

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

A. 510(k) Number:

k063232

B. Purpose for Submission:

New device for intact parathyroid hormone (PTH), calibrator and control materials

C. Measurand:

PTH

D. Type of Test:

Quantitative chemiluminescent microparticle immunoassay

E. Applicant:

BIOKIT S.A.

F. Proprietary and Established Names:

ARCHITECT Intact PTH reagents, calibrators (A-F) and controls (Low, Medium, High), models 8K25-20, 8K25-25, 8K25-01

G. Regulatory Information:

1. Regulation section:

21CFR Sec. 862.1545-Parathyroid hormone test system

21CFR Sec. 862.1150 Calibrator

21CFR Sec. 862.1660 Quality control material (assayed and unassayed)

2. Classification:

Class 2, 2, 1 (reserved), respectively

3. Product code:

CEW - radioimmunoassay, parathyroid hormone

JIT - calibrator, secondary

JJX - single (specified) analyte controls (assayed and unassayed)

4. Panel:

Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indication(s) for use below

2. Indication(s) for use:

Reagents

The ARCHITECT Intact PTH assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of intact parathyroid hormone (PTH) in human serum and plasma on the ARCHITECT i System. The ARCHITECT Intact PTH assay is intended to be used as an aid in the differential diagnosis of hypercalcemia, hypocalcemia and parathyroid disorders.

Calibrators

The ARCHITECT Intact PTH Calibrators are for the calibration of the ARCHITECT i System when used for the quantitative determination of intact PTH in human serum and plasma.

Controls

The ARCHITECT Intact PTH Controls are for the use in quality control to monitor the accuracy and precision of the ARCHITECT Intact PTH assay on the ARCHITECT i System for human serum and plasma.

For in vitro diagnostic use

3. Special conditions for use statement(s):

Prescription use only

The ARCHITECT Intact PTH assay has not been clinically validated for intra-operative use.

4. Special instrument requirements:

ARCHITECT i System

I. Device Description:

ARCHITECT Intact PTH Reagent Kit

- MICROPARTICLES 1 or 4 Bottle(s) (6.6 mL each)
- Anti-PTH (goat, polyclonal) coated microparticles in TRIS buffer
Preservative: sodium azide
- CONJUGATE 1 or 4 Bottle(s) (5.9 mL each) Anti -PTH (goat, polyclonal) acridinium -labeled conjugate in MES buffer with protein (bovine, goat) stabilizer. Preservative: sodium azide
- ASSAY DILUENT 1 or 4 Bottle(s) (10.0 mL each) Intact PTH Assay Diluent containing phosphate buffer with protein (bovine, goat) stabilizer
Preservative: sodium azide

ARCHITECT® Intact PTH Calibrators contents:

6 bottles (4.0 mL each) of ARCHITECT Intact PTH Calibrators

Calibrator A contains Bis Tris Propane buffer with protein (bovine) stabilizer

Calibrators B-F contain PTH (synthetic peptide) in Bis Tris Propane buffer

with protein (bovine) stabilizer. Preservatives: sodium azide and ProClin®

300

The calibrators yield the following concentrations:

Calibrator	Target concentration (pg/mL)
A.	0.0
B.	4.8
C.	24.0
D.	120.0
E.	600.0
F.	3000.0

ARCHITECT® Intact PTH control contents:

3 x 1 Bottle (8.0 mL each) of ARCHITECT Intact PTH controls contain PTH (synthetic peptide) in Bis Tris Propane buffer with protein (bovine) stabilizer. Preservatives: sodium azide and ProClin® 300.

The following concentration ranges may be used for individual replicate control specifications on the ARCHITECT i System when used with the Routine protocol:

Control	Target Concentration (pg/mL)	Range (pg/mL)
Low	10.0	6.0 – 14.0
Med	65.0	42.3 – 87.8
High	250.0	162.5 – 337.5

The following concentration ranges may be used for individual replicate control specifications on the ARCHITECT i System when used with the STAT protocol:

Control	Target Concentration (pg/mL)	Range (pg/mL)
Low	8.3	5.0 – 11.7
Med	54.2	35.2 – 73.1
High	208.3	135.4 – 281.2

Although control materials produced different target values and ranges, human serum and plasma specimens tested with the STAT or Routine protocol will produce equivalent results. The different ranges for the Controls in the STAT and Routine protocol are associated with the matrix used for the Intact PTH Controls.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Roche Elecsys Parathyroid Hormone Test System
2. Predicate 510(k) number(s):
k992680
3. Comparison with predicate:

Reagents: ARCHITECT vs. ROCHE Elecsys

Similarities:

CHARACTERISTICS	DEVICE		PREDICATE
	STAT	ROUTINE	Intact PTH
Product Type	Immunoassay	Immunoassay	Immunoassay
Methodology	Chemiluminescent Microparticle Immunoassay (CMIA)	Chemiluminescent Microparticle Immunoassay (CMIA)	Electrochemiluminescence Immunoassay (ECLIA)
Intended Use	The ARCHITECT® Intact PTH assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of intact parathyroid hormone (PTH) in human serum and plasma on the ARCHITECT i System.	The ARCHITECT® Intact PTH assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of intact parathyroid hormone (PTH) in human serum and plasma on the ARCHITECT i System.	The Roche Elecsys Immunoassay for the in vitro quantitative determination of intact parathyroid hormone in human serum and plasma for the differential diagnosis of hypercalcemia and hypocalcemia. The Electrochemiluminescence Immunoassay (ECLIA) is intended for use on the Roche Elecsys 1010/2010 and modular analyticas E170 (Elecsys module) immunoassay analyzers.
Assay Protocol	Direct sandwich immunoassay	Direct sandwich immunoassay	Sandwich principle
Interpretation of Results	Standard Curve	Standard Curve	Standard Curve

Differences:

Characteristics	Device		Predicate
	STAT	ROUTINE	
Components	<p>Microparticles - 1or 4 Bottle(s) (6.6 mL each) Anti-PTH (goat, polyclonal) coated microparticles in TRIS buffer. Preservative: sodium azide</p> <p>Conjugate -1or 4 Bottle(s) (5.9 mL each) Anti-iPTH (goat, polyclonal) acridinium-labeled conjugate in MES buffer with protein</p>	<p>Microparticles - 1or 4 Bottle(s) (6.6 mL each) Anti-PTH (goat, polyclonal) coated microparticles in TRIS buffer. Preservative: sodium azide</p> <p>Conjugate - 1or 4 Bottle(s) (5.9 mL each) Anti-iPTH (goat, polyclonal) acridinium-labeled conjugate in MES buffer</p>	<p>Microparticles - 1 bottle 6.5mL: Streptavidin-coated microparticles, 0.72 mg/mL; binding capacity: 470 ng biotin/mg microparticles; preservative</p> <p>R1 – Anti -PTH-Ab-biotin -1 bottle (10.0 mL) Biotinylated monoclonal anti-PTH antibody (mouse) 2.3 mg/L; phosphate buffer</p>

Characteristics	Device		Predicate
	STAT	ROUTINE	
	(bovine, goat) stabilizer. Preservative: sodium azide. Assay Diluent - 1or 4 Bottle(s) (10.0 mL each) Intact PTH Assay Diluent containing phosphate buffer With protein (bovine, goat) stabilizer. Preservative: sodium azide.	with protein (bovine, goat) stabilizer. Preservative: sodium azide. Assay Diluent - 1or 4 Bottle(s) (10.0 mL each) Intact PTH Assay Diluent containing phosphate buffer with protein (bovine, goat) stabilizer. Preservative: sodium azide.	100 mmol/L, pH 7.0; preservative. R2 – Anti -PTH-Ab-Ru 1 bottle, 10 mL: Monoclonal anti-PTH antibody (mouse) labeled with ruthenium complex 2.0 mg/L; phosphate buffer 100mmol/L, pH 7.0; preservative
Specimen Type	K+ EDTA, Na Heparin, Li Heparin and Serum	K+ EDTA, Na Heparin, Li Heparin and Serum	K+ EDTA plasma, Serum
Incubation time	STAT mode the first incubation is 4 minutes (18 minutes to first result)	Routine mode the first incubation is 18 minutes (29 minutes to first result)	18 minutes to first result (Elecsys 2010) 9 minutes to first result (Elecsys 1010)

Calibrators:

Similarities:

Characteristics	Device	Predicate
Intended Use	The ARCHITECT® PTH Calibrators are for the calibration of the ARCHITECT i System when used for the quantitative determination of Intact PTH in human serum and plasma.	Elecsys® PTH CalSet is used for calibrating the PTH assay on the Elecsys immunoassay systems.
Standardization/Traceability	Against a commercial PTH test and anchored to the WHO Standard Material NIBSC CODE: 79/500.	Against a commercial PTH test (RIA)

Differences:

Characteristics	Device	Predicate
Calibrator Components	Synthetic peptide PTH in a Bis Tris Propane buffer	Synthetic peptide in a human serum matrix
Calibrator Concentrations	6 levels	2 levels

Controls:

Similarities:

Characteristics	Device	Predicate
Intended Use	The ARCHITECT® Intact PTH Controls are for the use in quality control to monitor the accuracy and precision of the ARCHITECT Intact PTH assay on the ARCHITECT i System for human serum and plasma.	Elecsys® PreciControl Bone is used for the quality control of PTH on Elecsys immunoassay systems.
Control Concentrations	3 levels	3 levels

Differences:

Characteristics	Device	Predicate
Control Components	PTH synthetic peptide in Bis Tris Propane buffer	Lyophilized control serum based equine serum

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

CLSI - Interference Testing in Clinical Chemistry - EP07-A2

CLSI - Evaluation of Precision Performance of Clinical Chemistry Devices - EP05-A2

FDA - Points to Consider Guidance Document on Assayed and Unassayed Quality Control Material; Draft

L. Test Principle:

The ARCHITECT Intact PTH assay is a two-step sandwich immunoassay for the quantitative determination of intact PTH in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology.

In the first step, sample, assay diluent, and anti-PTH coated paramagnetic microparticles are combined. Intact PTH present in the sample binds to the anti-PTH coated microparticles. After washing, anti-PTH acridinium-labeled conjugate is added to create a reaction mixture in the second step. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs).

The ARCHITECT Intact PTH can be used with both STAT and Routine Protocols. The STAT protocol has a shorter incubation time in comparison to the Routine protocol. Routine and STAT protocols require separate calibrations due to different incubation time but require only one reagent kit.

A direct relationship exists between the amount of intact PTH in the sample and the RLUs detected by the ARCHITECT i System optics.

M. Performance Characteristics (if/when applicable):

- 1. Analytical performance:
 - a. *Precision/Reproducibility:*

A study was performed for the ARCHITECT Intact PTH assay, based on guidance from the Clinical Laboratory Standards Institute (CLSI) Protocol EP5-A. Multiple ARCHITECT Intact PTH control lots were assayed using two lots of reagents in replicates of two at two separate times per day for 20 days at one site on two instruments using the STAT protocol and at a second site on two instruments using the Routine protocol.

In addition, a second precision study was performed, where two lots of reagents were assayed in four replicates per run at two separate times per day over 10 days on one instrument at a third site using the STAT protocol and on one instrument at a fourth site using the Routine protocol. Each reagent lot used a single calibration curve throughout the study. Data from both studies are summarized in the following tables.

ARCHITECT Intact PTH Precision Using STAT Protocol

Sample	n	Mean Conc. (pg/mL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	878	8.5	0.74	8.7	0.74	8.7
Medium Control	880	56.5	2.34	4.1	2.35	4.2
High Control	880	208.9	8.62	4.1	8.62	4.1

ARCHITECT Intact PTH Precision Using Routine Protocol

Sample	n	Mean Conc. (pg/mL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	880	10.7	0.65	6.1	0.69	6.4
Medium Control	880	69.6	2.28	3.3	2.31	3.3
High Control	880	255.8	7.40	2.9	7.56	3.0

A third study was performed with high concentrated samples with one lot of reagents in replicates of two at two separate times per day for 20 days at one site on one instrument using the STAT protocol and the Routine protocol. Each reagent lot used a single calibration curve throughout the study. Data from both studies are summarized in the following tables.

ARCHITECT Intact PTH Precision Using STAT Protocol						
		Mean Conc.	Within Run		Total	
Sample	n	(pg/mL)	SD	%CV	SD	%CV
High Concentration	80	828.6	25.9	3.2	31.8	4.0
High Concentration	80	2039.9	49.5	2.5	67.4	3.4

ARCHITECT Intact PTH Precision Using Routine Protocol						
		Mean Conc.	Within Run		Total	
Sample	n	(pg/mL)	SD	%CV	SD	%CV
High Concentration	80	988.7	36.8	4.6	41.7	5.2
High Concentration	80	2392.4	78.5	3.9	88.8	4.4

b. *Linearity/assay reportable range:*

MEASUREMENT RANGE

The measurement for the ARCHITECT Intact PTH assay is

STAT: 4.0 pg/mL to 2227 pg/mL

Routine: 3.0 pg/mL to 2257 pg/mL

The range of measurement was established with dilution recovery studies and detection limit (functional sensitivity) below.

The high and low calibrators have been diluted to yield the below expected values dilutions. The obtained dilutions have been measured with the ARCHITECT Instrument using both STAT and Routine protocols. The percent recovery has been calculated.

	Routine expected observed		% recovery	% CV
dil 1	3000	2994	99.8	0.1
dil 2	1502.4	1551	103.3	0.5
dil 3	2251.2	2312	102.7	0.1
dil 4	1876.8	1841	98.1	6.2
dil 5	1689.6	1680	99.5	0.2
dil 6	1596.1	1647	103.2	1.4
dil 7	753.6	762	101.2	0.2
dil 8	379.2	362	95.6	3.8
dil 9	192	181	94.4	1.1
dil 10	98.4	92	93.6	0.5
dil 11	4.8	5	109.4	6.7

	STAT expected observed		% recovery	% CV
	dil 1	2500	2480	99.2
dil 2	1252	1263	100.8	0.4
dil 3	1876	1796	95.7	1.2
dil 4	1564	1447	92.5	0.1
dil 5	1408	1349	95.8	0.5
dil 6	1330	1285	96.6	1.6
dil 7	628	584	93.0	15.8
dil 8	316	306	97.0	4.3
dil 9	160	154	96.1	0.6
dil 10	82	76	93.2	1.2
dil 11	4	4	98.8	1.8

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Calibrators and controls are manufactured using Human Parathyroid Hormone and are traceable to WHO International reference preparation of Parathyroid Hormone, Human, for Immunoassay code: 79/500.

Value assignments and verification processes for ARCHITECT Intact PTH calibrators and controls are done using an internal protocol.

A study was conducted to determine the shelf-life integrity of the ARCHITECT Intact PTH Reagent Kit, Calibrator, and Controls when stored at the recommended storage condition of 2 to 8°C.

A real-time stability study supports a shelf life of 13 months for the ARCHITECT Intact PTH Reagent, Calibrator, and Control kit at the recommended storage condition of 2 to 8°C. The expiration date of 12 months is being assigned for the ARCHITECT Intact PTH Reagent, Calibrator and Control kit.

- d. *Detection limit:*

A study was performed using human samples with concentrations targeted at 3 pg/mL, 4 pg/mL and 5 pg/mL of intact PTH. Those samples were tested in replicates of two over 10 days using two reagent lots on two instruments using the STAT protocol and on one instrument using the Routine protocol.

Functional sensitivity (lowest concentration with a CV ≤ 20%) was determined to be = 3 pg/mL for the Routine protocol and = 4 pg/mL for the STAT protocol.

- e. *Analytical specificity:*

Specificity

The specificity of the ARCHITECT Intact PTH assay is designed to have a

cross-reactivity = 0.01% when tested with structurally similar compounds listed in the table below. A study was performed with the ARCHITECT Intact PTH assay based on guidance from the for Clinical Laboratory Standards Institute (CLSI) Protocol EP7-A. Aliquots of ARCHITECT Intact PTH Calibrator A were supplemented with potential cross-reactants at the concentrations listed and tested for intact PTH. Data from this study are summarized in the following table.

PTH fragment	Concentrations	% Cross-Reactivity
1-34	100000 pg/mL	0.00
39-68	100000 pg/mL	0.00
53-84	100000 pg/mL	0.00
44-68	100000 pg/mL	0.00
39-84	100000 pg/mL	0.00

$$\% \text{ Cross-Reactivity} = \frac{\text{Mean Value spiked} - \text{Mean Value non spiked (pg/mL)}}{\text{Concentration of Cross-Reactant (pg/mL)}} \times 100$$

Interference studies

Potential interference in the ARCHITECT Intact PTH assay from hemoglobin, bilirubin, triglycerides, and protein at the levels indicated below. Interference was demonstrated by a study based on guidance from the Clinical Laboratory Standards Institute (CLSI) Protocol EP7-A. There was no significant interference observed. Data from this study are summarized in the following table.

Potentially Interfering Substance	Concentration	% Mean Recovery
Hemoglobin	500 mg/dL	102
Bilirubin	20 mg/dL	98
Triglycerides	5000 mg/dL	105
Protein low	4 g/dL	106
Protein high	9.5 g/dL	93
Protein high (Routine protocol)	10.5 g/dL	94*

When using the STAT protocol, interference with high levels of protein may be observed.

Limitations to the procedure

The applicant states Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with in vitro immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed. Additional information may be required for diagnosis. The ARCHITECT Intact PTH assay has not been clinically validated for intra-operative use.

f. Assay cut-off:
Not Applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

The comparison studies were comprised of Serum and EDTA plasma samples.

A study was performed comparing the ARCHITECT Intact PTH assay to the predicate assay. In the study 467 specimens were analyzed with the STAT Protocol and 442 with the Routine Protocol,

In this evaluation, specimen concentrations ranged from ≤ 4 to 2027.2 pg/mL using the STAT Protocol, from ≤ 3 to 2326.9 pg/mL using the Routine Protocol and from 1.2 to 1813.0 pg/mL with the predicate.

**ARCHITECT Intact PTH vs. Predicate Assay
Using STAT Protocol**

Regression Method	n	Slope	Intercept	Correlation Coefficient
Passing-Bablok	467	1.28	0.45	0.99
Least Squares	467	1.20	11.00	

**ARCHITECT Intact PTH vs. Predicate Assay
Using Routine Protocol**

Regression Method	n	Slope	Intercept	Correlation Coefficient
Passing-Bablok	442	1.29	-0.66	0.99
Least Squares	442	1.19	11.40	

200 EDTA plasma specimens were tested in singlicate using both, the STAT and the ROUTINE protocols and the predicate device. The results ranged from 5.5 pg/mL to 1252.5 pg/mL and are presented in the table below:

		Intercept	Slope	r
STAT	Passing Bablok	3.003	1.192	0.9946
STAT	Linear	16.898	1.096	0.9946
Routine	Passing Bablok	3.978	1.263	0.9956
Routine	Linear	19.235	1.152	0.9956

b. *Matrix comparison:*

To evaluate the use of different anticoagulants, a study was conducted using 20 lithium heparin samples, 20 sodium heparin samples, and 20 serum samples collected in serum separator tubes (SST) and analyzed in both the stat and routine mode. The results were compared to serum samples collected in

plain tube with no additives. Ten of the twenty samples were spiked with PTH to cover the assay range. The results are presented below:

For the STAT protocol:

Test Condition	N	Range of % differences	
Normal range (24.9 pg/mL to 97.1 pg/mL)			
Serum no additive	10	Control Condition	
SST	10	-15.9 % to -6.3 %	
Li-Heparin	10	-3.6 % to 6.4 %	
Sodium-Heparin	10	-8.4 % to 9.7 %	
Upper range (121.7 pg/mL to 2681.1 pg/mL)			
Serum no additive	10	Control Condition	
SST	10	-10.4 % to 6.4 %	
Li-Heparin	10	-8.4 % to 3.3 %	
Sodium-Heparin	10	-8.3 % to 6.2 %	

For the ROUTINE protocol:

Test Condition	N	Range of % differences	
Normal range (22.7 pg/mL to 92.6 pg/mL)			
Serum no additive	10	Control Condition	
SST	10	-20.5 % to -5.6 %	
Li-Heparin	10	-11.1 % to 9.0 %	
Sodium Heparin	10	-17.8 % to 5.3 %	
Upper range (120.4 pg/mL to 2641.1 pg/mL)			
Serum no additive	10	Control Condition	
SST	10	-10.1 % to 4.9 %	
Li-Heparin	10	-7.5 % to 6.6 %	
Sodium-Heparin	10	-7.8 % to 6.0 %	

3. Clinical studies:
 - a. *Clinical Sensitivity:*
Not Applicable
 - b. *Clinical specificity:*
Not Applicable
 - c. Other clinical supportive data (when a. and b. are not applicable):
Not Applicable

4. Clinical cut-off:
Not Applicable

5. Expected values/Reference range:

A reference range study was conducted with USA population samples, testing a total of 168 samples from apparently healthy adults. These samples gave the values summarized in the following table.

	N	Intact PTH (pg/mL)					
		Median		2.5 th percentile		97.5 th percentile	
		STAT	Routine	STAT	Routine	STAT	Routine
Healthy Adults	168	27.2	28.9	8.5	8.7	72.5	77.1

A reference range study was conducted with European population for the ARCHITECT Intact PTH assay to establish the reference range from apparently healthy adults. Data from this study are summarized in the following table.

	N	Intact PTH (pg/mL)					
		Median		2.5 th percentile		97.5 th percentile	
		STAT	Routine	STAT	Routine	STAT	Routine
Healthy Adults	143	37.25	35.70	15.64	14.04	69.95	67.84

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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