510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT

I Background Information:

A 510(k) Number

K210254

B Applicant

MeMed Diagnostics Ltd.

C Proprietary and Established Names

MeMed BV

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QPS	Class II	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	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for the MeMed BV device.

B Measurand:

Three host immune protein biomarkers: TRAIL, IP-10, and CRP.

C Type of Test:

Chemiluminescent immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) 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. The 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.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

For prescription use only.

D Special Instrument Requirements:

MeMed Key Instrument

IV Device/System Characteristics:

A 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.

B Principle of Operation:

The test system is composed of the analyzer (MeMed Key) and the cartridge, and their respective sub-components. The product is designed to allow straightforward sample-to-answer testing, with a test run time of approximately 15 minutes.

The patient's serum specimen is pipetted by the user into the designated cartridge area. The users are instructed to fill 100 µl of sample. Each single-use cartridge is provided in a package that contains all necessary components for conducting a single patient test. This consists of the cartridge itself, all disposables (pipette tips), reagents and a waste collection well. The cartridge assembly contains both the reagents for the different assays and the pipette tips. The cartridge is

a multi-cavity plastic container that is sealed off with foil and covered with a label on the foil that indicates the sample type, the test name, indication to the user where to input the sample, required sample volume, lot number, cartridge expiry date and a barcode with test data and parameters that are intended to be read by the analyzer.

The cartridge contains the several reagents in separate cavities, which are required to perform the test. Upon insertion of the cartridge, the analyzer conducts three immunoassays on a single serum sample of 100 µL. The cartridge also securely stores all waste materials collected during the test.

The user inserts the cartridge with sample into the analyzer and is guided by the carriage caddy. The analyzer auto-reads the cartridge's barcode and verifies that the requested test matches the cartridge type, cartridge expiration date, and that the calibration curve matches the cartridge lot number. The analyzer notifies the user when specimen processing is initiated and when the user should expect the test result.

After the cartridge has been inserted, the carriage caddy system locks and guides the cartridge during the insertion phase. Once loaded, the cartridge holder is driven by the robot to the left, in position for processing.

The liquids are handled through the pipettor, which operates through measurement of displaced air volumes by means of a flow sensor, integrated directly in the pipetting head that is connected to a high-speed solenoid valve. The flow sensor is based on a differential pressure measurement across flow restriction. The cartridge is then heated through the heater block. A software-driven Proportional Integral Derivative (PID) control system is used to set and regulate the temperature of the heater block, using the center thermistor for feedback.

Once the sample has been diluted and mixed with magnetic particles, it is processed by the bead immobilizer magnet, which generates a high magnetic field strength, and allows both the reduction of immobilization time and a high percentage of bead retention per immobilization to be achieved. The sample is then washed and the chemiluminescence step takes place.

The chemiluminescence of the assay is measured by a Photo Multiplier Tube (PMT) Module, a highly sensitive light detection device. The selected PMT Module has a spectral range which matches the expected wavelength generated by the chemistry luminescence. When a PMT reading is required, the software then turns the PMT Module on and a reading is taken. Once readings have been completed, the software automatically turns the PMT Module off.

Each RLU measurement for each of the analytes is processed and translated to a concentration measurement using a calibration curve that is generated using calibration materials provided by MeMed. When a clinical serum sample is run, the resulting concentrations are also processed to apply a clinical correction factor, which is pre-determined for each of the analytes. This clinical correction factor exists primarily because of matrix-effects (in the serum) which may impact the generated signal compared to the calibration which is run on recombinant proteins. Final concentrations for each analyte are then processed to generate a Score result which places the specimen into one of five distinct bins, with higher score values corresponding to increasing likelihood of a bacterial infection.

The MeMed BV™ test result is a score between 0 and 100 derived from computational integration of the measurements of the three proteins TRAIL, IP-10, and CRP, where low scores are indicative of viral infection and high score of bacterial infection.

- 0 ≤ score ≤10: High likelihood of viral infection (or other non-bacterial etiology)
- 10 < score <35: Moderate likelihood of viral infection (or other non-bacterial etiology)
- 35 ≤ score ≤65: Equivocal
- 65 < score <90: Moderate likelihood of bacterial infection (or co-infection)
- 90 ≤ score ≤100: High likelihood of bacterial infection (or co-infection)

C Instrument Description Information:

1. Instrument Name:

   MeMed Key

2. Specimen Identification:

   The cartridge is a multi-cavity plastic container that is sealed off with foil and covered with a label on the foil that indicates the sample type, the test name, indication to the user where to input the sample, required sample volume, lot number, cartridge expiry date and a barcode with test data and parameters that are intended to be read by the analyzer.

3. Specimen Sampling and Handling:

   The patient's serum specimen is pipetted by the user into the designated cartridge area. The users are instructed to fill 100µl of sample. Each single-use cartridge is provided in a package that contains all necessary components for conducting a single patient test.

4. Calibration:

   A calibration is unique to a device and a cartridge lot. The calibration process assures that the unique characteristics of each device and the unique state of each cartridge lot – are accounted for in the calibration and that the concentration results are consistent and accurate. The calibration is valid only for a limited amount of time after the calibration takes place because the cartridge itself is decaying, producing different RLU measurements after a certain period of time (currently the calibration is valid for a period of 2 weeks). Every two weeks, or whenever a new lot needs to be used – the calibration process needs to be repeated. This is also monitored by the device which prevents the user from running on a lot which was never calibrated or a lot which has an expired calibration by displaying an error message.

   The calibration is a process used to generate the calibration curve. The calibration curve translates RLU measurements to concentration of each analyte. A calibration is unique to a device and a cartridge lot. Each calibrator is a solution of the 3 analytes introduced as recombinant proteins. The calibrators are in effect a synthetic sample which can be measured by the device using the normal cartridge.

5. Quality Control:

External controls are available through MeMed Diagnostics. The control set includes two control vials containing purified TRAIL, IP-10, and CRP antigens in a protein buffer. One vial corresponds to a bacterial MeMed BV test score (expected score 90-100) and one vial corresponds to a viral MeMed BV test score (expected score 0-10). The software evaluates each control and notifies the user whether the evaluation is completed successfully.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Vidas B.r.a.h.m.s. Pct (pct)

B Predicate 510(k) Number(s):
K162827

C Comparison with Predicate(s):

Device & Predicate Device(s):	K210254	K162827
Device Trade Name	MeMed BV	VIDAS B·R·A·H·M·S PCT
General Device Characteristic Similarities		
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. The MeMed BV is indicated for use in patients presenting to the emergency department or urgent care center and with	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:

	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.	• 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
Assay Principle	Same	Sandwich immunoassay technology
Assay Type	Same	Automated
Test Result Reporting	Same	Numerical values with risk bins
General Device Characteristic Differences		
Specimen	Human serum	Human serum or plasma
Measurand(s)	TRAIL, IP-10, and CRP	Procalcitonin (PCT)
Detection Method	Chemiluminescence-based analyte measurement using MeMed Key instrument	Fluorescence-based analyte measurement using VIDAS instrument
Time to result	Approximately 15 minutes	Approximately 20 minutes
Calibration frequency	Every two weeks	Every 28 days
Sample volume	100 µL	200 µL

VI Standards/Guidance Documents Referenced:

CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures

CLSI EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline

CLSI EP06-A Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

62304 IEC Medical Device Software - Software life cycle processes 1.1

CLSI EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

CLSI EP07 Interference testing in clinical chemistry
CLSI EP37 Supplemental tables for interference testing in clinical chemistry

CLSI EP28-A3c Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A multi-site reproducibility study was performed across three laboratories. The measurements were performed over five non-consecutive days. At each site, a single operator conducted the tests on two different analyzers using one cartridge lot, with three runs performed each day per panel member.

Calibration was performed on the first day on each analyzer; one calibrator lot was used. External controls (ECs) were also run daily using one lot of ECs.

The 'infectious' specimens were collected from non-U.S. individuals recruited to an infectious cohort as defined by the MeMed BV test intended use/indications for use under an appropriate clinical study protocol. The 'healthy' specimens were collected from non-U.S. individuals recruited to the healthy cohort recruited from a) patients' family members, b) medical staff not affiliated with the study, and c) elective pre-operative children and adults. The determination that the participant is healthy was adjudicated by an expert based on the patient data provided to them in an anonymized electronic case report form. The expert decided if the patient can be included in the healthy cohort in line with the healthy cohort eligibility criteria.

The samples were collected, centrifuged within 1 hr after blood withdrawal, aliquoted (120 µL) and frozen at -80°C. Prior initiation of the reproducibility study, the aliquots were sent on dry ice to the participating laboratories. Each aliquot was thawed 10-15 min on a roller prior to measurement on the MeMed Key instrument.

The following panel members were utilized for the reproducibility study:

Table 1. Reproducibility Study 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	Low (Score = 4)

Results from the reproducibility study are summarized in the table below including repeatability (between-run variation), intermediate precision, and reproducibility.

Table 2. Reproducibility Study Results

Panel Member	Measurand or Score	Mean	N	Repeatability		Intermediate Precision		Reproducibility	
				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	N/A[1]	1.3	N/A[1]	1.8	N/A[1]
B	Score	53.4	90	7.5	N/A[1]	7.7	N/A[1]	9.4	N/A[1]
C	Score	0.9	90	0.3	N/A[1]	0.3	N/A[1]	0.4	N/A[1]
D	Score	3.6	90	1.0	N/A[1]	1.2	N/A[1]	1.4	N/A[1]

[1]CV analysis was not considered for the logistic scale of the MeMed BV Score. The acceptance criterion for the score was set to be SD < 12.5 score units which reflects a small probability of scores falling into nonadjacent bins.

An additional study was performed to estimate lot-to-lot variance for each measurand and the test result for four panel members. The lot-to-lot study was performed on 3 days as follows: Operator 1 at Site 1 conducted three runs per day for each of the four panel members using two lots of cartridges on the same Analyzer. Two calibration lots were used, one for each cartridge lot. External controls were run daily using one lot of EC reagents. Results from the lot variability study are included in Table 3 below.

Table 3. Lot-to-Lot Variability Study Results

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
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	N/A[1]
B	Score	54.2	18	0.0	N/A[1]
C	Score	1.0	18	0.0	N/A[1]
D	Score	3.8	18	0.0	N/A[1]

[1]CV analysis was not considered for the logistic scale of the MeMed BV Score. The acceptance criterion for the score was set to be SD < 12.5 score units which reflects a small probability of scores falling into nonadjacent bins.

2. Linearity:

A study was performed to assess the linearity of measurement for each of the three measurands (TRAIL/IP-10/CRP) with acceptance criteria for bias due to non-linearity or less than 10% or, alternatively, 10 mg/L for CRP, 10 pg/mL for TRAIL, and 50 pg/mL for IP-10. Linearity is not applicable to the Test result (score), as it is calculated using a pre-defined weighted multinomial logistic regression model. The study was performed in a single laboratory with one analyzer, two lots of cartridges, and one lot of calibration and external control reagents. Eleven dilutions of individual analytes were prepared in protein rich buffer and measured four times. The range of concentrations tested spanned the applicable range for determination of the MeMed BV score and were 15-290 pg/mL for TRAIL, 96-1930 pg/mL for IP-10, and 1-289 µg/mL for CRP. Linearity for all MeMed BV measurands fell within the acceptance criteria.

3. Analytical Specificity/Interference:

Interference Study

An interference study was performed to evaluate the impact of select interferents and cross-reactants on the test score. Each interferent and cross-reactant was tested using two panel members that represent score bins 1 and 5 (a 'low' score, and 'high' score, respectively). Interference was assessed by estimating the bias for each specimen when compared to a sample without interferent. Each interferant was tested using eight replicates for each spiked and non-spiked (no interferent) specimen. Results from the interference study are included in the below table.

Table 4. Interference Study Results

Interferant	Test Level	High Score Bias	High Score Bias CI	Low Score Bias	Low Score Bias CI
Acetaminophen	0.156 mg/mL	0.1	-0.4-0.6	-0.1	-0.4-0.1
Amoxicillin	54 µg/mL	-0.1	-0.6-0.4	-0.1	-0.4-0.1
Ampicillin	75 µg/mL	0	-0.5-0.5	0	0-0
Aspirin	0.03 mg/mL	-0.4	-1.4-0.6	-0.5	-0.9-(-0.1)
Azithromycin	11.1 µg/mL	0	-0.5-0.5	0.1	-0.5-0.7
Caffeine	108 µg/mL	0.4	-0.9-1.7	0.3	-1-1.5
Cetirizine	4.35 µg/mL	0	-0.5-0.5	0.1	-0.1-0.4
Conjugated Bilirubin	0.4 mg/mL	0.1	-0.3-0.6	1.0	-2.2-4.2
Dextramethorphan	15.6 ng/mL	0	-0.5-0.5	0.4	0-0.7
Doxycycline	18 µg/mL	0.1	-0.4-0.6	0.1	-0.1-0.4
Ethanol	0.5% v/v	-0.1	-0.8-0.5	-0.4	-0.7-0
Hemoglobin	10% v/v	0.7	-1.1-0.4	-0.4	-2.3-3.6
Heparin	3300 U/L	-0.7	-1.3-(-0.2)	0.2	-0.6-0.1
Human Serum Albumin	60 mg/mL	-1.5	-2.7-(-0.3)	-0.3	-2.4-1.7
Ibuprofen	219 µg/mL	0.5	0-1	0.1	-0.1-0.4
Levoflaxacin	36 µg/mL	0	-1.4-1.4	0	-1.5-1.5
Loratidine	87 ng/mL	0	-0.5-0.5	0	-0.8-0.8
Nicotine	969 ng/mL	-0.2	-0.5-0.3	0.6	0-1.2
Oxymetazoline	0.0006 µg/mL	-0.1	-1.3-1.1	-0.3	-1.7-0.9
Phenylephrine	30 ng/mL	-0.9	-2.5-0.8	-0.1	-1.8-1.5
Prednisolone	1200 ng/mL	0.2	-0.2-0.7	-0.3	-0.8-0.3
Rheumatoid factor	500 IU/mL	0.4	-0.6-1.4	0.7	-1.1-2.6
Triglyceride	15 mg/mL	1.0	0.2-1.8	0.8	-1.2-3
Unconjugated Bilirubin	0.4 mg/mL	1.6	0-3.2	-3.6	-6.7-(-0.6)
4-1BB Ligand	50 ng/mL	-0.8	-1.9-0.4	0.1	-0.5-0.7
Adiponectin	50 ng/mL	0.1	-2.8-3	0.5	-0.2-1.2
CXCL1/GRO\alpha	50 ng/mL	-0.1	-1.3-1.1	0.1	-0.4-0.6
CXCL11/I-TAC	50 ng/mL	-0.6	-3-1.7	0.2	-0.6-1.1
CXCL12/SDF1a	50 ng/mL	0.5	-1.4-2.4	1.4	-2.2-5
CXCL13/BLC/BCA-1	50 ng/mL	-0.4	-1.7-1	-0.3	-0.6-0.1
CXCL3/GRO\gamma	50 ng/mL	0.5	-1.6-2.6	-0.1	-3.6-3.3

CXCL5/ENA-78	50 ng/mL	1.1	-0.5-2.7	0.3	-0.2-0.7
CXCL7/NAP-1	50 ng/mL	-1.2	-4.4-2.1	-1.1	-3.5-1.2
CXCL8/IL8	50 ng/mL	1.2	-0.9-3.4	-0.5	-3.5-2.5
CXCL9/MIG	50 ng/mL	-0.5	-2.5-1.5	-0.2	-3.2-2.7
CXCL6/GCP-2	50 ng/mL	1.6	0.1-3.1	0.4	-0.2-1
IFN gamma	50 ng/mL	-0.4	-2.9-2.2	0	-0.8-0.8
LT alpha1 beta2	50 ng/mL	1.0	-0.5-2.5	-0.4	-0.8-0.1
LTalpha2beta1	50 ng/mL	0	-1.1-1.1	0	-0.5-0.5
PTX2	50 ng/mL	-2.0	-5.2-1.2	0	-0.5-0.5
PTX3	50 ng/mL	0.6	-1.3-2.6	0.6	-0.1-1.3
SDF1b	50 ng/mL	-0.1	-2.2-2	0	-0.8-0.8
TNF alpha	50 ng/mL	0.5	-1.6-2.6	-0.1	-0.6-0.4
TNF beta	50 ng/mL	1.1	-0.1-2.3	-0.2	-0.5-0.3

These data demonstrate that the presence of commonly encountered interferants does not significantly alter the MeMed BV score. For all evaluated specimens, 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.

Interference by Human Anti-Mouse Antibody (HAMA) was also assessed by evaluating 3 contrived serum specimens that contained different amounts of HAMA. To generate these specimens a clinical serum sample (Level 1) was intermixed with a commercially available serum sample that contained high concentrations of HAMA (Level 5). Each individual specimen was run on two analyzers with a total of eight repeats for each sample. Acceptance criteria were that individual TRAIL, CRP, and IP-10 concentrations in the presence of HAMA should fall within 10% of the concentration without interferant. All samples successfully met the acceptance criteria demonstrating a lack of interference from HAMA.

Table 5. HAMA Interference Testing Results

		TRAIL		CRP		IP10		Score	
		Mean	**% Recovery**	**Mean**	**% Recovery**	**Mean**	**% Recovery**	**Mean**	**Nominal**
Sample 1	**Level 1**	132.3		109.5		1338.6		16	
	Level 2	103.8	97%	78.1	92%	991.8	98%	21	21
	Level 3	81.7	97%	59.8	108%	681.7	90%	34	29
	Level 4	57.3	98%	32.1	106%	409.7	96%	52	49
	Level 5	35.8		1.0		175.0		36	
Sample 2	**Level 1**	138.1		109.7		1293.6		14	
	Level 2	115.5	100%	83.7	98%	967.0	99%	17	17
	Level 3	93.4	93%	60.4	109%	661.1	95%	25	18
	Level 4	79.9	103%	31.9	103%	355.5	93%	28	28
	Level 5	62.3		1.5		101.1		9	

Cumulatively, these data establish that HAMA exhibits minimal interference in the detection of target analytes measured by the MeMed BV assay and does not significantly impact the MeMed BV Score.

4. Assay Reportable Range:

Not applicable.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Calibration

The calibration is a process used to generate the calibration curve and must be repeated every two weeks and/or when introducing a new test cartridge lot. The calibration curve translates RLU measurements to concentration of each analyte. A calibration is unique to a device and a cartridge lot. The calibrators are in effect synthetic samples which can be measured by the device using the normal cartridge. Each calibrator is a solution of the 3 analytes introduced as recombinant proteins. Each calibration set includes three vials that represent high, medium, and low values of the analyte ranges that impact the MeMed BV test score. Calibrators are provided by MeMed in vials which need to be stored in normal refrigerators (2-8°C). All three analytes are traceable to a standard. The TRAIL analyte is traced to international biological reference standard, NIBSC code: 04/166. The CRP analyte is traced to international standard, IFCC/BCR/CAP CRM 474. The IP-10 analyte is traced to an internal standard prepared by R&D Systems (Cat. #890836) due to the unavailability of international standards for IP-10.The material was produced following ISO Guide 34:2009.

The quality indicators (i.e., max/min slope, max/min intercept, min slope, and R^2) represent specifications for calibration curves created with released cartridges. These thresholds are established for each lot of cartridges during manufacturing (based on actual performance of the produced lot). The data is then encoded to the cartridge barcode, to be read by the analyzer when running a calibration. Failure to meet these thresholds (during run-time of a calibration) will fail the calibration. In case of a calibration failure the device will issue a failure message to the user and will prevent the failed cartridge-lot from running. The device will only run with cartridges from a lot which has a valid calibration. It is possible to calibrate more than one cartridge lot.

Controls

The MeMed BV External controls are intended for quality control testing in clinical laboratories. The control set includes two control vials containing purified TRAIL, IP-10, and CRP antigens in a protein buffer. One vial corresponds to a bacterial MeMed BV test score (expected score 90-100) and one vial corresponds to a viral MeMed BV test score (expected score 0-10). The software evaluates each control and notifies the user whether the evaluation is completed successfully.

Specimen Stability Study

A stability study was conducted to demonstrate appropriate handling conditions from blood draw to serum sample input to a MeMed BV cartridge. Four panel members were evaluated

as part of this study which was performed in a single laboratory over four days (one day per panel member). The stability study panel included two clinical samples that represent score bin 1 (i.e., a low score ~ 5) and two clinical samples that represent score bin 5 (i.e., a high score, ~95).

Each panel member was subjected to the following incubations at room temperature in the SST tube before centrifugation and running of the MeMed BV test. Three repeat runs were performed in parallel for each timepoint on three independent analyzers.

Table 6. Specimen Stability Study Room Temperature Storage Conditions

Sample #	Incubation Time (Min)
1	30
2	60
3	90
4	120
5	150

Table 7. Specimen Stability Study Results

Sample	Incubation Time (min)	Mean Concentration TRAIL	Mean Concentration CRP	Mean Concentration IP-10	Mean Score
High Score 1	30	65	162	211	92
	60	63	158	182	92
	90	61	167	197	94
	120	58	170	194	95
	150	62	164	176	94
High Score 2	30	33	119	220	97
	60	35	133	211	97
	90	38	130	226	96
	120	41	115	228	94
	150	39	126	246	95
Low Score 1	30	104	14	144	8
	60	103	13	174	8
	900	97	13	172	10
	120	92	12	166	12
	150	94	13	198	11
Low Score 2	30	156	87	2,170	5
	60	165	97	2,036	5
	900	164	86	2,025	4
	120	153	100	1,983	6
	150	157	101	2,100	6

Results from the stability study were analyzed via linear regression to identify whether slopes of best fit lines were statistically different from 0. If a slope was determined to have a statistically significant non-zero, slope, the earliest acceptable time point would be determined by the intersection of the 95% confidence interval bands with cutoff thresholds that correspond to a 20% increase or decrease in the value at 30 minutes, the shortest time for coagulation in the SST tubes instructions for use. Separate acceptance criteria were applied to the MeMed BV score that correspond to a maximal change of 12.5 score units. The TRAIL regression from the High Score 2 sample met these criteria with an acceptable storage limit of 120 minutes. These data cumulatively support a 120 minute storage claim before final processing and testing of serum specimens. No significant changes in MeMed Score were observed.

An additional stability study was performed to identify potential effects of storage of centrifuged and collected serum specimens on MeMed BV test scores. Four clinical samples representing two high score and two low score specimens were measured after storage at either room temperature or 4°C. No significant changes were observed and which supports the recommended storage claims in labeling.

Freeze-thaw Stability Study

An additional stability study was performed to establish equivalence between fresh and frozen specimens and support the use of archived frozen specimens in the clinical validation study. A total of 40 clinical specimens were evaluated that spanned the entire assay range as indicated in the table below.

Table 8. Freeze-thaw Stability Study Specimens

Bin Index	Score Bin	Interpretation	# of Specimens Evaluated
5	$90 \leq s \leq 100$	High likelihood of bacterial infection	12
4	$65 < s < 90$	Moderate likelihood of bacterial infection	6
3	$35 < s < 65$	Equivocal	4
2	$10 < s < 35$	Moderate likelihood of viral infection	6
1	$0 \leq s \leq 10$	High likelihood of viral infection	12

All collected serum aliquots were evaluated in triplicate on the MeMed BV test both fresh and after being stored frozen for the following time points: 24 hours, 1 month, 2 months, 3 months, 6 months, and 9 months. No significant changes in MeMed Score were observed after a single freeze thaw cycle over the duration of this study which successfully demonstrated stability of frozen specimens when tested with the MeMed BV assay.

Stability of MeMed BV Calibrators

Stability of calibrators for the MeMed BV Key instrument were evaluated in Real-Time, Transport, In-use, and open vial stability studies.

Real-time Stability Study

Real time stability testing was performed on three production lots when stored at 2-8°C and demonstrated stability of up to 3.5 months.

Transport Stability Study

A transport stability study was performed that evaluated the stability of one calibrator lot after exposure to several temperatures that simulate possible temperature deviations during shipment. Stability of the calibrators was demonstrated when exposed to room temperature for up to 48 hours or 30°C for up to 24 hours.

In-use Stability

An in-use stability study was conducted to evaluate the effect of calibrator exposure to ambient working conditions for a predefined period before running the MeMed BV test. Individual calibrators retained their activity for up to 4 hours at room temperature before running the BV test.

Open Vial Stability

Testing was conducted to evaluate the shelf-life of the calibrator vials after first being opened and used. Overall protein instability and decay was addressed in the real-time stability study. To demonstrate that opening vials did not affect calibrator homogeneity, precision of opened vials were compared to unopen vials after storage at the recommended conditions for various timepoints. No significant differences in calibrator precision were observed.

Stability of MeMed BV Cartridges

Shelf-life of the MeMed BV cartridge has been established in real-time, transport, and in-use stability studies.

Real-time Stability Study

Stability of MeMed BV cartridges was demonstrated at the recommended storage conditions (2-8°C) for 12 months from the manufacturing date.

Transport Stability

MeMed BV cartridges were exposed to temperature variations to simulate potential temperature deviations during shipment. Cartridges demonstrated stability after exposure to 25°C for up to 48 hours and 30°C for up to 24 hours.

In-use Stability

In-use stability was assessed for MeMed BV cartridges after removal from recommended storage conditions (2-8°C). The study demonstrated in-use stability of up to 5 minutes after removal from cold storage. MeMed BV test cartridges should be kept at 2-8°C until just before use.

6. Detection Limit:

Limit of Quantitation

For evaluated specimens with analyte levels below the limit of quantitation, the limit of quantitation value will be used to generate the MeMed BV score. Therefore a limit of detection and a limit of blank was not evaluated.

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 9 below. Each sample was tested three times on three non-consecutive days.

Table 9. LoQ Study Panel Members

Sample	TRAIL (pg/mL)	IP-10 (pg/mL)	CRP (mg/L)
1	12	80	0.8
2	13.5	90	0.9
3	15	100	1
4	16.5	110	1.1

The Total Error was calculated for each of the four concentration levels for three analytes as 2X the observed SD.

Table 10. LoQ Study Results

Cartridge Lot		Lot 1			Lot 2		
Sample	**Parameter**	**TRAIL (pg/mL)**	**IP-10 (pg/mL)**	**CRP (mg/L)**	**TRAIL (pg/mL)**	**IP-10 (pg/mL)**	**CRP (mg/L)**
1	**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%
	TE (%)	11%	15%	13%	16%	27%	16%
2	**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%
	TE (%)	16%	28%	14%	12%	27%	22%
3	**Mean**	17.3	106.2	1.1	16.9	93.6	1.1
	STD	2.5	5.4	0.03	1.6	2.8	0.1
	CV (%)	14%	5%	3%	10%	3%	13%
	TE (%)	29%	10%	7%	19%	6%	26%
4	**Mean**	18.1	111.1	1.2	18.1	103.3	1.2
	STD	1.1	4.4	0.1	1.6	15.7	0.1
	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 the following values TRAIL -15pg/mL, CRP-1 mg/mL, IP-10 – 100 pg/mL as is set in MeMed Key analyzer.

7. Assay Cut-Off:

   See clinical cut-off.

8. Accuracy (Instrument):

   Not applicable.

9. Carry-Over:

   A study was performed to evaluate the risk of carry-over between multiple cartridges evaluated on the MeMed Key instrument. Specifically, a low score ("L") and high score ("H") clinical specimen were evaluated according to the following sequences:

   1) H, H, H, H, H, L, H, L, H, L, H, L, H, L, H
   2) L, L, L, L, L, H, L, H, L, H, L, H, L, H, L.

   For both sequences evaluated, no significant difference was observed in assay score for either the high or low clinical specimens. These data support that no carry over occurs in the MeMed Key instrument with the MeMed BV assay cartridges.

10. Hook Effect:

Contrived samples containing high levels of each measurand were prepared by spiking protein rich buffer with recombinant proteins. For each concentration level, three runs were measured on one analyzer on the same day.

Table 11. Hook Effect Study Analyte Concentrations

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

Table 12. Hook Effect Study Results.

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

No significant loss of signal was observed for the evaluated specimens containing high analyte concentrations. Therefore, no Hook effect has been identified for the MeMed BV test.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Not applicable.

2. Matrix Comparison:

   Not applicable.

C Clinical Studies:

1. Clinical Sensitivity:

   The diagnostic performance of the MeMed BV test was established by a prospective, multi-center, observational, blinded study (Apollo, Clinicaltrials.gov identifier: NCT04690569) across 11 medical centers (9 in the US and 2 in Israel). Prospectively enrolled cases were further supplemented with archived cases randomly drawn from two previously completed prospective clinical studies conducted outside the U.S. (Observer, NCT03011515; and AutoPilot, NCT03052088).The primary analysis of the complete clinical study cohort

established the diagnostic performance of the MeMed BV test for differentiating bacterial from viral infection in patients with suspected acute bacterial or viral infection using forced expert adjudication as the comparator method (in which physicians were forced to make a bacterial, viral, or noninfectious diagnosis with categorization of patients as indeterminate not allowed). In this analysis, experts were blinded to both C-reactive protein (CRP) and procalcitonin (PCT) values. A secondary analysis was also performed using consensus expert adjudication as a comparator method (in which indeterminate cases were removed from analysis and with the experts given CRP and PCT values). Data from the secondary objective is also presented below and should be considered supplementary information. Patients classified as indeterminate span the complete range of MeMed BV score values (0-100).

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. The primary objective cohort (forced adjudication) comprised 1016 patients (476 prospectively recruited adult and pediatric patients and 540 archived cases). Enrolled patients ranged in age from 3 months to 98.3 years, with mean age 28.6 years and 49.9% female. The race and ethnicity representation in the U.S. patients of this cohort (Hispanic/Latino 15.6%, Asian 5.4%, Black or African American 22.0% and White American 62.9%) is comparable to that given in the 2019 U.S. Census (Hispanic/Latino 18.5%, Asian 5.9%, Black or African American 13.4% and White American 76.3%). Almost half of the cohort (46.0%) presented by the second day of symptom onset and one third (33.0%) were hospitalized. Prior to enrollment 3.9% received antibiotics. The most common clinical syndrome was respiratory tract infection (RTI; 76.3%).

The demographics of the forced adjudication study population are found in Table 13 below.

Table 13. Demographics of the Primary Objective Clinical Study Cohort (Forced Adjudication)

Demographic/Clinical Category		Study Population (N = 1016)	Forced Bacterial Adjudication (N = 160)	Forced Viral/Noninfectious Adjudication (N = 856)
Gender	Female	507 (49.9%)	73 (45.6%)	434 (50.7%)
	Male	509 (50.1%)	87 (54.4%)	422 (49.3%)
Age	3 months to ≤ 2 years	167 (16.4%)	12 (7.5%)	155 (18.1%)
	> 2 to ≤ 12 years	223 (21.9%)	30 (18.8%)	193 (22.5%)
	> 12 to ≤ 18 years	42 (4.1%)	4 (2.5%)	38 (4.4%)
	> 18 years	584 (57.5%)	114 (71.3%)	470 (54.9%)
Ethnicity	Hispanic/Latino	59 (5.8%)	4 (2.5%)	55 (6.4%)
Race[1]	Native American	0 (0.0%, 0.0%)	0 (0.0%, 0.0%)	0 (0.0%, 0.0%)
	Asian	20 (2.0%, 5.4%)	1 (0.6%, 2.4%)	10 (2.2%, 5.7%)
	Black or African American	82 (8.1%, 22.0%)	10 (6.3%, 24.4$)	72 (8.4%, 21.8%)
	Native Hawaiian	0 (0.0%, 0.0%)	0 (0.0%, 0.0%)	0 (0.0%, 0.0%)

	White	234 (23.0%, 62.9%)	25 (15.6%, 61.0%)	209 (24.4%, 63.1%)
	Other	36 (3.5%, 9.7%)	5 (3.1%, 12.2%)	31 (3.6%, 9.4%)
	Non-US	644 (63.4%)	119 (74.4%)	525 (61.3%)
Medical History	Maximal Temperature °C, (Mean [SD])	38.6 (1.03)	38.9 (0.86)	38.6 (1.05)
	Received antibiotics prior to enrollment	40 (3.9%)	6 (3.8%)	34 (4.0%)
	Days from symptom onset (median [IQR])	3.0 (2.00)	3.0 (2.00)	3.0 (2.00)
	≤ 2 days from symptom onsent	467 (46.0%)	72 (45.0%)	395 (46.1%)
	Hospital admission	335 (33.0%)	94 (58.8%)	241 (28.2%)
	Days hospitalized (median [IQR])	4.0 (3.0)	5.0 (3.0)	4.0 (3.0)
Comorbidity	Diabetes	94 (9.3%)	33 (20.6%)	61 (7.1%)
	Hypertension	164 (16.1%)	46 (28.8%)	118 (13.8%)
	Ischemic heart disease	46 (4.5%)	17 (10.6%)	29 (3.4%)
	COPD	34 (3.3%)	15 (9.4%)	19 (2.2%)
	Hyperlipidemia	115 (11.3%)	39 (24.4%)	76 (8.9%)
Clinical Syndrome[2]	CNS infection	1 (0.1%)	1 (0.6%)	0 (0.0%)
	Fever without source	6 (0.6%)	1 (0.6%)	5 (0.6%)
	LRTI	292 (28.7%)	82 (51.3%)	210 (24.5%)
	URTI	505 (49.7%)	44 (27.5%)	461 (53.9%)
	UTI	18 (1.8%)	14 (8.8%)	4 (0.5%)
	Other	219 (21.6%)	20 (12.5%)	199 (23.2%)

[1]Each patient can only be included in one category. Patients labeled as having more than one race are included in the other category. Percentages are relative to all patients and all US patients, respectively.
[2]Patients can be included in more than one clinical syndrome category except for "Other". The Other category includes abdominal pain, appendicitis, asthma, cellulitis, febrile convulsions, fever, gastroenteritis, headache, and unspecified viral infection.

The cohort for the secondary study objective (in which indeterminate cases were removed from the analysis) comprised 872 patients ranging in age from 3 months to 98.3 years, with mean age 28.2 years and 49.9% female. The race and ethnicity representation in the US patients of this cohort (Hispanic/Latino 15.5%, Asian 5.6%, Black or African American 22.6% and White American 62.8%) is comparable to that given in the 2019 US Census (Hispanic/Latino 18.5%, Asian 5.9%, Black or African American 13.4% and White American 76.3%). Almost half of the cohort (45.9%) presented by the second day of symptom onset and one third (32.5%) were hospitalized. Prior to enrollment 3.6% received antibiotics. The most common clinical syndrome was URTI (50.9%) followed by LRTI (26.9%).

The demographics of the consensus adjudication study population are found in Table 14 below.

Table 14. Demographics of the Secondary Objective Clinical Study Cohort (Consensus Adjudication)

Demographic/Clinical Category		Study Population (N = 872)	Consensus Bacterial Adjudication (N = 128)	Consensus Viral/Noninfectious Adjudication (N = 744)
Gender	Female	435 (49.9%)	61 (47.7%)	374 (50.3%)
	Male	437 (50.1%)	67 (52.3%)	370 (49.7%)
Age	3 months to ≤ 2 years	147 (16.9%)	7 (5.5%)	140 (18.8%)
	> 2 to ≤ 12 years	195 (22.4%)	20 (15.6%)	175 (23.5%)
	> 12 to ≤ 18 years	37 (4.2%)	2 (1.6%)	35 (4.7%)
	> 18 years	493 (56.5%)	99 (77.3%)	394 (53.0%)
Ethnicity	Hispanic/Latino	51 (5.8%)	4 (3.1%)	47 (6.3%)
Race[1]	Native American	0 (0.0%, 0.0%)	0 (0.0%, 0.0%)	0 (0.0%, 0.0%)
	Asian	18 (2.1%, 5.6%)	0 (0.0%, 0.0%)	18 (2.4%, 6.1%)
	Black or African American	73 (8.4%, 22.6%)	6 (4.7%, 22.2%)	67 (9.0%, 22.6%)
	Native Hawaiian	0 (0.0%, 0.0%)	0 (0.0%, 0.0%)	0 (0.0%, 0.0%)
	White	203 (23.3%, 62.8%)	18 (14.1%, 66.7%)	185 (24.9%, 62.5%)
	Other	29 (3.3%, 9.0%)	3 (2.3%, 11.1%)	26 (3.5%, 8.8%)
	Non-US	549 (63.0%)	101 (78.9%)	448 (60.2%)
Medical History	Maximal Temperature °C, (Mean [SD])	38.6 (1.03)	38.9 (0.84)	38.6 (1.05)
	Received antibiotics prior to enrollment	31 (3.6%)	4 (3.1%)	27 (3.6%)
	Days from symptom onset (median [IQR])	3.0 (2.00)	3.0 (2.00)	3.0 (2.00)
	≤ 2 days from symptom onsent	400 (45.9%)	53 (41.4%)	347 (46.6%)
	Hospital admission	283 (32.5%)	85 (66.4%)	198 (26.6%)
	Days hospitalized (median [IQR])	4.0 (3.00)	6.0 (4.00)	4.0 (2.00)
Comorbidity	Diabetes	82 (9.4%)	31 (24.2%)	51 (6.9%)
	Hypertension	140 (16.1%)	40 (31.3%)	100 (13.4%)
	Ischemic heart disease	35 (4.0%)	15 (11.7%)	11 (1.5%)
	COPD	26 (3.0%)	15 (11.7%)	11 (1.5%)
	Hyperlipidemia	99 (11.4%)	39 (30.5%)	60 (8.1%)

Clinical Syndrome[2]	CNS infection	1 (0.1%)	1 (0.8%)	0 (0.0%)
	Fever without source	4 (0.5%)	0 (0.0%)	4 (0.5%)
	LRTI	235 (26.9%)	73 (57.0%)	162 (21.8%)
	URTI	505 (49.7%)	44 (27.5%)	461 (53.9%)
	UTI	18 (1.8%)	14 (8.8%)	4 (0.5%)
	Other	219 (21.6%)	20 (12.5%)	199 (23.2%)

[1]Each patient can only be included in one category. Patients labeled as having more than one race are included in the other category. Percentages are relative to all patients and all US patients, respectively.
[2]Patients can be included in more than one clinical syndrome category except for "Other".

The Other category includes abdominal pain, appendicitis, asthma, cellulitis, febrile convulsions, fever, gastroenteritis, headache, and unspecified viral infection.

The distribution of scores among different demographic groups for both the U.S. primary cohort (forced adjudication) and the U.S. secondary cohort (consensus adjudication) are presented in Tables 15 and 16 below.

Table 15. Forced Physician Diagnosis Score Distribution Among Demographic Groups

Race	N	MeMed BV Score Bin									
		0 ≤ score ≤ 10		10 < score < 35		35 ≤ score ≤ 65		65 < score < 90		90 ≤ score ≤ 100	
		Bacterial	Viral/ NI[1]	Bacterial	Viral/ NI[1]	Bacterial	Viral/ NI[1]	Bacterial	Viral/ NI[1]	Bacterial	Viral/ NI[1]
Asian	20	0	12	0	2	1	3	0	0	0	2
Black	82	0	51	1	10	1	6	3	3	5	2
White	234	2	128	5	40	4	19	3	18	11	4
Hispanic or Latino	58	0	36	0	7	1	5	0	4	3	2

[1]NI, non-infectious

Table 16. Consensus Physician Diagnosis Score Distribution Among Demographic Groups

Race	N	MeMed BV Score Bin									
		0 ≤ score ≤ 10		10 < score < 35		35 ≤ score ≤ 65		65 < score < 90		90 ≤ score ≤ 100	
		Bacterial	Viral/ NI[1]	Bacterial	Viral/ NI[1]	Bacterial	Viral/ NI[1]	Bacterial	Viral/ NI[1]	Bacterial	Viral/ NI[1]
Asian	18	0	12	0	2	0	3	0	0	0	1
Black	73	0	49	0	9	0	5	3	2	3	2
White	203	2	122	1	37	1	13	3	13	11	0
Hispanic or Latino	51	0	35	0	6	1	3	0	3	3	0

[1]NI, non-infectious

The clinical study results show a relationship between the MeMed BV Score and the increasing probability of bacterial infection across each MeMed Score Bins. The Likelihood Ratios (LR) in Tables 17-18 (below) were calculated using the standard definition where LR equals the probability that an individual with disease has the test result divided by the probability that an individual without disease has the test result. This formula was applied to each MeMed Score Bin separately. These predictive values depend on the likelihood ratios and the prevalence of disease. Laboratories and other users should establish their own reference intervals for their patient populations using the MeMed BV test to reflect potential sources of variability, such as patient gender, race, age, and preparation techniques. Results from prospectively collected samples are included in Table 17 and results from testing of frozen archived specimens are included in Table 18.

Table 17. Likelihood Ratios for Prospective Clinical Study Population Using the Forced Diagnosis (N = 476)

MeMed BV Score Bin	N	Forced Bacterial Diagnosis	Forced Viral/ Noninfectious Diagnosis	% Total Patients	% Patients Bacterial	% Patients Viral/ Noninfectious	LR (95% CI)
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	0.1 (0.0-0.3)
Total	476	61	415	100			

Table 18. Likelihood Ratios for Archived Specimens Using the Forced Diagnosis (N = 540)

MeMed BV Score Bin	N	Forced Bacterial Diagnosis	Forced Viral/ Noninfectious Diagnosis	% Total Patients	% Patients Bacterial	% Patients Viral/ Noninfectious	LR (95% CI)
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 (0.0-0.2)
0 ≤ score ≤ 10	206	3	203	38.2	1.5	98.5	0.07 (0.0-0.2)
Total	540	99	441	100			

The Cochran Armitage test demonstrated a significant trend between the MeMed BV Score and the increasing likelihood of bacterial infection across the MeMed BV Score Bins ($p < 0.0001$). Across both study cohorts, a high percentage of patients are found in the outer bins (bin 1[$0 \leq$ score ≤ 10] and bin 5 [$90 \leq$ score ≤ 100]), representing a very high likelihood of viral or bacterial infection, respectively.

Table 19. Likelihood Ratios for Prospective Clinical Study Population Using the Consensus Diagnosis (N = 416)

MeMed BV Score Bin	N	Forced Bacterial Diagnosis	Forced Viral/ Noninfectious Diagnosis	% Total Patients	% Patients Bacterial	% Patients Viral/ Noninfectious	LR (95% CI)
$90 \leq$ score ≤ 100	30	24	6	7.2	80.0	20.0	33.8 (14.6-78.2)
$65 <$ score < 90	31	12	19	7.5	38.7	61.3	5.3 (2.8-10.2)
$35 \leq$ score ≤ 65	30	4	26	7.2	13.3	86.7	1.3 (0.5-3.6)
$10 <$ score < 35	66	1	65	15.9	1.5	98.5	0.13 (0.0-0.9)
$0 \leq$ score ≤ 10	259	3	256	62.3	1.2	98.8	0.1 (0.0-0.3)
Total	416	44	372	100			

Table 20. Likelihood Ratios for Archived Clinical Study Population Using the Consensus Diagnosis (N = 456)

MeMed BV Score Bin	N	Forced Bacterial Diagnosis	Forced Viral/ Noninfectious Diagnosis	% Total Patients	% Patients Bacterial	% Patients Viral/ Noninfectious	LR (95% CI)
$90 \leq$ score ≤ 100	92	75	17	20.2	81.5	18.5	19.5 (12.2-31.3)
$65 <$ score < 90	34	7	27	7.5	20.6	79.4	1.2 (0.5-2.5)
$35 \leq$ score ≤ 65	42	2	40	9.2	4.8	95.2	0.2 (0.1-0.9)
$10 <$ score < 35	89	0	89	19.5	0.0	100.0	0.0
$0 \leq$ score ≤ 10	199	0	199	43.6	0.0	100.0	0.0
Total	456	84	372	100			

The Cochran Armitage test demonstrated a significant trend between the MeMed BV Score and the increasing likelihood of bacterial infection across the MeMed BV Score Bins ($p < 0.0001$). Once again, across both study cohorts, a large percentage of patients are found in the outer bins (bin 1[$0 \leq$ score ≤ 10] and bin 5 [$90 \leq$ score ≤ 100], representing a very high likelihood of viral or bacterial infection, respectively.

To further demonstrate whether the MeMed BV test will provide clinically significant results in the intended use population, the sponsor also considered analysis of the area under the receiver operating characteristic curve for the MeMed BV test and also for comparison biomarkers (i.e., PCT, CRP, WBC, and absolute neutrophil count [ANC]). For the primary objective cohort, where the adjudicators were blinded to CRP, PCT, and MeMed BV, the MeMed BV (AUC 0.9; 95% CI:0.87-0.94) test outperformed WBC (AUC 0.77; 95% CI: 0.73-0.82), ANC (AUC 0.80; 95% CI:0.76-0.85), CRP (AUC 0.86; 95% CI:0.82-0.90.), and PCT (AUC 0.7; 95% CI:0.65-0.74) across the patients with all biomarker measurements (N=1011).

MeMed BV Performance Across Viral Detections

57.6% (N = 585) and 60.7% (N = 529) of the clinical study patients had at least one viral detection by Polymerase Chain Reaction or rapid antigen testing in the primary (Figure 1) and secondary (Figure 2) objective cohorts, respectively.

Every dot is a patient; blue indicates RV (viral physician diagnosis) and RNI (non-Infectious physician diagnosis) patients and red indicates RB (bacterial physician diagnosis) patients. The x-axis is each viral detection and the y-axis is the MeMed BV score. The black line denotes the group median and the purple circle corresponds to group mean. The box indicates patients with values between the 25 and 75 percentiles.

Figure 1. MeMed BV Score Values in Patients with Viral Detections (Primary Cohort)

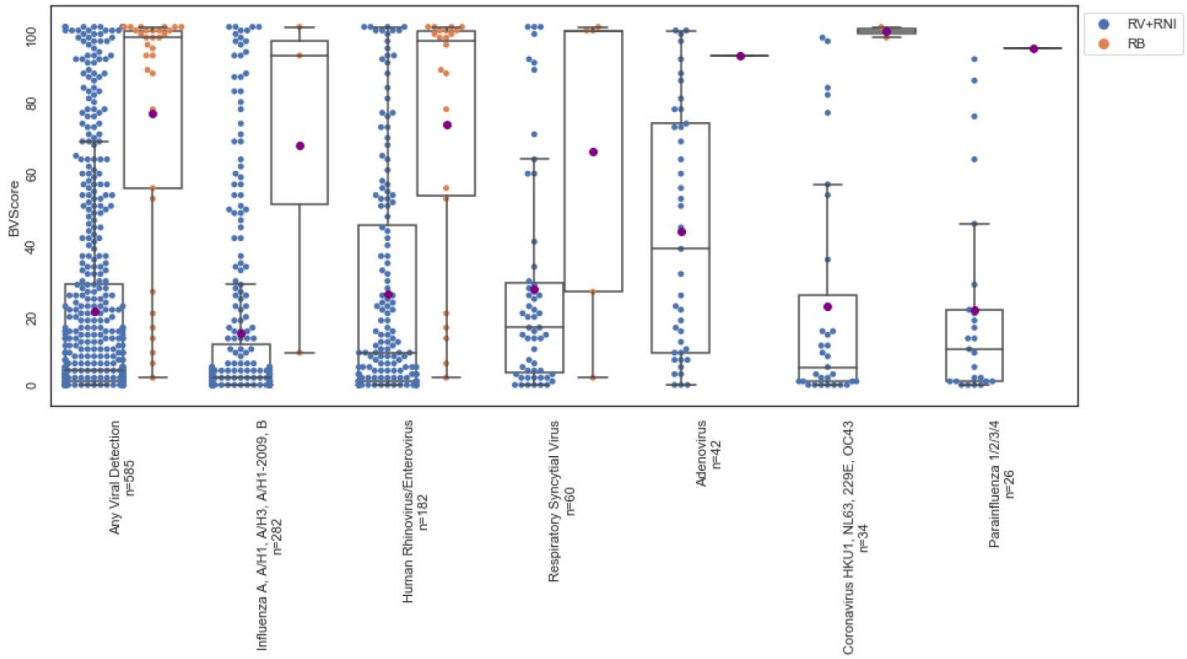
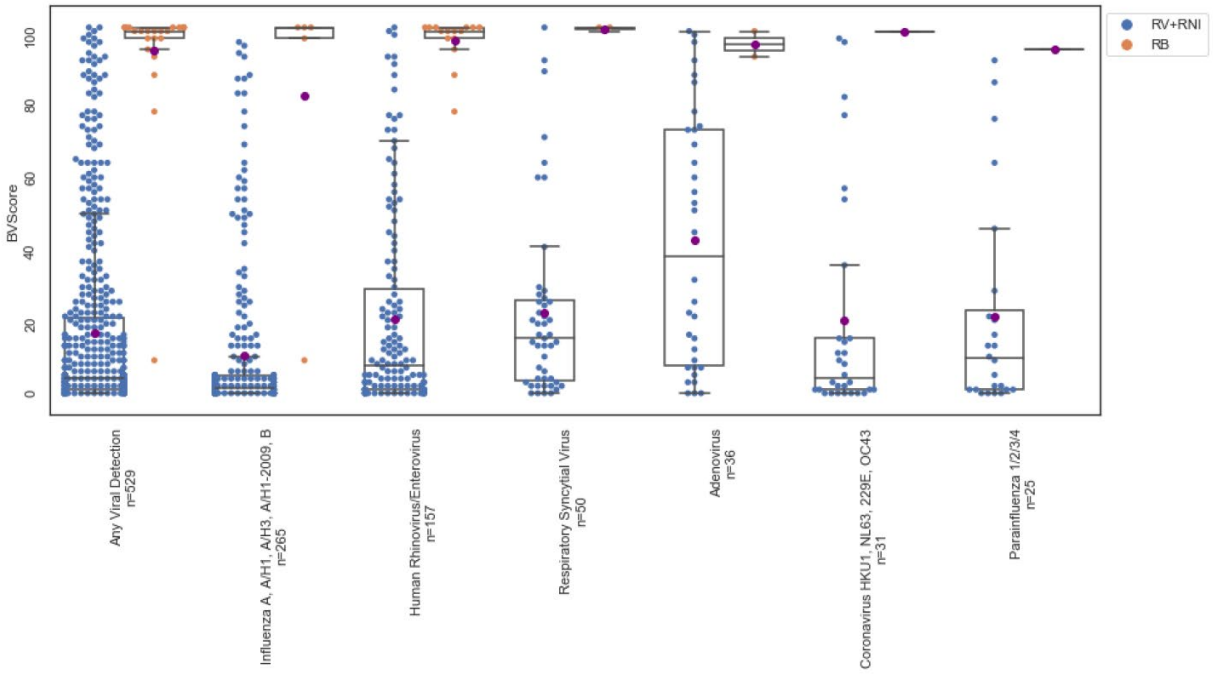


Figure 2. MeMed BV Score Values in Patients with Viral Detections (Secondary Cohort)



Across the viral PCR detections that included adenovirus, influenza, parainfluenza, respiratory syncytial virus, coronavirus and human rhinovirus/enterovirus, 33 and 26 were adjudicated as bacterial infections in the primary and secondary objective cohorts respectively, with 24 and 25 of these correctly receiving a bacterial score, respectively.

These data show that a bacterial immune response can be detected irrespective of viral detection, supporting that MeMed BV can complement direct viral detection tests by identifying bacterial-viral co-infection.

2. Clinical Specificity:

See Clinical Sensitivity above.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

121 healthy individuals with demographic characteristics similar to the Intended Use population were recruited at several U.S. and Israeli clinical sites. The distribution of age of the healthy individuals was 8.9-71.9 years. The determination that the participant is healthy was adjudicated by an expert based on the patient data provided to them in an anonymized electronic case report form. Results from the study are included in the table below and stratified by demographic group.

Table 21. Reference Interval for the MeMed BV Score in Healthy Individuals

Race		MeMed BV Score Band				
		1 (0 ≤ score ≤ 10)	2 (10 < score < 35)	3 (35 ≤ score ≤ 65)	4 (65 < score < 90)	5 (90 ≤ score ≤ 100)
Asian	N	4	3	1	0	0
	%	50.0%	37.5%	12.5%	0.0%	0.0%
Black	N	10	3	0	0	0
	%	76.9%	23.1%	0.0%	0.0%	0.0%
Hispanic	N	7	3	0	0	0
	%	70.0%	30.0%	0.0%	0.0%	0.0%
White	N	58	20	5	1	0
	%	69.0%	23.8%	6.0%	1.2%	0%

According to the CLSI guideline EP28, lower limit of the reference interval corresponds to the 2.5th percentile and the upper limit corresponds to the 97.5th percentile. The corresponding MeMed BV score values for the lower and upper limits across the entire healthy population are 0 and 46, respectively.

D Clinical Cut-Off:

MeMed BV cut-off values were established prior to the clinical trial. Specifically, the host biomarker signature used in the MeMed BV test was developed in the Curiosity study (Clinicaltrials.gov identifier: NCT01917461). Candidate proteins were screened from 1,002 prospectively enrolled patients with acute infections to identify differentially expressed biomarkers of infection. Multiple feature selection algorithms and computational models were evaluated to identify the optimal combination of proteins to discriminate bacterial and viral infection. The current signature was further validated in two independent studies: Pathfinder (NCT01911143) and Opportunity (NCT01931254).

The following MeMed BV Score Bin Interpretation tables are the results from non-interventional observational clinical trials. U.S. patients were prospectively enrolled in the Apollo trial (NCT04690569). Prospective cases were supplemented with archived cases randomly drawn from two previously completed prospective clinical studies conducted outside the U.S. (Observer, NCT03011515; and AutoPilot, NCT03052088). Data from the clinical study establish a trend between increasing MeMed BV Score value and the likelihood of a bacterial infection.

Table 22. Recommendations for interpretation of MeMed BV Score Bins using Forced Diagnosis

MeMed BV Score Band	Interpretation	Prevalence (%)		Bacterial Infection Likelihood Ratio (95% CI)
		Bacterial Infection	Viral Infection/ Noninfectious	
Bin 5 90 ≤ score ≤ 100	High likelihood of bacterial infection (or co-infection)	60.4	39.6	8.1 (6.3-10.5)

MeMed BV Score Band	Interpretation	Prevalence (%)		Bacterial Infection Likelihood Ratio (95% CI)
		Bacterial Infection	Viral Infection/ Noninfectious	
Bin 4 65 < score < 90	Moderate Likelihood of Bacterial Infection (or co-infection)	27.7	72.3	2.1 (1.3-3.1)
Bin 3 35 ≤ score ≤ 65	Equivocal	15.7	84.3	1.0 (0.6-1.7)
Bin 2 10 < score < 35	Moderate likelihood of viral infection (or other non-bacterial etiology)	5.2	94.8	0.3 (0.2-0.6)
Bin 1 0 ≤ score ≤ 10	High Likelihood of viral infection (or other non-bacterial etiology)	1.5	98.5	0.1 (0.0-0.2)

Table 23. Recommendations for interpretation of MeMed BV Score Bins using Consensus Diagnosis

MeMed BV Score Band	Interpretation	Prevalence (%)		Bacterial Infection Likelihood Ratio (95% CI)
		Bacterial Infection	Viral Infection/ Noninfectious	
Bin 5 90 ≤ score ≤ 100	High likelihood of bacterial infection (or co-infection)	81.2	18.9	25.0 (16.6-37.8)
Bin 4 65 < score < 90	Moderate Likelihood of Bacterial Infection (or co-infection)	29.2	70.8	2.4 (1.5-4.0)
Bin 3 35 ≤ score ≤ 65	Equivocal	8.3	91.7	0.5 (0.2-1.2)
Bin 2 10 < score < 35	Moderate likelihood of viral infection (or other non-bacterial etiology)	0.7	99.4	0.0 (0.0-0.3)
Bin 1 0 ≤ score ≤ 10	High Likelihood of viral infection (or other non-bacterial etiology)	0.7	99.3	0.0 (0.0-0.1)

E Expected Values/Reference Range:

See Clinical cut-off. Predictive values depend on the likelihood ratios and the prevalence of disease. Laboratories and other users should establish their own reference intervals for their patient populations using the MeMed BV test to reflect potential sources of variability, such as patient gender, race, or age.

F Other Supportive Instrument Performance Characteristics Data:

Not applicable.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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