510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K192380

B Applicant

Fujirebio Diagnostics, Inc.

C Proprietary and Established Names

ST AIA-PACK BNP

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:

New Device

B Measurand:

B-type Natriuretic Peptide (BNP)

C Type of Test:

Quantitative Immunoenzymometric Assay

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
The Tosoh ST AIA-PACK BNP assay is designed for IN VITRO DIAGNOSTIC USE ONLY for the quantitative measurement of BNP in human K2EDTA plasma on Tosoh AIA System analyzers. BNP is used as an aid in the diagnosis of heart failure (HF) in patients presenting to the emergency department (ED) with clinical suspicion of new onset HF, acutely decompensated or exacerbated HF.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

The ST AIA-PACK BNP should only be used for patients presenting to the emergency department (ED)

D Special Instrument Requirements:

TOSOH AIA Analyzer 2000

IV Device/System Characteristics:

A Device Description:

The ST AIA-PACK BNP set consists of 5 trays x 20 test cups. Each kit contains plastic test cups containing twelve magnetic lyophilized beads coated with anti-BNP mouse monoclonal antibody and 100 µL of anti-BNP mouse monoclonal antibody conjugated to alkaline phosphatase with sodium azide as a preservative.

B Principle of Operation:

The ST AIA-PACK BNP is a two-site immunoenzymometric assay which is performed entirely in the ST AIA-PACK BNP test cups. BNP present in the test sample is bound with monoclonal antibody immobilized on magnetic beads and enzyme-labeled monoclonal antibody. The magnetic beads are washed to remove unbound enzyme-labeled monoclonal antibody and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled monoclonal antibody that binds to the beads is directly proportional to the BNP concentration in the test sample. A standard curve is constructed, and unknown sample concentrations are calculated using the curve.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Advia Centaur B-type Natriuretic Peptide (BNP) Assay

B Predicate 510(k) Number(s):
K031038

C Comparison with Predicate(s):

Device & Predicate Device(s):	K192380	K031038
Device Trade Name	ST AIA-PACK BNP	SIEMENS ADVIA Centaur BNP
General Device Characteristic Similarities		
Intended Use/Indications for Use	For in vitro diagnostic use only for the quantitative measurement of BNP in human (EDTA) plasma	Same
Cut-off	100 pg/mL	Same
Type of Specimen	Human EDTA plasma	Same
General Device Characteristic Differences		
Instrument System	TOSOH AIA Analyzer 2000	ADVIA Centaur and ADVIA Centaur XP Systems
Principle of Operation	Immunoenzymometric Assay	Chemiluminescence immunoassay
Assay Range	4.0 – 2000pg/mL	<2.0 – 5000pg/mL
Test Principle	One-step sandwich assay	Delayed one-step sandwich assay
Intended Use Setting	For use on patients presenting to the Emergency Department (ED)	Not specified

VI Standards/Guidance Documents Referenced:

CLSI EP28-A3c: Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline
CLSI EP06-A: Evaluation of Linearity of Quantitative Measurement Procedures, A Statistical Approach: Approved Guideline
CLSI EP07: Interference Testing in Clinical Chemistry; Approved Guideline – Third Edition
CLSI EP37: Supplemental Tables for Interference Testing in Clinical Chemistry; Approved Guideline – First Edition
CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition
Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable; Guidance for Sponsors, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff (April 25, 2006)
Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications; Final Guidance for Industry and FDA Reviewers. Document issued on: November 30, 2000

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

The study was conducted at 1 site using three lots of ST AIA-PACK BNP Reagents and Calibrator Sets on three AIA-2000 analyzers to assess the precision of the ST AIA-PACK BNP assay. Six EDTA plasma samples were tested. A high concentration sample was prepared by spiking an EDTA plasma base pool with BNP. This sample was then diluted using a base EDTA plasma pool to create 3 pools with BNP concentrations of approximately 500, 1000, and 2000 pg/mL. The lower concentration samples were patient samples with approximate BNP concentrations of 10, 50 and 100 pg/mL. The six samples were tested in replicates of two, at two separate times per day, for twenty days. The two runs per day were separated by a minimum of two hours.

Within run, between run, between day and total precision was calculated for each lot and all lots combined. Results for a representative lot and the combined lots are shown below.

ST AIA-PACK BNP Precision one lot (n=80)

Sample		**EDTA Plasma-1**	**EDTA Plasma-2**	**EDTA Plasma-3**	**EDTA Plasma-4**	**EDTA Plasma-5**	**EDTA Plasma-6**
Mean Conc. (pg/mL)		10.896	49.919	104.864	495.956	988.208	1951.419
Within Run	**SD**	0.609	1.450	1.997	11.611	25.244	33.062
	%CV	5.6	2.9	1.9	2.3	2.6	1.7
Between Run	**SD**	0.000	0.307	1.777	7.232	15.589	21.281
	%CV	0.0	0.6	1.7	1.5	1.6	1.1
Between Day	**SD**	0.361	0.722	0.541	0.000	5.415	13.418
	%CV	3.3	1.4	0.5	0.0	0.5	0.7
Total	**SD**	0.708	1.648	2.728	13.679	30.159	41.546
	%CV	6.5	3.3	2.6	2.8	3.1	2.1

ST AIA-PACK BNP Precision Combined Lots (n=240)

Sample	Overall Mean (pg/mL)	Source of Variation	SD	%CV
EDTA Plasma-1	10.588	Within Run Between Run Between Day Between Lot	0.547 0.000 0.217 0.982	5.2 0.0 2.0 9.3
Total			**1.145**	**10.8**
EDTA Plasma-2	49.873	Within Run Between Run Between Day Between Lot	1.592 0.000 0.219 0.807	3.2 0.0 0.4 1.6
Total			**1.798**	**3.6**
EDTA Plasma-3	106.718	Within Run Between Run Between Day Between Lot	2.637 0.739 0.000 1.700	2.5 0.7 0.0 1.6
Total			**3.223**	**3.0**
EDTA Plasma-4	519.429	Within Run Between Run Between Day Between Lot	10.127 5.613 0.000 23.664	1.9 1.1 0.0 4.6
Total			**26.346**	**5.1**
EDTA Plasma-5	1050.712	Within Run Between Run Between Day Between Lot	21.451 13.823 3.329 58.632	2.0 1.3 0.3 5.6
Total			**64.031**	**6.1**

The EDTA Plasma-6 sample was excluded from this analysis because the results with all lots combined were above the measuring range of the assay.

2. Linearity:

The claimed assay range is 4.0 to 2000 pg/mL. A study was conducted to determine the linearity of the Tosoh ST AIA-PACK BNP assay using low and high EDTA plasma samples. The low sample was prepared by making a 1:99 dilution of a higher EDTA plasma sample. The ST AIA-PACK BNP sample diluting solution was used to prepare the dilutions. The high sample was spiked EDTA plasma. The intermediate concentrations were made by dilutions that would be related to each other and the high and low samples by constant intervals. A total of fourteen (14) samples each for EDTA plasma ranging from 3.1 – 2271.54 pg/mL were assayed on one (1) Tosoh AIA-2000 analyzer in replicates of four (4).

The sponsor performed the analyses recommended in the CLSI guideline EP06-A and the results support that the assay is linear from 4.0 to 2000 pg/mL.

3. Analytical Specificity/Interference:

Endogenous Interfering Substances:
Studies were conducted to evaluate the potential interference from the endogenous substance summarized below with the Tosoh ST AIA-PACK BNP assay. EDTA plasma samples with known concentrations of BNP, at approximately 35 pg/mL, 90 pg/mL and 1,000 pg/mL were spiked with varying concentrations of the potential interferents. The criterion for no interference was defined as a mean percent recovery for each interferent within 100±10% of the control. When the substances listed below were tested, no interference was observed up to the concentration listed in the table.

Substance	Highest Concentration Tested With No Interference
Hemoglobin	130 mg/dL
Unconjugated (Free) Bilirubin	15 mg/dL
Conjugated bilirubin	19 mg/dL
Lipemia (represented by triglycerides)	1600 mg/dL
Protein (represented by human albumin)	14 g/dL
Rheumatoid factor	500 IU/mL
Ascorbic Acid	20 mg/dL
Human IgG	5.3 g/dL
Creatinine	15 mg/dL
Cholesterol	400 mg/dL
Alkaline Phosphatase	2000 U/L
HAMA IgG	500 ng/mL

In addition, the labeling includes the following limitations:

- Hemolyzed samples should be avoided for the measurement due to the possibility to give erroneously lower concentrations.

- Lipemia has an insignificant effect on the assay except in the case of gross lipemia where spatial interference may occur.

- Tosoh Automated Immunoassays utilizing alkaline phosphatase-based technologies should not be used with samples from patients under Asfotase Alfa treatment.

- Patient samples may also contain human anti-mouse antibody (HAMA) due to either natural antibody production or antibodies produced in response to therapy regimens. HAMA may cause either false-positive or false-negative results in assays using

mouse monoclonal antibodies. Other heterophile antibodies are also known to interfere in assays of this type. ST AIA-PACK BNP has been designed to minimize the effects of heterophile antibodies, but interference from high titers cannot be ruled out.

Cross reactants:

Studies were conducted to evaluate the potential interference from various compounds with the Tosoh ST AI-PACK BNP assay. EDTA plasma samples of known BNP concentrations targeting 100 pg/mL and 300-500pg/mL were spiked with each cross reactant at a concentration of 50, 600 or 1000 pg/mL. Results are summarized below.

Cross Reactant	Concentration (pg/mL)	% Cross Reactivity
Adrenomedullin 52 Human	1000	0.17
Aldosterone	1000	0.11
Angiotensin I	600	0.02
Angiotensin II	600	0.13
Angiotensin III	1000	0.37
ANP	1000	0.03
Arg^8-Vasopressin	1000	0.02
CNP	1000	0.00
DNP	1000	0.43
Endothelin	1000	0.08
NT-proBNP	1000	0.05
Renin	50	0.18
Urodilatin	1000	0.00
VNP	1000	5.09

Drug Interference:

Studies were conducted to evaluate the potential interference from therapeutic drugs with the Tosoh ST AIA-PACK BNP assay. Interference testing was performed with 2 different EDTA samples of known BNP concentrations, targeting 100 pg/mL and 300 – 500 pg/mL. The criterion for no interference was defined as a mean percent recovery for each therapeutic within 100±10% of the control. When the substances listed below were tested, no interference was observed up to the concentration listed in the table.

Compound	Highest Concentration Tested With No Interference
Acetaminophen (4-Acetamidophenol)	1456 µmol/L
Acetylsalicylic Acid	200 µg/mL
Allopurinol	240 ug/mL
Amiodarone	4.2 mg/dL
Amlodipine besylate	4 µg/mL
Ampicillin	200 µg/mL
L-Ascorbic Acid	376 µmol/L

Compound	Highest Concentration Tested With No Interference
Atenolol	40 µg/mL
Atorvastatin	32 µg/mL
Biotin	30 µg/mL
Caffeine	10.8 mg/dL
Carvedilol	74 µmol/L
Captopril	40 µg/mL
Chloramphenicol	7.8 mg/dL
Clopidogrel Bisulfate	30 µg/mL
Cyclosporine	40 µg/mL
Diclofenac sodium salt	60 µg/mL
Digitoxin	60 µg/mL
Digoxin	0.0039 mg/dL
(+)-cis-Diltiazem hydrochloride	120 µg/mL
Dipyridamole	30 µg/mL
Disopyramide	1.68 mg/dL
Dobutamine	100 µg/mL
Dopamine hydrochloride	116 µg/mL
Enalaprilat dehydrate (hydrolyzed from enalapril maleate)	16 µg/mL
Erythromycin	13.8 mg/dL
Fenofibrate	45 µg/mL
Furosemide	199 µmol/L
Heparin	330 units/dL
Hydralazine	20 µg/mL
Hydrochlorothiazide	20 µg/mL
Ibuprofen	2425 µmol/L
Indomethacin	36 µg/mL
Isosorbide dinitrate	0.593 mg/dL
Levothyroxine	0.042 mg/dL
Lidocaine	1.5 mg/dL
Lisinopril x 2H2O	16 µg/mL
Losartan potassium	130 µmol/L
Lovastatin	0.021 mg/dL
Methyldopa	100 µg/mL
(±)-Metoprolol (+)-tartrate salt	18.7 µmol/L
Naproxen	2170 µmol/L
Nicotine	1.6 µg/mL
Nicotinic acid	40 µg/mL
Nifedipine	36 µg/mL
Nitrofuratoin	40 µg/mL
Oxazepam	12 µg/mL
Oxytetracycline	100 µg/mL

Compound	Highest Concentration Tested With No Interference
Phenobarbital	69 mg/dL
Phenytoin	6.00 mg/dL
Probenecid	600 µg/mL
Procainamide	4.80 mg/dL
Propanolol	64 µg/mL
Quinidine	20 µg/mL
Ramipril	14.4 µmol/L
Simvastatin	32 µg/mL
Spironolactone	600 µg/mL
Sulfamethoxazole	1.7 µmol/L
Theophylline	6.00 mg/dL
Trymethoprim	64 µg/mL
Verapamil hydrochloride	96 µg/mL
Warfarin	7.5 mg/dL
Trasylol/Aprotinin	100 KIE/mL

High-Dose Hook Effect:
Hook effect was evaluated using one (1) BNP positive EDTA plasma sample spiked to 60,000 pg/mL and diluted 1:2, 1:5, and 1:10 with ST AIA-PACK BNP sample diluting solution. No high dose hook effect was observed when samples up to approximately 50,000 pg/mL of BNP were assayed.

The following information will be included in the limitations section of the labeling.

- The ST AIA-PACK BNP has been designed so that the high dose "hook effect" is not a problem for the vast majority of samples. The "hook effect" phenomenon may occur at BNP concentrations higher than 50,000 pg/mL.

4. Assay Reportable Range:

   4.0 – 2000 pg/mL

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

   Traceability:
   The ST AIA-PACK BNP CALIBRATOR SET contains assigned concentrations of BNP. The assigned value is determined on a lot-by-lot basis and is designed to provide an assay calibration range of 4.0 to 2,000 pg/mL of BNP. The calibrators are prepared through serial dilution of a gravimetrically prepared internal reference standards made with commercially available BNP.

   Sample Stability:
   The sponsor provided data to support sample stability at different temperatures:

   Refrigerated samples 35.6 – 46.4 °F (2 - 8 °C) are stable for up to 8 hours.

Room Temperature samples are stable for up to 3 hours.

Frozen plasma at – 4 °F (-20 °C) are stable for 65 days.

6. Detection Limit:

The CLSI EP17-A guideline was used to design the limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies.

LoB was determined by running sixty replicates of Calibrator 1 (Buffered Solution; Blank Sample) over five days, measuring one run per day, three replicates per run and four lots using the Tosoh ST AIA-PACK BNP assay on one Tosoh AIA-2000 instrument. Non-parametric principle based on ordered values was used.

Low level samples selected from concentrations in the range from 1.3 to 17.0 pg/mL (LoB to 4x LoB) were prepared by dilution of specimens with known BNP concentrations. The samples were assayed in replicates of two (2) over five (5) days on one instrument for a total of ten (10) replicates per sample. The standard deviation (SD) and coefficient of variation (CV%) were calculated.

LoQ was calculated as the functional sensitivity at 20% CV. To determine the functional sensitivity, a precision profile was plotted using the values of CV% and the mean concentration of the samples in pg/mL from the LoD study.

The data provided supports the following claims:

LoB = 0.9 pg/mL

LoD = 1.9 pg/mL

LoQ = 3.5 pg/mL.

7. Assay Cut-Off:

See Clinical Cutoff in Section D.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Not Applicable: see clinical studies in Section C.

2. Matrix Comparison:

Not Applicable: human K2 EDTA plasma is the only sample type claimed for use with this assay.

C Clinical Studies:

1. Clinical Sensitivity:

See section 3 below.

2. Clinical Specificity:

See section 3 below.

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

A study was conducted in the U.S. to support the use of the assay. Compared to clinical studies for previously cleared BNP devices, this study prospectively recruited males and females who presented to the ED with clinical suspicion of new onset HF, acutely decompensated or exacerbated HF. A total of 825 samples were assayed for BNP using the Tosoh AIA 2000 Analyzer were recruited from 8 different ED sites. The analysis is based on 724 patients that met the inclusion criteria and the outcome (new onset HF, acutely decompensated or exacerbated HF) was based on adjudication. The samples were frozen prior to analysis. Data supporting the stability of the samples for the storage time and conditions were provided by the sponsor.

The cross tabulation of results between HF and BNP at the cutoff of 100 pg/mL is below.

Adjudicated	BNP		
	≥100 pg/mL	<100 pg/mL	Total
HF	291	38	329
Not HF	116	279	395
Total	407	317	724

Using the traditional single cutoff of 100 pg/mL, the sensitivity of the ST AIA-PACK BNP assay is 88.4% and the specificity is 70.6%. The Positive Predictive Value (PPV) is 71.5% and the Negative Predictive Value (NPV) is 88.0%.

Measure	Value	Low CI	High CI
Sensitivity	88.4%	84.5%	91.5%
Specificity	70.6%	66.0%	74.9%
Sensitivity + Specificity	159.1%	153.0%	164.3%
Concordance	78.7%	75.6%	81.6%
PPV, CI	71.5%	66.9%	75.7%
NPV, CI	88.0%	84.0%	91.1%
Positive Likelihood Ratio (PLR), CI	3.012	2.572	3.527
Negative Likelihood Ratio (NLR), CI	0.164	0.120	0.222

The performance for the device in the cohort was calculated for age above and below 75 years old. The clinical performance of the ST AIA-PACK BNP assay using the cutoff of 100 pg/mL for the two different age groups is described below.

	Age <75	Age ≥75
Sensitivity **95% CI**	86.9% (172/198) (81.5-90.9%)	90.8% (119/131) (84.7-94.7%)
Specificity **95% CI**	78.1% (218/279) (72.9-82.6%)	52.6% (61/116) (43.6-61.4%)
PPV **95% CI**	73.8% (172/233) (67.8-79.0%)	68.4% (119/174) (61.1-74.8%)
NPV **95% CI**	89.3% (218/244) (84.8-92.6%)	83.6% (61/73) (73.4-90.3%)
Prevalence **95% CI**	41.5% (37.2-46.0%)	53.0% (46.8-59.2%)
1-Prevalence **95% CI**	58.5% (54.0-62.8%)	47.0% (40.8-53.2%)
PLR **95% CI**	3.973 (3.162-4.992)	1.916 (1.570-2.338)
NLR **95% CI**	0.168 (0.117-0.242)	0.174 (0.099-0.307)

The performance for the device in the cohort was calculated for sex. The clinical performance of the ST AIA-PACK BNP assay using the cutoff of 100 pg/mL for males and females is described below.

	Females	Males
Sensitivity **95% CI**	89.1% (122/137) (82.7-93.3%)	88.0% (169/192) (82.7-91.9%)
Specificity **95% CI**	67.4% (128/190) (60.4-73.6%)	73.7% (151/205) (67.2-79.2%)

	Females	Males
PPV **95% CI**	66.3% (122/184) (59.2-72.7%)	75.8% (169/223) (69.8-80.9%)
NPV **95% CI**	89.5% (128/143) (83.4-93.5%)	86.8% (151/174) (80.9-91.0%)
Prevalence **95% CI**	41.9% (36.7-47.3%)	48.4% (43.5-53.3%)
1-Prevalence **95% CI**	58.1% (52.7-63.3%)	51.6% (46.7-56.5%)
PLR **95% CI**	2.729 (2.206-3.375)	3.342 (2.642-4.226)
NLR **95% CI**	0.163 (0.100-0.265)	0.163 (0.110-0.241)

The performance was further broken down by history of heart failure, BMI and Estimated Glomerular Filtration Rate (eGFR) values. The clinical performance is summarized in the following tables.

	History of HF	No History of HF
Sensitivity **95% CI**	89.5% (170/190) (84.3-93.1%)	87.1% (121/139) (80.5-91.6%)
Specificity **95% CI**	44.9% (48/107) (35.8-54.3%)	80.2% (231/288) (75.2-84.4%)
PPV **95% CI**	74.2% (170/229) (68.2-79.5%)	68.0% (121/178) (60.8-74.4%)
NPV **95% CI**	70.6% (48/68) (58.9-80.1%)	92.8% (231/249) (88.9-95.4%)
Prevalence **95% CI**	64.0% (58.4-69.2%)	32.6% (28.3-37.1%)
1-Prevalence **95% CI**	36.0% (30.8-41.6%	67.4% (62.9-71.7%)
PLR	1.623	4.398

	History of HF	No History of HF
95% CI	(1.358-1.938)	(3.456-5.598)
NLR **95% CI**	0.235 (0.147-0.373)	0.161 (0.105-0.249)

	eGFR <60*	eGFR ≥60
Sensitivity **95% CI**	89.4% (135/151) (83.5-93.4%)	87.6% (156/178) (82.0-91.7%)
Specificity **95% CI**	58.7% (54/92) (48.5-68.2%)	74.1% (223/301) (68.9-78.7%)
PPV **95% CI**	78.0% (135/173) (71.3-83.6%)	66.7% (156/234) (60.4-72.4%)
NPV **95% CI**	77.1% (54/70) (66.0-85.4%)	91.0% (223/245) (86.8-94.0%)
Prevalence **95% CI**	62.1% (55.9-68.0%)	37.2% (33.0-41.6%)
1-Prevalence **95% CI**	37.9% (32.0-44.1%)	62.8% (58.4-67.0%)
PLR **95% CI**	2.165 (1.686-2.778)	3.382 (2.772-4.126)
NLR **95% CI**	0.181 (0.110-0.296)	0.167 (0.112-0.248)

* patients with eGFR values < 30 were excluded from the study

	BMI <30	BMI 30-36	BMI ≥37
Sensitivity **95% CI**	96.1% (124/129) (91.2-98.3%)	90.3% (84/93) (82.6-94.8%)	75.3% (64/85) (65.2-83.2%)
Specificity **95% CI**	65.5% (114/174) (58.2-72.2%)	74.2% (72/97) (64.7-81.9%)	74.4% (64/86) (64.3-82.5%)
PPV **95% CI**	67.4% (124/184) (60.3-73.7%)	77.1% (84/109) (68.3-84.0%)	74.4% (64/86) (64.3-82.5%)
NPV **95% CI**	95.8% (114/119) (90.5-98.2%)	88.9% (72/81) (80.2-94.0%)	75.3% (64/85) (65.2-83.2%)
Prevalence **95% CI**	42.6% (37.1-48.2%)	48.9% (41.9-56.0%)	49.7% (42.3-57.1%)
1-Prevalence **95% CI**	57.4% (51.8-62.9%)	51.1% (44.0-58.1%)	50.3% (42.9-57.7%)
PLR **95% CI**	2.788 (2.265-3.431)	3.505 (2.484-4.944)	2.943 (2.012-4.306)
NLR **95% CI**	0.059 (0.025-0.141)	0.130 (0.069-0.245)	0.332 (0.224-0.491)

There are potentially confounding comorbidities that may influence BNP results. These comorbidities include diabetes, renal insufficiency, hypertension (HTN) and/or chronic obstructed pulmonary disease (COPD). Among the 724 patients in the study, 577 patients presented with comorbidities and 147 presented with no comorbidities. Performance of the BNP, broken down by the presence or absence of these comorbidities. In the subset of patients without comorbidities the sensitivity was 89.3% and the specificity was 74.7%. Conversely in the patients with comorbidities the sensitivity and specificity were 88.3% and 69.4% respectively.

	Without comorbidities	With comorbidities
Sensitivity **95% CI**	89.3% (50/56) (78.5-95.0%)	88.3% (241/273) (83.9-91.6%)
Specificity	74.7%	69.4%

	Without comorbidities	With comorbidities
95% CI	(68/91) (64.9-82.5%)	(211/304) (64.0-74.3%)
PPV **95% CI**	68.5% (50/73) (57.1-78.0%)	72.2% (241/334) (67.1-76.7%)
NPV **95% CI**	91.9% (68/74) (83.4-96.2%)	86.8% (211/243) (82.0-90.5%)
Prevalence **95% CI**	38.1% (30.6-46.2%)	47.3% (43.3-51.4%)
1-Prevalence **95% CI**	61.9% (53.8-69.4%)	52.7% (48.6-56.7%)
PLR **95% CI**	3.533 (2.453-5.088)	2.886 (2.423-3.437)
NLR **95% CI**	0.143 (0.067-0.308)	0.169 (0.121-0.236)

The following limitations are in the device labeling:

- This test has low sensitivity (76%) in patients with severe obesity (BMI ≥37). In the study, 24% of patients with an adjudicated diagnosis of new onset heart failure, exacerbated heart failure or acutely decompensated heart failure and a BMI ≥37 had BNP values below the cut-off (false negatives)
- This test has low specificity (59%) in patients with eGFR < 60. In the study, 41% of patients without an adjudicated diagnosis of new onset heart failure, exacerbated heart failure or acutely decompensated heart failure and eGFR < 60 had BNP values above the cut-off (false positives).
- This test has low specificity (53%) in patients in the higher age group (age ≥75). In the study, 47% of patients with an adjudicated diagnosis of new onset heart failure, exacerbated heart failure or acutely decompensated heart failure and aged ≥75 years had BNP values above the cut-off (false positives)
- This test has low specificity (45%) in patients with a history of HF. In the study, 55% of patients with an adjudicated diagnosis of new onset heart failure, exacerbated heart failure or acutely decompensated heart failure and a history of HF had BNP values above the cut-off (false positives)

D Clinical Cut-Off:

As recommended in the American Heart Association guidelines for acute heart failure (Weintraub NL, et al. Acute Heart Failure Syndromes: Emergency Department Presentation, Treatment, and Disposition: Current Approaches and Future Aims: A Scientific Statement from the American

Heart Association. Circulation. 2010; 122:1975-1996.), 100 pg/mL has been used as the cutoff for this assay.

E Expected Values/Reference Range:

To establish the reference range for subjects without HF BNP, concentrations from a total of 430 apparently healthy individuals were evaluated. The descriptive statistics for BNP concentrations in the population without heart failure are shown below.

Age	All	<45	45-54	55-64	65-74	75+
N	430	92	83	88	87	80
Mean pg/ml	34.6	10.4	11.9	15.1	58.1	81.6
SD pg/ml	73.8	11.0	11.2	18.1	106.6	110.2
Median pg/ml	10.8	5.9	7.9	8.5	14.7	39.1
95 percentile pg/ml	143.2	26.0	39.8	42.5	241.2	273.6
% < 100 pg/ml	91.4	100.0	100.0	98.9	82.8	73.8
Minimum pg/ml	<4	<4	<4	<4	<4	<4
Maximum pg/ml	627.5	80.0	51.6	121.3	619.1	627.5

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.