January 16, 2025

Axis-Shield Diagnostics Limited
Claire Dora
Associate Director, Regulatory Affairs
17 Luna Place, The Technology Park
Dundee, Scotland DD 1XA
United Kingdom

Re: K241176
Trade/Device Name: Alere NT-proBNP for Alinity i Reagent Kit
Regulation Number: 21 CFR 862.1117
Regulation Name: B-Type Natriuretic Peptide Test System
Regulatory Class: Class II
Product Code: NBC
Dated: December 11, 2024
Received: December 11, 2024

Dear Claire Dora:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device"

(https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these requirements, please see the UDI System webpage at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Paula V. Caposino -S

Paula Caposino, Ph.D.
Division Deputy Director
Division of Chemistry and
Toxicology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K241176

Device Name
Alere NT-proBNP for Alinity i

Indications for Use *(Describe)*
The Alere NT-proBNP for Alinity i assay is a chemiluminescent microparticle immunoassay (CMIA) used for the in vitro quantitative determination of N-terminal pro B-type natriuretic peptide (NT-proBNP) in human serum and plasma on the Alinity i system.
In the emergency department, measurements of NT-proBNP are used as an aid in the diagnosis of heart failure (HF) in patients with clinical suspicion of new onset or worsening HF.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Administrative Documentation – 510(k) Summary

This summary of the 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR §807.92.

I. 510(k) Number

K241176

II. Applicant Name

Axis-Shield Diagnostics Limited
Luna Place, The Technology Park,
Dundee DD2 1XA
United Kingdom

Primary contact:

Claire Dora, Associate Director, Regulatory Affairs
Axis-Shield Diagnostics Ltd
Phone: +44(0)790994098
Email: claire.dora@abbott.com

Date Summary Prepared: January 16, 2025

III. Device Name

Trade Name: Alere NT-proBNP for Alinity i

Alere NT-proBNP for Alinity i
Device Classification: Class II
Classification Name: BNP Test System
Governing Regulation: 21 CFR Part 862.1117
Product Code: NBC

IV. Predicate Device

Roche Elecsys proBNP II (K092649)

V. Description of Device

A. Reagents

The various configurations of the Alere NT-proBNP for Alinity i Reagent Kit are described below.

	List Number	
	04S7921	**04S7931**
Tests per cartridge	100	500
Number of cartridges per kit	2	2
Tests per kit	200	1000
Microparticle volume	6.7 mL	27.0 mL
Conjugate volume	6.1 mL	26.5 mL

Microparticles: Anti-NT-proBNP (sheep, monoclonal) coated microparticles in Bis-TRIS buffer with protein (bovine) stabilizer, non-specific binding blocking agents, and surfactant. Minimum concentration: 0.05% solids. Preservative: sodium azide.

Conjugate: Anti-NT-proBNP (mouse, monoclonal) acridinium-labeled conjugate in MES buffer with protein (bovine) stabilizer and surfactant. Minimum concentration: 0.12 µg/mL. Preservatives: antimicrobial agents.

B. Biological Principles of the Procedure

The Alere NT-proBNP for Alinity i assay is an automated, two-step immunoassay for the *in vitro* quantitative determination of NT-proBNP in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology.

Sample and anti-NT-proBNP coated paramagnetic microparticles are combined and incubated. The NT-proBNP present in the sample binds to the anti-NT-proBNP coated microparticles. The mixture is washed. Anti-NT-proBNP acridinium-labeled conjugate is added to create a reaction mixture and incubated. Following a wash cycle, Pre-Trigger and Trigger Solutions are added.

The resulting chemiluminescent reaction is measured as a relative light unit (RLU). There is a direct relationship between the amount of NT-proBNP in the sample and the RLU detected by the system optics.

Assay Standardization

There is currently no international recognized reference method or reference material for standardization. The Alere NT-proBNP for Alinity i Calibrators are traceable to internal reference standards at every concentration level that were value assigned on and made traceable to the predicate device by transference, as described by Clinical and Laboratory Standards Institute (CLSI) Document EP32-R.*

C. Interpretation of Results

Emergency Department

For patients presenting to the emergency department (ED) with clinical suspicion of heart failure (HF), the results should be interpreted as indicated in the table below.

Age Group (Years)	NT-proBNP (pg/mL)	NT-proBNP (pmol/L)	Interpretation
All	< 300.0	< 35.4	Negative: HF unlikely
18 to < 50	≥ 300.0 to < 450.0	≥ 35.4 to < 53.1	Grayzone: Indeterminate
50 to 75	≥ 300.0 to < 900.0	≥ 35.4 to < 106.2	Consider other causes of NT-proBNP elevation.
> 75	≥ 300.0 to < 1800.0	≥ 35.4 to < 212.4	
18 to < 50	≥ 450.0	≥ 53.1	Positive: HF likely
50 to 75	≥ 900.0	≥ 106.2	
> 75	≥ 1800.0	≥ 212.4	

* Clinical and Laboratory Standards Institute (CLSI). *Metrological Traceability and Its Implementation; A Report.* CLSI document EP32-R. Wayne, PA: CLSI; 2006.

VI. Intended Use of the Device

The Alere NT-proBNP for Alinity i assay is a chemiluminescent microparticle immunoassay (CMIA) used for the *in vitro* quantitative determination of N-terminal pro B-type natriuretic peptide (NT-proBNP) in human serum and plasma on the Alinity i system.

In the emergency department, measurements of NT-proBNP are used as an aid in the diagnosis of heart failure (HF) in patients with clinical suspicion of new onset or worsening HF.

VII. Comparison with the Predicate Device

The similarities and differences between the subject device and the predicate device are presented in the table below.

	Subject Device: **Alere NT-proBNP for Alinity i**	**Predicate Device:** **Roche Elecsys proBNP II (K092649)**
General Device Characteristic Similarities		
Intended Use/Indications for Use	Immunoassay used for the *in vitro* quantitative determination of N-terminal pro B-type natriuretic peptide (NT-proBNP) in human serum and plasma. In the emergency department, measurements of NT-proBNP are used as an aid in the diagnosis of heart failure (HF) in patients with clinical suspicion of new onset or worsening HF.	Immunoassay for the in vitro quantitative determination of N-terminal pro-Brain natriuretic peptide in human serum and plasma. This 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. 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.
Specimen Type	Human serum and plasma	Same
Test Principle	Sandwich immunoassay	Same
Measurement Type	Quantitative	Same
Analyte	NT-proBNP	Same

	Subject Device: Alere NT-proBNP for Alinity i	Predicate Device: Roche Elecsys proBNP II (K092649)
Detection Technology	Chemiluminescence	Same
General Device Differences		
Principle of Operation	CMIA	Electro chemiluminescent microparticle immunoassay (ECLIA)
Intended Use Setting	Emergency department	Not specified
Measuring Interval	Analytical Measuring Interval (AMI): 15.8 to 35,000.0 pg/mL (1.9 to 4130.0 pmoL/L)	5 to 35,000 pg/mL
Hook Effect	No hook effect up to 372,620 pg/mL	No hook effect up to 300,000 pg/mL
Results Interpretation	Negative: HF unlikely for all patients: < 300.0 pg/mL Gray Zone: Indeterminate; consider other causes of NT-proBNP elevation: Age (Years) — NT-proBNP (pg/mL) 18 to < 50 — ≥ 300.0 to < 450.0 50 to 75 — ≥ 300.0 to < 900.0 > 75 — ≥ 300.0 to < 1800.0 Positive: HF likely: Age (Years) — NT-proBNP (pg/mL) 18 to < 50 — ≥ 450.0 50 to 75 — ≥ 900.0 > 75 — ≥ 1800.0	125 pg/mL for < 75 years 450 pg/mL for ≥ 75 years

VIII. Summary of Nonclinical Performance

A. Reportable Interval

Based on representative data for the limit of quantitation (LoQ), the ranges over which results can be reported are provided below.

	pg/mL	pmol/L
Analytical Measuring Interval (AMI)[a]	15.8 – 35,000.0	1.9 - 4130.0
Extended Measuring Interval (EMI)[b]	35,000.0 – 350,000.0	4130.0 – 41,300.0
Reportable Interval[c]	15.8 – 350,000.0	1.9 – 41,300.0

[a] AMI: The AMI extends from the LoQ to the upper limit of quantitation (ULoQ). This is determined by the range of values in pg/mL (pmol/L) that demonstrated acceptable performance for linearity, imprecision, and bias.

[b] EMI: The EMI extends from the ULoQ to the ULoQ × dilution factor. The value reflects a 1:10 dilution factor.

[c] The reportable interval extends from the LoQ to the upper limit of the EMI.

B. Within-Laboratory Precision (20-Day)

A study was performed based on guidance from CLSI EP05-A3.* Testing was conducted using 3 lots of the Alere NT-proBNP for Alinity i reagents, 1 lot of the Alere NT-proBNP for Alinity i Calibrators, 1 lot of the Alere NT-proBNP for Alinity i Controls, and 1 instrument. Three controls and 8 human plasma panels (7 native panels and 1 panel supplemented with NT-proBNP analyte) were tested in 2 replicates at 2 separate times per day on 20 days.

* Clinical and Laboratory Standards Institute (CLSI). *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition*. CLSI Document EP05-A3. Wayne, PA: CLSI; 2014.

Sample	n	Mean (pg/mL)	Repeatability		Within-Laboratory[a]		Between-Lot		Overall Within-Laboratory[b]	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Low Control	240	143.0	6.40	4.5	7.63	5.3	4.42	3.1	8.82	6.2
Medium Control	240	503.4	16.26	3.2	18.21	3.6	9.29	1.8	20.44	4.1
High Control	240	5144.2	177.02	3.4	202.18	3.9	21.47	0.4	203.32	4.0
Panel A	240	18.8	1.39	7.4	1.72	9.2	0.75	4.0	1.88	10.0
Panel B	240	55.6	2.64	4.7	3.02	5.4	1.60	2.9	3.41	6.1
Panel C	240	130.4	4.28	3.3	5.44	4.2	4.87	3.7	7.30	5.6
Panel D	240	449.1	13.10	2.9	18.68	4.2	14.02	3.1	23.36	5.2
Panel E	240	1011.4	28.31	2.8	34.49	3.4	21.92	2.2	40.87	4.0
Panel F	240	1938.0	54.02	2.8	65.28	3.4	22.56	1.2	69.07	3.6
Panel G	240	14,939.8	417.56	2.8	518.88	3.5	296.61	2.0	597.67	4.0
Panel H (Supplemented)	240	31,711.0	989.02	3.1	1185.11	3.7	2118.19	6.7	2427.19	7.7

[a] Includes repeatability (within-run), between-run, and between-day variability.

[b] Includes repeatability (within-run), between-run, between-day, and between-lot variability.

C. Linearity

A study was performed based on guidance from CLSI EP06, 2nd ed.[*] This assay is linear across the AMI of 15.8 to 35,000.0 pg/mL (1.9 to 4130.0 pmol/L).

D. Lower Limits of Measurement

A study was performed based on guidance from CLSI EP17-A2.[†] Testing was conducted using 3 lots of the Alere NT-proBNP for Alinity i reagents on each of 2 instruments over a minimum of 3 days. The maximum observed limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) values are summarized below.

	pg/mL	pmol/L
LoB[a]	0.1	0.0
LoD[b]	3.6	0.4
LoQ[c]	15.8	1.9

[a] The LoB represents the 95th percentile from n ≥ 60 replicates of zero-analyte samples.

[b] The LoD represents the lowest concentration at which the analyte can be detected with 95% probability based on n ≥ 60 replicates of low-analyte level samples.

[c] The LoQ is defined as the lowest concentration at which a maximum allowable precision of 20 %CV was met and was determined from n ≥ 60 replicates of low-analyte level samples.

E. Analytical Specificity

1. Potentially Interfering Endogenous Substances

A study was performed based on guidance from CLSI EP07, 3rd ed. [‡] Each substance was tested at 2 levels of the analyte (approximately 125 pg/mL and 2000 pg/mL).

[*] Clinical and Laboratory Standards Institute (CLSI). *Evaluation of the Linearity of Quantitative Measurement Procedures.* 2nd ed. CLSI Guideline EP06. Wayne, PA: CLSI; 2020.

[†] Clinical and Laboratory Standards Institute (CLSI). *Evaluation of Detection Capability for Clinical Measurements; Approved Guideline—Second Edition*. CLSI Document EP17-A2. Wayne, PA: CLSI; 2012.

[‡] Clinical and Laboratory Standards Institute (CLSI). *Interference Testing in Clinical Chemistry. 3rd ed*. CLSI Guideline EP07. Wayne, PA: CLSI; 2018.

No significant interference (interference within ± 10.0%) was observed at the following concentrations.

No Significant Interference (Interference within ± 10.0%)	
Potentially Interfering Substance	**Interferent Level**
Bilirubin (conjugated)	60 mg/dL
Bilirubin (unconjugated)	60 mg/dL
Biotin	4250 ng/mL
Cholesterol	700 mg/dL
Human Anti-mouse Antibodies (HAMA)	1500 ng/mL
Hemoglobin	1 g/dL
IgG	6 g/dL
Intralipid	3000 mg/dL
Rheumatoid Factor (RF)	600 IU/mL
Total Protein	12.6 g/dL

Interference beyond ± 10.0% (based on 95% confidence interval [CI]) was observed at the concentrations shown below for the following substances.

Interference beyond ± 10.0% (based on 95% CI)			
Potentially Interfering Substance	**Interferent Level**	**Analyte Level**	**% Interference (95% CI)**
RF	1520 IU/mL	125 pg/mL	-8.9% (-10.4%, -7.5%)
	1520 IU/mL	2000 pg/mL	-11.4% (-12.4%, -10.4%)
Total Protein	15.2 g/dL	125 pg/mL	-12.7% (-14.7%, -10.7%)
	15.5 g/dL	2000 pg/mL	-9.9% (-11.4%, -8.5%)

2. Potentially Interfering Drugs

A study was performed based on guidance from CLSI EP07, 3rd ed.[*] Each substance was tested at 2 levels of the analyte (approximately 125 pg/mL and 2000 pg/mL).

No significant interference (interference within ± 10.0%) was observed at the following concentrations.

No Significant Interference (Interference within ± 10.0%)			
Potentially Interfering Drug	**Interferent Level**	**Potentially Interfering Drug**	**Interferent Level**
Acetaminophen	15.6 mg/dL	Lidocaine	8.0 mg/dL
Acetylsalicylic Acid	60 mg/dL	Lisinopril	1.6 mg/dL
Allopurinol	6.0 mg/dL	Lithium	4.20 mg/dL
Amikacin	15 mg/dL	Losartan potassium	5.99 mg/dL
Amiodarone	4.2 mg/dL	Lovastatin	2.0 mg/dL
Amlodipine Besylate	0.4 mg/dL	L-Thyroxine	0.06 mg/dL
Ampicillin	7.5 mg/dL	Methyldopa	2.5 mg/dL
Ascorbic acid	5.25 mg/dL	Methylprednisolone	0.75 mg/dL
Atenolol	1.0 mg/dL	Metoprolol	1.5 mg/dL
Atorvastatin	32 mg/dL	Milrinone	0.183 mg/dL
Caffeine	10.8 mg/dL	Naproxen	49.97 mg/dL
Captopril	5.0 mg/dL	Nicotine	0.1 mg/dL
Carbamazepine	4.5 mg/dL	Nicotinic acid	4.0 mg/dL
Carvedilol	3.75 mg/dL	Nifedipine	6.0 mg/dL
Chloramphenicol	7.8 mg/dL	Nitrofurantoin	4.0 mg/dL
Chlordiazepoxide	1.0 mg/dL	Nitroglycerin	0.016 mg/dL
Chlorpromazine	0.33 mg/dL	Oxazepam	1.2 mg/dL
Cimetidine	3.0 mg/dL	Oxytetracycline	10 mg/dL

[*] Clinical and Laboratory Standards Institute (CLSI). *Interference Testing in Clinical Chemistry. 3rd ed*. CLSI Guideline EP07. Wayne, PA: CLSI; 2018.

No Significant Interference (Interference within ± 10.0%)			
Potentially Interfering Drug	**Interferent Level**	**Potentially Interfering Drug**	**Interferent Level**
Cinnarizine	3.1 mg/dL	Penicillin G	25 U/mL
Clopidogrel bisulfate	7.5 mg/dL	Pentobarbital	12.6 mg/dL
Creatinine	30 mg/dL	Phenobarbitol	69 mg/dL
Cyclosporine A	0.4 mg/dL	Phenprocoumon (Marcumar)	1.53 mg/dL
Dextran 40	6000 mg/dL	Phenytoin	6.0 mg/dL
Diazepam	3.0 mg/dL	Primidone	5.7 mg/dL
Diclofenac	6.0 mg/dL	Probenecid	60 mg/dL
Digoxin	0.025 mg/dL	Procainamide	4.8 mg/dL
Diltiazem	12 mg/dL	Propafenone	30 mg/dL
Dipyridamole	8.0 mg/dL	Propanolol	0.2 mg/dL
Disopyramide	4.0 mg/dL	Propoxyphene	0.321 mg/dL
Dobutamine	10 mg/dL	Quinidine	2.0 mg/dL
Dopamine	65 mg/dL	Ramipril	0.6 mg/dL
Enalapril Maleate	1.6 mg/dL	Retaplase	3.33 mg/dL
Epinephrine	0.05 mg/dL	Simvastatin	3.2 mg/dL
Erythromycin	13.8 mg/dL	Spironolactone	7.5 mg/dL
Ethanol	600 mg/dL	Sulfamethoxazole	112 mg/dL
Ethosuximide	30 mg/dL	Theophylline	6.0 mg/dL
Fenofibrate	4.5 mg/dL	Tolbutamide	150 mg/dL
Furosemide	6.0 mg/dL	Torasemide	1.5 mg/dL
Gentamicin	12 mg/dL	Trandolapril	4.0 mg/dL
Heparin	8 U/mL	Trasylol/Aprotinin	501.8 KIE/mL
Hydralazine	2.0 mg/dL	Trimethoprim	6.4 mg/dL
Hydrochlorothiazide	2.0 mg/dL	Uric Acid	23.5 mg/dL
Insulin	0.16 mg/dL	Valproic Acid	50 mg/dL
Ibuprofen	50 mg/dL	Verapamil	24 mg/dL

No Significant Interference (Interference within ± 10.0%)			
Potentially Interfering Drug	**Interferent Level**	**Potentially Interfering Drug**	**Interferent Level**
Indomethacin	3.6 mg/dL	Warfarin	7.5 mg/dL
Isosorbide dinitrate	6.0 mg/dL		

3. Cross-Reactants

A study was performed based on guidance from CLSI EP07, 3rd ed.[*] Samples with NT-proBNP target concentrations of 125 pg/mL and 2000 pg/mL containing the cross-reactants at the concentration listed below were tested with the Alere NT-proBNP for Alinity i assay on the Alinity i system. For each cross-reactant, the % recovery was calculated as: (NT-proBNP concentration with cross-reactant) / (NT-proBNP concentration without cross-reactant) × 100%. The observed % recovery of NT-proBNP was within 100% ± 10% for all cross-reactants evaluated at each analyte level.

Potential Cross-Reactant	Cross-Reactant Concentration
Adrenomedullin	1000 pg/mL
Aldosterone	600 pg/mL
Angiotensin I	600 pg/mL
Angiotensin II	600 pg/mL
Angiotensin III	1000 pg /mL
ANP 28	3100 ng/mL
Arg-Vasopressin	1000 pg/mL
BNP 32	3500 ng/mL
CNP 22	2200 ng/mL
Endothelin	20 pg/mL
NT-proANP 1-30 (preproANP26-55)	3500 ng/mL

[*] Clinical and Laboratory Standards Institute (CLSI). *Interference Testing in Clinical Chemistry. 3rd ed*. CLSI Guideline EP07. Wayne, PA: CLSI; 2018.

Potential Cross-Reactant	Cross-Reactant Concentration
NT-proANP 31-67 (preproANP56-92)	1000 pg/mL
NT-proANP 79-98 (preproANP104-123)	1000 pg/mL
Renin	50,000 pg/mL
Urodilatin	3500 ng/mL

F. High Dose Hook

High dose hook effect was not observed on samples up to 372,620 pg/mL.

G. Expected Values (Reference Interval)

A reference interval study was performed based on guidance from CLSI EP28-A3c.[*] Testing was performed with a US-based general population from apparently healthy individuals (≥ 18 years old). The specimens were tested with the Alere NT-proBNP for Alinity i assay on the Alinity i system. Based on the results, the 95% reference interval of an apparently healthy population for each sex and age range was determined to be as follows:

Age Range	Sex	n	Median (pg/mL)	Reference Interval (2.5th to 97.5th Percentile) (pg/mL)
18 to < 50 years old	Female	181	30.7	< 15.8 to 104.8
	Male	137	< 15.8	< 15.8 to 180.3
50 to 75 years old	Female	134	51.7	< 15.8 to 334.1
	Male	146	39.9	< 15.8 to 451.6
> 75 years old	Female	127	81.4	< 15.8 to 956.1
	Male	136	65.1	< 15.8 to 683.0

[*] Clinical and Laboratory Standards Institute (CLSI). *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition.* CLSI document EP28-A3c. Wayne, PA: CLSI; 2008.

IX. Summary of Clinical Performance

A. Reproducibility

A study was performed based on guidance from CLSI EP05-A3.* Testing was conducted at each of 3 testing sites using 3 lots of the Alere NT-proBNP for Alinity i reagents, 2 lots of the Alere NT-proBNP for Alinity i Calibrators, 2 lots of the Alere NT-proBNP for Alinity i Controls, and 1 instrument. Three controls and 8 human plasma panels (6 native panels and 2 panels supplemented with NT-proBNP analyte) were tested in a minimum of 3 replicates at 2 separate times per day on 5 different days.

* Clinical and Laboratory Standards Institute (CLSI). *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition*. CLSI Document EP05-A3. Wayne, PA: CLSI; 2014.

Sample	n	Mean (pg/mL)	Repeatability		Within-Laboratory[a]		Between-Site		Between-Lot		Overall Reproducibility[b]	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Low Control	360	136.6	4.75	3.5	5.75	4.2	2.63	1.9	1.45	1.1	6.49	4.7
Medium Control	360	477.1	12.24	2.6	15.35	3.2	14.20	3.0	8.88	1.9	22.72	4.8
High Control	359	4932.2	201.01	4.1	311.08	6.3	105.17	2.1	0.00	0.0	328.38	6.7
Panel 1	359	14.5	2.10[c]	14.5	2.74[c]	18.9	0.00	0.0	0.00	0.0	2.74[c]	18.9
Panel 2	360	51.9	2.14	4.1	3.07	5.9	0.49	0.9	0.00	0.0	3.11	6.0
Panel 3	360	127.1	4.67	3.7	5.95	4.7	1.36	1.1	0.78	0.6	6.15	4.8
Panel 4	360	436.9	10.46	2.4	18.67	4.3	3.18	0.7	0.00	0.0	18.94	4.3
Panel 5	360	996.5	21.86	2.2	43.45	4.4	17.12	1.7	0.00	0.0	46.70	4.7
Panel 6	360	1891.1	33.18	1.8	79.86	4.2	35.96	1.9	0.00	0.0	87.58	4.6
Panel 7 (Supplemented)	359	15,664.6	319.91	2.0	974.61	6.2	281.81	1.8	217.28	1.4	1037.54	6.6
Panel 8 (Supplemented)	360	25,630.5	601.42	2.3	1654.86	6.5	220.39	0.9	807.19	3.1	1854.37	7.2

[a] Includes repeatability (within-run), between-run, and between-day variability.

[b] Includes repeatability (within-run), between-run, between-day, between-site, and between-lot variability.

[c] An outlying run was observed. Based on guidance from CLSI EP05-A3, a replacement run was performed and the results are shown in the preceding table. Without the replacement run, the repeatability SD was 9.53 pg/mL (1.12 pmol/L), within-laboratory precision SD was 9.64 pg/mL (1.14 pmol/L), and the overall reproducibility SD was 9.64 pg/mL (1.14 pmol/L).

B. Clinical Performance

A multi-center prospective study including 17 collection sites across the US was conducted to establish the performance characteristics of the Alere NT-proBNP for Alinity i assay. Subjects 18 years and older presenting to the ED with signs and symptoms consistent with a clinical suspicion of new onset or acute exacerbation of HF were included in the study. Subjects with renal insufficiency requiring dialysis or known estimated glomerular filtration rate (eGFR) < 15.0 mL/min/1.73 m^2 and subjects with dyspnea after chest trauma were excluded from the study. An adjudicated diagnosis was determined by a panel of board-certified cardiologists.

The results were determined from 2127 ED subjects. Of the 2127 ED subjects, 1030 (48.4%) were female and 1097 (51.6%) were male, ranging in age from 19 to 97 years. Individuals in the population were White (53.1%), Black or African American (39.5%), Asian (1.7%), American Indian or Alaska Native (0.8%), Native Hawaiian or Other Pacific Islander (0.3%), or represented by other races (0.9%), with the remaining 3.6% of Unknown / Not Reported race. A total of 1934 (90.9%) ED subjects were not Hispanic or Latino, and 168 (7.9%) ED subjects were Hispanic or Latino, with the remaining 25 (1.2%) ED subjects of Unknown / Not Reported ethnicity.

The descriptive statistics for the Alere NT-proBNP for Alinity i test results (pg/mL) were determined within and across sex by age group and are summarized in the following table.

Adjudicated Diagnosis	**HF**				**Non-HF**			
Age Group (Years)	**< 50**	**50 to 75**	**> 75**	**All**	**< 50**	**50 to 75**	**> 75**	**All**
All Subjects								
N	160	553	167	880	300	799	148	1247
Mean	4354.5	6092.9	6891.3	5928.3	437.9	760.4	1738.8	798.9
SD	5454.61	8144.69	6860.32	7521.45	1686.57	1833.48	3494.96	2100.93
Median	2664.9	3297.2	4787.6	3420.7	70.1	198.9	565.9	181.8

Adjudicated Diagnosis	HF				Non-HF			
Age Group (Years)	**< 50**	**50 to 75**	**> 75**	**All**	**< 50**	**50 to 75**	**> 75**	**All**
Minimum	22.8	19.8	158.9	19.8	0.0	0.0	4.2	0.0
Maximum	38,880.9	60,716.9	38,938.4	60,716.9	24,737.1	17,988.9	31,154.0	31,154.0
Female Subjects								
N	55	236	85	376	165	407	82	654
Mean	4034.7	5370.1	6814.2	5501.2	273.5	614.8	1320.8	617.2
SD	6302.82	7732.10	7042.32	7417.01	732.64	1543.13	2403.63	1556.92
Median	1851.5	2541.7	4787.6	2786.4	73.1	174.9	499.7	161.2
Minimum	22.8	24.9	158.9	22.8	0.0	0.9	25.7	0.0
Maximum	38,880.9	47,385.1	38,938.4	47,385.1	5633.9	14,849.5	18,827.7	18,827.7
Male Subjects								
N	105	317	82	504	135	392	66	593
Mean	4522.0	6631.0	6971.2	6247.0	638.8	911.6	2258.0	999.4
SD	4977.78	8410.52	6708.84	7590.10	2369.85	2084.06	4464.35	2557.26
Median	2780.1	4066.5	4773.9	3904.3	64.1	221.0	701.8	203.2
Minimum	58.3	19.8	186.9	19.8	0.0	0.0	4.2	0.0
Maximum	26,986.3	60,716.9	32,286.4	60,716.9	24,737.1	17,988.9	31,154.0	31,154.0

The pretest probability of adjudicated HF (prevalence of adjudicated HF in the study), posttest probabilities, and likelihood ratios of the Alere NT-proBNP for Alinity i result vs adjudicated diagnosis (along with the 95% CIs) were determined based on guidance from CLSI EP12, 3rd ed.,[*] for all subjects and by sex using the age-dependent positive cutoffs (450 pg/mL for subjects 18 to < 50 years of age, 900 pg/mL for subjects 50 to 75 years of age, and 1800 pg/mL for subjects > 75 years of age) and age-independent negative cutoff (300 pg/mL).

[*] Clinical and Laboratory Standards Institute (CLSI). *Evaluation of Qualitative, Binary Output Examination Performance.* 3rd ed. CLSI Guideline EP12. Wayne, PA: CLSI; 2023.

The results for all subjects are presented in the following table.

	All Subjects					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 34.78% (160/460)						
Positive	140	48	188	**74.5 (140/188) (67.8, 80.2)**	-	5.47 (4.19, 7.13)
Grayzone	7	13	20	35.0 (7/20) (18.1, 56.7)	65.0 (13/20) (43.3, 81.9)	1.01 (0.41, 2.48)
Negative	13	239	252	-	**94.8 (239/252) (91.4, 97.0)**	0.10 (0.06, 0.17)
Total	160	300	460			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 40.90% (553/1352)						
Positive	437	148	585	**74.7 (437/585) (71.0, 78.1)**	-	4.27 (3.67, 4.96)
Grayzone	80	147	227	35.2 (80/227) (29.3, 41.7)	64.8 (147/227) (58.3, 70.7)	0.79 (0.61, 1.01)
Negative	36	504	540	-	**93.3 (504/540) (90.9, 95.1)**	0.10 (0.07, 0.14)
Total	553	799	1352			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 53.02% (167/315)						

	All Subjects					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Positive	131	38	169	**77.5 (131/169) (70.6, 83.2)**	-	3.06 (2.30, 4.06)
Grayzone	34	59	93	36.6 (34/93) (27.5, 46.7)	63.4 (59/93) (53.3, 72.5)	0.51 (0.36, 0.73)
Negative	2	51	53	-	**96.2 (51/53) (87.2, 99.0)**	0.03 (0.01, 0.14)
Total	167	148	315			
All Subjects[c]						
Pretest Probability of HF (Prevalence of HF in Study): 41.37% (880/2127)						
Positive	708	234	942	**75.2 (708/942) (72.3, 77.8)**	-	4.29 (3.80, 4.83)
Grayzone	121	219	340	35.6 (121/340) (30.7, 40.8)	64.4 (219/340) (59.2, 69.3)	0.78 (0.64, 0.96)
Negative	51	794	845	-	**94.0 (794/845) (92.2, 95.4)**	0.09 (0.07, 0.12)
Total	880	1247	2127			

The results for female subjects are presented in the following table.

	Female Subjects					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 25.00% (55/220)						
Positive	45	20	65	**69.2 (45/65) (57.2, 79.1)**	-	6.75 (4.39, 10.37)
Grayzone	3	7	10	30.0 (3/10) (10.8, 60.3)	70.0 (7/10) (39.7, 89.2)	1.29 (0.34, 4.80)
Negative	7	138	145	-	**95.2 (138/145) (90.4, 97.6)**	0.15 (0.08, 0.31)
Total	55	165	220			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 36.70% (236/643)						
Positive	173	56	229	**75.5 (173/229) (69.6, 80.7)**	-	5.33 (4.13, 6.88)
Grayzone	35	76	111	31.5 (35/111) (23.6, 40.7)	68.5 (76/111) (59.3, 76.4)	0.79 (0.55, 1.15)
Negative	28	275	303	-	**90.8 (275/303) (87.0, 93.5)**	0.18 (0.12, 0.25)
Total	236	407	643			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 50.90% (85/167)						
Positive	64	19	83	**77.1 (64/83) (67.0, 84.8)**	-	3.25 (2.15, 4.91)

	Female Subjects					
	Adjudicated Diagnosis					
NT-proBNP Result	**HF**	**Non-HF**	**Total**	**Posttest Probability of HF % (n/N) (95% CI)[a]**	**Posttest Probability of Non-HF % (n/N) (95% CI)[a]**	**Likelihood Ratio (HF) (95% CI)[b]**
Grayzone	20	34	54	37.0 (20/54) (25.4, 50.4)	63.0 (34/54) (49.6, 74.6)	0.57 (0.36, 0.90)
Negative	1	29	30	-	**96.7 (29/30) (83.3, 99.4)**	0.03 (0.00, 0.24)
Total	85	82	167			
All Female Subjects[c]						
Pretest Probability of HF (Prevalence of HF in Study): 36.50% (376/1030)						
Positive	282	95	377	**74.8 (282/377) (70.2, 78.9)**	-	5.16 (4.25, 6.27)
Grayzone	58	117	175	33.1 (58/175) (26.6, 40.4)	66.9 (117/175) (59.6, 73.4)	0.86 (0.65, 1.15)
Negative	36	442	478	-	**92.5 (442/478) (89.7, 94.5)**	0.14 (0.10, 0.19)
Total	376	654	1030			

The results for male subjects are presented in the following table.

	Male Subjects					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 43.75% (105/240)						
Positive	95	28	123	**77.2 (95/123) (69.1, 83.8)**	-	4.36 (3.12, 6.10)
Grayzone	4	6	10	40.0 (4/10) (16.8, 68.7)	60.0 (6/10) (31.3, 83.2)	0.86 (0.25, 2.96)
Negative	6	101	107	-	**94.4 (101/107) (88.3, 97.4)**	0.08 (0.03, 0.17)
Total	105	135	240			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 44.71% (317/709)						
Positive	264	92	356	**74.2 (264/356) (69.4, 78.4)**	-	3.55 (2.95, 4.27)
Grayzone	45	71	116	38.8 (45/116) (30.4, 47.9)	61.2 (71/116) (52.1, 69.6)	0.78 (0.56, 1.10)
Negative	8	229	237	-	**96.6 (229/237) (93.5, 98.3)**	0.04 (0.02, 0.09)
Total	317	392	709			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 55.41% (82/148)						
Positive	67	19	86	**77.9 (67/86) (68.1, 85.4)**	-	2.84 (1.92, 4.20)

	Male Subjects					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Grayzone	14	25	39	35.9 (14/39) (22.7, 51.6)	64.1 (25/39) (48.4, 77.3)	0.45 (0.26, 0.80)
Negative	1	22	23	-	**95.7 (22/23) (79.0, 99.2)**	0.04 (0.01, 0.26)
Total	82	66	148			
All Male Subjects[c]						
Pretest Probability of HF (Prevalence of HF in Study): 45.94% (504/1097)						
Positive	426	139	565	**75.4 (426/565) (71.7, 78.8)**	-	3.61 (3.10, 4.19)
Grayzone	63	102	165	38.2 (63/165) (31.1, 45.8)	61.8 (102/165) (54.2, 68.9)	0.73 (0.54, 0.97)
Negative	15	352	367	-	**95.9 (352/367) (93.4, 97.5)**	0.05 (0.03, 0.08)
Total	504	593	1097			

The pretest probability of adjudicated HF (prevalence of adjudicated HF in the study), posttest probabilities, and likelihood ratios of the Alere NT-proBNP for Alinity i result vs adjudicated diagnosis (along with the 95% CIs) were also determined for relevant clinical subgroups using the age-dependent positive cutoffs and age-independent negative cutoff.

The results for subjects with a history of HF are presented in the following table.

	Subjects With History of HF					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 71.70% (114/159)						
Positive	103	17	120	**85.8 (103/120) (78.5, 91.0)**	-	2.39 (1.64, 3.50)
Grayzone	5	3	8	62.5 (5/8) (30.6, 86.3)	37.5 (3/8) (13.7, 69.4)	0.66 (0.16, 2.64)
Negative	6	25	31	-	**80.6 (25/31) (63.7, 90.8)**	0.09 (0.04, 0.22)
Total	114	45	159			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 65.09% (427/656)						
Positive	344	82	426	**80.8 (344/426) (76.7, 84.2)**	-	2.25 (1.88, 2.69)
Grayzone	58	45	103	56.3 (58/103) (46.7, 65.5)	43.7 (45/103) (34.5, 53.3)	0.69 (0.48, 0.99)
Negative	25	102	127	-	**80.3 (102/127) (72.6, 86.3)**	0.13 (0.09, 0.20)
Total	427	229	656			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 69.31% (131/189)						
Positive	107	22	129	**82.9 (107/129) (75.5, 88.5)**	-	2.15 (1.53, 3.02)

	Subjects With History of HF					
	Adjudicated Diagnosis					
NT-proBNP Result	**HF**	**Non-HF**	**Total**	**Posttest Probability of HF % (n/N) (95% CI)[a]**	**Posttest Probability of Non-HF % (n/N) (95% CI)[a]**	**Likelihood Ratio (HF) (95% CI)[b]**
Grayzone	24	21	45	53.3 (24/45) (39.1, 67.1)	46.7 (21/45) (32.9, 60.9)	0.51 (0.31, 0.83)
Negative	0	15	15	-	**100.0 (15/15) (79.6, 100.0)**	0.01 (0.00, 0.24)
Total	131	58	189			
All Subjects With History of HF[c]						
Pretest Probability of HF (Prevalence of HF in Study): 66.93% (672/1004)						
Positive	554	121	675	**82.1 (554/675) (79.0, 84.8)**	-	2.26 (1.95, 2.62)
Grayzone	87	69	156	55.8 (87/156) (47.9, 63.3)	44.2 (69/156) (36.7, 52.1)	0.62 (0.47, 0.83)
Negative	31	142	173	-	**82.1 (142/173) (75.7, 87.1)**	0.11 (0.07, 0.16)
Total	672	332	1004			

The results for subjects without a history of HF are presented in the following table.

	Subjects Without History of HF					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 15.28% (46/301)						
Positive	37	31	68	**54.4 (37/68) (42.7, 65.7)**	-	6.62 (4.62, 9.48)
Grayzone	2	10	12	16.7 (2/12) (4.7, 44.8)	83.3 (10/12) (55.2, 95.3)	1.11 (0.25, 4.90)
Negative	7	214	221	-	**96.8 (214/221) (93.6, 98.5)**	0.18 (0.09, 0.36)
Total	46	255	301			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 18.10% (126/696)						
Positive	93	66	159	**58.5 (93/159) (50.7, 65.9)**	-	6.37 (4.97, 8.18)
Grayzone	22	102	124	17.7 (22/124) (12.0, 25.4)	82.3 (102/124) (74.6, 88.0)	0.98 (0.64, 1.48)
Negative	11	402	413	-	**97.3 (402/413) (95.3, 98.5)**	0.12 (0.07, 0.22)
Total	126	570	696			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 28.57% (36/126)						
Positive	24	16	40	**60.0 (24/40) (44.6, 73.7)**	-	3.75 (2.27, 6.19)

	Subjects Without History of HF					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Grayzone	10	38	48	20.8 (10/48) (11.7, 34.3)	79.2 (38/48) (65.7, 88.3)	0.66 (0.37, 1.17)
Negative	2	36	38	-	**94.7 (36/38) (82.7, 98.5)**	0.14 (0.04, 0.55)
Total	36	90	126			
All Subjects Without History of HF[c]						
Pretest Probability of HF (Prevalence of HF in Study): 18.52% (208/1123)						
Positive	154	113	267	**57.7 (154/267) (51.7, 63.5)**	-	6.00 (4.96, 7.25)
Grayzone	34	150	184	18.5 (34/184) (13.5, 24.7)	81.5 (150/184) (75.3, 86.5)	1.00 (0.71, 1.40)
Negative	20	652	672	-	**97.0 (652/672) (95.4, 98.1)**	0.13 (0.09, 0.21)
Total	208	915	1123			

Patients with a history of HF had a higher rate of false positives compared to patients without a history of HF. Of the 332 total patients with a history of HF and adjudicated as non-HF, 121 (36.4%) had NT-proBNP concentrations greater than or equal to age-dependent cutoffs. Of the 915 total patients with no history of HF and adjudicated as non-HF, 113 (12.3%) had NT-proBNP concentrations greater than or equal to age-dependent cutoffs. This difference is likely due to long-standing chronic elevation of NT-proBNP in patients with a previous diagnosis of HF. Results should always be

assessed in conjunction with patient's medical history, clinical examination, and other findings.

The results for subjects with an eGFR less than 60 mL/min/1.73 m^2 are presented in the following table. This group was comprised of 548 patients with an eGFR between 30 and less than 60 mL/min/1.73 m^2 and 80 patients with an eGFR less than 30 mL/min/1.73 m^2.

	Subjects With eGFR < 60 mL/min/1.73 m^2					
	Adjudicated Diagnosis					
NT-proBNP Result	**HF**	**Non-HF**	**Total**	**Posttest Probability of HF % (n/N) (95% CI)[a]**	**Posttest Probability of Non-HF % (n/N) (95% CI)[a]**	**Likelihood Ratio (HF) (95% CI)[b]**
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 72.22% (39/54)						
Positive	37	5	42	**88.1 (37/42) (75.0, 94.8)**	-	2.85 (1.39, 5.84)
Grayzone	1	0	1	100.0 (1/1) (20.7, 100.0)	0.0 (0/1) (0.0, 79.3)	1.18 (0.05, 27.37)
Negative	1	10	11	-	**90.9 (10/11) (62.3, 98.4)**	0.04 (0.01, 0.28)
Total	39	15	54			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 57.11% (237/415)						
Positive	201	58	259	**77.6 (201/259) (72.1, 82.3)**	-	2.60 (2.09, 3.24)
Grayzone	27	50	77	35.1 (27/77) (25.3, 46.2)	64.9 (50/77) (53.8, 74.7)	0.41 (0.26, 0.62)

	Subjects With eGFR < 60 mL/min/1.73 m^2					
	Adjudicated Diagnosis					
NT-proBNP Result	**HF**	**Non-HF**	**Total**	**Posttest Probability of HF % (n/N) (95% CI)[a]**	**Posttest Probability of Non-HF % (n/N) (95% CI)[a]**	**Likelihood Ratio (HF) (95% CI)[b]**
Negative	9	70	79	-	**88.6 (70/79) (79.7, 93.9)**	0.10 (0.05, 0.19)
Total	237	178	415			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 59.12% (94/159)						
Positive	78	22	100	**78.0 (78/100) (68.9, 85.0)**	-	2.45 (1.72, 3.49)
Grayzone	16	22	38	42.1 (16/38) (27.9, 57.8)	57.9 (22/38) (42.2, 72.1)	0.50 (0.29, 0.88)
Negative	0	21	21	-	**100.0 (21/21) (84.5, 100.0)**	0.02 (0.00, 0.26)
Total	94	65	159			
All Subjects With eGFR < 60 mL/min/1.73 m^2 [c]						
Pretest Probability of HF (Prevalence of HF in Study): 58.92% (370/628)						
Positive	316	85	401	**78.8 (316/401) (74.5, 82.5)**	-	2.59 (2.17, 3.10)
Grayzone	44	72	116	37.9 (44/116) (29.6, 47.0)	62.1 (72/116) (53.0, 70.4)	0.43 (0.30, 0.60)
Negative	10	101	111	-	**91.0 (101/111) (84.2, 95.0)**	0.07 (0.04, 0.13)
Total	370	258	628			

The results for subjects with an eGFR greater than or equal to 60 mL/min/1.73 m^2 are presented in the following table.

	Subjects With eGFR ≥ 60 mL/min/1.73 m^2					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 30.25% (121/400)						
Positive	103	43	146	**70.5 (103/146) (62.7, 77.3)**	-	5.52 (4.15, 7.34)
Grayzone	6	13	19	31.6 (6/19) (15.4, 54.0)	68.4 (13/19) (46.0, 84.6)	1.06 (0.41, 2.73)
Negative	12	223	235	-	**94.9 (223/235) (91.3, 97.1)**	0.12 (0.07, 0.21)
Total	121	279	400			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 33.51% (312/931)						
Positive	232	90	322	**72.0 (232/322) (66.9, 76.7)**	-	5.11 (4.18, 6.26)
Grayzone	53	97	150	35.3 (53/150) (28.1, 43.3)	64.7 (97/150) (56.7, 71.9)	1.08 (0.80, 1.47)
Negative	27	432	459	-	**94.1 (432/459) (91.6, 95.9)**	0.12 (0.09, 0.18)
Total	312	619	931			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 46.45% (72/155)						

NT-proBNP Result	Adjudicated Diagnosis: HF	Adjudicated Diagnosis: Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Subjects With eGFR ≥ 60 mL/min/1.73 m²						
Positive	52	16	68	**76.5 (52/68) (65.1, 85.0)**	-	3.75 (2.36, 5.95)
Grayzone	18	37	55	32.7 (18/55) (21.8, 45.9)	67.3 (37/55) (54.1, 78.2)	0.56 (0.35, 0.89)
Negative	2	30	32	-	**93.8 (30/32) (79.9, 98.3)**	0.08 (0.02, 0.31)
Total	72	83	155			
All Subjects With eGFR ≥ 60 mL/min/1.73 m² [c]						
Pretest Probability of HF (Prevalence of HF in Study): 33.98% (505/1486)						
Positive	387	149	536	**72.2 (387/536) (68.3, 75.8)**	-	5.05 (4.32, 5.89)
Grayzone	77	147	224	34.4 (77/224) (28.5, 40.8)	65.6 (147/224) (59.2, 71.5)	1.02 (0.79, 1.31)
Negative	41	685	726	-	**94.4 (685/726) (92.4, 95.8)**	0.12 (0.09, 0.16)
Total	505	981	1486			

Patients with an eGFR less than 60 mL/min/1.73 m^2 had a higher rate of false positives compared to patients with an eGFR greater than or equal to 60 mL/min/1.73 m^2. Of the 258 total patients with an eGFR less than 60 mL/min/1.73 m^2 and adjudicated as non-HF, 85 (32.9%) had NT-proBNP concentrations greater than or equal to age-dependent cutoffs. Of the 981 total patients with an eGFR greater than or equal to

60 mL/min/1.73 m^2 and adjudicated as non-HF, 149 (15.2%) had NT-proBNP concentrations greater than or equal to age-dependent cutoffs. Eight patients adjudicated as non-HF (0.6%) had an unknown eGFR. Patients with an eGFR less than 60 mL/min/1.73 m^2 had a higher rate of false negatives (9.0% [10/111]) compared to patients with an eGFR greater than or equal to 60 mL/min/1.73 m^2 (5.6% [41/726]). All 10 of the false negatives in the eGFR less than 60 mL/min/1.73 m^2 group were from patients with a BMI greater than or equal to 30 kg/m^2. In patients with eGFR less than 60 mL/min/1.73 m^2, caution should be used when interpreting NT-proBNP results. Results should always be assessed in conjunction with the patient's medical history, clinical examination, and other findings.

The results for subjects with a BMI greater than or equal to 30 kg/m^2 are presented in the following table.

	Subjects With BMI ≥ 30 kg/m^2					
	Adjudicated Diagnosis					
NT-proBNP Result	**HF**	**Non-HF**	**Total**	**Posttest Probability of HF % (n/N) (95% CI)[a]**	**Posttest Probability of Non-HF % (n/N) (95% CI)[a]**	**Likelihood Ratio (HF) (95% CI)[b]**
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 40.75% (108/265)						
Positive	90	26	116	**77.6 (90 / 116) (69.2, 84.2)**	-	5.03 (3.51, 7.22)
Grayzone	7	8	15	46.7 (7 / 15) (24.8, 69.9)	53.3 (8 / 15) (30.1, 75.2)	1.27 (0.48, 3.40)
Negative	11	123	134	-	**91.8 (123 / 134) (85.9, 95.4)**	0.13 (0.07, 0.23)
Total	108	157	265			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 46.92% (328/699)						

	Subjects With BMI ≥ 30 kg/m²					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Positive	231	54	285	**81.1** **(231 / 285)** **(76.1, 85.2)**	-	4.84 (3.74, 6.25)
Grayzone	67	64	131	51.1 (67 / 131) (42.7, 59.5)	48.9 (64 / 131) (40.5, 57.3)	1.18 (0.87, 1.61)
Negative	30	253	283	-	**89.4** **(253 / 283)** **(85.3, 92.5)**	0.13 (0.09, 0.19)
Total	328	371	699			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 59.81% (64/107)						
Positive	48	5	53	**90.6** **(48 / 53)** **(79.7, 95.9)**	-	6.45 (2.80, 14.88)
Grayzone	16	19	35	45.7 (16 / 35) (30.5, 61.8)	54.3 (19 / 35) (38.2, 69.5)	0.57 (0.33, 0.97)
Negative	0	19	19	-	**100.0** **(19/19)** **(83.2, 100.0)**	0.02 (0.00, 0.28)
Total	64	43	107			
All Subjects With BMI ≥ 30 kg/m² [c]						
Pretest Probability of HF (Prevalence of HF in Study): 46.69% (500/1071)						
Positive	369	85	454	**81.3** **(369/454)** **(77.4, 84.6)**	-	4.96 (4.05, 6.07)

	Subjects With BMI ≥ 30 kg/m^2					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Grayzone	90	91	181	49.7 (90/181) (42.5, 56.9)	50.3 (91/181) (43.1, 57.5)	1.13 (0.87, 1.47)
Negative	41	395	436	-	**90.6 (395/436) (87.5, 93.0)**	0.12 (0.09, 0.16)
Total	500	571	1071			

The results for subjects with a BMI less than 30 kg/m^2 are presented in the following table.

	Subjects With BMI < 30 kg/m^2					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 30.41% (45/148)						
Positive	44	16	60	**73.3 (44/60) (61.0, 82.9)**	-	6.29 (4.00, 9.90)
Grayzone	0	4	4	0.0 (0/4) (0.0, 49.0)	100.0 (4/4) (51.0, 100.0)	0.25 (0.01, 4.60)
Negative	1	83	84	-	**98.8 (83/84) (93.6, 99.8)**	0.03 (0.00, 0.19)
Total	45	103	148			

NT-proBNP Result	Subjects With BMI < 30 kg/m²					
	Adjudicated Diagnosis			Posttest Probability of HF % (n/N)	Posttest Probability of Non-HF % (n/N)	Likelihood Ratio (HF)
	HF	Non-HF	Total	(95% CI)[a]	(95% CI)[a]	(95% CI)[b]
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 36.46% (198/543)						
Positive	185	80	265	**69.8 (185/265) (64.0, 75.0)**	-	4.03 (3.31, 4.90)
Grayzone	9	69	78	11.5 (9/78) (6.2, 20.5)	88.5 (69/78) (79.5, 93.8)	0.23 (0.12, 0.45)
Negative	4	196	200	-	**98.0 (196/200) (95.0, 99.2)**	0.04 (0.01, 0.09)
Total	198	345	543			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 51.08% (95/186)						
Positive	76	31	107	**71.0 (76/107) (61.8, 78.8)**	-	2.35 (1.73, 3.18)
Grayzone	17	32	49	34.7 (17/49) (22.9, 48.7)	65.3 (32/49) (51.3, 77.1)	0.51 (0.30, 0.85)
Negative	2	28	30	-	**93.3 (28/30) (78.7, 98.2)**	0.07 (0.02, 0.28)
Total	95	91	186			
All Subjects With BMI < 30 kg/m² [c]						
Pretest Probability of HF (Prevalence of HF in Study): 38.54% (338/877)						
Positive	305	127	432	**70.6 (305/432) (66.1, 74.7)**	-	3.83 (3.28, 4.48)

	Subjects With BMI < 30 kg/m^2					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Grayzone	26	105	131	19.8 (26/131) (13.9, 27.5)	80.2 (105/131) (72.5, 86.1)	0.39 (0.26, 0.59)
Negative	7	307	314	-	**97.8 (307/314) (95.5, 98.9)**	0.04 (0.02, 0.08)
Total	338	539	877			

Patients with a BMI greater than or equal to 30 kg/m^2 had a higher rate of false negatives compared to patients with a BMI less than 30 kg/m^2. Of the total observed false negatives (51/880), 41 (80.4%) were from patients with a BMI greater than or equal to 30 kg/m^2, 7 (13.7%) were from patients with a BMI less than 30 kg/m^2, and 3 (5.9%) were from patients with an unknown BMI. In patients with a BMI less than 30 kg/m^2, the age greater than 75 years group had a higher rate of false negatives (6.7% [2/30]) than the other age groups. Results should always be assessed in conjunction with the patient's medical history, clinical examination, and other findings. In patients with obesity, natriuretic peptides should be interpreted with caution.

The results for subjects with comorbidities are presented in the following table. Comorbidities include at least one of the following: diabetes, renal dysfunction (eGFR less than 60 mL/min/1.73 m^2), hypertension, and/or chronic obstructive pulmonary disease (COPD). Patients with these comorbidities had a higher rate of false positives compared to patients without these comorbidities.

	Subjects With Comorbidities					
	Adjudicated Diagnosis					
NT-proBNP Result	HF	Non-HF	Total	Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 43.67% (131/300)						
Positive	115	34	149	**77.2 (115/149) (69.8, 83.2)**	-	4.36 (3.21, 5.93)
Grayzone	7	10	17	41.2 (7/17) (21.6, 64.0)	58.8 (10/17) (36.0, 78.4)	0.90 (0.35, 2.31)
Negative	9	125	134	-	**93.3 (125/134) (87.7, 96.4)**	0.09 (0.05, 0.18)
Total	131	169	300			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 43.23% (527/1219)						
Positive	415	136	551	**75.3 (415/551) (71.6, 78.7)**	-	4.01 (3.42, 4.69)
Grayzone	78	133	211	37.0 (78/211) (30.7, 43.7)	63.0 (133/211) (56.3, 69.3)	0.77 (0.60, 0.99)
Negative	34	423	457	-	**92.6 (423/457) (89.8, 94.6)**	0.11 (0.08, 0.15)
Total	527	692	1219			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 55.25% (163/295)						
Positive	128	36	164	**78.0 (128/164) (71.1, 83.7)**	-	2.88 (2.15, 3.85)

	Subjects With Comorbidities					
	Adjudicated Diagnosis					
NT-proBNP Result	**HF**	**Non-HF**	**Total**	**Posttest Probability of HF % (n/N) (95% CI)[a]**	**Posttest Probability of Non-HF % (n/N) (95% CI)[a]**	**Likelihood Ratio (HF) (95% CI)[b]**
Grayzone	33	48	81	40.7 (33/81) (30.7, 51.6)	59.3 (48/81) (48.4, 69.3)	0.56 (0.38, 0.81)
Negative	2	48	50	-	**96.0 (48/50) (86.5, 98.9)**	0.03 (0.01, 0.14)
Total	163	132	295			
All Subjects With Comorbidities[c]						
Pretest Probability of HF (Prevalence of HF in Study): 45.26% (821/1814)						
Positive	658	206	864	**76.2 (658/864) (73.2, 78.9)**	-	3.86 (3.41, 4.38)
Grayzone	118	191	309	38.2 (118/309) (32.9, 43.7)	61.8 (191/309) (56.3, 67.1)	0.75 (0.61, 0.92)
Negative	45	596	641	-	**93.0 (596/641) (90.7, 94.7)**	0.09 (0.07, 0.12)
Total	821	993	1814			

The results for subjects without comorbidities are presented in the following table.

	Subjects Without Comorbidities					
	Adjudicated Diagnosis			Posttest Probability of HF % (n/N) (95% CI)[a]	Posttest Probability of Non-HF % (n/N) (95% CI)[a]	Likelihood Ratio (HF) (95% CI)[b]
NT-proBNP Result	HF	Non-HF	Total			
Age Group: 18 to < 50 Years						
Pretest Probability of HF (Prevalence of HF in Study): 18.13% (29/160)						
Positive	25	14	39	**64.1 (25/39) (48.4, 77.3)**	-	8.07 (4.81, 13.51)
Grayzone	0	3	3	0.0 (0/3) (0.0, 56.1)	100.0 (3/3) (43.9, 100.0)	0.64 (0.03, 12.00)
Negative	4	114	118	-	**96.6 (114/118) (91.6, 98.7)**	0.16 (0.06, 0.39)
Total	29	131	160			
Age Group: 50 to 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 19.55% (26/133)						
Positive	22	12	34	**64.7 (22/34) (47.9, 78.5)**	-	7.54 (4.32, 13.18)
Grayzone	2	14	16	12.5 (2/16) (3.5, 36.0)	87.5 (14/16) (64.0, 96.5)	0.59 (0.14, 2.43)
Negative	2	81	83	-	**97.6 (81/83) (91.6, 99.3)**	0.10 (0.03, 0.39)
Total	26	107	133			
Age Group: > 75 Years						
Pretest Probability of HF (Prevalence of HF in Study): 20.00% (4/20)						
Positive	3	2	5	**60.0 (3/5) (23.1, 88.2)**	-	6.00 (1.46, 24.69)

	Subjects Without Comorbidities					
	Adjudicated Diagnosis					
NT-proBNP Result	**HF**	**Non-HF**	**Total**	**Posttest Probability of HF % (n/N) (95% CI)[a]**	**Posttest Probability of Non-HF % (n/N) (95% CI)[a]**	**Likelihood Ratio (HF) (95% CI)[b]**
Grayzone	1	11	12	8.3 (1/12) (1.5, 35.4)	91.7 (11/12) (64.6, 98.5)	0.36 (0.06, 2.05)
Negative	0	3	3	-	**100.0 (3/3) (43.9, 100.0)**	0.52 (0.03, 8.39)
Total	4	16	20			
All Subjects Without Comorbidities[c]						
Pretest Probability of HF (Prevalence of HF in Study): 18.85% (59/313)						
Positive	50	28	78	**64.1 (50/78) (53.0, 73.9)**	-	7.69 (5.33, 11.08)
Grayzone	3	28	31	9.7 (3/31) (3.3, 24.9)	90.3 (28/31) (75.1, 96.7)	0.46 (0.15, 1.47)
Negative	6	198	204	-	**97.1 (198/204) (93.7, 98.6)**	0.13 (0.06, 0.28)
Total	59	254	313			

[a] The Wilson score method was used to calculate 95% CI for posttest probability.

[b] The log method was used to calculate 95% CI for likelihood ratio.

[c] The analysis across age groups used the pooled result based on age-dependent positive cutoff and age-independent rule-out cutoff.

The formulas below were used to calculate the pretest probabilities, posttest probabilities, and likelihood ratios in the tables above.

	Adjudicated Diagnosis	
Alere NT-proBNP for Alinity i Result	**HF**	**Non-HF**
Positive (≥ age-dependent cutoff)	A	B
Grayzone (≥ 300 pg/mL to < age-dependent cutoff)	C	D

	Adjudicated Diagnosis	
Alere NT-proBNP for Alinity i Result	**HF**	**Non-HF**
Negative (< 300 pg/mL [age-independent rule-out cutoff])	E	F

Posttest probability of HF:

- Posttest probability of HF for positive test results = A/(A+B)
- Posttest probability of HF for grayzone test results = C/(C+D)

Posttest probability of non-HF:

- Posttest probability of non-HF for grayzone test results = D/(C+D)
- Posttest probability of non-HF for negative test results = F/(E+F)

Likelihood ratios of HF given Alere NT-proBNP for Alinity i test result category:

- Positive: (A/(A+C+E))/(B/(B+D+F))
- Grayzone: (C/(A+C+E))/(D/(B+D+F))
- Negative: (E/(A+C+E))/(F/(B+D+F))

New York Heart Association (NYHA) Functional Classification

A total of 880 subjects had an NYHA functional classification. Descriptive statistics for the Alere NT-proBNP for Alinity i test results (pg/mL) by NYHA classification for subjects adjudicated to have HF are presented in the table below.

	NYHA Functional Class[a]		
Descriptive Statistics	**II**	**III**	**IV**
All Subjects			
N	12	369	499
Mean	5535.8	5187.5	6485.6
SD	6834.18	7056.92	7829.43
Minimum	89.5	27.1	19.8
5th Percentile	89.5	244.0	303.0
25th Percentile	1319.5	989.4	1492.8
Median	2846.4	2817.5	3928.2
75th Percentile	7399.7	6230.9	8349.3
95th Percentile	23734.0	20653.1	22086.6
Maximum	23734.0	60716.9	59178.1
Female Subjects			

	NYHA Functional Class[a]		
Descriptive Statistics	**II**	**III**	**IV**
N	4	163	209
Mean	5667.6	4216.4	6500.1
SD	6135.91	6073.57	8222.56
Minimum	264.5	27.1	22.8
5th Percentile	264.5	149.2	159.4
25th Percentile	492.6	749.2	1266.5
Median	4542.9	2172.1	3713.5
75th Percentile	11967.5	5022.1	8159.8
95th Percentile	13320.3	19295.7	24566.4
Maximum	13320.3	38880.9	47385.1
Male Subjects			
N	8	206	290
Mean	5469.9	5955.9	6475.2
SD	7566.03	7674.86	7547.84
Minimum	89.5	166.7	19.8
5th Percentile	89.5	365.8	375.5
25th Percentile	1954.8	1221.8	1599.4
Median	2846.4	3702.6	4094.2
75th Percentile	5415.8	7202.5	8515.5
95th Percentile	23734.0	21410.7	21598.1
Maximum	23734.0	60716.9	59178.1

[a] No NYHA Class I subjects were included in the study.

X. Conclusion

The information presented in this 510(k) premarket notification demonstrate that the subject device, Alere NT-proBNP for Alinity i (List Number 04S79), is substantially equivalent to the predicate device, Roche Elecsys proBNP II (K092649).