510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

The Elecsys BRAHMS PCT assay has been reformulated to address a 2017 FDA Safety Communication[1] alerting the public, health care providers, lab personnel, and lab test developers that biotin can significantly interfere with certain lab tests and cause incorrect test results which may go undetected.

A 510(k) Number

K192815

B Applicant

Roche Diagnostics

C Proprietary and Established Names

Elecsys BRAHMS PCT

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
PRI	Class II	21 CFR 866.3215 - Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

The purpose of this Traditional 510(k) Premarket Notification is to obtain FDA clearance for new reagents which have been added to the Elecsys BRAHMS PCT Test System. Additional reagents intended to minimize potentially interfering effects of biotin in a patient specimen have been added to the previously cleared product.

B Measurand:

[1] https://www.fda.gov/medical-devices/safety-communications/fda-warns-biotin-may-interfere-lab-tests-fda-safety-communication

Procalcitonin (PCT)

C Type of Test:

Quantitative, Electrochemiluminescence Immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

Immunoassay for the in vitro quantitative determination of PCT (procalcitonin) in human serum and plasma (K2 –EDTA, K3-EDTA and Li-Heparin).

The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

Used in conjunction with other laboratory findings and clinical assessments, Elecsys BRAHMS PCT is intended for use as follows:

- to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock,
- to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission,
- to aid in decision making on antibiotic therapy, for inpatients or patients in the emergency department with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD),
- to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Warnings and Precautions

The Elecsys BRAHMS PCT is not indicated to be used as a stand-alone diagnostic assay and should be used in conjunction with clinical signs and symptoms of infection and other diagnostic evidence. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be

performed. Changes in PCT should always be interpreted in the context of the clinical status of the patient and other laboratory results. Decisions regarding antibiotic therapy should NOT be based solely on procalcitonin concentrations.

There is no uniformly recognized interpretation of the change in PCT concentration levels for the prediction of mortality, and overall mortality is strongly dependent on many factors, including pre-existing patient risk factors and clinical course. The need to continue ICU care at Day 4 and other covariates (e.g., age, SOFA score) are also significant predictors of 28 day cumulative mortality risk. Validation of the Elecsys BRAHMS PCT test as an aid in predicting mortality was performed in a study population with an overall 28 day mortality of 22 %.

Certain patient characteristics, such as severity of renal failure or insufficiency, may influence procalcitonin values and should be considered as potentially confounding clinical factors when interpreting PCT values. Increased PCT levels may be observed in severe illness such as polytrauma, burns, major surgery, prolonged or cardiogenic shock. PCT levels may not be elevated in patients infected by certain atypical pathogens, such as Chlamydia pneumoniae and Mycoplasma pneumoniae. The safety and performance of PCT-guided therapy for individuals younger than age 17 years, pregnant women, immunocompromised individuals or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.

D Special Instrument Requirements:

The submission demonstrates performance on the cobas e 601 immunoassay analyzer.

IV Device/System Characteristics:

A Device Description:

The Elecsys BRAHMS PCT assay is intended for use with the cobas e immunoassay analyzers, PCT Cal1 and Cal2 reagents, and the PreciControl PCT1 and PCT2 as part of the Elecsys BRAHMS PCT Kit. An optional Procalcitonin CalCheck product is also available.

B Principle of Operation:

The Elecsys BRAHMS PCT assay is a two-step sandwich immunoassay with streptavidin microparticles, biotinylated antibody and antibody labeled with ruthenium as well as an electrochemiluminescence detection system. Procalcitonin (PCT) in the sample reacts with these labeled antibodies to form a sandwich complex. This complex binds to streptavidin coated magnetic microparticles, which are magnetically captured onto an electrode. Application of voltage to the electrode induces chemiluminescence which is measured by a photomultiplier tube. Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Total duration of assay: 18 minutes.

- 1st incubation: Antigen in the sample (30 µL), a biotinylated monoclonal PCT-specific antibody, and a monoclonal PCT-specific antibody labeled with a ruthenium complex*) react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

(*):Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

C Reagents

The reagent working solutions include:

Rackpack (kit placed on analyzer)

- M: Streptavidin-coated microparticles,
- R1: Anti-PCT-Ab~biotin
- R2: Anti-PCT-Ab~$Ru(bpy)_3^{2+}$

The following change is proposed to block the interference of biotin with the Elecsys BRAHMS PCT assay: Roche is taking a one-step approach by adding an antibody to bind free biotin in the sample. For the neutralization of free biotin in serum and plasma, Roche developed an antibody which binds to free biotin. The antibodies are specific for free biotin and do not bind to, or interact with, the biotin-linker conjugates.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Elecsys BRAHMS PCT

B Predicate 510(k) Number(s):

K173927

C Comparison with Predicate(s):

Device & Predicate Device(s):	K192815	K173927
Device Trade Name	Elecsys BRAHMS PCT	Same

Device & Predicate Device(s):	K192815	K173927
General Device Characteristic Similarities		
Intended Use/ Indications for Use	Immunoassay for the in vitro quantitative determination of PCT (procalcitonin) in human serum and plasma (K2 –EDTA, K3-EDTA and Li-Heparin). The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers. Used in conjunction with other laboratory findings and clinical assessments, Elecsys BRAHMS PCT is intended for use as follows: • to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock, • to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, • to aid in decision making on antibiotic therapy, for inpatients or patients in the emergency department with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD), • to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.	Same with the exception of intended analyzers, Elecsys BRAHMS PCT with biotin update is only intended for use on cobas e immunoassay analyzers.

Device & Predicate Device(s):	K192815	K173927
Assay Protocol	The Elecsys BRAHMS PCT assay is a two-step sandwich immunoassay with streptavidin microparticles and an electrochemiluminescence detection system. The test system reagents contain a biotinylated monoclonal PCT-specific antibody and a ruthenium labeled monoclonal PCT-specific antibody.	Same
Detection Protocol	Electrochemiluminescent immunoassay	Same
Applications	18-minute application	Same
Sample Volume	30 µL	Same
Sample Type	Human serum and plasma (Li-Heparin, K2/K3 EDTA)	Same
Calibrator	PCT Cal1 and PCT Cal2	Same
Calibration Interval	Calibration must be performed once per reagent lot using PCT Cal1, PCT Cal2 and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer). Renewed calibration is recommended as follows: • after 8 weeks when using the same reagent lot • after 7 days (when using the same reagent kit on the analyzer) • as required: e.g. quality control findings outside the specified limits	Same
Controls	PC PCT1 and PC PCT2	Same
Traceability/ Standardization	This method has been standardized against the BRAHMS PCT LIA assay.	Same

Device & Predicate Device(s):	K192815	K173927
Reagent Stability	Store at 2-8 °C. Do not freeze. Store the Elecsys reagent kit upright in order to ensure complete availability of the microparticles during automatic mixing prior to use. Stability: • unopened at 2-8 °C: up to the stated expiration date • after opening at 2-8 °C: 12 weeks on the analyzers: 4 weeks	Same
Measuring Range	0.02 – 100 ng/mL	Same
LoB	0.015 ng/mL	Same
LoD	0.02 ng/mL	Same
LoQ	0.06 ng/mL	Same
Hook Effect	No hook effect up to 1000 ng/mL	Same
General Device Characteristic Differences		
Biotin Limitations	Specimens with biotin concentrations up to 1200 ng/mL did not demonstrate bias in measured PCT values. Specimens with biotin concentrations > 1200 ng/mL and ≤ 2600 ng/mL demonstrated ≤ 10 % negative bias in measured PCT levels. Pharmacokinetic studies have shown that serum concentrations of biotin can reach up to 355 ng/mL within the first hour after biotin ingestion for subjects consuming supplements of 20 mg biotin per day and up to 1160 ng/mL for subjects after a single dose of 300 mg biotin.	Biotin interference can produce either falsely high or low results. Though the risk of misclassifying a test result due to biotin interference is lower than the risks from average assay imprecision, biological variability, or other known interference, patient biotin intake and the resulting % bias should be taken into account when interpreting PCT assay values. (See Interference study below). Do not test samples from patients who have indicated or whose clinical status or history would indicate they are currently taking high doses of biotin (> 10 mg per day). If biotin interference is suspected, follow your established internal procedures to investigate the interference per CLIA and GLP recommendations. Serial draws are indicated for procalcitonin measurements. Biotin will metabolize and clear, serum levels will reduce over time.

Device & Predicate Device(s):	K192815	K173927
Reagents	M: Streptavidin-coated microparticles: Steptavidin-coated microparticles; preservative R1: Anti-PCT-Ab~biotin: Biotinylated monoclonal anti-PCT antibody (mouse), phosphate buffer, preservative R2: Anti-PCT – Ab~Ru(bpy)$_3^{2+}$ a monoclonal anti-PCT antibody (mouse) labeled with ruthenium complex, Biotin Scavenger Antii-body, phosphate buffer, preservative Roche is taking a one-step approach by adding an antibody to bind free biotin in the sample. For the neutralization of free biotin in serum and plasma, Roche developed an antibody which binds to free biotin. The antibodies are specific for free biotin and do not bind to, or interact with, the biotin-linker conjugates.	M: Streptavidin-coated microparticles: Steptavidin-coated microparticles; preservative R1: Anti-PCT-Ab~biotin: Biotinylated monoclonal anti-PCT antibody (mouse), phosphate buffer, preservative R2: Anti-PCT – Ab~Ru(bpy)$_3^{2+}$ a monoclonal anti-PCT antibody (mouse) labeled with ruthenium complex, phosphate buffer, preservative
Instrument Platform	**cobas e** 601 analyzer	**cobas e** 411 analyzer

VI Standards/Guidance Documents Referenced:

1) CLSI EP05-A3; Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

The repeatability and intermediate precision of the Elecsys BRAHMS PCT assay was conducted using the cobas e 601 analyzer. Studies were performed in accordance with CLSI guideline EP5-A3, "*Evaluation of Precision Performance of Quantitative Measurement Methods*". One reagent lot was evaluated. The precision study was conducted using the study design of 21 days x 2 runs per day x 2 replicates per sample. One (1) instrument was used for the study and calibration was performed according to the Instructions for Use. Aliquots of seven (7) human serum samples and two (2) QC samples (PC PCT 1 and PC PCT 2) distributed over the measuring range were assayed in duplicate and randomized order on the cobas e 601 analyzer using one lot of reagent. Data is summarized in Table 1 below. An analysis was also performed to calculate % Total Error across the measuring range. The total error was calculated using the one-sided Westgard-Model as:

TE = 1.65* CV + %bias

The %CV used corresponds to the intermediate precision.

Table 1: Summary of Elecsys BRAHMS PCT Repeatability and Intermediate Precision

Sample	Mean (ng/mL)	Repeatability (CV%)		Intermediate Precision (CV%)		% Total Error
		Within Run		Within Lab		
		SD (ng/mL)	CV%	SD (ng/mL)	CV%	
Control1	0.478	0.012	2.5	0.020	4.2	10.6
Control2	10.0	0.119	1.2	0.306	3.1	7.44
Sample1	0.045	0.006	13.2	0.007	16.1	39.9
Sample2	0.112	0.007	6.3	0.010	8.6	21.3
Sample3	0.249	0.008	3.0	0.011	4.3	10.4
Sample4	0.495	0.013	2.7	0.021	4.2	10.3
Sample5	1.71	0.031	1.8	0.058	3.4	8.09
Sample6	31.4	0.326	1.0	0.985	3.1	7.38
Sample7	93.0	1.52	1.6	3.40	3.7	8.71

2. Linearity:

Please refer to previously FDA-cleared 510(k) K160729 and K173927 for Linearity performance. No additional testing was conducted.

3. Analytical Specificity/Interference:

Analytical Specificity

The specificity of the Elecsys BRAHMS PCT was determined using native human serum samples spiked with potential cross-reactant compounds. The samples were tested on a cobas e 601 Immunoassay Analyzer. Recovery within ± 15 % of initial value at PCT concentrations of ~0.5 ng/mL and ~2 ng/mL were verified for the following cross-reactant concentrations:

Table 2: Analytical Specificity/Cross-Reactivity Data

Cross Reactant		Serum Sample		
		Measured PCT (ng/mL)		Recovery
Type	Conc (ng/mL)	Reference	Spiked	%
Human Katacalcin	30	0.051	0.049	96%
	30	0.188	0.176	94%
	30	0.372	0.357	96%
	30	1.39	1.31	94%

Cross Reactant		Serum Sample		
		Measured PCT (ng/mL)		Recovery
Type	Conc (ng/mL)	Reference	Spiked	%
Human Calcitonin	10	0.049	0.050	102%
	10	0.182	0.191	105%
	10	0.396	0.409	103%
	10	1.31	1.38	105%
Human alpa CGRP1	10000	0.055	0.053	96%
	10000	0.189	0.178	94%
	10000	0.393	0.385	98%
	10000	1.41	1.41	100%
Human beta CGRP	10000	0.048	0.052	108%
	10000	0.187	0.189	101%
	10000	0.389	0.379	97%
	10000	1.38	1.40	101%
Calcitonin Salmon	30000	0.082	0.081	99%
	30000	0.216	0.218	101%
	30000	0.390	0.392	101%
	30000	1.98	2.01	102%
Calcitonin Eel	30000	0.084	0.082	98%
	30000	0.223	0.222	100%
	30000	0.394	0.394	100%
	30000	1.74	1.84	106%

Endogenous Interferences

The effect on quantitation of PCT in the presence of five endogenous interfering substances (Hemoglobin, Biotin, Intralipid, Bilirubin, and Rheumatoid Factor) was tested using one cobas e 601 analyzer at clinically relevant concentrations. One aliquot of each serum sample was spiked with the interfering substance, another aliquot was spiked with the same volume of the respective solvent (dilution pool). The interfering pool was then incrementally diluted into the dilution pool. The recovery for each sample was calculated by comparison to the analyte concentration of the respective dilution pools.

The following substances evaluated with the Elecsys BRAHMS PCT assay were found not to affect the test performance at concentrations reasonably and consistently found in clinical situations.

Table 3:Endogenous Substances

Potential Interferent	Claimed level where no interference was observed	Maximum Value with No Interference Observed
Intralipid	1500 mg/dL	2000 mg/dL
Biotin	1200 ng/mL	2600 ng/mL
Bilirubin	25 mg/dL	66 mg/dL
Hemoglobin	900 mg/dL	1287 mg/dL
Rheumatic Factor	1500 IU/mL	1500 IU/mL

Exogenous Interference

Thirty-four pharmaceutical compounds were spiked into human serum sample pools at clinically relevant PCT concentrations (0.10 ng/mL, 0.25 ng/mL, 0.5 ng/mL and 2.0 ng/mL) and tested with the Elecsys BRAHMS PCT assay on the cobas e 604 analyzer.

The following substances evaluated with the Elecsys BRAHMS PCT assay were found not to affect the test performance at concentrations reasonably and consistently found in clinical situations.

Table 4: Exogenous Interference

Potential Interferent	Drug Level Tested (mg/L)
Acetylcysteine	150
Ampicillin	75
Ascorbic acid	52.5
Cyclosporine	1.8
Cefoxitin	750
Heparin	3300 U/L
Levodopa	7.5
Methyldopa	22.5
Metronidazole	123
Phenylbutazone	321
Doxycycline	18
Acetylsalicylic acid	30
Rifampicin	48
Acetaminophen	156
Ibuprofen	219
Theophylline	60
Imipenem	1180
Cefotaxime	900
Vancomycin	3500
Dopamine	130
Noradrenaline	2
Dobutamine	11.2
Furosemide	20
Cromolyn	24
Alcohol	4000
Azithromycin	11.5
Cetirizine HCl	3.6
Dextromethorphan	1.4
Levofloxacin	17.5
Loratadine	0.3
Nicotine	1

Potential Interferent	Drug Level Tested (mg/L)
Oxymetazoline HCl	0.09
Phenylephrine	0.18
Tiotropium	0.0216

Hama Effect

Please refer to previously FDA-cleared 510(k) K160729 and K173927 for Hama Effect performance. No additional testing was conducted.

4. High-Dose Hook Effect:

Please refer to previously FDA-cleared 510(k) K160729 and K173927 for High Dose Hook Effect performance. No additional testing was conducted.

5. Assay Reportable Range:

Please refer to previously FDA-cleared 510(k) K160729 and K173927 for Assay Reportable Range/Linearity performance. No additional testing was conducted.

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

Sample Stability

Please refer to previously FDA-cleared 510(k) K160729 and K173927 for Sample Stability Effect performance. No additional testing was conducted.

Reagent On-Board Stability

A fresh Elecsys BRAHMS PCT test kit was placed on the cobas e 601 analyzer and calibrated. Reference values for the samples tested were determined (day 0). After 8, 15, 22 and 29 days (1, 2, 3 and 4 weeks) the same samples were measured with the same reagent kit kept under on- board condition. Re-calibration was performed at every measuring time point.

Samples tested include eight (8) human serum (HS) sample pools. Each sample was tested in two-fold determination. Samples were targeted with values near medical decision levels of 0.1 ng/mL, 0.25 ng/mL, 0.5 ng/mL and 2.0 ng/mL as one sample range, along with sample ranges at low, medium and high PCT concentration ranges relative to the measuring range. Mean recovery values for each sample range were calculated. Elecsys BRAHMS PCT reagent kits can be kept on board of the instruments for up to 4 weeks (28 days). A new calibration of the kit kept on board is recommended every 7 days.

Calibration Stability

The Elecsys BRAHMS PCT assay was calibrated with a fresh reagent kit on Day 0 using one cobas e 601 analyzer. After 3, 6, and 9 weeks a new reagent kit of the same lot was used with recovery of samples being determined using the calibration curve established on Day 0 for that reagent kit lot. Fourteen (14) human serum samples were tested in duplicate. Recovery compared to the reference value was calculated as absolute deviation in ng/mL or relative deviation in %. Samples were targeted with values near medical decision levels of 0.1 ng/mL, 0.25 ng/mL, 0.5 ng/mL and 2.0 ng/mL along with samples spread across the measuring range. Mean recovery values for each sample range were calculated. The resulting data support the package-insert claim of 8 weeks lot calibration stability when using the same reagent kit lot.

7. Detection Limit:

Limit of Detection

Please refer to previously FDA-cleared 510(k) K160729 and K173927 for Limit of Detection performance. No additional testing was conducted.

Limit of Quantitation

The Limit of Quantitation (LoQ) of the Elecsys BRAHMS PCT assay was determined according to CLSI EP17-A2. The LoQ represents the lowest amount of analyte that can be quantitatively determined with stated accuracy, precision, and experimental conditions. The LoQ was calculated based on intermediate precision according to CLSI EP17-A2. The LoQ was determined as the lowest concentration of analyte that can be quantified with an intermediate precision of no more than 20%.

A five-day LoQ experiment was carried out with one reagent lot on one cobas e 601 analyzer. Samples tested included seven native human serum (HS) samples and were measured in five-fold determination for each run. A total of 150 measuring points were collected.

The mean values and the intermediate precision (coefficient of variation and standard deviation) for each LoQ sample were calculated. To determine the LoQ, samples were sorted according to the concentration of their measured mean value. The LoQ is defined as the mean value of the sample that is first to fulfill the specification for intermediate precision, and for which there is no lower-concentration sample that exceeds the specification. The LoQ data are represented in the table below.

Table 5. LoQ Data – cobas e 601 analyzer

Sample Type	Day					Mean (ng/mL)	SD (ng/mL)	CV (%)
	1	2	3	4	5			
HS 1	0.032 0.030 0.022 0.033 0.029	0.029 0.021 0.023 0.020 0.024	0.026 0.031 0.022 0.032 0.025	0.021 0.028 0.021 0.023 0.022	0.021 0.028 0.020 0.024 0.018	0.025	0.004	18.0
HS 2	0.042 0.046 0.050 0.038 0.048	0.041 0.044 0.039 0.047 0.045	0.043 0.037 0.043 0.037 0.044	0.041 0.041 0.043 0.040 0.043	0.045 0.041 0.044 0.045 0.045	0.043	0.003	7.7
HS 3	0.056 0.050 0.051 0.047 0.053	0.057 0.046 0.048 0.043 0.054	0.052 0.048 0.048 0.045 0.050	0.052 0.040 0.044 0.045 0.046	0.057 0.046 0.052 0.049 0.050	0.049	0.004	9.0
HS 4	0.066 0.068 0.067 0.069 0.068	0.063 0.058 0.068 0.065 0.064	0.067 0.070 0.064 0.071 0.065	0.059 0.064 0.073 0.073 0.062	0.062 0.064 0.062 0.067 0.061	0.066	0.004	5.8
HS 5	0.069 0.068 0.072 0.072 0.072	0.062 0.067 0.063 0.065 0.065	0.068 0.058 0.073 0.063 0.069	0.067 0.058 0.066 0.064 0.064	0.068 0.056 0.068 0.062 0.067	0.066	0.004	6.8
HS 6	0.088 0.091 0.092 0.095 0.090	0.090 0.092 0.091 0.085 0.095	0.088 0.089 0.090 0.094 0.086	0.083 0.093 0.084 0.091 0.083	0.089 0.089 0.084 0.097 0.085	0.089	0.004	4.4
Overall Device LoQ: 0.025 ng/mL								

HS: human serum

The LoQ was determined to be 0.025 ng/mL. The LoQ claim for the Elecsys BRAHMS PCT assay is 0.06 ng/mL.

Based on LoQ testing the following total error values were calculated.

Table 6: Total Error

Expected value (ng/ml)	Elecsys BRAHMS PCT		
	%CV	**%Bias**	**%TE**
2.00	0.19	0.12	0.43
0.50	0.77	0.54	1.81
0.30	1.30	0.94	3.08
0.25	1.56	1.15	3.72
0.15	2.64	2.00	6.34
0.10	3.99	3.10	9.69
0.05	8.12	6.56	19.97

Limit of Blank

Please refer to previously FDA-cleared 510(k) K160729 and K173927 for Limit of Blank performance. No additional testing was conducted.

8. Assay Cut-Off:

28-day mortality:

- **ΔPCT ≤ 80%**

  A decrease in the PCT levels below or equal to 80% defines a positive ΔPCT test result representing a higher risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

- **ΔPCT > 80%**

  A decrease in the PCT levels of more than 80% defines a negative ΔPCT test result representing a lower risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

NOTE: The combination of the first PCT level (≤ 2.0 ng/mL or > 2.0 ng/mL) at initial diagnosis of severe sepsis or septic shock with the patient's clinical course and the change in PCT level over time until Day 4 provides important additional information about the mortality risk.

Progression Risk:

- **PCT > 2 µg/L**

  A PCT level above 2.0 µg/L on the first day of ICU admission is associated with a high risk for progression to severe sepsis and/or septic shock.

- **PCT < 0.5 µg/L**

  A PCT level below 0.5 µg/L on the first day of ICU admission is associated with a low risk for progression to severe sepsis and/or septic shock.

LRTI Antibiotic Decision Making:

- **PCT < 0.10 ng/mL**

  Antibiotic therapy strongly discouraged.

- **PCT 0.10-0.25 ng/mL**

  Antibiotic therapy discouraged.

- **PCT 0.26-0.50 ng/mL**

  Antibiotic therapy encouraged.

- **PCT >0.50 ng/mL**

  Antibiotic therapy strongly encouraged.

Sepsis Antibiotic Discontinuation:

- **ΔPCT > 80%**

  Antibiotic therapy may be discontinued

- **PCT ≤ 0.50 ng/mL**

  Antibiotic therapy may be discontinued

Recommendations for Laboratory Reports for Initiation and Discontinuation**:**

The Change in Procalcitonin Calculator is available at http://www.brahms-pct-calculator.com. The Change in Procalcitonin Calculator can be used to determine ΔPCT results. It is suggested to report the numerical PCT values (individual or paired). For paired PCT values the report should also indicate if the ΔPCT(%) was ≤ 80% or > 80%. The laboratory report should include a reference or a link to the package insert for a guided interpretation of the test results.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A method comparison of the Elecsys BRAHMS PCT assay and the predicate was performed using 496 native serum human clinical samples. A concordance analysis was performed with the predicate device. Only samples in which the result from the candidate and the predicate device were within the measuring range were included in the concordance analysis. The clinical concordance analysis of the Elecsys BRAHMS PCT clinical performance study shows more than 96% total agreement between the Elecsys BRAHMS PCT and the predicate device at the medical decision points 0.1, 0.25, 0.5 and 2.0

ng/mL. The regression slopes are within +/- 10% of identity in Passing-Bablok and Weighted Deming Analysis. This demonstrates equivalence to the predicate device to include all currently cleared claims of the predicate device in the labeling of the candidate device.

Further clinical performance study data can be found referenced in K173927 and K160729.

Table 7: PCT Agreement between Elecsys BRAHMS PCT and Predicate at 0.1 ng/mL

Elecsys BRAHMS PCT on cobas e 601	Predicate		Total
	> 0.1 ng/mL	≤ 0.1 ng/mL	
> 0.1 ng/mL	354	1	355
≤ 0.1 ng/mL	7	134	141
Total	361	135	496

Table 8: PCT Agreement between Elecsys BRAHMS PCT and Predicate at 0.25 ng/mL

Elecsys BRAHMS PCT on cobas e 601	Predicate		Total
	> 0.25 ng/mL	≤ 0.25 ng/mL	
> 0.25 ng/mL	278	1	279
≤ 0.25 ng/mL	6	211	217
Total	284	212	496

Table 9: PCT Agreement between Elecsys BRAHMS PCT and Predicate at 0.5 ng/mL

Elecsys BRAHMS PCT on cobas e 601	Predicate		Total
	> 0.5 ng/mL	≤ 0.5 ng/mL	
> 0.5 ng/mL	220	0	220
≤ 0.5 ng/mL	4	272	276
Total	224	272	496

Table 10:PCT Agreement between Elecsys BRAHMS PCT and Predicate at 2.0 ng/mL

Elecsys BRAHMS PCT on cobas e 601	Predicate		Total
	> 2.0 ng/mL	≤ 2.0 ng/mL	
> 2.0 ng/mL	141	2	143
≤ 2.0 ng/mL	3	350	353
Total	144	352	496

Table 11:Comparison Elecsys BRAHMS PCT vs Predicate

Cutoff (> vs. ≤)	Positive Agreement (95% CI)	Negative Agreement (95% CI)	Total Agreement	Cohen's Kappa
0.10 ng/mL	98.1%	99.3%	98.4%	0.960
	(96.1 – 99.1)	(95.9 – 99.9)		
0.25 ng/mL	97.9%	99.5%	98.6%	0.971
	(95.5 – 99.0)	(97.4 – 99.9)		
0.50 ng/mL	98.2%	100.0%	99.2%	0.984
	(95.5 – 99.3)	(98.6 -100.0)		
2.00 ng/mL	97.9%	99.4%	99.0%	0.975
	(94.1 - 99.3)	(98.0 – 99.8)		

Table 12: Weighted Deming and Passing Bablok Regression Analysis

Parameter	Passing Bablok Regression	Weighted Deming (λ=1) Regression Analysis
n	474	474
Slope	0.990	0.969
95% CI	[0.984; 0.994]	[0.963; 0.975]
Intercept	-0.003	0.004
95% CI	[-0.004; -0.001]	[0.002; 0.005]
Pearson Correlation Coefficient (R)	1.000	1.000
Sample Range	[0.02; 85.69]	[0.02; 85.69]

Figure 1: Weighted Deming Regression plots of Elecsys BRAHMS PCT versus Predicate

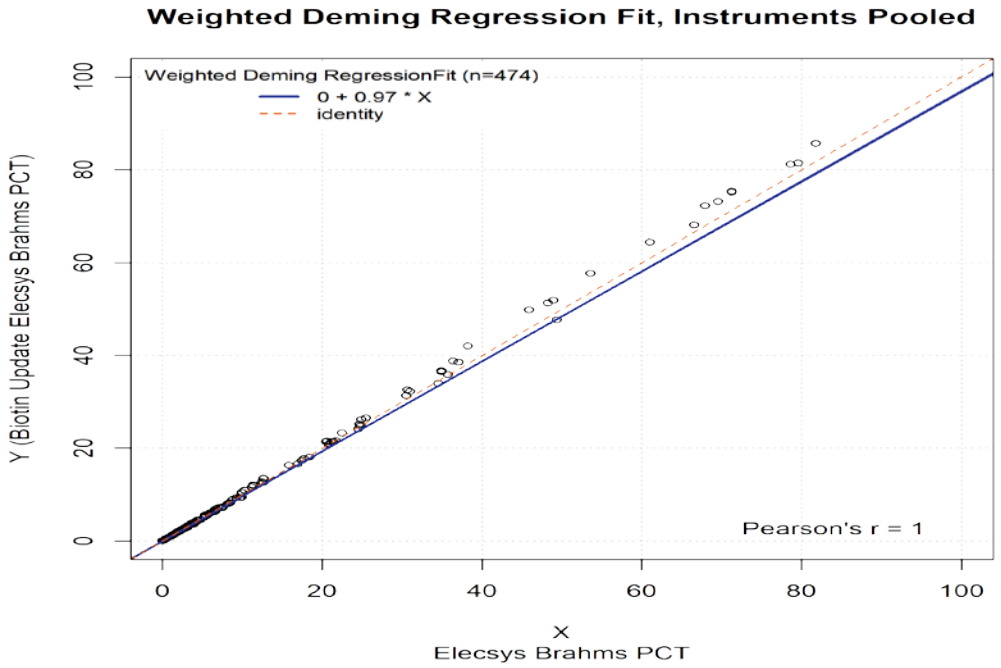
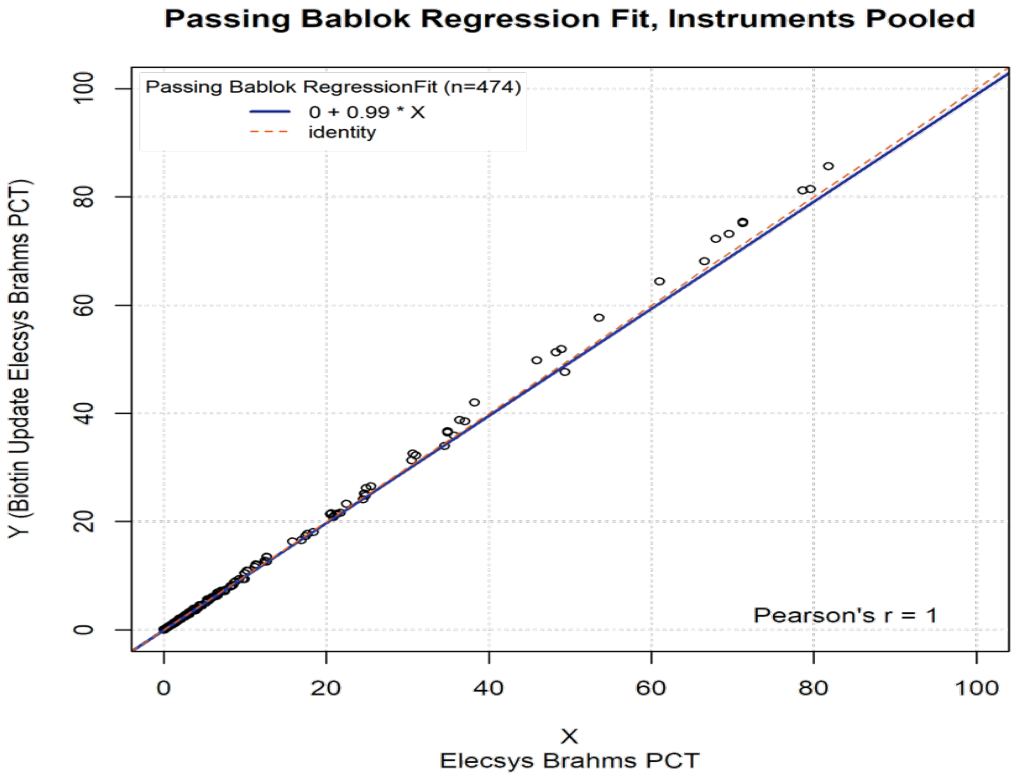


Figure 2: Passing Bablok Regression plots of Elecsys BRAHMS PCT versus Predicate



2. Matrix Comparison:

The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys BRAHMS PCT immunoassay was determined by comparing values obtained from samples (native human serum samples, single donors as well as pools) drawn into serum and Li-Heparin, K2-EDTA, K3-EDTA plasma tubes. A minimum of 40 serum/plasma pairs per sample material were tested in singleton with one reagent lot on one cobas e 601 analyzer. Data were evaluated using a regression analysis according to Passing/Bablok.

The results are acceptable and supports the following package-insert claim:

- SST is an acceptable sample type for use with the Elecsys PCT assay
- Li-Heparin plasma is an acceptable sample type for use with the Elecsys BRAHMS PCT assay
- K2-EDTA plasma is an acceptable sample type for use with the Elecsys BRAHMS PCT assay.
- K3-EDTA plasma is an acceptable sample type for use with the Elecsys BRAHMS PCT assay.

C Clinical Studies:

Not Applicable

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.