July 16, 2018

Siemens Healthcare Diagnostics Inc.
Fatima Pacheco
Regulatory Affairs Clinical Specialist
511 Benedict Ave
Tarrytown, New York 10591-5097

Re: K181002
Trade/Device Name: Atellica IM BRAHMS Procalcitonin (PCT)
Regulation Number: 21 CFR 866.3215
Regulation Name: Device to detect and measure non-microial analytes in human clinical specimens to aid in assessment of patients with suspected sepsis.
Regulatory Class: Class II
Product Code: PRI, PMT, PTF
Dated: April 13, 2018
Received: April 16, 2018

Dear Fatima Pacheco:

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 Part 801 and Part 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.

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 comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Steven R. Gitterman -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: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K181002

Device Name
Atellica IM B.R.A.H.M.S Procalcitonin (PCT)

Indications for Use *(Describe)*
The Atellica® IM BRAHMS Procalcitonin (PCT) assay is for in vitro diagnostic use in the quantitative determination of procalcitonin in human serum and plasma (EDTA, lithium heparin, and sodium heparin) using the Atellica® IM Analyzer. The Atellica IM BRAHMS PCT assay is intended for use, in conjunction with other laboratory findings and clinical assessments, as an aid in:

• The risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.
• 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, using percent change in PCT level over time.
• Decision-making on antibiotic therapy for patients 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) – in an inpatient setting or an emergency department.
• Decision-making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

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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510K SUMMARY

Atellica® IM B.R.A.H.M.S Procalcitonin (PCT)

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

1. 510(k) Number: k181002

2. Purpose for Submission:

To obtain a substantial equivalence determination for the Atellica® IM B.R.A.H.M.S Procalcitonin (PCT) assay.

3. Applicant:

Contact: Fatima Pacheco
Regulatory Clinical Affairs Specialist
Address: Siemens Healthcare Diagnostics Inc.
511 Benedict Ave,
Tarrytown, NY 10591
Phone: (914) 374-3770
Email: fatima.pacheco@siemens-healthineers.com

Date: June 04, 2018

4. Proprietary and Established Names:

Atellica® IM B.R.A.H.M.S Procalcitonin (PCT)

5. Measurand

Procalcitonin

6. Regulatory Information:

Regulatory Information for Atellica® IM B.R.A.H.M.S Procalcitonin (PCT)

Trade Name	Atellica® IM B.R.A.H.M.S Procalcitonin (PCT)
Common Name	Immunoassay, Procalcitonin
Classification Name	Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis.
FDA Classification	Class II
Review Panel	Microbiology (83)
Product Code	PMT
Regulation Number	21 CFR 866.3215

Regulatory Information for Atellica® IM B.R.A.H.M.S Procalcitonin Calibrator (Included in assay kit)

Trade Name	Atellica® IM B.R.A.H.M.S Procalcitonin Calibrator
Common Name	Single (specified) analyte calibrators (assayed and unassayed)
Classification Name	Calibrator (assayed and unassayed)
FDA Classification	Class II (Exempt)
Review Panel	Clinical Chemistry (75)
Product Code	JIT
Regulation Number	21 CFR 862.1150

Regulatory Information for Atellica® IM B.R.A.H.M.S Procalcitonin QC & MCM (Sold Separately)

Trade Name	Atellica® IM B.R.A.H.M.S Procalcitonin Quality Control (QC) Atellica® IM B.R.A.H.M.S Procalcitonin Master Curve Material (QC)
Common Name	Single (specified) analyte calibrators (assayed and unassayed)
Classification Name	Calibrator (assayed and unassayed)
FDA Classification	Class II (Exempt)
Review Panel	Clinical Chemistry (75)
Product Code	JIT
Regulation Number	21 CFR 862.1150

7. Predicate Devices:

Device Name: B.R.A.H.M.S PCT sensitive KRYPTOR
510(k) Number: DEN150009; k171338
Manufacturer: B.R.A.H.M.S GmbH (Thermo Fisher Scientific)

8. Intended Use:

Same as Indications for Use

9. Indications for Use:

The Atellica® IM BRAHMS Procalcitonin (PCT) assay is for *in vitro* diagnostic use in the quantitative determination of procalcitonin in human serum and plasma (EDTA, lithium heparin, and sodium heparin) using the Atellica® IM Analyzer.

The Atellica IM BRAHMS PCT assay is intended for use, in conjunction with other laboratory findings and clinical assessments, as an aid in:

• The risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

• 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, using percent change in PCT level over time.
• Decision-making on antibiotic therapy for patients 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) – in an inpatient setting or an emergency department.
• Decision-making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

10. Special Conditions for use statement(s):

For Prescription Use Only

11. Warnings and Precautions for Test Interpretation:

The Atellica® IM BRAHMS Procalcitonin (PCT) assay 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.

Decisions regarding antibiotic therapy should NOT be based solely on PCT concentrations.

PCT results should always be interpreted in the context of the clinical status of the patient and other laboratory results. Changes in PCT levels for the prediction of mortality, and overall mortality, are 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, such as age and Sequential Organ Failure Assessment (SOFA) score, are also significant predictors of 28‑day cumulative mortality risk.

PCT levels may not be elevated in patients infected by certain atypical pathogens, such as Chlamydophila pneumoniae and Mycoplasma pneumoniae.

Certain patient characteristics, such as severity of renal failure or insufficiency, may influence PCT values and should be considered as potentially confounding clinical factors when interpreting PCT values.
The safety and performance of PCT-guided therapy for individuals younger than 18 years of age, pregnant women, immunocompromised individuals, or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.

Increased PCT levels may not always be related to systemic infection. These conditions include, but are not limited to:

• Patients experiencing major trauma and/or recent surgical procedure, including extracorporeal circulation or burns;
• 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;
• 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 (such as candidiasis and aspergillosis) or acute attacks of plasmodium falciparum malaria; and
- Neonates during the first 2 days of life.

12. Special Instrument Requirement:

For use on the Atellica® IM Analyzer

13. Device Description:

The Atellica IM BRAHMS PCT assay is comprised of the following reagents:

Component	Volume	Ingredients
Atellica IM BRAHMS PCT Primary Reagent ReadyPack (assay kit)		
PCT Lite Reagent	5.0 mL/pack	Mouse monoclonal anti-PCT antibody (~0.5 µg/mL) labeled with acridinium ester in protein buffer; bovine serum albumin; surfactant; preservatives
PCT Solid Phase Reagent	10.0 mL/pack	Mouse monoclonal anti-fluorescein antibody coated paramagnetic particles (~0.15 mg/mL) in buffer; surfactant; preservatives
PCT Ancillary Reagent	4.5 mL/pack	Mouse monoclonal anti-PCT antibody (~13.3 µg/mL) labeled with fluorescein in protein buffer; bovine serum albumin; surfactant; preservatives
PCT Calibrator (Kitted-included in assay kit)		
PCT Low and High Calibrators	2.0 mL/vial	Lyophilized; after reconstitution, recombinant PCT; equine serum; preservatives
Atellica IM BRAHMS PCT Quality Control (sold separately)		
PCT Low and High Quality Controls	2.0 mL/vial	Lyophilized; after reconstitution recombinant PCT; equine serum; preservatives
Atellica IM BRAHMS PCT Master Curve Material (sold separately)		
PCT MCM1-5	1.0 mL/vial	Lyophilized; after reconstitution, various levels of recombinant PCT; equine serum; preservatives

14. Substantial Equivalence Information

The following table describes the similarities and differences between the Atellica IM BRAHMS PCT (Candidate Device) and the B.R.A.H.M.S PCT sensitive KRYPTOR® (Predicate Device).

Trade Name	Candidate Device	Predicate Device
	Atellica® IM B.R.A.H.M.S Procalcitonin (PCT)	B.R.A.H.M.S PCT sensitive KRYPTOR®
Intended Use	The Atellica® IM BRAHMS Procalcitonin (PCT) assay is for *in vitro* diagnostic use in the quantitative determination of procalcitonin in human serum and plasma (EDTA, lithium heparin, and sodium heparin) using the Atellica® IM Analyzer. The Atellica IM BRAHMS PCT is intended for use, in conjunction with other laboratory findings and clinical assessments as an aid 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. 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, using percent change in PCT level over time. Decision making on antibiotic therapy for patients 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) – in an inpatient setting or an	The B·R·A·H·M·S PCT sensitive KRYPTOR® is an immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACE®) technology to determine the concentration of PCT (procalcitonin) in human serum and EDTA or heparin plasma. The B·R·A·H·M·S PCT sensitive KRYPTOR® is intended to be performed on the B·R·A·H·M·S KRYPTOR® analyzer family. Used in conjunction with other laboratory findings and clinical assessments, B·R·A·H·M·S PCT sensitive KRYPTOR® 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

	emergency department. Decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.	exacerbation of chronic obstructive pulmonary disease (AECOPD), to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.
Analyte	Procalcitonin (PCT)	Same
Automated	Automated assay	Same
Measurement	Quantitative	Same
Sample Type	Human Serum, Plasma (EDTA, Lithium, Heparin, Sodium Heparin)	Human Serum, Plasma (EDTA and Heparin)
Assay Measuring Interval	0.04 – 50.00 ng/mL	0.02 – 50 µg/L
Operating Principle	Sandwich	Sandwich
Technology	Direct Chemiluminescent technology	Immunofluorescence TRACE® technology
Instrument	Atellica IM Analyzer	KRYPTOR® Test System
Sample Volume	100 µL	50 µL
Calibrators	Atellica IM B.R.A.H.M.S PCT Calibrators (lyophilized) 2 levels (Low and High); After reconstitution, recombinant PCT; equine serum; preservatives	B.R.A.H.M.S PCT sensitive KRYPTOR® Calibrator: 1 vial of lyophilized recombinant PCT in defibrinated human plasma (range 22.50-27.50µg/L)
Controls	Atellica IM B.R.A.H.M.S PCT Quality Control (lyophilized) 2 levels (Low and High); After reconstitution, recombinant PCT; equine serum; preservatives	B.R.A.H.M.S PCT sensitive KRYPTOR® QC Kit: 6 vials (3 of each control): Control 1 (0.20-0.40µg/L) Control 2 (8.00-12.00µg/L)

15. Standard/Guidance Document Referenced

The following recognized standards from Clinical Laboratory Standards Institute (CLSI) were used as a basis of the study procedures described in this submission:

- Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition (CLSI EP05-A3, 2014; Recognition Number 7-251)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (CLSI EP06-A, 2003; Recognition Number 7-193)
- Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition (CLSI EP07-A2, 2005; Recognition Number 7-127)
- Measurement Procedure Comparison And Bias Estimation Using Patient Samples -- Third Edition (CLSI EP09-A3, 2013; Recognition Number 7-245)
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline -- Second Edition (CLSI EP17-A2, 2012; Recognition Number 7-233)
- Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition (CLSI EP28-A3c – formerly C28-A3c, 2010; Recognition Number 7-224)
- Medical devices – Application of risk management to medical devices (ANSI/AAMI/ISO 14971:2007/(R)2010; Recognition Number 5-70)

16. Test Principle

The Atellica IM BRAHMS PCT assay is a 2-site sandwich immunoassay using direct chemiluminescent technology that uses 3 mouse monoclonal antibodies specific for PCT. The first antibody, in the Lite Reagent, is a mouse monoclonal anti-PCT antibody labeled with acridinium ester. The second and third antibodies, in the ancillary reagent, are mouse monoclonal anti-PCT antibodies labeled with fluorescein. The immunocomplex formed with PCT is captured with mouse monoclonal anti-fluorescein antibody coupled to paramagnetic particles in the Solid Phase.

A direct relationship exists between the amount of PCT present in the patient sample and the amount of relative light units (RLUs) detected by the system.

17. Performance Characteristics

1. Analytical Performance

A. Precision

The precision of the Atellica IM B.R.A.H.M.S PCT assay precision study was performed in accordance with CLSI EP05-A3 - *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

A single site study was conducted with a panel of five (5) contrived human serum samples, calibrators, and controls were tested. The panel of human samples was prepared by spiking normal serum samples with recombinant PCT spiking material. Samples were frozen in aliquots prior to the start of the study. Each sample was assayed in two (2) replicates per run, with two (2) runs per day separated by at least 2 hours, for 20 days yielding a total of 40 runs, and 80 replicates per sample. For each analyte concentration level, the mean value with variance components (standard deviation and %CV) was determined. The following results were obtained:

Sample	No. of replicates	Mean (ng/mL)	Repeatability (Within-Run)		Within-Lab (Total Precision)	
			SD	%CV	SD	%CV
Serum 1	80	0.05	0.00	9.7	0.01	12.1
Serum 2	80	0.27	0.00	1.8	0.01	2.8
Serum 3	80	0.75	0.01	1.2	0.02	2.1
Serum 4	80	1.52	0.02	1.4	0.04	2.6
Serum 5	80	19.14	0.29	1.5	0.43	2.2
Control 1	80	0.23	0.01	3.4	0.01	5.6
Control 2	80	7.85	0.11	1.4	0.60	7.7

A modeling analysis was conducted to estimate the %Bias, %CV, and % Total Error at each medical decision point. %Bias was calculated relative to reference values derived using the slope and the intercept derived experimentally from the method comparison study between Atellica IM BRAHMS PCT and BRAHMS sensitive KRYPTOR. The %CV measurement was derived using the precision profile; the %Total Error was calculated as 1.65*(%CV) + (%Bias). The results from each of three regressions (%Bias, %CV, and %TE) are summarized in the table below.

PCT Level (ng/mL)	Bias (%)	CV (%)	Total Error (%)
0.10	22%	6.1	32%
0.25	6%	2.6	11%
0.5	2%	1.4	4%
2.0	-1%	0.4	1%

B. Linearity/Assay Measuring Range

Linearity of the Atellica IM B.R.A.H.M.S PCT assay was performed according to CLSI EP06-A - Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline. The study was performed using 9 samples spanning the assay range, prepared using high and low human serum pools. Testing was performed on one (1) Atellica IM Analyzer with 2 PCT reagent lots, 3 replicates per level. The mean dose value of each sample was used in data analysis. The results were analyzed by % Deviation from Linear Fit.

Regression analysis using the first, second, and third order models were conducted to assess the linearity of the assay. Regression statistics (i.e., deviation from linearity for non-linear pools) at all levels tested demonstrated a ≤10% deviation from linear fit.

Linearity was confirmed in the range of 0.03 – 63.24 ng/mL. The measuring range claim for the Atellica IM BRAHMS PCT assay is 0.04 – 50.00 ng/mL. For PCT concentrations greater than 50.00 ng/mL, the measurement range can be extended up to 1000 ng/mL by 1:20 dilution of the sample.

C. Dilution Recovery

To evaluate the degree of bias introduced when the instrument auto-dilution is used on samples within the assay measuring range or above.

Five (5) human serum samples spiked with recombinant PCT stock. The samples were diluted to 1:20 with Atellica IM Multi-Diluent 1 both manually and automatically onboard the system. Recoveries ranged from 96% to 102% with a mean of 99%.

The samples were diluted (1:20) with Atellica IM Multi-Diluent 1 using the auto-dilution protocol. Recoveries ranged from 92% to 107%.

D. Hook Effect

A study was performed to evaluate the hook effect. In this assay, patient samples with procalcitonin concentrations as high as 2000 ng/mL will report > 50.00 ng/mL.

E. Detection Limits

Detection capability was determined in accordance with CLSI Document EP17‑A2. The assay is designed to have a limit of blank (LoB) < 0.03 ng/mL, a limit of detection (LoD) < 0.04 ng/mL, and a limit of quantitation (LoQ) ≤ 0.06 ng/mL. Representative detection capability data are presented below.

The LoB corresponds to the highest measurement result that is likely to be observed for a blank sample. The LoB of the Atellica IM BRAHMS PCT assay is 0.00 ng/mL.

The LoD corresponds to the lowest concentration of procalcitonin that can be detected with a probability of 95%. The LoD for the Atellica IM BRAHMS PCT assay is 0.03 ng/mL and was determined using 360 determinations, with 160 blank and 200 low-level replicates, and LoB of 0.00 ng/mL.

The LoQ corresponds to the lowest amount of procalcitonin in a sample at which the within-lab CV is ≤ 20%. The LoQ of the Atellica IM BRAHMS PCT assay is 0.04 ng/mL, and was determined using multiple patient samples in the interval 0.01–0.05 ng/mL. All samples were assayed in duplicate in each of 2 runs per day using 2 reagent lots, over a period of 20 days.

F. Endogenous Interference

Endogenous interference studies were performed according to CLSI EP07-A2. The assay was designed to have ≤ 10% interference from the following substances. Interference (bias) is the difference in the results between the control sample (does not contain the interferent) and the test sample (contains the interferent) expressed in percent. Potential interference from the following substances was tested by adding these substances to serum pools containing PCT ranging from 0.32–2.59 ng/mL.

The interference with biotin was not evaluated since Atellica IM BRAHMS PCT reagents architecture does not use biotin:streptavidin. Therefore interference with biotin is not possible.

Endogenous Substance	Concentration Tested (mg/dL)	Results
Bilirubin (Conjugated)	40 mg/dL	No interference observed
Bilirubin (Unconjugated)	40 mg/dL	No interference observed
Cholesterol	400 mg/dL	No interference observed
Hemoglobin	500 mg/dL	No interference observed
Triglycerides	1000 mg/dL	No interference observed
Fluorescein	0.1 µg/mL	No interference observed
Human Immunoglobulin	3.6 g/dL	No interference observed
Total Protein (as low as)	3.5 g/dL	No interference observed
Total Protein (as high as)	up to 12.0 g/dL	No interference observed

G. Heterophile Interference

Testing was performed to determine whether the presence of HAMA (Human anti-mouse antibody) may interfere with Atellica IM BRAHMS PCT assay results.

HAMA and RF positive patient samples were divided in half and spiked with PCT to a “Level 1” (0.4-0.7 ng/mL) and a “Level 2” (1.5-2.0 ng/mL) concentrations. A control sample negative for HAMA and RF (“serum control” and “plasma control”) was spiked with equal amounts of PCT. Acceptance criteria were met for the HAMA spiking study. The presence of HAMA in the samples did not influence the performance of the Atellica IM BRAHMS PCT assay. No HAMA/RF interference was observed for PCT analyte with the presence of HAMA at the concentrations tested.

H. Therapeutic Drug Interference

Therapeutic drug interference studies were performed according to CLSI EP07-A2. The assay was designed to have ≤ 10% interference from the following substances. Interference (bias) is the difference in the results between the control sample (does not

contain the interferent) and the test sample (contains the interferent) expressed in percent. Potential interference from the following substances was tested by adding these substances to serum pools containing PCT ranging from 0.42–1.99 ng/mL. All the therapeutic drugs evaluated did not affect the test performance at concentrations evaluated.

Drug	Concentration Tested (mg/dL)	Results
Acetaminophen	20	No interference observed
Acetylsalicylic Acid	100	No interference observed
Alcohol	405	No interference observed
Azithromycin	1.17	No interference observed
Caffeine	6	No interference observed
Celecoxib	24	No interference observed
Cetirizine HCl	0.36	No interference observed
Dextramethorphan	0.14	No interference observed
Doxycycline	5	No interference observed
Epinephrine	1.79	No interference observed
Fentanyl	1	No interference observed
Ibuprofen	50	No interference observed
Levofloxacin	1.75	No interference observed
Loratadine	0.03	No interference observed
Nicotine	0.1	No interference observed
Oxymetazoline HCl	0.01	No interference observed
Phenylephrine	0.02	No interference observed
Prednisolone	0.3	No interference observed
Salmeterol	0.006	No interference observed
Tiotropium	0.0022	No interference observed

I. Cross Reactivity

Potential cross-reactivity of drugs and metabolites were evaluated in accordance with CLSI document EP07-A2. The following substances were evaluated for cross-reactivity and do not interfere with the Atellica IM BRAHMS PCT assay when present in serum and plasma at the concentrations indicated. Testing was performed with serum, EDTA plasma, sodium heparin, and lithium heparin plasma matrices. The results are presented in the table below:

Substance	Concentration Tested (mg/dL)	Results
Calcitonin-human	8	No interference observed
Calcitonin salmon	30	No interference observed
Calcitonin eel	30	No interference observed
α-CGRP	30	No interference observed
β-CGRP	30	No interference observed
Katacalcin	30	No interference observed
Cefotaxim	900,000	No interference observed
Dobutamine	11,200	No interference observed

Substance	Concentration Tested (mg/dL)	Results
Dopamine	130,000	No interference observed
Furosemide	20,000	No interference observed
Heparin	40,000	No interference observed
Imipenem	1,180,000	No interference observed
Noradrenaline	2000	No interference observed
Vancomycin	3,500,000	No interference observed

J. Method Comparison with Predicate Device

The method comparison study was performed according to the guidance of CLSI Guideline EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples.

A total of 623 native human serum samples with assigned BRAHMS Kryptor does values (0-1000 ng/mL) were tested with the Atellica IM BRAHMS PCT assay. Samples > 50.00 ng/mL were auto-diluted (1:20) by the Atellica IM Analyzer.

Two separate data analysis for this was performed, one with analysis of all samples with BRAHMS PCT sensitive KRYPTOR assay with sample range 0.06–49.20 ng/mL (N=522) and one with an extended analysis including all samples tested (N=623). Weighted Deming and Passing & Bablok regression analyses including slope and intercept with 95% CI were calculated for N=522 samples. Regression analysis comparing the Atellica IM BRAHMS PCT assay results to the predicate assay results are summarized in table below and illustrated in Figures below.

Parameter	Weighted Deming Regression	Passing & Bablok Regression
N	522	522
Slope	1.02	1.06
95% CI two sided	0.99 to 1.05	1.04 to 1.09
Intercept	-0.02	-0.04
95% CI two sided	-0.03 to -0.01	-0.06 to -0.03
Correlation coefficient (r)	0.98	0.98
Sample Range (ng/mL)	0.06–49.20	0.06–49.20

Figure 1: Weighted Deming Regression Analysis Atellica IM BRAHMS PCT vs. Predicate

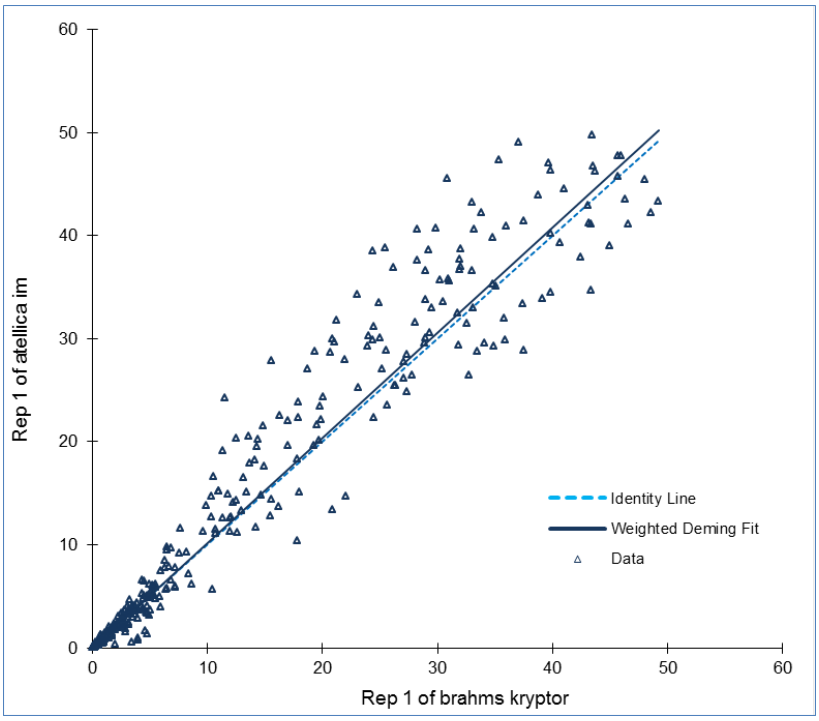
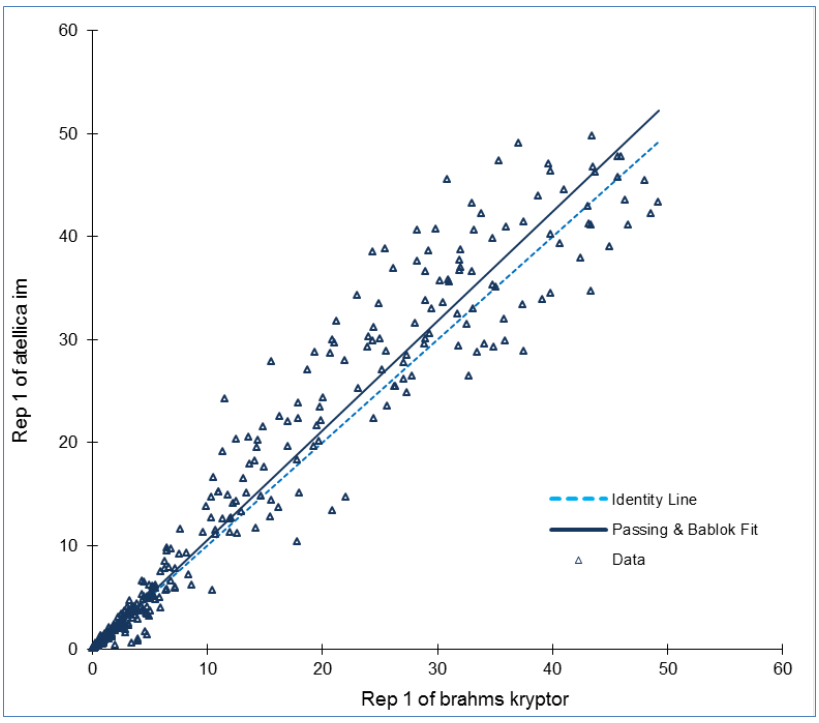


Figure 2: Passing & Bablock Regression Analysis Atellica IM BRAHMS PCT vs. Predicate



Data was further analyzed for concordance at the 0.1, 0.25, 0.5, and 2.0 ng/mL clinical cutoffs. From the total N=623 samples tested, the percent agreement between the Atellica IM BRAHMS PCT and the predicate BRAHMS sensitive KRYPTOR PCT at the cutoffs obtained are presented in Tables below.

Atellica IM BRAHMS PCT vs Predicate at 0.1 ng/mL cutoff

Atellica IM BRAHMS PCT	BRAHMS sensitive KRYPTOR		Total
	> 0.1 ng/mL	≤ 0.1 ng/mL	
> 0.1 ng/mL	539	4	543
≤ 0.1 ng/mL	4	76	80
Total	543	80	623

Positive percent agreement (PPA) = 539/543 (99.3%); 95% two sided CI 98.1%–99.7%
Negative percent agreement (NPA) = 76/80 (95.0%); 95% two sided CI 87.8%–98.0%
Overall percent agreement = 98.7%; 95% Confidence Interval: 97.5%–99.4%

Atellica IM BRAHMS PCT vs Predicate at 0.25 ng/mL cutoff

Atellica IM BRAHMS PCT	BRAHMS sensitive KRYPTOR		Total
	> 0.25 ng/mL	≤ 0.25 ng/mL	
> 0.25 ng/mL	488	7	495
≤ 0.25 ng/mL	5	123	128
Total	493	130	623

Positive percent agreement (PPA) = 488/493 (99.0%); 95% two sided CI 97.7%–99.6%
Negative percent agreement (NPA) = 123/130 (94.6%); 95% two sided CI 89.3%–97.4%
Overall percent agreement = 98.1%; 95% Confidence Interval: 96.7%–98.9%

Atellica IM BRAHMS PCT vs Predicate at 0.50 ng/mL cutoff

Atellica IM BRAHMS PCT	BRAHMS sensitive KRYPTOR		Total
	> 0.50 ng/mL	≤ 0.50 ng/mL	
> 0.50 ng/mL	414	5	419
≤ 0.50 ng/mL	14	190	204
Total	428	195	623

Positive percent agreement (PPA) = 414/428 (96.7%); 95% two sided CI% 94.6–98.0%
Negative percent agreement (NPA) =190/195 (97.4%); 95% two sided CI 94.1%–98.8%
Overall percent agreement = 97.0%; 95% Confidence Interval: 95.3%–98.0%

Atellica IM BRAHMS PCT vs Predicate at 2.0 ng/mL cutoff

Atellica IM BRAHMS PCT	BRAHMS sensitive KRYPTOR		Total
	> 2.0 ng/mL	≤ 2.0 ng/mL	
> 2.0 ng/mL	279	8	287
≤ 2.0 ng/mL	8	328	336
Total	287	336	623

Positive percent agreement (PPA) =279/287 (97.2%); 95% two sided CI 94.6%–98.6%
Negative percent agreement (NPA) = 328/336 (97.6%); 95% two sided CI 95.4%–98.8%
Overall percent agreement = 97.4%; 95% Confidence Interval: 95.9%–98.4%

Cross Tabulation of all Samples (n=623) Atellica IM BRAHMS PCT vs Predicate

Atellica IM BRAHMS PCT (ng/mL)	BRAHMS sensitive KRYPTOR (ng/mL)					
	≤ 0.10	> 0.10 - ≤ 0.25	> 0.25 - ≤ 0.50	> 0.50 - ≤ 2.0	> 2.0	Total
≤ 0.10	76	4	0	0	0	80
> 0.10 – ≤ 0.25	4	39	7	0	0	50
> 0.25 – ≤ 0.50	0	5	55	5	0	65
> 0.50 – ≤ 2.0	0	0	14	119	8	141
> 2.0	0	0	0	8	279	287
Total	80	48	76	132	287	623

K. Matrix Comparison

Specimen equivalency was determined using the Passing-Bablok regression model in accordance with CLSI Document EP09-A3. Fifty-one (51) matched specimen sets in 4 tube types (Serum, EDTA plasma, Lithium Heparin Plasma, Sodium Heparin Plasma) were obtained from a vendor and spiked with equal amounts of recombinant PCT stock. Each sample as tested in singlicate per sample matrix and compared to the serum tube. Regression analysis demonstrated that no significant matrix effect between Serum, EDTA plasma, Lithium Heparin Plasma, Sodium Heparin Plasma tubes. The following results were obtained.

Specimen Type (x)	Comparison Sample Type (y)	N	Sample Range (ng/mL)	Regression Equation	Correlation Coefficient
Serum	EDTA	51	0.05–44.72	y = 1.04x + 0.03 ng/mL	1.00
Serum	Li Heparin	51	0.05–44.72	y = 1.05x + 0.02 ng/mL	1.00
Serum	Na Heparin	51	0.05–44.72	y = 1.03x + 0.02 ng/mL	1.00

L. Expected Values/ Reference Interval

To establish the reference interval of a normal population, one-hundred and forty-four (144) serum samples from normal subjects were tested using the Atellica IM BRAHMS PCT assay on the Atellica IM Analyzer according to the CLSI Guideline EP28-A3c. In a population of N=144 self-reported healthy subjects, the PCT value corresponding to the 99th percentile was <0.05 ng/mL.

Age Range	N	Ethnicity				
		African American	Asian	Caucasian	Hispanic	Other
<60 years	132	59	1	44	25	3
≥60 years	12	2	1	8	1	0

2. Clinical Studies

The Atellica IM BRAHMS PCT clinical performance study was conducted with banked specimens that were collected from subjects(>18 years of age) diagnosed with severe sepsis or septic shock, admitted to the ICU and included as part of the intention-to-diagnose population from the BRAHMS MOSES study (DEN150009).

a. Cumulative 28-day mortality in patients with Severe Sepsis and Septic Shock

- **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.

  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.

b. Risk Assessment for progression to Severe Sepsis and Septic Shock

- **PCT > 2.0 ng/mL:** A PCT level above 2.0 ng/mL 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 ng/mL:** A PCT level below 0.5 ng/mL on the first day of ICU admission is associated with a low risk for progression to severe sepsis and/or septic shock.

PCT levels < 0.5 ng/mL do not exclude an infection, because localized infections (without systemic signs) may also be associated with such low levels.

The Atellica IM BRAHMS PCT assay was evaluated for the prediction of cumulative 28-day all-cause mortality in a study of 858 adult patients diagnosed with severe sepsis or septic shock recruited across 13 investigational sites in the US. The analysis population (598 subjects) comprised 44% female and 56% male patients with a mean age of 64 years. About half of the patients had severe sepsis (51%) vs. 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 = 0.009). 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 = 0.044). 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 as follows:

Prediction performance 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					
		28-Day Mortality Risk		Prognostic Accuracy[a]	
Day 4 Patient Location	PCT Interval	ΔPCT > 80% (95% CI)[b]	ΔPCT ≤ 80% (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
ICU	ΔPCT4.0	21.1 (12.2–30.0)	29.9 (23.2–36.6)	75.8 (65.7–85.9)	33.8 (26.9–40.7)
	ΔPCT4.1	19.0 (10.4–27.6)	31.1 (24.2–37.9)	77.3 (67.1–87.5)	36.1 (29.1–43.1)
Non-ICU	ΔPCT4.0	5.7 (1.7–9.8)	10.7 (6.4–15.0)	73.7 (57.1–90.3)	41.3 (35.5–47.2)
	ΔPCT4.1	7.4 (2.7–12.0)	9.5 (5.5–13.6)	67.9 (50.6–85.2)	38.5 (32.7–44.3)

[a] Prognostic accuracy refers to how accurate the ΔPCT (≤ 80% vs. > 80%) can predict mortality risk.

[b] Confidence interval.

Additional stratification of patients based on absolute initial PCT levels (> or ≤ 2.0 ng/mL) at Day 0 (ΔPCT4.0) or Day 1 (ΔPCT4.1) revealed subgroups with particularly reduced or elevated mortality risk considering their hospital disposition on Day 4. Mortality risk and prognostic performance are given for the following subgroups in the tables below:

1. Patients with PCT > 2.0 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4.
2. Patients with PCT ≤ 2.0 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4.
3. Patients with PCT > 2.0 ng/mL at Day 0 (or Day 1) without ICU care on Day 4.
4. Patients with PCT ≤ 2.0 ng/mL 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					
		28-Day Mortality Risk		Prognostic Accuracy[a]	
Day 4 Patient Location	PCT at Day 0	ΔPCT > 80% (95% CI)[b]	ΔPCT ≤ 80% (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
ICU	≤ 2.0 ng/mL	12.8 (0.0–36.7)	23.2 (13.9–32.5)	94.8 (84.9–100.0)	10.3 (2.4–18.2)
	> 2.0 ng/mL	22.0 (12.5–31.6)	35.2 (25.8–44.6)	68.6 (55.7–81.5)	46.9 (37.8–55.9)
Non-ICU	≤ 2.0 ng/mL	0.0 (0.0–21.8)	8.1 (3.5–12.7)	100.0 (71.5–100.0)	10.5 (4.9–16.2)
	> 2.0 ng/mL	6.4 (1.9–11.0)	16.1 (6.8–25.3)	57.6 (33.7–81.4)	67.2 (59.5–74.9)

[a] Prognostic accuracy refers to how accurate the ΔPCT (≤ 80% vs. > 80%) can predict mortality risk.

[b] Confidence interval.

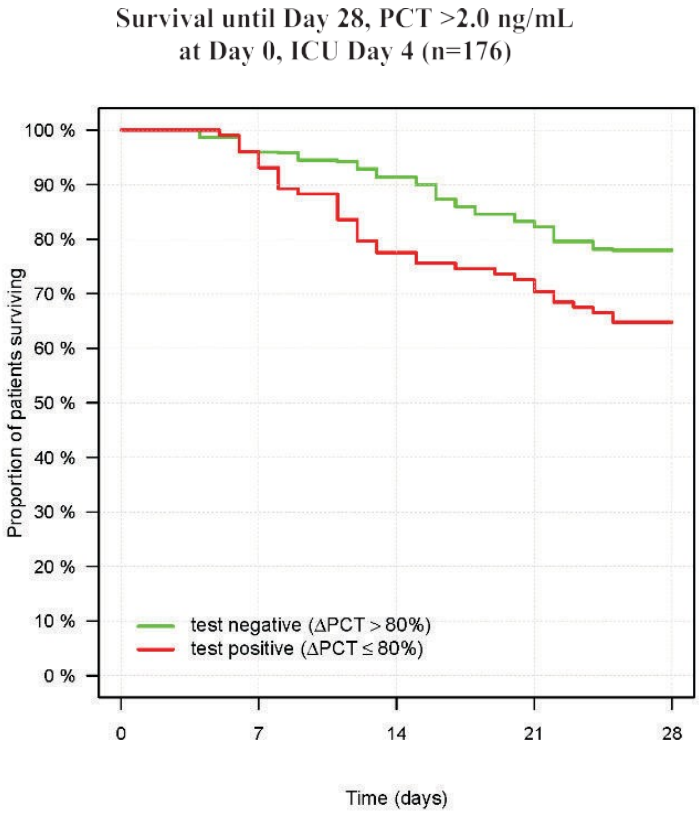
28-Day Mortality Risk Stratified by Patient Location on Day 4

Absolute PCT Value on Day 1
ΔPCT > 80% = Test Negative
ΔPCT ≤ 80% = Test Positive

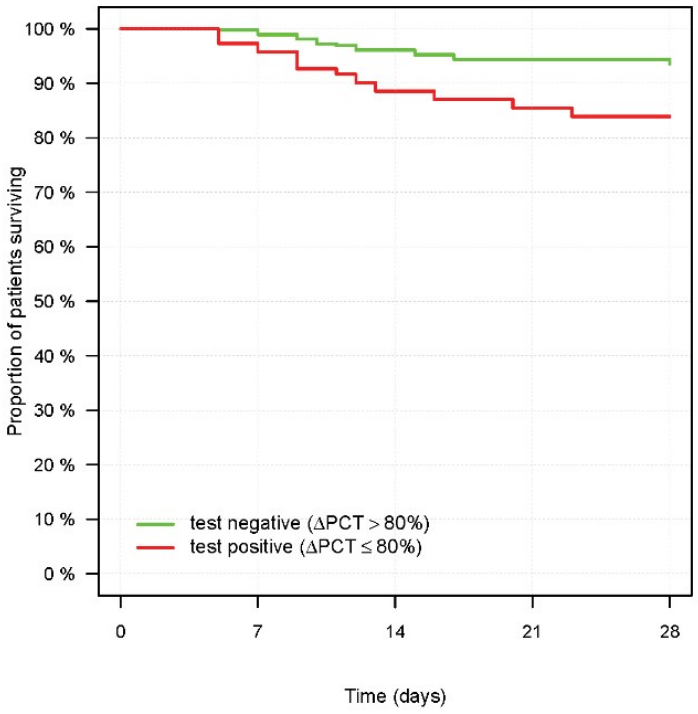
Day 4 Patient Location	PCT at Day 1	28-Day Mortality Risk		Prognostic Accuracy[a]	
		ΔPCT > 80% (95% CI)[b]	ΔPCT ≤ 80% (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
ICU	≤ 2.0 ng/mL	20.2 (0.0–57.2)	26 (16.2–35.8)	95.2 (86.0–100.0)	6.9 (0.0–14.3)
	> 2.0 ng/mL	19.0 (10.1–27.9)	35.0 (25.5–44.5)	69.8 (56.4–83.1)	49.9 (41.1–58.6)
Non-ICU	≤ 2.0 ng/mL	0.1 (0.0–26.5)	6.4 (2.3–10.4)	99.9 (66.4–100.0)	8.5 (3.2–13.7)
	> 2.0 ng/mL	8.2 (3.1–13.3)	16.4 (7.2–25.5)	53.4 (31.1–75.8)	65.7 (57.7–73.7)

[a] Prognostic accuracy refers to how accurate the ΔPCT (≤ 80% vs. > 80%) can predict mortality risk.

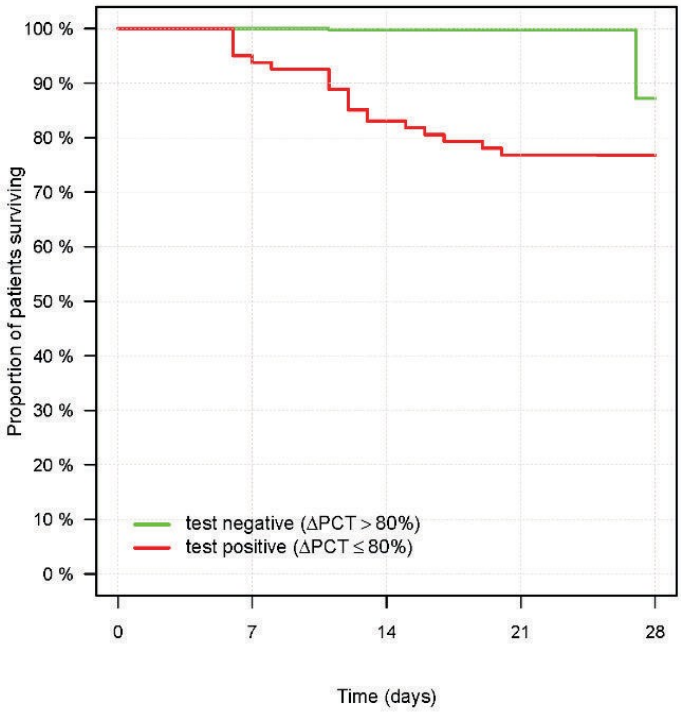
[b] Confidence interval.

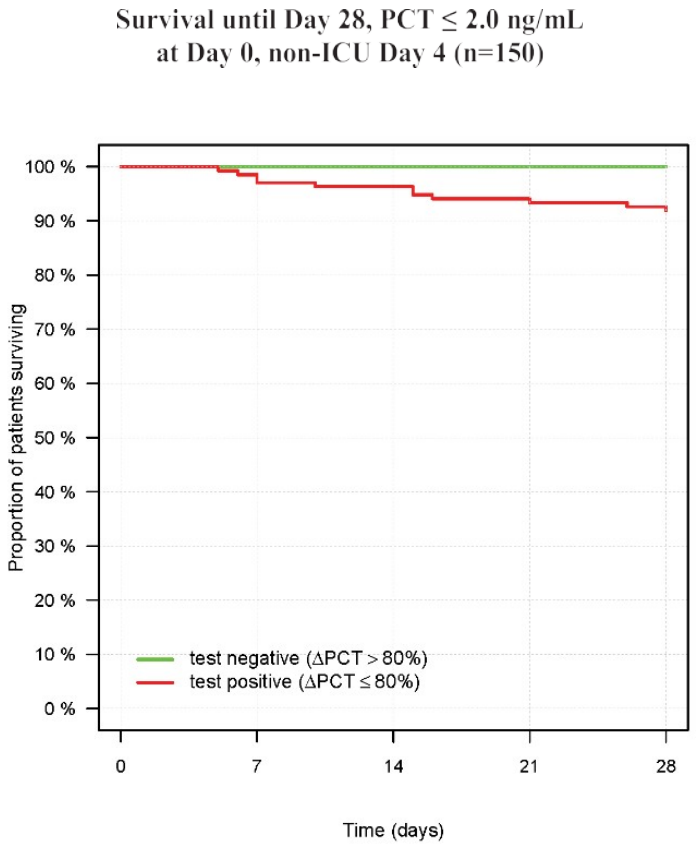


Survival until Day 28, PCT >2.0 ng/mL at Day 0, non-ICU Day 4 (n=183)



Survival until Day 28, PCT ≤ 2.0 ng/mL at Day 0, ICU Day 4 (n=89)





Time-to-event analysis illustrated by the Kaplan-Meier curves above shows that patients in the ICU, or with an initial PCT value > 2.0 ng/mL, had a lower survival probability (higher cumulative mortality risk) from study Day 4 until the end of follow-up time (28 days) when the ΔPCT test result was positive compared to when the ΔPCT result was negative (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 ratios for ΔPCT positive vs. ΔPCT negative patient subgroups were:

- 1.92 for patients with PCT > 2.0 ng/mL at Day 0 receiving ICU care on Day 4
- 2.11 for patients with PCT ≤ 2.0 ng/mL at Day 0 receiving ICU care on Day 4
- 2.78 for patients with PCT > 2.0 ng/mL at Day 0 without ICU care on Day 4
- ---* for patients with PCT ≤ 2.0 ng/mL at Day 0 without ICU care on Day 4

*Mortality ratio cannot be calculated due to 0 fatalities in the ΔPCT negative group. Mathematically, it tends towards infinite

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:

- An initial PCT level ≤ 2.0 ng/mL on Day 0 followed by a PCT decline of more than 80% until Day 4 indicates an almost 2-fold lower cumulative 28-day mortality risk (12.8%) 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 ng/mL (22.0%). 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 23.2–35.2%.

• An initial PCT level > 2.0 ng/mL that does not decline by more than 80% until Day 4 signals that such patients remain at a high mortality risk (16.1%) even when they are no longer receiving ICU care on Day 4. Mortality was otherwise observed between 0.0–8.1% for patients discharged from the ICU by Day 4.

Performance of ΔPCT from Day 0 to Day 4 (≤ 80% vs. > 80%) as a prognostic for 28-day cumulative risk of mortality was quantified by Cox proportional hazards regression analysis with a hazard ratio of 1.82 (95% CI: 1.14–2.89; p-value = 0.012). That is, the relative risk of cumulative 28-day mortality is about 1.8‑fold higher if an individual tests positive for ΔPCT (≤ 80%) than if an individual tests negative (> 80%). As a comparison, the table below lists the univariate hazard ratios for other clinical factors evaluated as separate predictors of mortality in the study population.

Univariate Hazard Ratios for 28-Day All-Cause Mortality of ΔPCT and Clinical Covariates

Factor	Comparison	Hazard Ratio Per-Protocol	p-Value Per-Protocol
ΔPCT4.0	≤ 80% vs. > 80%	1.82 (1.14–2.89)	0.012
ΔPCT4.1	≤ 80% vs. > 80%	1.72 (1.08–2.75)	0.023
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
Biol. Infection Type	Gram Pos vs. Gram Neg	0.83 (0.48–1.45)	0.522
Biol. Infection Type	Other vs. Gram Neg	0.99 (0.63–1.54)	0.960
Biol. 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	> 2.0 ng/mL vs. ≤ 2.0 ng/mL	1.62 (1.04–2.50)	0.031
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 the hazard ratio is adjusted for other mortality predictors in Cox multiple regression 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 1 standard deviation (SD) change in the predictor. For binary predictors, the risk estimate compares the hazards for the 2 binary results.

Hazard Ratios for ΔPCT and Selected Predictors from Multivariate Cox Regression Models

Model		Hazard Ratio (95% Confidence Interval)				
		Binary Predictors		Continuous Predictors (HR per 1 SD)		
ΔPCT Interval	Score + Covariates[a]	ΔPCT (≤ 80% vs. > 80%)	Day 4 Patient Location (ICU vs. Non-ICU)	APACHE (1SD = 8.13)	max SOFA (1SD = 3.98)	Age (1SD = 16.18)
Day 0 until Day 4	APACHE	1.91 (1.09–3.35)	2.65 (1.65–4.24)	1.23 (0.98–1.55)	—	1.59 (1.27–1.98)
	max SOFA	1.75 (1.01–3.02)	1.69 (1.02–2.78)	—	1.96 (1.53–2.52)	1.69 (1.35–2.10)
Day 1 until Day 4	APACHE	1.91 (1.12–3.28)	2.64 (1.65–4.22)	1.27 (1.02–1.59)	—	1.58 (1.26–1.97)
	max SOFA	1.73 (1.02–2.95)	1.74 (1.06–2.84)	—	1.95 (1.52–2.50)	1.67 (1.34–2.09)

[a] 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, and Gender. 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.

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 = 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 < 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 < 0.2 indicates a lower risk for mortality within 28 days. On a continuous scale, the relative mortality risk for such patients is higher the larger the PCT ratio. The following table lists the hazard ratios for an increase by the factor 2 in PCT ratio (that is, 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).

Hazard Ratios for ΔPCT and Selected Predictors from Multivariate Cox Regression Models

Model		Hazard Ratio (95% Confidence Interval)				
		Continuous Predictors (HR per 2-fold increase in PCT ratio or per equivalent in SD)				Binary Predictor
ΔPCT Interval Covariates	Score +	PCT ratio (2-fold increase) equivalent)[b]	APACHE (SD equivalent)[b]	max SOFA (SD equivalent)[b]	Age (SD	Day 4 Patient Location (ICU vs. Non-ICU)
Day 0 until Day 4	APACHE	1.29 (1.14–1.45)	1.07 (0.95–1.21)	—	1.31 (1.16–1.47)	2.56 (1.59–4.11)
	max SOFA	1.22 (1.08–1.38)	—	1.38 (1.20–1.58)	1.34 (1.19–1.51)	1.68 (1.02–2.77)
Day 1 until Day 4	APACHE	1.35 (1.17–1.57)	1.19 (1.02–1.40)	—	1.40 (1.19–1.64)	2.56 (1.60–4.10)
	max SOFA	1.29 (1.11–1.51)	—	1.58 (1.32–1.89)	1.46 (1.25–1.71)	1.74 (1.06–2.86)

[a] 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, and Gender. 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.

[b] A unit change of ΔPCT on log-2-scale corresponded to 0.54 SD of ΔPCT from Day 0 until Day 4 (0.71 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, that is, 0.54 or 0.71, respectively

Cumulative 28-day all-cause mortality did not differ significantly for male vs. female patients. Demographics with outcome information are shown below:

Comparison of Clinical Covariates by 28-Day Outcome

		All	Dead	Alive	% Dead
Variable	Class	N[a]	N	N	%
Gender	Female	264	46	218	17.4
	Male	334	55	279	16.5
Age, years (categorized)	≤ 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

Variable	Class	All	Dead	Alive	% Dead
		N[a]	N	N	%
	> 75	166	41	125	24.7
Ethnicity	African-American	202	32	170	15.8
	Asian	7	0	7	0.0
	Caucasian	362	64	298	17.7
	Hispanic	23	5	18	21.7
	Other	4	0	4	0.0
Sepsis Classification on Admission	Septic Shock	291	53	238	18.2
	Severe Sepsis	307	48	259	15.6
Baseline PCT, ng/mL	< 0.5	114	16	98	14.0
	≥ 0.5, ≤ 2.0	114	12	102	10.5
	> 2.0	338	66	272	19.5
	Missing	32	7	25	21.9

[a] Number of patients.

c. Decision-making on antibiotic therapy for patients with suspected or confirmed LRTI

- **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.

d. Sepsis Antibiotic Discontinuation:

- **ΔPCT > 80%**
  Antibiotic therapy may be discontinued
- **PCT ≤ 0.50 ng/mL**
  Antibiotic therapy may be discontinued

Two systematic literature reviews were performed to produce both study- and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results (FDA public docket FDA-2016-N-2880).

The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from

the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs), and 95% confidence intervals as appropriate. The endpoints evaluated were: proportion of subjects initiating antibiotics, duration of antibiotic therapy, exposure to antibiotics, length of hospital stay, mortality, and complications (patient-level only).

The study-level meta-analysis encompassed 11 randomized control trials (RCTs), which were published between 2004–2016, and included 4090 patients.

The patient-level meta-analysis encompassed 13 RCTs, which were published between 2004–2011 and included 3142 patients as listed below.

Publication	N[a]	PCT Device
Bouadma, 2010	630	B·R·A·H·M·S PCT sensitive KRYPTOR®
Briel, 2008	300	B·R·A·H·M·S PCT sensitive KRYPTOR
Burkhardt, 2010	550	B·R·A·H·M·S PCT sensitive KRYPTOR
Christ-Crain, 2004	243	B·R·A·H·M·S PCT sensitive KRYPTOR
Christ-Crain, 2006	302	B·R·A·H·M·S PCT sensitive KRYPTOR
Hochreiter, 2009	110	B·R·A·H·M·S PCT LIA®
Kristoffersen, 2009	223	B·R·A·H·M·S PCT sensitive KRYPTOR
Long, 2011	172	B·R·A·H·M·S PCT sensitive KRYPTOR
Long, 2009	127	B·R·A·H·M·S PCT LIA
Nobre, 2008	79	B·R·A·H·M·S PCT sensitive KRYPTOR
Schroeder, 2009	27	B·R·A·H·M·S PCT LIA
Schuetz, 2009	1381	B·R·A·H·M·S PCT sensitive KRYPTOR
Stolz, 2007	226	B·R·A·H·M·S PCT sensitive KRYPTOR

[a] Number of patients.

These meta-analyses concluded that PCT-guided antibiotic therapy resulted in:

- 19.2% reduction in relative antibiotic initiation for all patients.
- 38% reduction in overall antibiotic exposure (that is, total days of antibiotic therapy) for inpatients.
- 51% reduction in overall antibiotic exposure (that is, total days of antibiotic therapy) for patients who presented to the emergency department and other associated clinics, but were not admitted.
- 2.9-day reduction in antibiotic duration [1.25-day reduction in study-level].
- 3.6-day reduction in total antibiotic exposure [2.79-day reduction in study-level].
- No negative effects in regards to mortality, complications, or length of stay.

Overview of the Patient-Level Meta-Analysis

Parameter	Standard Care Therapy		PCT-Guided Therapy	
	N[a]	N (%) or Days, median (IQR)	N	N (%) or Days, median (IQR)
Initiation of antibiotics	1606	1420 (88.4%)	1536	1096 (71.4%)
Duration of antibiotics	1420	10 (7, 12)	1096	7 (4, 10)
Total exposure of antibiotics	1606	9 (8, 12)	1536	5 (0, 8)
30-day mortality	1606	119 (7.4%)	1536	103 (6.7%)
Complications	1606	339 (21.1%)	1536	276 (18.0%)
Hospital length of stay	1583	6 (0, 13)	1508	7 (0, 12)

[a] Number of patients included.

Decision-Making on Antibiotic Discontinuation for Suspected or Confirmed Septic Patients

Two systematic literature reviews were performed along with study- and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results. The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs), and 95% confidence intervals as appropriate (see tables below). The endpoints evaluated were: duration of antibiotic therapy (study-level only), exposure to antibiotics (patient-level only), length of ICU stay, length of hospital stay (patient-level only), and mortality.

The study-level meta-analysis encompassed 10 RCTs, which were published between 2008-2016 and included 3489 patients. (See FDA public docket FDA-2016-N-2880).

The above patient-level meta-analysis encompassed 5 RCTs, which were published between 2008-2010 and included 598 patients as listed below.

Publication	N[a, b]	PCT Device
Bouadma, 2010	630	B·R·A·H·M·S PCT sensitive KRYPTOR
Hochreiter, 2009	110	B·R·A·H·M·S PCT LIA
Nobre, 2008	79	B·R·A·H·M·S PCT sensitive KRYPTOR
Schroeder, 2009	27	B·R·A·H·M·S PCT LIA
Stolz, 2007	101	B·R·A·H·M·S PCT sensitive KRYPTOR

[a] Number of patients.

[b] Patients that did not classify as sepsis were removed prior to analysis (185 for PCT group and 164 for control group), leaving 598 patients.

Using this subset of meta-analyses, it was concluded that PCT-guided antibiotic therapy resulted in:

- 1.5-day reduction in antibiotic duration.
- 3.2-day reduction in total antibiotic exposure.
- 23% reduction in overall antibiotic exposure (that is, total days of antibiotic therapy) for patients who presented to the emergency department and other associated clinics, but were not admitted.
- No negative effects in regards to mortality, hospital length of stay, or ICU length of stay.

Overview of the Patient-Level Meta-Analysis

		Standard Care Therapy	PCT-Guided Therapy	
Parameter	**N[a]**	**N (%) or Days, median (IQR)**	**N**	**N (%) or Days, median (IQR)**
Total exposure of antibiotics	311	12 (8, 18)	287	8 (5, 15)
30-day mortality	311	74 (23.8%)	287	57 (19.9%)
Hospital length of stay	288	23 (13, 38)	259	21 (11, 37)
ICU length of stay	311	12 (6, 22)	287	12 (6, 23)

[a] Number of patients included.

Recommendations for Laboratory Reports for Initiation and Discontinuation:

The Change in Procalcitonin Calculator is available at www.BRAHMS-PCT-Calculator.com.
It is suggested to report the absolute PCT values (single or serial). For serial 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 Atellica IM BRAHMS PCT package insert for a guided interpretation of the test results.

3. Traceability and Value Assignment

The Atellica IM BRAHMS PCT assay is standardized using a reference preparation antigen as master standard. Assay standardization is verified through regression analysis of a PCT-positive patient population. Assigned values for calibrators and controls are traceable to this standardization.

4. Stability

Reagent Stability – Shelf-life

To establish the shelf-life claims for the Atellica IM BRAHMS PCT reagents and Calibrator (kit), the reagents and calibrators stored at 2-8°C and were tested with various samples at multiple time points. Sets of calibrators were also stored at or below -40°C and were tested at the same time points.

Testing demonstrated that the Atellica IM BRAHMS PCT reagents are stable up to 12 months when properly stored at 2-8°C. Unopened Atellica IM BRAHMS PCT reagents and calibrators are stable at 2-8°C until expiration date printed on the product packaging.

Reagent Stability – On-Board

The onboard stability of the Atellica IM BRAHMS PCT reagents is 60 days onboard, pack calibration interval of 35 days, and lot calibration interval of 82 days.

Calibrator Stability– Shelf-life

Testing demonstrated that the Atellica IM BRAHMS PCT reagents are stable up to 12 months when properly stored at 2-8°C. Lyophilized calibrators are stable until the expiration date on the product when stored at 2–8°C.

*Calibrator Stability– Reconstituted In use (*2-8°C/OBS)

Reconstituted calibrators are stable for 24 hours at 2–8°C or for 8 hours at room temperature (package insert claims).

Specimen Stability

a. Room temperature

Studies demonstrated that serum samples specimens are stable for 8 hours at room temperature.

b. Refrigerated (2–8°C)

Studies demonstrated that serum samples are stable for 24 hours at 2-8°C.

c. Freeze/Thaw cycles (≤ -20°C)

The recommended specimen handling are provided below.

- Do not use samples that have been stored at room temperature for longer than 8 hours.
- Tightly cap and refrigerate specimens at 2–8°C if the assay is not completed within 8 hours.
- Freeze samples at ≤ -20°C if the sample is not assayed within 48 hours.
- Freeze samples up to 5 times, and mix thoroughly after thawing.

Additional sample stability studies were performed on the MOSES clinical samples as described in DEN150009.

18. Proposed Labeling

The labeling is sufficient and it meets the requirements of 21 CFR Parts 801 and 809, as applicable and the special controls for this device under 21 CFR 866.3215.

19. Conclusion

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