510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

I Background Information:

A 510(k) Number

K213936

B Applicant

DiaSorin Inc.

C Proprietary and Established Names

LIAISON MeMed BV, LIAISON MeMed BV Control Set

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 LIAISON MeMed BV device and the LIAISON MeMed BV Control Set

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 DiaSorin LIAISON MeMed BV is an automated in vitro diagnostic semi-quantitative assay that uses chemiluminescent immunoassay (CLIA) technology to measure 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 LIAISON MeMed BV assay 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 seven days or less. The LIAISON MeMed BV assay generates a numeric score that falls within discrete interpretation ranges based on the increasing likelihood of bacterial infection. The assay has to be performed on the automated LIAISON XL Analyzer.

The DiaSorin LIAISON MeMed BV Control Set is intended for use as assayed quality control to monitor the performance of the DiaSorin LIAISON MeMed BV assay. The performance characteristics of the LIAISON controls have not been established for any other assays or instrument platforms different from the automated LIAISON Analyzer family. The control set is intended for in vitro diagnostic use in a professional laboratory only.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

The LIAISON MeMed BV Assay is performed on the LIAISON XL Analyzer.

IV Device/System Characteristics:

A Device Description:

The LIAISON MeMed BV assay 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 that conducts chemiluminescence-based analyte measurements of patient serum samples and their computational integration. Reagents are provided in individual compartments within a plastic container called the Reagent Integral. The assembled kit includes one each of the TRAIL Reagent Integral, IP-10 Reagent Integral, CRP Reagent Integral and two levels of calibrators for each specific assay. The assay configuration allows for the performance of 100 tests.

The LIAISON MeMed BV Control Set is quality control material that is available for purchase separately and that consists of two vials each of two control levels (viral and bacterial) provided lyophilized. The volume of each vial is sufficient for at least 10 determinations. The LIAISON

MeMed BV Control Set is intended to monitor for substantial reagent failure. The controls should be evaluated on each day of testing or as required by guidelines or requirements of local regulations or accredited organizations.

B Principle of Operation:

The LIAISON MeMed BV assay consists of three individual chemiluminescence immunoassays (CLIAs) for quantitative determination of TRAIL, IP-10, and CRP. All three reagent packs must be the same lot and present at the same time on the same instrument used for sample testing. All three reagent packs are individually calibrated and quality controlled.

Each individual reagent pack for TRAIL, IP-10, and CRP utilizes monoclonal antibodies for capture and antibody-conjugates for the detection of the specific assay target. The assay incubates sample, calibrator, or control with assay buffer and paramagnetic particles coated with a monoclonal antibody that specifically recognizes the target of interest. Following the incubation, an isoluminol conjugated antibody specific for each analyte is then added to the reaction and incubated. The unbound conjugate is removed with a wash step. Starter reagents are then added and a flash chemiluminescent reaction is initiated. The light signal is measured by a photomultiplier as relative light units (RLU) and is proportional to the concentration of analyte present in the calibrators, controls or samples.

The LIAISON 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.

- $0 \leq$ 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)
- $35 \leq$ score ≤ 65: Equivocal
- $65 <$ score < 90: Moderate likelihood of bacterial infection (or co-infection)
- $90 \leq$ score ≤ 100: High likelihood of bacterial infection (or co-infection)

C Instrument Description Information:

1. Instrument Name:

   LIAISON XL Analyzer

2. Specimen Identification:

   The LIAISON MeMed BV test is intended to be performed on human serum specimens To prevent confusion, a distinct identification number must be assigned to every sample in the LIAISON XL software. This sample ID can be entered either by scanning the bar-code using the barcode scanner located in the loading bay for sample racks or typing it manually.

3. Specimen Sampling and Handling:

The loading bay for sample racks allows continuous loading of the LIAISON XL system with samples. The samples in the tubes are placed in special racks and loaded in one of the 10 lanes afterwards. As support, a LED below each lane indicates the relevant usage status.

4. Calibration:

Two point kit calibrators specific to each Reagent Integral lot are used to establish specific working curves for each of the three assays based on assay master curves stored on the analyzer. In order to correctly run the test, the TRAIL, IP-10, and CRP Reagent Integrals must be calibrated.

Calibration is required every 21 days, or

- With each new lot of reagents (Reagent Integral or Starter Reagents)
- If Quality Control results are out of the acceptable range
- After each servicing of the LIAISON XL Analyzer

5. Quality Control:

The LIAISON MeMed BV Controls are representative of patient specimens intended for use with the LIAISON MeMed BV assay. Control 1 represents a low viral score and Control 2 represents a high bacterial score.

V Substantial Equivalence Information:

A Predicate Device Name(s):
MeMed BV

B Predicate 510(k) Number(s):
K210254

C Comparison with Predicate(s):

Device & Predicate Device(s):	K213936	K210254
Device Trade Name	LIAISON MeMed BV	MeMed BV
General Device Characteristic Similarities		
Intended Use/Indications For Use	The DiaSorin LIAISON MeMed BV is an automated in vitro diagnostic semi-quantitative assay that uses chemiluminescent immunoassay (CLIA) technology to measure three non-microbial (host) proteins (TRAIL,	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

	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 LIAISON MeMed BV assay 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 seven days or less. The LIAISON MeMed BV assay generates a numeric score that falls within discrete interpretation ranges based on the increasing likelihood of bacterial infection.	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.
Results	Same	Semi-quantitative
Measurand	Same	Three non-microbial host proteins (TRAIL, IP-10, and CRP)
Sample Type	Same	Human serum
Measurement System	Same	Photomultiplier
Output	Same	SCORE result
General Device Characteristic Differences		
Antibody Conjugate	Isoluminol Derivative	Alkaline Phosphatase
Sample volume	200 µL	100 µL
Instrument System	LIAISON XL Analyzer	MeMed Key Analyzer
Calibration	Low and High calibrators for each	High, Medium, and Low calibrators for

	analyte	each analyte
Calibration Interval	3 weeks	2 weeks

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: 2019 – Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline, 3rd Edition

CLSI EP15-A3: 2019 – User Verification of Precision and Estimation of Bias; Approved Guideline, 3rd Edition

CLSI EP06-Ed2: 2020 – Evaluation of Linearity of Quantitative Measurement Procedures

CLSI EP07-3rd Edition: 2018 – Interference Testing in Cilnical Chemistry

CLSI EP37-1st Edition: 2018 – Suplpemental Tables for Interference Testing in Clinical Chemistry

CLSI EP17-A2: 2012 – Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures

CLSI EP28-A3c: 2010 – Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory

ISO 14971: 2019 – Medical devices. Application of risk management to medical devices

IEC 62304:2006/A1: 2016 – Medical Device Software – Software life cycle processes

CLSI LIS01 – A2; Standard Spec for Low-Level Protocol to Transfer Messages Between Clinical Lab Instruments and Computer Systems

CLSI LIS02-A2; Standard Specification for Transferring Information Between Clinical Instruments and Computer Systems

AAMI TIR57: 2016 – Principles for medical device security – Risk Management

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision Study

A 20-day within-laboratory precision study was conducted at DiaSorin Inc. The study was performed for 20 days with two assay runs per day and two replicates per run by multiple

technicians for a total of 80 replicates per panel member. The test days spanned two calibration cycles. The test panel included the LIAISON MeMed BV Control set (Control 1 and Control 2 with two levels containing three analytes) and four serum specimens. Three of the serum specimens were contrived by spiking neat serum to generate target SCORE values that correspond to one viral (Low Score), one bacterial (High Score), and one equivocal assay (Medium Score) result. The final serum specimen was a native patient sample (Native) that corresponded to a low (viral/non-infectious) score.

Table 1. Precision Study Summary Results

TRAIL									
Sample ID	Mean (pg/mL)	Repeatability		Between-Run		Between Days		Total	
		SD	% CV	SD	% CV	SD	% CV	SD	% CV
Control 1	131	2.6	2.0	1.4	1.1	4.8	3.7	5.6	4.3
Control 2	24.7	0.5	2.1	0.2	2.2	1.1	4.5	1.3	5.4
Low Score	182	3.7	2.0	6.4	3.5	2.3	1.3	7.7	4.2
High Score	28.1	0.99	3.5	0.6	1.9	1.41	5.0	1.8	6.4
Medium Score	59.8	1.1	1.8	1.1	1.8	2.3	3.8	2.7	4.6
Native	68.2	1.7	2.4	0	0.0	2.6	3.8	3.02	4.4
IP-10									
Sample ID	Mean (pg/mL)	Repeatability		Between-Run		Between Days		Total	
		SD	% CV	SD	% CV	SD	% CV	SD	% CV
Control 1	1207	20.7	1.7	14.4	1.2	25.3	2.1	35.8	3.0
Control 2	191	2.8	1.5	2.8	1.4	9.4	4.9	10.2	5.3
Low Score	782	19.7	2.5	11	1.4	14.0	1.8	26.5	3.4
High Score	1244	26.1	2.1	0	0.0	22.8	1.8	33.5	2.7
Medium Score	537	10.4	1.9	8.0	1.5	16.8	3.1	21.4	4.0
Native	79.0	2.2	2.8	1.2	1.5	5.0	6.3	5.6	7.0
CRP									
Sample ID	Mean (mg/L)	Repeatability		Between-Run		Between Days		Total	
		SD	% CV	SD	% CV	SD	% CV	SD	% CV
Control 1	15.9	0.3	2.0	0.2	1.1	0.6	3.5	0.67	4.1
Control 2	139	4.1	2.9	2.0	1.4	5.2	3.7	6.9	4.9
Low Score	13.7	0.4	2.7	0.2	1.1	0.7	4.9	0.8	5.7
High Score	188	2.8	1.5	3.9	2.1	6.9	3.7	8.5	4.5
Medium Score	47	1.2	2.5	1.7	3.6	1.2	2.6	2.4	5.1
Native	2.4	0.09	3.9	0.06	2.8	0.2	10.4	0.3	11.4

Score									
Sample ID	Mean	Repeatability		Between-Run		Between Days		Total	
		SD	% CV[1]	SD	% CV[1]	SD	% CV[1]	SD	% CV[1]
Control 1	2.9	0.4	N/A	0.0	N/A	0.3	N/A	0.5	N/A
Control 2	99	0.0	N/A	0.0	N/A	0.0	N/A	0.0	N/A
Low Score	1	0.0	N/A	0.0	N/A	0.0	N/A	0.0	N/A
High Score	99	0.0	N/A	0.0	N/A	0.0	N/A	0.0	N/A
Medium Score	54.7	1.9	N/A	1.8	N/A	2.6	N/A	3.6	N/A
Native	7.9	0.8	N/A	0.0	N/A	0.6	N/A	0.9	N/A

[1]CV analysis was not considered for the logistic scale of the LIAISON MeMed BV Score.

Reproducibility Study

A five-day reproducibility study was conducted at DiaSorin Inc. and two external laboratories. Testing was performed over five days with one run per day and six replicates per run, for a total of 90 replicates per panel member. IP-10 values below the established measuring range were observed for the Native panel member in the reproducibility study; therefore, IP-10 Nateve panel member data are presented both as concentration and Relative Light Unit (RLU) values.

Table 2. Reproducibility Study Summary Results

TRAIL											
Sample ID	Mean (pg/mL)	Repeatability		Between-Days		Within-Laboratory		Between-Sites		Reproducibility	
		SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
Control 1	134	2.5	1.9	8.0	6.0	8.5	6.3	2.0	1.5	8.7	6.5
Control 2	27.8	0.6	2.1	1.7	6.0	1.8	6.3	0.0	0.0	1.6	5.8
Low Score	189	5.0	2.6	3.1	1.7	5.9	3.1	1.2	0.7	6.0	3.2
High Score	27.9	0.6	2.1	0.7	2.4	0.9	3.2	0.7	2.5	1.1	4.0
Medium Score	60.4	1.1	1.8	0.9	1.5	1.4	2.3	0.0	0.0	1.4	2.2
Native	70.1	1.6	2.3	0.8	1.2	1.8	2.6	1.1	1.5	2.1	3.0
IP-10											
Sample ID	Mean (pg/mL)	Repeatability		Between-Days		Within-Laboratory		Between-Sites		Reproducibility	
		SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
Control 1	1368	27.0	2.0	57.9	4.2	63.9	4.7	191.8	14.0	202.2	14.8
Control 2	186	4.5	2.4	8.9	4.8	10.0	5.4	26.1	14.0	28.0	15.0
Low Score	815	24.3	3.0	11.6	1.4	26.9	3.3	81.2	10.0	85.6	10.5
High Score	1348	33.6	2.5	31.7	2.4	46.2	3.4	151.5	11.2	158.4	11.7
Medium Score	567	13.6	2.4	11.6	2.1	17.9	3.2	52.5	9.3	55.5	9.8

Native (concentration)[1]	75.4	2.5	3.4	1.1	1.4	2.7	3.6	8.2	10.8	8.6	11.4
Native (RLU)	9698	255.2	2.6	117.7	1.2	281.1	2.9	429.2	4.4	513.1	5.3
CRP											
Sample ID	**Mean (mg/L)**	**Repeatability**		**Between-Days**		**Within-Laboratory**		**Between-Sites**		**Reproducibility**	
		SD	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**
Control 1	13.7	0.4	2.9	0.6	4.4	0.7	5.2	0.6	4.6	1.0	7.0
Control 2	129	4.3	3.3	4.8	3.8	6.5	5.0	3.9	3.0	7.6	5.9
Low Score	14.7	0.3	1.9	0.4	2.6	0.5	3.2	0.8	5.4	0.9	6.3
High Score	201	4.2	2.1	5.1	2.5	6.6	3.3	6.2	3..1	9.1	4.5
Medium Score	50.0	2.4	4.8	1.6	3.2	2.9	5.8	2.7	5.4	4.0	7.9
Native	2.6	0.1	3.6	0.1	4.9	0.2	6.1	0.2	9.3	0.3	11.1
Score											
Sample ID	**Mean**	**Repeatability**		**Between-Days**		**Within-Laboratory**		**Between-Sites**		**Reproducibility**	
		SD	**% CV[1]**	**SD**	**% CV[1]**	**SD**	**% CV[1]**	**SD**	**% CV[1]**	**SD**	**% CV[1]**
Control 1	2.2	0.2	N/A	0.7	N/A	0.0	N/A	0.0	N/A	0.7	N/A
Control 2	98.3	0.2	N/A	0.3	N/A	0.3	N/A	0.3	N/A	0.5	N/A
Low Score	1.0	0.0	N/A	0.0	N/A	0.0	N/A	0.0	N/A	0.0	N/A
High Score	99.0	0.0	N/A	0.0	N/A	0.0	N/A	0.0	N/A	0.0	N/A
Medium Score	55.0	1.9	N/A	1.3	N/A	1.5	N/A	1.5	N/A	2.8	N/A
Native	7.8	0.5	N/A	0.4	N/A	0.9	N/A	0.9	N/A	1.1	N/A

[1]IP-10 values for the Native Panel Member were below the assay measuring range.

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 of less than 15%. Linearity is not applicable to the test result (Score), as it is calculated using a pre-defined weighted multinomial logistic regression model. Serial dilutions of specimens containing high levels of each analyte were evaluated on the LIAISON MeMed BV Test. Specifically, two serum specimens (CRP and IP-10) and a high-concentration buffer spiked sample (TRAIL), were diluted to prepare a dilution series that spanned the relevant measuring range for each analyte (15-300 pg/mL for TRAIL, 100-2000 pg/mL for IP-10, and 1-250 mg/L for CRP). Linearity for each of the MeMed BV measurands fell within the acceptance criteria with no deviations above 5.5% observed throughout the relevant range for all analytes.

3. Analytical Specificity/Interference:

An interference study was performed to evaluate the impact of select interferents and cross-reactants on the test score. Performance in the presence of potentially interfering substances was evaluated using two serum samples, one that corresponded to a low score value (5) and one that corresponded to a high score value (95). Each sample was divided into equal

aliquots and spiked with the known amount of potential interferant or with the same volume of vehicle control. Matched spiked and vehicle control aliquots were evaluated in five replicates in the same run.

Table 3. Interference Study Results

Substance	Conc. Tested	Sample ID	Mean Vehicle Score	Mean Test Score	Absolute Difference
Bilirubin (conjugated)	0.4 mg/mL	1	99	99	0
		2	1	1	0
Bilirubin (unconjugated)	0.4 mg/mL	1	99	99	0
		2	1	1	0
Cholesterol	4 mg/mL	1	99	99	0
		2	1	1	0
Hemoglobin	10 mg/mL	1	99	99	0
		2	1	1	0
Human serum Albumin	60 mg/mL	1	99	99	0
		2	1	1	0
Triglycerides	15 mg/mL	1	99	99	0
		2	1	1	0
Acetaminophen	0.156 mg/mL	1	99	99	0
		2	1	1	0
Acetyl Salicylic Acid	0.03 mg/mL	1	99	99	0
		2	1	1	0
Amoxicillin	54 µg/mL	1	99	99	0
		2	1	1	0
Ampicillin	75 µg/mL	1	99	99	0
		2	1	1	0
Azithromycin	11.1 µg/mL	1	99	99	0
		2	1	1	0
Biotin	3600 ng/mL	1	99	99	0
		2	1	1	0
Caffeine	108 µg/mL	1	99	99	0
		2	1	1	0
Cetirizine HCL	4.35 µg/mL	1	99	99	0
		2	1	1	0
Dextramethorphan	15.6 ng/mL	1	99	99	0
		2	1	1	0
Doxycycline	18 µg/mL	1	99	99	0
		2	1	1	0
Ethanol	0.5% v/v	1	99	99	0
		2	1	1	0
Heparin	3300 U/L	1	99	99	0
		2	1	1	0
Ibuprofen	219 µg/mL	1	99	99	0
		2	1	1	0
Levofloxacin	36 µg/mL	1	99	99	0
		2	1	1	0

Loratidine	87 ng/mL	1	99	99	0
		2	1	1	0
Oxymetazoline HCl	0. 6 ng/mL	1	99	99	0
		2	1	1	0
Phenylephrine	30 ng/mL	1	99	99	0
		2	1	1	0
Prednisolone	1200 ng/mL	1	99	99	0
		2	1	1	0

These results demonstrate that the presence of the evaluated exogenous and endogenous interferants do not significantly impact the LIAISON MeMed BV Score values.

Additional interference testing was performed to establish whether the presence of human anti-mouse antibodies (HAMA) interfere with LIAISON MeMed BV assay results. Potential HAMA interference was assessed by evaluating three independent clinical samples that each contained HAMA levels varying from 316 to >600 ng/mL as determined by a sample vendor certificate of analysis. Samples were tested both before and after processing with heterophilic blocking tubes to remove HAMA. Results from testing are displayed below.

Table 4. HAMA Interference Testing Results

Substance	Conc. Tested	Sample ID	Mean Vehicle Score	Mean Test Score	Absolute Difference
HAMA	>600 ng/mL	1	39	51	12
	>600 ng/mL	2	75	77	2
	316 ng/mL	3	9	14	5

The observed difference in Score for each HAMA sample met acceptance criteria of less than 12.5 score units and indicate a low likelihood of specimens shifting to a non-adjacent bin.

Additional interference testing was performed to determine whether the presence of rheumatoid factor interferes with the LIAISON MeMed BV assay results. Again, two serum samples including one low Score (5) and one high score (95) were divided into equal aliquots and spiked with high RF Concentrations. Results are displayed in the table below.

Table 5. Rheumatoid Factor Interference Testing Results

Substance	Conc. Tested	Sample ID	Mean Vehicle Score	Mean Test Score	Absolute Difference
Rheumatoid Factor	500 IU/mL	1	99	99	0
		2	1	1	0

These results demonstrate that the presence of the evaluated RF concentrations do not significantly impact the LIAISON MeMed BV Score Values.

Cross-reactivity Testing

Evaluation of potential cross-reactants was performed similarly to the interefence testing described previously. Briefly, tesitng included two serum samples, one high score and one low score, in the presence and absence of the potential cross-reactant.

Table 6. Cross-reactivity Testing Summary Results

Substance	Conc. Tested	Sample ID	Mean Vehicle Score	Mean Test Score	Absolute Difference
4-1BB Ligand	50 ng/mL	1	99	99	0
		2	1	1	0
CD40 Ligand (carrier)	50 ng/mL	1	99	99	0
		2	1	1	0
CD40 Ligand (carrier-free)	50 ng/mL	1	99	99	0
		2	1	1	0
LT α1/β2	50 ng/mL	1	99	99	0
		2	1	1	0
LT α2/β1 (recombinant mouse)	50 ng/mL	1	99	99	0
		2	1	1	0
LT α2/β1	50 ng/mL	1	99	99	0
		2	1	1	0
TNF-α	50 ng/mL	1	99	99	0
		2	1	1	0
TNF-β	50 ng/mL	1	99	99	0
		2	1	1	0
BLC/BCA-1	50 ng/mL	1	99	99	0
		2	1	1	0
ENA-78	50 ng/mL	1	99	99	0
		2	1	1	0
GCP-2	50 ng/mL	1	99	99	0
		2	1	1	0
GRO α	50 ng/mL	1	99	99	0
		2	1	1	0
GRO γ	50 ng/mL	1	99	99	0
		2	1	1	0
IFN γ	50 ng/mL	1	99	99	0
		2	1	1	0
IL-8	50 ng/mL	1	99	99	0
		2	1	1	0
I-TAC	50 ng/mL	1	99	99	0
		2	1	1	0
NAP-2	50 ng/mL	1	99	99	0
		2	1	1	0
MIG	50 ng/mL	1	99	99	0
		2	1	1	0
SDF-1α (recombinant mouse)	50 ng/mL	1	99	99	0
		2	1	1	0

SDF-1α	50 ng/mL	1	99	99	0
		2	1	1	0
SDF-1β (aa 19-93)	50 ng/mL	1	99	99	0
		2	1	1	0
SDF-1β (aa 22-93)	50 ng/mL	1	99	99	0
		2	1	1	0
Pentraxin 2/SAP	500 ng/mL	1	99	99	0
		2	1	1	0
Pentraxin 3/TSG-14	500 ng/mL	1	99	99	0
		2	1	1	0
Adiponectin	50 ng/mL	1	99	99	0
		2	1	1	0

No cross-reactivity or significant impact of LIAISON MeMed BV test score was observed.

Hook Effect Study

A study was performed to evaluate whether a high dose hook effect occurs in samples containing high amounts of analyte. Samples containing analyte levels above the upper end of the analytical measuring range were evaluated using one reagent lot. All samples demonstrated an increasing amount of chemiluminescence with increasing concentration of analyte. No hook effect was observed for TRAil up to 1,000 pg/mL, IP-10 up to 10,000 pg/mL, and CRP up to 500 mg/L.

4. Assay Reportable Range:

Not applicable.

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

Calibration

The LIAISON MeMed BV assay consists of three separate reagent integrals, TRAIL, IP-10, and CRP that generate a continuous response (relative light units, RLU) which is used in sample grading to provide a reportable quantitative result. Sample grading is based on the use of a calibration curve referenced to 'In-house' TRAIL, IP-10, and CRP reference standards (master standards). Each calibration curve (master curve) is controlled by the use of two lyophilized calibrators (Calibrator 1 and Calibrator 2) provided with the Reagent Integral. Calibrator 1 and 2 are assayed by the user to transform the master curve into a working curve and further used to calculate sample results. The LIAISON XL Analyzer working curve is obtained by the user during assay calibration by assigning a curve to the two point kit calibrators based upon the master curve. This working curve is used to calculate the patient sample results.

Recalibration in triplicate is mandatory whenever at least one of the following conditions occurs: new lot of reagents are being used, previous calibration was performed more than 21 days prior, quality control results are out of the acceptable range, or the analyzer has been serviced.

Controls

The LIAISON MeMed BV Controls are representative of patient specimens intended for use with the LIAISON MeMed BV assay. Control 1 represents a low viral score specimen and control 2 represents a high bacterial score specimen. The range of concentrations for each analyte present in each control is reported on the certificate of analysis and indicates the limits established by DiaSorin for control values that can be obtained in reliable assay runs.

Specimen Stability

Several studies were performed to assess stability of serum samples exposed to different storage conditions.

To demonstrate room temperature sample storage stability, five serum samples that spanned the entire LIAISON MeMed BV score range were aliquoted and stored at 22°C across several timepoints before being tested in duplicate on the LIAISON MeMed BV assay. Mean values were calculated for each sample and mean percent differences from the baseline were evaluated by linear regression to demonstrate a deviation of less than 10% from samples at baseline. The study data support a room temperature sample stability claim of three hours.

To demonstrate refrigerated sample storage stability, five serum samples spanning the entire LIAISON MeMed BV score range were aliquoted and stored at 2-8°C. Mean values were plotted and evaluated over several timepoints to demonstrate a deviation of less than 10% from baseline. These study data support a refrigerated sample storage claim of eight hours.

To demonstrate frozen sample storage stability, five serum samples that spanned the entire range of the LIAISON MeMed BV assay were aliquoted and stored at both -20°C and -70°C before being tested in duplicate. Mean values were calculated for each sample and mean percent differences from the baseline were evaluated by linear regression to demonstrate a deviation of less than 10% from samples at baseline. Data from these studies support a frozen sample storage claim of four weeks at -20°C or-70°C.

Freeze/Thaw Stability

To evaluate the effect of freeze-thawing serum samples on the LIAISON MeMed BV assay results, five serum samples that spanned the entire LIAISON MeMed BV score range were aliquoted, frozen, and thawed for up to five freeze/thaw cycles before being tested in triplicate on the LIAISON MeMed BV assay. Mean values for each sample were evaluated at each time point and analyzed via linear regression to determine the point at which a 10% or greater deviation from baseline occurs. Results from these studies demonstrate sample stability for up to three freeze/thaw cycles.

Stability of LIAISON MeMed BV Calibrators

Stability of reconstituted calibrators for the LIAISON MeMed BV assay were evaluated across multiple storage conditions: room temperature on board the LIAISON XL instrument, refrigerated at 2-8°C, and frozen at -20°C. Performance was evaluated by re-calibrating the assay with the reconstituted calibrators at designated intervals. Samples tested included unexpired kit controls and four internal controls that spanned the LIAISON MeMed BV

Score range. Results from these stability studies support storage of controls at room temperature for 48 hours, refrigerated for up to four weeks, and frozen for up to 8 weeks. Additionally, calibrator stability was demonstrated for up to 4 freeze/thaw cycles.

Stability of LIAISON MeMed BV Controls

Stability of reconstituted LIAISON MeMed BV controls was evaluated using two lots of control materials across multiple storage conditions: room temperature on board the LIAISON XL instrument, refrigerated at 2-8°C, and frozen at -20°C. Controls were evaluated in triplicate at designated intervals after storage. Mean values were analyzed via linear regression to identify the point where deviation greater than 10% occurs. Results from these studies demonstrate control stability for up to 72 hours at room temperature, eight weeks when refrigerated, and eight weeks when stored frozen. Additionally, stability of the LIAISON MeMed BC controls were also demonstrated for up to four freeze/thaw cycles.

Fresh vs. Frozen Study

A study was conducted to establish that fresh and frozen serum samples are equivalent and can be used interchangeably in the assay. Forty-three fresh serum samples were collected from patients and spiked with recombinant TRAIL, IP-10, and/or CRP to span the entire range of the LIAISON MeMed BV Score. Samples were tested fresh in triplicate and then frozen, thawed, and tested again in triplicate. Sample results were analyzed by Passing Bablock regression with overall acceptance criteria for the study requiring a slope 0.9-1.1 and $R^2 \geq 0.9$. Results for all individual analytes and Score values met the acceptance criteria and establish equivalent assay results for both fresh and frozen specimens.

6. Detection Limit:

Limit of Blank

Five blank samples were tested on the LIAISON MeMed BV assay on one analyzer, with two reagent lots and two technicians over six runs. Testing spanned three days and included 2 replicates per run for a total of 60 results per reagent lot. LoB was calculated as described in CLSI EP17-A2. Results are summarized in the table below.

Table 7. Limit of Blank Test Results

	Limit of Blank					
	CRP (mg/L)		IP-10 (pg/mL)		TRAIL (pg/mL)	
	Lot 1	Lot 2	Lot 1	Lot 2	Lot 1	Lot 2
Mean	0.000	0.002	0.000	0.067	4.73	3.75
SD	0.000	0.014	0.000	0.309	0.366	0.35
Concentration	0.000	0.024	0.000	0.578	5.33	4.33

The assay's LoB was defined as the higher of the two kit lots (0.024 mg/L for CRP, 0.578 pg/mL for IP-10, and 5.33 pg/mL for TRAIL).

Limit of Detection

Four samples containing low levels of CRP, IP-10, and TRAIL were evaluated on the LIAISON MeMed BC assay on one analyzer, with two reagent lots and two technicians over six runs. Testing spanned three days and included 2 replicates per run for a minimum of 96 dose results. LoD was calculated as described in CLSI EP17-A2. Results are summarized in the table below.

Table 8. Limit of Detection Study Results

	Limit of Detection					
	CRP (mg/L)		IP-10 (pg/mL)		TRAIL (pg/mL)	
	Lot 1	Lot 2	Lot 1	Lot 2	Lot 1	Lot 2
Mean	0.392	0.375	30.95	48.57	8.21	7.13
SD	0.022	0.026	2.296	2.254	1.025	0.437
Concentration	0.037	0.067	3.8	4.31	7.03	5.05

The overall assay LoD for each analyte was defined as the higher of the two kit lots (0.067 mg/L for CRP, 4.31 pg/mL for IP-10, and 7.03 pg/mL for TRAIL).

Limit of Quantitation

Seven serum samples for CRP, seven serum and/or spiked matrix samples for TRAIL and eight serum samples for IP-10 containing low concentrations of each analyte were evaluated to determine the assay limit of quantitation as described in CLSI EP17-A2. The % CV for each individual sample was plotted against the mean dose result and a best fit curve was applied to determine when the regression line crossed the 20% CV threshold. The assay LoQ for each analyte was defined as the higher of the two kit lots. LoQ for the LIAISON MeMed BV test was identified as 1.0 mg/L for CRP, 100 pg/mL for IP-10, and 15 pg/mL for TRAIL. When one of the three proteins (CRP, IP-10 and TRAIL) is detected below the respective assay LoQ or above the assay specific maximum measurable value, the LoQ value or the maximum is used as the input into the formula.

7. Assay Cut-Off:

See clinical cut-off.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Clinical validation for the LIAISON MeMed BV assay was performed utilizing a subset of samples used to support clearance of the predicate MeMed BV assay (K210254). Briefly, samples were collected in a multicenter, observational, blinded study (Apollo, Clinicaltrials.gov identifier: NCT04690569) across 11 medical centers (9 in the US and 2 in Israel). The study population included hospital admitted, Emergency Department (ED) and Urgent Care patients with suspected acute bacterial or viral infections.

The primary analysis of the complete clinical study cohort established the diagnostic performance 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.

A subset of the original Apollo study cohort consisting of 300 samples (delinked and de-identified specimen aliquots) was utilized to demonstrate equivalent clinical performance of the LIAISON MeMed BV test. Fifteen specimens were not evaluated due to sample integrity errors on the LIAISON XL Anlayzer due to low serum volume which precluded the possibility of repeat testing. Of the remaining 285 subjects considered, 51 resided in Israel and 234 in the U.S. Age, gender, ethnicity and racial diversity are summarized in Table 9 below.

Table 9. Demographics of Clinical Samples Evaluated

Demographic/Clinical Category		**Study Population (N = 285)**
Gender	Female	156 (54.7%)
	Male	129 (45.3%)
Age	5 months to ≤ 2 years	14 (4.9%)
	> 2 to ≤ 12 years	44 (15.4%)
	> 12 to ≤ 18 years	17 (6.0%)
	> 18 years	210 (73.7%)
Ethnicity	Hispanic/Latino	38 (13.3%)
Race	Native American	0 (0.0%)
	Asian	16 (5.6%)
	Black or African American	60 (21.1%)
	Native Hawaiian	0 (0.0%, 0.0%)
	White	143 (50.2%)
	Other	15 (5.3%)
	Non-US	51 (17.9%)
Comorbidity	Diabetes	18 (6.3%)
	Hypertension	16 (5.6%)
	COPD	5 (1.8%)
	Hyperlipidemia	13 (4.6%)
	None Reported	233 (81.8%)
Clinical Syndrome	LRTI	29 (10.2%)
	URTI	149 (52.3%)
	LRTI/URTI	12 (4.2%)

	LRTI, UTI	1 (0.4%)
	UTI	7 (2.5%)
	UTI; URTI	2 (0.7%)
	Other	85 (29.8%)

All specimens were shipped frozen on dry ice to DiaSorin Inc. Specimen aliquots were randomized and shipped frozen to two additional external sites for testing. Results of the LIAISON MeMed BV assay for internal assay concentration values for individual analytes and score values were compared directly to the predicate results utilizing Deming Regression Analysis. Results are summarized in the table below.

Table 10. Deming Regression Analysis Results – LIAISON MeMed BV Test Results Compared to the Predicate Device.

Analyte	N	Range	Slope (95% CI)	Y-intercept (95% CI)	R^2 (Spearman)	R (Spearman)
TRAIL	238	15.6 - 300 pg/mL	0.98 (0.91 – 1.05)	-2.47 (-8.03 to 3.09)	0.86	0.93
IP-10	211	100 – 2000 pg/mL	1.13 (1.05 – 1.21)	-13.67 (-45.08 to 17.7)	0.94	0.97
CRP	259	1.0 – 229.3 mg/L	1.15 (1.10 – 1.20)	-0.92 (-2.08 to 0.23)	0.98	0.99
Score	285	0.0 - 100	1.03 (1.0 – 1.05)	0.84 (0.02 to 1.65)	0.94	0.97

Additional analyses were performed to calculate the bias at each relevant cut-off across the LIAISON MeMed BV Score range as detailed below.

Table 11. Deming Regression Bias Analysis – Bias estimates at relevant cutoffs

	LIAISON MeMed BV Score Bias	95% CI	
10	1.1	0.3	2.1
35	1.7	0.5	3.1
65	2.5	0.6	4.7
90	3.2	0.7	6.0

The bias at each bin cut-off met acceptance criteria of less than 12.5 score units, and ensure a low likelihood of specimens shifting to a non-adjacent bin. A comparison of the LIAISON MeMed BV Bin result to that obtained with the predicate device on the same clinical samples is summarized below.

Table 12. Clinical Sample Bin Results – LIAISON MeMed BV Comparison to the Predicate

LIAISON MeMed BV Bin Results	Predicate Bin Results				
	Bin 1	Bin 2	Bin 3	Bin 4	Bin 5
Bin 1	146	7	0	0	0
Bin 2	13	28	7	0	0
Bin 3	0	12	8	5	0
Bin 4	0	1	9	15	1
Bin 5	0	0	0	4	29
Agreement	91.8% (146/159)	58.3% (28/48)	33.3% (8/24)	62.5% (15/24)	96.7% (29/30)

Out of all clinical samples evaluated, only 1 sample exhibited a shift to a non-adjacent bin when tested with the LIAISON MeMed BV test.

Additional analyses of the LIAISON MeMed BV Results were performed by comparing results from the LIAISON test to forced expert adjudication result utilized as the comparator in the Apollo clinical study.

Table 13. LIAISON MeMed BV Comparison to Physician Adjudication Result – Forced Adjudication

LIAISON 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	33	22	11	11.6	66.7	33.3	13.0 (7.09-25.83)
65 < score < 90	26	8	18	9.1	30.8	69.2	2.89 (1.27-5.95)
35 ≤ score ≤ 65	25	6	19	8.8	24.0	76.0	2.05 (0.79-4.51)
10 < score < 35	48	1	47	16.8	2.1	94.7	0.14 (0.01-0.6)
0 ≤ score ≤ 10	153	1	152	53.7	0.7	99.3	0.043 (0.002-0.18)
Total	285	38	247	100			

A significant trend was demonstrated between the LIAISON MeMed BV Score and increasing likelihood of bacterial infection across Score bins. Additionally, individuals with Scores in the lowest bin have a high likelihood of viral or non-bacterial etiology and the individuals with scores in the highest bin have a high likelihood of bacterial infection. To further demonstrate equivalent performance to the predicate device, a similar analysis was performed for the predicate device results on the same clinical samples evaluated as part of this study.

Table 14. Predicate Performance Comparison to Physician Adjudication Result – Forced Adjudication

Predicate Score Bin	N	Forced Bacterial Diagnosis	Forced Viral/ Noninfectious Diagnosis	% Total Patients	% Patients Bacterial	% Patients Viral/ Noninfectious	LR (95% CI)
90 ≤ score ≤ 100	30	20	10	10.5	66.7	33.3	13.0 (6.83-27.01)
65 < score < 90	24	10	14	8.4	41.7	58.3	4.64 (2.16-9.63)
35 ≤ score ≤ 65	24	5	19	8.4	20.8	79.2	1.71 (0.6-3.96)
10 < score < 35	48	2	46	16.8	4.2	95.8	0.28 (0.05-0.85)
0 ≤ score ≤ 10	159	1	158	55.8	0.6	99.4	0.041 (0.002-0.173)
Total	285	38	247	100			

Overall, these results demonstrate equivalent performance between the LIAISON MeMed BV test and the predicate device.

Additional analyses of the LIAISON MeMed BV test was performed according to the secondary analysis in which the adjudicators were un-blinded to PCT and CRP results. Individuals for whom adjudicators could not agree were labeled indeterminate and excluded from this analysis. Twenty eight of the 285 samples were excluded.

Table 15. LIAISON MeMed BV Comparison to Physician Adjudication Result – Consensus Adjudication

LIAISON MeMed BV Score Bin	N	Consensus Bacterial Diagnosis	Consensus Viral/ Noninfectious Diagnosis	% Total Patients	% Patients Bacterial	% Patients Viral/ Noninfectious	LR (95% CI)
90 ≤ score ≤ 100	24	21	3	9.3	87.5	12.5	52.97 (19.9-214.87)
65 < score < 90	20	5	15	7.8	25.0	75.0	2.52 (0.87-5.99)
35 ≤ score ≤ 65	23	3	20	9.0	13.0	87.0	1.14 (0.28-3.07)
10 < score < 35	42	0	42	16.3	0.0	100.0	0.0 (0.0-0.341)
0 ≤ score ≤ 10	148	1	147	57.6	0.7	99.3	0.051 (0.003-0.214)
Total	257	30	227	100			

Similar analyses were performed for the predicate device in these samples.

Table 16. Predicate Performance Comparison to Physician Adjudication Result – Consensus Adjudication

Predicate Score Bin	N	Consensus Bacterial Diagnosis	Consensus Viral/ Noninfectious Diagnosis	% Total Patients	% Patients Bacterial	% Patients Viral/ Noninfectious	LR (95% CI)
90 ≤ score ≤ 100	21	18	3	8.2	85.7	14.3	45.4 (16.75-185.3)
65 < score < 90	20	9	11	7.8	45	55.0	6.19 (2.72-13.77)
35 ≤ score ≤ 65	19	2	17	7.4	10.5	89.5	0.89 (0.15-2.89)
10 < score < 35	44	0	44	17.1	0.0	100.0	0.0 (0.0-0.326)
0 ≤ score ≤ 10	153	1	152	59.5	0.7	99.3	0.050 (0.003-0.207)
Total	257	30	227	100			

Cumulatively, the results from clinical sample testing demonstrate equivalent performance between the LIAISON MeMed BV test and the predicate device.

2. Matrix Comparison:

   Not applicable.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

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

   See section B.1 above.

D Clinical Cut-Off:

The Score algorithm of the LIAISON MeMed BV test is identical to that of the predicate device (K210254). See the K210254 decision summary for additional details regarding establishment of clinical cut-offs.

E Expected Values/Reference Range:

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 LIAISON MeMed BV test to reflect potential sources of variability, such as patient gender, race, or age.

To assess the expected reference range for the LIAISON MeMed BV assay, serum samples from 150 apparently healthy asymptomatic adults were collected and evaluated on a single lot of LIAISON MeMed BV reagents. Study subjects were 65% female and 35% male and ranged in age from 21-71.

Table 14. Reference Interval for the LIAISON MeMed BV Score in Healthy Individuals

Race		LIAISON MeMed BV Score Band				
		1 (0 ≤ score ≤ 10)	2 (10 < score < 35)	3 (35 ≤ score ≤ 65)	4 (65 < score < 90)	5 (90 ≤ score ≤ 100)
American Indian	N	5	0	0	0	0
	%	100%	0	0	0	0
Asian	N	8	2	0	0	0
	%	80%	20%	0	0	0
Black	N	6	1	0	0	0
	%	85.7%	14.3%	0	0	0
Hispanic	N	49	7	2	1	0
	%	83.1%	11.9%	3.4%	1.7%	0
White	N	94	14	1	1	0
	%	85.5%	12.7%	0.9%	0.9%	0

The Mean Score value in the healthy population was 6.9, the median score was 4, and the central 95% interval spanned the range 1-33.

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.