DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

June 28, 2016

BIOMERIEUX, INC.
THI DANG
REGULATORY AFFAIRS SPECIALIST
595 ANGLUM RD.
HAZELWOOD, MO 63042

Re: K160911
Trade/Device Name: VIDAS® BRAHMS PCT™ (PCT)
Regulation Number: 21 CFR 866.3215
Regulation Name: Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis
Regulatory Class: II
Product Code: PMT
Dated: March 31, 2016
Received: April 1, 2016

Dear Ms. Dang:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

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

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

Sincerely yours,

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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K160911

Device Name
VIDAS B•R•A•H•M•S PCT (PCT)

Indications for Use *(Describe)*

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.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(K) SUMMARY

This 510(k) summary of safety and effectiveness information is being submitted in accordance with the requirement of Safe Medical Devices Act of 1990 and 21 CFR 807.92.

VIDAS® B·R·A·H·M·S PCT™

A. Submitter Information

Submitter's Name:	bioMérieux, Inc.
Address:	595 Anglum Road Hazelwood, MO 63042
Contact Person:	Thi My Lan Dang
Phone Number:	314-731-8799
Fax Number:	314-731-8689
Date of Preparation:	March 31, 2016

B. Device Name

Trade Name:	VIDAS® B·R·A·H·M·S PCT™ (PCT)
Common Name:	Endotoxin Assay
Classification Name:	Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis (21 CFR 866.3215, Product Code PMT) – Class II in vitro Diagnostic device

C. Predicate Devices

Predicate device 1, trade name: B·R·A·H·M·S PCT Sensitive KRYPTOR® (DEN150009)

Predicate device 2, trade name: VIDAS® B·R·A·H·M·S PCT™ (K071146)

D. Device Description

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.

E. 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.

F. Technological Characteristics Summary

A general comparison of the similarities and differences of the assay with the predicates is presented in the following table.

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)
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	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	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. The 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.

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)
	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.	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 µg/L are associated with a higher risk for progression to severe sepsis and/or septic shock than PCT levels below 0.5 µg/L. 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 µg/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

G. Nonclinical Test

A summary of the non-clinical (analytical) results is presented below.

Dilution for sample volumes between 50 µL and 200 µL
A dilution study was performed on the VIDAS® according to a protocol based on the CLSI EP6-A guideline. 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 volume of diluent) before testing with the VIDAS® B·R·A·H·M·S PCT assay.

Limits of detection and quantitation
The Limit of Blank (LoB), the limit of Detection (LoD) and the Limit of Quantitation (LoQ) were determined on the VIDAS® and VIDAS®3 instruments according to the CLSI® EP17-A2 recommendations. The limits reported below apply for all the instruments of the VIDAS family:

Limit of Blank (LoB)	0.01 ng/mL
Limit of Detection (LoD)	0.03 ng/mL
Limit of Quantitation (LoQ)	0.05 ng/mL

The Limit of Quantitation (LoQ) is the lowest concentration of PCT measured with a level of acceptable precision of 20% CV.

Precision
The study was performed according to the recommendations of CLSI® document EP5-A3. A panel of 9 human samples covering the measuring range were tested in duplicate in 2 runs per day, over 20 days using 3 VIDAS® and 3 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. The repeatability, between-day precision, within-laboratory precision and reproducibility/total precision (between-laboratory precision) were estimated for each sample and are reported 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%

Linearity

The test linearity was studied on the VIDAS® and VIDAS® 3 instruments according to a procedure taken from the CLSI EP6-A guideline. The test is linear over the complete measurement range.

H. Clinical Testing

A study was conducted on a population of 858 adult patients recruited across 13 investigational sites in the US to assess the performance of VIDAS® B·R·A·H·M·S PCT™ (PCT) on VIDAS®3 and VIDAS® for the prediction of cumulative 28-day all-cause mortality.

In the per protocol population (598 patients) was comprised of 44% female and 56% male patients with a mean age of 64 years, diagnosed either with severe sepsis (51%) or septic shock (49%), presenting mainly with community acquired infections (91%) and less frequently with nosocomial infections (9%). 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).

Demographics with patients outcome and % mortality information are shown below:

Variable	Class	N*	Dead	Alive	% Mortality
Gender	**Female**	264	46	218	17.4%
	Male	334	55	279	16.5%
Age (years)	**≤ 30**	39	1	38	2.6%
	31-45	45	4	41	8.9%
	46-55	74	8	66	10.8%
	56-65	149	26	123	17.4%
	66-75	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%

*per protocol population

Cumulative 28-day all-cause mortality did not differ significantly for male vs. female patients (χ^2 p-value = 0.84).

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

Variable	Class	VIDAS® 3				VIDAS®			
		N	Dead	Alive	% Mortality	N	Dead	Alive	% Mortality
PCT on Day 0	**< 0.5**	101	17	84	16.8%	97	16	81	16.5%
(ng/mL)	**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 (VIDAS 3 n = 24, VIDAS n = 29), or were below assay measuring range of 0.05 ng/mL (VIDAS 3 n = 11, VIDAS n = 13).

The study demonstrated that **for patients diagnosed with severe sepsis or septic shock, the 28-Day mortality was statistically significantly increased for patients with ΔPCT ≤ 80% compared to patients with ΔPCT > 80%**:

- Binary ΔPCT was significantly associated with 28-day cumulative mortality (Two-sided Fisher's Exact Test p-value 0.0003 and 0.002 for VIDAS®3 and VIDAS® respectively for ΔPCT based on Day 0 and p-value = 0.003 and 0.019 for VIDAS®3 and VIDAS® respectively for ΔPCT based on Day 1) and this association remained significant in each patient location subgroup, ICU vs. non ICU at Day 4 (for VIDAS®3 and VIDAS® respectively Cochran-Mantel-Haenszel Test p-value =0.006 and 0.016 using ΔPCT based on Day 0 and p-value = 0.023 and 0.073 using ΔPCT based on Day 1). The mortality in the group with ΔPCT ≤ 80 % was increased by a factor of 2.1 on VIDAS®3 and 1.9 on VIDAS® compared to the group with ΔPCT > 80% using ΔPCT based on Day 0 (factor 1.8 on VIDAS®3 and 1.6 on VIDAS® using ΔPCT based on Day 1). The observed mortality risk was generally higher in the ICU subgroup than in the non-ICU group (5.4 to 11.4% vs. 18.4 to 31.6%). In each subgroup, the mortality was even higher for patients with a ΔPCT ≤ 80% than for patients with a ΔPCT > 80%.

- Supplementary classification of patients based on the patient location on Day 4 and initial PCT level (< 2.0 vs. ≥ 2.0 ng/mL) at Day 0 (or Day 1) showed that in each patient location and initial PCT level subgroup, a PCT decrease ≤ 80% from Day 0 (or Day 1) to Day 4 constitutes a higher risk for mortality within 28 days compared to a higher PCT decline (> 80%). **For the prediction of absolute mortality risks, ICU disposition at Day 4 and initial PCT level at Day 0 (or Day 1) should be considered in addition to binary ΔPCT (≤ 80% or > 80%).**

Significantly reduced or increased mortality were observed by patient location and initial PCT level subgroups:

a) Patients still receiving ICU care on Day 4 or patients with initial PCT level > 2.0 ng/mL have a higher mortality risk from study Day 4 to the end of follow-up time (28 days) when the ΔPCT is ≤ 80% compared to when the ΔPCT is > 80%.

b) among patients who are still in the ICU on Day 4, patients with ΔPCT > 80% and an initial PCT level of ≤ 2.0 ng/mL on Day 0 have a particularly lower cumulative 28-day mortality risk compared to patients with an initial PCT level at Day 0 of > 2.0 ng/mL (2.2% vs. 20.3% on VIDAS®3; 1.8% vs. 21.4% on VIDAS®). In addition, regardless of the initial PCT level, patients in the ICU on Day 4

which have ΔPCT ≤ 80% (Day 0 to Day 4) have an even higher mortality risk (26.4% to 34.1% on VIDAS3; 27.0% to 33.5% on VIDAS®).

c) even when they are no longer in the ICU on Day 4, patients with an initial PCT level > 2.0 ng/mL and with a ΔPCT ≤ 80% (Day 0 to Day 4) remain at high mortality risk (14.1% on VIDAS®3; 13.4% on VIDAS®). Overall, a lower mortality risk was observed for patients discharged from the ICU before or on Day 4 with an initial PCT level ≤ 2.0 ng/mL than for patients with an initial PCT level of > 2.0 ng/mL (3.7% to 9.5% vs. 5.8% to 14.1% on VIDAS3; 4.2% to 9.2% vs. 6.5% to 13.4% on VIDAS®).

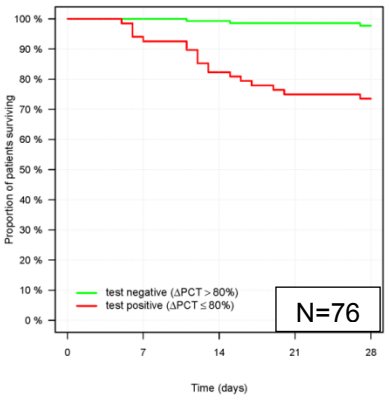
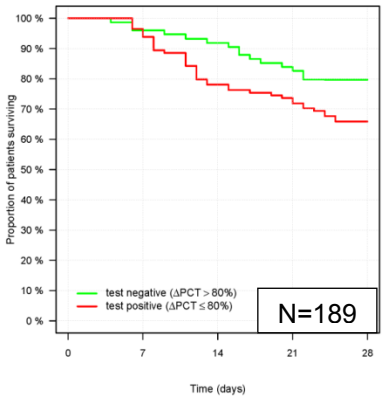
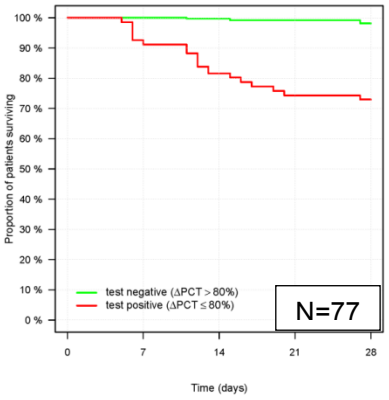
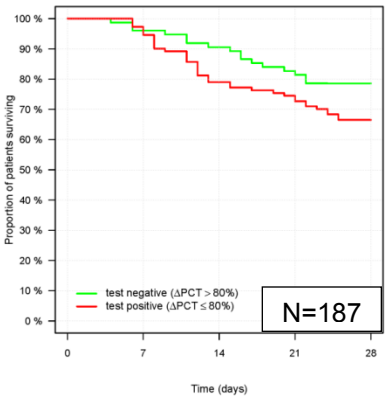
The table below shows the 28-day cumulative mortality risk and prognostic accuracy by binary ΔPCT group (≤ 80% or > 80%), by the selection of either Day 0 or Day 1 for the ΔPCT calculation, by patient location at Day 4, and by initial PCT level.

	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%)

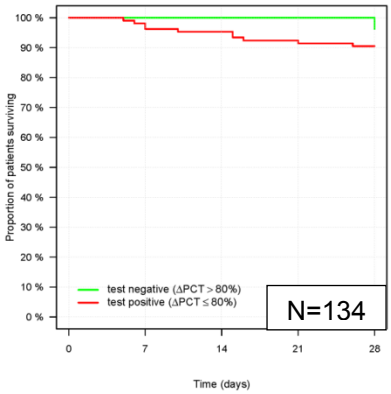
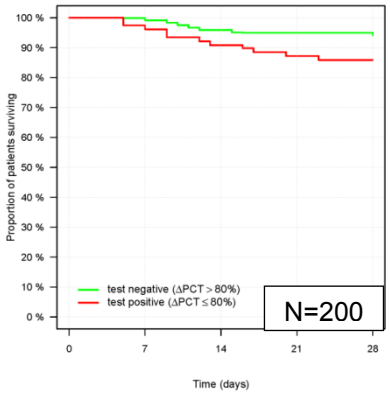
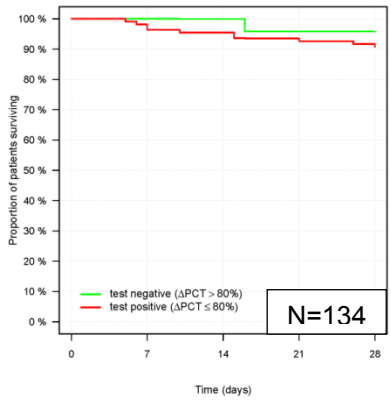
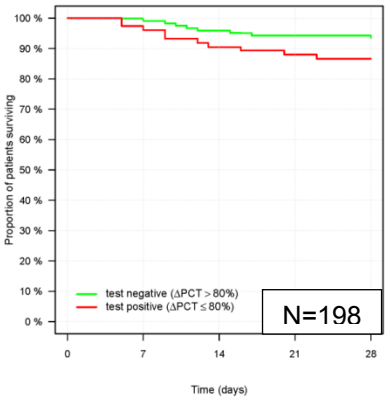
*Prognostic accuracy refers to how the binary ΔPCT can accurately predict mortality risk.

Time-to-event analysis is illustrated by the Kaplan-Meier survival probability curves below.

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

	PCT ≤ 2.0 ng/mL at Day 0	PCT > 2.0 ng/mL at Day 0
VIDAS®3		
VIDAS®		

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®		

Performance of binary ΔPCT from Day 0 to Day 4 for the prognosis of 28-day cumulative mortality risk was quantified by Cox proportional hazards regression. Hazard ratio 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.

	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)
VIDAS® 3	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 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.

Note: For binary predictors, the risk estimate compares the hazards for the two binary results. For continuous predictors, the hazard ratio (HR) was calculated for one standard deviation (SD) change in the predictor.

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

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

A ΔPCT of 80% corresponds to a PCT ratio of 0.2 (i.e. PCT level at Day 4 is 5 times less than PCT level at Day 0, or Day 1). When ΔPCT is ≤ 80%, the PCT ratio is ≥ 0.2, 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 larger the PCT ratio, the higher the relative mortality risk is.
In the following table, the relative increase in mortality risk (hazard ratio) are reported for a patient with any given PCT ratio compared to a patient with a 2-fold lower PCT ratio. For comparison, other selected predictors (APACHE, max SOFA, Age, Patient location at Day 4) are indicated with corresponding equivalents in standard deviation (0.50 SD on VIDAS3 and 0.51 SD on VIDAS for Day 0 to Day 4; 0.69 SD on VIDAS3 and 0.67 SD on VIDAS for Day 1 to 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.

I. Conclusion

The results from the non-clinical and clinical studies submitted in this premarket notification are complete and demonstrate that the VIDAS® B·R·A·H·M·S PCT assay is substantially equivalent to the predicate devices.