510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k073091

B. Purpose for Submission:

Addition of NT-proBNP to bioMerieux VIDAS instruments

C. Measurand:

N-terminal pro-B type Natriuretic Peptide

D. Type of Test:
Quantitative, enzyme-linked fluorescent assay (ELFA)

E. Applicant:

bioMerieux, Inc

F. Proprietary and Established Names:

VIDAS® NT-proBNP

G. Regulatory Information:

1. Regulation section:

   21 CFR § 862.1117 B-type natriuretic peptide test system

2. Classification:

   Class II (special controls)

3. Product code:

   NBC

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:

   VIDAS® NT-proBNP assay is an automated quantitative test for use on the VIDAS instruments for the determination of N-terminal fragment of B-type natriuretic peptide in human serum or plasma (lithium heparin) using the ELFA (Enzyme-Linked Fluorescent Assay) technique. The VIDAS® NT-proBNP test is used as an aid in the diagnosis of suspected congestive heart failure.

3. Special conditions for use statement(s):

   For prescription use

4. Special instrument requirements:

   bioMerieux VIDAS and miniVIDAS instruments

I. Device Description:

Each VIDAS® NT-proBNP (PBNP) kit contains 60 tests. The kit is comprised of: 60 PBNP Reagent Strips, 60 Solid Phase Receptacles (SPR), PBNP controls (C1 and C2), PBNP calibrators (S1 and S2), Sample Diluent, and one Master Lot Entry (MLE) Card.

The PBNP Reagent Strips consist of 10 wells covered with a labeled foil seal. Five of the wells contain either conjugate (alkaline phosphatase-labeled polyclonal sheep anti-NT-proBNP antibody and preservative), wash buffer, or a cuvette with substrate (4-Methyl-umberlliferyl phosphate, dietholamine, and preservative). One well is designated for the sample and the remaining wells are empty.

The interior of the Solid Phase Receptacles (SPR) are coated with sheep polyclonal NT-proBNP antibody.

The PBNP controls (C1 and C2) are supplied with the kit as four, 2 mL vials of lyophilized human serum, NT-proBNP, and preservative; 2 vials of C1 and 2 vials of C2.

The PBNP calibrators (S1 and S2) are supplied with the kit as four, 2 mL vials of lyophilized human serum, NT-proBNP, and preservative; 2 vials of C1 and 2 vials of C2.

The PBNP diluent is ready-to-use as one 2 mL vial and contains human serum with

preservatives.

Human source material was tested and found negative for HIV-1/2, HBsAg, and HCV by FDA or European Union approved methods.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Roche Elecsys pro-BNP Immunoassay

2. Predicate K number(s):

   k022516

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Quantitative determination of N-terminal fragment of B-type natriuretic peptide in human serum or lithium heparin plasma. The VIDAS NT-proBNP test is used as an aid in the diagnosis of suspected congestive heart failure	Same as initial claim by Roche (k022516)
Antibody	Sheep NT-proBNP antibody	Same
Cut-off	125 pg/mL for patients < 75 years old 450 pg/mL for patients ≥ 75 years old	Same
Specimen Type	Serum and plasma	Same

Differences		
Item	Device	Predicate
Assay Principle	Enzyme-Linked Fluorescent Assay (ELFA)	Electrochemiluminescence
Sample Volume	200 mcL	20 mcL
Hook Effect	No hook effect found up to 500,000 pg/mL	No hook effect found up to 300,000 pg/mL
Measurement range	20-25,000 pg/mL	5-35,000 pg/mL
Traceability	Roche NT-proBNP	Purified synthetic NTG-proBNP (1-76) in human serum matrix

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

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation

CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples

CLSI EP6-A: Evaluation of Linearity of Quantitative Measurement Procedures: A Statistical Approach

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

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 FDA Staff (April 25, 2006)

L. Test Principle:

The VIDAS® NT-proBNP Assay is one-step, sandwich enzyme-linked fluorescent immunoassay (ELFA) performed with an automated VIDAS or a miniVIDAS instrument. A pipette tip-like disposable device, the Solid Phase Receptacle (SPR), serves as the solid phase as well as a pipettor for the assay. Reagents for the assay are pre-dispensed in the sealed PBNP Reagent Strips.

All assay steps and assay temperatures are controlled by the instrument. The sample is transferred into the wells containing the conjugate (alkaline phosphatase-labeled sheep polyclonal NT-proBNP antibody). The sample and conjugate mixture is cycled in and out of the SPR several times. Unbound sample is removed from the SPR during the wash step. During the detection step, the fluorescent substrate (4-Methyl-umberlliferyl phosphate) is cycled in and out of the SPR. The conjugate enzyme remaining in the SPR catalyzes the hydrolysis of the substrate into a fluorescent product 4-methylumbellferone. Fluorescence is measured at 450 nm wavelength by the optical scanner in the instrument. The intensity of the fluorescence is directly proportional to the concentration of analyte present in the sample.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

a. Precision/Reproducibility:

The precision study was performed over 10 days using five samples covering the measurement range (116.58, 508.55, 1407.06, 7,126.53, 14,528.62) assayed in duplicate in 40 different runs (2 runs per day) with two reagent lots using the same VIDAS instrument at three different sites—2 European and 1 US. Each site performed modified randomized precision studies following CLSI EP5-A2 Guidelines. 80 values per sample were generated per site (n=240 values for each sample). The results presented below were evaluated for the following: repeatability, between-run within-day precision, between-day within-site precision, between-site within-lot precision, and lot-to-lot precision.

Source of Variation	Statistics Mean (pg/mL)	C001 116.85	C002 513.47	C003 1066.82	C004 7143.73	C005 14528.62
Repeatability or within-run	SD (pg/mL)	2.84	8.29	16.38	179.03	408.49
	CV (%)	2.43	1.61	1.54	2.51	2.81
Run-to-run or between-run	SD (pg/mL)	4.32	13.26	22.60	230.71	543.08
	CV (%)	3.69	2.58	2.12	3.23	3.74
Day-to-day or between-day	SD (pg/mL)	4.48	14.52	26.05	242.09	602.08
	CV (%)	3.84	2.83	2.44	3.39	4.14
Inter-site or site-to-site or between site	SD (pg/mL)	5.13	18.84	35.71	278.39	743.47
	CV (%)	4.39	3.67	3.35	3.90	5.12
Inter-lot or lot-to-lot Or between-lot	SD (pg/mL)	6.32	21.43	37.79	599.82	1083.20
	CV (%)	5.41	4.17	3.54	8.40	7.46

b. Linearity/assay reportable range:

The reportable range is 20-25,000 pg/mL. 2 samples were tested for linearity. One sample was a high pool (28,459 pg/mL) and the other was a lower pool (1583 pg/mL). Each pool was diluted 13 times using the reagent kit diluent, and a pool of human samples mixed with other samples in variable proportions to cover the measurement range down to 30 pg/mL. Samples were assayed in duplicate. 30 pg/mL was the lowest concentration obtainable because the diluent is composed of human serum pool with preservatives so there is always some NT-proBNP present. The percent deviation from linearity was 10%.

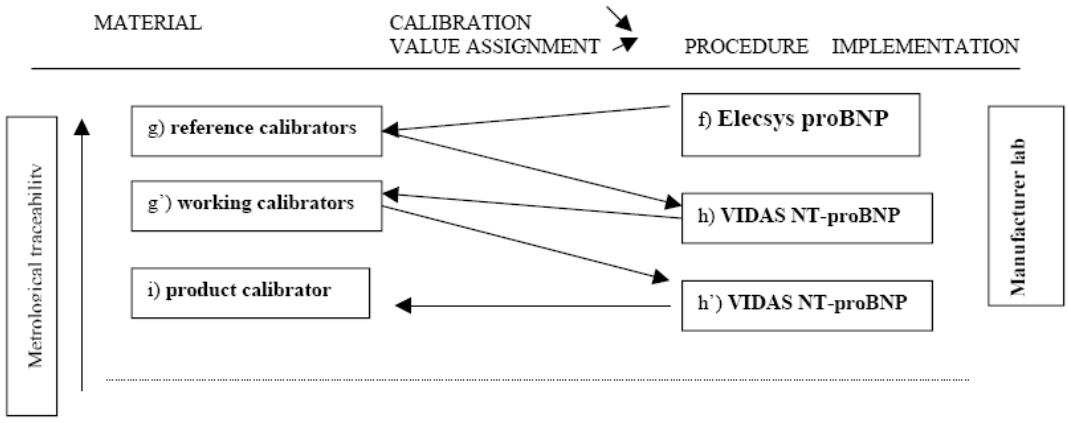
Recovery studies were performed on samples with NT-proBNP concentrations of 70-24,400 pg/mL. Recoveries ranged from 86.9.0% to 112.9%.

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

Traceability

The assay is metrologically traceable to Roche purified synthetic NT-proBNP

using a modification of ISO 17511.



Stability

The calibrators and controls are lyophilized and are stable for 12 months when stored at 2-8°C. After reconstitution, they are stable for up to 8 hours at 2-8°C or up to the expiration date of the kit when stored at -25±6°C. Calibrators and controls may be frozen and thawed up to 6 times.

The stability protocols and acceptance criteria were reviewed and found to be acceptable.

d. Detection limit:

Four samples were analyzed over a period of 4 days on one instrument using one lot of reagents. They consisted of 2 standards, a blank containing no NT-proBNP, and a high standard with a concentration of 51.8 pg/mL of NT-proBNP. Two low level samples with values of 13.64 pg/mL and 14.16 pg/mL were also analyzed.

Limit of Blank (LoB) was defined as corresponding to the 95th percentile of blank signal values. 6 replicates were assayed 10 times for n=60. Based on the sponsor's analysis and acceptance criteria, the LoB = 3.4 pg/mL.

Limit of Detection (LoD) was defined as the concentration corresponding to the signals from the two low level samples along a curve drawn between the blank and the high standard, rounded to the upper value. 2 replicates of each sample were assayed 15 times for a total of 30 measurements per sample (n=60). The LoD signal for the two samples was calculated using the formula LoD = LoB signal + c_β SDs where the SDs are the estimated pooled standard deviation of the low level sample signals and c_β is derived from the 95th percentile of the standard Gaussian distribution and corrected for degrees of freedom of the estimated standard deviations. Based on the sponsor's analysis

and acceptance criteria, the LoD = 6.7 pg/mL. The sponsor claims a limit of detection of < 20 pg/mL.

Limit of Quantitation (LoQ) was defined as the lowest concentration that can be measured with an inter-assay CVof 20%. Twelve samples ranging from 10 to 39 pg/mLwere tested in duplicate on one instrument for 9 days over a period of 15 days. The value obtained for LoQ was 21.9 pg/mL.

e. Analytical specificity:

Analytical specificity (cross-reactivity) was evaluated by spiking each cross-reactant into serums containing target concentrations of 0, 255, 1483 pg/mL NT-proBNP. A control for each cross-reactant was prepared by spiking the samples with the same volume of the solvent used for reconstituting the cross-reactant. The cross-reactant test samples and the control samples were measured on the VIDAS and the cross-reactivity was calculated. Acceptance criteria was the percent of cross-reactivity must be < 0.1% for all samples, interference ratios are within 99.8% confidence interval (CI) for the within lot precision profile. The following compounds do not cross-react.

Tested compound	Tested concentration	Cross-reactivity %
Adrenomodullin	1.0 ng/mL	< 0.1%
Aldosterone	0.6 ng/mL	< 0.1%
Angiotensin I	0.6 ng/mL	< 0.1%
Angiotensin II	0.6 ng/mL	< 0.1%
Angiotensin III	1.0 ng/mL	< 0.1%
ANP_{28},	3.1 µg/mL	< 0.1%
Arg-vasopressin	1.0 ng/mL	< 0.1%
BNP_{32}	3.5 µg/mL	< 0.1%
CNP_{22}	2.2 µg/mL	< 0.1%
Endothelin	20 pg/mL	< 0.1%
NT-proANP$_{1-30}$	3.5 µg/mL	< 0.1%
NT-proANP$_{31-67}$	1.0 ng/mL	< 0.1%
NT-proANP$_{79-98}$	1.0 ng/mL	< 0.1%
Renin	50 ng/mL	< 0.1%
Urodilatin	3.5 µg/mL	< 0.1%

Interference from endogenous substances were evaluated for hemoglobin, triglycerides, bilirubin, human serum albumin (HSA), human IgG, IgM, rheumatoid factors (RF), anti-alkaline phosphatase (anti-ALP) and dialysis patients.

Hemoglobin, Bilirubin, Triglycerides

Samples containing approximately 24, 325, 3600 and 14,500 pg/mL NT pro-BNP were spiked with the appropriate concentration of the test substance. NT-proBNP recovery of the sample was compared to that of a control sample. Hemoglobin up to 300 micM (485 g/dL), bilirubin up to 510 micM (29 mg/dL), and triglycerides up to 30 g/L did not interfere with the test. As a further precaution, the device labeling recommends that samples appearing hemolyzed, icteric, or lipemic not be used and that, if possible, a new sample be collected.

HSA, IgG, IgM, rheumatoid factors, anti-ALP and dialysis samples

Recovery studies were performed to determine interference from HSA, IgG, IgM, RF, anti-ALP and dialysis. A NT-proBNP positive sample (1278.6-1585.8 pg/mL) and a NT-proBNP negative sample (<20-39.8 pg/mL) were used for the studies. There was no IgG, or IgM interference at 1.7 g/dL and 0.6 g/dL respectively.

HSA was evaluated at three doses, 10.5 g/dL, 14.5 g/dL and 19.5 g/dL in the negative and positive NT-proBNP samples. The negative NT-proBNP sample showed interference at the 10.5 g/dL dose of HSA. There was no interference in the positive NT-proBNP sample.

Recovery studies were performed for rheumatoid factor-positive samples, dialysis samples and anti-alkaline phosphatase samples using positive and negative NT-proBNP samples. Dialysis and the anti-alkaline phosphatase (ant-ALP) samples were evaluated by spiking them with known concentrations of the positive and negative NT-proBNP samples from above. These were compared to a "reference sample" composed of a mixture of the positive and negative NT-proBNP samples.

Interferent	Interferent dose range	Recovery range of all samples
Rheumatoid factor	40 IU/mL-1,560 IU/mL	84.6%-101.9%
Dialysis	NA	88.2%-102.1%
Anti-ALP	NA	88.4%-94.4%

Drug Interference

The effect of 39 frequently administered drugs was tested *in vitro*. No interference was observed.

f. Assay cut-off:

Assay cutoffs were established based on the Roche Elecsys proBNP assay which the VIDAS assay claims traceable to.

125 pg/mL for < 75 years old

450 pg/mL for > 75 years old

2. Comparison studies:

a. Method comparison with predicate device:

713 clinical samples from 3 sites were analyzed on the VIDAS and the predicate device, Roche Elecsys across the measurement range of 20-25,000 pg/mL. For method comparison against the predicate, 104 samples were included although they had values <20 pg/mL or were beyond the measurement range and had to be diluted. 224 samples were from a biochemical laboratory in Europe (Site 1), 203 samples from a European hospital (Site 2) and 182 samples from a medical center in the USA (Site 3). Slope = 0.905 and intercept = -14.599 for the combined sites met the sponsor's acceptance criteria of 95% confidence interval (slope 0.896-0.915, intercept -19.031 – -12.120). r = 0.989.

Total concordance between the VIDAS and the predicate using the 713 clinical samples at the cutoffs of 125 pg/mL for subjects < 75 years old and 450 pg/mL for subjects > 75 years old are shown in the table below.

Concordance-all sites combined

		Elecsys pro- BNP		
		+	-	Total
VIDAS	+	505	1	506
NT-proBNP	-	15	192	207
Total		520	193	713

Concordance met the sponsor's acceptance criteria of 95% confidence interval.

Negative Percent Agreement = 97.12% (95.29%-98.38%)

Positive Percent Agreement = 99.48% (97.15%-99.99)

Overall Agreement = 97.76% (96.38%-98.71%)

b. Matrix comparison:

In order to demonstrate equivalence between serum and plasma, three different tube types, gel separator, EDTA, and lithium heparin, were compared to a plain tube (no anticoagulants or gel). Two manufacturers' products were used. 63 patient samples were collected. Samples were native and spiked to cover the entire measurement range (<20-24,499.2 pg/mL).

Results were compared to those of the plain tube. Passing and Bablock regression data of lithium heparin plasma and gel separator tubes to the plain tubes had slopes of 0.98 and1.00, intercepts of -2.2 and 7.2 respectively. The sponsor's acceptance criteria were: slope 0.9-1.1, intercept < 20 pg/mL, CV > 0.95. Based on these studies it was determined that the gel separator (serum) or lithium heparin were appropriate preservatives. EDTA showed nonconformity and is not recommended for use in the labeling.

3. Clinical studies:

Clinical studies were performed at 3 sites, 2 European and 1 US, which represented 407 samples with confirmed congestive heart failure (CHF). 147 samples were from European Site 1, 139 samples were from European Site 2, and 119 were from the US Site. The reference group consisted of 411 samples from prospective subjects that presented to the Emergency Department or Clinical Investigation Center at a European site with neither a history of CHF nor cardiac nor circulatory diseases. Sensitivities, specificities and positive and negative predictive values are shown with the 95% CI and are broken down by site, age and gender.

a. Clinical Sensitivity:

European Site 1

Statistics	All patients	< 75 yrs.	≥ 75 yrs.
Sensitivity (%)	94.63 (89.64-97.29)	100 (94.81-100)	89.47 (80.36-94.64)
Specificity (%)	97.39 (93.36-99.00)	97.27 (92.14-99.09)	97.67 (87.63-99.6)

European Site 2

Statistics	All patients	< 75 yrs.	≥ 75 yrs.
Sensitivity (%)	94.96 (89.84-97.57)	94.23 (84.08-98.06)	95.4 (88.58-98.23)
Specificity (%)	96.69 (92.37-98.6)	96.36 (90.87-98.6)	97.56 (87.09-99.58)

US Site

Statistics	All patients	< 75 yrs.	≥ 75 yrs.
Sensitivity (%)	84.87 (77.18-90.3)	82.86 (72.14-90.02)	87.76 (75.46-94.35)
Specificity (%)	81.31 (72.69-87.67)	81.82 (72.88-88.28)	75 (40.31-93.02)

Males: All sites combined

Statistics	Males	Males < 75 yrs.	Males ≥ 75 yrs.
Sensitivity (%)	92.92 (88.85-95.57)	94.07 (88.6-97.01)	91.43 (84.33-95.48)
Specificity (%)	95.67 (92.13-97.66)	95.31 (91.23-97.55)	97.44 (86.49-99.56)

Females: All sites combined

Statistics	Females	Females < 75 yrs.	Males ≥ 75 yrs.
Sensitivity (%)	90.42 (84.87-94.07)	88.33 (77.56-94.31)	91.59 (84.61-95.57)
Specificity (%)	89.44 (83.98-93.2)	87.4 (80.35-92.17)	94.34 (84.36-98.1)

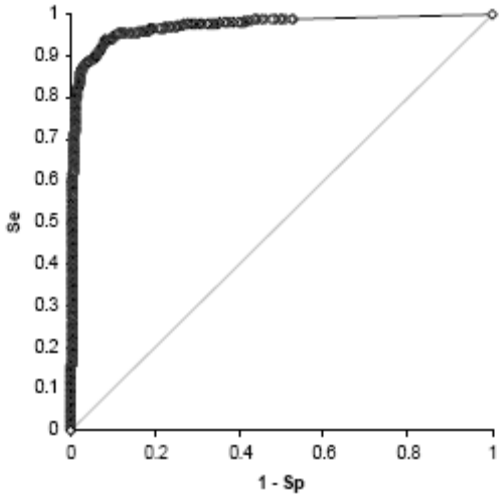
*b. Clinical specificity**:***

See Clinical Sensitivity above.

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

4. Clinical cut-off**:**

Assay cutoffs were established based on the Roche Elecsys proBNP assay which the VIDAS assay is traceable to. Recommended clinical thresholds are 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older. Since the incidence of CHF increases with age, age matched Receiver Operator Curves (ROC) were calculated for each stratification: <45, 45-54, 55-64, 65-75 and ≥ 75 years old. The optimum cut-off maximizes the area under the curve (AUC) and represents the highest sensitivity and specificity for the assay. The overall area under the curve (AUC) for the VIDAS NT-proBNP assay was 0.965.



5. Expected values/Reference range:

Assay cutoffs were established based on the Roche Elecsys proBNP assay which the VIDAS assay is traceable to.

125 pg/mL for < 75 years old

450 pg/mL for > 75 years old

Results were stratified by age groups and genders. Patients with results < 20 pg/mL were not included in the mean and standard deviation calculations.

Males	< 45 years	45 – 54 years	55 – 64 years	65 – 74 years	< 75 years	≥ 75 years
Mean*	332.6	62.2	110.9	57.9	151.2	147.0
Standard deviation*	971.8	42.8	206.2	32.1	532.7	131.6
Median	< 20	< 20	< 20	40	< 20	90
95th percentile	334.5	107.5	153.5	123	131.5	438
% < Cut-off	93.2	97.0	95.0	100.0	95.3	97.4
N	74	67	40	11	192	39

Females	< 45 years	45 – 54 years**	55 – 64 years	65 – 74 years	< 75 years**	≥ 75 years
Mean*	141.5	637.7	73.3	107.7	253.7	178.6
Standard deviation*	309.3	2208.5	29.4	42.7	1146.3	141.1
Median	20.5	< 21	41	92.5	25	131
95th percentile	618.5	4909	116.5	191	251.5	533
% < Cut-off	91.4	77.8	96.0	75.0	87.4	94.3
N	58	36	25	8	127	53

Males and Females	< 45 years	45 – 54 years**	55 – 64 years	65 – 74 years	< 75 years**	≥ 75 years
Mean*	213.1	334.8	93.3	79.7	204.8	165.2
Standard*deviation	639.8	1525.4	150.8	43.9	905.0	137.3
Median	< 20	< 20	< 20	63	< 20	120
95th percentile	263	173.5	123	191	174	469
% < Cut-off	92.4	90.3	95.4	89.5	92.2	95.7
N	132	103	65	19	319	92

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.