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

I Background Information:

A 510(k) Number

K213611

B Applicant

CAIRE Diagnostics Inc.

C Proprietary and Established Names

Fenom Pro

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
MXA	Class II	21 CFR 862.3080 - Breath Nitric Oxide Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

Modification of a previously cleared device

B Measurand:

Breath Nitric Oxide

C Type of Test:

Quantitative, amperometric

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

Fenom Pro is a portable, non-invasive device to measure fractional exhaled nitric oxide (FENO) in human breath. FENO is increased in some airway inflammatory processes, such as asthma, and decreases in response to anti-inflammatory treatment. Fenom Pro measures fractional exhaled nitric oxide according to guidelines established by the American Thoracic Society.

Measurement of FENO by Fenom Pro is a non-invasive quantitative method to measure the decrease in FENO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy as an indication of therapeutic effect in patients with elevated FENO levels. FENO measurements are to be used as an adjunct to established clinical assessments. Fenom Pro is suitable for adults and children 6 years and older.

Fenom Pro should be used in a point-of-care healthcare setting under professional supervision. Fenom Pro should not be used in critical care, emergency care or in anesthesiology.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Fenom Pro may not be used by children under the age of 6 years, including infants, or by patients who are unable to understand and execute the instructions given by healthcare providers, as measurement requires patient cooperation.

Fenom Pro should not be used in critical care, emergency care, or in anesthesiology.

All subjects should refrain from eating or drinking for at least 60 minutes before the FENOM test. Recent intake of nitrate rich food, such as lettuce, spinach, beets, walnuts, peanuts, and animal organs, can lead to increased FeNO levels.

Smoking reduces exhaled NO levels. Fenom results obtained from subjects who smoke should only be considered after considering the subject's smoking history and the potential impact on NO levels.

D Special Instrument Requirements:

Fenom Pro

IV Device/System Characteristics:

A Device Description:

Fenom Pro is a point-of-care (POC) breath analyzer that quantitatively measures fractional exhaled nitric oxide (NO) in expired human breath.

The device is comprised of three major components (main unit, handpiece, and mouthpiece). The main unit contains a touch screen interface for the user as well as the nitric oxide sensor and pneumatics needed to sample the patient's breath. The patient interfaces with the device through the mouthpiece which is attached to the handpiece. The handpiece is connected to the main unit via a breath tube. The mouthpiece is a single patient use, disposable component that contains an anti-bacterial/anti-viral filter. The mouthpiece has an ergonomically designed oval interface to aid in creating a proper seal during the breath maneuver.

To measure the fraction of exhaled FeNO in human exhaled breath using the Fenom Pro, the patient performs a breath maneuver by grasping the handpiece attached to the main unit of the device and exhaling into it. A graphical user interface (GUI) display assists the patient in keeping their breath flow rate within acceptable limits.

B Principle of Operation:

The candidate device uses solid-state electrochemical sensor technology sensitive to nitric oxide (NO) compounds. The solid state sensor is preceded by a reactive filter material that renders (oxidizes) potentially confounding species such as carbon monoxide (CO), ammonia (NH_4), and methanol (CH_4O) inactive, or inert, to the NO sensor. Fenom Pro provides visual and audible feedback during its use. A user performs a breath maneuver by exhaling into the device, and the graphical user interface (GUI) displays an indication of the user's breath flow rate, such that the user can modulate their breath flow rate to be within the acceptable limits. An electrochemical potential difference between the electrodes of the sensor develops and is proportional to the amount of NO in the breath sample.

C Instrument Description Information:

1. Instrument Name:

   Fenom Pro

2. Specimen Identification:

   There is no mechanism to identify the specimen, as it is analyzed at the point and time of collection. Results are stored in the order they are performed, cataloged by date and time. No patient information is entered or stored on the device.

3. Specimen Sampling and Handling:

   The user obtains a breath sample by having the subject exhale into the device.

4. Calibration:

   The device is calibrated by the manufacturer; no calibration is required by customers.

5. Quality Control:

The device utilizes internal and external quality control procedures. For external quality control, two measurements (a positive and a negative control) are required to validate device performance. Quality control should be performed each day of device use.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Fenom Pro Nitric Oxide Test

B Predicate 510(k) Number(s):
K182874

C Comparison with Predicate(s):

Device & Predicate Device(s):	K213611	K182874
Device Trade Name	Fenom Pro	Fenom Pro Nitric Oxide Test
General Device Characteristic Similarities		
Intended Use/Indications For Use	Same	For the measurement of fractional exhaled nitric oxide (FeNO) in human breath.
Sample Type	Same	Exhaled human breath
Measurement Range	Same	10-200 ppb NO
Analysis Time	Same	Approximately 30 seconds
Limit of Detection	Same	10 ppb
General Device Characteristic Differences		
Sensor Type	Amperometric Sensor Technology	Potentiometric Sensor Technology
Measurement Mode	6-second and 10-second breath maneuver	10-second breath maneuver
Intended Users	Suitable for children and adults 6 years and older.	Suitable for children and adults 7 years and older.

VI Standards/Guidance Documents Referenced:

- ISO 14971 Third Edition 2019-12 Medical devices - Application of risk management to medical devices
- CLSI EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition

- ISTA 3A 2018 Packaged-Products for Parcel Delivery System Shipment 70 kg (150 lb) or Less

- ISO 10993-5 Third edition 2009-06-01 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity

- ISO 10993-11 Third edition 2017-09 Biological evaluation of medical devices - Part 11: Tests for systemic toxicity

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Analytical precision

The sponsor performed studies to evaluate the within-device precision and repeatability of the candidate device, based on CLSI EP05-A3. Target values for the precision samples were measured using a chemiluminescence device calibrated against a NIST traceable NO tank. Data were collected using 5 candidate devices, over 5 operating days, 2 sessions per day, 4 runs per session with 2 replicates for each concentration, at concentrations of 10, 25, 75 and 200 ppb, by multiple operators. Repeatability is an estimate of variation within one test run in one day. Within-device precision is an estimate of variation between test runs and days. The repeatability and within-device precision over the five days was determined for each concentration.

Precision was evaluated for the 10-second mode and 6-second mode separately and the results are summarized in the tables below:

Precision Study Summary (10-second mode)

	Repeatability				Within-Device Precision			
	SD (ppb)	SD (ppb)	CV(%)	CV(%)	SD (ppb)	SD (ppb)	CV(%)	CV(%)
NO Conc.	10 ppb	25 ppb	75 ppb	200 ppb	10 ppb	25 ppb	75 ppb	200 ppb
Device 1	1.1	1.5	2.4%	1.4%	2.0	3.2	3.7%	1.3%
Device 2	0.8	1.3	2.1%	1.4%	1.0	1.9	3.5%	1.5%
Device 3	0.8	1.2	1.8%	1.1%	1.5	2.0	3.8%	1.3%
Device 4	1.2	1.7	5.0%	4.5%	1.5	2.5	5.5%	4.5%
Device 5	0.8	1.1	1.9%	1.7%	1.4	1.5	2.4%	1.8%

Precision Study Summary (6-second mode)

	Repeatability				Within-Device Precision			
	SD (ppb)	SD (ppb)	CV(%)	CV(%)	SD (ppb)	SD (ppb)	CV(%)	CV(%)
NO Conc.	10 ppb	25 ppb	75 ppb	200 ppb	10 ppb	25 ppb	75 ppb	200 ppb
Device 1	1.5	1.2	2.4%	1.8%	1.3	1.8	5.1%	6.4%
Device 2	2.2	0.7	2.1%	1.0%	1.3	1.4	6.4%	6.7%
Device 3	2	1.3	3.1%	2.6%	2.0	2.3	4.3%	4.2%
Device 4	1.6	1.3	2.2%	1.7%	1.3	1.1	3.9%	5.0%
Device 5	1.6	0.9	2.3%	1.5%	1.5	3.2	7.7%	8.9%

Clinical precision

The clinical precision of the candidate device was evaluated as part of a clinical study which included a total of 11 point of care sites. Across all sites, 17 healthcare providers (operators) assisted with the data collection. Each of the 70 subjects provided duplicate samples using both the 6-second and 10-second measurement modes at each of two visits. The clinical precision results per mode and visit are summarized in the tables below:

10-second mode – visit 1

Median Concentrations	Number of subjects	Within Subject Mean SD (ppb)	95% CI for SD (ppb)	Within Subject Mean CV (%)	95% CI for CV (%)
<10	--	n/a	n/a	n/a	n/a
10 to <20	--	n/a	n/a	n/a	n/a
20 to <30	6	1.650	0.971, 3.317	5.86	3.45, 11.78
30 to <40	16	1.989	1.434, 2.931	5.88	4.24, 8.66
40 to <50	16	2.696	1.944, 3.973	5.88	4.24, 8.67
≥ 50	32	3.027	2.396, 3.941	3.54	2.80, 4.60

10-second mode – visit 2

Median Concentrations	Number of subjects	Within Subject Mean SD (ppb)	95% CI for SD (ppb)	Within Subject Mean CV (%)	95% CI for CV (%)
<10	2	0.000	0.000, 0.000	0.00	0.00, 0.00
10 to <20	22	0.964	0.729, 1.333	6.08	4.59, 8.41
20 to <30	19	1.675	1.240, 2.381	6.79	5.03, 9.66
30 to <40	10	2.33	1.547, 3.885	6.60	4.38, 10.99
40 to <50	5	2.404	1.342, 5.274	5.40	3.02, 11.85
≥ 50	12	2.239	1.537, 3.539	3.36	2.31, 5.31

6-second mode – visit 1

Median Concentrations	Number of subjects	Within Subject Mean SD (ppb)	95% CI for SD (ppb)	Within Subject Mean CV (%)	95% CI for CV (%)
<10	--	n/a	n/a	n/a	n/a
10 to <20	--	n/a	n/a	n/a	n/a
20 to <30	10	1.980	1.312, 3.296	7.00	4.64, 11.65
30 to <40	10	2.263	1.500, 3.767	6.52	4.32, 10.86
40 to <50	15	2.310	1.648, 3.454	5.07	3.62, 7.58
≥ 50	35	2.889	2.310, 3.714	3.48	2.78, 4.48

6-second mode – visit 2

Median Concentrations	Number of subjects	Within Subject Mean SD (ppb)	95% CI for SD (ppb)	Within Subject Mean CV (%)	95% CI for CV (%)
<10	--	n/a	n/a	n/a	n/a
10 to <20	23	0.953	0.724, 1.308	6.03	4.58, 8.27
20 to <30	18	1.139	0.837, 1.637	4.69	3.44, 6.74
30 to <40	10	2.051	1.359, 3.414	6.00	3.98, 10.00
40 to <50	7	3.435	2.102, 6.472	7.71	4.72, 14.52
≥ 50	12	2.946	2.023, 4.656	4.44	3.05, 7.01

2. Linearity:

The sponsor performed studies to evaluate the linearity performance of the candidate device. Nitric oxide was mixed to create simulated breath gas to obtain 10 NO concentration levels ranging from 5-330 ppb (5, 10, 15, 30, 50, 100, 150, 200, 300, and 330 ppb).

Five replicates were obtained at each level, and ten candidate devices were evaluated in both the 6-second and the 10-second modes. The range of slope, intercept, and R^2 values obtained are listed in the tables below.

	Range of Slopes	Range of Intercepts	Range of R^2
6-second mode	0.96 – 1.03	-1.11 – 1.87	0.99 – 1.00
10-second mode	0.96 – 1.05	-1.58 – 1.23	0.99 – 1.00

Effect of extreme temperature and relative humidity

The sponsor performed a study to evaluate the effects of extreme temperature and humidity conditions on the performance of the candidate device. Two devices were tested in an environmentally controlled chamber at the four corners of temperature and humidity extremes (15-30° C and 20-80% RH) at three NO concentrations (15, 75, and 200 ppb) in air with 5 replicates at each combination of temperature and humidity:

Condition	Temperature (°C)	Relative Humidity (%RH)
low temperature/low humidity	15°	20%
high temperature/low humidity	30°	20%
low temperature/high humidity	15°	80%
high temperature/high humidity	30°	80%

The results support the claimed operating conditions for the candidate device of 15°C-30°C and 20-80% RH .

3. Analytical Specificity/Interference:

Interference from endogenous compounds and exogenous substances

The sponsor performed a study to evaluate potential interference from endogenous compounds and exogenous substances.

The following endogenous compounds were tested at the concentrations listed below:

Substance	**Concentration Tested**
Acetaldehyde	923 ppb
Acetone	102 ppm
Acetonitrile	500 ppb
Ammonia	100 ppm
Carbon Dioxide	8% vol
Carbon Monoxide	249 ppm
Ethanol	1000 ppm
Hydrogen	480 ppm
Hydrogen Sulfide	5 ppm
Isoprene	1.5 ppm
Hydrogen Peroxide	500 ppm
Nitrogen Dioxide	1 ppm
Oxygen	100% vol

All of the compounds tested met the sponsor's acceptance criteria and were determined not to interfere with the NO measurement.

Exogenous substances

The sponsor also performed a study at a single site by testing FeNO levels after use of seven common substances that are orally consumed or utilized and could potentially interfere with the device. Each subject performed one baseline measurement before the exogenous

substance was introduced and one measurement 60 minutes post exposure or consumption. All subjects refrained from eating or drinking for 60 minutes prior to the baseline testing. The results of the study are shown below and support that there is no significant effect of these exogenous substances on the measurement of FeNO by the candidate device, if users allow one hour to pass before a FeNO measurement. The device labeling recommends that no food or beverage be consumed, and no smoking be done, for at least one hour before taking a FeNO measurement.

Exogenous Substance	No. of subjects	Mean difference (ppb)	95% Confidence Intervals (ppb)
Alcohol Free Mouthwash	16	0.3	[-1.8, 2.3]
Caffeinated Soda	15	-0.9	[-4.3, 2.6]
Caffeine Free Soda	16	-1.1	[-3.0, 0.7]
Menthol Mint	17	-0.1	[-2.4, 2.2]
Mouthwash with Alcohol	16	2.4	[0.2, 4.7]
Mint (no menthol)	15	-1.0	[-2.3, 0.3]
Toothpaste	16	0.8	[-1.1, 2.7]

Effect of altitude

The sponsor performed a study to evaluate the effect of altitude on the candidate device. Four devices were tested using both 6-second and 10-second modes at 25, 50, and 200 ppb NO in seven replicates each at 330 feet (the nominal condition) and at 6550 feet. For all devices at all conditions the difference between the nominal condition and 6550 feet was ≤ 8.8% and the %CVs were all ≤ 6.7%.

4. Assay Reportable Range:

The results of the sponsor's detection limit and linearity studies support the claimed measuring range of 10-200 ppb FeNO.

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

Calibration stability

The manufacturer performs calibration for each Fenom Pro device. No calibration is required by the user.

Mouthpiece shelf life

The claimed shelf-life for the mouthpiece is 23 months.

6. Detection Limit:

   The sponsor provided data collected with both the 6-second and 10-second modes that supported the claimed detection limit of 10 ppb.

7. Assay Cut-Off:

   Not applicable.

8. Accuracy (Instrument):

   Please see Comparison Studies section below.

9. Carry-Over:

   The sponsor performed a study to evaluate the potential for carryover from a high concentration FeNO sample to a subsequent sample. Five devices were evaluated using both the 6-second and 10-second modes and the FeNO concentrations applied to assess carryover ranged from approximately 10 to 200 ppb. The results showed no carryover effect.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Not applicable. A clinical study was conducted to validate the clinical performance of the candidate device.

2. Matrix Comparison:

   Not applicable. The assay can be run using breath 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):

   The sponsor provided the results of a study incorporating both the 6-second and 10-second modes to evaluate the clinical accuracy of the candidate device. A total of 70 patients (38

adults 18 years of age and older and 32 children ages 6 – 17) participated in the study where measurements for FeNO, spirometry, and asthma control questionnaires (ACQ) were completed at baseline (Visit 1) and two weeks later (Visit 2) after therapeutic agents were administered. The study included data from a total of 11 sites, and 17 healthcare providers (operators) assisted with the data collection.

The American Thoracic Society (ATS) defines elevated FENO as >25 ppb for adults and > 20 ppb for children. The initial (visit 1) FENO inclusion criteria for this study were >30 ppb for adults and >25 ppb for children.

A meaningful decline is defined by ATS as >20% for initial FENO values >50 ppb and >10 ppb for initial FENO values <50 ppb. Among the pediatric subjects, 84.4% showed a meaningful decline in FeNO. Among the adult subjects, 70.3% showed a meaningful decline in FeNO. Overall results showed a mean FeNO change of -28.2 ppb (-41.12%) with a mean SD of 30.89 ppb.

The decline in FeNO was accompanied by the following changes in subjective and objective asthma measures.

The following secondary outcome measures showed the following after 2 weeks of corticosteroid therapy that accompanied the fall in FeNO described above.

ACQ: Mean ACQ score fell by 50.0% after corticosteroids.

FEV1: There was a mean FEV_1 change of 12.5% after corticosteroids.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The sponsor states the following in the labeling: The fractional NO concentration in expired breath can be measured by the Fenom Pro device according to guidelines for NO measurement established by the American Thoracic Society (ATS) and European Respiratory Society (ERS).

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.