecsys proBNP II, Elecsys proBNP II STAT

B Predicate 510(k) Number(s):
K210546

C Comparison with Predicate(s):

Device & Predicate Device(s):	K223637	K210546
Device Trade Name	Elecsys proBNP II, Elecsys proBNP II STAT	Elecsys proBNP II, Elecsys proBNP II STAT
General Device Characteristic Similarities		
Intended Use	For the quantitative determination of NT-proBNP in human serum and plasma.	Same
Test principle	Quantitative immunoassay	Same

Device & Predicate Device(s):	K223637	K210546
General Device Characteristic Differences		
Result interpretation	Emergency Department setting for ADHF: Negative < 300 pg/mL for all age groups Indeterminate • ≥ 300 to ≤ 450 pg/mL for < 50 years of age • ≥ 300 to ≤ 900 pg/mL for 50-75 years of age • ≥ 300 to ≤ 1800 pg/mL for > 75 years of age Positive • > 450 pg/mL for < 50 years of age • > 900 pg/mL for 50-75 years of age • >1800 pg/mL for > 75 years of age	Positive • 125 pg/mL for < 75 years of age • 450 pg/mL for patients ≥ 75 years of age

VI Standards/Guidance Documents Referenced:

Clinical and Laboratory Standards Institute (CLSI) EP05-A3: Evaluation of Precision of Quantitative Measuring Procedures-Third Edition.

CLSI EP06: Evaluation of the Linearity of Quantitative Measurement Procedure - Second Edition.

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures-Second Edition.

B-Type Natriuretic Peptide Premarket Notifications - Final Class II Special Control Guidance Document for Industry and FDA Reviewers

VII Performance Characteristics (if/when applicable):

The performance characteristics of the Elecsys ProBNP II STAT on the cobas e 601 analyzer are described in K210456.

A Analytical Performance:

1. Repeatability and Intermediate Precision:

The precision of the Elecsys proBNP II assay was evaluated on one cobas e 601 analyzer at one internal site with three reagent lots over 21 days.

Testing was conducted with eight 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 the recommendations in the CLSI EP05-A3 guideline.

Human serum samples 1, 2, 3, 4, 5, and 6 are pooled unaltered human serum samples. Samples 7 and 8 are human serum sample pools spiked with a synthetic NT-proBNP peptide. Results from a representative lot are described below.

		Repeatability		Within laboratory precision	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	68.3	1.96	2.9	3.26	4.8
Human serum 2	145	3.24	2.2	5.95	4.1
Human serum 3	314	4.31	1.4	11.5	3.7
Human serum 4	467	12.8	2.7	17.6	3.8
Human serum 5	1004	20.0	2.0	34.6	3.5
Human serum 6	2075	38.9	1.9	68.6	3.3
Human serum 7	15985	371	2.3	579	3.6
Human serum 8	34624	609	1.8	1367	3.9
PreciControl Cardiac II 1	140	2.48	1.8	4.94	3.5
PreciControl Cardiac II 2	4721	70.2	1.5	156	3.3

2. Linearity:

The linearity study was conducted using the Elecsys proBNP II on the cobas e 601 analyzer following the recommendations in the CLSI guideline EP06 second edition. 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 10 concentrations were prepared that spanned the measuring range. Samples were assayed in 3-fold determination within a single run.

The maximum deviation from linearity observed within the claimed measuring range for the Elecsys proBNP II was -16.8%.

The results of the linearity study support the claimed measuring range of 36 pg/mL to 35000 pg/mL

3. Analytical Specificity/Interference:

Analytical specificity studies were conducted using the Elecsys proBNP II assay on the cobas e 601 analyzer and support the same analytical specificity claims established in K210546 for the Elecsys proBNP II assay on the e 411 analyzer.

4. Assay Reportable Range:

The claimed assay reportable range is 36-35,000 pg/mL.

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

The traceability of the assays is the same as described in K210546.

6. Detection Limit:

LoB (Limit of blank), LoD (Limit of detection) and Limit of Quantitation (LoQ) of the Elecsys proBNP II on the cobas e 601 analyzer were determined according to CLSI EP17-A2 and support the claims described in K210546 for the Elecys proBNP II assay on the e 411 analyzer.

7. Assay Cut-Off:

See clinical cut-off (Section VII.D.) below.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A method comparison was conducted using the Elecsys NT proBNP II assay on the cobas e 411 and the cobas e 601analyzers. One hundred fifty-seven (157) human serum samples containing between 54 and 33,544 pg/mL of NTproBNP were tested in the study. One hundred fifty-three (153) samples were native and 4 samples were spiked. There were no diluted samples.

The results of the Passing-Bablok regression analysis are summarized below:

Slope	95% CI	Intercept	95% CI	Pearsons r
0.988	0.980 to 0.995	1.03	-2.98 to 4.96	0.999

2. Matrix Comparison:

The sponsor claims the same matrix types for the Elecsys proBNP II on the cobas e 601 as described in K210546.

C Clinical Studies:

1. Clinical Sensitivity:

   See Section VII.C.3. below.

2. Clinical Specificity:

   See Section VII.C.3. below.

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

   A multi-center prospective study including 17 sites in the United States was conducted to establish the clinical performance characteristics of the Elecsys proBNP II and Elecsys proBNP II STAT assays. Subjects 22 years and older admitted to the emergency department (ED) suspected of or with symptoms of acute decompensated heart failure (ADHF) that included acute dyspnea of a duration no longer than several days were enrolled in the study. Subjects with renal insufficiency requiring dialysis or known estimated glomerular filtration rate (eGFR) < 15.0 mL/min/1.73 m^2 and subjects with dyspnea after chest trauma were excluded from the study. The final clinical diagnosis was adjudicated by cardiologists or ED physicians. The Elecsys proBNP II and Elecsys proBNP II STAT results were determined on the Roche cobas e601 immunoassay analyzer using samples collected from 1485 ED subjects consisting of 741 (49.9%) female subjects and 744 (50.1%) male subjects ranging in age from 22 to 97 years. Individuals in the population were Caucasian (57.4%), Black or African American (37.2%), Asian (1.3%), American Indian or Alaska Native (0.3%), Native Hawaiian or Other Pacific Islander (0.6%), or other race (1.3%) with the remaining 1.9% of unknown race. 1238 (83.4%) ED subjects were not Hispanic or Latino and 190 (12.8%) ED subjects were Hispanic or Latino with the remaining 57 (3.8%) ED subjects of unknown ethnicity.

   The descriptive statistics for the Elecsys proBNP II and Elecsys proBNP II STAT results (pg/mL) were determined within and across sex by age group. The results using the Elecsys proBNP II STAT assay are summarized below and are similar to the results obtained using the Elecsys proBNP II:

   Elecsys proBNP II STAT – All subjects

	ADHF				No ADHF			
Age group	< 50	50-75	>75	All	< 50	50-75	>75	All
N	36	182	57	275	442	660	108	1210
Mean (SD)	3175.8 (2640.3)	5204.3 (6569.9)	7689.5 (8796.2)	5453.8 (6854.2)	159.8 (428.6)	819.0 (2721.4)	1751.5 (2472.2)	661.4 (2203.7)
Median	2554.0	2832.0	4473.0	3054.0	45.1	148.7	847.2	104.9
Min - Max	90.4 - 9900.0	36.0 - 33746.0	316.4 - 35000.0	36.0 - 35000.0	36.0 - 5921.0	36.0 - 35000.0	39.4 - 16896.0	36.0 - 35000.0

Elecsys proBNP II STAT – Females

	ADHF				No ADHF			
Age group	< 50	50-75	>75	All	< 50	50-75	>75	All
N	15	74	21	110	252	326	53	631
Mean (SD)	3559.7 (3173.3)	5106.0 (7371.8)	9179.4 (10912.0)	5672.8 (7920.7)	132.8 (399.0)	761.0 (2638.8)	1972.5 (2877.1)	611.8 (2144.3)
Median	2990.0	2762.5	4941.0	2912.5	54.5	124.8	885.7	98.8
Min - Max	202.5 - 9900.0	67.6 - 32615.0	929.1 - 35000.0	67.6 - 35000.0	36.0 - 5921.0	36.0 - 35000.0	60.7 - 16896.0	36.0 - 35000.0

Elecsys proBNP II STAT – Males

	ADHF				No ADHF			
Age group	< 50	50-75	>75	All	< 50	50-75	>75	All
N	21	108	36	165	190	334	55	579
Mean (SD)	2901.6 (2227.4)	5271.6 (5994.1)	6820.3 (7324.4)	5307.9 (6061.3)	195.7 (463.7)	875.6 (2802.5)	1538.6 (2011.4)	715.5 (2267.4)
Median	2470.0	2907.5	4143.0	3123.0	36.0	182.9	840.0	112.8
Min - Max	90.4 - 7544.0	36.0 - 33746.0	316.4 - 34670.0	36.0 - 34670.0	36.0 - 3405.0	36.0 - 35000.0	39.4 - 10326.0	36.0 - 35000.0

Elecsys proBNP II STAT results versus adjudicated diagnosis

Age (years)	Elecsys proBNP II STAT Test Result Interpretation	Adjudicated diagnosis		Total
		ADHF	No ADHF	
<50	Positive	31	27	58
	Gray	0	23	23
	Negative	5	392	397
	Total	36	442	478
50-75	Positive	146	114	260
	Gray	25	117	142
	Negative	11	429	440
	Total	182	660	842
>75	Positive	43	31	74
	Gray	14	52	66
	Negative	0	25	25
	Total	57	108	165
All	Positive	220	172	392
	Gray	39	192	231
	Negative	16	846	862
	Total	275	1210	1485

The pretest probability of ADHF (prevalence of ADHF in the study), posttest probabilities, likelihood ratios and the 95% confidence intervals (CIs) of the Elecsys proBNP II result versus adjudicated diagnosis and the Elecsys proBNP II STAT result versus adjudicated diagnosis were determined across and within sex using the age-dependent positive (450 pg/mL for subjects <50 years of age; 900 pg/mL for subjects 50–75 years of age; 1800 pg/mL for subjects > 75 years of age) and age-independent negative (300 pg/mL) cutoffs. The results using the Elecsys proBNP II STAT assay are summarized below and are similar to the results obtained using the Elecsys proBNP II:

Elecsys proBNP II STAT all subjects

Age Group	Prevalence of ADHF (% (n/N))	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (% (n/N))	95% CI (%)*	Estimate (% (n/N))	95% CI (%)*	LR	95%-CI**
<50	7.5 (36/478)	Positive	**53.4 (31/58)**	40.0-66.5	–	–	14.10	9.56-20.79
		Gray	0.0 (0/23)	0.0-17.8	100.0 (23/23)	82.2-100.0	0.00	0.00-NaN
		Negative	–	–	**98.7 (392/397)**	96.9-99.5	0.16	0.07-0.35
50-75	21.6 (182/842)	Positive	**56.2 (146/260)**	49.9-62.2	–	–	4.64	3.87-5.57
		Gray	17.6 (25/142)	11.9-25.1	82.4 (117/142)	74.9-88.1	0.77	0.52-1.16
		Negative	–	–	**97.5 (429/440)**	95.4-98.7	0.09	0.05-0.17
>75	34.5 (57/165)	Positive	**58.1 (43/74)**	46.1-69.3	–	–	2.63	1.89-3.66
		Gray	21.2 (14/66)	12.5-33.3	78.8 (52/66)	66.7-87.5	0.51	0.31-0.84
		Negative	–	–	**100.0 (25/25)**	83.4-100.0	0.00	0.00-NaN

N/A = not applicable. NaN = not a number due to empty cells.
*Wilson Score confidence intervals with continuity correction
**Log method confidence intervals

Elecsys proBNP II STAT – Females

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	5.6 (15/267)	Positive	**61.9 (13/21)**	38.7-81.0	--	--	27.30	13.42-55.54
		Gray	0.0 (0/15)	0.0-25.3	100.0 (15/15)	74.7-100.0	0.00	0.00-NaN
		Negative	--	--	**99.1 (229/231)**	96.6-99.8	0.15	0.04-0.53
50-75	18.5 (74/400)	Positive	**52.7 (58/110)**	43.0-62.2	--	--	4.91	3.73-6.48
		Gray	19.6 (11/56)	10.7-32.8	80.4 (45/56)	67.2-89.3	1.08	0.59-1.98
		Negative	--	--	**97.9 (229/234)**	94.8-99.2	0.10	0.04-0.22
>75	28.4 (21/74)	Positive	**46.9 (15/32)**	29.5-65.0	--	--	2.23	1.38-3.58
		Gray	18.8 (6/32)	7.9-37.0	(26/32)	63.0-92.1	0.58	0.28-1.21
		Negative	--	--	**100.0 (10/10)**	65.5-100.0	0.00	0.00-NaN

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*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

Elecsys proBNP II STAT – Males

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	10.0 (21/211)	Positive	**48.6 (18/37)**	32.2-65.3	--	--	8.57	5.41-13.59
		Gray	0.0 (0/8)	0.0-40.2	100.0 (8/8)	59.8-100.0	0.00	0.00-NaN

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
		Negative	--	--	**98.2 (163/166)**	94.4-99.5	0.17	0.06-0.48
50-75	24.4 (108/442)	Positive	**58.7 (88/150)**	50.3-66.6	--	--	4.39	3.45-5.59
		Gray	16.3 (14/86)	9.5-26.1	83.7 (72/86)	73.9-90.5	0.60	0.35-1.02
		Negative	--	--	**97.1 (200/206)**	93.5-98.8	0.09	0.04-0.20
>75	39.6 (36/91)	Positive	**66.7 (28/42)**	50.4-80.0	--	--	3.06	1.88-4.96
		Gray	23.5 (8/34)	11.4-41.6	76.5 (26/34)	58.4-88.6	0.47	0.24-0.92
		Negative	--	--	**100.0 (15/15)**	74.7-100.0	0.00	0.00-NaN

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*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

The pretest probability of ADHF (prevalence of ADHF in the study), posttest probabilities, likelihood ratios and the 95% CIs of the Elecsys proBNP II result versus adjudicated diagnosis and Elecsys proBNP II STAT result versus adjudicated diagnosis were determined for the relevant clinical subgroups using the age-dependent positive (450 pg/mL for subjects <50 years of age; 900 pg/mL for subjects 50–75 years of age; 1800 pg/mL for subjects ≥ 75 years of age) and age-independent negative (300 pg/mL) cutoffs. The results using the Elecsys proBNP II STAT assay are summarized below and are similar to the results obtained using the Elecsys proBNP II:

Elecsys proBNP II STAT – Subjects with a history of heart failure

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	45.2 (28/62)	Positive	**67.2 (25/37)**	50.1-81.4	--	--	2.53	1.58-4.06
		Gray	0.0 (0/6)	0.0-48.3	100.0 (6/6)	51.7-100	0.00	0.00-NaN
		Negative	--	--	**84.2 (16/19)**	59.5-95.8	0.23	0.07-0.7
50-75	52.6 (113/215)	Positive	**68.9 (93/135)**	60.3-76.4	--	--	2.00	1.56-2.56
		Gray	40.6 (13/32)	24.2-59.2	59.4 (19/32)	40.8-75.8	0.62	0.32-1.19
		Negative	--	--	**85.4 (41/48)**	71.6-93.5	0.15	0.07-0.33
>75	50.7 (35/69)	Positive	**65.9 (29/44)**	50.0-79.1	--	--	1.88	1.25-2.82
		Gray	27.3 (6/22)	11.6-50.4	72.7 (16/22)	49.6-88.4	0.36	0.16-0.82
		Negative	--	--	**100.0 (3/3)**	31.0-100.0	0.00	0.00-NaN

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*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

Elecsys proBNP II STAT – Subjects with no history of heart failure

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	1.8 (7/396)	Positive	**26.3 (5/19)**	10.1-51.4	--	--	19.85	9.9-39.8
		Gray	0.0 (0/17)	0.0-22.9	100.0 (17/17)	77.1-100	0.00	0.00-NaN
		Negative	--	--	**99.4 (358/360)**	97.8-99.9	0.31	0.10-1.00
50-75	10 (57/569)	Positive	**40 (42/105)**	30.7-50	--	--	5.99	4.53-7.91
		Gray	12 (12/100)	6.6-20.4	88 (88/100)	79.6-93.4	1.22	0.72-2.1
		Negative	--	--	**99.2 (361/364)**	97.4-99.8	0.07	0.02-0.22
>75	20.0 (16/80)	Positive	**45.5 (10/22)**	25.1-67.3	--	--	3.33	1.77-6.29
		Gray	16.7 (6/36)	7.0-33.5	83.3 (30/36)	66.5-93	0.80	0.4-1.59
		Negative	--	--	**100.0 (22/22)**	81.5-100.0	0.00	0.00-NaN

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*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

The sponsor included the following information in the labeling.
"Patients with a history of prior HF have a substantially lower performance for positive cut-points compared to the performance in all evaluable subjects of the ICON-Reloaded cohort, which is likely due to a chronic biological elevation of NT-proBNP in these conditions. Higher false positive rates were observed in all subjects and higher false negative rates were seen in

those subjects who were less than 50 and between 50-75 years of age. Use caution when interpreting test results in these patients due to a higher false positive and false negative rate."

Elecsys proBNP II STAT – Subjects with eGFR <60 mL/min/1.73 m2

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	40.9 (9/22)	Positive	**81.8 (9/11)**	47.8-96.8	--	--	6.50	1.82-23.26
		Gray	0.0 (0/4)	0.0-60.4	100.0 (4/4)	39.6-100.0	0.00	0.00-NaN
		Negative	- -	--	**100.0 (7/7)**	56.1-100.0	0.00	0.00-NaN
50-75	40.5 (85/210)	Positive	**64.2 (77/120)**	54.8-72.6	--	--	2.63	2.05-3.39
		Gray	22.6 (7/31)	10.3-41.5	77.4 (24/31)	58.5-89.7	0.43	0.19-0.95
		Negative	- -	--	**98.3 (58/59)**	89.7-99.9	0.03	0.00-0.18
>75	40.4 (38/94)	Positive	**60.0 (33/55)**	45.9-72.7	--	--	2.21	1.56-3.13
		Gray	16.1 (5/31)	6.1-34.5	83.9 (26/31)	65.5-93.9	0.28	0.12-0.67
		Negative	- -	--	**100.0 (8/8)**	59.8-100.0	0.00	0.00-NaN

NaN due to empty cells

*Wilson Score confidence intervals with continuity correction

**log method confidence interval

Elecsys proBNP II STAT – Subjects with eGFR ≥60 mL/min/1.73 m2

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	6.9 (25/361)	Positive	**48.8 (21/43)**	33.6-64.3	--	--	12.83	8.27-19.89
		Gray	0.0 (0/16)	0.0-24.1	100.0 (16/16)	75.9-100.0	0.00	0.00-NaN
		Negative	--	--	**98.7 (298/302)**	96.4-99.6	0.18	0.07-0.44
50-75	15.5 (92/592)	Positive	**50.0 (65/130)**	41.5-58.5	--	--	5.43	4.18-7.06
		Gray	16.4 (18/110)	10.2-24.9	83.6 (92/110)	75.1-89.8	1.06	0.68-1.67

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
		Negative	--	--	**97.4 (343/352)**	95.0-98.7	0.14	0.08-0.27
>75	26.9 (18/67)	Positive	**50.0 (9/18)**	29.0-71.0	--	--	2.72	1.29-5.76
		Gray	27.3 (9/33)	13.9-45.8	72.7 (24/33)	54.2-86.1	1.02	0.59-1.76
		Negative	--	--	**100.0 (16/16)**	75.9-100.0	0.00	0.00-NaN

NaN due to empty cells

*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

Elecsys proBNP II STAT – Subjects with BMI ≥30 kg/m2

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	11.8 (30/255)	Positive	**62.5 (25/40)**	45.8-76.8	--	--	12.50	7.47-20.91
		Gray	0.0 (0/11)	0.0-32.1	100.0 (11/11)	67.9-100.0	0.00	0.00-NaN
		Negative	--	--	**97.5 (199/204)**	94.1-99.1	0.19	0.08-0.42
50-75	25.6 (104/407)	Positive	**60.2 (77/128)**	51.1-68.6	--	--	4.40	3.34-5.79
		Gray	25.8 (17/66)	16.1-38.2	74.2 (49/66)	61.8-83.9	1.01	0.61-1.67
		Negative	--	--	**95.3 (203/213)**	91.3-97.6	0.14	0.08-0.26
>75	32.3 (20/62)	Positive	**55.0 (11/20)**	32.0-76.2	--	--	2.57	1.27-5.18
		Gray	29.0 (9/31)	14.9-48.2	71.0 (22/31)	51.8-85.1	0.86	0.49-1.51
		Negative	--	--	**100.0 (11/11)**	67.9-100.0	0.00	0.00-NaN

NaN due to empty cells

*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

Elecsys proBNP II STAT – Subjects with BMI <30 kg/m2

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	2.8 (5/177)	Positive	**33.3 (5/15)**	13.0-61.3	--	--	17.20	9.43-31.39
		Gray	0.0 (0/12)	0.0-30.1	100.0 (12/12)	69.9-100.0	0.00	0.00-NaN
		Negative	- -	--	**100.0 (150/150)**	96.9-100.0	0.00	0.00-NaN
50-75	18.9 (70/370)	Positive	**51.6 (63/122)**	42.5-60.7	--	--	4.58	3.59-5.83
		Gray	11.1 (7/63)	5.0-22.2	88.9 (56/63)	77.8-95.0	0.54	0.26-1.12
		Negative	- -	--	**100.0 (185/185)**	97.5-100.0	0.00	0.00-NaN
>75	36.6 (37/101)	Positive	**59.3 (32/54)**	45.1-72.1	--	--	2.52	1.75-3.61
		Gray	15.2 (5/33)	5.7-32.7	84.8 (28/33)	67.3-94.3	0.31	0.13-0.73
		Negative	- -	--	**100.0 (14/14)**	73.2-100.0	0.00	0.00-NaN

NaN due to empty cells

*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

The sponsor included the following information in the labeling:
"In this study, 15 of the 16 subjects with false negative results had an elevated BMI. In turn, however, patients with low BMI that were tested negative are characterized by a high NPV of 100 % (95 % CI 98.7-100.0)".

Elecsys proBNP II STAT – Subjects with Comorbidities (i.e., subjects with at least one of the following: diabetes, renal insufficiency (eGFR values < 60), hypertension and/or chronic obstructive pulmonary disease (COPD)).

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	14 (31/221)	Positive	**57.8 (26/45)**	42.2-72	--	--	8.39	5.33-13.2
		Gray	0.0 (0/18)	0.0-21.9	100.0 (18/18)	78.1-100.0	0.00	0.00-NaN
		Negative	- -	--	**96.8 (153/158)**	92.4-98.8	0.20	0.00-NaN
50-75	23.8 (161/677)	Positive	**57 (127/223)**	50.2-63.5	--	--	4.24	3.48-5.17
		Gray	20.5 (24/117)	13.8-29.2	79.5 (93/117)	70.8-86.2	0.83	0.55-1.25
		Negative	- -	--	**9 7 (327/337)**	94.4-98.5	0.10	0.05-0.18
>75	35.8 (53/148)	Positive	**63.5 (40/63)**	50.4-75	--	--	3.12	2.12-4.59
		Gray	21.3 (13/61)	12.3-34	78.7 (48/61)	66-87.7	0.49	0.29-0.81
		Negative	- -	--	**100.0 (24/24)**	82.8-100	0.00	0.00-NaN

NaN due to empty cells

*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

proBNP II STAT – Subjects without Comorbidities

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
<50	1.7 (4/232)	Positive	**36.4 (4/11)**	12.4-68.4	--	--	32.57	15.7-67.5
		Gray	0.0 (0/5)	0.0-53.7	100.0 (5/5)	46.3-100	0.00	0.00-NaN
		Negative	- -	--	**100 (216/216)**	97.8-100	0.00	0.00-NaN

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Posttest Probability of ADHF		Posttest Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%)*	Estimate (%) (n/N)	95%-CI (%)*	LR	95%-CI**
50-75	12 (15/125)	Positive	**52 (13/25)**	31.8-71.7	--	--	7.94	4.49-14.04
		Gray	5.6 (1/18)	0.3-29.4	94.4 (17/18)	70.6-99.7	0.43	0.06-3.01
		Negative	--	--	**98.8 (81/82)**	92.5-99.9	0.09	0.01-0.60
>75	0.0 (0/7)	Positive	**0.0 (0/6)**	0.0-48.3	--	--	NaN	NaN-NaN
		Gray	NaN (0/0)	NA-NA	NaN (0/0)	NA-NA	NaN	NaN-NaN
		Negative	--	--	**100.0 (1/1)**	5.5-100	NaN	NaN-NaN

NaN due to empty cells

*Wilson Score confidence intervals with continuity correction

**log method confidence intervals

New York Heart Association (NYHA) Functional Classification

586 subjects had a NYHA functional classification. NT-proBNP values in this group are presented below for the Elecsys proBNP II STAT assay. The results based on the Elecsys proBNP II were similar.

All Subjects:

proBNP II STAT	All HF	NYHA II	NYHA III	NYHA IV
Mean	1400	1067	1485	1631
SD	3712	3087	3044	4973
Median	155	111	270	161
5th Percentile	36	36	36	36
95th Percentile	7781	4952	8585	7774
% above cut-point	26.3	20.8	31.7	24.4
Minimum	36	36	36	36
Maximum	35000	27776	21402	35000
N	586	178	240	168

Female Subjects:

proBNP II STAT	All HF	NYHA II	NYHA III	NYHA IV
Mean	1090	522	1175	1558
SD	3317	1247	2486	5077
Median	115	105	121	132
5th Percentile	36	36	36	36
95th Percentile	5160	2426	6310	7750
% above cut-point	20.3	13.7	27	18.9
Minimum	36	36	36	36
Maximum	35000	9832	14061	35000
N	301	95	111	95

Male Subjects:

proBNP II STAT	All HF	NYHA II	NYHA III	NYHA IV
Mean	1727	1692	1752	1725
SD	4068	4248	3441	4867
Median	279	115	403	228
5th Percentile	36	36	36	36
95th Percentile	8852	9793	8768	7030
% above cut-point	32.6	28.9	35.7	31.5
Minimum	36	36	36	36
Maximum	34670	27776	21402	34670
N	285	83	129	73

The sponsor also provided information to support the use of the frozen samples in this study.

D Clinical Cut-Off:

In this submission, the sponsor added the following cut-offs for use as an aid in the diagnosis of ADHF in patients presenting to emergency departments:

Age Group	Elecsys proBNP II / Elecsys proBNP II STAT Cut-Points	Interpretation
All ages	300 pg/mL	NT-proBNP < 300 pg/mL indicates ADHF not likely
< 50 years	450 pg/mL	NT-proBNP > 450 pg/mL indicates ADHF is likely
50 to 75 years	900 pg/mL	NT-proBNP > 900 pg/mL indicates ADHF is likely
> 75 years	1800 pg/mL	NT-proBNP > 1800 pg/mL indicates ADHF is likely
All ages	Results within the gray zone for the patient's age group	Indeterminate. Further clinical information is needed to determine if ADHF is present

E Expected Values/Reference Range:

Reference ranges for individuals without heart failure were previously established in K022516.

Also see Section VII.C.3., which describes NT-proBNP levels in subjects without ADHF presenting to the ED.

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.