October 29, 2025

Ortho-Clinical Diagnostics, Inc.
Kristine Tkacs
Senior Manager, Regulatory Affairs
100 Indigo Creek Drive
Rochester, NY 14626

Re: K252393
Trade/Device Name: VITROS Immunodiagnostic Products hs Troponin I Reagent Pack
Regulation Number: 21 CFR 862.1215
Regulation Name: Creatine phosphokinase/creatine kinase or isoenzymes test system
Regulatory Class: Class II
Product Code: MMI
Dated: July 31, 2025
Received: July 31, 2025

Dear Kristine Tkacs:

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.
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: 07/31/2026
See PRA Statement below.

510(k) Number *(if known)*
K252393

Device Name
VITROS Immunodiagnostic Products hs Troponin I Reagent Pack

Indications for Use *(Describe)*
For In Vitro Diagnostic Use

For the quantitative measurement of cardiac troponin I (cTnI) in human plasma (heparin) using the VITROS 5600 Integrated System.

Cardiac troponin I is used to aid in the diagnosis of myocardial infarction (MI).

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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510(k) Summary

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

The assigned 510(k) number is: K252393

Applicant	Ortho-Clinical Diagnostics, Inc. 100 Indigo Creek Drive Rochester, NY 14626 Contact Person: Kristine Tkacs Phone: +1 (908) 218-8085
Device Name	**Trade or Proprietary Names:** VITROS® Immunodiagnostic Products hs Troponin I Reagent Pack **Common Name:** VITROS hs Troponin I Assay **Classification:** Creatine phosphokinase/creatine kinase or isoenzymes test system (862.1215), Class II **Product Code:** MMI
Predicate Device	VITROS Immunodiagnostic Products hs Troponin I Reagent Pack referred to as the VITROS hs Troponin I assay (test) in the remainder of this document, is substantially equivalent to the VITROS Immunodiagnostic Products Troponin I ES Reagent Pack K062838.
Device Description	The VITROS hs Troponin I assay is performed using the VITROS Immunodiagnostic Products hs Troponin I Reagent Pack and the VITROS Immunodiagnostic Products hs Troponin I Calibrators on the VITROS 5600 Integrated System. An immunometric immunoassay technique is used. Cardiac troponin I present in the sample reacts simultaneously with streptavidin-conjugated antibody (mouse monoclonal anti- cTnI), bound by biotin-BSA on the wells, and a horseradish peroxidase (HRP)-labeled antibody conjugate (mouse monoclonal anti-cTnI). The antigen-antibody complex is captured by the antibody on the wells. Unbound materials are removed by washing. The bound HRP conjugate is measured by a luminescent reaction. A reagent containing

	luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The amount of HRP conjugate bound is directly proportional to the concentration of cardiac troponin I present.
Device Intended Use	For in vitro diagnostic use only. For the quantitative measurement of cardiac troponin I (cTnI) in human plasma (heparin) using the VITROS 5600 Integrated System. Cardiac troponin I is used to aid in the diagnosis of myocardial infarction (MI).
Comparison to Predicate Device	Table 1 provides a summary of the key features of the new device assessed against the predicate.

Table 1: Summary of Key Features of VITROS Immunodiagnostic Products hs Troponin I Reagent Pack compared to the Predicate Device

Device Characteristic	Predicate Device VITROS Immunodiagnostic Products Troponin I ES Reagent Pack, K062838	New Device VITROS Immunodiagnostic Products hs Troponin I Reagent Pack, K252393
Similarities		
Indication for Use	For *in vitro* diagnostic use only. For the quantitative measurement of cardiac troponin I (cTnI) in human plasma (heparin) using the VITROS 5600 Integrated System. Cardiac troponin I is used to aid in the diagnosis of myocardial infarction (MI).	Same
Analyte	Cardiac Troponin I	Same
Antibody	Mouse Monoclonal	Same
Type of immunoassay	Sandwich immunoassay	Same

Device Characteristic	Predicate Device VITROS Immunodiagnostic Products Troponin I ES Reagent Pack, K062838	New Device VITROS Immunodiagnostic Products hs Troponin I Reagent Pack, K252393
Similarities		
Detection technology	Chemiluminescence	Same
Traceability	Calibration of the VITROS Troponin I ES test is traceable to in-house reference calibrators, which have been value assigned to correlate to another commercially available test.	Same

Device Characteristic	Predicate Device VITROS Immunodiagnostic Products Troponin I ES Reagent Pack, K062838	New Device VITROS Immunodiagnostic Products hs Troponin I Reagent Pack, K252393
Differences		
Indication for Use	For the quantitative measurement of cardiac Troponin I (cTnI) in human serum (EDTA) Indicated for the risk stratification of patients with non-ST-segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction (MI) or increased probability of ischemic events requiring urgent revascularization procedures	Not indicated for these uses
Sample Type	Serum and plasma (EDTA and lithium heparin)	Lithium heparin plasma
Measuring Range	12-80,000 ng/L	2.25–30,000 ng/L
Detection Limit	LoB: 0.007 ng/mL LoD: 0.012 ng/mL LoQ: 0.012 ng/mL	LoB: 0.19 ng/L LoD: 0.59 ng/L LoQ: 2.25 ng/L
Upper 99th percentile cut-off	34 ng/L	Female: 9 ng/L Male: 12 ng/L Overall: 11 ng/L

Nonclinical performance

The following nonclinical tests were performed.

Precision

Precision was evaluated consistent with CLSI document EP05-A3. Two replicates each of four

human lithium heparin plasma patient pools and two controls were tested on two separate occasions per day on at least 20 different test days. The experiment was performed using three reagent lots on one VITROS 5600 Integrated System. The test was designed to have within-laboratory precision of ≤20% at or near the LoQ, ≤10% at the 99th percentile, and <7% between the 99th percentile and 30,000 ng/L. Representative performance data are shown below.

VITROS System	Conc. Units - ng/L (pg/mL)							No. Observe.	No. Days
	Mean hs Troponin I Conc.	Within-run*		Within-calibration**		Within-lab***			
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
5600	5.48	0.141	2.7	0.254	4.9	0.422	7.4	80	20
	11.66	0.308	2.7	0.566	4.9	0.633	5.4	80	20
	65.27	1.143	1.8	1.907	3.0	2.602	3.9	80	20
	309.2	3.42	1.1	9.15	3.0	9.56	3.0	80	20
	14,090	262.7	1.9	415.8	3.0	764.8	5.4	80	20
	18,460	236.3	1.3	565.0	3.1	544.8	2.9	80	20

* Within-run (repeatability). Between Duplicate precision averaged over all runs.
** Within-calibration. Total precision with weighted components of within-run, between-run, and between-day variation.
*** Within-lab. A measure of the effect of recalibration on total precision, calculated within reagent lot, using data from at least 4 calibrations.

Detection Limit

The Limit of Detection (LoD) for the VITROS hs Troponin I test was consistent with CLSI document EP17-A2. The observed LoD was determined to be 0.59 ng/L. The observed Limit of Quantitation (LoQ) at 20% CV was determined to be 0.59 ng/L, consistent with CLSI document EP17-A2. The claimed LoQ is set at 0.59 ng/L.

LoD	LoQ (20% CV)
0.59 ng/L	0.59ng/L

Linearity

Linearity studies were performed in line with CLSI document EP06 2nd edition. The linearity of the VITROS hs Troponin I test was established following CLSI EP06-ED2. For cTnI, the measurement procedure shows linearity for the interval from 2.25 to 30,000 ng/L, with deviations from linearity within +/- 10%.

Two studies were conducted. The first study used test fluids comprised of human plasma (troponin-stripped/low protease/buffer matrix) and spanned the entire measuring interval using 11 levels with a minimum of 3 replicates for each level, the observed % deviation from linearity ranged from -4.2% to 2.3%. The second study used lithium heparin plasma patient samples and spanned the low end up to 4799 ng/L with 12 levels and a minimum of 5 replicates for each level, the observed % deviation from linearity ranged from -9.0% to 8.5%.

Analytical Specificity

Known Interferences

The VITROS hs Troponin I test was evaluated for interference in lithium heparin plasma samples with cTnI concentrations of approximately 10.00 ng/L and 350.0 ng/L, consistent with CLSI EP07 3rd edition and EP37 1st edition. The following compounds, when tested at the concentrations indicated, caused the biases shown.

Substance	Interferent concentration	cTnI conc.	Effect when above the concentration limit	% Interference
Bilirubin, unconjugated	40 mg/dL	11.2 ng/L	Decreased cTnI results	-10%
	40 mg/dL	330 ng/L	Decreased cTnI results	-6%
Cefoxitin Sodium	523 mg/dL	11.2 ng/L	Decreased cTnI results	-8%
Dextran	600 mg/dL	13.1 ng/L	Increased cTnI results	+8%
	600 mg/dL	385 ng/L	Increased cTnI results	+5%
Fibrinogen	500 mg/dL	8.8 ng/L	Decreased cTnI results	-3%
Hemoglobin	750 mg/dL	320 ng/L	Decreased cTnI results	-9%
Streptokinase*	37,500 U/dL	12.0 ng/L	Decreased cTnI results	-79%
	37,500 U/dL	390 ng/L	Decreased cTnI results	-65%
tPA (alteplase)	0.6 mg/dL	11.8 ng/L	Decreased cTnI results	-9%
	0.3 mg/dL	386 ng/L	Decreased cTnI results	-5%
Total protein**	10.2 g/dL	10.3 ng/L	Decreased cTnI results	-1%
	10.1 g/dL	390 ng/L	Increased cTnI results	+3%

*Streptokinase is not commercially available in the United States.

**Test results compared to a control sample with total protein concentration of 7.3 g/dL.

Note: These results are representative. The degree of interference at concentrations other than those listed might not be predictable from these results. Other interfering substances may be encountered in the patient population.

Other Limitations

- Dextran at therapeutic doses significantly interferes with this test. This test should not be used on patients taking Dextran. An alternate method not subject to Dextran interference should be used.

- Heterophile as well as human anti-animal antibodies (most common human anti-mouse antibodies or HAMA) in serum or plasma of certain individuals are known to cause interference with immunoassays.[1] The anti-animal antibodies may be present in blood samples from individuals regularly exposed to animals or who have received preparations

[1] Tate J, Ward G. Interferences in Immunoassay. Clin Biochem Rev. Vol 25: 105-120; May 2004.

of mouse monoclonal antibodies for diagnosis or therapy. Results inconsistent with clinical observations indicate the need for additional testing.

- Troponin autoantibodies have been reported to be present in approximately 10% to 20% of patients presenting to the emergency department (ED) and may lead to falsely low troponin assay results and delay in treatment of acute coronary syndrome.[2,3]Therefore, a test result that is inconsistent with the clinical picture and patient history should be interpreted with caution.

Substances that do not Interfere

The VITROS hs Troponin I test was evaluated for interference in lithium heparin plasma samples consistent with CLSI EP07 and EP37. Of the compounds tested, none was found to cause a bias of >10% with the test at the concentrations indicated at nominal cTnI concentrations of 10.00 ng/L and 350.0 ng/L.

Compound	Concentration	
Acetaminophen	156 µg/mL	1030 µmol/L
Acetylcysteine	15 mg/dL	919 µmol/L
Adrenaline (epinephrine)	20 µg/dL	1.09 µmol/L
Allopurinol	6.0 mg/dL	441 µmol/L
Alprazolam	0.0258 mg/dL	0.835 µmol/L
Ambroxol	63 µg/dL	1.52 µmol/L
Amlodipine besylate	0.0104 mg/dL	0.183 µmol/L
Amoxicillin	5.40 mg/dL	148 µmol/L
Ascorbic acid	5.25 mg/dL	298 µmol/L
Atorvastatin calcium	0.162 mg/dL	1.34 µmol/L
Benazepril HCl	0.044 mg/dL	0.954 µmol/L
Bilirubin, conjugated	40 mg/dL	475 µmol/L
Biotin	3510 ng/mL	14,300 nmol/L
Bivalirudin	2.18 mg/dL	10.0 µmol/L
Caffeine	10.8 mg/dL	556 µmol/L
Carvedilol	43.2 µg/dL	1.06 µmol/L
Ceftriaxone disodium hemi(heptahydrate)	100 mg/dL	1510 µmol/L
Cephalexin sodium	13.4 mg/dL	363 µmol/L
Cholesterol	400 mg/dL	10.3 mmol/L
Cinnarizine	108 µg/dL	2.93 µmol/L
Clopidogrel	2.4 µg/dL	0.057 µmol/L
Cocaine	0.6 mg/dL	17.7 µmol/L
Cotinine	0.24 mg/dL	4.89 µmol/L
Cyclosporin A	0.18 mg/dL	1.50 µmol/L
Digoxin	0.0039 mg/dL	0.0499 µmol/L

[2] Park JY, Jaffe AS. Troponin autoantibodies: from assay interferent to mediator of cardiotoxicity. Clin Chem 2017; 63(1):30-32.
[3] Nussinovitch U, Shoenfeld Y. Anti-troponin autoantibodies and the cardiovascular system. Heart 2010;96(19):1518-1524

Compound	Concentration	
Diphenhydramine	0.0774 mg/dL	3.03 µmol/L
Dopamine	0.0621 mg/dL	4.06 µmol/L
Enalaprilat	0.0819 mg/dL	2.35 µmol/L
Enoxaparin (LMWH)	360 U/dL	N/A
Eptifibatide	1.44 mg/dL	17.3 µmol/L
Erythromycin	13.8 mg/dL	188 µmol/L
Ethanol	600 mg/dL	130,000 µmol/L
Fondaparinux	0.39 mg/dL	2.26 µmol/L
Furosemide	1.59 mg/dL	48.1 µmol/L
HAMA (human anti-mouse antibodies)	800 µg/L	0.005 µmol/L
Heparin (Sodium), UFH	330 U/dL	N/A
Ibuprofen	21.9 mg/dL	1060 µmol/L
Insulin	3.12 µg/dL	0.005 µmol/L
L-dopa (Levodopa)	0.75 mg/dL	38.0 µmol/L
Levothyroxine	0.0429 mg/dL	0.552 µmol/L
Lidocaine	1.5 mg/dL	64.0 µmol/L
Methylprednisolone	0.783 mg/dL	20.9 µmol/L
Metronidazole	12.3 mg/dL	719 µmol/L
Naproxen sodium	39.3 mg/dL	1560 µmol/L
Nifedipine	0.0588 mg/dL	1.70 µmol/L
Nitrofurantoin	0.213 mg/dL	8.94 µmol/L
Nitroglycerin (Nitrostat)	1.2 µg/dL	0.053 µmol/L
Omeprazole	0.84 mg/dL	24.3 µmol/L
Oxycodone	0.0324 mg/dL	1.03 µmol/L
Oxytetracycline	1.2 mg/dL	24.2 µmol/L
Phenytoin	6.0 mg/dL	238 µmol/L
Propranolol HCl	0.115 mg/dL	3.88 µmol/L
Pseudoephedrine	0.330 mg/dL	20.0 µmol/L
Quinidine	1.5 mg/dL	46.2 µmol/L
Rheumatoid Factor	900 IU/mL	N/A
Rifampicin (Rifampin)	4.8 mg/dL	58.3 µmol/L
Rivaroxaban	0.270 mg/dL	6.19 µmol/L
Salicylic acid	2.86 mg/dL	207 µmol/L
Spironolactone	0.0555 mg/dL	1.33 µmol/L
Theophylline	6.0 mg/dL	333 µmol/L
Total Protein	10.1 g/dL	101 g/L
Triglycerides	1500 mg/dL	16.9 mmol/L
Vancomycin hydrochloride	12.3 mg/dL	82.8 µmol/L
Verapamil	0.16 mg/dL	3.51 µmol/L
Vorapaxar	36 µg/dL	0.731 µmol/L
Warfarin sodium	8.0 mg/dL	259 µmol/L

Cross-Reactivity

The cross-reactivity of the VITROS hs Troponin I test was evaluated in lithium heparin plasma by adding the following substances to the respective plasma pools containing no cTnI.

Cross-Reactant	Cross Reactant Concentration		Mean Result of Control Pool	Mean Result of Cross-Reactant Pool	% Cross-Reactivity
	ng/mL	ng/L	ng/L (pg/mL)	ng/L (pg/mL)	
Actin (from Rabbit Muscle)	1000	1000000	*	*	*
Cardiac Troponin C (Recombinant)	1000	1000000	*	11.01	0.0
Cardiac Troponin T (Recombinant)	1000	1000000	*	*	*
CK-MB (Recombinant)	1000	1000000	*	*	*
Myoglobin (Recombinant)	1000	1000000	*	*	*
Myosin (Recombinant)	1000	1000000	*	*	*
Skeletal Troponin I	1000	1000000	*	*	*
Tropomyosin (from porcine muscle)	1000	1000000	*	*	*

* Not Detectable. Concentration was below the measuring range of the test, 2.25 - 30,000 ng/L (pg/mL).

The cross-reactivity of the VITROS hs Troponin I test was evaluated in lithium heparin plasma by adding the following substances to the respective plasma pools containing cTnI at a concentration of approximately 10.00 ng/L.

Cross-Reactant	Cross Reactant Concentration		Mean Result of Control Pool	Mean Result of Cross-Reactant Pool	% Cross-Reactivity
	ng/mL	ng/L	ng/L (pg/mL)	ng/L (pg/mL)	
Actin (from Rabbit Muscle)	1000	1000000	11.65	11.94	0.0
Cardiac Troponin C (Recombinant)	1000	1000000	11.65	26.70	0.0
Cardiac Troponin T (Recombinant)	1000	1000000	11.65	11.64	0.0
CK-MB (Recombinant)	1000	1000000	12.39	14.53	0.0
Myoglobin (Recombinant)	1000	1000000	12.39	11.73	0.0
Myosin (Recombinant)	1000	1000000	12.39	11.35	0.0
Skeletal Troponin I	1000	1000000	11.65	15.31	0.0
Tropomyosin (from porcine muscle)	1000	1000000	12.39	13.69	0.0

Cross-reactivity was expressed as the mean result obtained for the cross-reactant pool minus the mean result obtained for the control sample divided by the cross-reactant concentration in percentage terms.

$$\% \text{ Cross-reactivity} = \frac{(\text{Mean Troponin I Result Cross-reactant Pool}) - (\text{Mean Troponin I Result Control Sample})}{\text{Concentration of Cross-reactant}} \times 100$$

cTnC was spiked into one Lithium Heparin plasma pool with endogenous cTnI at approximately 10.00 ng/L. cTnC (Purified from Human heart tissue, 98% purity) was prepared as a concentrate before spiking into the sample pool to yield a cTnC concentration of 80,000 ng/L. An equal volume of the relevant solvent was added to each of the control pools for comparison. Interim dilutions were also prepared at 75%, 50% and 25% of the high pool, yielding concentrations of 60,000 ng/L, 40,000 ng/L and 20,000 ng/L.

Five replicates were collected for each fluid level. The percent bias between the test/interim dilutions and control samples was calculated: 100 * (Spike – Control Sample)/Control Sample.

	VITROS hsTnI						
Cardiac Troponin C (ng/L)	**Rep 1 (ng/L)**	**Rep 2 (ng/L)**	**Rep 3 (ng/L)**	**Rep 4 (ng/L)**	**Rep 5 (ng/L)**	**Mean (ng/L)**	**% Difference (Mean - Mean_Blank)/Mean_Blank**
0	10.04	10.63	10.24	10.63	10.29	10.37	N/A
20000	10.56	11.03	10.50	10.77	10.57	10.69	3.1%
40000	11.95	12.30	11.39	11.65	11.34	11.73	13.1%
60000	12.40	12.24	12.28	12.29	12.14	12.27	18.3%
80000	11.93	11.89	11.85	11.89	11.76	11.87	14.5%

The results of these tests demonstrate that the performance of the VITROS hs Troponin I assay is not affected by the presence of cTnC up to 20,000 ng/L.

High Dose Hook

The VITROS hs Troponin I test has no high dose hook effect up to a concentration of 100,000ng/L.

Expected Values

The VITROS hs Troponin I 99th percentile URLs were established from lithium heparin plasma of nine hundred fifty-two (952) apparently healthy adults,including 486 female and 466 male subjects. The results included variation from reagent lots, systems, operators, and reagent age. The subjects ranged in age from 22 to 91 years old, with fifty-nine percent of the subjects ≥ 50 years of age.

Subjects were excluded if they met any of the following exclusion criteria:

- History of kidney disease, diabetes, heart disease, cancer, lung disease,thyroid disease, or stroke
- High blood pressure, cholesterol or triglycerides
- Muscle or skeletal injury or surgery in the last 3 months
- Current smoker
- Pregnancy
- Additional exclusion criteria:
- Hemoglobin A1c ≥ 6.5%
- NT-proBNP > 125 pg/mL for subjects < 75 years of age or > 450 pg/mLfor subjects ≥ 75

years of age
- eGFR < 60 mL/min/1.73m^2

The overall observed 99th percentile URL from the 952 lithium heparin plasma samples is 11 ng/L (90% CI of 8.2 – 14.3 ng/L). The 99th percentile URL values and respective 90% Confidence Intervals (CI), determined for lithium heparin plasma (females, males, and overall) using the non -parametric statistical method, are shown in the table below.

Sample Type	Gender	Number of Subjects	99th Percentile URL ng/L (pg/mL)	90% CI* ng/L (pg/mL)
Lithium Heparin Plasma	Female	486	9	3.9 - 17.5
	Male	466	12	8.8 - 20.9
	Overall	952	11	8.2 - 14.3

*CI = Confidence Interval

High Sensitivity Determination

For a troponin test to be labelled as high sensitivity it must fulfil the two IFCC TF-CB established criteria:

- The test should have analytical imprecision (% CV) at the 99th percentile ≤ 10% and
- The test should measure troponin concentrations above the Limit of Detection (LoD) in ≥ 50% of healthy male and subjects ≥ 50% of healthy female subjects.

Data from a Limit of Quantitation (LoQ) study was used to create a best fit regression expressing the relationship between %CV and cTnI concentration in the clinically relevant range. The analytical imprecision around the 99th percentile URL concentrations was estimated using the regression analysis.

Sample Type	Gender	99th PercentileURL ng/L (pg/mL)	%CV Based on LoQ Imprecision Profile
Lithium Heparin Plasma	Female	9	4.7
	Male	12	4.5
	Overall	11	4.5

Greater than 50% of the healthy male subjects and greater than 50% of the healthy female subjects used to establish the 99th percentile had cTnI results equal to or above the claimed LoD. The VITROS hs troponin I test meets the IFCC TF-CB criteria for a high sensitivity cardiac troponin test.[4]

[4] Wu AHB, Christenson RH, Greene DN, et al. Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical

Clinical performance

Results of this test should be used in conjunction with the patient's history, risk factors, clinical presentation, other diagnostic tests, such as electrocardiogram (ECG), and in accordance with the appropriate clinical guidelines to aid in the diagnosis of MI.

A multi-center prospective study was conducted to assess the diagnostic accuracy of the VITROS hs Troponin I test in lithium heparin plasma.

The study included 2145 evaluable subjects from patients presenting with symptoms consistent with acute coronary syndrome (ACS) at 24 Emergency Departments (ED) across the United States. Each subject's diagnosis was determined by an independent adjudication committee consisting of US board-certified cardiologists according to the Fourth Universal Definition of Myocardial Infarction – consensus guideline.[5] The prevalence of adjudicated MI in the study was 8.16% (175/2145).

The diagnostic accuracy of the VITROS hs Troponin I test was determined by quantifying the area under the Receiver Operating Characteristic (ROC)[6] curves (AUC)[7] for each time bracket relative to the time of patient ED presentation, within and across genders. The AUC and the two-tailed 95% confidence intervals (CIs) are presented in the table below: AUC Analysis Results for the VITROS hs Troponin I Test.

AUC Analysis Results for the VITROS hs Troponin I Test

Gender	Time Bracket	N	AUC	95% Confidence Interval
Female	0-2 hours	1042	0.947	0.911- 0.983
	≥2-4 hours	858	0.979	0.966- 0.992
	≥4-6 hours	508	0.963	0.930- 0.996
	≥6-11 hours	541	0.976	0.962- 0.991
Male	0-2 hours	1214	0.902	0.868- 0.937
	≥2-4 hours	979	0.914	0.875- 0.952
	≥4-6 hours	648	0.920	0.876- 0.963
	≥6-11 hours	799	0.937	0.906- 0.969

Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem. 2018;64(4):645–655. doi:10.1373/clinchem.2017.277186.

[5] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation 2018; 138: e618-e651. https://doi.org/10.1161/CIR.0000000000000617

[6] Zweig MH, Campbell G, Receiver-Operating Characteristic (ROC) Plots: A Fundamental Evaluation Tool in Clinical Medicine. Clinical Chemistry, 1993; 39(4):561-577.

[7] Bamber D, The Area Above the Ordinal Dominance Graph and the Area Below the Receiver Operating Characteristic Graph. Journal of Mathematical Psychology. 1975; 12:387-415.

AUC Analysis Results for the VITROS hs Troponin I Test

Gender	Time Bracket	N	AUC	95% Confidence Interval
All Subjects	0-2 hours	2256	0.923	0.898- 0.948
	≥2-4 hours	1837	0.941	0.918- 0.965
	≥4-6 hours	1156	0.935	0.905- 0.965
	≥6-11 hours	1340	0.952	0.931- 0.972

Clinical performance was determined by the following analyses:

VITROS hs Troponin I Test Result	Adjudicated Diagnosis	
	MI	No MI
cTnI >99th percentile cutoff	A	B
cTnI ≤99th percentile cutoff	C	D

- Sensitivity = 100xA/(A+C);
- Specificity = 100xD/(B+D);
- Negative predictive value (NPV), probability of no MI diagnosis in patients with cTnI ≤99th percentile cutoff =100xD/(C+D);
- Positive predictive value (PPV), probability of MI diagnosis in patients with cTnI >99th percentile cutoff = 100xA/(A+B);
- Negative likelihood ratio (LR-), the ratio of the likelihood of false negative results to the likelihood of true negative results= (1-sensitivity)/specificity;
- Positive likelihood ratio (LR+), the ratio of the likelihood of true positive results to the likelihood of false positive results =sensitivity/(1-specificity).

Predictive value analysis is directly related to the prevalence of the disease in the intended use population. Likelihood ratiosare not directly related to the prevalence of the disease in the intended use population and are applicable across populations with varying MI prevalence.

Data analyses were conducted with samples categorized into four time brackets related to patient ED presentation: 0-2 hours, ≥2-4 hours, ≥4-6 hours, and ≥6-11 hours.

The clinical performance of the VITROS hs Troponin I test versus adjudicated diagnosis was determined by time brackets after ED presentation for all subjects using the overall (11 ng/L) 99th percentile cutoff.

All Subjects using 11 ng/L Cutoff (Overall 99th Percentile)

Time Bracket	N	Sensitivity (%) (n/N)	95% CI* (%)	Specificity (%) (n/N)	95% CI* (%)	NPV (%) (n/N)	95% CI* (%)	PPV (%) (n/N)	95% CI* (%)
0-2 hours	2256	85.64 (155/181)	79.78 - 90.00	86.60 (1797/2075)	85.07 - 88.00	98.57 (1797/1823)	97.92 - 99.02	35.80 (155/433)	31.42 - 40.42
≥2-4 hours	1837	90.00 (144/160)	84.37 - 93.75	85.45 (1433/1677)	83.68 - 87.06	98.90 (1433/1449)	98.21 - 99.32	37.11 (144/388)	32.45 - 42.02
≥4-6 hours	1156	92.00 (115/125)	85.90 - 95.60	81.57 (841/1031)	79.09 - 83.82	98.82 (841/851)	97.85 - 99.36	37.70 (115/305)	32.45 - 43.27
≥6-11 hours	1340	93.30 (167/179)	88.65 - 96.12	78.55 (912/1161)	76.10 - 80.82	98.70 (912/924)	97.74 - 99.26	40.14 (167/416)	35.54 - 44.92

* 95% Wilson Score Confidence Interval

Time Bracket	N	LR-	95% CI**	LR+	95% CI*
0-2 hours	2256	0.17	0.12 - 0.24	6.39	5.64 - 7.24
≥2-4 hours	1837	0.12	0.07 - 0.19	6.19	5.45 - 7.02
≥4-6 hours	1156	0.10	0.05 - 0.18	4.99	4.35 - 5.73
≥6-11 hours	1340	0.09	0.05 - 0.15	4.35	3.87 - 4.89

* 95% Confidence Interval

The clinical performance of the VITROS hs Troponin I test versus adjudicated diagnosis was determined by time brackets after ED presentation for female subjects using the gender-specific (9 ng/L) and overall (11 ng/L) 99th percentile cutoffs. Using the female gender-specific (9 ng/L) 99th percentile cutoff instead of the overall (11 ng/L) 99th percentile cutoff may result in a higher proportion of positive test results for females that are not having an MI.

Female Subjects Using Overall (11 ng/L) versus Gender-specific (9 ng/L) 99th Percentile Cutoffs

Time Bracket	99th Percentile Cutoff	Sensitivity (%) (n/N)	95% CI* (%)	Specificity (%) (n/N)	95% CI* (%)	NPV (%) (n/N)	95% CI* (%)	PPV (%) (n/N)	95% CI* (%)
0-2 hours (N=1042)	Gender-specific	88.71 (55/62)	78.48 - 94.42	90.31 (885/980)	88.29 - 92.00	99.22 (885/892)	98.39 - 99.62	36.67 (55/150)	29.38 - 44.62
	Overall	87.10 (54/62)	76.55 - 93.31	91.63 (898/980)	89.73 - 93.21	99.12 (898/906)	98.27 - 99.55	39.71 (54/136)	31.87 - 48.10
≥2-4 hours (N=858)	Gender-specific	95.08 (58/61)	86.51 - 98.31	88.58 (706/797)	86.19 - 90.61	99.58 (706/709)	98.76 - 99.86	38.93 (58/149)	31.47 - 46.94
	Overall	91.80 (56/61)	82.21 - 96.45	90.21 (719/797)	87.95 - 92.09	99.31 (719/724)	98.39 - 99.70	41.79 (56/134)	33.78 - 50.26
≥4-6 hours (N=508)	Gender-specific	97.62 (41/42)	87.68 - 99.58	84.98 (396/466)	81.45 - 87.94	99.75 (396/397)	98.59 - 99.96	36.94 (41/111)	28.54 - 46.21
	Overall	95.24 (40/42)	84.21 - 98.68	86.48 (403/466)	83.08 - 89.29	99.51 (403/405)	98.22 - 99.86	38.83 (40/103)	29.99 - 48.49
≥6-11 hours (N=541)	Gender-specific	96.77 (60/62)	88.98 - 99.11	84.76 (406/479)	81.27 - 87.70	99.51 (406/408)	98.23 - 99.87	45.11 (60/133)	36.91 - 53.59
	Overall	93.55 (58/62)	84.55 - 97.46	86.01 (412/479)	82.62 - 88.83	99.04 (412/416)	97.55 - 99.63	46.40 (58/125)	37.90 - 55.12

*95% Wilson Score Confidence Interval

Time Bracket	99th Percentile Cutoff	LR-	95% CI*	LR+	95% CI**
0-2 hours (N=1042)	Gender-specific	0.13	0.06 - 0.25	9.15	7.41 - 11.30
	Overall	0.14	0.07 - 0.27	10.41	8.28 - 13.08
≥2-4 hours (N=858)	Gender-specific	0.06	0.02 - 0.17	8.33	6.81 - 10.19
	Overall	0.09	0.04 - 0.21	9.38	7.50 - 11.73
≥4-6 hours (N=508)	Gender-specific	0.03	0.00 - 0.19	6.50	5.21 - 8.11
	Overall	0.06	0.01 - 0.21	7.04	5.54 - 8.95
≥6-11 hours (N=541)	Gender-specific	0.04	0.01 - 0.15	6.35	5.12 - 7.88
	Overall	0.08	0.03 - 0.19	6.69	5.31 - 8.43

*95% Confidence Interval

The lower bound of the CI for PPV for female subjects using the gender-specific 99th percentile (9 ng/L) cutoff was as low as 28.54% (≥4-6 hours). Cardiac troponin test results should always be interpreted in conjunction with the patient's signs, symptoms, and other clinical information.

The lower bound of the CI for PPV for female subjects using the overall 99th percentile (11 ng/L) cutoff was as low as 29.99% (at ≥4-6 hours). Cardiac troponin test results should always be interpreted in conjunction with the patient's signs, symptoms, and other clinical information.

The clinical performance of the VITROS hs Troponin I test versus adjudicated diagnosis was determined by time brackets after ED presentation for male subjects using the gender-specific (12 ng/L) and overall (11 ng/L) 99th percentile cutoffs. Using the male gender-specific (12 ng/L) 99th percentile cutoff instead of the overall (11 ng/L) 99th percentile cutoff may result in a higher proportion of negative test results for males that are having an MI.

Male Subjects Using Overall (11 ng/L) versus Gender-specific (12 ng/L) 99th Percentile Cutoffs

Time Bracket	99th Percentile Cutoff	Sensitivity (%) (n/N)	95% CI* (%)	Specificity (%) (n/N)	95% CI* (%)	NPV (%) (n/N)	95% CI* (%)	PPV (%) (n/N)	95% CI* (%)
0-2 hours (N=1214)	Gender-specific	84.03 (100/119)	76.40 - 89.53	83.11 (910/1095)	80.77 - 85.21	97.95 (910/929)	96.83 - 98.69	35.09 (100/285)	29.78 - 40.79
	Overall	84.87 (101/119)	77.35 - 90.21	82.10 (899/1095)	79.72 - 84.26	98.04 (899/917)	96.92 - 98.75	34.01 (101/297)	28.85 - 39.57
≥2-4 hours (N=979)	Gender-specific	88.89 (88/99)	81.19 - 93.68	81.48 (717/880)	78.78 - 83.91	98.49 (717/728)	97.31 - 99.15	35.06 (88/251)	29.42 - 41.15
	Overall	88.89 (88/99)	81.19 - 93.68	81.14 (714/880)	78.42 - 83.58	98.48 (714/725)	97.30 - 99.15	34.65 (88/254)	29.06 - 40.69
≥4-6 hours (N=648)	Gender-specific	89.16 (74/83)	80.66 - 94.19	78.41 (443/565)	74.83 - 81.60	98.01 (443/452)	96.26 - 98.95	37.76 (74/196)	31.27 - 44.72
	Overall	90.36 (75/83)	82.12 - 95.03	77.52 (438/565)	73.90 - 80.77	98.21 (438/446)	96.50 - 99.09	37.13 (75/202)	30.76 - 43.97
≥6-11 hours (N=799)	Gender-specific	93.16 (109/117)	87.09 - 96.49	75.07 (512/682)	71.69 - 78.17	98.46 (512/520)	96.99 - 99.22	39.07 (109/279)	33.53 - 44.90
	Overall	93.16 (109/117)	87.09 - 96.49	73.31 (500/682)	69.87 - 76.50	98.43 (500/508)	96.92 - 99.20	37.46 (109/291)	32.09 - 43.15

*95% Wilson Score Confidence Interval

Time Bracket	99th Percentile Cutoff	LR-	95% CI**	LR+	95% CI**
0-2 hours (N=1214)	Gender-specific	0.19	0.13 - 0.29	4.97	4.27 - 5.80
	Overall	0.18	0.12 - 0.28	4.74	4.09 - 5.50
≥2-4 hours (N=979)	Gender-specific	0.14	0.08 - 0.24	4.80	4.11 - 5.60
	Overall	0.14	0.08 - 0.24	4.71	4.04 - 5.50
≥4-6 hours (N=648)	Gender-specific	0.14	0.07 - 0.26	4.13	3.47 - 4.91
	Overall	0.12	0.06 - 0.24	4.02	3.40 - 4.76
≥6-11 hours (N=799)	Gender-specific	0.09	0.05 - 0.18	3.74	3.25 - 4.30
	Overall	0.09	0.05 - 0.18	3.49	3.05 - 3.99

**95% Confidence Interval

The lower bound of the CI for PPV for male subjects using the gender-specific 99th percentile (12 ng/L) cutoff was as low as 29.42% (≥2-4 hours). Cardiac troponin test results should always be interpreted in conjunction with the patient's signs, symptoms, and other clinical information.

The lower bound of the CI for PPV for male subjects using the overall 99th percentile (11 ng/L) cutoff was as low as 28.85% (0-2 hours). Cardiac troponin test results should always be interpreted in conjunction with the patient's signs, symptoms, and other clinical information.

Non-elevated VITROS hs Troponin I Test Results in Patients Adjudicated as Having MI (False Negatives)

Among the 62 female subjects adjudicated as having MI, there were 4 for whom none of the VITROS hs Troponin I test results exceeded the overall cutoff of 11 ng/L. When using the gender-specific cutoff of 9 ng/L, the number of false negatives for females was reduced from 4 to 2.

Among the 113 male subjects adjudicated as having MI, there were 8 for whom none of the VITROS hs Troponin I test results exceeded the overall cutoff of 11 ng/L. When using the gender-specific cutoff of 12 ng/L, the number of false negatives for males increased from 8 to 9.

Serial blood samples for subjects in the VITROS hs Troponin I study were drawn no more than 11 hours after ED presentation; however, clinical information of the study subjects, including standard of care (SOC) troponin test results, were collected for the subjects' entire hospital stay.

The standard of care (SOC) troponin tests were the tests used by each clinical study site and were reviewed by the adjudicators for the adjudicated diagnosis.

For 2 of the male false negative subjects, the earliest SOC troponin test results that exceeded the SOC troponin cutoff were from samples drawn more than 26 hours after the final VITROS hs Troponin I sample was collected. For 2 of the female false negative subjects, the earliest SOC troponin test results that exceeded the SOC cutoff were from samples drawn more than 17 hours after the final VITROS hs Troponin I sample was collected. The adjudicated MI diagnosis for some of these subjects could therefore have been based on SOC troponin test results from samples drawn beyond the VITROS hs Troponin I study period.

Elevated VITROS hs Troponin I Test Results in Patients Adjudicated as Not Having MI (False Positives)

There are conditions other than MI that are known to cause acute or chronic myocardial injury and lead to elevated troponin values. The VITROS hs Troponin I clinical trial enrolled all subjects presenting to the emergency department with symptoms consistent with ACS. Some of these subjects had an acute or chronic condition other than MI. In the clinical trial, 15.79% (311/1970) of subjects without an MI diagnosis had at least one VITROS hs Troponin I test result above the overall 99th percentile cutoff on one or more serial draws. 91.96% (286/311) of these subjects were found to have decreased kidney function (eGFR < 60 mL/min/1.73m^2, Stage 3 chronic kidney disease or renal failure) or one or more of the following cardiac conditions: angina, atrial fibrillation, cardiomyopathy, coronary artery disease, heart failure or tachycardia

(heart rate > 100 BPM).

Conclusions

The nonclinical and clinical data presented in the submission provides a reasonable assurance that the VITROS hs Troponin I Reagent Pack is substantially equivalent to the cleared predicate device.