510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K191360

B Applicant

Abbott Point of Care, Inc.

C Proprietary and Established Names

i-STAT CHEM8+ cartridge with the i-STAT 1 System

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JFP	Class II	21 CFR 862.1145 - Calcium Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

Modification of a previously cleared device - modification to the i-STAT CHEM8+ (blue) cartridge run on the i-STAT 1 Analyzer

B Measurand:

Ionized Calcium (Ca++)

C Type of Test:

Quantitative, Ion Specific Electrode (Potentiometric method)

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The i-STAT CHEM8+ cartridge with the i-STAT 1 System is intended for use in the in vitro quantification of ionized calcium in arterial or venous whole blood in point of care or clinical laboratory settings.

Ionized calcium measurements are used in the diagnosis and treatment of parathyroid disease, a variety of bone diseases, chronic renal disease and tetany.

C Special Conditions for Use Statement(s):

For Prescription Use Only

Intended for use at point of care and clinical laboratory settings

D Special Instrument Requirements:

i-STAT 1 Analyzer

IV Device/System Characteristics:

A Device Description:

The i-STAT 1 System consists of the i-STAT 1 Analyzer and the i-STAT CHEM+ (blue) cartridges. The system is designed for use by trained medical professionals at the patient point of care or in the clinical laboratory and is for prescription use only.

The i-STAT 1 Analyzer (previously cleared under k103195 as the i-STAT 1 Wireless Analyzer) is a handheld device designed to run only i-STAT test cartridges. The instrument interacts with the cartridge to move fluid across the sensors and generate a quantitative result.

The single-use, disposable i-STAT CHEM8+ cartridge contains test reagents to analyze whole blood at the point of care or in the clinical laboratory for ionized calcium and other analytes. The cartridge format allows all the tests in the cartridge to be performed simultaneously. The cartridges contain the required sensors, a fluid pouch, a sample entry well and closure, fluid channels, waste chamber, and the necessary mechanical features for controlled fluid movement within the cartridge. Cartridges require two to three drops of whole blood which are typically applied to the cartridge using a transfer device, by the trained user before the cartridge is placed within the analyzer.

B Principle of Operation:

The sensors are microfabricated thin film electrodes on a silicon chip. A lead line connects the sensors to contact pads. The sensors and lead line are contained within the cartridge; the contact pads are exposed to allow direct contact with the analyzer. The contact pads conduct the signals generated by the sensors to the analyzer. The analyzer connects to the contact pads of the sensor via contact pins that lower inside the analyzer upon insertion of the cartridge. When the sensor generates an electrical signal (in response to contact with the patient sample and the presence or absence of each analyte of interest), the signal is carried by the lead line to the contact pad where the signal generated by the sensor is read by the analyzer.

Ion selective methods are based on the measurement of potential difference (voltage) between the ion selective electrode and the reference electrode (both are found on the biosensors within the cartridge). The biosensor chips convert the activity of the ion dissolved in the patient sample into an electrical signal which can be measured. The concentration of ionized calcium and other analytes in the patient sample is calculated (derived from the Nernst equation) from the difference between the patient sample and the calibrant solution electrical signals.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Epoc Blood Analysis System

B Predicate 510(k) Number(s):

K061597

C Comparison with Predicate(s):

Device & Predicate Device(s):	K191360	K061597
Device Trade Name	**i-STAT CHEM8+ cartridge with the i-STAT 1 System (Calcium)**	**Epoc Blood Analysis System**
General Device Characteristic Similarities		
Intended Use/Indications For Use	Quantitation of ionized calcium Ionized calcium measurements are used in the diagnosis and treatment of parathyroid disease, a variety of bone diseases, chronic renal disease and tetany	Same

Device & Predicate Device(s):	K191360	K061597
Intended use settings	Point of care and clinical laboratory settings	Same
Measurement principle	Ion selective electrode	Same
Traceability	NIST SRM 956	Same
General Device Characteristic Differences		
Reportable range	0.25 – 2.50 mmol/L	0.25 – 4.00 mmol/L
Sample volume	95 µL	92 µL
Reagent format	Cartridge	Test Card

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition.

CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline–Second Edition.

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Internal site precision
A single-site precision study for the ionized calcium assay was conducted following the recommendations in CLSI EP05-A3. Five concentration levels of commercially available i-STAT calibration verification samples were tested using one lot of i-STAT CHEM8+ (blue) cartridges and twelve i-STAT 1 Analyzers. Each sample was measured in duplicates per run, with two runs per day for 20-days resulting in a total of 80 test results per level. The results are summarized below.

Level	Mean (mmol/L)	Repeatability		Between Run		Between Day		Total	
		SD	% CV	SD	% CV	SD	% CV	SD	% CV
L 1	2.328	0.0121	0.5	0.0037	0.2	0.0038	0.2	0.0132	0.6
L 2	1.484	0.0096	0.6	0.0025	0.2	0.0026	0.2	0.0103	0.7
L 3	1.299	0.0062	0.5	0.0020	0.2	0.0018	0.1	0.0067	0.5
L 4	0.725	0.0036	0.5	0.0009	0.1	0.0008	0.1	0.0038	0.5

Level	Mean (mmol/L)	Repeatability		Between Run		Between Day		Total	
		SD	% CV	SD	% CV	SD	% CV	SD	% CV
L 5	0.262	0.0035	1.3	0.0015	0.6	0.0010	0.4	0.0040	1.5

Internal precision study - whole blood
An internal precision study was conducted with lithium heparinized venous whole blood samples. Whole blood from a healthy subject (normal sample) was collected in lithium heparinized tubes and altered to create a low abnormal sample and a high abnormal sample. Each sample (high abnormal, normal, and low abnormal) was tested with one lot of CHEM8+ cartridges on 54 i-STAT 1 Analyzers. The results are shown below.

Sample	N	Mean (mmol/L)	SD	% CV
High Abnormal	15	2.879	0.0495	1.7
Normal	20	1.214	0.0165	1.4
Low abnormal	33	0.446	0.0067	1.5

Point of Care precision - aqueous control material
A three-site precision study was performed using a panel of five levels of aqueous control solutions, containing a different level of ionized calcium. Each sample was assayed at each site once per day for five days across each of six i-STAT 1 Analyzers for a total of 90 measurements. At each site, all testing was conducted by one operator using 6 i-STAT 1 Analyzers and one lot of i-STAT CHEM8+ cartridges for a total of 90 measurements. The results were analyzed for within-day, within-site, and overall (summation of within-day and within-site) and provided in the tables below:

Level	N	Mean (mmol/L)	Within-day		Within-site		Overall	
			SD	% CV	SD	% CV	SD	% CV
1	90	2.336	0.0134	0.6	0.0142	0.6	0.0152	0.7
2	90	1.467	0.0081	0.6	0.0081	0.6	0.0084	0.6
3	90	1.283	0.0065	0.5	0.0076	0.6	0.0076	0.6
4	90	0.686	0.0050	0.7	0.0053	0.8	0.0053	0.8
5	90	0.262	0.0036	1.4	0.0040	1.5	0.0041	1.6

Point of Care precision - whole blood
A whole blood repeatability analysis was conducted using the data collected across three point of care sites. One hundred and thirty-two (132) whole blood venous samples and 109 whole blood arterial samples were measured in duplicate using one lots of i-STAT CHEM8+ cartridges and 23 i-STAT 1 Analyzers by multiple POC operators at each site. The mean values for each sample were divided into four subintervals for each sample type based on the lower and upper limits of the reference range (1.12-1.32 mmol/L). Note that these estimates of SDs and %CVs present the estimates of repeatability together with variability from different analyzers.

The results are provided in the tables below:

Precision for Venous Samples

Sample Range (mmol/L)	N	Mean (mmol/L)	SD	%CV
[0.25-0.75]	10	0.438	0.0097	2.2
[0.75- 1.2]	93	1.094	0.0173	1.6
[1.2-1.5]	22	1.278	0.0134	1.0
[1.5-2.5]	7	2.109	0.0183	0.9

Precision for Arterial Samples

Sample Range (mmol/L)	N	Mean (mmol/L)	SD	%CV
[0.25-0.75]	3	0.445	0.0041	0.9
[0.75- 1.2]	73	1.110	0.0329	3.0
[1.2-1.5]	27	1.244	0.0105	0.8
[1.5-2.5]	6	1.725	0.0183	0.5

2. Linearity:

The linearity of the ionized calcium assay on i-STAT CHEM8+ (blue) cartridge was evaluated following the recommendations in CLSI EP06-A. Lithium heparin venous whole blood was obtained from a healthy subject and was altered to produce a high sample pool and a low sample pool. Samples of intermediate concentrations were prepared by intermixing the low and high pools. Each sample was measured in replicates of three using five lots of i-STAT CHEM8+ (blue) cartridges. An assessment of linearity was performed using polynomial regression analysis.

For ionized calcium, regression analysis found that at each level, the deviation from linearity was 0.003 mmol/L or 0.27%.

Linear regression analysis results for all five lots combined are presented in the tables below.

Ionized calcium:

Range tested (mmol/L)	Slope	Intercept	R^2
0.25 – 2.82	0.988	0.031	0.9992

The observed proportional response supports the claim that the ionized calcium assay on the i-STAT CHEM8+ (blue) are linear across the following measurement range: 0.25 - 2.50 mmol/L.

3. Analytical Specificity/Interference:

The analytical specificity of the ionized calcium assay on the i-STAT CHEM8+ (blue) cartridge was established by conducting interference studies following the recommendations in CLSI EP07-ED3 and CLSI EP37. Interference from certain exogenous and endogenous substances was assessed using lithium heparin venous whole blood spiked at two concentrations of the ionized calcium at low and high: 1.15±0.10 mmol/L and 1.50±0.10

mmol/L. Each low and high sample was further divided into two aliquots: control (with no added interferent) and test (with added interferent). Each sample was measured in replicates of 10 using one lot of the i-STAT CHEM8+ (blue) cartridges. A substance was identified as an interferent if the difference in the means between the control and spiked test samples was outside of the predefined allowable error of ±0.05 mmol/L or ±5%. For any substances identified as an interferent, a dose response analysis was performed to assess the highest concentration without significant error, as defined above.

The following table lists the concentrations of each substance at which no significant interference was found:

Substance	Highest concentration at which no interference was observed
Acetaminophen	15.6 mg/dL
N-Acetyl-L-Cysteine	15.0 mg/dL
Ascorbic Acid	5.25 mg/dL
β-Hydroxybutyric Acid	62.5 mg/dL
Bilirubin	40 mg/dL
Cholesterol	400 mg/dL
Hemoglobin	1000 mg/dL
Lithium Bromide	325.69 mg/dL
Lithium Salicylate	2.86 mg/dL
Magnesium Chloride	10 mg/dL
Potassium Chloride	59.6 mg/dL
Sodium Chloride	993.48 mg/dL
Sodium Iodide	44.82 mg/dL
Triglyceride	1500 mg/dL

For those substances that on initial screening where found to interfere, dose response testing was conducted to establish the concentration limit below which no significant interference is expected. The results are summarized in the table below:

Substance	Concentration	Interference
Leflunomide	≥ 0.4 mmol/L	Decreased results
Lithium Lactate	≥ 6.3 mmol/L	Decreased results
Lithium Thiocyanate	≥ 0.874 mmol/L	Decreased results
pH*	An increase of ~0.10 pH units decrease the ionized Ca results by 0.070 mmol/L	
Sodium Thiosulfate	≥ 5.5 mmol/L	Decreased results
Sodium Thiosulfate	≥ 4.19 mmol/L	Increased results
Teriflunomide	≥ 0.1 mmol/L	Decreased results

*The concentration of ionized calcium in blood is dependent on the pH of the specimen and therefore is considered a factor affecting results.

The sponsor includes the following statements in the labeling for the device and relevant literature reference:

Nithiodote (sodium thiosulfate) at ≥3.1 mmol/L shows increased sodium results. Sodium thiosulfate is indicated for the treatment of acute cyanide poisoning. The journal article titled "Falsely increased chloride and missed anion gap elevation during treatment with sodium thiosulfate" indicated that sodium thiosulfate could be used in the treatment of calciphylaxis indicating that "the highest concentration likely to be seen in plasma [is] after infusion of a 12.5 g dose of sodium thiosulfate pentahydrate. Assuming that the 12.5 g dose of sodium thiosulfate pentahydrate is distributed in a typical blood volume of 5 L with a hematocrit of 40%, the peak sodium thiosulfate plasma concentration expected is 16.7 mmol/L.

Leflunomide is an isoxazole immunomodulatory agent that inhibits dihydroorotate dehydrogenase, an enzyme involved in de novo pyrimidine synthesis, and that has antiproliferative activity. It is used in the treatment of some immune diseases. Following oral administration, leflunomide is metabolized to an active metabolite, teriflunomide, which is responsible for essentially all its in vivo activity. The active metabolite teriflunomide reaches a plasma concentration of 8.5 μg/mL (0.031 mmol/L) after a 100 mg loading dose and the steady state concentration is maintained at 63 μg/mL (0.23 mmol/L) after 24 weeks of maintenance dose at 25 mg/day (16) when treating inflammatory polyarthropathy.

Thiocyanate is a major metabolite of cyanide produced in the liver. The cyanide compound sodium nitroprusside may be used in emergency medical situations to produce a rapid decrease in blood pressure in humans and most of the cyanide produced during metabolism of sodium nitroprusside is eliminated in the form of thiocyanate. Additionally, cyanide elimination is accelerated by the co-infusion of thiosulfate, thiocyanate production is increased as in the case of thiosulphate treatment of cyanide poisoning. The highest drug concentration under therapeutic treatment reported by CLSI EP37 is 0.299 mmol/L. However, concentrations in patients receiving nitroprusside and co-infusion of thiosulfate may be much higher. Thiocyanate is mildly neurotoxic (tinnitus, miosis, hyperreflexia) at serum levels of 1 mmol/L. Thiocyanate toxicity is life-threatening when levels are 3 or 4 times higher. Thiocyanate concentrations greater than 0.874 mmol/L will lead to falsely low ionized calcium results.

4. Assay Reportable Range:

   See section A.2. Linearity.

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

   The ionized calcium assays on the i-STAT CHEM8+ (blue) cartridges and ionized calcium assigned to i-STAT controls and calibration verification materials are traceable to the U.S. National Institute of Standards and Technology (NIST) standard reference material NIST SRM 956.

6. Detection Limit:

Detection capability studies of limit of blank (LoB), limit of detection (LoD) and a limit of quantitation (LoQ) for the ionized calcium assay on the i-STAT CHEM8+ cartridge with the i-STAT 1 Analyzer was conducted following the recommendations in CLSI EP17-A2.

LoB
The LoB for the i-STAT CHEM8+ (blue) cartridge for the ionized calcium assay was evaluated using lithium heparin venous whole blood samples that were collected from four healthy subjects, each altered to create a blank sample. Each sample was tested in 20 replicates using two i-STAT CHEM8+ lots for a total of 40 test results per sample. Testing was conducted by five operators over three days. The LoB was calculated using a parametric data analysis for each of the two lots. The higher of the two LoB values from each lot is reported in the labeling as the LoB.

LoD
The LoD for ionized calcium was evaluated using lithium heparin venous whole blood samples that were collected four healthy subjects of different days and altered to two low samples. Each sample was tested in 20 replicates using two i-STAT CHEM8+ lots for a total of 40 test results per sample. Testing was conducted by five operators over three days. The LoD was calculated using a parametric data analysis for each of the two lots. The higher of the two LoD values from each lot is reported in the labeling as the LoD.

LoQ
The LoQ for ionized calcium was evaluated using four lithium heparin venous blood samples that were collected each day from a unique healthy subject over four days. The whole blood samples were altered to low concentrations each day. Each of the four samples was measured in 15 replicates per day for four days across each of two i-STAT CHEM8+ (blue) cartridge lots for a total of 120 cartridges. The sponsor defined LoQ as the greater of the two lots at which the lowest concentration met the pre-defined total error goal of 0.05 mmol/L.

The results are summarized in the table below.

Reportable Range	LoB	LoD	LoQ
0.25 - 2.50 mmol/L	0.14 mmol/L	0.15 mmol/L	0.21 mmol/L

7. Assay Cut-Off:

Not applicable.

8. Carry-Over

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The accuracy of the ionized calcium assay with the i-STAT CHEM8+ (blue) cartridge on the i-STAT 1 Analyzer was evaluated by a method comparison study for agreement with the predicate device. The study was conducted across three point of care sites. A total of 250 specimens, 136 lithium heparin venous whole blood specimens and 114 lithium heparin arterial whole blood specimens were tested. Twenty four of 250 samples (9.6%) were contrived. The data were analyzed by Passing-Bablok regression analysis comparing the first replicate of the candidate deice results to the singlicate result of the predicate device.

Venous Samples

Site	N	Sample Range Tested (mmol/L)	Regression Equation	r
1	76	0.82 – 1.49	y= -0.11+1.08x	0.96
2	42	0.81 – 1.42	y= -0.07+1.04x	0.96
combined	136*	0.25 – 2.43	y= -0.05+1.03x	1.00

*Includes 18 contrived samples

Arterial Samples

Site	N	Sample Range Tested (mmol/L)	Regression Equation	r
1	66	0.76 – 1.61	y = 0.02 + 0.96x	0.95
2	48	0.33 – 2.32	y = 0.00 + 0.98x	1.00
combined	114*	0.33 – 2.32	y = 0.01 + 0.97x	0.99

*Includes 6 contrived samples

2. Matrix Comparison:

Not applicable. Lithium heparin venous and arterial whole blood are the only acceptable sample types for this device.

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

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

Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

Expected values for the ionized calcium assay on the i-STAT CHEM8+ (blue) cartridge are cited from literature*:

Analyte	Unit	Reference Range
Ionized calcium (iCa)	mmol/L	1.12 – 1.32

*****P.C. Painter, J.Y. Cope, J.L. Smith, "Reference Ranges, Table 41–20" in Tietz Textbook of Clinical Chemistry—Second Edition, C.A. Burtis and E.R. Ashwood, eds. (Philadelphia: W.B. Saunders Company, 1994).

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.