510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K160911

B. Purpose for Submission:

To obtain a substantial equivalence determination for the VIDAS® B·R·A·H·M·S PCT™ (PCT).

C. Measurand:

Procalcitonin

D. Type of Test:

Quantitative, Enzyme-Linked Fluorescent Assay (ELFA)

E. Applicant:

bioMérieux Inc.

F. Proprietary and Established Names:

VIDAS® B·R·A·H·M·S PCT™ (PCT)

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.3215; Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis

2. Classification:

   Class II (Special Controls)

3. Product codes:

   PMT

4. Panel:

   83 - (Microbiology)

H. Intended Use/ Indications for Use:

1. Intended Use/Indications for Use:

VIDAS® B·R·A·H·M·S PCT™ (PCT) is an automated test for use on the instruments of the VIDAS® family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique.

VIDAS® B·R·A·H·M·S PCT™ (PCT) 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.

VIDAS® B·R·A·H·M·S PCT™ (PCT) is also intended for use to determine the change of PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality in conjunction with other laboratory findings and clinical assessments 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.

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 also aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock.

PCT levels on the first day of ICU admission above 2.0 ng/mL are associated with a higher risk for progression to severe sepsis and/or septic shock than PCT levels below 0.5 ng/mL.

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.

2. Special conditions for use statement(s):

For prescription use only

Warnings and Precautions:

The VIDAS B·R·A·H·M·S PCT assay should not be used as a sole basis for diagnosis for determining the risk of 28 day all-cause mortality. Changes in PCT should always be interpreted in the context of the clinical status of the patient and other laboratory results.

There is no uniformly recognized interpretation of the change in PCT levels for the prediction of mortality, and overall mortality is strongly dependent on many factors, including pre-existing patient risk factors and clinical course. The need for continued ICU care at Day 4 and other covariates (e.g., age, sepsis-related organ failure assessment (SOFA score) are also significant predictors of 28-day cumulative mortality risk. Validation of the VIDAS B·R·A·H·M·S PCT assay as an aid in predicting mortality was performed in a study population with an overall 28-day mortality of 22%.

3. Special instrument requirements:

For use with VIDAS family of instruments

I. Device Description:

Reagents

Materials provided in VIDAS B·R·A·H·M·S PCT:

The VIDAS B·R·A·H·M·S PCT contains sufficient reagents for 60 determinations.

60 PCT strips	STR	Ready-to-use.
60 PCT SPR®s 2 x 30	SPR®	Ready-to-use. Interior of SPR®s coated with mouse monoclonal anti-human procalcitonin immunoglobulins.
PCT controls C1 control 2 x 2 mL (lyophilized) C2 control 2 x 2 mL (lyophilized)	C1 C2	Reconstitute with 2 mL distilled water. Let stand for 5 - 10 minutes then mix. Stable after reconstitution for 8 hours at 2-8°C, or until the expiration date on the kit at - 25 ± 6°C. 5 freeze/thaw cycles are possible. TRIS NaCl buffer (pH 7.3) + recombinant human PCT + preservatives. MLE data indicate the confidence interval in ng/mL ("Control C1 Dose Value Range" or "Control C2 Dose Value Range").
PCT calibrators S1 calibrator 2 x 2 mL (lyophilized) S2 calibrator 2 x 2 mL (lyophilized)	S1 S2	Reconstitute with 2 mL distilled water. Let stand for 5 - 10 minutes then mix. Stable after reconstitution for 8 hours at 2-8°C, or until the expiration date on the kit at - 25 ± 6°C. 5 freeze/thaw cycles are possible. TRIS NaCl buffer (pH 7.3) + recombinant human PCT + preservatives. MLE data indicate the calibrator concentration in ng/mL ("Calibrator (S1) Dose Value" or "Calibrator (S2) Dose Value") and the confidence interval in "Relative Fluorescence Value ("Calibrator (S1) RFV Range" or "Calibrator (S2) RFV Range").
Specifications for the factory master data required to calibrate the test: • MLE data (Master Lot Entry) provided in the kit or • MLE barcodes printed on the box label.		
1 package insert provided in the kit or downloadable from www.biomerieux.com/techlib.		

J. Substantial Equivalence Information:

1. Predicate device name(s):

B·R·A·H·M·S PCT sensitive KRYPTOR®
VIDAS® B·R·A·H·M·S PCT™

2. Predicate 510(k) number(s):

DEN150009
K071146

4. Comparison with predicate:

Item	Proposed Device: VIDAS® B·R·A·H·M·S™ PCT	Predicate device 1: B·R·A·H·M·S PCT Sensitive KRYPTOR® (DEN150009)	Predicate device 2: VIDAS® B·R·A·H·M·S PCT™ (K071146)
Intended Use and indications for use	VIDAS B·R·A·H·M·S PCT is an automated test for use on the instruments of the VIDAS family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique. VIDAS B·R·A·H·M·S PCT 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. VIDAS B·R·A·H·M·S PCT is also intended for use to determine the change of PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality in conjunction with other laboratory findings and clinical assessments 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. 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 also aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock. PCT levels on the first day of ICU admission above 2.0 ng/mL are associated with a higher risk for progression to severe sepsis and/or septic shock than PCT levels below 0.5 ng/mL. 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	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. The B·R·A·H·M·S 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 Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock. The B·R·A·H·M·S PCT sensitive KRYPTOR is also intended for use to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all cause mortality in conjunction with other laboratory findings and clinical assessments 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. 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 also aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock. PCT level on the first day of ICU admission above 2.0 µg/L is associated with a higher risk for progression to severe sepsis and/or septic shock than a PCT level below 0.5 µg/L. A PCT level that declines ≤ 80% from	VIDAS B·R·A·H·M·S PCT is an automated test for use on the instruments of the VIDAS® family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique. The VIDAS B·R·A·H·M·S PCT 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.

Item	Proposed Device: VIDAS® B·R·A·H·M·S™ PCT	Predicate device 1: B·R·A·H·M·S PCT Sensitive KRYPTOR® (DEN150009)	Predicate device 2: VIDAS® B·R·A·H·M·S PCT™ (K071146)
	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 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 PCT level (≤ 2.0 ug/L or > 2.0 µg/L) 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.	
Specimen	Human serum or plasma (lithium heparinate).	Human serum, plasma (EDTA, heparin)	Same as the proposed device
Analyte	Procalcitonin (PCT)	Same as the proposed device	Same as the proposed device
Automated	Automated assay	Same as the proposed device	Same as the proposed device
Assay Technique	ELFA (Enzyme-Linked Fluorescent Assay) technique.	Immunofluorescent assay	Same as the proposed device
Assay principle	Immunoassay based on sandwich principle	Immunofluorescent assay based on sandwich principle	Same as the proposed device
Detection method	Fluorescence (ELFA) of 4-methyl-umbelliferyl measured at 450 nm	Measuring principle based on TRACE® technology which measures the signal emitted from an immunocomplex with time delay	Same as the proposed device

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

Standard No.	Standards Title	Page #
EP17-A2	Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures	12 - 2
EP5-A3	Evaluation of Precision of Quantitative Measurement Procedures	12 - 4
EP6-A	Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline	12 - 6
EP9-A3	Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline	12 - 8

L. Test Principle:

The assay principle combines a one-step immunoassay sandwich method with a final fluorescent detection (ELFA).

The Solid Phase Receptacle (SPR®) serves as the solid phase as well as the pipetting device. Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips. All of the assay steps are performed automatically by the instrument. The sample is transferred into the wells containing anti-procalcitonin antibodies labeled with alkaline phosphatase (conjugate). The sample/conjugate mixture is cycled in and out of the SPR® several times. This operation enables the antigen to bind with the immunoglobulins fixed to the interior wall of the SPR® and the conjugate to form a sandwich. Unbound compounds are eliminated during washing steps.

Two detection steps are performed successively. During each step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR®. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone) the fluorescence of which is measured at 450 nm. The intensity of the fluorescence is proportional to the concentration of antigen present in the sample.

At the end of the assay, results are automatically calculated by the instrument in relation to two calibration curves corresponding to the two detection steps. A fluorescence threshold value determines the calibration curve to be used for each sample. The results are then printed out.

M. Performance Characteristics:

1. Analytical performance:

a. Reproducibility/Precision:

The precision study of the VIDAS B·R·A·H·M·S PCT assay was conducted on the VIDAS and VIDAS 3 instrument by using 2 assay reagent lots over 20 days of testing at the 3 sites. The performance was compared to the requirements specified in the Product Requirements Document (PRD). The protocol was based on the CLSI EP5-A3 guideline, "Evaluation of Precision of Quantitative Measurement Procedures."

A panel of 9 human samples covering the measuring range were tested in duplicate in 2 runs per day, over 20 days using three VIDAS and three VIDAS 3 instruments (N=240 values for each sample) at 3 sites (one instrument per site). Two reagent lots were used: 10 days of tests and 6 calibrations were performed for each lot. Calibrations (cal) were distributed as follows, cal 1: days 1-2, cal 2: days 3-4, cal 3: day 5, cal 4: days 6-7, cal 5: days 8-9, cal 6: day 10. Repeatability, between-day precision, within-laboratory precision and reproducibility/total precision (between-laboratory precision) were estimated for each sample.

The precision study demonstrated %CV repeatability ranging from 1.3% to 9.0% on the VIDAS and 2.0% to 8.6% on the VIDAS 3; between-day precision ranging from 2.3% to 10.9% on the VIDAS and 3.0% to 9.2% on the VIDAS 3; reproducibility ranging from 3.8% to 14.6% on the VIDAS and 4.4% to 12.6% VIDAS 3.

See summary data in the following tables:

VIDAS

Sample	N	Mean concentration (ng/mL)	Repeatability		Between-Day precision		Within-Laboratory precision		Reproducibility / Total precision	
			Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)
Sample 1	240	0.12	0.011	9.0%	0.013	10.9%	0.018	14.6%	0.018	14.6%
Sample 2	240	0.16	0.010	6.6%	0.013	8.5%	0.020	12.7%	0.020	12.7%
Sample 3	240	0.20	0.011	5.4%	0.013	6.1%	0.017	8.2%	0.017	8.2%
Sample 4	240	0.53	0.013	2.4%	0.017	3.2%	0.023	4.2%	0.023	4.2%
Sample 5	240	2.14	0.027	1.3%	0.048	2.3%	0.081	3.8%	0.081	3.8%
Sample 6	240	23.20	0.506	2.2%	0.749	3.2%	0.962	4.1%	0.962	4.1%
Sample 7	240	93.01	3.136	3.4%	5.343	5.7%	6.962	7.5%	6.962	7.5%
Sample 8	240	129.86	5.368	4.1%	8.436	6.5%	12.664	9.8%	12.664	9.8%
Sample 9	240	164.85	7.364	4.5%	10.613	6.4%	18.445	11.2%	18.445	11.2%

VIDAS 3

Sample	N	Mean concentration (ng/mL)	Repeatability		Between-Day precision		Within-Laboratory precision		Reproducibility / Total precision	
			Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)
Sample 1	240	0.12	0.010	8.6%	0.010	8.6%	0.015	12.6%	0.015	12.6%
Sample 2	239	0.15	0.013	8.3%	0.014	9.2%	0.017	11.2%	0.017	11.2%
Sample 3	239	0.20	0.012	6.2%	0.013	6.6%	0.016	8.2%	0.017	8.5%
Sample 4	239	0.52	0.020	3.8%	0.022	4.2%	0.026	5.0%	0.031	6.1%
Sample 5	240	2.06	0.042	2.0%	0.061	3.0%	0.095	4.6%	0.100	4.9%
Sample 6	240	21.85	0.583	2.7%	0.694	3.2%	0.844	3.9%	0.955	4.4%
Sample 7	240	83.60	3.365	4.0%	3.520	4.2%	4.791	5.7%	5.815	7.0%
Sample 8	240	110.83	5.494	5.0%	5.750	5.2%	7.884	7.1%	8.669	7.8%
Sample 9	240	140.35	6.470	4.6%	7.329	5.2%	11.301	8.1%	13.026	9.3%

b. Linearity/Assay Reportable Range:

Linearity:

Linearity of the VIDAS B·R·A·H·M·S PCT was assessed according to CLSI guideline EP6-A, "Evaluation of the Linearity of Quantitative Measurement Procedures." The linearity was determined using one (1) VIDAS 3 instrument. Three high concentration human samples (H1, H2 and H5) were diluted intone low concentration sample pool to generate eleven (H1 and H2) and thirteen (H5) levels respectively.

Samples were assayed in triplicate within a single run, using one reagent lot. 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 higher order models (quadratic and cubic).

Linearity was confirmed in the range of 0.05 ng/mL to 200 ng/mL. The measuring-range claim for the VIDAS B·R·A·H·M·S PCT assay is 0.02–100 ng/mL.

c. Traceability, Stability, Expected Values (controls, calibrators, or methods):

Reagent Stability: Real-Time Shelf Life

The VIDAS B·R·A·H·M·S PCT kit retain the same expiration dating as currently assigned to the kit (12 months when stored at 2-8°C).

Real time monitoring is performed per internal procedure ref. 001791 "Stability Testing", which follow the requirements from standard ISO EN 23640:2011 "In vitro diagnostic medical devices – Evaluation of stability of in vitro diagnostic reagents", and consists in testing one batch per year stored at recommended storage conditions through expiration.

Control (Post-Reconstitution) Stability:

Controls were shown to be stable after reconstitution for 8 hours at 2-8°C, or until expiration date on the kit at – 25 ± 6°C. Five freeze/thaw cycles are possible.

Calibrators (Post-Reconstitution) Stability:

Calibrators are stable after reconstitution for 8 hours at 2-8°C, or until expiration date on the kit at – 25 ± 6°C. Five freeze/thaw cycles are possible.

Expected Values:

Controls. VIDAS B·R·A·H·M·S PCT assay controls contain 2 levels of antigen concentration. Each vial contains lyophilized recombinant PCT in TRIS NaCl buffer (pH 7.3) and preservatives.

Calibrators. VIDAS B·R·A·H·M·S PCT assay calibrators contain 2 levels of antigen concentration. Each vial contains lyophilized recombinant PCT in TRIS NaCl buffer (pH 7.3) and preservatives.

d. Detection Limit:

The Limit of Blank (LoB) for the VIDAS and VIDAS 3 instruments was determined according to CLSI EP17-A2 guideline "Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline, Second Edition".

For LoB determination on 2 assay lots, 6 blank samples were each tested in 4 replicates in a single run per day for 4 days with each lot on one VIDAS and one VIDAS 3 instrument.

For LoD/LoQ determinations on 2 assay lots, 6 low-level samples were each tested in 6 replicates, 2 runs per day, for 5 days, with each lot on one VIDAS and one VIDAS 3 instrument. The LoB, LoD and LoQ determinations for each instrument were based on 912 results, including 192 results from blank samples and 720 results from low-level samples both assay lots combined. The accuracy goal associated to LoQ was defined as a 20%CV within-laboratory precision, based upon the precision profile established on low-level samples. The LoB, LoD, LoQ of the VIDAS B·R·A·H·M·S PCT assay when tested with the VIDAS instrument are 0.01 ng/mL, 0.03 ng/mL and 0.05 ng/mL respectively.

The LoB, LoD, LoQ of the VIDAS B·R·A·H·M·S PCT assay when tested with the VIDAS 3 instrument are 0.007 ng/mL, 0.022 ng/mL and 0.043 ng/mL respectively.

The claimed LoD of the VIDAS B·R·A·H·M·S PCT assay for all VIDAS family instruments is as follows:

- LoB = 0.01 ng/mL
- LoD = 0.03 ng/mL
- LoQ = 0.05 ng/mL

e. Matrix Equivalency Study:

See K071146

f. Analytical Specificity/ Cross-Reactivity:

See K071146

g. Interfering Substances:

See K071146

h. High-dose Hook Effect:

See K071146

i. Diluent Study:

The objective of this study was to recommend a dilution ratio with serum free diluent allowing the testing with VIDAS B·R·A·H·M·S PCT assay of patient samples with volume less than 200µL and unknown PCT concentration. The study was performed according to the CLSI EP6-A guideline “Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline”

Six (6) dilutions series composed of nine (9) samples each (the initial undiluted sample + 8 dilutions with the diluent) were tested with each diluent lot. Each dilution series was tested in triplicate in a random order in the same single run and the results were analyzed using the polynomial analysis method. Statistically nonlinear series was further evaluated by comparing deviation from linearity to predefined acceptance criteria. The acceptance criteria are that the assay is statistically linear (alpha = 0.05) or, if the assay is statistically nonlinear, deviation from linearity is within ± 12% for sample with PCT concentration from 2 ng/mL to 200 ng/mL, ± 20% for sample with PCT concentration from 0.05 ng/mL to 2 ng/mL and ± 100% for sample with PCT concentration lower than 0.05 ng/mL.

For the VIDAS B·R·A·H·M·S PCT assay, the recommended diluent serum free with a dilution ratio 1:10 has been demonstrated to be appropriate for samples with PCT concentrations inside the measuring range (0.05 - 200 ng/mL) or above the assay upper limit of quantitation (200 ng/mL), with acceptable deviation from linearity. To support the testing samples with insufficient volume (i.e., <200 uL) the recommended dilution ratio is 1:4.

j. Method Comparison:

Using human based materials, the objective of this study was to demonstrate equivalency of the VIDAS 3 to the current VIDAS instrument in terms of Accuracy (method comparison) on the VIDAS B·R·A·H·M·S PCT assay. The protocol was based upon the CLSI EP09 guideline "*Method Comparison and Bias Estimation Using Patient Samples."*

A total of 69 natural human samples appropriately distributed over the entire measurement range of the VIDAS B·R·A·H·M·S PCT assay were tested once with both systems.

The predetermined acceptance criteria was, the estimated difference observed between the VIDAS and the VIDAS 3 should be +/- 10% at the medical decision level of the assay (0.5 ng/mL & 2 ng/mL) and should have no clinical impact at additional level(s).

The VIDAS testing was conducted as described in the VIDAS B·R·A·H·M·S PCT product Instructions For Use (IFU) between the December 15, 2014 and the April 29, 2015.A single replicate of each sample was randomly tested with one VIDAS 3 (test method) and with one VIDAS (comparative method) on the same assay batch. Three (3) calibrations were performed for the VIDAS and VIDAS 3 during the study. Kit control materials were run with each run on both systems.

Repeat testing was performed for the following situations:

- In the event of invalid control(s): the entire run was repeated according to the same Methodology.
- In the event of established human error, or if the system does not give any results, repeat testing was performed.

In both cases, only the valid repeat result was taken into account for the statistical analysis.

The analysis estimate difference at levels of interest, a Weighted Deming regression was performed between the concentration result observed on VIDAS system and the concentration

result observed on VIDAS 3 system. The 95% CI of the estimated differences was also calculated. Data analysis were performed on all samples; there were no statistical outliers.

Results were as follows:
The 69 samples covered the range of 0.07 to 175.47 ng/mL and 0.08 to 196.61 ng/mL for the VIDAS 3 and VIDAS respectively.

A weighted Deming line equation was fit to the data along and presented along with the observed difference at levels of interest with associated 95% Confidence Interval (CI); study requirements and result disposition are summarized below:

VIDAS B·R·A·H·M·S PCT				
Weighted Deming line equation is : VIDAS 3 = 1.0089 VIDAS-0.0130 Correlation coefficient is equal to : r = 0.9946				
Sample Level (ng/mL)	**Difference**	**95% CI**	**Clinical Requirement**	**Disposition**
0.5	-1.7%	[-6.3% ;2.8%]	10 %	Passed
2	0.2%	[-2.1% ; 2.6%]	10 %	Passed
180*	0.9%	[-1.9% ; 3.7%]	No clinical impact	Passed

*A result at 181.62 (180 + 0.9%) has no impact on the patient management and on clinical interpretation based on expected range values for patients admitted to intensive care units. Moreover, the VIDAS B·R·A·H·M·S PCT assay should be interpreted as part of a complete clinical profile and taking into account the patient's history.

2. Clinical Studies:

The VIDAS B·R·A·H·M·S PCT assay performed on VIDAS 3 and VIDAS was evaluated for the prediction of cumulative 28-day all-cause mortality in a prospective clinical trial (MOSES study - Procalcitonin Monitoring Sepsis Study; ClinicalTrials.gov Identifier: NCT01523717) 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) comprised 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%). All patients were admitted into ICU at some point during their hospital stay, 44% were still located in ICU at Day 4 of the study ("ICU" group), whereas 56% were at Day 4 already transferred to a location outside of the ICU ("non-ICU" group). The mortality rate in the per protocol population (598 subjects) was 16.8% as compared to the entire study population (858 subjects) where the mortality rate was 22%. Clinical performance data summarized below was determined based on the per protocol population.

A two-sided Fisher's Exact Test analysis was performed, using change in PCT (ΔPCT) (> 80% or ≤ 80%) versus vital status on Day 28. Change in PCT levels was determined at time 0 and Day 1 which were then compared to PCT values at Day 4.

The table below presents the data with additional stratification of patients based on initial PCT level, above 2.0 µg/L less than or equal to 2.0 µg/L at Day 0 or Day 1.

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 tables 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

Please note, differences in results, relative to the predicate device, reflect the impact of the number of samples available for testing (e.g., insufficient sample volume).

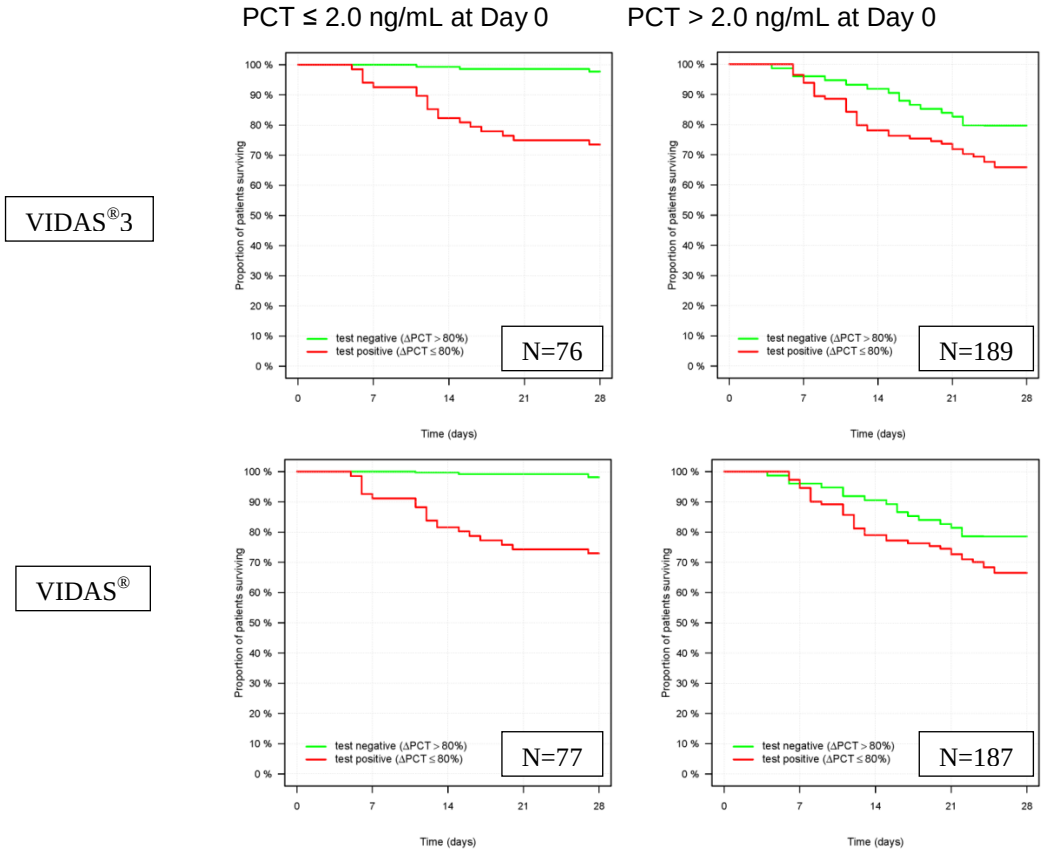
	Mortality Risk by binary ΔPCT group and Prognostic Accuracy* by Patient Location on Day 4 and by initial PCT level						
	ΔPCT Interval	**Day 4 Patient Location**	**Initial PCT level**	**28 Day Mortality Risk**		**Prognostic Accuracy**	
				ΔPCT > 80% (95% CI)	**ΔPCT ≤ 80% (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
VIDAS 3	**Day 0 to Day 4**	**ICU**	**All PCT levels**	**18.4%** (10.0-26.8%)	**31.3%** (24.5-38.1%)	**78.4%** (68.7-88.1%)	**35.7%** (28.7-42.7%)
			≤ 2.0 ng/mL	**2.2%** (0.0-15.1%)	**26.4%** (15.8-37.1%)	**98.8%** (91.7-100.0%)	**14.9%** (5.1-24.7%)
			> 2.0 ng/mL	**20.3%** (11.1-29.5%)	**34.1%** (25.3-42.9%)	**71.6%** (59.4-83.8%)	**44.6%** (36.0-53.3%)
		non ICU	**All PCT levels**	**5.4%** (1.8-9.1%)	**11.4%** (6.8-16.1%)	**71.7%** (55.0-88.3%)	**47.0%** (40.9-53.0%)
			≤ 2.0 ng/mL	**3.7%** (0.0-11.0%)	**9.5%** (3.9-15.1%)	**91.0%** (74.2-100.0%)	**21.2%** (13.2-29.1%)
			> 2.0 ng/mL	**5.8%** (1.6-10.0%)	**14.1%** (6.1-22.1%)	**59.6%** (36.4-82.8%)	**64.3%** (56.7-72.0%)
	Day 1 to Day 4	**ICU**	**All PCT levels**	**18.4%** (10.1-26.7%)	**31.6%** (24.7-38.5%)	**77.2%** (67.2-87.2%)	**37.7%** (30.6-44.7%)
			≤ 2.0 ng/mL	**12.6%** (0.0-34.0%)	**22.2%** (11.6-32.7%)	**90.6%** (74.1-100.0%)	**16.8%** (6.4-27.2%)
			> 2.0 ng/mL	**19.2%** (10.3-28.1%)	**36.8%** (27.8-45.7%)	**73.6%** (61.9-85.3%)	**46.7%** (38.0-55.3%)
		non ICU	**All PCT levels**	**7.0%** (2.8-11.2%)	**10.1%** (5.7-14.5%)	**63.8%** (45.8-81.8%)	**45.8%** (39.6-52.0%)
			≤ 2.0 ng/mL	**0.0%** (0.0-13.2*%)	**8.1%** (2.9-13.3%)	**100.0%** (66.4-100.0*%)	**20.7%** (12.9-28.4%)
			> 2.0 ng/mL	**8.5%** (3.5-13.5%)	**13.0%** (5.2-20.9%)	**48.1%** (25.7-70.5%)	**63.5%** (55.6-71.5%)
VIDAS	**Day 0 to Day 4**	**ICU**	**All PCT levels**	**19.2%** (10.7-27.6%)	**31.0%** (24.2-37.8%)	**77.0%** (67.1-87.0%)	**36.1%** (29.1-43.1%)
			≤ 2.0 ng/mL	**1.8%** (0.0-12.8%)	**27.0%** (16.3-37.8%)	**98.9%** (92.4-100.0%)	**16.4%** (6.4-26.5%)
			> 2.0 ng/mL	**21.4%** (12.1-30.7%)	**33.5%** (24.6-42.3%)	**69.5%** (56.9-82.0%)	**44.8%** (36.1-53.5%)
		non ICU	**All PCT levels**	**6.1%** (2.2-10.0%)	**10.9%** (6.3-15.4%)	**68.2%** (51.0-85.4%)	**46.6%** (40.6-52.7%)
			≤ 2.0 ng/mL	**4.2%** (0.0-12.2%)	**9.2%** (3.8-14.7%)	**91.0%** (74.1-100.0%)	**19.0%** (11.4-26.6%)
			> 2.0 ng/mL	**6.5%** (2.1-10.8%)	**13.4%** (5.3-21.5%)	**53.9%** (30.3-77.6%)	**65.5%** (57.9-73.2%)
	Day 1 to Day 4	**ICU**	**All PCT levels**	**20.2%** (11.7-28.6%)	**30.8%** (23.9-37.7%)	**74.6%** (64.3-85.0%)	**37.5%** (30.4-44.5%)
			≤ 2.0 ng/mL	**2.2%** (0.0-14.2%)	**22.2%** (11.8-32.7%)	**98.2%** (88.5-100.0%)	**17.7%** (7.3-28.1%)
			> 2.0 ng/mL	**22.5%** (13.3-31.8%)	**35.6%** (26.6-44.5%)	**68.9%** (56.7-81.1%)	**46.2%** (37.5-54.8%)
		non ICU	**All PCT levels**	**7.3%** (2.9-11.6%)	**9.8%** (5.5-14.2%)	**63.6%** (45.5-81.7%)	**44.3%** (38.2-50.4%)
			≤ 2.0 ng/mL	**0.2%** (0.0-14.2%)	**6.9%** (2.1-11.8%)	**99.5%** (85.8-100.0%)	**19.0%** (11.5-26.4%)
			> 2.0 ng/mL	**8.7%** (3.5-13.8%)	**13.9%** (6.0-21.8%)	**50.8%** (28.9-72.6%)	**62.3%** (54.3-70.2%)

*Prognostic accuracy refers to how the binary ΔPCT can accurately predict mortality risk.

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

Time-to-event analysis illustrated by the Kaplan-Meier curves below shows that patients who remained in the ICU at day 4 with an initial PCT value > 2.0 µg/L 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).

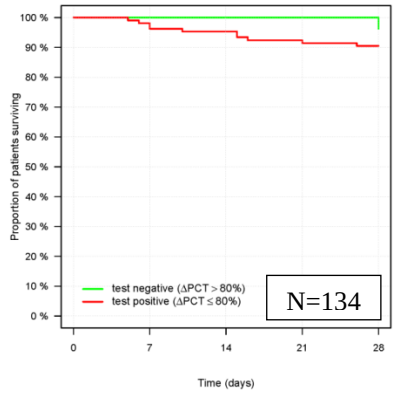
Survival probability until Day 28 for Patients still receiving ICU Care on Day 4

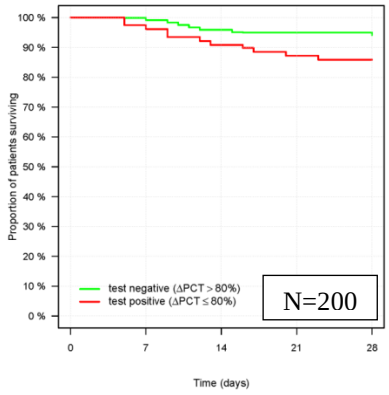


Survival probability until Day 28 for Patients without ICU Care on Day 4

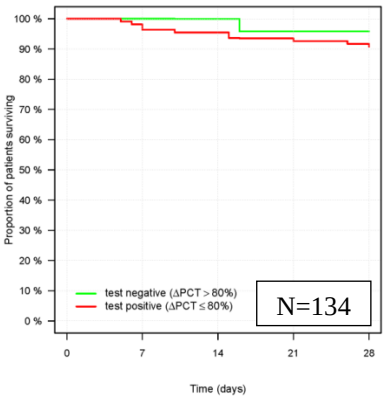
PCT ≤ 2.0 ng/mL at Day 0 | PCT > 2.0 ng/mL at Day 0

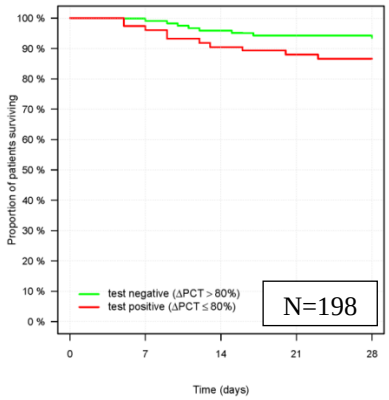
VIDAS 3





VIDAS





The performance of ΔPCT from Day 0 to Day 4 (≤80% vs. >80%) as prognostic for 28-day cumulative risk of mortality was quantified by Cox proportional hazards regression analysis. Hazard ratios of 2.27 and 2.05 were observed for VIDAS 3 and VIDAS respectively: patients with ΔPCT ≤ 80% have about a 2-fold higher 28-day mortality risk than patients with ΔPCT > 80%.

In the table below, the relative mortality risk (univariate hazard ratios) are shown for binary ΔPCT, and for other clinical factors evaluated as separate predictors of mortality, for indication.

	Predictors	Comparison	Hazard Ratio	95% CI	p-Value
VIDAS 3	**ΔPCT (Day 0 to Day 4)**	**≤ 80% vs. > 80%**	**2.27**	**1.41 - 3.63**	**0.0007**
	ΔPCT (Day 1 to Day 4)	≤ 80% vs. > 80%	1.96	1.24 - 3.11	0.004
	PCT on Day 0	>2 ng/mL vs. ≤ 2 ng/mL	1.38	0.89 - 2.14	0.149
VIDAS	**ΔPCT (Day 0 to Day 4)**	**≤ 80% vs. > 80%**	**2.05**	**1.30 - 3.23**	**0.002**
	ΔPCT (Day 1 to Day 4)	≤ 80% vs. > 80%	1.74	1.11 - 2.73	0.015
	PCT on Day 0	>2 ng/mL vs. ≤ 2 ng/mL	1.39	0.89 - 2.15	0.145
	APACHE on Day 1	difference of 5 units	1.36	1.22 - 1.53	< 0.001
	Max SOFA of Day 0-Day 4	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
	ICU Care on Day 4	yes vs. no	3.45	2.24 - 5.31	< 0.001
	Biological Infection Type	gram positive vs. gram negative	0.83	0.48 - 1.45	0.522
	Biological Infection Type	Fungal vs. gram negative	2.44	0.87 - 6.84	0.09
	Clinical Infection Type	Nosocomial vs. community acquired	0.76	0.35 - 1.64	0.481
	Positive Blood Culture	yes vs. no	1.05	0.69 - 1.58	0.834
	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

The binary ΔPCT was shown to have an added-value related to other mortality predictors in the prognosis of the risk of 28-day mortality in patients diagnosed with severe sepsis or septic shock. The relative mortality risk (Hazard ratio) for binary ΔPCT and selected predictors (Patient location at Day 4, APACHE, max SOFA, Age) reported below were estimated with 95% confidence intervals using Cox multiple regression models adjusted for scores and other mortality predictors. 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 as shown in the table below:

	Model		Hazard Ratio (95% Confidence Interval)				
			Binary Predictors		Continuous Predictors (HR per 1 SD)		
	ΔPCT Interval	Score + covariates*	ΔPCT (≤80% vs. >80%)	Patient Location at Day 4 (ICU vs. non ICU)	APACHE (1 SD = 8.13)	max SOFA (1 SD = 3.98)	Age (1 SD = 16.18)
VIDAS3	**Day 0 to Day 4**	**APACHE**	2.11 (1.24-3.59)	2.59 (1.62-4.16)	1.23 (0.98-1.54)	---	1.61 (1.28-2.01)
		max SOFA	1.81 (1.06-3.07)	1.68 (1.02-2.77)	---	1.93 (1.50-2.49)	1.69 (1.35-2.11)
	Day 1 to Day 4	**APACHE**	1.72 (1.05-2.82)	2.60 (1.62-4.16)	1.29 (1.03-1.61)	---	1.56 (1.25-1.95)
		max SOFA	1.60 (0.97-2.63)	1.70 (1.04-2.79)	---	1.99 (1.55-2.55)	1.65 (1.32-2.06)
VIDAS	**Day 0 to Day 4**	**APACHE**	1.82 (1.08-3.05)	2.60 (1.62-4.17)	1.24 (0.99-1.56)	---	1.59 (1.27-2.00)
		max SOFA	1.59 (0.95-2.67)	1.68 (1.02-2.77)	---	1.96 (1.52-2.51)	1.69 (1.35-2.11)
	Day 1 to Day 4	**APACHE**	1.58 (0.97-2.57)	2.61 (1.63-4.17)	1.30 (1.04-1.63)	---	1.57 (1.25-1.96)
		max SOFA	1.42 (0.87-2.34)	1.72 (1.05-2.82)	---	1.99 (1.56-2.56)	1.67 (1.33-2.08)

* The models also included the following predictors (hazard ratio results not shown): Antibiotic Adequacy, Sepsis Severity, Biological Infection Type, Clinical Infection Type, Positive Blood Culture, PCT on Day 0, 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 (Rubin D.B.,Wiley New York 1987; Multiple Imputation for Nonresponse in Surveys).

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):

$$PCT_{ratio} = \frac{PCT_{Day4}}{PCT_{Day0\ (or\ Day1)}}$$

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 (cf. 6.3). The following Table lists 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.

	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	**Score + covariates***	**PCT ratio (2-fold increase)**	**APACHE (SD equivalent)**	**max SOFA (SD equivalent)**	**Age (SD equivalent)**	**Patient Location at Day 4 (ICU vs. non ICU)**
VIDAS 3	**Day 0 to Day 4**	APACHE	1.28 (1.14-1.44)	1.07 (0.95-1.20)	---	1.28 (1.14-1.43)	2.50 (1.55-4.03)
		max SOFA	1.21 (1.08-1.36)	---	1.34 (1.18-1.52)	1.31 (1.17-1.46)	1.68 (1.02-2.77)
	Day 1 to Day 4	APACHE	1.27 (1.09-1.48)	1.19 (1.02-1.39)	---	1.37 (1.18-1.60)	2.60 (1.62-4.17)
		max SOFA	1.21 (1.03-1.42)	---	1.58 (1.33-1.87)	1.43 (1.23-1.67)	1.75 (1.06-2.87)
VIDAS	**Day 0 to Day 4**	APACHE	1.29 (1.14-1.45)	1.08 (0.96-1.21)	---	1.28 (1.14-1.44)	2.49 (1.54-4.02)
		max SOFA	1.22 (1.08-1.37)	---	1.35 (1.19-1.54)	1.31 (1.17-1.47)	1.68 (1.02-2.76)
	Day 1 to Day 4	APACHE	1.26 (1.08-1.46)	1.18 (1.02-1.37)	---	1.36 (1.17-1.58)	2.60 (1.62-4.17)
		max SOFA	1.19 (1.02-1.39)	---	1.56 (1.32-1.84)	1.42 (1.22-1.64)	1.75 (1.06-2.86)

*The models also included the following predictors considered as covariates (hazard ratio results not shown): Antibiotic Adequacy, Sepsis Severity, Biological Infection Type, Clinical Infection Type, Positive Blood Culture, PCT on Day 0, 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.

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

Variable Class		Per Protocol Population (N=598)			
		All	Dead	Alive	Mortality
		N	N	N	%
Gender	**Female**	264	46	218	17.4%
	Male	334	55	279	16.5%
Age	**< 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	17.7%
	Hispanic	23	5	18	21.7%
	Other	4	0	4	0.0%

Initial PCT levels at Day 0 with patient outcome and % mortality were as follows:

Variable	Class	VIDAS 3				VIDAS			
		N	Dead	Alive	%	N	Dead	Alive	%
PCT on Day 0 (ng/mL)	**< 0.5**	101	17	84	16.8%	97	16	81	16.5%
	0.5-2.0	89	10	79	11.2%	92	10	82	10.9%
	> 2.0	373	70	303	18.8%	367	69	298	18.8%
	Unavailable*	35	4	31	11.4%	42	6	36	14.3%

* Unavailable patients results were either not available for testing, or were below assay measuring range of 0.05 ng/mL.

3. Clinical Cut-off:

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 result representing a lower risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

PCT > 2 µg/L
A PCT level above 2.0 µg/L on the first day of ICU admission is associated with a high risk for progression to severe sepsis and/or septic shock.

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

Note: A PCT level below 0.5 µg/L does not exclude infection. If the PCT measurement is done very early after the systemic infection process has started (usually < 6 hours), these values may still be low.

Various non-infectious conditions are known to induce changes in PCT level. PCT levels between 0.5 µg/L and 2.0 µg/L should be interpreted in the context of the specific clinical background and condition(s) of the individual patient. It is recommended to retest PCT as clinically indicated within 6-24 hours if any concentrations <2 µg/L are obtained.

4. Expected Values/Reference Range:

A study was performed using the VIDAS B·R·A·H·M·S PCT test on serum samples from apparently healthy male (N=98) and female (N=102) subjects. The normal values corresponding to the 95th and 99th percentiles were respectively found at < 0.05 ng/mL and 0.09 ng/mL.

		Ethnicity				
Age Range	N	African American	Asian	Caucasian	Hispanic	Other
<60 years	189	179	0	9	1	0
>60 years	11	11	0	0	0	0

N. Instrument Names:

VIDAS family of instruments

O. System Descriptions:

1. Modes of Operation:

See Device Description (Section I) above

2. Software

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes ____X___ or No _____

In addition to the device, to minimize manual user calculation errors, an on-line 'Change in Procalcitonin Calculator' was developed (www.BRAHMS-PCT-Calculator.com). The on-line calculator is a simple web-based software application; the requirement specifications for the Change in Procalcitonin Calculator focus on functional specifications of the software. The software handles all data on the client-side only (i.e., no transfer of any data from user's local computer). Browsers evaluated included:

Android Browser (on Android)	Microsoft Internet Explorer 7.0
Chrome 31.0	Microsoft Internet Explorer 8.0
Chrome 36.0	Microsoft Internet Explorer 9.0
Chrome 44.0	Microsoft Internet Explorer 11.0
Chrome 45.0	Safari 8.0
Firefox 40	Safari (on iOS)
Microsoft Edge 12	

The user inputs the patient location on day 4 (ICU or not ICU) and the absolute PCT concentrations of a patient obtained on the day severe sepsis or septic shock was first diagnosed (or 24 hours later) and four days thereafter to determine ΔPCT results. (See www.BRAHMS-PCT-Calculator.com). Once data input is completed, the user selects 'calculate' and a summary cross tab table displays calculation results and mortality risk prognosis classification as determined by the clinical trial. If incorrect information is entered, corresponding error messages are displayed. These include:

- If no value is entered, 'Required field.' will appear.
- If no numeric value is entered, 'Values must be between 0.02 and 5000.' will appear
- If date of collection is incorrect, 'Range between Day 0 and Day 4 is too long.' will appear

A link to the device package labeling is provided within the on-line calculator page. The user is only able to Print/Download results without transmission of any data away from the local computer. Usability testing was conducted.

Absolute PCT values on the laboratory report should be reported with a link to the Change in Procalcitonin Calculator (www.BRAHMS-PCT-Calculator.com) for a guided interpretation of the test results. In addition the laboratory report should also include the 'Change in Procalcitonin Result' (> 80% or ≤ 80%) if Day 0 (or Day 1) and Day 4 values are available.

3. Specimen Identification:

   Specimens are identified by unique bar codes.

4. Specimen Sampling and Handling:

   Specimen type and collection

   Human serum or plasma (lithium heparinate).
   Since EDTA causes a decrease in the values measured, plasma collected in EDTA tube should not be used. For a given patient, the PCT assays must be performed on the same type of sample tube.

   Sample preparation

   Dry tubes: wait for samples to coagulate and centrifuge according to the tube

manufacturer’s recommendations to eliminate fibrin.
Other tubes: follow the tube manufacturer’s recommendations for use.
Frozen-stored samples: after thawing, all these samples must be clarified by centrifuging.

Note**:** Blood sampling tube results may vary from one manufacturer to another depending on the materials and additives use.

It is the responsibility of each laboratory to validate the type of sample tube used and to follow the manufacturer’s recommendations for use.

Sample preparation

Follow the tube manufacturer’s recommendations for use.

The pre-analytical step, including the preparation of blood samples, is an essential first step when performing laboratory testing and should be in accordance with Good Laboratory Practice.

For serum specimens, ensure that complete clot formation has taken place prior to centrifugation**.** Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting times.

Samples containing suspended fibrin particles or erythrocyte stroma should be centrifuged before testing. The presence of fibrin, red blood cells, or suspended particles can lead to erroneous results.

Sample stability

The sera or plasma separated from the clot can be stored at 2-8°C in stoppered tubes for up to 48 hours; if longer storage is required, freeze at -25 ± 6°C. Six-month storage of frozen samples does not affect the quality of results. Three freeze/thaw cycles were validated.

Special case for sample volumes between 50 µL and 200 µL

Sample volumes between 50 µL and 200 µL can be tested after performing a manual dilution up to 1/4 (1 volume of test sample + 3 volumes of PCT negative sample or Serum Free reagent no more than two hours after dilution. Dilution of sample would be required if the sample volume is less than 200 µL or if the PCT concentration of the sample is above 200 ng/mL.

Sample-related interferences

It is recommended not to use samples that are hemolyzed, lipemic or icteric and, if possible, to collect a new sample when these conditions are known to be present.

5. Calibration:

   Calibration, using the two calibrators provided in the kit, must be performed each time a new lot of reagents is opened, after the master lot data (MLE) has been entered, and then every 28 days. This operation provides instrument-specific calibration curves and compensates for possible minor variations in assay signal throughout the shelf-life of the kit.

   The calibrators, identified by S1 and S2, must be tested in duplicate (see VIDAS Operator's Manual) in the same run. The calibration values must be within the set RFV ("Relative Fluorescence Value"). If this is not the case, recalibrate using S1 and S2.

6. Quality Control:

   See "Traceability, Stability, Expected Values (controls, calibrators, or methods)" Section (M.1.c) above.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In the "Performance Characteristics" Section above:

See K071146

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809 and the specials controls for this device type.

R. Conclusion:

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