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

I   Background Information:

A   510(k) Number

K223085

B   Applicant

Miris AB

C   Proprietary and Established Names

Miris Human Milk Analyzer (HMA)

D   Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QEI	Class II	21 CFR 862.1493 - Breast Milk Macronutrients Test System	CH - Clinical Chemistry

II   Submission/Device Overview:

A   Purpose for Submission:

Modification to a previously authorized device

B   Measurand:

Fat, carbohydrate, and protein

C   Type of Test:

Quantitative, mid-infrared spectroscopy

III   Intended Use/Indications for Use:

A   Intended Use(s):
See Indications for Use below.

B   Indication(s) for Use:
The Miris Human Milk Analyzer (HMA) quantitatively measures the concentration of fat, protein, and carbohydrate in human milk. The Miris HMA also provides calculated values for total solids and energy. These measurements, in conjunction with other clinical assessments, may be used to aid in the nutritional management of newborns, including preterm, and infants. This device is intended for use in healthcare by trained healthcare personnel at clinical laboratories. The Miris HMA is also intended for use by personnel trained in the use of the device at Human Milk Banking Association of North America (HMBANA) accredited human milk banks, for the purpose of labeling milk donations and in the processing of milk donations.

C   Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

The Miris Human Milk Analyzer (HMA) is not the sole basis for nutritional management of the newborn. Use of the Miris HMA device is intended as part of an overall treatment plan and nutritional measures for newborns. The Miris HMA is an aid to the healthcare providers' standard of care assessment of nutritional management of newborns through monitoring of weight gain and growth.
Do not use the HMA with fortified human milk or infant formula.
Clinicians should follow clinical practice guidelines and standard of care when supplementing or fortifying human breast milk.

D   Special Instrument Requirements:

Miris Human Milk Analyzer

IV   Device/System Characteristics:

A   Device Description:

The Miris Human Milk Analyzer (HMA) is a system for the quantitative measurement of fat, protein, and total carbohydrate content in human milk. The measurements of fat, protein and carbohydrate are also used in calculating the total solids and the energy content of human milk samples. The HMA unit includes a mid-infrared (mid-IR) spectroscopy system and a user interface. The user is guided by the interactive interface, via the screen, through the measurement process by use of the six-button controlled menu system. Milk samples (3 mL) are injected into the measuring unit (cuvette) via the instrument inlet using a syringe, with excess sample and waste exiting via the outlet.

The HMA device is comprised of a sample cuvette, hardware consisting of a mainboard and central processing unit (CPU) board, a display, touch button, fan, case, and consumables. The hardware consists of a mainboard with a CPU-board, detector board, and emitter board.

Consumables:

- Miris Check (provided) -This is a solution to be used during start up to check zero-level transmission.
- Miris Calibration Control Kit (provided)
- Miris Cleaner (provided)
- Syringes (provided)
- Distilled or deionized water (not provided)

B   Principle of Operation:

The Miris Human Milk Analyzer (HMA) detector contains four waveband filters, where three are used for detection of the macronutrients and one is a reference filter. The wavebands used for the macronutrients are specific for the functional carbonyl groups (5.7μm) for fat determination, amide groups (6.5 μm) for protein determination, and hydroxyl groups (9.6 μm) for carbohydrate determination. The fourth waveband is a reference filter to correct, according Lambert-Beer's law, for variations in the optical path length in the liquid phase in the gap between the calcium fluoride windows. For determination of each component, the quantity of radiation absorbed by the functional groups is used, and estimations are made by reference to the amount of infrared radiation absorbed by water at the same waveband. The reference waveband is used to adjust for the background absorbance that is not derived from the presence of functional groups.

At a measurement, the HMA software application processes the transmission data via an internal calibration and presents values for fat, crude protein, true protein, and total carbohydrate concentrations (g/100 mL milk), and also calculated values for total solids (g/100 mL milk) and energy (kcal/100 mL milk), on the instrument display.

C   Instrument Description Information:

1. Instrument Name:

   Miris Human Milk Analyzer (HMA)

2. Specimen Identification:

   Milk samples are given a unique identifier prior to analysis.

3. Specimen Sampling and Handling:

   Human milk, in liquid form, is the only type of sample that should be used in this assay. Thawed milk can be kept at room temperature (20-30°C) for a maximum of 2 hours or refrigerated for a maximum of 48 hours (unpreserved) or 72 hours (preserved). Frozen samples maximum recommended storage duration is 6 months (unpreserved) and up to 12 months (preserved). Recommendations are provided in the labeling for sample handling and processing for storage.

4. Calibration:

The instrument is calibrated at the manufacturer site. Calibration is performed using calibration samples designed to cover the instrument calibration range of each analyte (fat, protein, carbohydrates). The calibration samples are prepared, and values are assigned using validated methods.

5. Quality Control:

The sponsor recommends running quality control (QC) materials prior to analyzing patient samples to ensure the Miris Human Milk Analyzer is working as intended. Laboratories should follow federal, state, and local guidelines for testing QC.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Miris Human Milk Analyzer (HMA)

B Predicate 510(k) Number(s):
DEN180007

C Comparison with Predicate(s):

Device & Predicate Device(s):	K223085	DEN180007
Device Trade Name	Miris Human Milk Analyzer (HMA)	Same
General Device Characteristic Similarities		
Intended Use/Indications For Use	The Miris Human Milk Analyzer (HMA) quantitatively measures the concentration of fat, carbohydrate, and protein in human milk.	Same
User Population	Newborns, including preterm, and infants	Same
Methodology	Mid-infrared transmission spectroscopy system	Same
Measured Parameters	Fat, Crude Protein, True Protein, Carbohydrate	Same
Calculated Parameters	Total Solids, Energy	Same
General Device Characteristic Differences		
Environment of Use	Clinical Laboratories and HMBANA accredited Human Milk Banks	Clinical Laboratories

Device & Predicate Device(s):	K223085	DEN180007
Dimensions	11 x 26 x 31 cm	9 x 26 x 31 cm
Weight	3.8 kg	3.1 kg
Fat measuring range (g/100 mL)	0.6 – 6.0	0.6 – 4.0

VI   Standards/Guidance Documents Referenced:

- ISO 14971:2019 Medical devices - applications of risk management to medical devices

- IEC 60601-1-2:2014 Medical electrical equipment -- part 1-2: general requirements for basic safety and essential performance -- collateral standard: electromagnetic disturbances -- requirements and tests

- IEC 62304:2006+A1:2015 Edition 1.1 Medical device software - software life cycle processes

- IEC 62366-1:2015 Medical devices - part 1: application of usability engineering to medical devices

- ISO 15223-1 Fourth edition 2021-07 Medical devices - symbols to be used with information to be supplied by the manufacturer - part 1: general requirements

- CLSI EP05-A3 Evaluation of precision of quantitative measurement procedures; approved guideline - third edition

- CLSI EP06 2nd Edition Evaluation of the linearity of quantitative. measurement procedures

- CLSI EP09c 3rd Edition Measurement procedure comparison and bias estimation using patient samples

- CLSI EP17-A2 Evaluation of detection capability for clinical laboratory measurement procedures; approved guideline - second edition

VII   Performance Characteristics (if/when applicable):

A Analytical Performance:

1. <u>Precision/Reproducibility:</u>

The precision of the Miris Human Milk Analyzer (HMA) for measuring fat, crude protein (CP), true protein (TP), and carbohydrate (CHO) content was evaluated following the CLSI EP05-A3 guideline. A precision study was conducted at site 1 by testing five milk samples on one device by one operator over 20 different days, with duplicate measurements per run and two runs per day for a total of 80 measurements per sample.

Additional precision studies were conducted at sites 2 and 3, where milk samples were analyzed using one device by 2-3 operators over five days with triplicate measurements per

run and two runs per day for a total of 30 measurements per sample. All three sites were
HMBANA accredited human donor milk bank sites.

Results of the studies are provided in the tables below.

FAT				Repeatability (within-run variation)		Intermediate Precision (within-lab variation)	
Site	Sample	N	Mean (g/100 mL)	SD (g/100 mL)	CV%	SD (g/100 mL)	CV%
Site 1	1	80	0.7	0.02	2.4	0.04	6.7
	2	80	5.4	0.07	1.3	0.07	1.3
	3	80	2.7	0.03	1.2	0.05	1.7
	4	80	3.4	0.06	1.6	0.07	1.9
	5	80	4.1	0.10	2.6	0.11	2.8
Site 2	1	*29	0.6	0.03	5.2	0.05	8.5
	2	30	5.9	0.08	1.4	0.09	1.5
	3	30	3.0	0.00	0.0	0.06	2.0
	4	30	3.8	0.04	1.0	0.05	1.2
	5	30	4.5	0.06	1.3	0.07	1.6
Site 3	1	30	0.6	0.03	5.3	0.06	8.6
	2	30	5.4	0.07	1.3	0.08	1.5
	3	30	2.7	0.05	1.8	0.06	2.2
	4	30	3.5	0.04	1.3	0.07	1.9
	5	30	4.3	0.10	2.4	0.11	2.5

* The number of results is reduced because one sample was unintentionally not tested and no
results were obtained.

CRUDE PROTEIN				Repeatability (within-run variation)		Intermediate Precision (within-lab variation)	
Site	Sample	N	Mean (g/100 mL)	SD (g/100 mL)	CV%	SD (g/100 mL)	CV%
Site 1	1	80	2.9	0.04	1.2	0.04	1.4
	2	80	1.3	0.03	2.5	0.05	3.6
	3	80	0.9	0.02	2.5	0.04	4.5
	4	80	1.1	0.04	3.5	0.05	4.6
	5	80	1.7	0.03	1.5	0.05	2.8
Site 2	1	*29	2.9	0.04	1.4	0.05	1.8
	2	30	1.4	0.02	1.3	0.02	1.3
	3	30	1.0	0.04	4.5	0.05	4.9
	4	30	1.2	0.02	2.1	0.03	2.8
	5	30	1.8	0.02	1.0	0.02	1.0
Site 3	1	30	3.0	0.04	1.2	0.04	1.2
	2	30	1.3	0.03	2.5	0.05	3.5
	3	30	0.9	0.04	4.1	0.04	4.1
	4	30	1.1	0.00	0.0	0.00	0.0
	5	30	1.8	0.05	2.9	0.06	3.4

TRUE PROTEIN				Repeatability (within-run variation)		Intermediate Precision (within-lab variation)	
Site	Sample	N	Mean (g/100 mL)	SD (g/100 mL)	CV%	SD (g/100 mL)	CV%
Site 1	1	80	2.3	0.02	0.8	0.02	1.0
	2	80	1.1	0.04	3.3	0.04	3.4
	3	80	0.7	0.03	3.6	0.05	6.2
	4	80	0.9	0.04	3.9	0.04	4.7
	5	80	1.4	0.03	2.0	0.04	2.8
Site 2	1	*29	2.4	0.05	1.9	0.05	2.1
	2	30	1.1	0.02	1.7	0.02	1.7
	3	30	0.8	0.04	5.0	0.04	4.8
	4	30	0.9	0.04	4.1	0.04	4.2
	5	30	1.4	0.02	1.3	0.02	1.3
Site 3	1	30	2.4	0.03	1.1	0.03	1.1
	2	30	1.1	0.04	3.5	0.04	3.9
	3	30	0.7	0.04	5.5	0.04	5.7
	4	30	0.9	0.00	0.0	0.00	0.0
	5	30	1.4	0.03	1.8	0.03	1.9

* the number of results is reduced because one sample was unintentionally not tested and no results were obtained.

CARBOHYDRATE				Repeatability (within-run variation)		Intermediate Precision (within-lab variation)	
Site	Sample	N	Mean (g/100 mL)	SD (g/100 mL)	CV%	SD (g/100 mL)	CV%
Site 1	1	80	8.6	0.04	0.5	0.05	0.6
	2	80	8.0	0.05	0.6	0.05	0.7
	3	80	6.8	0.04	0.6	0.05	0.8
	4	80	7.6	0.05	0.5	0.06	0.8
	5	80	7.8	0.05	0.6	0.05	0.7
Site 2	1	*29	9.3	0.04	0.5	0.05	0.6
	2	30	8.4	0.05	0.5	0.06	0.7
	3	30	7.2	0.05	0.7	0.05	0.7
	4	30	8.0	0.05	0.7	0.06	0.7
	5	30	8.3	0.05	0.6	0.05	0.6
Site 3	1	30	9.3	0.06	0.6	0.07	0.8
	2	30	8.3	0.04	0.5	0.07	0.8
	3	30	7.1	0.06	0.8	0.08	1.1
	4	30	8.0	0.06	0.8	0.07	0.8
	5	30	8.2	0.09	1.1	0.12	1.4

* the number of results is reduced because one sample was unintentionally not tested and no results were obtained.

2. Linearity:

A linearity study was performed to evaluate the fat measuring range from 0.6 – 6.0 g/100 mL. Nine levels with fat concentrations spanning the reportable range were analyzed on one device over one day, and each linearity sample was analyzed in duplicate. The observed values were plotted against the expected values and linear regression analysis was performed. The results are provided in the table below.

Concentrations tested (g/100 mL)	R^2	Slope	Intercept
0.3 – 7.3	0.9981	1.0284	-0.1122

The results of this study support the claimed measuring range of 0.6 – 6.0 g/100 mL for the fat parameter.

See DEN180007 for the linearity evaluation for the other parameters (i.e., crude protein and carbohydrates).

3. Analytical Specificity/Interference:

See DEN180007 for the Analytical Specificity and Interference performance for the HMA device.

4. Assay Reportable Range:

Fat   0.6 – 6 g/100 mL
Crude Protein   0.8 – 3 g/100 mL
True Protein   0.6 – 2.4 g/100 mL
Carbohydrates   6.6 – 8.7 g/100 mL

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

See DEN180007.

6. Detection Limit:

See DEN180007 for the Detection Limit performance for the HMA device.

7. Assay Cut-Off:

Not applicable.

8. Accuracy (Instrument):

Not applicable. Refer to section B Comparison Studies.

9. Carry-Over:

See DEN180007 for the evaluation of carry-over with the HMA device.

B   Comparison Studies:

1. Method Comparison with Predicate Device:

The sponsor performed an accuracy study to determine the bias of fat measured on the Miris Human Milk Analyzer (HMA) against validated comparative chemical methods to support the measuring range of fat from 0.6 – 6.0 g/100 mL.

Samples were unmodified, native human milk samples where each study sample was from an individual mother. The study samples covered the following concentration range for fat of 0.6 – 5.9 g/100 mL (measuring range 0.6 – 6 g/100 mL). The results are presented below.

Parameter	N	Corr Coeff	Slope	y-intercept
Fat	105	0.9662	1.08	-0.0097

See DEN180007 for the evaluation of analytes other than fat.

2. Matrix Comparison:

Not applicable. The candidate device can be used with human milk samples only.

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):

Not applicable.

D   Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The sponsor states the following in their labeling:

The composition of human milk is highly variable and affected by multiple factors such as diurnal variation, longitudinal changes associated with postpartum duration, time since last feed, volume of milk consumed at the prior feed, time during feed, and maternal physiological let down.

The sponsor also included in the labeling the variability which can be seen in macronutrients in human milk, based upon a meta-analysis results reported in the literature. The following tables are not intended to be used as expected values for milk supplementation.

Meta-analysis results of the macronutrient composition of term (37-42 weeks of gestation) human milk [1].

Time After Delivery	Fat (g/100 mL)		Crude Protein (g/100 mL)		True Protein (g/100mL)		Lactose (g/100mL)		Oligo-saccharides (g/100mL)		Energy (kcal/100mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 1-3	1.8	0.7	2.0	0.6	2.0	0.9	5.6	0.6	1.6	0.2	54	8
Day 4-7	2.6	0.8	2.0	0.5	1.6	0.3	6.0	1.0	1.9	0.4	66	9
Week 2	3.0	0.9	1.8	0.4	1.3	0.2	6.2	0.6	1.9	0.4	66	9
Week 3-4	3.4	0.8	1.5	0.3	1.1	0.2	6.7	0.7	1.6	0.3	66	8
Week 5-6	3.6	1.1	1.1	0.2	1.0	0.1	6.1	1.0	1.4	0.3	63	7
Week 7-9	3.4	0.8	1.3	0.2	0.9	0.1	6.5	0.5	1.3	0.3	63	7
Week 10-12	3.4	0.9	1.2	0.2	1.0	0.1	6.7	0.7	-		63	8
Colostrum (day1-3)	1.8				2.0		5.6				54	
Mature milk (week 5-12)	3.4				1.0		6.5				63	

Meta-analysis results of the macronutrient composition of preterm (<37 weeks of gestation) human milk [1].

Time After Delivery	Fat (g/100 mL)		Crude Protein (g/100 mL)		True Protein (g/100mL)		Lactose (g/100mL)		Oligo-saccharides (g/100mL)		Energy (kcal/100mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 1-3	2.2	0.9	2.8	1.1	2.7	1.5	5.1	0.7	-		49	7
Day 4-7	3.0	1.2	2.1	0.5	1.7	0.5	6.3	1.1	2.1	0.4	71	9
Week 2	3.5	1.1	1.9	0.4	1.5	0.4	5.7	0.8	2.1	0.5	71	12
Week 3-4	3.5	1.0	1.6	0.4	1.4	0.4	6.0	0.5	1.7	0.3	77	8

Time After Delivery	Fat (g/100 mL)		Crude Protein (g/100 mL)		True Protein (g/100mL)		Lactose (g/100mL)		Oligo-saccharides (g/100mL)		Energy (kcal/100mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Week 5-6	3.2	0.8	1.4	0.3	1.1	0.2	5.8	0.6	-		70	5
Week 7-9	3.3	0.9	1.1	0.2	1.1	0.2	6.3	0.4	-		76	8
Week 10-12	3.4	1.5	1.3	0.3	1.0	0.2	6.8	0.3	-		-	
Colostrum (day1-3)	2.2				2.7		5.1				49	
Mature milk (week 5-12)	3.3				1.1		6.2				73	

Macronutrient composition of donor human milk.

Reference	Fat (g/100 mL)		Crude Protein (g/100 mL)		True Protein (g/100mL)		Carbohydrate (g/100mL)		Energy (kcal/100mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	M	SD
[2]	3.2	1.0	1.2	0.5	-		7.7	0.9	65	9
[3]	3.6		0.9		-		7.2		67	

[1] D. Gidrewicz and T. Fenton. "A systematic review and meta-analysis of the nutrient content of preterm and term breast milk", BMC Pediatrics 14:216, 2014.
[2] K. Wojcik, D. Rechtman, M. Lee, A. Montoya, and E. Medo. "Macronutrient analysis of a nationwide sample of donor breast milk". J Am Diet Assoc, vol. 109, pp. 137-140, 2009.
[3] K. Michaelsen, L. Skafte, J. Badsberg, and M. Jorgensen. "Variation in macronutrients in human bank milk: Influencing factors and implications for milk banking". Journal of Pediatric Gastroenterology and Nutrition, vol. 11, pp. 229-239, 1990.

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.