July 21, 2023

Roche Diagnostics
Jane Phillips
Sr. Regulatory Program Manager
9115 Hague Road
Indianapolis, IN 46250

Re: K223637
Trade/Device Name: Elecsys proBNP II, Elecsys proBNP II STAT
Regulation Number: 21 CFR 862.1117
Regulation Name: B-type natriuretic peptide test system
Regulatory Class: Class II
Product Code: NBC
Dated: June 20, 2023
Received: June 21, 2023

Dear Jane Phillips:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR

803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

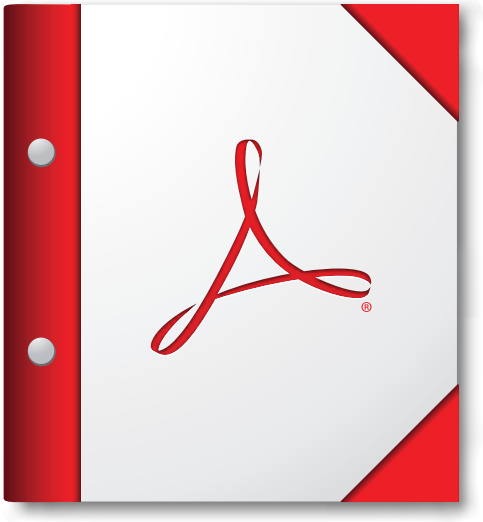
For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Paula V. Caposino -S

Paula Caposino, Ph.D.
Acting Deputy Director
Division of Chemistry
and Toxicology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure



For the best experience, open this PDF portfolio in Acrobat X or Adobe Reader X, or later.

Get Adobe Reader Now!

k223637 Elecsys proBNP II and proBNP II STAT

510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

In accordance with 21 CFR 807.87, Roche Diagnostics hereby submits official notification as required by Section 510(k) of the Federal Food, Drug and Cosmetics Act of our intention to market the device described in this Premarket Notification 510(k).

The purpose of this Traditional 510(k) Premarket Notification is to obtain FDA review and clearance for the new cut-offs for patients presenting with dyspnea to the emergency department for the Elecsys proBNP II STAT and the Elecsys proBNP.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0457
Contact	Jane Phillips, PhD Phone: (317) 521 3338 Email: jane.phillips@roche.com
Date Prepared	November 30th, 2022
Proprietary Name	Elecsys proBNP II and Elecsys proBNP II STAT
Common Name	proBNP II and proBNP II STAT
Classification Name	B-type natriuretic peptide test system
Product Codes, Regulation Numbers	NBC, 862.1117
Predicate Devices	Elecsys proBNP II and Elecsys proBNP II STAT (k210546)

Table 1: Similarities and Differences between the Elecsys proBNP II

Item	Elecsys proBNP II k210546	Elecsys proBNP II Candidate Device	Change description
Proprietary name	Elecsys proBNP II	Elecsys proBNP II	None
Technology	ECLIA	ECLIA	None
Test format	Sandwich	Sandwich	None
Test type	Quantitative	Quantitative	None
Assay protocol	R1 + R2 + sample, incubation, + beads, incubation	R1 + R2 + sample, incubation, + beads, incubation	None
Measuring Range	36-35000 pg/mL	36-35000 pg/mL	None

Table 2: Similarities and Differences between the Elecsys proBNP STAT

Item	Elecsys proBNP II STAT k210546	Elecsys proBNP II STAT Candidate Device	Change description
Proprietary name	Elecsys proBNP II STAT	Elecsys proBNP II STAT	None
Technology	ECLIA	ECLIA	None
Test format	Sandwich	Sandwich	None
Test type	Quantitative	Quantitative	None
Assay protocol	R1 + R2 + sample + beads, incubation	R1 + R2 + sample + beads, incubation	None
Measuring Range	36-35000 pg/ml	36-35000 pg/ml	None

1. DEVICE DESCRIPTION

Elecsys proBNP II and proBNP II STAT are second-generation assays by Roche Diagnostics for the in vitro quantitative determination of N-terminal pro-Brain natriuretic peptide (NT-proBNP) in human serum and plasma. The STAT and the 18 Minute assays are intended for use on the cobas e 601

The cobas e family of analyzers employs the electrochemiluminescence immunoassay "ECLIA" technology. The assays are sandwich principle methods using two monoclonal antibodies which are specifically directed against NT-proBNP. For the neutralization of free biotin in serum and plasma, Roche developed an antibody, which binds to free biotin. The antibodies are specific for free biotin and do not bind to or interact with the biotin-linker conjugates.

2. INDICATIONS FOR 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. 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 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.

3. PREDICATE DEVICE

The predicate for this submission are the Elecsys proBNP II and the Elecsys proBNP II STAT Immunoassays which we cleared in k210546. No changes have been made to the assay since clearance.

4. ANALYTICAL PERFORMANCE EVALUATION

Analytical experiments were run on the cobas e 601 using the Elecsys proBNP II.

PRECISION (CLSI EP05-A3)

Precision was evaluated on a single cobas e 601 for Elecsys proBNP II. The experiment was conducted according to CLSI guideline EP05-A3.

The protocol consisted of testing the 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). Testing was conducted at one internal site.

Results

Elecsys proBNP II

Lot MP01: Elecsys proBNP II

cobas e 601 analyzer									
		Repeatability				Intermediate precision			
Sample (Serum)	Mean pg/mL	SD pg/mL	SD 95% UCL pg/mL	CV %	CV 95% UCL %	SD pg/mL	SD 95% UCL pg/mL	CV %	CV 95% UCL %
Human serum 1	68.3	1.96	2.39	2.9	3.5	3.26	4.05	4.8	5.9
Human serum 2	145	3.24	3.96	2.2	2.7	5.95	7.42	4.1	5.1
Human serum 3	314	4.31	5.27	1.4	1.7	11.5	14.7	3.7	4.7
Human serum 4	467	12.8	15.7	2.7	3.4	17.6	21.2	3.8	4.5
Human serum 5	1004	20.0	24.4	2.0	2.4	34.6	42.0	3.5	4.2
Human serum 6	2075	38.9	47.6	1.9	2.3	68.6	84.8	3.3	4.1
Human serum 7	15985	371	454	2.3	2.8	579	712	3.6	4.5
Human serum 8	34624	609	744	1.8	2.1	1367	1725	3.9	5.0
PreciControl Cardiac II 1	140	2.48	3.03	1.8	2.2	4.94	6.13	3.5	4.4
PreciControl Cardiac II 2	4721	70.2	85.8	1.5	1.8	156	198	3.3	4.2

Conclusion

The results of precision studies performed with the Elecsys proBNP II assay met predetermined acceptance criteria.

ANALYTICAL SENSITIVITY

Limit of Blank (LoB) and Limit of Detection (LoD) (CLSI EP17-A2)

LoB of the Elecsys proBNP II on the **cobas e** 601 was determined according to CLSI EP17-A2. Limit of Blank determines the highest observed measurement values for samples free of analyte. The Limit of Blank was determined as the 95th percentile of measurements of blank samples.

LoD of the Elecsys proBNP II on the **cobas e** 601 analyzer was determined according to CLSI EP17-A2. The LoD determines the lower limit for samples with analyte. The LoD was determined as the lowest amount of analyte in a sample that can be detected with a 95% probability.

Methods LoB

In total 60 determinations of an analyte-free sample were obtained on one instrument over ≥ three days in 6 runs with 10-fold determination per run. Three lots of reagent were used in the experiment design.

As the analyzer does not report negative sample concentrations, the data set was truncated and the data were evaluated as the linear interpolation of the 57th and 58th ranked observation.

Methods LoD

Five low level human serum samples were measured on one instrument over ≥ three days in 6 runs with a two-fold determination per run. In total sixty determinations per sample per reagent lot. The experiment was conducted using three reagent lots.

A pooled estimate of the precision (SD total) for the 5 low level samples was calculated.

LoD was calculated according to EP17-A2, chapter 5.3.3.2 as:

LoD = LoB + 1.653 x SD total (of low analyte samples)

Results

Elecsys proBNP II

Lot MP01 Elecsys proBNP II (concentrations in pg/mL)

	Date Run	31-Jul-2019 1	31-Jul-2019 2	31-Jul-2019 3	01-Aug-2019 4	22-Aug-2019 5	23-Aug-2019 6	Instrument 1
Analyte-free	Value_1	0.0000	0.0000	0.0000	0.0000	0.0000	0.966	
	Value_2	0.0000	0.0000	0.0000	0.145	0.0000	0.0000	
	Value_3	0.0000	0.0000	0.783	0.0000	0.0000	0.844	
	Value_4	0.0000	0.0000	0.0000	0.343	0.407	1.44	
	Value_5	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	
	Value_6	0.0000	0.0000	0.0000	0.145	0.721	1.21	
	Value_7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	
	Value_8	0.0000	0.0000	0.0000	0.0000	0.0000	1.56	
	Value_9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	
	Value_10	0.0000	0.0000	0.471	0.0000	0.0000	0.0000	
	Date Run	31-Jul-2019 1	31-Jul-2019 2	31-Jul-2019 3	01-Aug-2019 4	22-Aug-2019 5	23-Aug-2019 6	
Analyte-low	Value_1	5.11	6.25	7.86	6.95	7.80	7.49	
	Value_2	7.70	4.41	4.52	5.27	5.64	5.64	
	Value_3	6.68	3.59	6.74	6.57	7.16	5.05	
	Value_4	4.46	6.41	5.16	5.22	6.01	6.36	
	Value_5	3.26	2.60	6.79	6.68	6.41	4.03	
	Value_6	6.03	4.45	3.70	4.62	4.41	6.47	
	Value_7	7.91	5.48	5.69	5.43	5.96	6.75	
	Value_8	5.54	7.11	9.18	8.71	7.91	8.81	
	Value_9	5.69	4.79	7.91	7.91	7.65	5.59	
	Value_10	7.65	6.79	5.48	5.75	6.01	7.65	

calculation factor ($c_ß$)	1.653
SD value 1/2	1.30
SD value 3/4	1.08
SD value 5/6	1.46
SD value 7/8	1.43
SD value 9/10	1.14
SD_{total}	1.29
$SD_{total} \times c_β$	2.13
LoD	3.22

Result:	LoB	1.48	LoD	2.57	pg/mL

Conclusion

The LoD claim in the labeling will be set to ≤ 10 pg/mL. LoB will be set to ≤ 8 pg/mL.

Limit of Quantitation (LoQ) (CLSI EP17-A2)

LoQ determines the lowest amount of analyte that can be quantitatively determined with stated accuracy and stated experimental conditions. The LoQ was determined as the lowest concentration of analyte which can be reproducibly measured with an intermediate precision of 20% CV.

Methods LoQ

A low level sample set of 10 native, unaltered serum samples using the **cobas e** 601 analyzer of known measurand concentration was tested in 5 replicates (aliquots) on one instrument in singleton per day, over 5 days with 1 run per day. Three lots of reagent were used in the LoQ experiment. A total of n=25 measured values were obtained for each sample. The mean value and the intermediate precision as coefficient of variation (CV) and standard deviation (SD) were calculated for each LoQ sample.

Results

Elecsys proBNP II

Lot MP01: Elecsys proBNP II

Day 1										
Date Run	11-Feb-2019									
Sample Type	Sample _1	Sample _2	Sample _3	Sample _4	Sample _5	Sample _6	Sample _7	Sample _8	Sample _9	Sample _10
Replicate	NT-proBNP concentrations in pg/mL									
1	12.1	11.6	17.3	16.4	30.1	46.2	53.0	74.1	63.9	77.4
2	11.9	8.70	19.8	17.1	29.8	47.4	56.1	68.6	60.7	80.9
3	8.26	11.8	16.2	17.2	33.6	48.7	55.5	59.0	71.8	98.9
4	10.4	10.5	23.5	16.3	29.7	47.6	58.4	66.9	73.8	97.3
5	9.25	13.7	18.4	22.7	33.3	46.7	57.3	60.4	72.4	99.2

Day 2										
Date Run	12-Feb-2019									
Sample Type	Sample _1	Sample _2	Sample _3	Sample _4	Sample _5	Sample _6	Sample _7	Sample _8	Sample _9	Sam ple - _10
Replicate	NT-proBNP concentrations in pg/mL									
1	13.1	14.1	18.3	22.0	33.1	45.5	59.6	65.9	80.8	103
2	9.64	10.5	19.2	18.6	30.2	45.8	58.5	63.9	82.8	103
3	10.1	10.3	21.4	24.1	33.9	46.8	60.6	64.9	82.6	105
4	13.9	10.6	22.2	22.8	29.9	49.7	55.2	63.1	78.6	107
5	10.5	10.1	20.1	13.7	22.6	30.1	49.6	57.8	64.6	78.9

Day 3										
Date Run	13-Feb-2019									
Sample Type	Sample _1	Sample _2	Sample _3	Sample _4	Sample _5	Sample _6	Sample _7	Sample _8	Sample _9	Sam ple _10
replicate	NT-proBNP concentrations in pg/mL									
1	12.1	12.0	18.1	21.3	31.5	42.6	54.9	58.3	76.0	99.8
2	11.4	8.64	18.8	21.7	31.7	42.8	54.2	60.1	77.4	99.6
3	8.37	12.5	17.7	21.7	27.9	46.5	52.9	65.4	76.1	98.4
4	12.3	12.5	21.1	22.0	33.2	45.9	53.1	60.3	79.5	102
5	8.98	12.5	16.8	18.2	33.4	46.3	57.0	62.9	79.4	101

Day 4										
Date Run	14-Feb-2019									
Sample Type	Sample _1	Sample _2	Sample _3	Sample _4	Sample _5	Sample _6	Sample _7	Sample _8	Sample _9	Sam ple _10
Replicate	NT-proBNP concentrations in pg/mL									
1	9.31	10.0	20.7	21.7	29.0	48.8	57.8	64.6	77.2	103
2	12.9	13.4	21.4	18.2	33.4	50.1	56.2	65.7	82.3	108
3	9.42	10.6	18.2	22.0	29.4	50.6	56.5	66.9	83.4	105
4	13.1	14.1	18.8	19.8	32.4	46.2	57.1	64.8	80.1	108
5	10.0	13.2	19.1	23.1	33.3	47.5	60.2	63.3	81.9	104

Day 5										
Date Run	18-Feb-2019									
Sample Type	Sample _1	Sample _2	Sample _3	Sample _4	Sample _5	Sample _6	Sample _7	Sample _8	Sample _9	Sample _10
Replicate	NT-proBNP concentrations in pg/mL									
1	12.4	9.14	21.7	18.7	31.4	48.1	53.8	62.8	78.8	102
2	10.0	9.69	21.1	21.0	33.1	45.1	54.6	60.5	75.4	104
3	8.87	12.6	17.6	21.2	29.0	48.6	54.9	65.2	81.7	98.1
4	9.53	12.9	21.4	21.5	29.4	49.6	58.0	65.9	80.6	107
5	12.8	13.6	21.8	18.6	28.0	51.3	56.2	65.1	78.1	104

Sample Type	Sample _1	Sample _2	Sample _3	Sample _4	Sample _5	Sample _6	Sample _7	Sample _8	Sample _9	Sample _10
Measured conc Mean of 5 days	10.8	11.6	19.6	20.1	30.9	46.6	56.0	63.9	76.8	99.9
SD of 5 days	1.70	1.70	1.91	2.60	2.59	4.05	2.55	3.59	6.09	8.43
Conc. CV% of 5 days	15.7	14.7	9.7	13.0	8.4	8.7	4.6	5.6	7.9	8.4

Conclusion

The LoQ claim in the labeling will be set to 36 pg/mL.

Linearity/Reportable Range (CLSI EP06-Ed2)

The linearity study was conducted on the proBNP II assays to demonstrate that measurements across the claimed measuring range for each parameter are linear. The study was performed according to CLSI guideline EP06-Ed2.

Methods

The experiment was initially designed for evaluation with the preceding edition of the guideline, i.e. CLSI guideline EP06-A. The evaluation was repeated according to the current guideline CLSI EP06-Ed2 using in-house software tool BioWarp.

A weighted least square regression by pooled variance was performed. As one high analyte human, native serum sample above measuring range was diluted with analyte free serum (CLSI Design A1), a regression without intercept was chosen. As variance increases with concentration, weighted linear regression was used. As only 3 replicates are available at each dilution step, the weights were computed based on the pooled variance including also the replicates of the next higher as well as the next lower dilution step ("moving window").

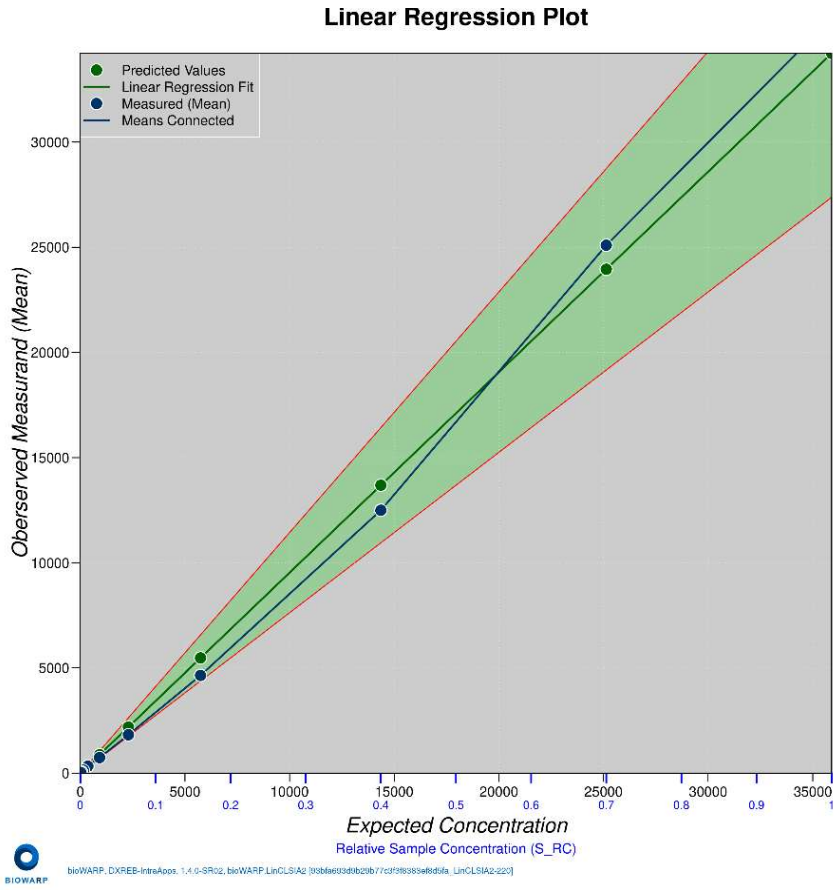
Results

Linearity Evaluation Summary

Category	Name	Value
Input Data	Unit	pg/mL
	Max Number of Replicates	3
	Number of Levels	10
	Range of Levels	0.000640 - 1.00
	Measured Range	24.3 - 35902
Model	CLSI Design	A1
	Weighting	yes
Precision Specs	Prec. Acc. Limits	Passed
SubRange 1 (21.9 - 50.0)	10.0 SD	1
SubRange 2 (50.0 - 100)	20.0 CV	1
SubRange 3 (100 - 35000)	10.0 CV	8
ADL Specs	Allowed Deviation	Passed
SubRange 1 (21.9 - 50.0)	10.0 [pg/mL] abs	1
SubRange 2 (50.0 - 35000)	20.0 [%] rel	9
Linearity evaluation	between: 24.3 - 35902 [pg/mL]	PASSED

Results of the linear regression analysis

Level	Relative Concentration	Mean	Expected	Predicted	SubRange	Diff. abs	Diff. rel	Criteria	Specs met
1	1.00	35902	35902	34218	2	1684	4.92	<=20%	yes
2	0.700	25096	25131	23953	2	1144	4.78	<=20%	yes
3	0.400	12497	14361	13687	2	-1191	-8.70	<=20%	yes
4	0.160	4646	5744	5475	2	-829	-15.1	<=20%	yes
5	0.0640	1821	2298	2190	2	-369	-16.8	<=20%	yes
6	0.0256	737	919	876	2	-139	-15.9	<=20%	yes
7	0.0100	324	359	342	2	-18.2	-5.33	<=20%	yes
8	0.00400	136	144	137	2	-1.06	-0.778	<=20%	yes
9	0.00160	56.5	57.4	54.7	2	1.71	3.12	<=20%	yes
10	0.000640	24.3	23.0	21.9	1	2.41	11.0	<=10	yes



Conclusion

The recommended measuring range is 36 to 35000 pg/mL. Linearity specifications were met.

Endogenous Interferences (CLSI EP07-A3)

The purpose of this study was to evaluate endogenous substances for potential interference with the parameters measured on the cobas e 601 for Elecsys proBNP II.

Methods

The effect on quantitation of analyte in the presence of endogenous interfering substances using the Elecsys proBNP II was determined on the **cobas e** 601.

Endogenous interferences were determined by testing three different analyte concentration levels (low about 130 pg/mL, medium about 900 pg/mL, high about 20000 pg/mL) in human native serum samples. The high concentrations were spiked with recombinant human NT-proBNP (1-76) for the bilirubin and lipemia testing.

One aliquot of each serum sample was spiked with the interfering substance (= interference pool) and another aliquot was spiked (if applicable) with the same volume of the solvent of the interfering substance (= dilution pool). The interfering pool was then diluted into the dilution pool in 10 % increments. The recovery for each sample was calculated by comparison to the reference (unspiked sample).

Results

Interfering substance	**No interference up to**
Bilirubin	≤ 428 µmol/L or ≤25 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤1000 mg/dL
Lipemia	≤ 1500 mg/dL
Biotin	≤ 3500 ng/mL
Rheumatoid Factor	≤ 1500 IU/mL

5. CLINICAL PERFORMANCE EVALUATION

Clinical data are required in this submission to support the use of the proposed cutoffs for aiding in the diagnosis of heart failure in acutely dyspneic patients. These patients may include a subset of those with acutely decompensated heart failure (ADHF).

Expected values: Acute care setting

To assess the performance of positive and negative cut-points for ADHF in patients presenting with signs and symptoms of ADHF to the ED, a multi-center trial was performed in the United States. 1485 subjects were enrolled at 17 sites, 744 males and 741 females. Subjects were ≥ 22 years of age with symptoms of suspected acute decompensated HF, presenting with dyspnea of a duration no longer than several days. 275 (19 %) were found to have acutely decompensated HF, based on adjudication by a clinical events committee.

As reported in previous studies, the age-based positive cut-points, and the negative cut-point for all ages were determined to be:

Age Group	Elecsys proBNP II/ Elecsys proBNP II STAT Cut-Points	Interpretation
<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

Elecsys proBNP II/ Elecsys proBNP II STAT Cut-Point	Interpretation
300 pg/mL	NT-proBNP < 300 pg/mL indicates ADHF is not likely

NT-proBNP values above the respective age-specific cut-points (450 / 900 / 1800 pg/mL) are denoted as positive test results, and NT-proBNP values below the universal age-independent cut-point (300 pg/mL) are denoted as negative test result. A gray zone exists between the negative and positive cut-points.

Age Range [years]	Result Interpretation	NT-proBNP concentration [pg/mL]
<50	Positive	> 450
	Gray	300-450
	Negative	<300
50-75	Positive	>900
	Gray	300-900
	Negative	<300
>75	Positive	>1800
	Gray	300-1800
	Negative	<300
All Age Groups	Positive	aggregated
	Gray	aggregated
	Negative	<300

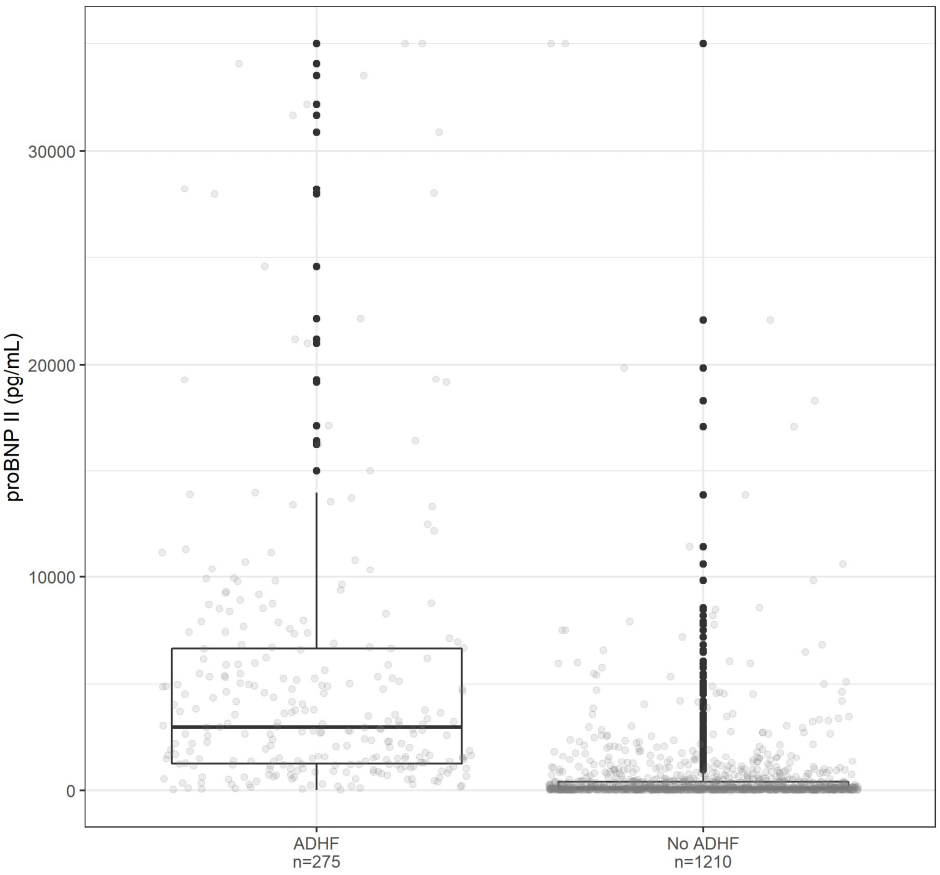
In this study, the following NT-proBNP values were found with Elecsys proBNP II (18min):

Diagnostic category	Median proBNP II	IQR[a]
Subjects without ADHF[b]	105 pg/mL	38.64 - 400.38 pg/mL
Subjects with ADHF	3012 pg/mL	1258.50 - 6673.50 pg/mL

a) IQR = interquartile range

b) ADHF = acute decompensated HF

Boxplot of proBNP values per ADHF group, all subjects – 18min assay.



Censoring into measuring range:
- ADHF: lower limit: 1 subjects; upper limit: 2 subjects.
- No ADHF: lower limit: 283 subjects; upper limit: 2 subjects.

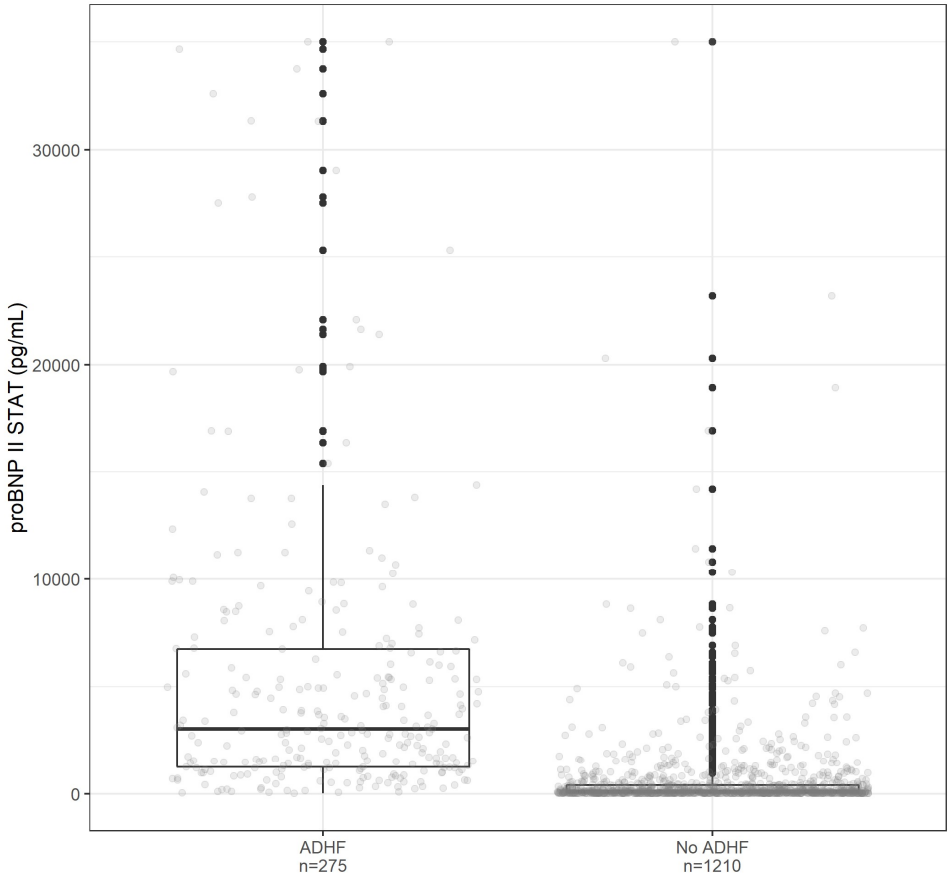
In this study, the following NT-proBNP values were found with Elecsys proBNP II STAT:

Diagnostic category	Median proBNP II STAT	IQR[a]
Subjects without ADHF[b]	105 pg/mL	37.86 - 402.80 pg/mL
Subjects with ADHF	3054 pg/mL	1255.50 - 6759.00 pg/mL

a) IQR = interquartile range

b) ADHF = acute decompensated HF

Boxplot of proBNP values per ADHF group, all subjects – STAT assay.



Censoring into measuring range:
- ADHF: lower limit: 1 subjects; upper limit: 2 subjects.
- No ADHF: lower limit: 291 subjects; upper limit: 2 subjects.

An analysis of the primary endpoint included the gray zone, which is the zone between the positive and negative thresholds for each subject age group. This gray zone included NT-proBNP levels ≥ 300 pg/mL but less than or equal to the cut-point for the rule-in for diagnosis (that is, 450 pg/mL for age < 50 years, 900 pg/mL for age 50-75 years and 1800 pg/mL for age > 75 years).

A total of only 228 subjects (15%) had NT-proBNP levels that fell into the gray zone between cut-points with Elecsys proBNP II. This analysis was performed to better understand the performance of the assay for values that fall between the cut-off for positive and the cut-off for negative.

The likelihood ratio (LR) for all 228 subjects (any age) who fell into the gray zone was 0.91 (95% CI: 0.66-1.25) suggesting no additive diagnostic value. For them, other clinical or diagnostic information would be necessary for the differential diagnosis of acute decompensated HF in patients presenting with acute dyspnea in the emergency department.

The performance of the NT-proBNP-based diagnosis of ADHF through the triple age-specific positive cut-points and the single universal negative cut-point was demonstrated through the calculation of Likelihood ratios (positive likelihood ratios (LR+) and negative likelihood ratios (LR-). Likelihood ratios can provide a quantification of the diagnostic capabilities of the assay for both subjects with reactive Elecsys NT-proBNP results (LR+) and non-reactive Elecsys NT-proBNP results (LR-). The likelihood ratio can be used to project the change in the probability of having ADHF from the general disease prevalence (the pre-test probability) to the probability after the test results are interpreted (the post-test probability). Establishing the likelihood ratios for the Elecsys proBNP II and proBNP II STAT assays performed on the cobas e 601 analyzer demonstrated the strength of the assays as an aid in diagnosing ADHF and the ability to understand the implications of the diagnosis in patients presenting emergently with dyspnea.
Analyses were conducted separately for each gender and age sub-population, as well for all age-groups combined and all genders combined.

Acutely decompensated cutoff performance

Three-by-Two Contingency Table for the ICON Cut-Points - Elecsys proBNP II 18min Assay - All Evaluable US Subjects

Age Group	Test Result Interpretation	ADHF	No ADHF	Total
<50	Positive	31	28	59
	Gray	0	20	20
	Negative	5	394	399
	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	173	393
	Gray	39	189	228
	Negative	16	848	864
	Total	275	1210	1485

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of Acute Decompensated Heart Failure - Elecsys proBNP II 18min Assay - All Evaluable US Subjects

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) c)	Estimate (%) (n/N)	95%-CI (%) c)	LR d)	95%-CI e)
< 50	7.5 (36/478)	Positive f)	**52.5 (31/59)**	39.2-65.5	--	--	13.6	9.28-19.9
		Gray g)	0.0 (0/20)	0.0-20.0	100 (20/20)	80.0-100	0.00	0.00-NaN h)
		Negative i)	--	--	**98.7 (394/399)**	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	0.00	0.00-NaN

c) Wilson score confidence intervals with continuity correction

d) LR = likelihood ratios

e) log method confidence intervals

f) Positive: > age-specific cut-point

g) Gray: ≥ 300 pg/mL and ≤ age-specific cut-point

h) NaN (Not a Number) due to empty cells

i) Negative: < 300 pg/mL

Three-by-Two Contingency Table for the ICON Cut-Points - Elecsys proBNP II 18min Assay- Females

Age Group	Test Result Interpretation	ADHF	No ADHF	Total
< 50	Positive	13	8	21
	Gray	0	15	15
	Negative	2	229	231
	Total	15	252	267
50 - 75	Positive	58	52	110
	Gray	11	46	57
	Negative	5	228	233
	Total	74	326	400
> 75	Positive	15	17	32
	Gray	6	26	32
	Negative	0	10	10
	Total	21	53	74
All	Positive	86	77	163
	Gray	17	87	104
	Negative	7	467	474
	Total	110	631	741

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II 18min Assay - Females

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) c)	Estimate (%) (n/N)	95%-CI (%) c)	LR d)	95%-CI e)
< 50	5.6 (15/267)	Positive f)	**61.9 (13/21)**	38.7-81.0	--	--	27.3	13.4-55.5
		Gray g)	0.0 (0/15)	0.0-25.3	100 (15/15)	74.7-100	0.00	0.00-NaN h)
		Negative i)	--	--	**99.1 (229/331)**	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	19.3 (11/57)	10.5-32.3	80.7 (46/57)	67.7-89.5	1.05	0.57-1.93
		Negative	--	--	**97.9 (228/233)**	94.8-99.2	0.10	0.04-0.23
> 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	81.3 (26/32)	63.0-92.1	0.58	0.28-1.21
		Negative	--	--	**100 (10/10)**	65.5-100	0.00	0.00-NaN

Three-by-Two Contingency Table for the ICON Cut-Points - Elecsys proBNP II 18min Assay - Males

Age Group	Test Result Interpretation	ADHF	No ADHF	Total
< 50	Positive	18	20	38
	Gray	0	5	5
	Negative	3	165	168
	Total	21	190	211
50 - 75	Positive	88	62	150
	Gray	14	71	85
	Negative	6	201	207
	Total	108	334	442
> 75	Positive	28	14	42
	Gray	8	26	34
	Negative	0	15	15
	Total	36	55	91
All	Positive	134	96	230
	Gray	22	102	124
	Negative	9	381	390
	Total	165	579	744

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II 18min Assay- Males

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) c)	Estimate (%) (n/N)	95%-CI (%) c)	LR d)	95%-CI e)
< 50	10.0 (21/211)	Positive f)	**47.4 (18/38)**	31.3-64.0	--	--	8.14	5.19-12.8
		Gray g)	0.0 (0/5)	0.0-53.7	100 (5/5)	46.3-100	0.00	0.00-NaN h)
		Negative i)	--	--	**98.2 (165/168)**	94.5-99.5	0.16	0.06-0.47
50-75	24.4 (108/442)	Positive	**58.7 (88/150)**	50.3-66.6	--	--	4.39	3.45-5.59
		Gray	16.5 (14/85)	9.6-26.4	83.5 (71/85)	73.6-90.4	0.61	0.36-1.04
		Negative	--	--	**97.1 (201/207)**	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 (15/15)**	74.7-100	0.00	0.00-NaN

Three-by-Two Contingency Table for the ICON Cut-Points - Elecsys proBNP II STAT Assay - All Evaluable US Subjects

Age Group	Test Result Interpretation	ADHF	No ADHF	Total
< 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

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II STAT Assay - All Evaluable US Subjects

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) c)	Estimate (%) (n/N)	95%-CI (%) c)	LR d)	95%-CI e)
< 50	7.5 (36/478)	Positive f)	**53.4 (31/58)**	40.0-66.5	--	--	14.10	9.56-20.79
		Gray g)	0.0 (0/23)	0.0-17.8	100.0 (23/23)	82.2-100.0	0.00	0.00-NaN h)
		Negative i)	--	--	**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

c) Wilson score confidence intervals with continuity correction

d) LR = likelihood ratios

e) log method confidence intervals

f) Positive: > age-specific cut-point

g) Gray: ≥ 300 pg/mL and ≤ age-specific cut-point

h) NaN (Not a Number) due to empty cells

i) Negative: < 300 pg/mL

Three-by-Two Contingency Table for the ICON Cut-Points - Elecsys proBNP II STAT Assay - Females

Age Group	Test Result Interpretation	ADHF	No ADHF	Total
< 50	Positive	13	8	21
	Gray	0	15	15
	Negative	2	229	231
	Total	15	252	267
50 - 75	Positive	58	52	110
	Gray	11	45	56
	Negative	5	229	234
	Total	74	326	400
> 75	Positive	15	17	32
	Gray	6	26	32
	Negative	0	10	10
	Total	21	53	74
All	Positive	86	77	163
	Gray	17	86	103
	Negative	7	468	475
	Total	110	631	741

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II STAT Assay - Females

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) c)	Estimate (%) (n/N)	95%-CI (%) c)	LR d)	95%-CI e)
< 50	5.6 (15/267)	Positive f)	**61.9 (13/21)**	38.7-81.0	--	--	27.30	13.42-55.54
		Gray g)	0.0 (0/15)	0.0-25.3	100.0 (15/15)	74.7-100.0	0.00	0.00-NaN h)
		Negative i)	--	--	**99.1 (229/331)**	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	81.3 (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

Three-by-Two Contingency Table for the ICON Cut-Points - Elecsys proBNP II STAT Assay - Males

Age Group	Test Result Interpretation	ADHF	No ADHF	Total
< 50	Positive	18	19	37
	Gray	0	8	8
	Negative	3	163	166
	Total	21	190	211
50 - 75	Positive	88	62	150
	Gray	14	72	86
	Negative	6	200	206
	Total	108	334	442
> 75	Positive	28	14	42
	Gray	8	26	34
	Negative	0	15	15
	Total	36	55	91
All	Positive	134	95	229
	Gray	22	106	128
	Negative	9	378	387

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II STAT Assay - Males

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

Renal cohort (ED)

Renal disease can alter NT-proBNP values because the peptide is known to be cleared by the kidneys. Below are analyses of performance in patients with and without compromised renal function.

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II 18min Assay - Renal Disease (eGFR < 60 mL/min/1.73 m^2)

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) j)	Estimate (%) (n/N)	95%-CI (%) j)	LR k)	95%-CI l)
< 50	40.9 (9/22)	Positive m)	**81.8 (9/11)**	47.8-96.8	--	--	6.50	1.82-23.26
		Gray n)	0.0 (0/4)	0.0-60.4	100.0 (4/4)	39.6-100.0	0.00	0.00-NaN o)
		Negative p)	--	--	**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

j) Wilson score confidence intervals with continuity correction

k) LR = likelihood ratios

l) log method confidence intervals

m) Positive: > age-specific cut-point

n) Gray: ≥ 300 pg/mL and ≤ age-specific cut-point

o) NaN (Not a Number) due to empty cells

p) Negative: < 300 pg/mL

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II 18min Assay - No Renal Disease (eGFR ≥ 60 mL/min/1.73 m^2)

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) j)	Estimate (%) (n/N)	95%-CI (%) j)	LR k)	95%-CI l)
< 50	6.9 (25/361)	Positive m)	**47.7 (21/44)**	32.7-63.1	--	--	12.27	7.98-18.86
		Gray n)	0.0 (0/13)	0.0-28.3	100.0 (13/13)	71.7-100.0	0.00	0.00-NaN o)
		Negative p)	--	--	**98.7 (300/304)**	96.4-99.6	0.18	0.07-0.44
50-75	15.5 (95/592)	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
		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

Of note, the overall positive likelihood ratio (LR+) with the Elecsys proBNP II STAT was found to be lower in patients with renal disease compared to patients without renal disease (LR+ 2.61 and 6.42, respectively). In this population, more false positives are observed. Caution should be used when interpreting NT-proBNP or Elecsys proBNP II STAT results in patients with renal dysfunction.

Body mass index (ED)

Prior studies concluded that the concentrations of BNP[6] and NT-proBNP[7] are lower in obese people, both without and with HF. The most likely biological reason for the lower natriuretic peptide level has been described by the lower release of natriuretic peptides in obesity and also involving pericardial fat, rather than increase in their clearance.[8] The observed natriuretic peptide reduction in obese (vs non-obese) patients was 10-50 %.[8] In line, the overall negative likelihood ratio (LR-) with the Elecsys proBNP II was observed to be higher (i.e., worse) in patients with high BMI compared to patients with low BMI (LR- 0.13 and 0.00, respectively). This is due to the fact that false negatives were characterized by a high BMI. 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).

In the context of obesity, natriuretic peptides should be interpreted with caution. For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II 18 Minute Assay - High BMI (≥ 30 kg/m^2)

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) q)	Estimate (%) (n/N)	95%-CI (%) q)	LR r)	95%-CI s)
< 50	11.8 (30/255)	Positive t)	**61.0 (25/41)**	44.5-75.4	--	--	11.72	7.12-19.29
		Gray u)	0.0 (0/9)	0.0-37.1	100.0 (9/9)	62.9-100.0	0.00	0.00-NaN v)
		Negative w)	--	--	**97.6 (200/205)**	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	25.4 (17/67)	15.9-37.7	74.6 (50/67)	62.3-84.1	0.99	0.60-1.64
		Negative	--	--	**95.3 (202/212)**	91.2-97.6	0.14	0.08-0.26

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) q)	Estimate (%) (n/N)	95%-CI (%) q)	LR r)	95%-CI s)
> 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

q) Wilson score confidence intervals with continuity correction
r) LR = likelihood ratios
s) log method confidence intervals
t) Positive: > age-specific cut-point
u) Gray: ≥ 300 pg/mL and ≤ age-specific cut-point
v) NaN (Not a Number) due to empty cells
w) Negative: < 300 pg/mL

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II 18 Minute Assay- Low BMI (< 30 kg/m^2)

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) q)	Estimate (%) (n/N)	95%-CI (%) q)	LR r)	95%-CI s)
< 50	2.8 (5/177)	Positive t)	**33.3 (5/15)**	13.0-61.3	--	--	17.20	9.43-31.39
		Gray u)	0.0 (0/11)	0.0-32.1	100.0 (11/11)	67.9-100.0	0.00	0.00-NaN v)
		Negative w)	--	--	**100.0 (151/151)**	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	11.3 (7/62)	5.0-22.5	88.7 (55/62)	77.5-95.0	0.55	0.26-1.15
		Negative	--	--	**100.0**	97.5-	0.00	0.00-

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) q)	Estimate (%) (n/N)	95%-CI (%) q)	LR r)	95%-CI s)
					(186/186)	100.0		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

History of heart failure (ED)

Heart failure is a chronic progressive disease. Below are the analyses showing the performance of NT-proBNP in patients with a previous diagnosis of heart failure when presenting to the ED with a suspicion of ADHF.

In addition, 346 subjects in this cohort had a previous diagnosis of heart failure.

Three-by-Two Contingency Table for the ICON Cut-Points - Elecsys proBNP II 18 Minute Assay – All Subjects with a Previous Diagnosis of Heart Failure

Age Group	Test Result Interpretation	ADHF	No ADHF	Total
< 50	Positive	25	13	38
	Gray	0	5	5
	Negative	3	16	19
	Total	28	34	62
50 - 75	Positive	93	42	135
	Gray	13	19	32
	Negative	7	41	48
	Total	113	102	215
> 75	Positive	29	15	44
	Gray	6	16	22

Age Group	Test Result Interpretation	ADHF	No ADHF	Total
	Negative	0	3	3
	Total	35	34	69
All	Positive	147	70	217
	Gray	19	40	59
	Negative	10	60	70
	Total	176	170	376

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II 18 Minute Assay - History of HF

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) x)	Estimate (%) (n/N)	95%-CI (%) x)	LR y)	95%-CI z)
< 50	45.2 (28/62)	Positive aa)	**65.8 (25/38)**	48.6-79.9	--	--	2.34	1.49-3.65
		Gray ab)	0.0 (0/5)	0.0-53.7	100.0 (5/5)	46.3-100.0	0.00	0.00-NaN ac)
		Negative ad)	--	--	**84.2 (16/19)**	59.5-95.8	0.23	0.07-0.70
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

x) Wilson score confidence intervals with continuity correction

y) LR = likelihood ratios

z) log method confidence intervals

aa) Positive: > age-specific cut-point

ab) Gray: ≥ 300 pg/mL and ≤ age-specific cut-point

ac) NaN (Not a Number) due to empty cells

ad) Negative: < 300 pg/mL

Pre- and Post-Test Probabilities as well as informative LRs for NT-proBNP Cut-Points for the Diagnosis or Exclusion of ADHF - Elecsys proBNP II 18 Minute Assay- No History of HF

Age Group	Prevalence of ADHF (%) (n/N)	Test Result Interpretation	Post-test Probability of ADHF		Post-test Probability of No ADHF		Likelihood Ratio (ADHF)	
			Estimate (%) (n/N)	95%-CI (%) x)	Estimate (%) (n/N)	95%-CI (%) x)	LR y)	95%-CI z)
< 50	1.8 (7/396)	Positive aa)	**26.3 (5/19)**	10.1-51.4	--	--	19.85	9.90-39.80
		Gray ab)	0.0 (0/15)	0.0-25.3	100.0 (15/15)	74.7-100.0	0.00	0.00-NaN ac)
		Negative ad)	--	--	**99.4 (360/362)**	97.8-99.9	0.31	0.10-1.00
50-75	10.0 (57/569)	Positive	**40.0 (42/105)**	30.7-50.0	--	--	5.99	4.53-7.91
		Gray	12.0 (12/100)	6.6-20.4	88.0 (88/100)	79.6-93.4	1.22	0.72-2.10
		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	0.80	0.40-1.59
		Negative	--	--	**100.0 (22/22)**	81.5-100.0	0.00	0.00-NaN

Patients with a history of prior HF have a substantially lower performance for rule-in 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. Use caution when interpreting test results in these patients due to a higher false positive and false negative rate.

6. CONCLUSIONS

The information provided in this 510(k) Premarket Notification supports the determination that the supplementation of the additional cut-points provides adequate performance when aiding in the diagnosis of acutely decompensated heart failure.

The information submitted in this Premarket Notification supports a substantial equivalent decision.

7. REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-3726.
2. Writing Committee M, Members AAJC. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. J Card Fail. 2022;28(5):e1-e167.
3. Daniels LB, Clopton P, Bhalla V, et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. Am Heart J. 2006;151(5):999-1005.
4. Kozhuharov N, Martin J, Wussler D, et al. Clinical effect of obesity on N-terminal pro-B-type natriuretic peptide cut-off concentrations for the diagnosis of acute heart failure. Eur J Heart Fail. 2022;24(9):1545-1554.
5. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019;21(6):715-731.
6. Daniels LB, Clopton P, Bhalla V, et al. How obesity affects the cutpoints for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. Am Heart J. 2006;151(5):999-1005.
7. Kozhuharov N, Martin J, Wussler D, et al. Clinical effect of obesity on N-terminal pro-B-type natriuretic peptide cut-off concentrations for the diagnosis of acute heart failure. Eur J Heart Fail. 2022;24(9):1545-1554.
8. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019;21(6):715-731.