510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K252169

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

Access BNP II

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:

Modifications to an existing device

B Measurand:

B-type natriuretic peptide (BNP)

C Type of Test:

Chemiluminescent Assay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Access BNP II test is intended for use with the Beckman Coulter Access Family of Immunoassay Systems for the In Vitro quantitative measurement of B-type natriuretic peptide (BNP) in plasma specimens using EDTA as the anticoagulant. The test is intended to be used for the following indications:

as an aid in the diagnosis of heart failure (HF) in patients presenting to the emergency department (ED) with clinical suspicion of new onset, acutely decompensated, or exacerbated heart failure

for the risk stratification of patients with acute coronary syndromes

for the risk stratification of patients with heart failure

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

DxI 9000 Access Immunoassay Analyzer

IV Device/System Characteristics:

A Device Description:

The Access BNP II assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of B-type natriuretic peptide (BNP) levels in human EDTA plasma using the DxI 9000 Access Immunoassay Analyzer.

The Access BNP II reagent pack includes:

Well	Contents	Ingredients
R1a	3.31 mL	Paramagnetic particles coated with mouse Omnioclonal anti-human BNP antibody suspended in TRIS buffered saline, with bovine serum albumin (BSA), 0.1% ProClin *300, and < 0.1% sodium azide.
R1b	3.10 mL	Purified mouse and goat IgG in TRIS buffered saline, with bovine serum albumin (BSA), 0.1% ProClin* 300, and < 0.1% sodium azide.
R1c	3.10 mL	Mouse monoclonal anti-human BNP antibody alkaline phosphatase bovine conjugate in PBS buffered saline with BSA, 0.1% ProClin* 300, and < 0.1% sodium azide.

*ProClin is a trademark of LANXESS Corp.
Materials needed but not supplied with reagent kit include Access BNP calibrators (provided at zero and approximately 25, 100, 500, 2500, and 5000 pg/mL), quality control materials, Lumi-Phos PRO, and UniCel DxI wash buffer II.

This device was previously cleared in K033383 and K052789.

B Principle of Operation:

The Access BNP II is a two-site immunoenzymatic ("sandwich") assay. A sample is added to the reaction vessel with mouse monoclonal anti-human BNP antibody-alkaline conjugate and paramagnetic particles coated with mouse Omniclonal anti-human BNP antibody. BNP in human plasma binds to the immobilized anti-human BNP antibody on the solid phase, while the mouse anti-BNP antibody alkaline phosphatase conjugates react with a different antigenic site on the BNP molecule.

After incubation, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of analyte in the sample. Analyte concentration is automatically determined from a stored calibration.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Triage BNP Test For Beckman Coulter Immunoassay Systems

B Predicate 510(k) Number(s):
K052789

C Comparison with Predicate(s):

Device & Predicate Device(s):	**K252169**	**K052789**
Device Trade Name	Access BNP II	Triage BNP Test For Beckman Coulter Immunoassay Systems
General Device Characteristic Similarities		
Intended Use/Indications For Use	In vitro quantitative measurement of B-type natriuretic peptide (BNP) in plasma specimens using EDTA as the anticoagulant.	Same
Technology	Chemiluminescent	Same

General Device Characteristic Differences		
Indications for Use	As an aid in the diagnosis of heart failure (HF) in patients presenting to the emergency department (ED) with clinical suspicion of new onset, acutely decompensated, or exacerbated heart failure	As an aid in the diagnosis and assessment of severity of congestive heart failure (also referred to as heart failure)
Measuring Range	5 - 5000 pg/mL	1 - 5000 pg/mL
Sample volume	13 µL	55 µL
Substrate	Lumi-Phos Pro Substrate	Access Substrate

VI Standards/Guidance Documents Referenced:

Clinical & Laboratory Standards Institute (CLSI) EP 09c: Measurement Procedure Comparison and Bias Estimation Using Patient Samples; 3rd Edition.

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; 3rd Edition. (Reaffirmed: September 2019).

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; 2nd Edition.

CLSI EP 07: Interference Testing In Clinical Chemistry; 3rd Edition.

CLSI EP 06: Evaluation of the Linearity of Quantitative Measurement Procedures; 2nd Edition.

CLSI EP 24-A2: Assessment of the Diagnostic Accuracy of Laboratory Tests using Receiver Operating Characteristic Curve; 2nd Edition.

CLSI EP28-A3c: Defining Establishing and Verifying Reference Intervals in the Clinical Laboratory; 3rd Edition.

Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications; Final Guidance for Industry and FDA Reviewers (November 30, 2000).

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Single Site Precision Study

A single site precision study was performed following the recommendations in the CLSI guideline EP05-A3. The precision of the Access BNP II assay was evaluated on three DxI 9000 Access Immunoassay Analyzers using three lots of reagents and three lots of calibrators over 20 days. Each of the seven patient K2-EDTA plasma pools was tested in replicates of two per run, two runs per day over each of 20 days on a unique instrument/reagent lot/calibrator lot combination for a total of 80 measurements per instrument/reagent lot/calibrator lot combination. The within-laboratory estimate includes within-run, between-run, and between-day variance components. Results from one representative combination are presented in the table below.

Sample	N	Mean (pg/mL)	Repeatability		Between-Run		Between-Day		Within-Laboratory	
			SD (pg/mL)	%CV	SD (pg/mL)	%CV	SD (pg/mL)	%CV	SD (pg/mL)	%CV
Sample 1	80	5.1	0.5	10	0.0	0	0.4	7	0.6	12
Sample 2	80	121	8.7	7	0.0	0	2.3	2	9.0	7
Sample 3	80	226	11.4	5	8.4	4	5.0	2	15.0	7
Sample 4	80	349	12.7	4	8.6	2	12.5	4	19.7	6
Sample 5	80	1030	45.1	4	36.1	4	29.9	3	65.0	6
Sample 6	80	1414	38.2	3	18.4	1	36.5	3	55.9	4
Sample 7	80	3854	94.4	2	78.3	2	103.5	3	160.5	4

Multisite Reproducibility Study

The reproducibility performance was established with a multi-site precision evaluation. The study was performed at three sites. Each of the seven patient K2-EDTA plasma pools was tested in three replicates per run, two (2) runs per day for five (5) days at each site. One calibrator lot and three reagent lots were used at three (3) sites, with each site receiving one reagent lot. The results are summarized below.

Sample	N	Mean (pg/mL)	Repeatability		Between-Run		Between-Day		Between Site/Lot	
			SD (pg/mL)	%CV	SD (pg/mL)	%CV	SD (pg/mL)	%CV	SD (pg/mL)	%CV
AS0	90	7.5	0.6	8%	0	0%	0.2	2%	0.9	12%
AS02	90	116.5	7.2	6%	0	0%	2.1	2%	5.2	5%

Sample	N	Mean (pg/mL)	Repeatability		Between-Run		Between-Day		Between Site/Lot	
			SD (pg/mL)	%CV	SD (pg/mL)	%CV	SD (pg/mL)	%CV	SD (pg/mL)	%CV
AS03	90	231.2	12.4	5%	2.8	1%	0.0	0%	15.3	7%
AS04	90	389.9	16.1	4%	0.0	0%	11.3	3%	23.2	6%
AS05	90	991.0	30.4	3%	7.9	1%	17.2	2%	39.8	4%
AS06	90	1883.4	54.3	3%	0.0	0%	17.4	1%	66.0	4%
AS07	90	3776.6	129.5	3%	0.0	0%	87.5	2%	95.6	3%

Sample	N	Mean	Reproducibility	
			SD (pg/mL)	%CV
AS01	90	7.5	1.1	15%
AS02	90	116.5	9.2	8%
AS0	90	231.2	19.9	9%
AS04	90	389.9	30.4	8%
AS05	90	991.0	53.5	5%
AS06	90	1883.4	87.2	5%
AS07	90	3776.6	183.2	5%

2. Linearity:

The linearity performance of the Access BNP II assay was established for K2-EDTA plasma in a study following the recommendations in the CLSI EP06, 2nd Edition guideline. A low sample was obtained from a single native sample by depleting of BNP antigen. A high sample was obtained from a single native sample above the upper end of the measuring range (> 5000 pg/mL). The low and high samples were mixed in pre-defined ratios to create an additional six samples. Each sample was measured on each of three reagent pack lots and a single calibrator lot on one DxI 9000 Access Immunoassay Analyzer. The low sample was run in replicates of eight, and all other samples were run in replicates of four. The linearity was analyzed separately for each reagent lot. Using a weighted linear regression model, the difference between the mean observed value and the value predicted by the weighted linear regression model was derived. Deviations from linearity were never observed to be greater than 6% within the claimed measuring range of 5 pg/mL to 5000 pg/mL. The sponsor also provided a sub-range linearity study results and the results were found to be similar to the full range studies. The results of two linearity studies support that Access BNP II is linear across the claimed range of 5 pg/mL to 5000 pg/mL.

Hook Effect

A study was performed to support the claim that the Access BNP II assay has no hook effect up to 150,000 pg/mL.

3. Analytical Specificity/Interference:

Endogenous and Exogenous Interference

The analytical specificity of the Access BNP II assay was established following the recommendations in the CLSI EP07, 3rd Edition guideline.

Each substance was tested using K2-EDTA plasma samples with BNP at approximate concentrations of 100 pg/mL and 500 pg/mL. Each of the high and low samples was further divided into two aliquots for a control sample (with no added interferent) and a test sample (with added interferent). Each sample was measured in replicates of five or more on each of three unique DxI 9000 Access Immunoassay Analyzer, reagent lot, and calibration lot combinations. No significant interference, defined by the sponsor as a difference within ±10% between the mean of the test sample versus the mean of the control samples, was observed at the following concentrations:

Substance	**Highest Concentration Added Without Significant Interference**
Endogenous Substance	
Conjugated Bilirubin	20 mg/dL
Unconjugated Bilirubin	20 mg/dL
Hemoglobin	500 mg/dL
Protein (human serum albumin) *	6000 mg/dL
Triglycerides	3000 mg/dL
HAMA	800 µg/L
Fibrinogen	800 mg/dL
Rheumatoid factor	500 IU/mL
Exogenous substance	
Acetaminophen	20 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Amiodarone	4.2 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	3 mg/dL
Aspirin	50 mg/dL
Atenolol	1 mg/dL
Biotin	3,510 ng/mL
Caffeine	10 mg/dL
Captopril	1.25 mg/dL
Chloramphenicol	7.8 mg/dl
Cinnarizine	40 mg/dL
Clopidogrel bisulfate	30 µg/mL
Cyclosporine	40 µg/mL
Diclofenac	2 mg/dL
Digoxin	0.02 mg/dL
Dipyridamole	30 µg/mL
Dopamine	65 mg/dL

Substance	Highest Concentration Added Without Significant Interference
Enalapril maleate	16 µg/mL
Erythromycin	20 mg/dL
Furosemide	40 mg/dL
Heparin	8 mg/dL
Hydralazine	20 µg/mL
Hydrochlorothiazide	20 µg/mL
Ibuprofen	40 mg/dL
Indomethacin	36 µg/mL
Isosorbide dinitrate	0.593 mg/dL
Lisinopril	16 µg/mL
Lovastatin	0.021 mg/dL
Methyldopa	2.5 mg/dL
Nicotine	1.6 µg/mL
Nifedipine	6 mg/dL
Nitrofurantoin	6.4 mg/dL
Oxazepam	12 µg/mL
Oxytetracycline	0.5 mg/dL
Phenobarbital	69 mg/dL
Phenytoin	10 mg/dL
Probenecid	600 µg/mL
Procainamide	4.8 mg/dL
Propranolol	0.5 mg/dL
Quinidine sulfate	5 mg/dL
Simvastatin	32 µg/mL
Spironolactone	600 mg/dL
Sulfamethoxazole	1.7 µmol/L
Theophylline	25 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	7.5 mg/dL

*The final protein concentrations in the test samples were 12.5 to 12.7 g/dL.

Cross-reactivity

A study was conducted to evaluate the performance of the Access BNP II assay in the presence of cross-reactants. In this study, two K2-EDTA plasma samples with BNP concentrations at 100 pg/mL and 500 pg/mL were used. Each sample was then spiked with the potential cross-reactive substance to form a test sample or spiked with solvent to form a control sample. Each sample was assayed in replicates of five on a single DxI 9000 Access Immunoassay Analyzer across three reagent pack lots and one calibrator lot.

No cross-reactivity, defined by the sponsor as a difference within ±10% between the mean of the test sample versus the mean of the control samples, was observed at the following concentrations:

Cross-reactant	Concentration
Adrenomedullin	1000 pg/mL
Aldosterone	600 pg/mL
α Atrial Natriuretic polypeptide 1-28	1000 pg/mL
Angiotensin I	600 pg/mL
Angiotensin II	600 pg/mL
Angiotensin III	1000 pg/mL
Arg-Vasopressin	1000 pg/mL
C type Natriuretic Peptide	1000 pg/mL
Endothelin	20 pg/mL
Prepro ANF 104-123	1000 pg/mL
Prepro ANF 26-55	1000 pg/mL
Prepro ANF 56-92	1000 pg/mL
Prepro BNP 1-21	1000 pg/mL
Prepro BNP 22-46	1000 pg/mL
Renin	50 ng/mL
Urodilatin 95-126	1000 pg/mL

The sponsor includes the following limitations in the labeling:

- For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce human anti-animal antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.

- Other potential interferences in the sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, fibrin, endogenous alkaline phosphatase, exogenous alkaline phosphatase (e.g., asfotase alfa, Strensiq), and proteins capable of binding to alkaline phosphatase. Carefully evaluate results if the sample is suspected of having these types of interferences.

- Nesiritide is a synthetic form of BNP; BNP measurements should not be performed during Nesiritide Infusion.

4. Assay Reportable Range:

The claimed measuring range is 5 to 5,000 pg/mL.

The sponsor provided information to support the following dilution claims:
- Diluted: up to approximately 10,000 pg/mL.

- For automated dilutions, the system dilutes one volume of sample with one volume of wash buffer.
- For manual dilutions, dilute one volume of sample with one volume of wash buffer.

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

Traceability

The traceability of the assay is the same as described in K033383.

Stability

The sponsor has provided information to support the following sample stability claims in their labeling:

- Separated K2-EDTA plasma samples are stable for up to 2 hours at room temperature (20 to 25ºC), and for up to 7 hours at 2-8°C.
- Separated samples are stable at -20°C or below for up to 60 days.
- Separated samples are stable for one freeze-thaw cycle.

6. Detection Limit:

The limit of blank (LoB), limit of detection (LoD), and limit of quantification (LoQ) were established following the recommendations in the CLSI EP17-A2 guideline.

Limit of Blank (LoB)
The LoB study was performed on five blank samples, using three reagent pack lots and one calibrator lot across three instruments. Each sample was analyzed across three days with one run per day and five replicates per run, for each pack lot/instrument. The LoB was determined non-parametrically for each reagent lot separately, and the highest value obtained from three lots was taken as the LoB value. The LoB for the Access BNP II assay was estimated to be 0.3 pg/mL.

Limit of Detection (LoD)
The LoD study was performed using five native EDTA plasma samples containing low levels of BNP analyte, using three reagent pack lots and one calibrator lot across three instruments. Each sample was analyzed over five days with one run per day and nine replicates per run on each reagent pack lot/instrument. The LoD was determined by parametric analysis, and the highest value obtained from three lots was claimed. The LoD for the Access BNP II assay was estimated to be 1 pg/mL.

Limit of Quantification (LoQ)
The LoQ study was performed using eleven EDTA plasma samples containing low levels of BNP analyte, using three reagent pack lots and one calibrator lot across three DxI 9000 Immunoassay Analyzer. The samples were each assayed in replicates of nine per run per day and five days per reagent pack lot/instrument. The LoQ was determined as the lowest concentration of analyte which can be measured with a within-laboratory precision of 20%

CV, and the highest value obtained from three lots was the reported LoQ for the assay. The LoQ for the Access BNP II assay was estimated to be 2 pg/mL.

7. Assay Cut-Off:

   Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
   A study was conducted comparing the values obtained with the Access BNP II assay on the DxI 9000 Access Immunoassay Analyzer to the values obtained with the predicate device (the Access BNP assay on the Access 2 Immunoassay Analyzer). A total of 144 native K2-EDTA plasma samples from the intended use patient population were evaluated. The study was run on three DxI 9000 Access Immunoassay Analyzers with three Access BNPII assay reagent pack lots and two Access 2 instruments with three Access BNP assay reagent pack lots. Each sample was tested in singleton. Weighted Deming Regression was used to analyze the data.

   Method Comparison Summary Access BNPII vs Access BNP (predicate) in pg/mL:

N	Concentration Range	Intercept (95% CI)	Slope (95% CI)	Bias (95% CI) at 100 pg/mL	%Bias (95% CI) at 100 pg/mL
144	7.5-4641	-6.8 (-9.5, -4.1)	1.06 (1.02, 1.10)	-1.1 (-3.7, 1.5)	-1.1% (-3.7%, 1.5%)

2. Matrix Comparison:

   K2-EDTA plasma is the only claimed sample type.

C Clinical Studies:

1. Clinical Sensitivity:

   See Section C.3 below.

2. Clinical Specificity:

   See Section C.3 below.

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

   A multi-center prospective study including 18 clinical collection sites and 3 clinical laboratory testing sites across the United States was conducted to establish the clinical performance characteristics of the Access BNP II assay run on the DxI 9000 Access Immunoassay Analyzer. In this study, subjects 22 years and older presenting with clinical suspicion of new onset heart failure or worsening symptoms suggestive of decompensated or exacerbated heart failure were prospectively enrolled in the study. Subjects on dialysis, on nesiritide infusion, and subjects with dyspnea clearly not secondary to heart failure (e.g.,

primary lung disease or chest trauma) were excluded from the study. The Access BNP II assay results were determined on the DxI 9000 Access Immunoassay Analyzer using stored frozen samples collected from 1323 emergency department (ED) subjects consisting of 43.2% (572/1323) female subjects and 56.7% (751/1323) male subjects. Individuals in the population were 37.4% Black or African American, 59% White, and 3.6% other. The sponsor provided information to support the use of the frozen samples in their study.

A diagnosis of whether a patient had new onset, decompensated or exacerbated HF (hereinafter referred to as HF) for each subject was determined by an independent central adjudication panel consisting of medical doctors with a specialty in cardiology. For all 1323 subjects enrolled in the study, a total of 449 subjects were adjudicated as subjects with HF, and 874 subjects with adjudicated as subjects without HF. The descriptive statistics for the Access BNP II results were determined within and across sex and age groups. The results are summarized below.

Adjudicated Diagnosis of No HF

Statistics	All Ages	Age < 45	Age 45-54	Age 55-64	Age 65-74	Age 75+
All Subjects						
N	874	141	145	232	203	153
Mean (pg/mL)	162	97	100	161	179	262
SD (pg/mL)	323.3	236.4	186.5	363.5	274.3	444.0
Median (pg/mL)	52	20	25	40	75	126
IQR 25^{th}-75^{th} percentile	17 – 159	10 – 51	11 – 91	14 – 135	31 – 219	59 – 304
Min (pg/mL)	<5	<5	<5	<5	5	8
Max (pg/mL)	4294	1363	1100	2879	1835	4294
Male						
N	469	71	81	132	107	78
Mean (pg/mL)	168	100	88	201	157	270
SD (pg/mL)	361.8	273.7	194.8	449.7	205.7	511.7
Median (pg/mL)	46	13	21	39	69	126
IQR 25^{th}-75^{th} percentile	15 – 155	5 – 29	9 – 63	14 – 170	35 – 201	67 – 304
Min (pg/mL)	<5	<5	<5	<5	6	8
Max (pg/mL)	4294	1363	1100	2879	1095	4294
Female						
N	405	70	64	100	96	75
Mean (pg/mL)	156	95	116	108	203	253
SD (pg/mL)	272.4	193.4	175.6	188.7	334.0	363.9
Median (pg/mL)	56	25	43	43	86	128
IQR 25^{th}-75^{th} percentile	20 – 176	13 – 60	12 – 134	16 – 97	29 – 233	56 – 318
Min (pg/mL)	< 5	<5	<5	<5	5	12
Max (pg/mL)	2317	932	840	1182	1835	2317

Adjudicated Diagnosis of HF

Statistics	All Ages	Age < 45	Age 45-54	Age 55-64	Age 65-74	Age 75+
All Subjects						
N	445	40	72	109	114	110
Mean (pg/mL)	1046	1163	1010	1123	1096	899
SD (pg/mL)	1080.0	1049.3	1042.8	1217.6	1130.5	904.9
Median (pg/mL)	729	919	660	800	831	626
IQR 25th -75th percentile	318 – 1419	336 – 1578	304 –1363	354 – 1450	326 –1492	318 –1105
Min (pg/mL)	10	54	20	10	30	13
Max (pg/mL)	>5000	4457	>5000	>5000	>5000	4618
Male*						
N	278	25	48	77	69	59
Mean (pg/mL)	1149	1393	1113	1145	1248	964
SD (pg/mL)	1118.3	1119.7	1107.5	1046.1	1292.9	996.6
Median (pg/mL)	819	982	772	857	864	630
IQR 25th -75th percentile	387 - 1515	718 - 1596	374 - 1426	394 - 1450	360 - 1719	360 - 1078
Min (pg/mL)	10	94	32	10	30	13
Max (pg/mL)	>5000	4457	>5000	>5000	>5000	4618
Female						
N	167	15	24	32	45	51
Mean (pg/mL)	875	780	803	1070	863	824
SD (pg/mL)	992.7	816.4	885.1	1574.1	779.2	788.8
Median (pg/mL)	615	356	390	659	680	580
IQR 25th -75th percentile	253 - 1151	191 -1440	265 - 1149	152 - 1315	276 - 1237	279 - 1118
Min (pg/mL)	20	54	20	56	47	48
Max (pg/mL)	>5000	2778	3325	>5000	3471	3858

*Four (4) male subjects with adjudicated diagnosis of Acute HF are excluded due to undetermined Access BNP II numerical values for descriptive statistics reporting.

The cross-tabulation of results between HF and BNP at the cutoff of ≥100 pg/mL is shown as below:

DxI 9000 Result	Adjudicated Diagnosis		
	Acute Heart Failure	No Acute Heart Failure	Total
>100 pg/mL	418	301	719
≤ 100 pg/mL	31	573	604
Total Subjects	449	874	1323

Using the single cutoff >100 pg/mL, the sensitivity of Access BNP II is 93.1% and the specificity is 65.6% for all subjects. The Positive Predictive Value (PPV) is 58.1% and the Negative Predictive Value (NPV) is 94.9%, as shown in the table below.

Statistics		All Ages	Age <50	Age 50-75	Age >75
All Subjects					
Sensitivity	Estimate (n/N)	93.1% (418/449)	93.7% (74/79)	91.8% (246/268)	96.1% (98/102)
	95% CI	(90.4-95.1%)	(86.0-97.3%)	(87.9-94.5%)	(90.3-98.5%)
Specificity	Estimate (n/N)	65.6% (573/874)	82.0% (168/205)	66.4% (352/530)	38.1% (53/139)
	95% CI	(62.3-68.6%)	(76.1-86.6%)	(62.3-70.3%)	(30.5-46.4%)
NPV	Estimate (n/N)	94.9% (573/604)	97.1% (168/173)	94.1% (352/374)	93.0% (53/57)
	95% CI	(92.8-96.4%)	(93.4-98.8%)	(91.3-96.1%)	(83.3-97.2%)
PPV	Estimate (n/N)	58.1% (418/719)	66.7% (74/111)	58.0% (246/424)	53.3% (98/184)
	95% CI	(54.5-61.7%)	(57.5-74.7%)	(53.3-62.6%)	(46.1-60.3%)
Male					
Sensitivity	Estimate (n/N)	94.3% (266/282)	98.0% (49/50)	93.2% (165/177)	94.5% (52/55)
	95% CI	(91.0-96.5%)	(89.5-99.6%)	(88.5-96.1%)	(85.1-98.1%)
Specificity	Estimate (n/N)	65.7% (308/469)	85.6% (89/104)	65.8% (194/295)	35.7% (25/70)
	95% CI	(61.3-69.8%)	(77.6-91.1%)	(60.2-70.9%)	(25.5-47.4%)
NPV	Estimate (n/N)	95.1% (308/324)	98.9% (89/90)	94.2% (194/206)	89.3% (25/28)
	95% CI	(92.1-96.9%)	(94.0-99.8%)	(90.1-96.6%)	(72.8-96.3%)
PPV	Estimate (n/N)	62.3% (266/427)	76.6% (49/64)	62.0% (165/266)	53.6% (52/97)
	95% CI	(57.6-66.8%)	(64.9-85.3%)	(56.1-67.7%)	(43.7-63.2%)
Female					
Sensitivity	Estimate (n/N)	91.0% (152/167)	86.2% (25/29)	89.0% (81/91)	97.9% (46/47)
	95% CI	(85.7-94.5%)	(69.4-94.5%)	(80.9-93.9%)	(88.9-99.6%)
Specificity	Estimate (n/N)	65.4% (265/405)	78.2% (79/101)	67.2% (158/235)	40.6% (28/69)
	95% CI	(60.7-69.9%)	(69.2-85.2%)	(61.0-72.9%)	(29.8-52.4%)
NPV	Estimate (n/N)	94.6% (265/280)	95.2% (79/83)	94.0% (158/168)	96.6% (28/29)
	95% CI	(91.4-96.7%)	(88.3-98.1%)	(89.4-96.7%)	(82.8-99.4%)
PPV	Estimate (n/N)	52.1% (152/292)	53.2% (25/47)	51.3% (81/158)	52.9% (46/87)
	95% CI	(46.3-57.7%)	(39.2-66.7%)	(43.5-58.9%)	(42.5-63.0%)

The performance of the device in the cohort was calculated for ages >75, 50-75, and <50 years. The clinical performance of the Access BNP II using the cutoff of ≥100 pg/mL for the two different age groups is described below.

Statistics		<50	50-75	>75
Sensitivity	Estimate (n/N)	93.7% (74/79)	91.8% (246/268)	96.1% (98/102)
	95% CI	(86.0-97.3%)	(87.9-94.5%)	(90.3-98.5%)
Specificity	Estimate (n/N)	82.0% (168/205)	66.4% (352/530)	38.1% (53/139)
	95% CI	(76.1-86.6%)	(62.3-70.3%)	(30.5-46.4%)
PPV	Estimate (n/N)	66.7% (74/111)	58.0% (246/424)	53.3% (98/184)
	95% CI	(57.5-74.7%)	(53.3-62.6%)	(46.1-60.3%)
NPV	Estimate (n/N)	97.1% (168/173)	94.1% (352/374)	93.0% (53/57)
	95% CI	(93.4-98.8%)	(91.3-96.1%)	(83.3-97.2%)
PLR	Estimate	5.19	2.73	1.55
	95% CI	(3.86-6.99)	(2.41-3.10)	(1.36-1.78)
NLR	Estimate	0.08	0.12	0.10
	95% CI	(0.03-0.18)	(0.08-0.19)	(0.04-0.28)

The performance of the device in the cohort was calculated per sex. The clinical performance of the Access BNP II using the cutoff of >100 pg/mL for males and females is described below.

Statistics		Females	Males
Sensitivity	Estimate (n/N)	91.0% (152/167)	94.3% (266/282)
	95% CI	(85.7 – 94.5%)	(91.0 – 96.5%)
Specificity	Estimate (n/N)	65.4% (265/405)	65.7% (308/469)
	95% CI	(60.7 – 69.9%)	(61.3 – 69.8%)
PPV	Estimate (n/N)	52.1% (152/292)	62.3% (266/427)
	95% CI	(46.3 – 57.7%)	(57.6 – 66.8%)
NPV	Estimate (n/N)	94.6% (265/280)	95.1% (308/324)
	95% CI	(91.4 – 96.7%)	(92.1 – 96.9%)
LR(+)	Estimate	2.63	2.75
	95% CI	(2.28 – 3.04)	(2.42 – 3.12)
LR(-)	Estimate	0.14	0.09
	95% CI	(0.08 – 0.22)	(0.05 – 0.14)

The performance was further broken down by history of heart failure, BMI, and estimated glomerular filtration rate (eGFR). The clinical performance is summarized in the following tables.

Statistics		Prior History of HF	No Prior History of HF
Sensitivity	Estimate (n/N)	93.6% (324/346)	91.1% (92/101)
	95% CI	(90.6 – 95.8%)	(83.9 – 95.2%)
Specificity	Estimate (n/N)	40.3% (116/288)	78.0% (454/582)
	95% CI	(34.8 – 46.0%)	(74.5 – 81.2%)
PPV	Estimate (n/N)	65.3% (324/496)	41.8% (92/220)
	95% CI	(61.0 – 69.4%)	(35.5 – 48.4%)
NPV	Estimate (n/N)	84.1% (116/138)	98.1% (454/463)
	95% CI	(77.0 – 89.2%)	(96.3 – 99.0%)
LR(+)	Estimate	1.57	4.14
	95% CI	(1.42 – 1.73)	(3.51 – 4.88)
LR (-)	Estimate	0.16	0.11
	95% CI	(0.10 – 0.24)	(0.06 – 0.21)

Statistics		eGFR <60* (mL/min/1.73m^2)	eGFR ≥60 (mL/min/1.73m^2)
Sensitivity	Estimate (n/N)	93.9% (215/229)	94.1% (191/203)
	95% CI	(90.0 – 96.3%)	(90.0 – 96.6%)
Specificity	Estimate (n/N)	46.4% (96/207)	70.8% (436/616)
	95% CI	(39.7 – 53.2%)	(67.1 – 74.2%)
PPV	Estimate (n/N)	66.0% (215/326)	51.5% (191/371)
	95% CI	(60.6-70.9%)	(46.4 – 56.5%)
NPV	Estimate (n/N)	87.3% (96/110)	97.3% (436/448)
	95% CI	(79.8 – 92.3%)	(95.4 – 98.5%)
LR(+)	Estimate	1.75	3.22
	95% CI	(1.54-2.00)	(2.83 – 3.66)
LR(-)	Estimate	0.13	0.08
	95% CI	(0.08 – 0.22)	(0.05 – 0.14)

*subjects on dialysis were excluded from the study

Statistics		BMI < 30	BMI ≥30
Sensitivity	Estimate (n/N)	98.1% (206/210)	89.7% (201/224)
	95% CI	(95.2 – 99.3%)	(85.1 – 93.1%)
Specificity	Estimate (n/N)	59.6% (255/428)	71.9% (300/417)
	95% CI	(54.9 – 64.1%)	(67.4 – 76.0%)
PPV	Estimate (n/N)	54.4% (206/379)	63.2% (201/318)
	95% CI	(49.3 – 59.3%)	(57.8 – 68.3%)
NPV	Estimate (n/N)	98.5% (255/259)	92.9% (300/323)
	95% CI	(96.1 – 99.4%)	(89.5 – 95.2%)
LR (+)	Estimate (n/N)	2.43	3.20
	95% CI	(2.16 – 2.73)	(2.73 – 3.75)
LR (-)	Estimate (n/N)	0.03	0.14
	95% CI	(0.01 – 0.08)	(0.10 – 0.21)

Statistics		No Comorbidities	Comorbidities*
Sensitivity	Estimate (n/N)	97.5% (39/40)	92.6% (377/407)
	95% CI	(87.1 – 99.6%)	(89.7 – 94.81%)
Specificity	Estimate (n/N)	77.3% (143/185)	62.3% (426/684)
	95% CI	(70.7 – 82.7%)	(58.6 – 65.8%)
PPV	Estimate (n/N)	48.1% (39/81)	59.4% (377/635)
	95% CI	(37.6 – 58.9%)	(55.5 – 63.1%)
NPV	Estimate (n/N)	99.3% (143/144)	93.4% (426/456)
	95% CI	(96.2-99.9%)	(90.8 – 95.4%)
LR (+)	Estimate (n/N)	4.29	2.46
	95% CI	(3.28 – 5.63)	(2.22 – 2.71)
LR (-)	Estimate (n/N)	0.03	0.12
	95% CI	(0.00 – 0.22)	(0.08 – 0.17)

* "Comorbidity" is defined as one or more of the following non-cardiac history conditions: chronic kidney disease (eGFR < 60 mL/min/1.73m^2, systemic hypertension, pulmonary disease (requiring chronic steroid therapy and/or supplemental home oxygen), and metabolic disorders (ex. diabetes, NAFLD, NASH).

The labeling includes the following limitations:

- The results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests, and other appropriate information. The results of different BNP assays are not comparable.

- Blood concentrations of BNP may be elevated in patients who are experiencing a heart attack, patients that are candidates for renal dialysis, and patients that have had renal dialysis.

The labeling includes these factors that may impact BNP results:

- Of the adjudicated HF subjects, 6.9% (31/449) were false negative (≤100 pg/mL cutoff, adjudicated HF). BNP levels are inversely correlated with obesity/body mass index (BMI) based on peer reviewed literature. Of the 31 false negative subjects, 74.2% (23/31) had BMI ≥ 30 kg/m^2, 12.9% (4/31) had BMI < 30 kg/m^2, and 12.9 % (4/31) had no BMI information.

- Of the adjudicated non-HF subjects, 34.4% (301/874) were false positive (>100 pg/mL cutoff, adjudicated non-HF). The AHA/ACC/HFSA guideline defines Stage C heart failure as structural heart disease with current or prior symptoms. Natriuretic peptides are elevated in heart failure due to myocardial wall stress; accordingly, patients with chronic HF may have persistently abnormal BNP values even when clinically stable. Of the 301 subjects with a false positive test result, 57.1% (172/301) had a prior heart failure diagnosis.

- As renal function worsens, the concentration of BNP increases, therefore the relationship between the two should be considered during the interpretation of BNP results based on peer reviewed literature. In this study, of the 301 false positive subjects, 36.9% (111/301) had eGFR < 60 mL/min/1.73m^2.

- As age increases, concentration of BNP increases, and therefore the relationship between the two should be considered during the interpretation of BNP results based on peer reviewed literature. In this study, of the 301 false positive subjects, 28.6% (86/301) were over the age of 75 years old.

Risk stratification of patients with heart failure (HF) and risk stratification of acute coronary syndrome (ACS)

The sponsor provided information to support the risk stratification of heart failure and acute coronary syndrome claims based on the following peer-reviewed literature references:

Reference 1: 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevated Acute Coronary Syndromes. Amsterdam, E., et al., Journal of the American College of Cardiology, 64 (24), pp e139-e228.

Reference 2: The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes, deLemos JA., et al., New Engl. J. Med., 345: 1014-1021, 2001

Reference 3: How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. Doust, J.A., et al., BMJ 330: 625-633, 2005.

Reference 4: Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. Vrtovec, B., et al., Circulation, 107:1764-1769, 2003.

Reference 5: B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. Harrison, A., et.al., Ann. Emerg. Med. 39: 131-138, 2002.

Reference 6: Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure, Logeart, D., et.al., J. Am. Coll. Cardiol., 43: 635-641, 2004.

BNP Correlation to New York Heart Association (NYHA) Classification: Descriptive Statistics

A total of 449 subjects were adjudicated as HF. Of the 449 subjects, 445 had BNP values within the measuring range. Descriptive statistics by the NYHA classification for the 445 subjects adjudicated to have HF for all subjects and for male and female subjects are presented in the table below.

Statistics	NYHA Functional Classification			
	Class I	Class II	Class III	Class IV
All Subjects				
N	11	111	179	144
Mean (pg/mL)	1186	977	1038	1099
SD (pg/mL)	982.7	982.6	1123.3	1110.1
Median (pg/mL)	900	661	712	808
5^{th} percentile (pg/mL)	277	104	65	74
95^{th} percentile (pg/mL)	3428	2809	3254	3471
Male				
N	1	36	71	59
Mean (pg/mL)	2557	611	977	884
SD (pg/mL)	n/a	670.6	1023.4	1086.5
Median (pg/mL)	2557	318	747	617
5^{th} percentile (pg/mL)	2557	64	71	56
95^{th} percentile (pg/mL)	2557	1873	2778	3471
Female				
N	10	75	108	85
Mean (pg/mL)	1049	1153	1078	1248
SD (pg/mL)	918.3	1061.2	1187.4	1108.2
Median (pg/mL)	761	785	697	953

Statistics	NYHA Functional Classification			
	Class I	Class II	Class III	Class IV
All Subjects				
5th percentile (pg/mL)	277	167	38	94
95th percentile (pg/mL)	3428	3149	3465	3622

D Clinical Cut-Off:

Same as described in K033383. The sponsor provides the following information in the labeling:

"BNP values less than or equal to 100 pg/mL are representative of normal values in patients without heart failure (HF). BNP results greater than 100 pg/mL are considered abnormal and suggestive of patients with HF."

E Expected Values/Reference Range:

Same as described in K033383.

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.