



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

I Background Information:

A 510(k) Number

K262109

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

Access NT-proBNP

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
NBC	Class II	21 CFR 862.1117 – B-Type Natriuretic Peptide Test System	Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

Modified device

B Measurand:

N-terminal pro 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 NT-proBNP assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of N-terminal pro B-type natriuretic peptide levels in human serum and plasma using the automated Access Immunoassay Analyzers to aid in the following:

1. Diagnosis of patients suspected of having acute heart failure in the Emergency Department
2. Assessment of heart failure severity
3. Risk stratification of patients with heart failure
4. Risk stratification of patients with acute coronary syndrome

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Access 2 Immunoassay Analyzer

IV Device/System Characteristics:

A Device Description:

The candidate device is the same as described in K232164 except for the chemiluminescent substrate, which was changed from Lumi-Phos PRO substrate to the Access substrate to support use on the Access 2 Immunoassay Analyzer.

B Principle of Operation:

The principle of operation is unchanged from the previous clearance described in K232164. The device has been modified to now use the Access substrate to support use on the Access 2 Immunoassay Analyzer.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Access NT-proBNP on DxI 9000 Immunoassay Analyzer

B Predicate 510(k) Number(s):

K232164

C Comparison with Predicate(s):

Device & Predicate Device(s):	<u>K262109</u>	<u>K232164</u>
Device Trade Name	Access NT-proBNP	Access NT-proBNP
General Device Characteristic Similarities		
Intended Use/Indications For Use	For the quantitative determination of N-terminal pro B-type natriuretic peptide (NT-proBNP) levels in human serum and plasma	Same
Antibody	Monoclonal anti-NT-proBNP	Same
General Device Characteristic Differences		
Instrument Required	Access 2 Immunoassay Analyzer	DxI 9000 Access Immunoassay Analyzer
Substrate	Access substrate	Lumi-Phos PRO substrate

VI Standards/Guidance Documents Referenced:

Clinical & Laboratory Standards Institute (CLSI) EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; 3rd Edition.

CLSI EP06-2nd Edition: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach.

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

CLSI EP09c 3rd Edition: Measurement Procedure Comparison and Bias Estimation using Patient Samples.

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:

The sponsor evaluated the precision of the Access NT-proBNP assay on the Access 2 Immunoassay Analyzer following the CLSI guideline EP05-A3.

Single Site Precision

The study was conducted at a single internal site using three Access 2 Immunoassay Analyzers, each paired with a unique reagent lot and calibrator lot.

Seven lithium heparin samples with concentrations of NT-proBNP spanning the measuring range were used in the study. Sample 1 to Sample 5 were pooled native human plasma samples. Sample 6 and Sample 7 were pooled native plasma samples supplemented with NT-proBNP antigen. Each sample was measured in 2 replicates per run, 2 runs per day over 20 days across the three instruments, yielding a total of 240 measurements per sample. The overall imprecision includes within-run, between-run, between-day, and between-reagent-lot variance components.

Sample	N	Mean (ng/L)	Repeatability		Between-Run		Between-Day		Between-Lot	
			SD (ng/L)	%CV	SD (ng/L)	%CV	SD (ng/L)	%CV	SD (ng/L)	%CV
S1	240	40	1.9	4.8%	0.7	1.8%	1.1	2.7%	0.1	0.3%
S2	240	139	2.8	2.0%	2.5	1.8%	3.1	2.3%	4.6	3.3%
S3	240	334	7.4	2.2%	3.9	1.2%	4.5	1.3%	7.9	2.4%
S4	240	461	9.5	2.1%	4.2	0.9%	8.2	1.8%	8.1	1.8%
S5	240	1866	45.8	2.5%	0.0	0.0%	27.1	1.5%	27.7	1.5%
S6	240	8249	146.6	1.8%	34.2	0.4%	93.0	1.1%	48.7	0.6%
S7	240	23160	464.2	2.0%	0.0	0.0%	286.4	1.2%	446.4	1.9%
Sample	N	Mean	Overall							
			SD (ng/L)	%CV						
S1	240	40	2.3	5.8%						
S2	240	139	6.7	4.8%						
S3	240	334	12.4	3.7%						
S4	240	461	15.5	3.4%						
S5	240	1866	60.0	3.2%						
S6	240	8249	183.5	2.2%						
S7	240	23160	704.8	3.0%						

Multi-Site Reproducibility Study

A multi-site study was conducted to evaluate the reproducibility of the Access NT-proBNP assay on the Access 2 Immunoassay Analyzer. One reagent lot and one calibrator lot were used for measurements taken at three sites.

Seven lithium heparin samples with concentrations of NT-proBNP spanning the measuring range were used in the study. Sample 1 to Sample 6 were pooled native human plasma samples. Sample 7 was a pooled native plasma supplemented with NT-proBNP antigen. Each sample was measured in 3 replicates per run, 2 runs per day, over 5 days at each site, yielding

a total of 90 measurements per sample. The results for this study are summarized in the table below.

Sample	N	Mean (ng/L)	Repeatability		Between-Run		Between-Day		Between-Site /Instrument	
			SD (ng/L)	%CV	SD (ng/L)	%CV	SD (ng/L)	%CV	SD (ng/L)	%CV
S1	90	34	1.5	4.4%	0.9	2.5%	1.3	3.9%	0.8	2.3%
S2	90	117	4.1	3.5%	3.1	2.6%	0.0	0.0%	1.8	1.5%
S3	90	353	9.7	2.8%	10.1	2.9%	1.1	0.3%	0.7	0.2%
S4	90	623	20.6	3.3%	17.1	2.7%	0.0	0.0%	10.1	1.6%
S5	90	1853	41.9	2.3%	30.5	1.6%	22.3	1.2%	0.0	0.0%
S6	90	12339	326.9	2.6%	46.1	0.4%	162.7	1.3%	263.9	2.1%
S7	90	31415	598.1	1.9%	531.9	1.7%	211.7	0.7%	775.8	2.5%
Sample	N	Mean	Reproducibility							
			SD (ng/L)	%CV						
S1	90	34	2.3	6.8%						
S2	90	117	5.4	4.6%						
S3	90	353	14.1	4.0%						
S4	90	623	28.7	4.6%						
S5	90	1853	56.5	3.0%						
S6	90	12339	452.9	3.7%						
S7	90	31415	1134.9	3.6%						

2. Linearity:

The linearity performance of the Access NT-proBNP assay run on the Access 2 Immunoassay Analyzer was established for lithium heparin plasma in a study following the recommendations of the CLSI EP06, 2nd Edition guideline.

Three Access 2 Immunoassay Analyzers, each paired with a unique reagent lot and calibrator lot, were used in this study. A native lithium heparin plasma sample containing a concentration of NT-proBNP below the lower end of measuring interval (< 10.0 ng/L) was obtained. A high sample was prepared by pooling high-concentration ($> 35,000$ ng/L) native lithium heparin plasma samples. The low and high pool samples were mixed in pre-defined ratios to create an additional seven samples for each sample type.

Each sample was measured on each Access 2 Immunoassay Analyzer. The low sample was run in replicates of eight, and all other samples were run in replicates of four. Linearity was analyzed separately for each reagent lot/instrument combination.

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. The maximum deviation from linearity was 6%. The sponsor concluded that the assay yields a linear response over the claimed NT-proBNP measuring range of 10 ng/L to 35,000 ng/L.

Additionally, the sponsor provided a sub-range linearity study (from lower measuring end up to 2000 ng/L) using native samples, and the results were found to be similar to the full-range studies. The maximum deviation from linearity was 3%.

These data support the sponsor's measuring range of 10 to 35,000 ng/L.

Hook Effect

The sponsor provided information to support that the hook effect claim is the same as the predicate device K232164.

3. Analytical Specificity/Interference:

The Analytical Specificity/Interference performance was evaluated in K232164. The sponsor provided information to support that the analytical specificity/interference claims are the same as described in K232164.

4. Detection Limit and Assay Reportable Range:

Detection Limit

The detection capability of the Access NT-proBNP assay run on the Access 2 Immunoassay Analyzer was evaluated. 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 with three Access 2 Immunoassay Analyzers, three reagent lots, and one calibrator lot, with each analyzer paired with a unique reagent lot.

Each sample was tested across three days with one run per day and five replicates per run on each analyzer. A total of 75 measurements were obtained from five samples per analyzer-reagent lot combination. The LoB was determined non-parametrically for each combination separately, and the highest value obtained across three lots was taken as the LoB value for the assay.

- The LoB for the Access NT-proBNP assay on the Access 2 Immunoassay Analyzer is estimated to be 1.8 ng/L.

Limit of Detection (LoD)

The LoD study was performed using nine lithium heparin plasma native samples containing low levels of NT-proBNP analyte with three Access 2 Immunoassay Analyzers, three reagent lots, and one calibrator lot, with each analyzer paired with a unique reagent lot.

Each sample was tested across five days with one run per day and nine replicates per run on each analyzer. A total of 45 measurements were obtained per sample per each analyzer-reagent lot combination. The parametric approach described in EP17-A2 was followed to

determine the LoD. The highest observed LoD across three lots was the reported LoD for the assay.

- The LoD for the Access NT-proBNP assay is estimated to be 3.5 ng/L.

Limit of Quantitation (LoQ)

The LoQ study was performed using twelve lithium heparin plasma samples containing low levels of NT-proBNP analyte with three Access 2 Immunoassay Analyzers, three reagent lots, and one calibrator lot, with each analyzer paired with a unique reagent lot.

Each sample was tested across five days with one run per day and nine replicates per run on each analyzer. A total of 45 measurements were obtained for each sample per each analyzer-reagent lot combination. The LoQ was determined independently for each analyzer-reagent lot using a precision profile approach as the concentration where the %CV was less than or equal to 20%. The highest LoQ values obtained across three lots were taken as the LoQ value of the assay.

- The LoQ for the Access NT-proBNP assay is estimated to be 3.1 ng/L.

The maximum observed LoQ for the Access NT-proBNP assay on the Access 2 Immunoassay Analyzer is lower than the reported LoD (3.5 ng/L). Following EP17-A2 recommendation, the LoQ value is reported as 3.5 ng/L to align with the LoD.

These studies support the following detection capability claims in the labeling:

Limit of Blank (LoB): 1.8 ng/L

Limit of Detection (LoD): 3.5 ng/L

Limit of Quantitation (LoQ) ($\leq 20\%$ within-lab CV): 3.5 ng/L

Assay Reportable Range

10.0 – 35,000 ng/L

The sponsor performed studies to demonstrate that the Access NT-proBNP assay is not susceptible to intra-assay carryover on the Access 2 Immunoassay Analyzer.

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

Traceability and sample stability are the same as described in K232164.

The sponsor provided data to support:

- Opened reagent onboard stability of 61 days at 2 to 10°C.
- Calibration stability of 61 days.

6. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The sponsor performed a method comparison study to demonstrate the equivalence between the candidate device and the predicate device (K232164).

This method comparison study was conducted following the recommendations outlined in CLSI EP09c, 3rd Edition. In this study, a total of 327 subjects aged 22 years and older presenting with clinical suspicion of acute heart failure across five geographically diverse clinical sites were prospectively enrolled. Subjects on dialysis and those with dyspnea clearly not secondary to heart failure (e.g., primary lung disease or chest trauma), were excluded from the study. The study cohort consisted of 42.8% (140/327) female subjects and 57.2% (187/327) male subjects. Individuals in the population were 40.1% (131/327) Black or African American, 57.8% (189/327) White or Caucasian, and 1.2% (4/327) Asian. In addition, the study cohort represented key demographic and clinical subgroups, with diverse representation across age, BMI, kidney function (eGFR), history of heart failure, and comorbidities.

For each subject, a lithium heparin plasma sample was collected to determine the NT-proBNP concentration on both the candidate device and the predicate device. All samples were stored and handled within validated conditions. Samples were tested on 3 Access 2 Immunoassay Analyzers using 3 reagent pack lots and 3 calibrator lots of the candidate device and 3 DxI 9000 Analyzers using 3 reagent pack lots and 3 calibrator lots of the predicate device. Results of this method comparison study were analyzed using Passing-Bablok regression and are summarized below:

N	Concentration Range by Comparator (ng/L)	Slope (95%CI)	Intercept (95%CI)	Correlation Coefficient R
327	12.6 – 34,397.4	0.99 [0.98, 1.00]	-1.62 [-3.25, -0.21]	1.00

Additional subgroup Passing-Bablok regression analyses were performed by stratifying subjects by age (<50, 50-75, and >75 years), sex (male and female), race (White and non-White), BMI (< 30 and ≥30 kg/m²), kidney function (eGFR <60 and ≥60 mL/min/1.73 m²), history of heart failure, acute heart failure status (n=94 with New York Heart Association (NYHA) functional class from I to IV), and comorbidity status. Across all evaluated subgroups, slope and intercept estimates demonstrated minimal deviation from the predicate device, with confidence intervals consistently supporting analytical accuracy in each subgroup.

The results of this method comparison study demonstrate analytical equivalence between the candidate device and the predicate device (K232164). These findings support the conclusion that the modification to the candidate device did not impact the clinical performance characteristics and all clinical claims described in K232164.

2. Matrix Comparison:

A study was conducted following the recommendations in the CLSI EP35, 1st edition guideline to demonstrate the equivalence between serum, K2EDTA plasma (candidate tubes), and lithium heparin plasma (comparator tube) using three reagent lots.

Matched samples were tested in replicates with each reagent lot. The results were analyzed using Passing-Bablok regression analysis comparing the first replicate of the candidate tube to the mean of the comparator tube (lithium heparin). The representative results of the analysis, including the slope with 95% confidence interval (CI), the intercept with 95% CI, and the correlation coefficient, are shown in the table below.

Matrix	N	Concentration by Comparator (ng/L)	Slope (95%CI)	Intercept (95%CI)	R (95% CI)
Serum (Y) vs Lithium Heparin (X)	58	10.8 – 28,228.9	1.01 (0.99, 1.02)	-0.72 (-1.78, 0.22)	1.00 (0.999, 1.000)
K2 EDTA (Y) vs Lithium Heparin (X)	58	10.8 – 28,228.9	1.01 (0.99, 1.02)	-1.00 (-1.85, 0.07)	0.999 (0.999, 1.000)

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Clinical Cut-Off:

For patients in the Emergency Department (ED) settings, the cut-offs are the same as described in K232164.

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

In addition to the analytical accuracy evaluation described above under “Method Comparison with Predicate Device”, all enrolled subjects were adjudicated for an acute heart failure (AHF) diagnosis by an independent clinical event committee (CEC). The sponsor conducted a clinical concordance analysis utilizing all 327 subjects to compare the agreement between the candidate device and the predicate device at age-dependent positive cutoffs (≥ 450 ng/L for subjects < 50 years old; ≥ 900 ng/L for subjects 50 – 75 years old; ≥ 1800 ng/L for subjects > 75 years old) and the age-independent negative (< 300 ng/L) cutoff. Among the subjects with a confirmed diagnosis of AHF (N=94), the total exact agreement between the candidate device and the predicate device was 100% (94/94). Among the subjects with a confirmed non-AHF diagnosis (N=233), 96.6% (225/233) showed exact agreement between

results and 3.4% (8/233) results were discordant. All discordant results were limited to one-degree discordance between adjacent categories (i.e., heart failure unlikely / grey zone or grey zone/heart failure likely). The 8 discordant results were near the cutoff values, and the discordance is consistent with the normal variation of the assays.

D Expected Values/Reference Range:

The sponsor provided information to support that the modification to the candidate device did not impact the expected values of NT-proBNP in healthy adults established in K232164.

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.