DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

August 3, 2016

Roche Diagnostics
Mr. Adam Clark
Regulatory Affairs Consultant
9115 Hague Road
Indianapolis, IN 46250

Re: K160729
Trade/Device Name: Elecys BRAHMS PCT, Elecys BRAHMS PCT CalCheck 5
Regulation Number: 21 CFR 866.3215
Regulation Name: Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis
Regulatory Class: II
Product Code: PMT, JJX
Dated: March 15, 2016
Received: March 16, 2016

Dear Mr. Clark:

This letter corrects our substantially equivalent letter of June 13, 2016.

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 (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. 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.

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 Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Kristian M. Roth -S

For: Uwe Scherf, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics and
Radiological Health
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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K160729

Device Name
Elecsys BRAHMS PCT

Indications for Use *(Describe)*
Immunoassay for the in vitro quantitative determination of PCT (procalcitonin) in human serum and plasma (K2 and K3 EDTA, Li-Heparin).
The Elecsys BRAHMS PCT assay is intended for use to determine the change of PCT 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 Intensive Care Unit (ICU) or when obtained in the emergency department or other medical wards prior to ICU admission.
The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.
Procalcitonin (PCT) is a biomarker associated with the inflammatory response to bacterial infection that aids in the risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock. The percent change in PCT level over time aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock.
A PCT level that declines ≤ 80 % from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is associated with higher cumulative 28-day risk of all-cause mortality than a decline > 80 %.
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.
The PCT level on Day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at Day 4 if the Day 0 measurement is unavailable.

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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K160729

Device Name
Elecsys BRAHMS PCT CalCheck 5

Indications for Use *(Describe)*

The Elecsys BRAHMS PCT Calcheck 5 is an assayed control for use in calibration verification and for use in verification of the assay range established for the Elecsys BRAHMS PCT assay on the Elecsys and cobas e analyzers,

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 21 CFR 807.92.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road Indianapolis, IN 46250
Contact	Adam Clark Phone: (317) 521-4371 FAX: (317) 521-2324 Email: adam.clark@roche.com
Date Prepared	March 15, 2016
Proprietary Name	1) Elecsys BRAHMS PCT 2) Elecsys BRAHMS PCT CalCheck 5
Common Name	1) PCT Test System (test system contains both controls and calibrators) 2) PCT CalCheck 5
Classification Name	1) Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis 2) Secondary, calibrator 3) Multi-Analyte Control, All Kinds (Assayed) 4) Single (specified) analyte Controls (assayed and unassayed)
Product Codes	1) PMT; 866.3215 2) JIT; 862.1150 3) JJY; 862.1660 4) JJX; 862.1660
Predicate Devices	1) BRAHMS PCT sensitive KRYPTOR® test system 2) Elecsys Progesterone III CalSet 3) Elecsys Progesterone III CalCheck 5 4) BRAHMS PCT sensitive KRYPTOR® QC Kit
Establishment Registration	Roche Diagnostics GmbH in Mannheim, Germany: 9610126 Roche Diagnostics GmbH in Penzberg, Germany: 9610529 Roche Diagnostics in the United States: 1823260

1. DEVICE DESCRIPTION

The Elecsys BRAHMS PCT assay is a two-step sandwich immunoassay with streptavidin microparticles and an electrochemiluminescence detection system. 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. An optional Procalcitonin CalCheck product is also available.

1.1. 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)$^{2+}_{3}$

1.2. Calibrator

PCT CalSet is a 2-level PCT calibrator consisting of lyophilized recombinant PCT in a human serum matrix. The CalSet includes:

- PCT Cal1: approximately 0.10 ng/mL, 1 bottle, containing 4 mL
- PCT Cal2: approximately 54 ng/mL, 1 bottle, containing 4 mL

1.3. Control

PreciControl PCT is a single analyte control that is used for quality control of the Elecsys BRAHMS PCT assay. The PreciControl PCT includes:

- PC PCT 1: approximately 0.5 ng/mL, 2 bottles each for 4 mL
- PC PCT 2: approximately 10 ng/mL, 2 bottles each for 4 mL

1.4. CalCheck

PCT CalCheck 5 is a lyophilized Human serum matrix with added PCT in five concentration ranges. The CalCheck includes:

- PCT CalCheck 1: approximately <0.06 ng/mL
- PCT CalCheck 2: approximately 0.5 ng/mL
- PCT CalCheck 3: approximately 40 ng/mL
- PCT CalCheck 4: approximately 80 ng/mL
- PCT CalCheck 5: approximately 100 ng/mL

2. INDICATIONS FOR USE

Immunoassay for the in vitro quantitative determination of PCT (procalcitonin) in human serum and plasma (K2 and K3 EDTA, Li-Heparin).
The Elecsys BRAHMS PCT assay is intended for use to determine the change of PCT 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 Intensive Care Unit (ICU) or when obtained in the emergency department or other medical wards prior to ICU admission.
The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.
Procalcitonin (PCT) is a biomarker associated with the inflammatory response to bacterial infection that aids in the risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock. The percent change in PCT level over time aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock.
A PCT level that declines ≤ 80 % from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is associated with higher cumulative 28-day risk of all-cause mortality than a decline > 80 %.
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.
The PCT level on Day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at Day 4 if the Day 0 measurement is unavailable.

3. DISCUSSION OF ANALYZER PLATFORMS

The following summary of the Elecsys platforms is provided.

The **cobas e** 411 analyzer is an updated version of the Elecsys 2010 analyzer. Roche Diagnostics pursued a conservative course and submitted a 510(k) for the analyzer under K062279. The submission was closed out under 'exempt' since the submission was only for the analyzer and the 'Joint Risk Assessment' performed internally identified no potential impact on reagent performance. However, to be on the conservative side, Roche Diagnostics conducted recovery and reproducibility testing with representative Elecsys assays, and those data are documented

internally. The modifications did not alter the measurement components of the analyzer or the means by which results are calculated. The systems are analytically identical. The majority of the hardware changes, outside of the obvious name change, were cosmetic (*e.g.*, change to color scheme, an external PC versus an internal PC) or related to safety (*e.g.*, protective shields added over moving parts), or were made to improve customer satisfaction (*e.g.*, a larger external waste container, flash drive replacement of floppy drive). The user-interface changes were made for aesthetics, customer satisfaction, or to bring the 'old' 2010 analyzer up to parity with those features already designed into the cobas 6000 series system.

The **cobas e** 601 analyzer is an updated version of the MODULAR ANALYTICS E170 analyzer. The MODULAR ANALYTICS E170 analyzer was acknowledged by FDA under Add-to-File K961481/A003 on May 23, 2001. The **cobas e** 601 analyzer was reviewed and cleared as a component of the cobas 6000 series system submission K060373. The submission was required to introduce the other component of the cobas 6000 series system: the **cobas c** 501 analyzer, a new clinical-chemistry analyzer.

The **cobas e** 602 analyzer, part of the cobas 8000 analyzer series, was cleared via Internal Documentation, in keeping with the Reagent Replacement and Instrument Family Policy, as a new member of the Roche/Elecsys family of analyzers. The **cobas e** 602 is analytically identical to the **cobas e** 601 analyzer, part of the cobas 6000 analyzer series cleared in K060373.

4. TECHNOLOGICAL CHARACTERISTICS

Table 1: Assay Comparison

Feature	Candidate Device: Elecsys BRAHMS PCT (K160729)	Predicate Device: BRAHMS PCT sensitive KRYPTOR®(DEN150009)
Intended Use/ Indications for Use	Immunoassay for the in vitro quantitative determination of PCT (procalcitonin) in human serum and plasma. The Elecsys BRAHMS PCT assay is intended for use to determine the change of PCT 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 Intensive Care Unit (ICU) or when obtained in the emergency department or other medical wards prior to ICU admission. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers. A PCT level that declines ≤ 80% from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is associated with higher cumulative 28-day risk of all-cause mortality than a decline > 80%. The combination of the first PCT level (≤ 2.0 ng/mL or > 2.0 ngmL) 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. The PCT level on Day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at Day 4 if the Day 0 measurement is unavailable.	The BRAHMS PCT sensitive KRYPTOR® is intended for use in conjunction with other laboratory findings and clinical assessments 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. The BRAHMS PCT sensitive KRYPTOR® test is also intended for use to determine the change of PCT over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with sever sepsis or septic shock in the Intensive Care Unit (ICU) or when obtained in the emergency department or other medical wards prior to the ICU admission.
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.	The BRAHMS PCT sensitive KRYPTOR® assay is a homogeneous sandwich immunoassay for detection of PCT in human serum or plasma. The measuring principle is based on Time-Resolved Amplified Cryptate Emission (TRACE®) technology, which measures the signal that is emitted from an immunocomplex with time delay.
Detection Protocol	Electrochemiluminescent Assay	Time-Resolved Amplified Cryptate Emission (TRACE®)
Applications	18-minute application	19-minute incubation

Feature	Candidate Device: Elecsys BRAHMS PCT (K160729)	Predicate Device: BRAHMS PCT sensitive KRYPTOR®(DEN150009)
Instrument Platform	**cobas e** 411 analyzer	BRAHMS KRYPTOR® analyzer
Sample Volume	30 µL	50 µL
Sample Type	Human serum and plasma (Li-Heparin, K2/K3 EDTA)	Human serum and plasma (EDTA, heparin)
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) 2/3+ a monoclonal anti-PCT antibody (mouse) labeled with ruthenium complex, phosphate buffer, preservative	• Cryptate conjugate, cryptate labeled, anti-PCT antibody (polyclonal, sheep), 3.2mL after reconstitution with KRYPTOR® Solution 2 • XL665 conjugate, XL665 labeled, anti-PCT antibody (monoclonal, mouse), 3.95 mL after reconstitution with KRYPTOR® Solution 1 and KRYPTOR® Solution 2 • Defibrinated human plasma, for diluting samples above 50µg/L, ready for use
Calibrator	Elecsys PCT CalSet	BRAHMS PCT sensitive KRYPTOR® Calibrator
Calibration Interval	Calibration must be performed once per reagent lot using 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	Before first use of each new BRAHMS PCT sensitive KRYPTOR® assay lot, then repeated on a regular basis automatically managed by the BRAHMS PCT sensitive KRYPTOR®.
Controls	Elecsys Precicontrol PCT	BRAHMS PCT sensitive KRYPTOR® Controls
Traceability/ Standardization	This method has been standardized against the BRAHMS PCT LIA assay.	N/P
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	• In original shipping containers unopened at 2-8 °C: up to the stated expiration date • after opening, onboard at 2-8 °C: 29 days

Feature	Candidate Device: Elecsys BRAHMS PCT (K160729)	Predicate Device: BRAHMS PCT sensitive KRYPTOR®(DEN150009)
Measuring Range	0.02 – 100ng/mL	0.02-50000µg/L
Precision	**cobas e** 411 Repeatability HS1: 5.03% CV @ 0.079 ng/mL HS2: 1.71% CV @ 0.442 ng/mL HS3: 2.35% CV @ 1.49 ng/mL HS4: 1.38% CV @ 27.5 ng/mL HS5: 2.23% CV @ 71.4 ng/mL HS6: 1.35% CV @ 88.1 ng/mL PC1: 1.91% CV @ 0.456 ng/mL PC2: 1.83% CV @ 9.07 ng/mL Intermediate Precision HS1: 6.44% CV @ 0.079 ng/mL HS2: 3.14% CV @ 0.442 ng/mL HS3: 3.40% CV @ 1.49 ng/mL HS4: 3.24% CV @ 27.5 ng/mL HS5: 3.66% CV @ 71.4 ng/mL HS6: 3.18% CV @ 88.1 ng/mL PC1: 3.21% CV @ 0.456 ng/mL PC2: 3.35% CV @ 9.07 ng/mL	Not Provided (N/P)
LoB	0.015 ng/mL	N/P
LoD	0.02 ng/mL	N/P
LoQ	0.06 ng/mL	0.075 µg/L
Lower Detection Limit	0.015 ng/mL	N/P
Hook Effect	No hook effect up to 1000ng/mL	N/A

Feature	Candidate Device: Elecsys BRAHMS PCT (K160729)	Predicate Device: BRAHMS PCT sensitive KRYPTOR®(DEN150009)
Limitations	The assay is unaffected by icterus (bilirubin < 428 µmol/L or < 25 mg/dL), hemolysis (Hb < 0.559 mmol/L or < 0.900 g/dL), lipemia (Intralipid < 1500 mg/dL) and biotin (< 123 nmol/L or < 30 ng/mL). Criterion: Recovery within ± 15 % of initial value. Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration. No interference was observed from rheumatoid factors up to a concentration of 1500 IU/mL. In vitro tests were performed on 27 pharmaceuticals compounds. No interference with the assay was found. Human Anti Mouse Antibody (HAMA) interference testing was completed with three PCT analyte concentrations using a high HAMA human serum pool. No interference was detected. Samples from patients routinely exposed to animals or animal serum products may contain heterophilic antibodies causing an atypical result. This assay has been formulated to mitigate the risk of this type of interference. However, potential interactions between rare sera and test components can occur. In rare cases, interference due to extremely high titers of antibodies to analyte specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design. For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.	Citrate plasma tubes should not be used as PCT concentrations are underestimated. • The prognostic value of PCT in the setting of sepsis has not been validated in US patients younger than 18. • Carefully follow the manufacturer's instructions. Improper handling of the reagents may falsify the test results. • Increased PCT levels may not always be related to systemic infection4,11,12,13. These conditions include, but are not limited to: o Patients experiencing major trauma and/or recent surgical procedure including extracorporeal circulation or burns; o Patients under treatment with OKT3 antibodies, OK-432, interleukins, TNF-alpha and other drugs stimulating the release of pro-inflammatory cytokines or resulting in anaphylaxis; o Patients diagnosed with active medullary C-cell carcinoma, small cell lung carcinoma, or bronchial carcinoid; o Patients with acute or chronic viral hepatitis and/or decompensated severe liver cirrhosis (Child-Pugh Class C); o Patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies or after resuscitation from cardiac arrest; o Patients receiving peritoneal dialysis or hemodialysis treatment; o Patients with biliary pancreatitis, chemical pneumonitis or heat stroke; o Patients with invasive fungal infections (e.g. candidiasis, aspergillosis) or acute attacks of plasmodium falciparum malaria; and o Neonates during the first 2 days of life. The results of the B·R·A·H·M·S PCT sensitive KRYPTOR® should be evaluated in context of all laboratory findings and the total clinical status of the patient. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.

Feature	Candidate Device: Elecsys BRAHMS PCT (K160729)	Predicate Device: BRAHMS PCT sensitive KRYPTOR®(DEN150009)
Limitations Continued	Increased PCT levels may not always be related to systemic infection. These include, but are not limited to: ▪Patients experiencing major trauma and/or recent surgical procedure including extracorporeal circulation or burns. ▪Patients undergoing treatment with OKT3 antibodies, OK 432, interleukins, TNF alpha and other drugs that stimulate the release of pro inflammatory cytokines or result in anaphylaxis. ▪Patients diagnosed with active medullary C cell carcinoma, small cell lung carcinoma, or bronchial carcinoid. ▪Patients with acute or chronic viral hepatitis and/or decompensated severe liver cirrhosis (Child Pugh Class C). ▪Patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, or after resuscitation from cardiac arrest. ▪Patients receiving peritoneal dialysis or hemodialysis treatment. ▪Patients with biliary pancreatitis, chemical pneumonitis, or heat stroke. Patients with invasive fungal infections (e.g. candidiasis, aspergillosis) or acute attacks of plasmodium falciparum malaria. ▪Neonates during the first 2 days of life. The results of the Elecsys BRAHMS PCT assay should be evaluated in the context of all laboratory findings and the total clinical status of the patient. In cases where laboratory results do not agree with the clinical picture or history, additional tests should be performed.	
Method Comparison	2617 samples were run on the Cobas e411 and the predicate device (BRAHMS PCT sensitive KRYPTOR®). Passing Bablok Slope: 0.959 (95% CI: 0.947; 0.972) Intercept: -0.023 (95% CI: -0.028; -0.018) Coefficient: 0.989 (95% CI: 0.988; 0.990)	

Table 2. CalSet Comparison

Characteristic	Candidate Device: PCT CalSet (K160729)	CalSet Predicate Device: Progesterone III CalSet (K152526)
Intended Use	PCT CalSet is used for calibrating the quantitative Elecsys BRAHMS PCT assay on the Elecsys and **cobas e** analyzers.	The Progesterone III CalSet is used for calibrating the quantitative Elecsys Progesterone III assay on the Elecsys and **cobas e** immunoassay analyzers.
Analyte	Recombinant PCT	Progesterone (plant-derived)
Matrix	Human serum matrix	Human serum matrix
Levels	Two	Two
Target Ranges	PCT Cal 1: 0.10 ng/mL PCT Cal 2: 54 ng/mL	Cal 1: 0.80 ng/mL Cal 2: 53 ng/mL
Format	Lyophilized	Lyophilized
Handling	Carefully dissolve the contents of one bottle by adding exactly 4 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding the foam formation. Transfer aliquots of the reconstituted calibrators into empty labeled snap-cap bottles (CalSet Vials). Attach the supplied labels to the additional bottles. Store the aliquots immediately at .15 to -25°C. Perform only one calibration procedure per aliquot.	Carefully dissolve the contents of one bottle by adding exactly 1.0mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding the foam formation. Transfer aliquots of the reconstituted calibrators into empty labeled snap-cap bottles (CalSet Vials). Attach the supplied labels to the additional bottles. Store the aliquots immediately at -20°C. Perform only one calibration procedure per aliquot.

Table 3. Control Comparison

Characteristic	Candidate Device: PreciControl PCT (K160729)	Predicate Device: BRAHMS PCT sensitive KRYPTOR® QC Kit (DEN150009)
Intended Use	PreciControl PCT is a single analyte control that is used for quality control of the Elecsys BRAHMS PCT assay.	The B·R·A·H·M·S PCT sensitive KRYPTOR® QC is designed for quality control on board the B·R·A·H·M·S KRYPTOR® analyzer for the B·R·A·H·M·S PCT sensitive KRYPTOR® assay.
Analyte	Recombinant PCT	Recombinant PCT
Matrix	Human plasma	Human plasma
Levels	Two	Two
Target Ranges	PC1: 0.5 ng/mL PC2: 10 ng/mL	PC1: 0.2-0.4 µg/L PC2: 8-12 µg/L
Format	Lyophilized	Lyophilized
Handling	Carefully dissolve the contents of one bottle by adding exactly 4 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation. Transfer the reconstituted controls into the empty labeled snap cap bottles supplied or into additional snapcap bottles (ControlSet Vials). Attach the supplied labels to these additional bottles. Aliquots intended for storage at .15 to -25°C should be frozen immediately. Perform only one control procedure per aliquot.	Reconstitute a vial with de-ionized water (2.0mL) as indicated on the vial label. Use de-ionized water with conductivity of less than 50 µS/cm. ☐ dissolution of the lyophilisate. ☐ the control sample using a Vortex. ☐ tubes. ☐ immediate measurements. Freeze the other tubes immediately at < –16 °C and store up to one month. ☐ using a Vortex and use immediately for measurement. A control tube will be processed like a sample tube.

Table 4. CalCheck Comparison

Characteristic	Candidate Device: Elecsys PCT CalCheck 5 (K160729)	Predicate Device: Elecsys Progesterone III CalCheck 5 (K150955)
Intended Use	The BRAHMS PCT CalCheck 5 is an assayed control for use in calibration verification and for use in the verification of the assay range established by the Elecsys BRAHMS PCT reagent on the indicated Elecsys and **cobas e** immunoassay analyzers.	The Elecsys Progesterone III CalCheck 5 is an assayed control for use in calibration verification and for use in the verification of the assay range established by the Elecsys Progesterone III reagent on the indicated Elecsys and **cobas** e immunoassay analyzers.
Analyte	Recombinant PCT	Progesterone (plant material)
Matrix	Human plasma	Human serum matrix
Levels	Five	Five
Assay measuring range	0.02 – 100 ng/mL	0.05 – 60 ng/mL
Target Ranges	Check 1: ≤ 0.06 ng/mL Check 2: 0.5 ng/mL Check 3: 40.0 ng/mL Check 4: 80.0 ng/mL Check 5: 100.0 ng/mL	Check 1: ≤ 0.15 ng/mL Check 2: 2.0 ng/mL Check 3: 30.0 ng/mL Check 4: 45.0 ng/mL Check 5: 60.0 ng/mL
Format	Lyophilized	Lyophilized
Handling	Reconstitute the contents of Check 1, Check 2, Check 3, Check 4 and Check 5 with exactly 1.0 mL distilled or deionized water. Allow the bottles to stand closed for 15 minutes. Mix gently by inversion to ensure homogeneity.	Reconstitute Check 1, Check 2, Check 3, Check 4, and Check 5 with exactly 1.0mL distilled or deionized water. Allow to stand closed for 15 minutes, then mix gently by inversion to ensure homogeneity.
Stability	Unopened: · Store at 2-8°C until expiration date Opened: · 20-25°C: 2 hours	Unopened: · Store at 2-8°C until expiration date Opened: · 20-25°C: 4 hours

5. NON-CLINICAL PERFORMANCE EVALUATION

Non-clinical performance evaluations for the Elecsys BRAHMS PCT assay executed with the study briefly summarized.

5.1. Precision (Human Sera)

Precision of the Elecsys BRAHMS PCT assay was evaluated on one **cobas e** 411 analyzer according to CLSI EP5-A3 guideline. One reagent lot was evaluated.

The protocol consisted of testing two replicates of each control (PC PCT 1 and PC PCT 2) and six human serum samples per run, two runs per day for 21 days. The samples were run in randomized order on the analyzer.

Repeatability and Intermediate precision were calculated according to CLSI EP5-A3.

5.2. Limit of Blank (LoB)

For the analytical sensitivity studies, the Limit of Blank was determined according to CLSI EP17-A2. The LoB was determined as the 95th percentile of blank-sample measurements. The distribution of values for five analyte-free serum samples was determined with one reagent lot on one **cobas e** 411 anaylzer over three days for six runs total.

The samples were measured in two-fold determination for each run. A total of 60 measuring points were collected.

5.3. Limit of Detection (LoD)

For the analytical sensitivity studies, the Limit of Detection was determined according is the smallest amount of analyte that can be detected with 95% probability. The distribution of values for five low-level human serum samples was determined with one reagent lot on one **cobas e** 411 anaylzer over three days for six runs total.

The samples were measured in two-fold determination for each run. A total of 60 measuring points were collected.

5.4. Limit of Quantitation (LoQ)

The Limit of Quantitation 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. For Procalcitonin, no reference material or reference method is available, thus bias cannot be calculated. Therefore, 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 precision experiment was carried out with one reagent lot on one **cobas e** 411 analyzer. Samples tested included five human serum (HS) samples with concentrations from LoB to two times the LoQ. Samples were measured in five-fold determination for each run. A total of 125 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.

5.5. Linearity

The linearity results were obtained with serum samples on one **cobas e** 411 analyzer. Three spiked human plasma samples and three spiked human serum samples were diluted into six dilution series with each series containing at least 14 dilutions. Samples were assayed in three-fold determination within a single run.

The linearity data were analyzed with regards to linear, quadratic, and cubic polynomials, according to CLSI EP6-A. In the first step, a linearity check was performed with a first order (linear) regression, and then with high order models (quadratic and cubic).

5.6. Dilution Study

To demonstrate the Elecsys BRAHMS PCT assay dilution study, three different dilutions with dilution factors between 1:1 and 1:5 were prepared. Three serum samples and one plasma sample were spiked with PCT to concentrations exceeding the measuring range. The samples were diluted with serum (low PCT concentrations) and recovery was investigated on the **cobas e** 411.

5.7. Analytical Specificity

The specificity of the Elecsys BRAHMS PCT assay was determined using native human serum samples spiked with potential cross-reacting compounds. The spiked and unspiked reference samples were measured in duplicate on one Elecsys 2010 analyzer. Specificity was determined using two human serum sample pools spiked with potential cross-reactant compounds at four different concentrations each. The analyte concentration of the samples was at approximately 0.4 and 1.5 ng/mL PCT. Cross-reactivity results will be reported in the method sheet.

5.8. 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 Elecsys 2010 analyzer. Spiked serum pools were used for testing.

For each potential interferent, three human serum samples (containing low, mid, and high concentrations of PCT) were tested.

5.9. HAMA Effect

The effect of the presence of human anti-mouse antibodies (HAMA) on the Elecsys BRAHMS PCT assay was assessed on the Elecsys 2010 analyzer.

A suitable HAMA serum was spiked with PCT analyte at multiple concentrations covering the clinically relevant range. In parallel, a control (human serum) sample was spiked with the same levels of analyte. For each analyte concentration, a series of 11 dilutions of the HAMA sample and control sample were each prepared and measured in duplicate. The recovery for each sample was calculated by comparison to the reference (no HAMA) sample.

5.10. High-Dose Hook Effect

The high-dose hook effect of the Elecsys BRAHMS PCT assay was assessed on the Elecsys 2010 analyzer. Human serum pools were spiked with analyte up to a concentration of 2,500 ng/mL. These samples were subsequently diluted with negative human serum.

The expected values for the diluted samples were calculated using the known spiked PCT analyte concentration of the undiluted sample and the appropriate dilution factor.

The hook concentration reported corresponds to the analyte concentration that generates a signal ≥10% above the upper limit of the measuring range

5.11. Exogenous Interferences – Drugs

The effect on quantitation of analyte in the presence of drugs was determined by comparing values obtained from samples spiked with 27 pharmaceutical compounds into two human serum samples at differing analyte concentrations and tested on the Elecsys 2010 analyzer.

The PCT concentration of the spiked aliquots was tested in two-fold determination and compared to the PCT concentration for the reference aliquot (also tested in two-fold determination).

5.12. Serum/Plasma Comparison

The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys BRAHMS PCT assay was determined by comparing values obtained from samples drawn into Serum Separator Tubes (SST), Serum, Li-Heparin Plasma, K2-, K3-EDTA and Plasma primary tubes and Plasma Separation Tubes (PST). Ten human serum samples were tested in duplicate on one Elecsys 2010 analyzer at three time points for SST. For remaining Serum/Plasma comparison studies, a minimum of 50 serum/plasma pairs were tested with one reagent lot on one **cobas e** 411 analyzer. Potential effects were assessed by Passing/Bablok regression analysis.

5.13. Method Comparison

A method comparison study was performed to compare the Elecsys BRAHMS PCT assay on the **cobas e** 601 analyzer with the Elecsys BRAHMS PCT assay on the **cobas e** 411 analyzer. A total of 137 human serum samples with PCT values from 0.0681 ng/mL to 99.1 ng/mL were measured.

The results were calculated using Passing/Bablok and Linear Regression analyses.

5.14. Reagent Stability

To test reagent stability, three studies were executed.

5.14.1. Study 1. Reagent Stability (On Board)

Reagent on-board stability for the Elecsys BRAHMS PCT assay was tested on one Elecsys 2010 analyzer.

A fresh reagent Rack Pack was placed on the analyzer and calibrated. Reference values for the samples tested were determined. On day 7 and day 28 the same samples were determined with the same reagent kit (kept on board the instrument) using the calibration curve of day 0 and day 21 respectively.

Samples tested in duplicate include five human serum samples and two controls.

5.14.2. Study 2. Reagent Stability (After Opening)

Reagent stability after first opening for the Elecsys BRAHMS PCt assay was tested on one Elecsys 2010 analyzer.

A fresh reagent Rack Pack was placed on the analyzer and calibrated. Reference values for the samples tested were determined. After measurement, the kit was removed from the analyzer and stored at 2–8°C for 12 weeks. The kit was again placed on the analyzer, calibrated, and the samples were tested.

Samples tested included five human serum samples and two controls.

5.14.3. Study 3. Reagent Stability (Real-Time Shelf Life)

In the real-time, shelf-life stability study, the Elecsys BRAHMS PCT assay reagent was stored at 2–8°C. The stored reagent was tested at time point 0 (at manufacture), then again at specified intervals over the shelf life of the device (up to the planned shelf life plus one month).

Samples tested in duplicate include human serum samples from three reagent lots and two controls.

5.15. Sample Stability

To test reagent stability, four studies were executed.

5.15.1. Study 1. Sample Stability (Freeze/Thaw Cycles)

Ten samples of each human serum and plasma types were aliquoted and measured fresh (reference value) and after one freeze/thaw cycle with the Elecsys BRAHMS PCT assay.

Measurements were performed in three-fold determination on one **cobas e** 601 analyzer, and recovery was calculated as percent of the reference value or as deviation in ng/mL.

5.15.2. Study 2. Sample Stability (at −20°C)

Ten samples of each human serum and plasma types were aliquoted and measured fresh (reference value) and after storage for up to 13 months at −20°C with the Elecsys BRAHMS PCT assay.

Measurement were performed in three-fold determination on one **cobas e** 601 analyzer, and recovery was calculated as percent of the reference value or as deviation in ng/mL.

5.15.3. Study 3. Sample Stability (at 2–8°C)

Ten samples of each human serum and plasma types were aliquoted and measured fresh (reference value) and after storage for up to 72 hours at 2-8°C with the Elecsys BRAHMS PCT assay.

Measurement were performed in three-fold determination on one **cobas e** 601 analyzer, and recovery was calculated as percent of the reference value or as a deviation in ng/mL.

5.15.4. Study 4. Sample Stability (at 15–25°C)

Ten samples of each human serum and plasma types were aliquoted and measured fresh (reference value) and after storage for up to 48 hours at 15-25°C with the Elecsys BRAHMS PCT assay.

Measurement were performed in three-fold determination on one **cobas e** 601 analyzer, and recovery was calculated as percent of the reference value or as a deviation in ng/mL.

5.16. Calibration Stability

To test calibration stability, two studies were executed.

5.16.1. Study 1. Calibration (Lot) Stability

Calibration of an Elecsys BRAHMS PCT reagent lot is recommended every 4 weeks. During that time period, fresh reagent kits of the same lot can be used in conjunction with the calibration curve established at Day 0 for that reagent kit lot.

The Elecsys BRAHMS PCT assay was calibrated with a fresh reagent kit on Day 0 using one Elecsys 2010 analyzer. After 4, 8, and 12 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.

Five human serum (HS) samples and two controls were tested in duplicate. Recovery compared to the reference value was calculated as either deviation (in ng/mL).

5.16.2. Study 2. Calibration (On Board) Stability

A fresh Elecsys BRAHMS PCT test kit was placed on an Elecsys 2010 analyzer and calibrated. Five native human serum (HS) sample pools and two control samples were tested with the fresh reagent kit; each sample was tested with 2-fold determination. On day 7 and day 28 the same samples were determined with the same reagent kit (kept on board of the instruments) using the

calibration curve of day 0 and day 21 respectively. Each sample was tested with 2-fold determination.

5.16. Calibrator Stability

The PCT CalSet was evaluated for value assignment and stability; three studies were executed.

5.17.1. Calibrator Value Assignment

Value assignment tested was conducted and passed pre-defined acceptance criteria. The target values for the two levels of the PCT Calset are chosen to obtain the best fit with the Master Calibration Curve, together with the Rodbard curve parameters encoded in the reagent barcode. For each Elecsys PCT CalSet lot manufactured, the calibrators are run in duplicate on at least six **cobas e** 411 analyzers and least three **cobas e** 601/**cobas e** 602/MODULAR ANALYTICS E170 analyzers with all Elecsys BRAHMS PCT reagent lots available. The assigned value of each calibrator is defined as the mean value obtained over at least six runs on at least three analyzers of the respective calibrator.

Measurement values for PreciControl PCT (Levels 1 and 2), a single-analyte control recommended for use to monitor accuracy and precision of the PCT analyte, are read from the calibration curves generated. The pre-defined acceptance criteria for PreciControl PCT have to be met to release the Assigned Values for the PCT CalSet.

5.17.2. Study 1. Calibrator Stability (Post Reconstitution at −20°C)

Reconstituted calibrators were stored for 3 months at −20°C.

The freshly reconstituted calibrators, and the reconstituted calibrators stored for 3 months at -20°C, were measured in one run on one Elecsys 2010 analyzer.

Recoveries of the stressed calibrators versus the freshly reconstituted calibrators were calculated.

5.17.3. Study 2. Calibrator Stability (Post Reconstitution at 20-25°C)

Reconstituted calibrators were stored for 5 hours at 20–25°C.

The freshly reconstituted calibrators, and the reconstituted calibrators stored for 5 hours at 20–25°C, were measured in one run on one Elecsys 2010.

Recoveries of the stressed calibrators versus the freshly reconstituted calibrators were calculated.

5.17.4. Study 3. Calibrator Stability (Real-Time Shelf Life part of Assay Testing)

In the real-time, shelf-life stability study, the PCT CalSet was stored at 2–8°C. The stored calibrator was tested at time point 0 (at manufacture), then again at specified intervals over the shelf life of the device (up to the planned shelf life plus one month).

5.18. PreciControl PCT

PreciControl PCT was evaluated for value assignment and stability; three studies were executed.

5.18.1. PreciControl Value Assignment

The PreciControl PCT assigned values are determined with the Elecsys BRAHMS PCT assay. A human serum sample panel (Master Calibrators) covering the entire measuring range is available, which is traceable to the PCT.

The assigned values for PreciControl PCT are read from the master calibration curve. Values are assigned for each lot of PreciControl PCT in combination with each Elecsys PCT assay reagent lot available. The controls are run in duplicate on at least six analyzers of the master analyzer platform. The assigned value of each control level is defined as the median value obtained over at least six determinations of the respective control level. For additional analyzer platforms, the same value assignment procedure is performed. The assigned values obtained on the additional analyzer are compared to those obtained on the master platform.

5.18.2. Study 1. PreciControl Stability (Post Reconstitution at −20°C)

Reconstituted calibrators were stored for 3 months at −20°C.

The freshly reconstituted calibrators, and the reconstituted calibrators stored for 3 months at −20°C, were measured in one run on one Elecsys 2010 analyzer.
Recovery of the stressed PreciControl PCT compared to the freshly reconstituted PreciControl PCT was calculated.

5.18.3. Study 2. PreciControl Stability (Post Reconstitution at 20-25°C)

Reconstituted controls were stored for 5 hours at 20–25°C.

The freshly reconstituted controls, and the reconstituted controls stored for 5 hours at 20–25°C, were measured in one run on one Elecsys 2010.

Recoveries of the stressed controls versus the freshly reconstituted controls.

5.18.4. Study 3. PreciControl Stability (Real-Time Shelf Life part of Assay Testing)

In the real-time, shelf-PCT samples were tested at time point 0 (at manufacture), then again at specified intervals over the shelf life of the device (up to the planned shelf life plus one month).

5.19. PCT CalCheck 5 Stability

PCT CalCheck 5 was evaluated for value assignment and stability; two studies were executed.

5.19.1. PCT CalCheck 5 Value Assignment

Value assignment testing was conducted and passed pre-defined acceptance criteria. For each Elecsys BRAHMS PCT CalCheck 5 lot manufactured, each CalCheck is run in duplicate on at

least six analyzers of the master analyzer platform. The assigned valued of each CalCheck level is defined as the mean value obtained over at least six determinations (duplicate runs on at least three analyzers) of the respective CalCheck level.

The CalCheck assigned range is calculated as ±30% of the assigned value for levels two through five. The label states that each laboratory should establish appropriate acceptance criteria when using this product for its intended use.

The same value assignment procedure is performed on the **cobas e** 601 analyzer. The assigned values obtained are compared to those obtained on the **cobas e** 411 analyzer. The mean value obtained on the additional analyzer must be within 10% of the master platform assigned value. After this acceptance criterion is met, the assigned values from the master platform are deemed valid for the Elecsys 2010, MODULAR ANALYTICS E170, **cobas e** 411, **cobas e** 601, and **cobas e** 602 analyzers.

5.19.2. Study 1. PCT CalCheck 5 Accelerated and Open Vial Stability

One PCT CalCheck 5 lot was evaluated, in duplicate, on one **cobas e** 411 analyzer. A set of PCT CalCheck 5 was stored for 3 weeks at 35°C. After the three week period the test material was reconstituted and stored for 3 hours at 25°C (in an open vial).

The reference material used was a freshly reconstituted set of PCT CalCheck 5. Recovery of the stressed PCT CalCheck 5 compared to the freshly reconstituted PCT CalCheck 5 was calculated.

5.19.3. Study 2. PCT CalCheck 5 Stability (Real-Time Shelf Life)

In the real-time shelf-life stability study (which is ongoing), the PCT CalCheck 5 will be stored at 2–8°C. The stored PCT CalCheck 5 will be tested at time point 0 (at manufacture), then again at specified intervals over the shelf life of the device (up to the planned shelf life plus one month).

Samples tested in duplicate include five CalCheck levels.

5.19.4. Study 3. PCT CalCheck 5* Stability (Real-Time Shelf Life)

In another real-time shelf-life stability study, a PCT CalCheck 5 lot (*with slightly different level 2 and 3 concentrations) was stored at 2–8°C for up to 37 months. The stored PCT CalCheck 5 was tested at time point 0 (at manufacture), then again at specified internals up to 37 months.

Samples tested in duplicate include five CalCheck levels.

6. CLINICAL PERFORMANCE EVALUATION

6.1 Reference Range

In a population of 282 self-reported healthy individuals, the 95th percentile, upper reference range limit was calculated at 0.08 ng/mL.

		assay								
		PCT study								
		unit								
		ng/mL								
		ResultStudyUnit								
		NMiss	N	Min	Median	P95	Mean	StdDev	CV	Max
total (all)		0	282	0.02	0.02	0.08	0.03	0.03	100.25	0.39
gender		0	139	0.02	0.02	0.04	0.03	0.01	46.86	0.12
female	total (all)									
male	total (all)	0	143	0.02	0.03	0.11	0.04	0.04	105.30	0.39
smoking		0	210	0.02	0.02	0.08	0.03	0.03	99.49	0.39
no	total (all)									
yes	total (all)	0	40	0.02	0.02	0.11	0.04	0.05	122.89	0.29
unknown	total (all)	0	32	0.02	0.03	0.08	0.04	0.02	67.85	0.13
race		0	101	0.02	0.02	0.09	0.03	0.02	81.44	0.16
African/black	total (all)									
Alaska Native/American Indian	total (all)	0	1	0.03	0.03	0.03	0.03	.	.	0.03
Asian	total (all)	0	4	0.02	0.03	0.15	0.06	0.06	99.45	0.15
Caucasian/white	total (all)	0	169	0.02	0.03	0.07	0.04	0.04	108.24	0.39
other	total (all)	0	7	0.02	0.02	0.05	0.03	0.01	42.75	0.05
age class		0	113	0.02	0.02	0.09	0.04	0.05	129.22	0.39
20-<30 years	total (all)									
30-<40 years	total (all)	0	97	0.02	0.02	0.08	0.03	0.02	65.56	0.15
40-<50 years	total (all)	0	43	0.02	0.02	0.11	0.03	0.02	71.93	0.11
50-<60 years	total (all)	0	23	0.02	0.03	0.08	0.04	0.03	72.37	0.12
60-<70 years	total (all)	0	4	0.02	0.02	0.04	0.02	0.01	38.38	0.04
70 years or older	total (all)	0	2	0.03	0.03	0.04	0.03	0.01	34.28	0.04

6.2 Clinical Performance

The Elecsys BRAHMS PCT assay was evaluated for the prediction of cumulative 28-day all-cause mortality in a prospective clinical trial[18] study of 858 adult patients diagnosed with severe sepsis or septic shock admitted to ICU care in which PCT levels were measured on Days 0, 1, and 4 across 13 investigational sites in the US. The per protocol analysis population (598 subjects) was comprised of 44 % female and 56 % male patients with a mean age of 64 years. About half of the patients had severe sepsis (51 %) versus septic shock (49 %). Infections were mainly community acquired (91%).

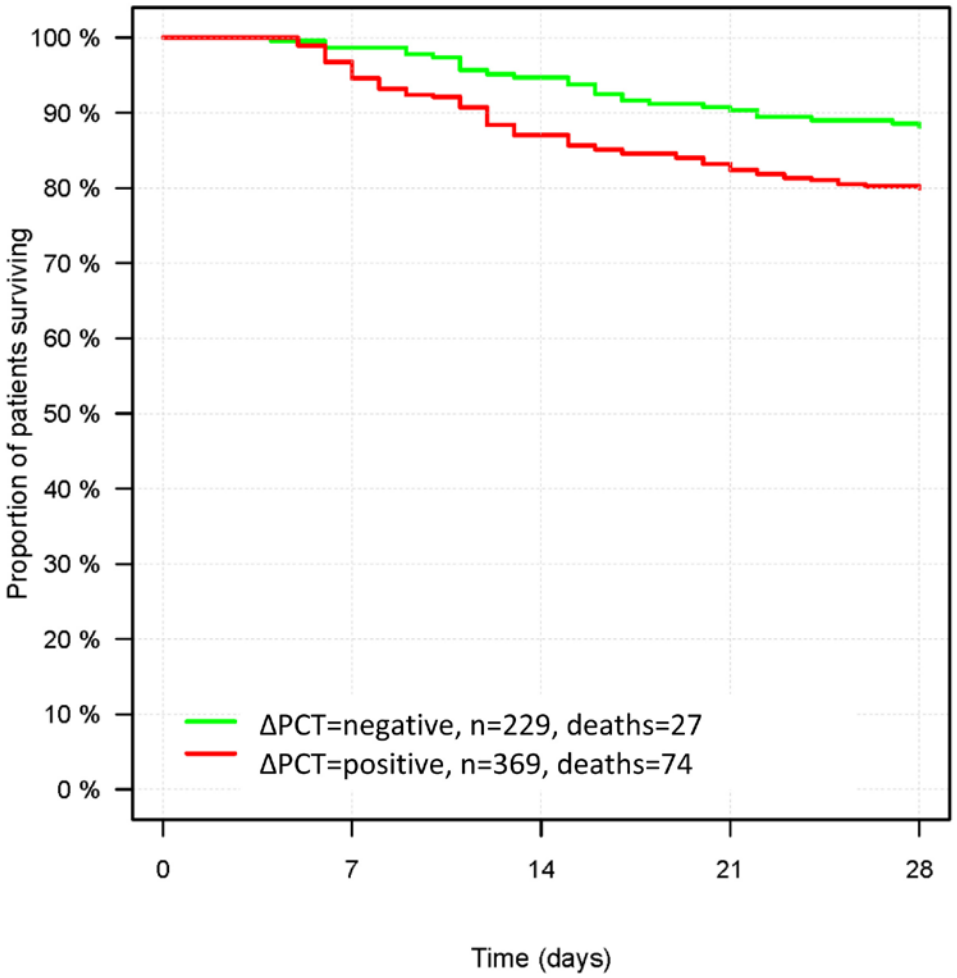
The binary test result (ΔPCT > 80 % or ≤ 80 %) was significantly associated with 28-day cumulative mortality (vital status on day 28) (Two-sided Fisher's Exact Test p-value = 0.002). Adjusted for ICU vs. non-ICU patient subgroups (based on hospital location at day 4 after initial diagnosis), the association remained significant (Cochran-Mantel-Haenszel Test p-value = 0.020). In each binary ΔPCT subgroup, the 28-day cumulative mortality rate was stratified by need to continue ICU care on day 4 and/or the selection of Day 0 vs. Day 1 as the baseline measurement day for the ΔPCT calculation. The data are as follows:

Prediction performances of binary ΔPCT stratified by ICU care on Day 4

28-day mortality risk stratified by patient location on Day 4: ΔPCT > 80 % = Test Negative; ΔPCT ≤ 80 % = Test Positive per-protocol population					
Day 4 patient location	**Measurement interval**	**28-day mortality risk (%)**		**Prognostic accuracy[b)]**	
		ΔPCT > 80 %	**ΔPCT ≤ 80 %**	**Sensitivity**	**Specificity**
ICU	ΔPCT 0-4	22.1 (13.3-31.0)	29.6 (22.9-36.4)	73.4 (62.9-83.8)	35.0 (28.2-41.8)
	ΔPCT 1-4	21.5 (13.0-29.9)	30.4 (23.4-37.3)	71.6 (60.8-82.3)	38.7 (31.7-45.7)
Non-ICU	ΔPCT 0-4	5.6 (1.8-9.4)	11.0 (6.6-15.5)	72.3 (55.9-88.6)	44.4 (38.4-50.3)
	ΔPCT 1-4	7.1 (2.8-11.3)	9.9 (5.7-14.2)	65.4 (48.0-82.7)	43.3 (37.3-49.2)

b) Prognostic accuracy refers to how accurate the ΔPCT (> 80 % vs. ≤ 80 %) can predict mortality risk using 28-day mortality as the clinical reference.

Kaplan Meier survival curves show that patients with a positive ΔPCT result (≤ 80 %) had a clearly lower survival probability from study Day 4 till the end of follow up time compared to ΔPCT negative (> 80 %) patients.



Additional stratification of patients based on absolute initial PCT levels (> or ≤ 2.0 µg/L) at Day 0 (or Day 1) revealed subgroups with particularly reduced or elevated mortality risk considering their hospital disposition on Day 4. Mortality rates and prognostic performance are given for the following subgroups in the table below:

1. Patients with PCT ≤ 2.0 µg/L at Day 0 (or Day 1) receiving ICU care on Day 4.
2. Patients with PCT > 2.0 µg/L at Day 0 (or Day 1) receiving ICU care on Day 4.
3. Patients with PCT ≤ 2.0 µg/L at Day 0 (or Day 1) without ICU care on Day 4.
4. Patients with PCT > 2.0 µg/L at Day 0 (or Day 1) without ICU care on Day 4.

28-day mortality risk stratified by patient location on Day 4, absolute PCT value on Day 0: ΔPCT > 80 % = Test Negative; ΔPCT ≤ 80 % = Test Positive					
Per-Protocol Population: ∆PCT 0-4 stratified PCT at Day 0					
Day 4 patient location	**Measurement interval**	**28-day mortality risk (%)**		**Prognostic accuracy***	
		ΔPCT Day 0-4 > 80 %	**ΔPCT Day 0-4 ≤ 80 %**	**Sensitivity (%)**	**Specificity (%)**
ICU	≤ 2.0 µg/L	10.4 (0.0-29.7)	24.9 (15.2-34.6)	94.9 (85.2-100)	13.3 (4.9-21.8)
	> 2.0 µg/L	23.6 (14.0-33.2)	33.2 (24.0-42.4)	65.1 (51.8-78.3)	46.3 (37.5-55.0)
Non-ICU	≤ 2.0 µg/L	5.6 (0.0-16.3)	8.3 (3.6-12.9)	91.7 (76.0-100)	12.3 (6.2-18.4)
	> 2.0 µg/L	5.6 (1.6-9.7)	17.5 (7.5-27.5)	58.6 (35.1-82.1)	71.4 (64.1-78.8)

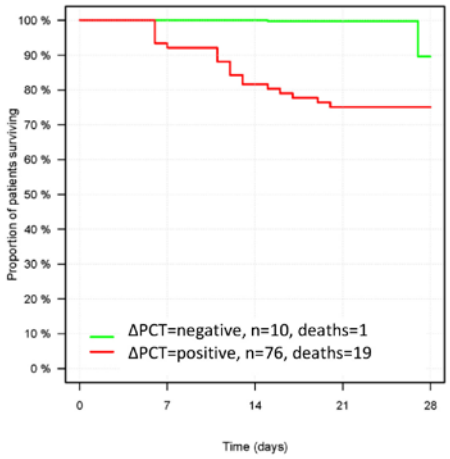
28-day mortality risk stratified by patient location on Day 4, absolute PCT value on Day 1: ΔPCT > 80 % = Test Negative; ΔPCT ≤ 80 % = Test Positive					
Per-Protocol Population: ∆PCT 1-4 stratified PCT at Day 1					
Day 4 patient location	**Measurement interval**	**28-day mortality risk (%)**		**Prognostic accuracy***	
		ΔPCT Day 1-4 > 80 %	**ΔPCT Day 1-4 ≤ 80 %**	**Sensitivity (%)**	**Specificity (%)**
ICU	≤ 2.0 µg/L	11.8 (0.0-33.6)	25.5 (15.4-35.6)	94.7 (84.6-100.0)	12.7 (3.8-21.7)
	> 2.0 µg/L	22.5 (13.5-31.5)	34.0 (24.4-43.5)	62.9 (49.4-76.5)	51.3 (42.4-59.7)
Non-ICU	≤ 2.0 µg/L	0.0 (0.0-17.6%)[c]	7.5 (3.0-12.0)	100.0 (69.2-100.0)[c]	13.4 (7.3-19.5)
	> 2.0 µg/L	8.2 (3.3-13.1)	15.3 (6.0-24.7)	47.2 (24.6-69.7)	69.4 (61.6-77.2)

c) Normality approximation of within-imputation variance not valid, therefore the estimate corresponds to within-imputation variation based on exact confidence intervals [Clopper & Pearson, 1934]

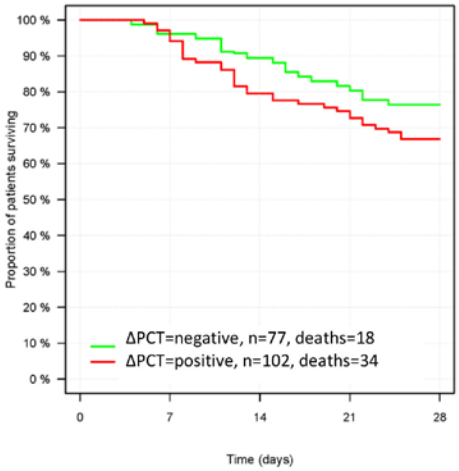
* Prognostic accuracy refers to how accurate the ΔPCT (≤ 80% vs. ≤ 80%) can predict mortality risk.

Kaplan-Meier Plots are depicted below to illustrate the time-to-event structure in the extended patient subgroups according to hospital location on Day 4 and initial PCT level.

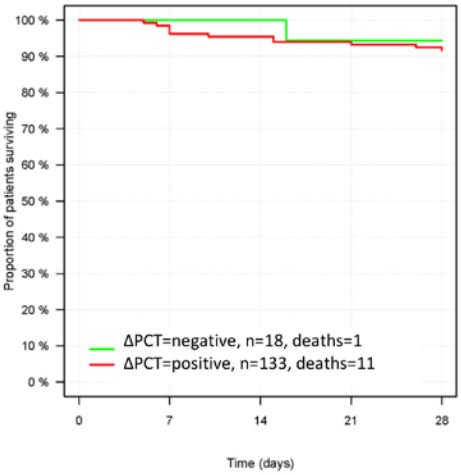
Survival until Day 28, PCT ≤ 2.0 µg/L at Day 0, ICU Day 4 (n=86)



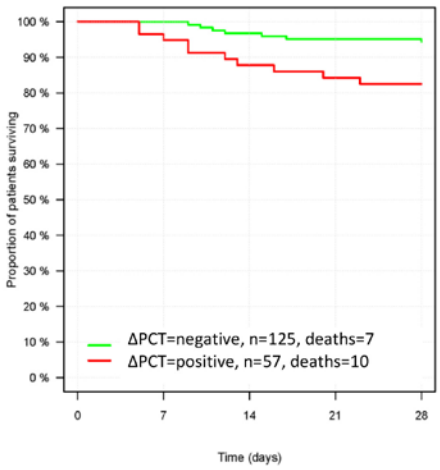
Survival until Day 28, PCT > 2.0 µg/L at Day 0, ICU Day 4 (n=179)



Survival until Day 28, PCT ≤ 2.0 µg/L at Day 0, non-ICU Day 4 (n=151)



Survival until Day 28, PCT > 2.0 µg/L at Day 0, non-ICU Day 4 (n=182)



Time-to-event analysis evidently reveals that patients in the ICU or with an initial PCT value > 2.0 µg/L had a lower survival probability from study Day 4 until the end of follow up time (28 days) when the ΔPCT test result was positive compared to ΔPCT negative patients as illustrated by the Kaplan-Meier curves above (patient subgroups according to hospital location on Day 4 and initial PCT level).

A generally lower mortality rate was observed in the non-ICU subgroup. The mortality rates for ΔPCT positive vs. ΔPCT negative patient subgroups were:

Patients with PCT ≤ 2.0 µg/L at Day 0 receiving ICU care on Day 4	10.4 % vs. 24.9 %
Patients with PCT > 2.0 µg/L at Day 0 receiving ICU care on Day 4	23.6 % vs. 33.2 %
Patients with PCT ≤ 2.0 µg/L at Day 0 without ICU care on Day 4	5.6 % vs. 8.3 %
Patients with PCT > 2.0 µg/L at Day 0 without ICU care on Day 4	5.6 % vs. 17.5 %

Based on relative mortality ratios a decrease by more than 80 % from Day 0 (or Day 1) to Day 4 constitutes a lower risk for mortality within 28 days compared to smaller declines in each subgroup. For the prediction of absolute mortality risks ICU disposition at Day 4 and initial PCT concentrations should be considered:

1. An initial PCT level ≤ 2.0 µg/L on Day 0 followed by a PCT decline of more than 80 % until Day 4 indicates an almost 2-fold lower mortality (10.4 %) for patients with severe sepsis or septic shock who are still in the ICU by Day 4 compared to those patients with an initial PCT level > 2.0 µg/L (23.6 %). Regardless of the initial PCT level, patients in the ICU on Day 4 that do not decline by more than 80 % in PCT plasma concentration from Day 0 to Day 4 have an even higher mortality risk of 24.9-33.2 %.
2. An initial PCT level > 2.0 µg/L that does not decline by more than 80 % until Day 4 signals that such patients remain at high mortality risk (17.5 %) even when they are no longer receiving ICU care on Day 4. Mortality was otherwise observed between 5.6 to 8.3 % for patients discharged from the ICU by Day 4.

In conclusion, hazard ratios for binary ΔPCT for both subgroups enrolled show an increase in mortality with ΔPCT. The mortality risk stratification using ΔPCT is valid when calculated from the day severe sepsis or septic shock is first diagnosed (Day 0) or the day thereafter (Day 1) and compared to the fourth day (Day 4) after diagnosis. The ΔPCT at Day 4 combined with the patient's clinical course provides important information for the 28-day all-cause mortality risk prediction after a diagnosis of severe sepsis or septic shock.

The prognostic value of ΔPCT was quantified by pooled p values of Wald statistics (Rubin's rule). The hazard ratio of binary ΔPCT4.0 in the univariate model is 1.80 (p = 0.011) for patients of the Per-Protocol population and similarly of the Intention to diagnose group (1.81; p = 0.008). That means **the risk of death is increased 1.8-fold if an individual has a positive test result for ΔPCT.**

As a comparison, the table below lists the univariate hazard ratios for other clinical factors evaluated as separate predictors of mortality in the per protocol study population.

Univariate hazard ratios for 28-day all-cause mortality of ΔPCT and clinical covariates			
Factor	**Comparison**	**Hazard ratio**	**p-Value**
ΔPCT4.0	≤ 80 % vs. > 80 %	1.80 (1.15-2.82)	0.011
ΔPCT4.1	≤ 80 % vs. > 80 %	1.61 (1.04-2.49)	0.034
APACHE	Difference of 5 units	1.36 (1.22-1.53)	< 0.001
Max SOFA	Difference of 3 units	1.73 (1.50-2.00)	< 0.001
Antibiotic adequacy	No vs. yes	1.59 (1.00-2.53)	0.051
Sepsis severity	Septic shock vs. severe sepsis	1.19 (0.80-1.76)	0.386
Biologic infection type	Gram pos vs. gram neg	0.83 (0.48-1.45)	0.522
Biologic infection type	Other vs. gram neg	0.99 (0.63-1.54)	0.960
Biologic infection type	Fungal vs. gram neg	2.44 (0.87-6.84)	0.090
Clinical infection type	Nosocomial vs. community	0.76 (0.35-1.64)	0.481
Positive blood culture	Yes vs. no	1.05 (0.69-1.58)	0.834
Baseline PCT	> 2 µg/L vs. ≤ 2 µg/L	1.43 (0.94-2.17)	0.095
Age	Difference of 5 years	1.16 (1.08-1.24)	< 0.001
Gender	Male vs. female	0.95 (0.64-1.40)	0.782
ICU care on Day 4	Yes vs. no	3.45 (2.24-5.31)	< 0.001

ΔPCT from Day 0 (or Day 1) to Day 4 remains a prognostic parameter for the risk of cumulative 28-day mortality in patients diagnosed with severe sepsis or septic shock even when hazard ratios are adjusted for other mortality predictors in multivariate models. The relative mortality risk estimates for ΔPCT and selected predictors are given below with 95 % confidence intervals. For continuous predictors, the hazard ratio (HR) was calculated for one standard deviation (SD) change in the predictor. For binary predictors, the risk estimate compares the hazards for the two binary results.

Hazard ratios for ΔPCT were calculated for each group as univariate and when applying certain covariates and are tabulated below.

Hazard ratios for ΔPCT per group	
Hazard ratio for ΔPCT ≤ 80 %	**Per-protocol**
ΔPCT 4.0 (univariate)	**1.80** [1.15-2.82]; p=0.0106
ΔPCT 4.0 with binary APACHE + covariates[d)]	**1.94** [1.14-3.31]; p=0.0140
ΔPCT 4.0 with numeric APACHE + covariates[c)]	**1.72** [1.00-2.95]; p=0.0487
ΔPCT 4.0 with binary SOFA + covariates[c)]	**1.76** [1.05-2.96]; p=0.0320
ΔPCT 4.0 with numeric SOFA + covariates[c)]	**1.46** [0.86-2.48]; p=0.1595
ΔPCT 4.1 (univariate)	**1.61** [1.04-2.49]; p=0.0345
ΔPCT 4.1 with binary APACHE + covariates[c)]	**1.68** [1.03-2.76]; p=0.0392
ΔPCT 4.1 with numeric APACHE + covariates[c)]	**1.61** [0.98-2.65]; p=0.0625
ΔPCT 4.1 with binary SOFA + covariates[c)]	**1.64** [1.00-2.69]; p=0.0483
ΔPCT 4.1 with numeric SOFA + covariates[c)]	**1.47** [0.89-2.42]; p=0.1300

d) Antibiotic adequacy, Sepsis severity, ICU Care on Day 4, Biological infection type, Clinical infection type, Positive blood culture, PCT on Day 0, Age, Gender

Hazard ratios for ΔPCT and selected predictors from multivariate Cox Regression Models			
Model		**Hazard ratio (95 % confidence interval)**	
		Binary predictors[e)]	
ΔPCT interval	**Score + Covariates[f)]**	**ΔPCT (≤ 80 % vs > 80 %)**	**Day 4 patient location (ICU vs. no ICU)**
Day 0 until Day 4	APACHE	1.72 (1.00-2.95)	2.61 (1.63-4.19)
	max SOFA	1.46 (0.86-2.48)	1.71 (1.04-2.81)
Day 1 until Day 4	APACHE	1.61 (0.98-2.65)	2.63 (1.64-4.21)
	max SOFA	1.47 (0.89-2.42)	1.73 (1.06-2.84)

e) In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules (Rubin D.B.,Wiley New York 1987; Multiple Imputation for Nonresponse in Surveys).

f) The models also included the following predictors (HR results not shown): Antibiotic adequacy, Sepsis severity, Biological infection type, Clinical infection type, Positive blood culture, PCT on Day 0, Gender.

Hazard ratios for ΔPCT and selected predictors from multivariate Cox Regression Models				
Model		**Hazard ratio (95 % confidence interval)**		
		Continuous predictors[g] (HR per 1 SD)		
ΔPCT interval	**Score + Covariates[h]**	**APACHE (1 SD=8.13)**	**max SOFA (1 SD=3.98)**	**Age (1 SD=16.18)**
Day 0 until Day 4	APACHE	1.25 (0.99-1.57)	----	1.59 (1.27-1.99)
	max SOFA	----	1.97 (1.53-2.53)	1.69 (1.35-2.10)
Day 1 until Day 4	APACHE	1.29 (1.04-1.62)	----	1.57 (1.25-1.96)
	max SOFA	----	2.00 (1.56-2.56)	1.67 (1.33-2.08)

g) In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules (Rubin D.B.,Wiley New York 1987; Multiple Imputation for Nonresponse in Surveys).

h) The models also included the following predictors (HR results not shown): Antibiotic adequacy, Sepsis severity, Biological infection type, Clinical infection type, Positive blood culture, PCT on Day 0, Gender.

The change of PCT over time can also be described by the ratio of PCT values from Day 4 and Day 0 (or Day 1):

$$PCT_{ratio} = \frac{PCT_{Day\ 4}}{PCT_{Day\ 0\ (or\ Day\ 1)}}$$

A decline of ΔPCT = 80 % translates into a PCT ratio of 0.2. The PCT ratio has values larger than 0.2 when the ΔPCT decline is below 80 % which is associated with a higher risk for cumulative 28-day all-cause mortality in patients diagnosed with severe sepsis or septic shock. Likewise, a PCT ratio below 0.2 indicates a lower risk for mortality within 28 days. On a continuous scale, the relative mortality risk for patients diagnosed with severe sepsis or septic shock is higher the larger the PCT ratio. The following tables list the hazard ratios for an increase by the factor 2 in PCT ratio, i.e. the relative increase in mortality risk for a patient with any given PCT ratio compared to a patient with a 2-fold lower PCT ratio. For comparison, selected predictors are indicated with corresponding equivalents in standard deviation. For the patient location at Day 4, the risk estimate compares the hazards for patients with vs. without ICU care on Day 4.

Hazard ratios for ΔPCT and selected predictors from multivariate Cox Regression Models		
Model		**Hazard ratio (95 % confidence interval)**
		Binary predictors[i)]
ΔPCT interval	**Score + Covariates[j)]**	**Day 4 patient location (ICU vs. no ICU)**
Day 0 until Day 4	APACHE	2.57 (1.59-4.13)
	Max SOFA	1.70 (1.03-2.80)
Day 1 until Day 4	APACHE	2.57 (1.60-4.11)
	Max SOFA	1.74 (1.06-2.86)

i) In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules (Rubin D.B.,Wiley New York 1987; Multiple Imputation for Nonresponse in Surveys).

j) The models also included the following predictors (HR results not shown): Antibiotic adequacy, Sepsis severity, Biological infection type, Clinical infection type, Positive blood culture, PCT on Day 0, Gender.

Hazard ratios for ΔPCT and selected predictors from multivariate Cox Regression Models					
Model		**Hazard ratio (95 % confidence interval)**			
		Continuous predictors[k)] (HR per 2-fold increase in PCT ratio or per equivalent in SD)			
ΔPCT interval	**Score + Covar[l),m)]**	**PCT ratio (2-fold increase)**	**APACHE (SD equiv[n)])[o)]**	**Max SOFA (SD equiv[i)])[j)]**	**Age (SD equiv[i)])[j)]**
Day 0 until Day 4	APACHE	1.26 (1.12-1.42)	1.08 (0.96-1.22)	----	1.29 (1.15-1.45)
	max SOFA	1.20 (1.07-1.35)	----	1.37 (1.20-1.57)	1.32 (1.18-1.49)
Day 1 until Day 4	APACHE	1.29 (1.11-1.49)	1.19 (1.02-1.39)	----	1.37 (1.18-1.60)
	max SOFA	1.23 (1.06-1.44)	----	1.58 (1.33-1.87)	1.43 (1.23-1.67)

k) In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules (Rubin D.B.,Wiley New York 1987; Multiple Imputation for Nonresponse in Surveys).

l) Covar = Covariates

m) The models also included the following predictors (HR results not shown): Antibiotic adequacy, Sepsis severity, Biological infection type, Clinical infection type, Positive blood culture, PCT on Day 0, Gender.

n) Equiv = Equivalent

o) A unit change of ΔPCT on log 2-scale corresponded to 0.52 SD of ΔPCT from Day 0 until Day 4 (0.69 SD for ΔPCT from Day 1 until Day 4). Accordingly, the reported ΔPCT hazard ratios refer to an increase of ΔPCT by a factor of 2. For comparability, hazard ratios of the other continuous predictors were estimated for the same fractional SDs, i.e. 0.52 or 0.69, respectively.

Cumulative 28-day all-cause mortality did not differ significantly for male vs. female patients ($\chi 2$ p-value = 0.84). Demographics with outcome information are shown below :

		Per-protocol population (N=598)			
Variable	**Class**	**All N**	**Dead N**	**Alive N**	**Mortality %**
Gender	Female	264	46	218	17.4
	Male	334	55	279	16.5
Age, years (catagorized)	< 30	39	1	38	2.6
	> 30, < 45	45	4	41	8.9
	> 45, < 55	74	8	66	10.8
	> 55, < 65	149	26	123	17.4
	> 65, < 75	125	21	104	16.8
	> 75	166	41	125	24.7
Ethnicity	African-American	202	32	170	15.8
	Asian	7	0	7	0.0
	Caucasian	362	64	298	17.72
	Hispanic	23	5	18	21.7
	Other	4	0	4	0.0
Baseline PCT, ug/L	< 0.5	125	19	106	15.2
	> 0.5, < 2.0	104	13	91	12.5
	> 2.0	353	69	284	19.5
	Missing	16	0	16	0.0

7. CONCLUSIONS

The information provided in this 510(k) Premarket Notification will support a determination of substantial equivalence for the Elecsys BRAHMS PCT test system. The data supports a safe, effective device which performs as well as or better than the predicate device.