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

A. 510(k) Number:

k060632

B. Purpose for Submission:

New device

C. Measurand:

N-terminal pro Brain Natriuretic Peptide (NT-proBNP)

D. Type of Test:

Quantitative

E. Applicant:

Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:

VITROS Immunodiagnostic NT-proBNP Reagent Pack

VITROS Immunodiagnostic Products NT-proBNP Calibrator

VITROS Immunodiagnostic Products NT-proBNP Range Verifier

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NBC	Class II	21 CFR 862.1117, B-type natriuretic peptide test system.	75, Clinical Chemistry (CH)
JIT	Class II	21 CFR 862.1150, Calibrator, Secondary	75, Clinical Chemistry (CH)
JJX	Class I	21 CFR 862.1660, Single (specified) analyte controls (assayed and unassayed)	75, Clinical Chemistry (CH)

H. Intended Use:

1. Intended use(s):

VITROS Immunodiagnostic NT-proBNP Reagent Pack

For the *in vitro* quantitative measurement of N-terminal pro Brain Natriuretic Peptide (NT-proBNP) in human serum and plasma (EDTA or heparin) to aid in the diagnosis of congestive heart failure and for the risk stratification of acute coronary syndrome and congestive heart failure. The test is further indicated as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease. The test can also be used in the assessment of heart failure severity in patients diagnosed with congestive heart failure.

VITROS Immunodiagnostic Products NT-proBNP Calibrator

For *in vitro* use in the calibration of the VITROS ImmunodiagnosticSystem for the quantitative measurement of N-terminal pro Brain Natriuretic Peptide (NT-proBNP) in human serum and plasma (EDTA or heparin).

VITROS Immunodiagnostic Products NT-proBNP Range Verifier

For the *in vitro* use in verifying the calibration range of the VITROS Immunodiagnostic System when used for the quantitative measurement of N-terminal pro Brain Natriuretic Peptide (NT-proBNP).

2. Indication(s) for use:

   See Intended Use section above

3. Special conditions for use statement(s):

   Prescription use only

4. Special instrument requirements:

   The device is intended for use with the VITROS Immunodiagnostics System (k962919).

I. Device Description:

One VITROS NT-proBNP Reagent Pack contains:

- 100 coated wells (streptavidin source, bacterial; binds ≥ 3 ng biotin/well)

- 8.2 mL conjugate reagent [HRP-sheep polyclonal anti-NT-proBNP, binds ≥ 37,000 pg NT-proBNP/mL (≥ 4,366 pmol NT-proBNP/L)] in buffer with bovine serum albumin and antimicrobial agent.
- 8.2 mL biotinylated antibody reagent [biotin-sheep polyclonal anti-NT-proBNP, binds ≥ 37,000 pg NT-proBNP/mL ≥ 4,366 pmol NT-proBNP/L)] in buffer with sheep serum, bovine serum albumin, bovine gamma globulin and antimicrobial agent.

NT-proBNP Calibrator contains 1 set of NT-proBNP Calibrators 1, 2, and 3 (2 mL, in buffer with bovine serum albumin and microbial agent).

NT-proBNP Range Verifier contains 2 sets of NT-proBNP range verifiers low and high (1 mL NT-proBNP in buffer with bovine serum albumin and antimicrobial agent).

Human source materials were tested by FDA approved methods and found to be negative /non-reactive for HCV, HIV-1/2, and HBsAg.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Roche Diagnostics Elecsys proBNP Immunoassay

2. Predicate K number(s):
   k053182

Comparison with predicate

Vitros NT-proBNP Reagent Pack Similarities		
Item	Vitros	Roche
Indications for Use	aid in the diagnosis of congestive heart failure and for the risk stratification of acute coronary syndrome and congestive heart failure. The test is further indicated as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease.	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. The test may also serve as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease.
Reportable Range	5.00-35,000 pg/mL	5.00-35,000 pg/mL

Vitros NT-proBNP Reagent Pack Similarities		
Item	Vitros	Roche
Antibody	polyclonal anti-NT-proBNP (sheep)	polyclonal anti-NT-proBNP (sheep)
Sample Type	serum and plasma	serum and plasma
Expected Values	125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older	125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older
Analytical Sensitivity	less than 5 pg/mL	5 pg/mL

Vitros NT-proBNP Reagent Pack Differences		
Item	Vitros	Roche
Indications for Use	The test can also be used in the assessment of heart failure severity in patients diagnosed with congestive heart failure	Does not include an indication for assessment of heart failure severity
Instrument	VITROS Immunodiagnostic System	Elecsys family of analyzers
Assay Principle	Chemiluminescence	Electrochemiluminescence
Hook Effect	No high dose hook up to 500,000 pg/mL	No high dose hook up to 300,000 pg/mL
Functional Sensitivity	less than 10 pg/mL	less than 50 pg/mL

VITROS NT-proBNP Calibrator Similarities		
Item	Vitros	Roche
Intended Use	used for calibrating the quantitative NT-proBNP assay	used for calibrating the quantitative NT-proBNP assay

VITROS Immunodiagnostic Products NT-proBNP Calibrator Differences		
Item	Vitros	Roche
Matrix	Liquid; NT-proBNP in buffer with bovine serum albumin and antimicrobial agent	Lyophilized equine serum matrix with added synthetic NT-proBNP
Levels	Cal 1 0 pg/mL; Cal 2 150 pg/mL; Cal 3 12,500 pg/mL	Cal 1 140 pg/mL; Cal 2 2700 pg/mL

VITROS NT-proBNP Range Verifier Similarities		
Item	Vitros	Roche
Intended Use	in vitro use in verifying the calibration range of the VITROS Immunodiagnostic System	in vitro use in verifying the calibration range of the VITROS Immunodiagnostic System
Levels	Low and High	Low and High

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

STANDARDS
Title and Reference Number
CLSI - Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP9-A 1995)
CLSI - Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)
CLSI - Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A)
CLSI – Evaluation of Linearity; Approved Guideline (EP6-A)
CLSI – Limits of Detection and Quantitation; Approved Guideline (EP17-A)

GUIDANCE			
Document Title	**Office**	**Division**	**Web Page**
Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications; Final Guidance for Industry and FDA Reviewers	OIVD	DCTD	http://www.fda.gov/cdrh/ode/guidance/1072.html

L. Test Principle:

The VITROS NT-proBNP assay is performed using the VITROS Immunodiagnostic Products NT-proBNP Reagent Pack and VITROS Immunodiagnostic Products NT-proBNP Calibrators on the VITROS Immunodiagnostic System. An immunometric technique is used. NT-proBNP present in the specimen reacts simultaneously with a biotinylated antibody and a horseradish peroxidase (HRP)-labeled conjugate. The antigen-antibody complex is captured by streptavidin on the wells. Unbound materials are removed by washing. A reagent containing luminogenic substrates (a luminol derivative and peracid salt) and an electron transfer agent (a substituted acetanilide) is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent increases the level and duration of the light produced. The light signals are read by the VITROS Immunodiagnostic System. The amount of HRP conjugate bound is directly proportional to the concentration of NT-proBNP present in the specimen.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision was evaluated according to CLSI protocol EP5. Two replicates of each of 3 frozen control sera and 4 frozen human sample pools were assayed on 2 separate occasions per day on at least 20 different days. The experiment was performed using 3 reagent lots on three different VITROS Immunodiagnostic Systems.

	Conventional Units = pg/mL								
	Mean NT-proBNP Conc.	Within-run*		Within-calibration**		Within-lab***		No. Observ.	No. Days
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
System 1	68.4	0.746	1.1	3.08	4.6	3.48	5.0	84	28
	112	0.825	0.7	6.66	6.0	6.26	5.5	84	28
	395	3.97	1.0	18.0	4.6	16.8	4.2	84	28
	26383	289	1.1	533	2.0	549	2.1	84	28
	212	2.03	1.0	5.24	2.5	5.67	2.6	84	28
	680	5.17	0.8	11.4	1.7	12.3	1.8	84	28
	7640	88.0	1.2	146	1.9	157	2.0	84	28
System 2	67.6	1.18	1.7	3.19	4.7	3.03	4.5	84	28
	111	1.27	1.1	6.20	5.6	6.31	5.7	84	28
	394	4.83	1.2	16.5	4.2	16.9	4.3	84	28
	26723	357	1.3	889	3.3	1053	4.0	84	28
	212	1.74	0.8	4.51	2.1	4.37	2.1	84	28
	692	6.74	1.0	11.7	1.7	12.6	1.8	84	28
	7826	63.2	0.8	122	1.6	155	2.0	84	28
System 3	71.2	0.817	1.2	3.11	4.4	3.04	4.2	84	28
	116	1.01	0.9	6.90	6.0	6.06	5.2	84	28
	406	3.48	0.9	20.1	5.0	16.8	4.1	84	28
	27449	342	1.3	831	3.1	705	2.5	84	28
	214	1.54	0.7	4.98	2.4	5.78	2.7	84	28
	685	4.48	0.7	13.4	2.0	14.2	2.0	84	28
	7702	79.3	1.0	170	2.3	179	2.3	84	28

* Within-run (Repeatability): Between-duplicate precision was determined using duplicate determinations.

** Within-calibration: Total within calibration precision was determined using a single lot of reagent over a single calibration interval.

***Within-lab: Total within-lab precision was estimated using a single reagent lot calibrated weekly

b. Linearity/assay reportable range:

The claimed measuring range of the assay is 5 – 35,000 pg/mL.

A linearity study was conducted using 10 pooled samples with values ranging from 3.97 to 30,727 pg/mL. The mean measured concentrations of pools 2 to 10, when expressed as a percentage of the calculated concentrations, gave a mean result of 99.2%, with a range of 95.1% to 105%. Analysis by linear regression also indicated that the assay is linear across the range tested (3.97 to 30,727 pg/mL) with the following regression equation: y = 0.9687x - 15.011, R = 0.9999. An additional linearity study was conducted to assess the linearity of the assay up to 35,000 pg/mL, which is the upper limit of the reportable range of the assay. In this study, the samples ranged from 2.29 to 44, 653 pg/mL. The mean measured concentrations of pools 2 to 10, when expressed as a percentage of the calculated concentrations, gave a mean result of 98.3%, with a range of 97.6% to 99.7%.

To assess the potential for high dose hook effect, a series of samples having NT-proBNP concentrations ranging from 8100 to 514,667 pg/mL were assayed in the VITROS NT-proBNP assay. Singleton determinations of each sample were made with each of 3 Master Lots. No high dose hook effect was observed in the VITROS NT-proBNP assay in samples containing up to 500,000 pg/mL NT-proBNP.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):
Both the Calibrators and Range Verifiers are value assigned by performing multiple determinations using several VITROS Immunodiagnostic Systems. The values for the calibrators are assigned by performing multiple determination of each calibrator. The calibrators are traceable to reference calibrators, which have been value assigned to correlate with the Roche Elecsys proBNP immunoassay. VITROS Immunodiagnostic Products NT-proBNP Range Verifiers and VITROS NT-proBNP Calibrators are supplied ready for use and are stored at 2-8 °C until the expiration date. Stability studies are ongoing.

To establish the open-vial stability of the VITROS NT-proBNP Range Verifiers, the verifiers were pooled and stored in sample cups at 2-8°C and -20°C. The pooled VITROS NT-proBNP Range Verifiers were tested at the initial time point (day 0) and days 4 (interim), 7 (expiry) and 10 (post expiry) of the trial using three Master Kit Lots and three lots of VITROS NT-proBNP Range Verifiers. All data for stored 2-8°C Range Verifiers and fresh Range Verifiers, returned results within acceptance limits up to and including the day 10 time-point, therefore, supporting the storage claim of 7 days at 2-8°C.

To establish the open-vial stability of the VITROS NT-proBNP Calibrators, the calibrators were opened, pooled and stored in sample cups at 2-8°C. The pooled calibrators were tested at the initial timepoint. The calibrators stored at 2-8°C were tested at weeks 0, 4, 8 and 10. The stored calibrators were

compared against fresh calibrators using 3 Master Lots. The data obtained demonstrates no differences between the fresh and stored calibrators. The data supports the storage of the calibrators at 2-8°C after opening for up to 8 weeks.

d. Detection limit:

The limit of detection (LoD) for NT-proBNP is 4.29 pg/mL, determined using methods consistent with the CLSI guideline EP17-A, with proportions of false positives (α) less than 1% and false negatives (β) less than 1%. This determination was based on 1049 determinations, with 150 blank and 899 low-level samples. The Limit of Blank (LoB) was determined to be 1.71 pg/mL. The limit of quantitation (LoQ) was set at 5.00 pg/mL to ensure acceptable precision within the lower range of the assay.

Analytical Sensitivity = < 5.00 pg/mL

LoB = 1.71 pg/mL, LoD = 4.29 pg/mL and LoQ = 5.00 pg/mL

Functional sensitivity = 10.0 pg/mL (The sponsor has defined function sensitivity as the concentration at which the assay achieves 20% CV.)

e. Analytical specificity:

Specificity of the VITROS NT-proBNP assay was evaluated by testing the following substances as recommended by the Clinical and Laboratory Standards Institute (CLSI) document EP7. They were found not to interfere (bias <10%) with the assay at a NT-proBNP concentration of approximately 125 pg/mL.

Acetaminophen	20 mg/dL	1.32 mmol/L	**Lisinopril**	4 mg/dL	0.099 mmol/L
N-Acetyl-L-cysteine	271 mg/dL	16.6 mmol/L	**Lovastatin (Mevinolin)**	8 mg/dL	0.198 mmol/L
Acetylsalicylic acid	100 mg/dL	5.55 mmol/L	**Marcumar (Warfarin)**	0.600 mg/dL	0.019 mmol/L
Adrenalin (Epinephrine HCl)	0.037 mg/dL	1.68 µmol/L	**Methyl Dopa**	2 mg/dL	0.084 mmol/L
Ampicillin	100 mg/dL	2.69 mmol/L	**6-alpha-Methylprednisolone**	8 mg/dL	0.214 mmol/L
Ascorbic acid	30 mg/dL	1.70 mmol/L	**Metoprolol +/- Tartrate**	1.5 mg/dL	0.022 mmol/L
Bilirubin	20 mg/dL	0.342 mmol/L	**Metronidazole**	20 mg/dL	1.17 mmol/L
Biotin	0.002 mg/dL	81.9 nmol/L	**Molsidomine**	2.4 mg/dL	0.099 mmol/L
Bisoprolol Hemifumarate	1 mg/dL	0.026 mmol/L	**Nicardipine HCl**	9 mg/dL	0.174 mmol/L
Captopril	15 mg/dL	0.690 mmol/L	**Nifedipine**	6 mg/dL	0.173 mmol/L
Carvedilol	5 mg/dL	0.123 mmol/L	**Phenylbutazone**	40 mg/dL	1.30 mmol/L
Cefoxitin Sodium	250 mg/dL	5.56 mmol/L	**Pravastatin**	4 mg/dL	0.090 mmol/L
Cyclosporin A	0.500	0.004	**Propafenone HCl**	90	2.38

	mg/dL	mmol/L		mg/dL	mmol/L
Clopidogrel Hydrogensulfate	7.5 mg/dL	0.179 mmol/L	**Propranolol HCl**	228 mg/dL	7.71 mmol/L
Digitoxin	0.030 mg/dL	0.392 µmol/L	**Retavase**	0.112 mg/dL	na
Digoxin	0.050 mg/dL	0.640 µmol/L	**Rifampicin**	6 mg/dL	0.073 mmol/L
Dipyrone	1000 mg/dL	30 mmol/L	**Simvastatin**	4 mg/dL	0.096 mmol/L
Doxycycline Hyclate	6.9 mg/dL	0.067 mmol/L	**Sodium Azide**	200 mg/dL	30.8 mmol/L
Enalapril Maleate	4 mg/dL	0.081 mmol/L	**Sotalol HCl**	32 mg/dL	1.04 mmol/L
Gentamicin sulfate	0.050 mg/dL	0.001 mmol/L	**Spironolactone**	40 mg/dL	0.960 mmol/L
Glycerylnitrate (Nitroglycerin)	19.2 mg/dL	0.845 mmol/L	**Streptokinase**	na	300 IE
Heparin (Sodium)	na	5000 U/L	**Theophylline**	100 mg/dL	5.54 mmol/L
Ibuprofen	50 mg/dL	2.42 mmol/L	**Tolbutamide**	64 mg/dL	2.37 mmol/L
Insulin	0.084 mg/dL	0.145 µmol/L	**Torsemide**	20 mg/dL	0.574 mmol/L
Intralipid	1 mg/dL	na	**Triolein**	3000 mg/dL	33.9 mmol/L
Levodopa	2 mg/dL	0.101 mmol/L	**Urokinase**	na	600 IE
Lidocaine	10 mg/dL	0.427 mmol/L	**Verapamil**	12 mg/dL	0.244 mm

The cross-reactivity of the VITROS NT-proBNP assay was evaluated by adding the following substances to samples containing 0 and approximately 125 pg/mL of analyte. Cross-reactivity was expressed as the mean result obtained for the cross-reactant pool divided by the cross-reactant concentration in percentage terms.

Test Substance	Concentration Tested		% Cross-Reactivity
ANP_{28}	3.1 µg/mL	1.01 µmol/L	< 0.1
NT-proANP $_{1-30}$ (preproANP $_{26-55}$)	3.5 µg/mL	0.998 µmol/L	< 0.1
NT-proANP $_{31-67}$ (preproANP $_{56-92}$)	1.0 ng/mL	0.258 nmol/L	< 0.1
NT-proANP $_{79-98}$ (preproANP $_{104-123}$)	1.0 ng/mL	0.458 nmol/L	< 0.1
BNP_{32} (Natrecor®)	3.5 µg/mL	1.01 µmol/L	< 0.1
CNP_{22}	2.2 µg/mL	1.00 µmol/L	< 0.1
Adrenomedullin	1.0 ng/mL	0.166 nmol/L	< 0.1
Aldosterone	0.6 ng/mL	1.66 nmol/L	< 0.1
Angiotensin I	0.6 ng/mL	0.463 nmol/L	< 0.1
Angiotensin II	0.6 ng/mL	0.574 nmol/L	< 0.1
Angiotensin III	1.0 ng/mL	1.29 nmol/L	< 0.1
Endothelin	20 pg/mL	8.45 pmol/L	< 0.1
Urodilatin	3.5 µg/mL	0.998 µmol/L	< 0.1
Arg-Vasopressin	1.0 ng/mL	0.922 nmol/L	< 0.1
Renin	50 ng/mL	21.9 nmol/L	< 0.1

Hemoglobin may interfere with the VITROS NT-proBNP assay. At an NT-proBNP level of 88.4 pg/mL (10.4 pmol/L), hemoglobin at 400

and 500 mg/dL caused a positive bias of 11.4 and 15.8 pg/mL respectively.

Interferent	Interferent Concentration		Units = pg/mL (pmol/L)	
			Analyte Conc*	Bias**
Hemoglobin	0.248 mmol/L	400 mg/dL	88.4 (10.4)	11.4 (1.34)
Hemoglobin	0.310 mmol/L	500 mg/dL	88.4 (10.4)	15.8 (1.86)

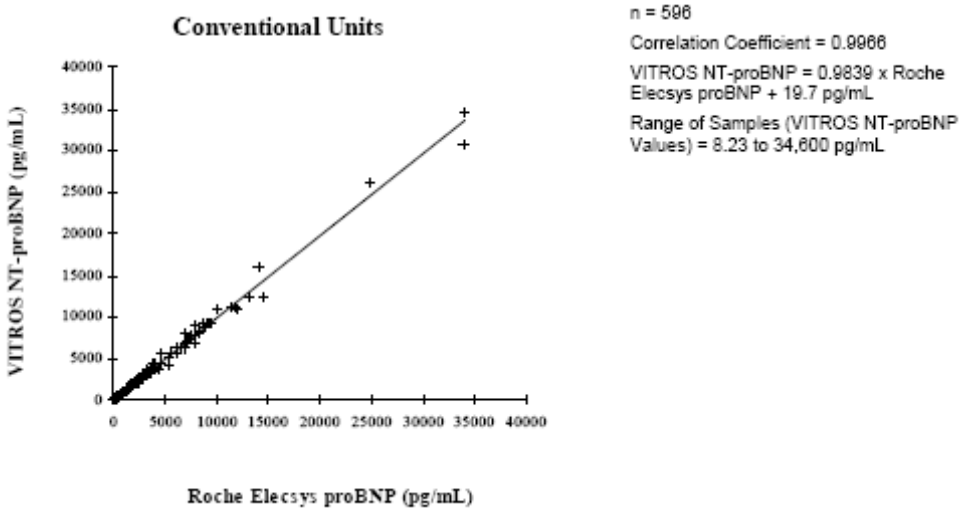
f. Assay cut-off:

The assay cutoffs are 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older.

2. <u>Comparison studies:</u>

a. Method comparison with predicate device:

Accuracy was evaluated based on CLSI Protocol EP9. The plots show the results of a method comparison study using patient samples analyzed on the VITROS System with those analyzed using the Roche Elecsys proBNP assay. The relationship between the two methods was determined by Deming's regression.



b. Matrix comparison:

Individual results from three determinations of each sample type (serum, EDTA plasma, and heparin plasma) and after storage at 2-8º C and after 1, 2 and 3 freeze/thaw cycles were tabulated. The mean value for each specimen type within each storage condition was calculated from the three determinations. The overall mean, SD and CV (%) for each sample type across storage conditions were also calculated. For each condition (sample type or storage), % differences were calculated from the baseline (serum for specimen type and fresh for storage condition). The mean and range of the % differences, across all samples, for each condition were calculated. The results indicated that all sample types are suitable (< 10% mean percent difference) for use in the VITROS NT-proBNP assay and that their suitability is not

affected by storage.

3. Clinical studies:

a. Clinical Sensitivity:

The clinical sensitivity and specificity of the VITROS NT-proBNP immunoassay using decision thresholds of 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older are presented below.

Males						
Age (yrs)	< 45	45-64	55-64	65-74	<75	>75
% Sensitivity	100.0	70.0	85.2	95.6	89.4	86.0
95% Confidence interval	29.2-100.0	34.8-93.3	66.3-95.8	84.9-99.5	80.8-95.0	73.3-94.9
N (total)	3	10	27	45	85	50
N (above decision threshold)	3	7	23	43	76	43
% Specificity	87.5	100.0	88.6	63.2	84.1	100.0
95% Confidence interval	61.7-98.4	73.5-100.0	73.3-96.8	38.4-83.7	74.4-91.3	75.3-100.0
N (total)	16	12	35	19	82	13
N (below decision threshold)	14	12	31	12	69	13

Females						
Age (yrs)	< 45	45-64	55-64	65-74	<75	>75
% Sensitivity	66.7	100.0	94.7	96.4	94.9	79.2
95% Confidence interval	9.43-99.2	66.4-100.0	74.0-99.9	81.7-99.9	85.9-98.9	65.0-91.4
N (total)	3	9	19	28	59	48
N (above decision threshold)	2	9	18	27	56	4338
% Specificity	92.0	80.6	66.0	68.0	75.0	84.2
95% Confidence interval	74.0-99.0	62.5-92.5	50.7-79.1	46.5-85.1	66.2-82.2	60.4-97.1
N (total)	25	31	47	25	128	19
N (below decision threshold)	23	25	31	17	96	16

b. Clinical specificity:

See Clinical Sensitivity section

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

Three peer reviewed literature references were provided demonstrating clinical support of the additional indications for use as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease. All three studies measured NT-proBNP using the Elecsys proBNP Immunoassay, to which the VITROS NT-proBNP assay is traceable. The VITROS NT-proBNP assay uses the same antibody as the Roche Elecsys assay. In the VITROS NT-proBNP assay, the calibrators are traceable to reference calibrators, which have been value assigned to correlate with the Roche Elecsys proBNP immunoassay. The Elecsys and VITROS assays have the same analytical range, 5-35,000 pg/mL. The method comparison between the Elecsys and VITROS assays shows that the two assays compare with the following regression equation: VITROS NT-proBNP (y) = 0.9839(x) Roche Elecsys proBNP + 19.7 pg/mL. The studies are:

Schnabel R, Rupprecht HJ, Lackner KJ, Lubos E, Bickel C, et al. Analysis of N-Terminal-pro-Brain Natriuretic Peptide and C-Reactive Protein for Risk Stratification in Stable and Unstable Coronary Artery Disease: Results from the AtheroGene Study. European Heart Journal, 2005. 26(3):241-249.

Kragelund C, Groenning B, Kober L, Hildebrandt P and Steffensen R. N-Terminal Pro-B-Type Natriuretic Peptide and Long-Term Mortality in Stable Coronary Heart Disease. The New England Journal of Medicine, 2005. 352(7):666-675.

Ndrepepa G, Braun S, Niemoller K, Mehilli J, von Beckerath N, et al. Prognostic Value of N-Terminal Pro-Brain Natriuretic Peptide in Patients with Chronic Stable Angina. Circulation, 2005. 112:2102- 2107.

Three literature references were provided which provide support for the claim for the use of the VITROS NT-proBNP assay for the risk stratification of acute coronary syndrome and CHF:

James SK, et al. NT-proBNP and Other Risk Markers for the Separate Prediction of Mortality and Subsequent Myocardial Infarction in Patients with Unstable Coronary Artery Disease. (GUSTO)-IV Substudy. Circulation 2003; 108: 275-281.

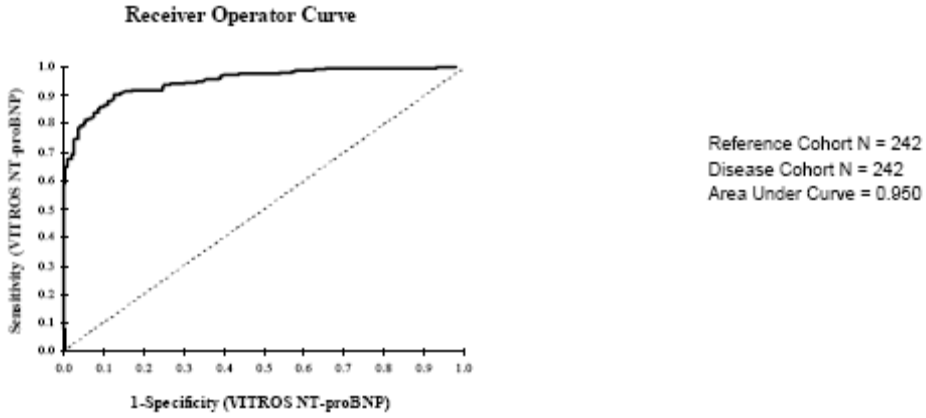
Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal Pro-Brain Natriuretic Peptide on Admission for Early Risk Stratification of Patients with Chest Pain and No ST-Segment Elevation. J Am Coll Cardiol 2002; 40:437-

445.

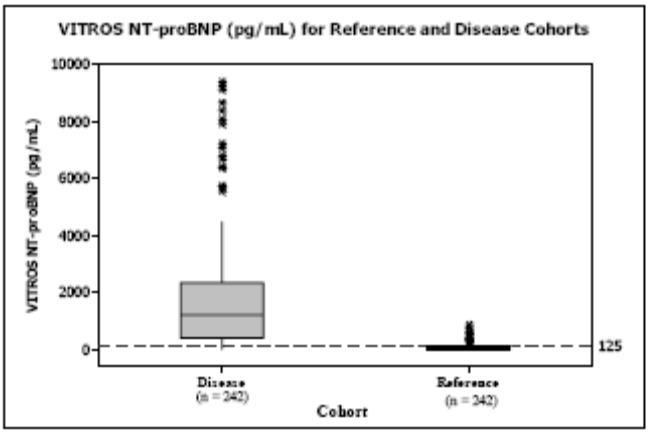
Fisher C, et al. NT-proBNP Predicts Prognosis in Patients with Chronic Heart Failure. Heart 2003; 89: 879-881.

4. Clinical cut-off:

Recommended clinical thresholds are 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older. The Receiver Operator Curve (ROC) compares clinical sensitivity and specificity at various decision thresholds. The optimum decision threshold maximizes the area under the curve (AUC) and represents the highest sensitivity and specificity for the assay. The ROC analysis for the VITROS NT-proBNP assay is presented below. The AUC for the VITROS NT-proBNP assay is 0.950 with a 95% Confidence Interval of 0.931 to 0.968.



A box and whisker plot for the clinical study population is presented below. Recommended clinical thresholds are 125 pg/mL (14.8 pmol/L) for patients younger than 75 years and 450 pg/mL (53.1 pmol/L) for patients 75 years and older.



5. Expected values/Reference range:

The circulating NT-proBNP concentration was determined from 242 individuals without CHF (95 men and 147 women). This population included apparently healthy individuals and individuals with diabetes, hypertension, pulmonary disease, and mild renal insufficiency. The descriptive statistics for NT-proBNP concentrations in the reference cohort are shown in the following tables.

All						
Age (yrs)	<45	45-54	55-64	65-74	<75	>=75
Mean (pg/mL)	64.0	61.5	102	120	90.2	249
SD	74.4	53.1	132	95.0	104	170
Median (pg/mL)	43.8	40.2	63.6	98.3	60.6	206
95th Percentile	251	158	288	288	271	598
% <125 pg/mL	90.2	86.0	75.6	65.9	78.6	-
% <450 pg/mL	-	-	-	-	-	90.6
N	41	43	82	44	210	32

Males						
Age (yrs)	<45	45-54	55-64	65-74	<75	>=75
Mean (pg/mL)	61.4	36.5	96.3	146	92.3	187
SD	89.0	34.0	173	127	138	128
Median (pg/mL)	32.6	22.4	48.0	107	52.2	145
95th Percentile	266	87.7	351	346	310	391
% <125 pg/mL	87.5	100.0	88.6	63.2	84.1	-
% <450 pg/mL	-	-	-	-	-	100.0
N	16	12	35	19	82	13

Females						
Age (yrs)	<45	45-54	55-64	65-74	<75	>=75
Mean (pg/mL)	65.6	71.2	106	101	88.9	292
SD	65.3	56.4	91.6	55.5	74.2	185
Median (pg/mL)	55.7	47.0	73.4	87.3	66.7	254
95th Percentile	168	162	288	213	228	615
% <125 pg/mL	92.0	80.6	66.0	68.0	75.0	-
% <450 pg/mL	-	-	-	-	-	84.2
N	25	31	47	25	128	19

Blood samples were obtained from 242 patients diagnosed with CHF (135 men and 107 women). The descriptive statistics for NT-proBNP concentrations in patients with CHF and NYHA Classifications I – IV are presented in the tables below.

CHF Population - All					
NYHA Functional Class					
	ALL	NYHA I	NYHA II	NYHA III	NYHA IV
Mean (pg/mL)	2124	1299	1467	3390	2956
SD	4165	1730	1638	7089	3179
Median (pg/mL)	1210	741	917	1870	1665
5th Percentile	109	137	85.3	191	260
95th Percentile	7193	2923	4514	10584	8993
% > cutoff	88.0	86.0	83.8	91.0	100.0
N	242	50	99	67	26
Minimum	15.3	78.1	15.3	48.0	139
Maximum	55600	9220	7900	55600	10800

CHF Population- Males					
NYHA Functional Class					
	ALL	NYHA I	NYHA II	NYHA III	NYHA IV
Mean (pg/mL)	2124	1338	1674	2905	3598
SD	2471	1761	1791	3232	3066
Median (pg/mL)	1490	802	960	2305	2115
5th Percentile	98.0	125	83.1	385	318
95th Percentile	7305	2941	5664	8044	8758
% > cutoff	88.1	85.7	83.1	93.8	100.0
N	135	28	59	32	16
Minimum	48.0	78.1	50.6	48.0	253
Maximum	16000	9220	7900	16000	9110

CHF Population - Females					
NYHA Functional Class					
	ALL	NYHA I	NYHA II	NYHA III	NYHA IV
Mean (pg/mL)	2125	1249	1161	3832	1929
SD	5632	1730	1344	9360	3241
Median (pg/mL)	862	658	735	1550	701
5th Percentile	138	301	103	259	202
95th Percentile	6957	2397	3100	9896	7348
% > cutoff	87.9	86.4	85.0	88.6	100.0
N	107	22	40	35	10
Minimum	15.3	133	15.3	56.3	139
Maximum	55600	8380	7200	55600	10800

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.