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

I Background Information:

A 510(k) Number

K233775

B Applicant

Bosch Healthcare Solutions GmbH

C Proprietary and Established Names

Vivatmo 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:

New device

B Measurand:

Fractional exhaled nitric oxide

C Type of Test:

Chemical field effect transistor (Chem-FET)

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

Vivatmo pro nitric oxide test 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 often decreases in response to anti-inflammatory treatment. Measurement of FeNO by Vivatmo pro is a 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.

Vivatmo pro is suitable for children, approximately 7-17 years, and adults 18 years and older.

Testing using the Vivatmo pro should only be done in a point-of-care healthcare setting under professional supervision. Vivatmo 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

Regardless of displayed measured results, monitor signs or symptoms of chest tightness, shortness of breath, coughing or wheezing for decisions about treatment. Do not use the device for subjects suffering from acute upper or lower respiratory infection disease or with current serious medical conditions (other than asthma).

Vivatmo pro should not be used in critical care, emergency care or in anesthesiology. The following conditions can influence correct measurement of results and shall be avoided: smoking or tobacco consumption for at least 1 hour before the measurement, eating or drinking at least 1 hour before the measurement, especially nitrate rich food (e.g., spinach), strenuous exercise, use of rescue inhaler or leukotriene modifier 1h before measurement.

The device is not indicated for children under the age of 7 years of age including infants, or by patients who are unable to understand and execute the instructions given by healthcare providers, as measurement requires patient cooperation.

D Special Instrument Requirements:

Vivatmo Pro

IV Device/System Characteristics:

A Device Description:

The Vivatmo pro device is comprised of the following main components:

1. A Vivatmo pro handheld, which holds the measuring module with electronics, display and the rechargeable battery. The handheld includes software to drive the handheld.
2. A Vivatmo pro basestation, which consists of a cradle to charge the Vivatmo pro handheld and a single board computer to run the Vivatmo pro software driving the touch screen and the interfaces. The basestation is provided with an external power supply.
3. The Vivatmo pro software that runs on the Vivatmo pro basestation.
4. A Vivatmo pro Oxycap, which is a disposable mouthpiece holding filters, desiccant and converter materials to prepare the exhaled breath for the measurement. Vivatmo pro Oxycap is for single use and must be replaced for every new patient and measurement occasion.
5. A Vivatmo pro Level 0 accessory, a disposable mouthpiece with filters, desiccant and reagent to remove NO to facilitate a measurement with 0 ppb FeNO for QC purposes.

B Principle of Operation:

Vivatmo pro nitric oxide test is a portable, non-invasive device to measure fractional exhaled nitric oxide (FeNO) in human breath.

The measurement procedure of the Vivatmo pro generates the fraction of the exhaled breath (FeNO). The last 3 second fraction of a 10 second exhalation is evaluated for average NO concentration. The exhalation flow is controlled to 50 ml/s ±5 ml/s at an applied pressure of 10 to 20 cm H2O.

The measurement method of Vivatmo pro is Chemical field effect transistor (Chem-FET). The measurement sample is internally taken after a bypass time period and directly forwarded onto the sensor. The nitrogen dioxide molecules are adsorbed on the sensor layer and the change in the binding energy creates an electrical signal, which is transferred into a quantifiable measurement signal. The nitrogen dioxide is converted from Nitric oxide in the breath by a potassium permanganate converter in the disposable mouthpiece.

NO2 is measured using Chem-FET detection with NO2 molecules accumulated to a sensitive layer changing the electrical field of the capacitor. The drop of voltage is proportional with the number of NO2 molecules accumulated.

C Instrument Description Information:

1. Instrument Name:

   Vivatmo Pro

2. Specimen Identification:

   The healthcare professional assists the patient, who performs the test in real-time and is identified by patient name

3. Specimen Sampling and Handling:

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

4. Calibration:

   The manufacturer performs calibration for each Vivatmo Pro device. Recalibration by the user is not possible.

5. Quality Control:

   QC is recommended weekly or after 50 measurements if Vivatmo pro is used in a clinical environment or point-of-care healthcare setting under professional supervision.

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):	K233775	K182874
Device Trade Name	Bosch Vivatmo pro	Fenom Pro
General Device Characteristic Similarities		
Intended Use/Indications For Use	Same	Device intended to measure fractional exhaled nitric oxide (FeNO) in human breath
Sample type	Same	Exhaled human breath
Intended Use Setting	Same	Point-of-care healthcare setting under professional supervision
Intended Users	Same	Children 7-17 years and adults
General Device Characteristic Differences		
Analysis Time	Approximately 5 seconds	Approximately 30 seconds
Measurement Range	5-300 ppb NO	10-200 ppb NO
Detection Limit	5 ppb NO	10 ppb NO

VI Standards/Guidance Documents Referenced:

- 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
- ISO 10993-5:2009 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity
- ISO 10993-12:2012 Biological evaluation of medical devices - Part 12: Sample preparation and reference materials
- Breath Nitric Oxide Test System - Class II Special Controls Guidance Document for Industry and FDA Staff, Document issued on: July 7, 2003
- CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A study was performed to assess the analytical precision of the candidate device.

A nested components-of-variance design with 20 testing days, three devices, two runs per day and two replicate measurements per run for each concentration was used. Five NO concentrations (in simulated breath) were evaluated at 15 ppb, 25 ppb, 50 ppb, 200 ppb and 275 ppb and the data was collected by three operators.

Repeatability and within-device precision were determined for each concentration as shown in the tables below:

Within-device Precision

NO Concentration	**15 ppb**	**25 ppb**	**50 ppb**	**200 ppb**	**275 ppb**
	SD (ppb)	SD (ppb)	SD (ppb)	CV %	CV/%
Device 1	3	4	5	4	5
Device 2	3	4	5	3	5
Device 3	3	3	5	4	4

Repeatability

NO Concentration	**15 ppb**	**25 ppb**	**50 ppb**	**200 ppb**	**275 ppb**
	SD (ppb)	SD (ppb)	SD (ppb)	CV/ %	CV/ %
Device 1	2	2	2	3	4
Device 2	1	1	2	2	2
Device 3	2	1	2	3	2

Clinical Precision

Clinical precision was assessed by studying the device in 65 children and 78 adults (143 subjects). At least 2 FeNO measurements per subject were collected by a total of 16 operators across seven different clinical sites.

Clinical repeatability was assessed together with the 95%-confidence interval as pooled standard deviation (mean of measurement pair within visit < 50 ppb) and CV (mean of measurement pair within visit ≥ 50 ppb), respectively, using the residual variance component resulting from a random effects ANOVA (as used in CLSI EP05 guideline). Results are summarized in the table below.

Median Concentration [ppb]	N	Within subject mean SD [ppb]	Within subject mean CV [%]	95% CI for SD	95% CI for CV
0 to <10	28	1.09	15.64%	0.93; 1.31	13.37%;18.85%
10 to <20	56	2.19	15.47%	1.95; 2.51	13.74%; 17.70 %
20 to <30	28	2.45	10.07%	2.12; 2.89	8.73%; 11.91 %
30 to <40	18	3.30	9.62%	2.64; 4.41	7.69 %; 12.86 %
40 to<50	8	4.46	9.80%	3.43; 6.37	7.54%; 14.00 %
>=50 ppb	45	6.54	7.75%	5.81; 7.47	6.88 %; 8.86 %

2. Linearity:
Linearity was evaluated within one single run, measuring a range of concentrations above and below the claimed measuring range with the concentrations known relative to each other. In total, nine NO concentrations and a negative control were tested in the following order: 50 ppb, 10 ppb, 300 ppb, 5 ppb, 100 ppb, 0 ppb, 150 ppb, 25 ppb, 330 ppb, 3 ppb, 3 ppb, 3 ppb.

For the determination of the linear range, the slope and r^2 coefficient of the linear fit of measurement values plotted against NO concentration in the claimed range of 5 - 300 ppb NO were calculated:

Slope	Intercept	R^2
0.97	2.23	0.999

3. Analytical Specificity/Interference:

The sponsor performed studies to evaluate the potential for interference from various endogenous and exogenous compounds that could be present in human breath or are consumed.

Endogenous Substances

Interference testing was performed using simulated breath. The following endogenous substances did not interfere with the FeNO measurement at the concentrations listed in the table below:

Endogenous Substance	Concentration Tested
Acetaldehyde	150 ppb
Acetone	5 ppm
Acetonitrile	150 ppb
Ammonia	1 ppm
Carbon Dioxide	8 %
Carbon Monoxide	50 ppm
Ethanol	165 ppm
Hydrogen	50 ppm
Hydrogen Sulfide	4 ppm
Isoprene	1.5 ppm
Oxygen	21%
Hydrogen Peroxide	600 ppm
Nitrogen Dioxide	13 ppb

Exogenous Substances:

The following exogenous substances did not interfere with the FeNO measurements when tested 60 minutes after consumption: alcohol free mouthwash, caffeinated soda, caffeine free soda, menthol lozenge, non-menthol lozenge, mouthwash with alcohol, and toothpaste.

Effect of Temperature and Humidity

A study was performed to assess the effects of temperature and humidity on the candidate device. Four combinations of temperature and humidity were evaluated using three devices with conditions slightly outside the claimed temperature and humidity ranges. Duplicate measurements were performed at NO concentrations of 15, 50, 275 ppb.

Baseline measurements at standard conditions (22 °C, 37 % r.h.) were performed, and the difference from baseline at each combination of temperature and humidity was calculated. No effect was seen at the combinations of temperature and humidity listed in the table below:

High temperature, high humidity	30 °C , 65 % r.h.
High temperature, low humidity	30 °C, 10 % r. h.
Low temperature, high humidity	10 °C, 65 % r. h.
Low temperature, low humidity	10 °C, 10 % r. h.

The sponsor additionally provided testing of the device when used at temperatures between 50-65°C and 65-80% relative humidity. Results indicate that the device either returned accurate results or were flagged as invalid (with no result reported).

Effect of Altitude
The sponsor provided information that was adequate to support the claimed operating pressure for the device (780-1100 hPa), corresponding to elevation up to 65,000 feet above sea level.

Assay Reportable Range:

The claimed range is 5 – 300 ppb.

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

   The device is traceable to commercially available materials.

5. Detection Limit:

   The sponsor performed a study based upon recommendation in CLSI EP17-A2 to characterize the lowest concentration that can be detected by the candidate device. The Limit of Blank (LoB) was calculated to be 2.6 ppb and the Limit of Detection (LoD) was calculated to be 3.8 ppb. The sponsor claims a lower limit of measurement of 5 ppb for the device.

6. Assay Cut-Off:

   Not applicable.

7. Accuracy (Instrument):

   Please see Comparison Studies section below.

8. Carry-Over:
   The sponsor performed a study to evaluate carry- over by analyzing a sample with a concentration below the measuring range immediately after a high concentration sample. Results were adequate to demonstrate that the risks of carryover were adequately mitigated.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Not applicable.

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):

   Clinical Accuracy
   A study was also performed to assess the clinical accuracy of the device. A total of 161 patients (n= 106 adults and n=55 children) participated in a longitudinal study where measurements for FeNO, spirometry, and asthma control questionnaires were completed at baseline (Visit 1) and two weeks later (Visit 2) after therapeutic agents were administered.

   For those with elevated initial FeNO levels >30 ppb for adults and > 25 ppb for children (total n=95), there was a fall in mean FeNO measured by Vivatmo Pro in patients with elevated FeNO levels for combined adult and pediatric treatment populations. Results showed a mean change of -39.1 ppb (-41.6%) with a mean SD of 43.9.

   The decline in FeNO after 2 weeks of corticosteroid therapy resulted in the following changes in subjective and objective asthma measures.
   • ACQ: Mean ACQ score fell by -51.1 % after corticosteroids
   • FEV1: There was a mean FEV1 change of 6.9 % after corticosteroids

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

In the labeling, the sponsor instructs the user to refer to the Official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications.

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.