

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY**

**ASSAY ONLY TEMPLATE**

**A. 510(k) Number:**

k061795

**B. Purpose for Submission:**

New device

**C. Measurand:**

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

**D. Type of Test:**

Quantitative

**E. Applicant:**

Dade Behring, Inc.

**F. Proprietary and Established Names:**

Dimension® Vista™ NT-proBNP (PBNP) Flex® reagent cartridge method

Dimension® Vista™ NT-proBNP (PBNP) calibrator

**G. Regulatory Information:**

1. Regulation section:

21 CFR 862.1117, B-type natriuretic peptide test system

21 CFR 862.1150, Calibrator secondary

2. Classification:

Class II

3. Product code:

NBC; JIT

4. Panel:

75 Chemistry

**H. Intended Use:**

1. Intended use(s):

See Indications for use below.

2. Indication(s) for use:

The PBNP method is an *in vitro* diagnostic assay for the quantitative measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human serum and plasma on the Dimension Vista™ System. In individuals suspected of having congestive heart failure (CHF), measurements of NT-proBNP are used as an aid in the diagnosis and assessment of severity. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure.

The Dimension Vista NT-proBNP(PBNP) calibrator is an *in vitro* diagnostic product for the calibration of the N-terminal pro-brain natriuretic peptide (PBNP) method on the Dimension Vista™ System.

3. Special conditions for use statement(s):

Prescription use

4. Special instrument requirements:

Dade Behring Dimension Vista™ Integrated System

**I. Device Description:**

The Flex® reagent cartridge contains reagents for 80 tests (2 x 40/catridge). Reagents contains biotinylated antibody, NT-proBNP Chemibeads, Streptavidin Sensibeads, and assay buffer in the following configuration:

Wells	Form	Ingredient	Concentration	Quantity	Source
1-2	Liquid	Biotinylated Antibody	9 µg/mL	670 µL	Sheep polyclonal
3-4	Liquid	NT-proBNP Chemibeads	150 µg/mL	670 µL	Sheep polyclonal
7-8	Liquid	Streptavidin Sensibead	1400 µg/mL	565 µL	Recombinant <i>E. coli</i>
9-12	Liquid	Assay Buffer	na	1300 µL	

The NT-proBNP (PBNP) Calibrator is a frozen liquid product containing synthetic human N-terminal pro-brain natriuretic peptide in a bovine albumin matrix with stabilizers and preservative. The kit consists of eight vials, two each of four levels (A, B, C and D), 1.0 mL per vial for levels A, C and D and 1.5mL per vial for level B.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

Roche Diagnostics Elecsys® proBNP Immunoassay

2. Predicate 510(k) number(s):

k022516

3. Comparison with predicate:

Similarities		
Item	Dimension® Vista™ NT-proBNP (PBNP) Flex®	Roche NT-proBNP
Assay type	Immunoassay (chemiluminescent)	Immunoassay (electrochemiluminescent)
Antibody	Polyclonal sheep antibody	Polyclonal sheep antibody
Cut-off	125 pg/mL for patients <75 years 450 pg/mL for patients ≥ 75 years	125 pg/mL for patients <75 years 450 pg/mL for patients ≥ 75 years Roche NT-proBNP antibody 5 – 35,000 pg/mL
Reference	Roche NT-proBNP antibody	
Reportable range	5-35,000 pg/mL	
Differences		
Item	Dimension® Vista™ NT-proBNP (PBNP) Flex®	Roche NT-proBNP
Indications for Use	The PBNP method is an in vitro diagnostic assay for the quantitative measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human serum and plasma on the Dimension Vista System. In individuals suspected of having congestive heart failure (CHF), measurements of NT-proBNP are used as an aid in the diagnosis and assessment of	For the <i>in vitro</i> quantitative determination of NT-proBNP in human serum and plasma. The Elecsys proBNP assay is used as an aid in the diagnosis of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and congestive heart failure.

	severity. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure.	
Sample volume	8 µL	20 µL

**K. Standard/Guidance Document Referenced (if applicable):**

CLSI EP5-A2; CLSI EP7-A; CLSI EP9-A; and Class II Special Controls Guidance Document for B-Type Natriuretic Peptide Premarket Notifications: Final Guidance for Industry and FDA Reviewers (11/30/2000)

**L. Test Principle:**

The PBNP method is a one-step sandwich chemiluminescent immunoassay based on Luminescent Oxygen Channeling Immunoassay (LOCI™) technology. LOCI™ reagents include two latex bead reagents and a biotinylated polyclonal antibody fragment which recognize an epitope located in the N-terminal part of proBNP. The first bead reagent (Sensibeads) is coated with streptavidin and contains photosensitive dye. The second bead reagent (Chemibeads) is coated with a second antibody specific for a second independent epitope on NT-proBNP and contains chemiluminescent dye. Sample is incubated with Chemibeads and biotinylated antibody to form a particle/NT-proBNP/biotinylated antibody sandwich. Sensibeads then are added and bind to the biotin to form a bead-aggregated immunocomplex. Illumination of the complex by light at 680 nm generates singlet oxygen from Sensibeads, which diffuses to the Chemibeads and triggers a chemiluminescent reaction. The resulting chemiluminescent signal is measured at 612 nm and is directly proportional to the concentration of NT-proBNP in the sample.

**M. Performance Characteristics (if/when applicable):**

1. Analytical performance:

*a. Precision/Reproducibility:*

CLSI EP5-A2 was used. During each day of testing, two separate runs, with two test samples, for each test material, were analyzed for 20 days. The results are presented in the table below.

Material	Mean pg/mL	Standard Deviation (%CV)			
		Repeatability	Within-Lab		
Serum Pool 1	124	3.04	2.5	5.49	4.4
Serum Pool 2	470	7.55	1.6	14.14	3.0
Serum Pool 3	2047	31.93	1.6	56.91	2.8
Internal QC Pool 1	11407	174.72	1.5	223.60	2.0
Internal QC Pool 2	26038	476.16	1.8	628.00	2.4
Bio-Rad LT Level 1	334	5.68	1.7	8.84	2.6

*b. Linearity/assay reportable range:*

The assay reportable range is 5-35,000 pg/mL. A patient plasma sample with a high NT-proBNP concentration was diluted across the assay range. An additional plasma sample was diluted linearly to confirm dilutional accuracy at the low end of the assay range. All samples were diluted with low level patient plasma pools.

The following table summarizes the results of these studies:

	Sample A	Sample B
Starting Concentration (pg/mL)	40500	1147
<b>Regression Statistics</b>		
Slope	1.007	1.002
Intercept	-425.2	11.0
Correlation Coefficient	0.999	0.999
N	5	5
<b>% Recovery</b>		
Average	98	102
Range	94-100	100-105

Hook effect was evaluated using samples containing NT-proBNP concentrations ranging from 0 to 400,000 pg/mL. The samples were prepared with Roche synthetic antigen spiked into 5% bovine serum base material. No hook effect was found up to 400,000 pg/mL.

*c. Traceability, Stability, Expected values (controls, calibrators, or methods):*

The assay is referenced to Roche purified synthetic NT-proBNP (1-76). The assigned values for the Dimension Vista Calibrator are referenced to a master pool containing synthetic human N-terminal pro-brain natriuretic peptide.

Un-open calibrators stored frozen at -20 to -10° C are stable until the stated expiration date. Calibrator stability is determined using Dade Behring's shelf life stability protocol and is ongoing. Open vial stability was set at 7 days to be consistent with other Dimension Vista® system calibrators, although

stability studies demonstrated that the calibrators were stable for longer than 7 days.

*d. Detection limit:*

The analytical sensitivity of the PBNP method is  $\leq 5$  pg/mL. Analytical sensitivity is defined as the concentration at two standard deviations (N=20) above a sample devoid of NT-proBNP, such as the PBNP Level 1 Calibrator (0 pg/mL). The analytical sensitivity was determined by assaying 20 consecutive replicates of the 0 pg/mL level calibrator. The analytical sensitivity was then calculated by determining the standard deviation (SD) of the 20 replicates, multiplying by 2 and adding it to the absolute value of the mean. The analytical sensitivity of the Dimension Vista PBNP method was 1.186. A claim of  $\leq 5$  pg/mL will be used to account for instrument variability.

Functional sensitivity for NT-proBNP is defined as the analyte detection concentration corresponding to a 20% CV. This was determined by performing a 20 day ANOVA experiment using samples prepared from normal human serum. Two replicates of each sample were analyzed once per day for 20 days. Total % CV was plotted vs. the target PBNP concentration. Although the functional sensitivity was determined to be 7 pg/mL, a claim of  $\leq 30$  pg/mL will be used to account for instrument to instrument variability.

*e. Analytical specificity:*

The NT-proBNP assay was evaluated for interference according to CLSI EP7-A. The following substances demonstrated no significant bias (defined as  $< 10$  %).

Substance Tested	Substance Concentration	NT-proBNP Concentration pg/mL	Bias %
Hemoglobin	680 mg/dL	114	-8.15
Bilirubin (unconjugated)	60 mg/dL	114	-5.77 %
Bilirubin (conjugated)	60 mg/dL	115	-6.52 %
Lipemia Intralipid®)	3000 mg/dL	121	1.96

An extensive list of other compounds was evaluated for interference and was found to have no significant interference or cross reactivity. A list of these compounds is present in the product labeling. The following substances have no significant cross-reactivity (less than 1 %) at the concentrations indicated when added to samples containing 0 and approximately 125 pg/mL NT-proBNP:

<b>Substance</b>	<b>Concentration</b>
ANP <sub>28</sub>	3.1 µg/mL
NT-proANP <sub>1-30</sub> (preproANP <sub>26-55</sub> )	3.5 µg/mL
NT-proANP <sub>31-67</sub> (preproANP <sub>56-92</sub> )	1.0 ng/mL
NT-proANP <sub>79-98</sub> (preproANP <sub>104-123</sub> )	1.0 ng/mL
BNP <sub>32</sub> (Natrecor <sup>®</sup> )	3.5 µg/mL
CNP <sub>32</sub>	2.2 µg/mL
DNP	1.0 ng/mL
VNP	1.0 ng/mL
Adrenomedullin	1.0 ng/mL
Aldosterone	1.0 ng/mL
Angiotensin I	1.0 ng/mL
Angiotensin II	0.6 ng/mL
Angiotensin III	0.6 ng/mL
Endothelin	0.6 ng/mL
Renin	1.0 ng/mL
Urodilatin	20 pg/mL
Arg-Vasopressin	50 ng/mL

*f. Assay cut-off:*

See clinical studies below. The recommended medical decision thresholds are the same as those recommended by the predicate device. They are by age group as follows:

Patients <75 years      125 pg/mL

Patients ≥ 75 years      450 pg/mL

2. Comparison studies:

*a. Method comparison with predicate device:*

A split sample comparison study was performed between the Dimension Vista NY-proBNP assay and the predicate Roche Elecsys proBNP assay with serum and heparinized plasma patient samples. CLSI EP9-A was used. Samples were obtained from patients known to have CHF (n = 269) and patients with no history available (n = 150). The range of NT-proBNP values in the correlation study was 5.1 to 32,779 pg/mL.

**Regression Statistics**

<b>Comparative Method</b>	<b>Slope</b>	<b>Intercept pg/mL</b>	<b>Correlation Coefficient</b>	<b>n</b>
Roche Elecsys <sup>®</sup>	1.018	3.616	0.99	411

b. *Matrix comparison:*

Comparison of 50 matched serum and lithium heparin plasma samples with values ranging from 33.2 pg/mL to 35,925 pg/mL on the Dimension Vista system gave a slope of 1.00, an intercept of -32.3, and a correlation coefficient of 0.999 using linear regression statistics.

Comparison of 72 matched serum and EDTA plasma samples with values ranging from 7.8 pg/mL to 29,272 pg/mL on the Dimension Vista system gave a slope of 0.99, an intercept of 2.3, and a correlation coefficient of 0.999 using linear regression statistics.

3. Clinical studies:

a. *Clinical Sensitivity:*

Clinical Studies: For the Reference Study Group, NT-proBNP concentrations were determined in 318 individuals without congestive heart failure (163 women and 155 men). This population included apparently healthy individuals and individuals with diabetes, hypertension, and pulmonary disease. For the Disease Study Group, NT-proBNP concentrations were determined in 269 patients diagnosed with congestive heart failure (CHF). This population included 78 women and 191 men.

The tables below show the clinical sensitivity and specificity of the Dimension Vista PBNP assay using a cutoff of 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years or older.

Males		
	<75 yrs	≥75 yrs
Sensitivity	94% (133/142)	96% (47/49)
95% Confidence Interval	90 – 98	90 – 100
Specificity	87% (81/93)	73% (45/62)
95% Confidence Interval	80 - 94	61 – 84

Females		
	<75 yrs	≥75 yrs
Sensitivity	89% (54/61)	88% (15/17)
95% Confidence Interval	81 – 97	73 – 100
Specificity	92% (95/103)	85% (51/60)
95% Confidence Interval	87 – 97	76 – 94



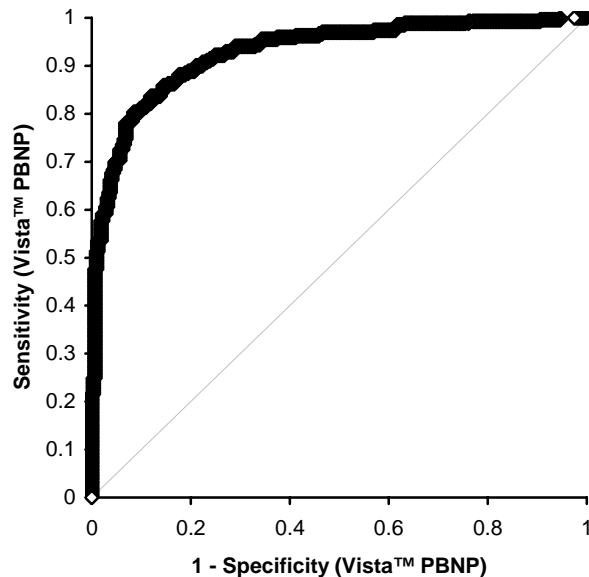
*b. Clinical specificity:*

See Clinical sensitivity section above.

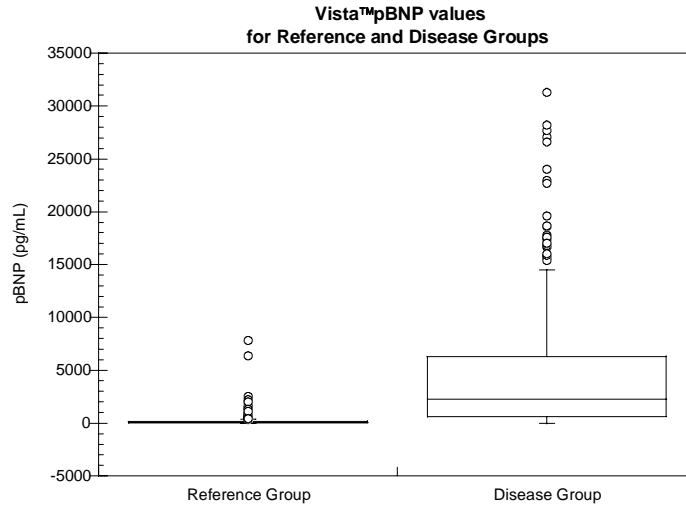
c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off:

The Receiver Operator Characteristics (ROC) Curve presents the clinical sensitivity and specificity at various cutoffs for the 269 patients diagnosed with CHF and 318 subjects without CHF. The ROC curve for the Dimension Vista PBNP assay is shown below. The area under ROC curve (AUC) for the Dimension Vista™ PBNP assay is 0.928 with a 95% confidence interval of 0.907 to 0.949.



A box and whiskers plot of the clinical study population is presented below. Recommended clinical thresholds are 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older.



5. Expected values/Reference range:

NT-proBNP concentrations in the Reference Group are shown in the following tables. The recommended medical decision thresholds, by age group, are:

Patients < 75 years    125 pg/mL

Patients ≥ 75 years    450 pg/mL

Reference Study Group

NT-proBNP concentrations were determined in 318 individuals without congestive heart failure (163 women and 155 men). This population included apparently health individuals and individuals with diabetes, hypertension, and pulmonary disease. The statistics for NT-proBNP concentrations in the reference study group are shown in the following table.

Reference Study Group

All				
	<55 yrs	55 - 64 yrs	65 – 74 yrs	≥ 75 yrs
Mean	45.9	54.6	175.5	451.3
SD	53.6	62.3	197.6	987.1
Median	27.2	28.8	106.2	173.5
95 <sup>th</sup> Percentile	131.2	206.6	880.8	1615.7
% < 125 pg/mL	94%	80%	61%	-
% < 450 pg/mL	-	-	-	79%
N	163	15	18	122

Males				
	<55 yrs	55 - 64 yrs	65 – 74 yrs	≥ 75 yrs
Mean	39.0	56.7	219.4	520.8
SD	57.8	58.2	242.4	1080.9
Median	16.6	25.4	123.6	173.5
95 <sup>th</sup> Percentile	168.8	154.7	880.8	1969.7
% < 125 pg/mL	93%	83%	55%	-
% < 450 pg/mL	-	-	-	73%
N	76	6	11	62

Females				
	<55 yrs	55 - 64 yrs	65 – 74 yrs	≥ 75 yrs
Mean	51.9	53.2	106.6	379.5
SD	49.2	68.3	60.8	883.1
Median	39.4	28.8	87.7	167.3
95 <sup>th</sup> Percentile	124.0	206.6	215.2	1453.2
% < 125 pg/mL	95%	78%	71%	-
% < 450 pg/mL	-	-	-	85%
N	87	9	7	60

### Disease Study Group

Blood samples were obtained from 269 patients diagnosed with congestive heart failure (CHF). The population included 78 women and 191 men. The descriptive statistics and New York Heart Association (NYHA) functional classes are provided below.

CHF Population – All				
	<55 yrs	55 – 64 yrs	65 – 74 yrs	≥75 yrs
Mean	6131.8	4455.5	6168.1	8142.7
SD	13470.3	9296.0	10950.5	12699.1
Median	1550.9	1639.5	2541.3	3780.5
95 <sup>th</sup> Percentile	28099.6	19481.5	17768.6	26923.1
% > 125 pg/mL	89%	92%	95%	-
% > 450 pg/mL	-	-	-	94%
N	72	72	59	66

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CHF Population – Males

	<55 yrs	55 – 64 yrs	65 – 74 yrs	≥75 yrs
Mean	7771.4	4954	6537.2	8827.3
SD	15797.2	10536.7	12383.9	12856.6
Median	2526.1	1699.8	2541.3	5529.2
95 <sup>th</sup> Percentile	31237.1	19481.5	17768.6	18634.8
% > 125 pg/mL	94%	94%	93%	-
% > 450 pg/mL	-	-	-	96%
N	48	51	43	49

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CHF Population – Females

	<55 yrs	55 – 64 yrs	65 – 74 yrs	≥75 yrs
Mean	2852.6	3244.9	5176.1	6169.7
SD	5774.0	5200.7	5727.8	12397.4
Median	452.3	1516.9	2270.8	1125.3
95 <sup>th</sup> Percentile	15569.3	7903.1	16889.9	45824.4
% > 125 pg/mL	79%	86%	100%	-
% > 450 pg/mL	-	-	-	88%
N	24	21	16	17

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CHF Population – All

NYHA Functional Class					
	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Mean	6184.5	3941.9	3648.8	6643.1	11089.2
SD	11737.8	8461.3	4897.0	13567.0	14428.2
Median	2282.2	1161.0	1091.7	2541.3	4537.7
5 <sup>th</sup> Percentile	101.1	100.4	46.6	143.1	74.6
95 <sup>th</sup> Percentile	22331.9	14184.1	14238.5	17497.1	28099.6
% > Cutoff	92%	93%	90%	94%	88%
Minimum	5.1	52.8	24.5	5.1	39.6
Maximum	91446.4	52327.0	18634.8	91446.4	78045.2
N	269	45	60	124	40

### CHF Population – Males

NYHA Functional Class					
	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Mean	7012.1	4567.5	4402.2	7298.4	14351.2
SD	12991.9	9204.3	5167.4	14789.5	17258.9
Median	3162.6	1639.5	2230.9	3442.2	6015.9
5 <sup>th</sup> Percentile	126.1	136.3	46.5	126.1	101.1
95 <sup>th</sup> Percentile	24004.7	19481.5	14238.5	17497.1	31237.1
% > Cutoff	94%	97%	93%	95%	91%
Minimum	5.1	72.5	44.7	5.1	74.6
Maximum	91446.4	52327.0	18634.8	91446.4	78045.2
N	191	37	40	91	23

### CHF Population – Females

NYHA Functional Class					
	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Mean	4157.8	1048.3	2142.1	4836.0	6676.0
SD	7561.7	1636.1	4008.9	9366.5	7864.9
Median	950.2	225.4	705.3	1286.7	3780.5
5 <sup>th</sup> Percentile	84.3	52.8	24.5	143.1	39.6
95 <sup>th</sup> Percentile	22331.9	4960.2	11020.8	26923.1	22997.0
% > Cutoff	87%	75%	85%	94%	82%
Minimum	24.5	52.8	24.5	126.8	39.6
Maximum	45824.4	4960.2	15893.8	45824.4	22997.0
N	78	8	20	33	17

The results demonstrate a relationship between the severity of the clinical signs and symptoms of CHF and the median NT-proBNP concentration.

### N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

**O. Conclusion:**

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