September 1, 2021

MeMed Diagnostics Ltd.
Efrat Hartog-David
Director of Regulatory Affairs and Quality Assurance
Nahum Heth 5
Tirat Carmel, 3508504
Israel

Re: K210254
Trade/Device Name: MeMed BV
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: Class II
Product Code: QPS
Dated: January 29, 2021
Received: January 29, 2021

Dear Efrat Hartog-David:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; 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 https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). 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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Kristian Roth, Ph.D.
Branch Chief
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
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: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K210254

Device Name
MeMed BV™

Indications for Use *(Describe)*
The MeMed BV test is an automated semi-quantitative immunoassay that measures three non-microbial (host) proteins (TRAIL, IP-10, and CRP) in adult and pediatric serum samples and is intended for use in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection. MeMed BV is indicated for use in patients presenting to the emergency department or urgent care center and with samples collected at hospital admission from patients with suspected acute bacterial or viral infection, who have had symptoms for less than seven days. The MeMed BV test generates a numeric score that falls within discrete interpretation bins based on the increasing likelihood of bacterial infection.

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

MeMed Diagnostics Ltd.'s MeMed BV™

Submitter

MeMed Diagnostics Ltd.
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Tirat Carmel, 3508504, Israel

Phone: +972-4-8500302
Contact Person: Efrat Hartog-David, Ph.D.

Date Prepared: January 29, 2021

Name of Device: MeMed BV™

Common or Usual Name: MeMed BV™

Classification Name: Immunoassay for host biomarkers of infection

Regulatory Class: Class II

Product Code: QPS

Predicate Devices

BioMerieux, Inc, VIDAS B.R.A.H.M.S. PCT (PCT) (K162827)

Device Description

The MeMed BV™ ("BV test" or the "test") is an In-Vitro-Diagnostic device that measures in parallel the blood concentrations of TRAIL, IP-10 and CRP. The test consists of an automated analyzer with built-in hardware and software that conduct chemiluminescence-based analyte measurements of patient serum samples and their computational integration (MeMed Key™), and a disposable cartridge that contains the reagents and controls needed to detect the analytes of interest (MeMed BV™ cartridge). The test generates an answer to each sample, with a test run time of approximately 15 minutes.

Intended Use / Indications for Use

The MeMed BV™ test is an automated semi-quantitative immunoassay that measures three non-microbial (host) proteins (TRAIL, IP-10, and CRP) in adult and pediatric serum samples and is intended for use in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection. MeMed BV™ is indicated for use in patients presenting to the emergency department or urgent care center and with samples collected at hospital admission from patients with suspected acute bacterial or viral infection, who have had symptoms for less than seven days. The MeMed BV™ test generates a numeric score that falls within discrete interpretation bins based on the increasing likelihood of bacterial infection.

Comparison with Predicate Device

The MeMed BV is substantially equivalent to the predicate device the VIDAS B.R.A.H.M.S. PCT (PCT) (K162827). The MeMed BV has similar intended and indications for use, as

well as similar basic technological principles to the predicate device. The minor differences in technological characteristics are supported by the performance testing and do not raise any new questions of safety and efficacy. A substantial equivalence table summarizing the similarities and differences between the MeMed BV and its predicate device is provided below.

Performance Data

1. Analytical performance:

a. Limit of Quantitation

The Total Error and precision for the lowest concentration of each measurand that could be reliably measured (i.e., Limit of Quantification or LoQ) by the MeMed BV test was evaluated in accordance with CLSI EP17-A2, *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.* The study used two cartridge lots with one MeMed Key analyzer and the samples described in **Table 1**. Each sample was tested three times on three non-consecutive days.

Table 1. Predefined acceptance criteria for LOQ

Analyte	Total Error Accuracy Goal
TRAIL	TE < 30%
IP-10	TE < 40%
CRP	TE < 30%

The TE (total error) was calculated for each of the four concentration levels for three analytes as 2 x SD observed.

The results obtained for LLOQ testing on two cartridge lots are summarized in **Table 2**.

Table 2. Total error for LLOQ measurements for two cartridge lots

Cartridge Lot		M21244			M21532		
Sample	Parameter	TRAIL (pg/ml)	IP-10 (pg/ml)	CRP (mg/L)	TRAIL (pg/ml)	IP-10 (pg/ml)	CRP (mg/L)
	MEAN	13.4	90.3	0.9	13.9	80.4	0.9
	STD	0.8	7.0	0.1	1.1	11.0	0.1
	CV	6%	8%	7%	8%	14%	8%
1	TE	11%	15%	13%	16%	27%	16%
	MEAN	15.0	98.7	1.0	15.8	85.8	1.0
	STD	1.2	14.0	0.1	1.0	11.6	0.1
	CV	8%	14%	7%	6%	13%	11%
2	TE	16%	28%	14%	12%	27%	22%
	MEAN	17.3	106.2	1.1	16.9	93.6	1.1
	STD	2.5	5.4	0.0	1.6	2.8	0.1
	CV	14%	5%	3%	10%	3%	13%
3	TE	29%	10%	7%	19%	6%	26%
	MEAN	18.1	111.1	1.2	18.1	103.3	1.2
4	STD	1.1	4.4	0.1	1.6	15.7	0.1

Cartridge Lot		M21244			M21532		
Sample	Parameter	TRAIL (pg/ml)	IP-10 (pg/ml)	CRP (mg/L)	TRAIL (pg/ml)	IP-10 (pg/ml)	CRP (mg/L)
	CV	6%	4%	9%	9%	15%	9%
	TE	12%	8%	18%	18%	30%	18%

The results show that for all the tested samples, MeMed BV test passes the acceptance criteria of TE. The formal LLOQ is established to values corresponding to TRAIL -15pg/mL, CRP-1 mg/mL, IP-10 – 100 pg/mL as is set in MeMed Key analyzer.

b. Reproducibility/Precision:

The repeatability, intermediate precision and reproducibility studies for each measurand (TRAIL/IP-10/CRP) of the MeMed BV™ test were conducted using the MeMed Key™ Analyzer. The MeMed BV test score used a panel of 4 scores representing infectious bacteria, infectious virus, equivocal and noninfectious scores during the studies. Studies were performed in accordance with CLSI EP05-A3 *Evaluation of Precision of Quantitative Measurement Procedures.*

The serum panel members representing the MeMed BV test scores used for these studies included the following:

Table 3. Patient Specimen Panel Members

Panel member	Sample type	Score
A	Infectious serum specimen	High (Score = 96)
B	Infectious serum specimen	Medium (Score = 53)
C	Infectious serum specimen	Low (Score = 1)
D	Healthy serum specimen	Healthy (Score = 4)

The study was performed in three laboratories. The measurements were performed over 5 non-consecutive days. At each site, a single operator conducted the tests on two different MeMed Key analyzers using one cartridge lot, with three runs performed each day per panel member. Calibration was performed on the first day for each MeMed Key analyzer using one calibrator lot. External Controls were run daily using one lot of external controls.

For each measurand, TRAIL, IP-10, and CRP, the acceptance criteria for measurements was CV ≤ 15 %. This acceptance criteria were not applicable to IP-10 and CRP concentration of healthy specimens since the concentrations were expected to be below the LoQ of IP-10 and CRP assays. The acceptance criterion for the MeMed BV test score was set at SD < 12.5 score units.

The results of the repeatability, intermediate precision and reproducibility studies are summarized below.

Table 4. Repeatability, Intermediate precision and reproducibility results for four panel members

				Repeatability		Intermediate Precision		Reproducibility	
Panel member	**Measurand or score**	**Mean**	**N**	**SD**	**CV%**	**SD**	**CV%**	**SD**	**CV%**
A	TRAIL	34.0	90	2.9	8.5	2.9	8.5	4.1	12.0
B	TRAIL	68.0	90	6.0	8.9	6.3	9.3	7.6	11.1
C	TRAIL	266.5	90	17.6	6.6	18.1	6.8	25.9	9.7
D	TRAIL	77.2	90	7.0	9.1	7.7	9.9	9.8	12.7
A	IP-10	930.7	90	40.1	4.3	43.2	4.7	48.6	5.2
B	IP-10	372.3	90	20.0	5.4	20.5	5.5	21.3	5.7
C	IP-10	558.4	90	22.3	4.0	24.4	4.4	25.8	4.6
D	IP-10	101.4	90	6.2	6.1	6.2	6.1	6.3	6.2
A	CRP	126.0	90	10.5	8.3	10.5	8.3	14.6	11.6
B	CRP	63.2	90	5.2	8.3	5.7	9.0	6.5	10.2
C	CRP	60.9	90	4.9	8.1	5.3	8.6	6.3	10.4
D	CRP	1.0	90	0.1	4.9	0.1	5.0	0.1	5.0
A	Score	96.0	90	1.3		1.3		1.8	
B	Score	53.4	90	7.5		7.7		9.4	
C	Score	0.9	90	0.3		0.3		0.4	
D	Score	3.6	90	1.0		1.2		1.4	

The reproducibility results complied with the pre-established acceptance criteria for score and individual analytes.

c. Lot-to-Lot Reproducibility

A lot-to-lot reproducibility study was conducted to estimate lot-to-lot variance, for each MeMed BV test measurand (TRAIL/IP-10/CRP) and the MeMed BV test score for the four panel members as described in **Table 4** above.

The lot-to-lot study was performed on 3 days with one operator at one site using three runs per day for each of the four panel members using two lots of cartridges on one MeMed Key Analyzer. Two calibration lots were used, one for each cartridge lot. External controls were run daily using one lot of External Control reagents.

For each of TRAIL, IP-10, and CRP, the acceptance criterion for measurement was set at CV ≤ 15 %. This acceptance criteria are not applicable to IP-10 and CRP concentration of healthy individual since it is expected to be below the LoQ of IP-10 and CRP assays. The acceptance criterion for the score was set at SD < 12.5 score units.

Table 5. Between lots analysis of components of variance

Panel member	Measurand or score	Mean	N	Between Lots	
				SD	CV%
A	TRAIL	33.1	18	0.5	1.6
B	TRAIL	66.4	18	0.0	0.0
C	TRAIL	258.8	18	0.0	0.0
D	TRAIL	74.5	18	0.0	0.0
A	IP-10	950.1	18	69.7	7.3

Panel member	Measurand or score	Mean	N	Between Lots	
				SD	CV%
B	IP-10	385.8	18	16.9	4.4
C	IP-10	575.2	18	44.4	7.7
D	IP-10	100.0	18	0.0	0.0
A	CRP	117. 6	18	0.8	0.7
B	CRP	60.8	18	0.0	0.0
C	CRP	58.5	18	0.7	1.2
D	CRP	1.0	18	0.0	0.6
A	Score	95.8	18	0.0	
B	Score	54.2	18	0.0	
C	Score	1.0	18	0.0	
D	Score	3.8	18	0.0	

The lot-to-lot reproducibility results comply with the pre-established acceptance criteria for score and individual analytes.

d. Linearity

Linearity of the MeMed BV test for each of the three measurands (TRAIL/IP-10/CRP) was evaluated in accordance with CLSI EP06-A *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*. The study was performed in one laboratory with one MeMed Key Analyzer, two lots of cartridges, one lot of calibration reagents and one lot of External Control reagents. Calibration was performed before initiating the study for each cartridge lot. External Controls were run daily.

Four replicates of eleven dilutions of each MeMed BV test measurand were measured in the linearity study. The order of measurement of the dilution series was random. The eleven dilutions used in the study are represented in **Table 6**.

Table 6. Preparation of dilutions for linearity testing

Dilution #	Volume of low positive material [mL]	Volume of high positive material [mL]	TRAIL (pg/mL)	IP-10 (pg/mL)	CRP (ug/mL)
1	2	0	15	96	1
2	1.8	0.2	49	301	27
3	1.6	0.4	80	500	52
4	1.4	0.6	111	699	78
5	1.2	0.8	142	898	103
6	1	1	173	1097	129
7	0.8	1.2	204	1295	154
8	0.6	1.4	235	1494	180
9	0.4	1.6	266	1693	205
10	0.2	1.8	297	1892	231
11	0	2	290	1930	289

The linearity criterion is that measurement bias due to non-linearity is less than 10% or 10mg/L for CRP, 10% or 10 pg/mL for TRAIL and 10% or 50 pg/mL for IP-10 of the value corresponding to the linear fit. The absolute value thresholds are intended to reflect differences at low concentrations for which defined relative errors result in extremely low absolute value.

Polynomial regression analysis was performed for first-, second- and third-order polynomials.

For CRP and IP-10 Lot 1 and IP-10 Lot 2 significance was identified for second order coefficients. However, the degree of non-linearity is within the acceptance criteria.

e. Hook Effect

A recombinant sample where each analyte was present at the upper limit of quantitation (ULOQ, sample #1) was used as well as three additional samples where each analyte was present at higher concentrations (samples 2-4).

The samples were prepared by spiking protein rich buffer with each of the three measurands (recombinant proteins). This approach was used to generate Sample 1 and 4 as indicated in **Table 7**. Sample 2 was prepared by mixing Sample 1 and 4 samples in a ratio of 2/3 and 1/3, respectively. Sample 3 sample was prepared by mixing Level 1 and 4 samples in a ratio of 1/3 and 2/3, respectively. For each concentration level, 3 runs were measured on one MeMed Key Analyzer, on the same day.

Table 7. Analyte concentrations levels to be tested for hook effect assessment

Samples	**TRAIL (pg/ml)**	**IP-10 (pg/ml)**	**CRP (mg/L)**
Sample 1 (ULOQ)	300	6000	250
Sample 2	533	7333	333
Sample 3	767	8666	417
Sample 4	1000	10000	500

Hook effect was determined to be excluded if the responses obtained for concentrations up to level 4 were no less than the response obtained for upper limit of quantification (ULoQ). If one or more of the assessed concentration levels deviated from this criterion, hook effect concentration was established as the lowest concentration for which the obtained response was lower than the response corresponding to ULoQ.

For each concentration level average signal was calculated and compared against the average response obtained for sample 1 (ULOQ). The results are summarized in **Table 8**.

Table 8. Measurements of high analyte concentration samples on MeMed Key Analyzer

Sample	Measurement by analyzer (RLUs)		
	TRAIL	IP-10	CRP
Sample 1 (ULOQ)	2018979	6645676	3656138
Sample 2	3209761	8029144	4693431
Sample 3	4448549	9508794	5348636
Sample 4	6111236	10904508	6125845

No hook effect was seen for concentrations up to TRAIL of 1,000 pg/mL, IP-10 of 10,000 pg/mL, and CRP of 500 mg/L.

f. Carry over

Because each specimen tested with the MeMed BV test is processed in a separate disposable cartridge and within the cartridge, each one of the three immunoassays is processed using a separate disposable filtered tip, with a unique tip dedicated to each measurand, the likelihood of carry over between specimens is negligible. A carry over study was, nonetheless, conducted to address the low risk of potential carry over. Sequential runs of ("L") and high score ("H") clinical samples were used in the study. No carry-over was assessed based on 1) the difference between average score of high score sample ran after low score sample and high score sample baseline average score of no more than 12.5 score units; and 2) the difference between average score of low score sample ran after high score sample and low score sample baseline average score of no more than 12.5 score units.

Two clinical samples were run in two sequences 1 and 2 of high to low scores and low to high scores, each sequence on a different MeMed Key analyzer: The high to low score (**Table 9**) and low to high score (**Table 10**) are represented below.

Table 9. High to low score series

1	High	95
2	High	88
3	High	95
4	High	96
5	High	95
6	Low	4
7	High	90
8	Low	2
9	High	93
10	Low	3
11	High	97
12	Low	7
13	High	97
14	Low	3
15	High	97
Baseline high score mean		93.8
Test high score mean		94.8
Difference		1

Table 10. Low to high score series

1	Low	3
2	Low	3
3	Low	5
4	Low	5
5	Low	4
6	High	96
7	Low	2
8	High	94
9	Low	3
10	High	94
11	Low	4
12	High	98
13	Low	5
14	High	97
15	Low	6
Baseline low score mean		4
Test low score mean		4
Difference		0

The maximal difference in score obtained for high score sample (1 score unit difference) demonstrates that no carry-over occurred with the MeMed BV test.

g. Interference/Cross Reactivity

Interfering substances and cross-reactants were evaluated for the MeMed BV test score. Each interferent and cross-reactant was tested using two serum panel members that represented score a 'low' score of approximately 5 and 'high' score of approximately 95. The study was performed in one laboratory using one lot of cartridges, one lot of calibration reagents and one lot of External Control reagents. Each interferant and cross-reactant was tested by 8 repeat runs of spiked and non-spiked sample for each clinical sample using 2 MeMed Key Analyzers.

Master stock interferant/cross reactant solutions were spiked into serum specimens at concentrations of less than 10% v/v of the total sample volume. Detailed descriptions of each interferant/cross-reactant concentration is provided in **Table 11** and **Table 12**. The Interference/cross reactivity was assessed by comparison of the spiked sample Test result to a non-spiked sample Test result (appropriate diluent/buffer was added to the non-spiked sample). Interference was determined as bias between spiked and non-spiked score results was ± 12.5 score units.

Table 11. Panel of interferents for screening[1]

Interferent	Stock concentration	Reference matrix	Volume spiked	Final Concentration tested
Acetaminophen (Tylenol)	312 mg/dL	Aqueous	5% v/v	0.156 mg/mL
Acetyl Salicylic Acid (Aspirin)	60 mg/dL	Ethanol	5% v/v	0.03 mg/mL
Alcohol	100%	Aqueous	5% v/v	0.5% V/V
Amoxicillin	108 mg/dL	Aqueous	5% v/v	54 µg/mL
Ampicillin	150 mg/dL	Aqueous	5% v/v	75 µg/mL
Azithromycin	22.2 mg/dL	Ethanol	5% v/v	11.1 µg/mL
Bilirubin (conjugated)	>400 mg/dL	Aqueous	10 % v/v	0.4 mg/mL
Bilirubin (unconjugated)	>400 mg/dL	0.1M NaOH	10 % v/v	0.4 mg/mL, in 0.1M NaOH
Caffeine	216 mg/dL	Aqueous	5% v/v	108 µg/ml
Cetirizine HCL	8.7 mg/dL	Aqueous	5% v/v	4.35 µg/ml
Dextramethorphan	0.0312 mg/dL	Aqueous	5% v/v	15.6 ng/ml
Doxycycline	36 mg/dL	Aqueous	5% v/v	18 µg/ml
HAMA (human α-mouse Ab)	168 ng/mL >640 (titer)	N/A	N/A	N/A
Hemoglobin	>10,000 mg/dL	Aqueous	10 % v/v	10 mg/ mL, zero spike: 0.9% NaCl
Heparin	66,000 U/L	Aqueous	5% v/v	3300 U/L
Human serum Albumin (HSA, total protein)	powder	Aqueous	10 % v/v	60 mg/mL, in serum
Ibuprofen (Motrin)	438 mg/dL	Ethanol	5% v/v	219 µg/ml
Levofloxacin	72 mg/dL	HCl	5% v/v	36 µg/ml
Loratidine	0.0174 mg/dL	Ethanol	5% v/v	87 ng/ml
Nicotine	0.1983 mg/dL	Ethanol	5% v/v	969 ng/ml
Oxymetazoline HCl	0.0012 µg/ml	Aqueous	5% v/v	0.0006 µg/ml
Phenylephrine	0.06 mg/dL	Aqueous	5% v/v	30 ng/ml
Prednisolone	0.198 mg/dL	Ethanol	5% v/v	1200 ng/ml
Rheumatoid Factor (RF)	25 kU	Aqueous	2% v/v	500 IU/mL
Triglycerides/Triolein	>15,000 mg/dL	Sucrose and NaCl	10 % v/v	15 mg/mL, in Ethanol

1. Concentrations based on recommended testing concentrations in CLSI EP7-A2 *Interference testing in clinical chemistry* and CLSI EP37 *supplemental tables for interference testing in clinical chemistry*)

Table 12. Panel of cross-reactants

Cross-reactant	Stock	Reconstitution volume	Reference matrix	Volume spiked	Final Concentration tested
Recombinant Human 4-1BB Ligand/TNFSF9 Protein	25 µg	250 µL	PBS	5% v/v	50 ng/mL
Recombinant Human CD40 Ligand/TNFSF5 (HEK293-expressed)	25 µg	250 µL	PBS	5% v/v	50 ng/mL
Recombinant Human Lymphotoxin alpha1/beta2 Protein	25 µg	100 µL	PBS	5% v/v	50 ng/mL
Recombinant Human Lymphotoxin alpha2/beta1 Protein	10 µg	100 µL	PBS	5% v/v	50 ng/mL
Recombinant Human TNF-alpha Protein	20 µg	200 µL	PBS	5% v/v	50 ng/mL
Recombinant Human	1**0** µg	100 µL	PBS	5% v/v	50 ng/mL

Cross-reactant	Stock	Reconstitution volume	Reference matrix	Volume spiked	Final Concentration tested
Lymphotoxin-alpha/TNF-beta Protein					
Recombinant Human Adiponectin/Acrp30 Protein	0.266 mg/mL	NA	PBS	5% v/v	50 ng/mL
Recombinant Human CXCL13/BLC/BCA-1 Protein	25 µg	250 µL	PBS	5% v/v	50 ng/mL
Recombinant Human CXCL5/ENA-78 Protein	25 µg	250 µL	PBS	5% v/v	50 ng/mL
Recombinant Human CXCL6/GCP-2 Protein	25 µg	250 µL	PBS	5% v/v	50 ng/mL
Recombinant Human CXCL1/GRO alpha Protein	10 µg	100 µL	PBS	5% v/v	50 ng/mL
Recombinant Human CXCL3/GRO gamma Protein	10 µg	100 µL	PBS	5% v/v	50 ng/mL
Recombinant Human IFN-gamma Protein	100 µg	500 µL	DDW	5% v/v	50 ng/mL
Recombinant Human IL-8/CXCL8 Protein	50 µg	500 µL	PBS	5% v/v	50 ng/mL
Recombinant Human CXCL11/I-TAC Protein	25 µg	250 µL	PBS	5% v/v	50 ng/mL
Recombinant Human CXCL7/NAP-2 Protein	10 µg	100 µL	PBS	5% v/v	50 ng/mL
Recombinant Human CXCL9/MIG Protein	10 µg	100 µL	PBS	5% v/v	50 ng/mL
Recombinant Human/Rhesus Macaque/Feline CXCL12/SDF-1a	10 µg	100 µL	PBS	5% v/v	50 ng/mL
Recombinant Human/Feline CXCL12/SDF-1 beta aa 22-93	10 µg	100 µL	PBS	5% v/v	50 ng/mL
Recombinant Human Pentraxin 2/SAP Protein	50 µg	200 µL	DDW	5% v/v	50 ng/mL
Recombinant Human Pentraxin 3/TSG-14 Protein	50 µg	100 µL	PBS	5% v/v	50 ng/mL

The data shows that the 95% confidence interval for the bias lies within +/-12.5 score units for all the interferants and cross-reactants in the indicated concentrations for both bacterial and viral clinical samples. Thus, it can be concluded that there is no interference or cross-reactivity caused by the above mentioned compounds at the indicated concentrations.

h. Human Anti-Mouse Antibody (HAMA) Interference

Interference of human anti-mouse antibody (HAMA) was conducted by a dose-response experimental design consisting of 5 serum levels with different amounts of HAMA: Low Pool as described in **Table 13** below. The Interference of HAMA was assessed by a comparison of TRAIL, CRP, and IP10 concentrations in the measured serum samples to their nominal concentration values.

Each sample was run on 2 MeMed Key Analyzers with a total of 8 repeats for each sample. The acceptance criterion was that TRAIL, CRP, and IP10 concentrations, when run on clinical serum sample mixed with HAMA positive sample, shall measure concentrations within +/- 10% compared to their nominal concentration. The interference of HAMA on analytes concentration was examined by two independent experiments using two different HAMA-positive samples.

Table 13. HAMA interference testing results

		TRAIL				CRP				IP10			
	Sample	Mean measured	Mean nominal	Recovery %	Pass /Fail	Mean measured	Mean nominal	Recovery %	Pass /Fail	Mean measured	Mean nominal	Recovery %	Pass /Fail
Sample 1	Level 1	132.3				109.5				1338.6			
	Level 2	103.8	107.0	97%	Pass	78.1	84.7	92%	Pass	991.8	1010.2	98%	Pass
	Level 3	81.7	84.0	97%	Pass	59.8	55.3	108%	Pass	681.7	756.8	90%	Pass
	Level 4	57.3	58.8	98%	Pass	32.1	30.4	106%	Pass	409.7	428.3	96%	Pass
	Level 5	35.8				1.0				175.0			
Sample 2	Level 1	138.1				109.7				1293.6			
	Level 2	115.5	115.7	100%	Pass	83.7	85.0	98%	Pass	967.0	977.3	99%	Pass
	Level 3	93.4	100.2	93%	Pass	60.4	55.6	109%	Pass	661.1	697.3	95%	Pass
	Level 4	79.9	77.8	103%	Pass	31.9	30.9	103%	Pass	355.5	381.1	93%	Pass
	Level 5	62.3				1.5				101.1			

For both HAMA samples the recovery of TRAIL, IP-10 and CRP are within the +/- 10%. The results show that the three assays are tolerant to high HAMA concentrations.

i. In-Use Stability

An in-use stability study was conducted to demonstrate the allowable handling conditions from blood draw to serum sample input into the cartridge. Stability was assessed for each MeMed BV test measurand (TRAIL/IP-10/CRP) and the MeMed BV test resulting score for four patient serum panel members representing two samples with 'low' scores of approximately 5 and two samples with 'high' scores of approximately 95 as described in **Table 14**.

The study was performed in one laboratory on four days, one day per panel member. Three MeMed Key analyzers and one lot of cartridges were used. Calibration was performed at the beginning of the study using one lot of calibration reagents.

Table 14. Patient specimens (panel members)

Panel member	Sample type	Score	Number of patients
A1, A2	Infectious serum specimen	High (score approximately 95)	2
B1, B2	Infectious serum specimen	Low (score approximately 5)	2

For each panel member, the incubations listed **Table 15** were performed with the package insert indicated SST tube before centrifugation and testing with the MeMed BV Test. There were three replicate runs for each time point performed in parallel on three MeMed Key analyzers.

Table 15. Incubation Time at Room Temperature

SST Tube #	Time at room temp before centrifugation (mins)
1	30 (shortest time for coagulation according to the IFU of BD SST Vacutainer)
2	60
3	90

SST Tube #	Time at room temp before centrifugation (mins)
4	120
5	150

The mean values, regression lines, confidence intervals and significance level of the difference of the slope from 0 were examined for each of the incubation times. The minimum acceptable incubation time was approximately 130 minutes and the incubation time before an observed failure was 120 minutes. Thus, the 120 minute time period at room temperature before centrifugation preparation for use in the MeMed BV test was established as 120 minutes.

j. Freeze-thaw stability

A study was conducted to validate stability between fresh and frozen specimens. This study examined the stability of the MeMed BV test result (score) using 40 paired fresh and frozen specimens as indicated in **Table 16**. The study was performed in one laboratory. Each sample was tested three times on the same MeMed Key analyzer using one lot of cartridges and one lot of calibrator reagents. Calibration was performed on the first day and repeated after two weeks.

Table 16. Sample Score Ranges and Specimen Numbers per Score

Score bin	Interpretation	# of specimen tested
90 ≤ s ≤100	High likelihood of bacterial infection	12
65 < s <90	Moderate likelihood of bacterial infection	6
35 ≤ s ≤ 65	Equivocal	4
10 < s <35	Moderate likelihood of viral infection	6
0 ≤ s ≤ 10	High likelihood of viral infection	12

The acceptance criteria for equivalency between fresh and frozen specimens for the score was that all scores within the 95% confidence interval are within a move of within the same or adjacent score categories and do not result in a move between non-adjacent scores.

Passing Bablok regression was used to compare the means of results from the fresh and the frozen specimens. A 95% confidence interval for the regression was calculated using bootstraping.

The confidence intervals do not intersect the lines representing the adjacent test scores and demonstrates the frozen and fresh samples demonstrated score results corresponding to the same or adjacent scores within the 95% confidence interval, thus demonstrating equivalency between fresh and frozen samples for the MeMed BV test.

k. Calibrator Traceability

The company conducted metrological traceability testing of the MeMed BV™ multi-standard calibrator material to ensure that analytical results used for patient care are accurate as well as consistent over time and when using different devices and systems.

All three analytes are traceable to a standard. The material was produced following ISO Guide 34:2009. The test was performed to assign the TRAIL, CRP and IP10 portion of the Master Lot-Calibrator a concentration that is based on their respective reference standard, in order to assign a value to the MeMed BV Calibrators. The test was performed with a calibration curve.

Lastly, testing was conducted to verify that the released calibrators are able to accurately quantify known samples on the MeMed Key analyzer using MeMed BV cartridges. The Lot was released only if all the parameters comply with the acceptance criteria.

l. Calibrator, External Controls, and Cartridges Stability Testing

MeMed BV calibrators (i.e., CAL1, CAL2, and CAL3), external controls (ECs), and cartridges were subjected to real time stability, in-use stability, transportation stability, shelf life validation, stability monitoring, and calibration interval testing (for ECs and calibrators only) in order to show that they maintain their respective performance characteristics over a defined time interval under indicated storage conditions. MeMed BV cartridges were also subjected to calibration interval testing.

The results of this testing demonstrated that the calibrators, ECs have a shelf life of 3.5 months and the cartridges have a shelf life of 12 months.

m. Reference Interval

Reference Interval study, conducted based on CLSI EP28-A3c Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory, demonstrated that:

The lower limit of the score (corresponding to the 2.5th percentile) is 0 [90% CI: 0-1].

The upper limit of the score (corresponding to the 97.5th percentile) is 46 [90% CI: 36-75].

Clinical Studies

a. Apollo Clinical Study

The diagnostic performance of the MeMed BV™ test was established by a prospective, multi-center, observational, blinded study. The primary objective of the Apollo clinical study was to establish the diagnostic performance of the MeMed BV™ test for differentiating bacterial from viral infection in patients with suspected acute bacterial or viral infection using expert adjudication comparator method (forced diagnosis for indeterminate cases) with the experts blinded to C-reactive protein (CRP) and procalcitonin (PCT) values. A secondary objective was to establish the diagnostic performance of MeMed BV™ for differentiating bacterial from viral infection using expert adjudication comparator method (indeterminate cases removed from analysis) with the experts given CRP and PCT values. This study included 1,016 infectious subjects (476 prospectively recruited adult and pediatric patients and 540 archived cases) from 11 medical centers (9 in the US and 2 in Israel). The study population comprised hospital admitted, Emergency Department

(ED) and urgent care center patients over the age of 90 days, with suspected acute bacterial or viral infection, and healthy subjects.

The bins used in the study correspond to **Table 16**.

Primary Objective Cohort (Forced Bacterial Viral Cohort Based on Adjudication Blinded to CRP and PCT)

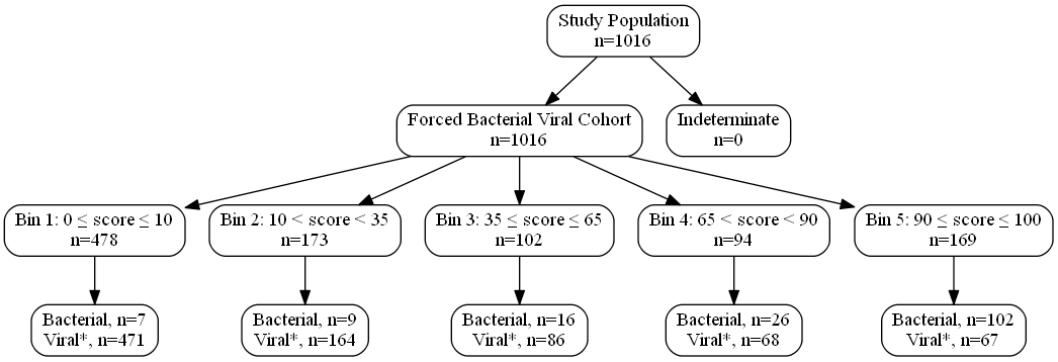

Figure 1: Primary Objective Cohort Disposition

*Viral includes viral and non-infectious comparator method outcomes

The performance of MeMed BV™ test in differentiating between bacterial and viral infection was assessed in the primary objective cohort using two pre-specified statistical tests:

- The Cochran–Armitage (CA) Test demonstrated a significant trend in increasing probability of bacterial infection with higher MeMed BV™ score ($p < 0.0001$).
- The 95% Confidence Interval (CI) of the Likelihood Ratio (LR) for some of the bins (Bins 1,2,4,5) excluded 1 (**Table 17**).

These statistical tests validate that the higher the score, the higher the likelihood of a bacterial infection and therefore the study successfully achieves its the primary objective**.**

Table 17: MeMed BV™ Performance in Primary Objective Cohort

Score Bin	N	N (Reference Bacterial)	N (Reference Viral and Non-Infectious)	% Patients	% Reference Bacterial Patients	% Reference Viral and Non-Infectious Patients	Likelihood Ratio (Confidence Interval)
90 ≤ score ≤100	169	102	67	16.6	60.4	39.6	8.1 (6.3-10.5)
65 < score <90	94	26	68	9.3	27.7	72.3	2.1 (1.3-3.1)
35 ≤ score ≤ 65	102	16	86	10.0	15.7	84.3	1.0 (0.6-1.7)
10 < score <35	173	9	164	17.0	5.2	94.8	0.3 (0.2-0.6)
0 ≤ score ≤10	478	7	471	47.1	1.5	98.5	0.1 (0.0-0.2)
Total	1016	160	856	100			

Secondary Objective Cohort (Suspected Bacterial Viral Cohort Based on Adjudication NOT Blinded to CRP and PCT)

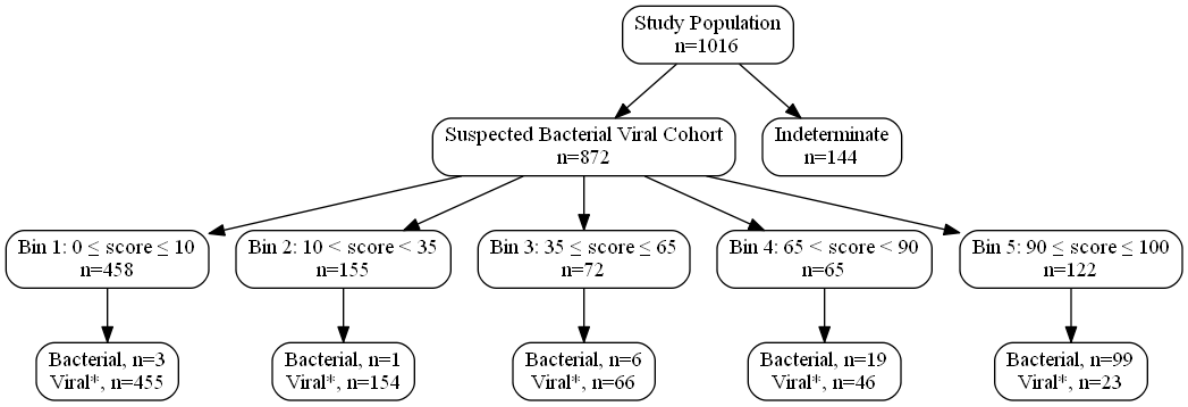

Figure 2: Secondary Objective Cohort Disposition

*Viral includes viral and non-infectious comparator method outcomes

The performance of MeMed BV™ test in differentiating between bacterial and viral infection was assessed in the secondary objective cohort using two statistical tests:

- The Cochran–Armitage (CA) Test demonstrated a significant trend in increasing probability of bacterial infection with higher MeMed BV™ score ($p < 0.0001$).
- The 95% Confidence Interval (CI) of the Likelihood Ratio (LR) for some of the bins (Bins 1,2,4,5) excluded 1 (**Table 18**).

These statistical tests validate that the higher the score, the higher the likelihood of a bacterial infection and therefore the study successfully achieves its secondary objective.

Table 18: MeMed BV™ Performance in Secondary Objective Cohort

Score Bin	N	N (Reference Bacterial)	N (Reference Viral and Non-Infectious)	% Patients	% Reference Bacterial Patients	% Reference Viral and Non-Infectious Patients	Likelihood Ratio (Confidence Interval)
90 ≤ score ≤100	122	99	23	14.0	81.2	18.9	25.0 (16.6-37.8)
65 < score <90	65	19	46	7.5	29.2	70.8	2.4 (1.5-4.0)
35 ≤ score ≤ 65	72	6	66	8.3	8.3	91.7	0.5 (0.2-1.2)
10 < score <35	155	1	154	17.8	0.7	99.4	0.0 (0.0-0.3)
0 ≤ score ≤10	458	3	455	52.5	0.7	99.3	0.0 (0.0-0.1)
Total	872	128	744	100			

Table 19 summarizes the results of a bin analysis for the prospectively recruited patients (primary objective), and **Table 20** summarizes the results of a bin analysis for the archived cases (primary objective).

Table 19: Diagnostic performance of MeMed BV™ for prospectively recruited patients (primary objective)

Score Bin	n	nBacterial	nViral	%Patients	%Bacterial Patients	%Viral Patients	Likelihood Ratio
90 ≤ score ≤100	42	27	15	8.8	64.3	35.7	12.25 (6.9-21.7)
65 < score <90	39	13	26	8.2	33.3	66.7	3.40 (1.8-6.3)
35 ≤ score ≤ 65	46	10	36	9.7	21.7	78.3	1.89 (1.0-3.6)
10 < score <35	77	7	70	16.2	9.1	90.9	0.68 (0.3-1.4)
0 ≤ score ≤10	272	4	268	57.1	1.5	98.5	0.10 (0.0-0.3)
Total	476	61	415	100			

Table 20: Diagnostic performance of MeMed BV™ for archived cases (primary objective)

Score Bin	n	nBacterial	nViral	%Patients	%Bacterial Patients	%Viral Patients	Likelihood Ratio
90 ≤ score ≤100	127	75	52	23.5	59.1	40.9	6.42 (4.9-8.5)
65 < score <90	55	13	42	10.2	23.6	76.4	1.38 (0.8-2.5)
35 ≤ score ≤ 65	56	6	50	10.4	10.7	89.3	0.53 (0.2-1.2)
10 < score <35	96	2	94	17.8	2.1	97.9	0.09 (0.0-0.4)
0 ≤ score ≤10	206	3	203	38.2	1.5	98.5	0.07 (0.0-0.2)
Total	540	99	441	100			

Subgroup Analyses

For both the primary and secondary objective cohort, the MeMed BV™ score increased significantly with the likelihood of bacterial infection irrespective of sex, age, ethnicity, race, pre-enrollment antibiotics, time from symptom onset, and comorbidities (hypertension, ischemic heart disease, hyperlipidemia, diabetes, and COPD adults). As expected, there was a difference in bacterial prevalence in children versus adults (e.g., in the primary objective cohort 10.6% versus 19.5%, respectively). Nevertheless, both statistical tests of performance were passed for all ages.

Based on the clinical performance as documented in the clinical study, the MeMed BV™ test has a safety and effectiveness profile that is similar to the predicate device.

Conclusions

The MeMed BV™ is as safe and effective as the VIDAS B.R.A.H.M.S. PCT (PCT) (K162827). The MeMed BV™ and the predicate test have the same general intended use and similar indications for use, technological characteristics and principles of operation.

In addition, the minor technological differences between the MeMed BV™ test and its predicate devices raise no new issues of safety or effectiveness. Performance data demonstrate that the MeMed BV™ is as safe and effective as the VIDAS B.R.A.H.M.S. PCT (PCT). Thus, the MeMed BV™ is substantially equivalent.

Table 21. MeMed Diagnostics, Ltd.'s MeMed BV test Substantial Equivalence Chart

	MeMed BV test	VIDAS® B·R·A·H·M·S PCT™ Test (K162827)
Intended Use / Indications for Use	The MeMed BV™ test is an automated semi-quantitative immunoassay that measures three non-microbial (host) proteins (TRAIL, IP-10, and CRP) in adult and pediatric serum samples and is intended for use in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection. MeMed BV™ is indicated for use in patients presenting to the emergency department or urgent care center and with samples collected at hospital admission from patients with suspected acute bacterial or viral infection, who have had symptoms for less than seven days. The MeMed BV™ test generates a numeric score that falls within discrete interpretation bins based on the increasing likelihood of bacterial infection.	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. Used in conjunction with other laboratory findings and clinical assessments, VIDAS B•R•A•H•M•S PCT is intended for use as follows: • to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock, • to 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, using a change in PCT level over time, • to aid in 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, • to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.
User Population	Health Care Providers requesting samples to be tested by clinical laboratory technicians	Health Care Providers requesting samples to be tested by clinical laboratory technicians
Specimen	Human serum	Human serum or plasma (lithium heparinate)
Assay Principle	Sandwich immunoassay technology	Sandwich immunoassay technology
Analytes of Interest	TRAIL, IP-10, and CRP	Procalcitonin (PCT)
Assay Technique	Chemiluminescent immunoassay (CLIA)	ELFA (Enzyme-Linked Fluorescent Assay)
Detection Method	Automated chemiluminescence-based analyte measurement using MeMed Key Instrument	Automated fluorescence-based analyte measurement using VIDAS instrument
Assessment Process	Software algorithm-based	Software algorithm-based

	MeMed BV test	VIDAS® B·R·A·H·M·S PCT™ Test (K162827)
Test Result Reporting	Numerical values with risk bins	Numerical values with risk bins
Time to Result	Approximately 15 minutes	Approximately 20 minutes
Calibration Frequency	Every two weeks	Every 28 days
Volume for Sample	100 µL	200 µL