

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

**A. 510(k) Number:**

k072816

**B. Purpose for Submission:**

New Device

**C. Measurand:**

Breath Nitric Oxide

**D. Type of Test:**

Quantitative

**E. Applicant:**

Aerocrine AB

**F. Proprietary and Established Names:**

NIOX MINO® Airway Inflammation Monitor

**G. Regulatory Information:**

1. Regulation section:  
21 CFR § 862.3080
2. Classification:  
Class II
3. Product code:  
MXA
4. Panel:  
Toxicology (91)

**H. Intended Use:**

1. Intended use(s):  
Refer to indications for use below.
2. Indication(s) for use:  
NIOX MINO® measures Nitric Oxide (NO) in human breath. Nitric Oxide is frequently increased in some inflammatory processes such as asthma. The fractional NO concentration in expired breath (FE<sub>NO</sub>), can be measured by NIOX MINO according to guidelines for NO measurement established by the American Thoracic Society.

Measurement of FE<sub>NO</sub> by NIOX MINO is a quantitative, non-invasive, simple and safe method to measure the decrease in FE<sub>NO</sub> concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy, as an indication of the therapeutic effect in patients

with elevated FE<sub>NO</sub> levels. NIOX MINO is suitable for children, approximately 7 - 17 years, and adults 18 years and older.

FE<sub>NO</sub> measurements provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to the established clinical and laboratory assessments in asthma. NIOX MINO should only be used as directed in the NIOX MINO User Manual and the NIOX MINO Quality Control Test User Manual, by trained physicians, nurses, respiratory therapists and laboratory technicians. NIOX MINO cannot be used with infants or by children approximately under the age of 7, as measurement requires patient cooperation. NIOX MINO should not be used in critical care, emergency care or in anaesthesiology.

3. Special conditions for use statement(s):

NIOX MINO should only be used as directed in the User Manual and by trained physicians, nurses, respiratory therapists and laboratory technicians. NIOX MINO cannot be used with infants or by children under the age of 7, as measurement requires patient cooperation. NIOX MINO should not be used in critical care, emergency care or in anaesthesiology. Subjects should not smoke in the hour before measurements, and short- and long-term active and passive smoking history should be recorded. In addition, subjects should refrain from eating and drinking for 1 hour before exhaled NO measurement. Alcohol ingestion reduces FE<sub>NO</sub> in patients with asthma and healthy subjects FE<sub>NO</sub>. It is prudent, where possible, to perform serial NO measurements in the same period of the day and to always record the time.

4. Special instrument requirements:

NIOX MINO® Airway Inflammation Monitor

**I. Device Description:**

NIOX MINO® is a hand held device intended to measure fractional exhaled Nitric Oxide (FE<sub>NO</sub>) in human breath. The NIOX MINO system includes a sampling and gas conditioning system and a man-machine interface (MMI). The user is guided on the built-in touch-screen display through the breathing maneuver by use of the interactive MMI. The NO concentration is detected by an electrochemical sensor. Results are processed using dedicated software and are expressed as NO concentration in parts per billion (ppb).

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

NIOX

2. Predicate 510(k) number(s):

k021133

3. Comparison with predicate:

<b>Characteristic</b>	<b>NIOX MINO®</b>	<b>NIOX®</b>
<b>Device type</b>	Hand held device	Stationary device
<b>Risks to health</b>	There are no known direct risks to patient health. However, failure of the test to perform as indicated or erroneous interpretation of results may lead to improper patient management. Therefore, use of FE <sub>NO</sub> measurement results to adjust a treatment regimen without consideration of other clinical factors could pose a risk.	There are no known direct risks to patient health. However, failure of the test to perform as indicated or erroneous interpretation of results may lead to improper patient management. Therefore, use of FE <sub>NO</sub> measurement results to adjust a treatment regimen without consideration of other clinical factors could pose a risk.
<b>Target population</b>	Suitable for children, 7 - 17 years, and adults 18 years and older.	Suitable for children, 4 - 17 years and adults 18 years and older.
<b>Measurement principles</b>	Measurement principle is based on ATS guidelines. The last three 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 H <sub>2</sub> O. The inhaled air is NO free. Electrochemical detection, NO concentration derived from proportional electrical current.	Measurement principle is based on ATS guidelines. The last three 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 H <sub>2</sub> O. The inhaled air is NO free. Chemiluminescence detection, NO concentration derived from proportional photon emission.
<b>Measurement range</b>	5 - 300 ppb	2 - 200 ppb
<b>Detection level</b>	5 ppb	2 ppb

**K. Standard/Guidance Document Referenced (if applicable):**

The sponsor states the use of the following standards:

- ISO 13485:2003 Medical Device – Quality Management Systems – Requirements for Regulatory Purposes.
- ISO 14971:2000 Medical Devices - Application of risk management to medical devices
- 93/42/EEG, Medical Device Directive conformity, certification Intertek- SEMKO
- EN/IEC 60601-1:1988 Medical Electrical Equipment Part 1 General requirements for safety
- EN/IEC 60601-1-1:2000 Collateral standard; Safety requirements for medical electrical systems
- EN/IEC 60601-1-2:2001 Collateral standard; Electromagnetic compatibility - Requirements and tests
- EN/IEC 60601-1-4:2000 Collateral standard; Programmable electrical medical systems
- 21CFR 862.3080 Class II Special Control Guidance Document Breath Nitric Oxide Test System, Food and Drug Administration, Centre for Devices and Radiological

Health, Division of Chemistry and Toxicology Devices, Office of In Vitro Diagnostic Device Evaluation and Safety, July 7, 2003.

- 21 CFR Part 820 - Quality System Regulation, US Federal Register, Food and Drug Administration, current version.
- Draft Guidance Total Product Life Cycle for Portable Invasive Blood Glucose Monitoring Systems, October 24, 2006
- Guidance for the content of premarket submission for Software Contained in Medical Devices, May 1998.
- General Principles of Software Validation, Final Guidance for Industry and FDA Staff, 2002
- CLSI EP5-A2, Vol 24 No. 25, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline.
- CLSI EP6-A, Vol 23, No. 16, Evaluation of the Linearity of Quantitative Measurement Procedures; Approved Guideline.
- CLSI EP7-A, Vol 22, No. 27, Interference Testing in Clinical Chemistry; Approved Guideline.
- CLSI EP9-A2, Vol 22, No. 19, Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

**L. Test Principle:**

The measurement principle is based on the American Thoracic Society (ATS) guidelines (ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. Am J Respir Crit Care Med. 2005;171:912-930). The last three second fraction of a 10 second exhalation is evaluated for average NO concentration. The exhalation flow is controlled to 50 ml/s  $\pm$ 5 ml/s at an applied pressure of 10 to 20 cm H<sub>2</sub>O. The inhaled air is NO free. Electrochemical detection, NO concentration derived from proportional electrical current.

**M. Performance Characteristics (if/when applicable):**

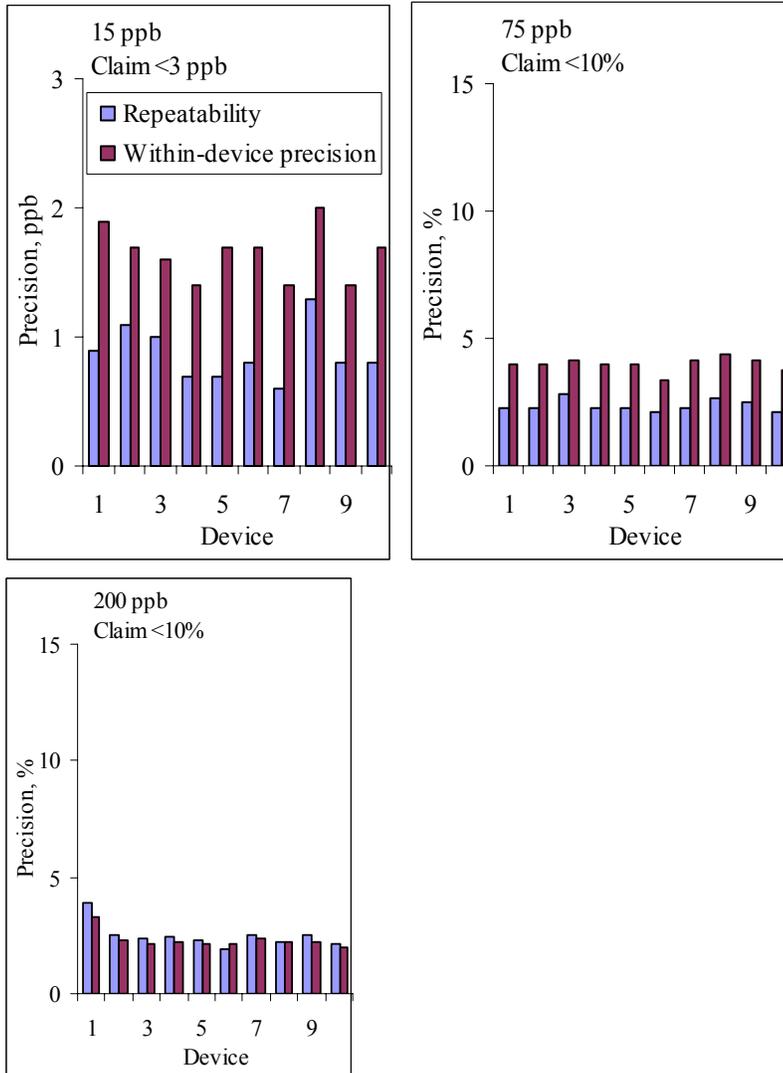
1. Analytical performance:

a. *Precision/Reproducibility:*

Analytical precision was determined in-house. Certified NO in N<sub>2</sub> calibration gas of 200 ppb was mixed with nitrogen gas in a gas mixer, connected in-line with the NIOX MINO instrument, to obtain three NO concentration levels (15, 75, and 200 ppb). Two replicate determinations of each concentration were made twice a day (more than 2 hours apart) for 20 days. 10 NIOX MINO sensors, continually mounted in 10 NIOX MINO instruments, respectively, were used in these tests. All NIOX MINO instruments were tested and stored at ambient room conditions. The NIOX MINO instruments were continuously powered during the test period.

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. Both repeatability and within-device precision were calculated for the 10 instruments. The results at 15 ppb are expressed as absolute values in ppb.

The results at the 75 and 200 ppb levels were expressed as percentage of the measured NO concentration. The results demonstrate that the repeatability and within-device precision are within the sponsor's specification limits: < 3 ppb of measured NO value < 30 ppb, < 10 % of measured NO value  $\geq$  30 ppb. The results are presented in the figure and table below.



Precision at 15, 75 and 200ppb.						
	Repeatability			Within-device precision		
NO concentration, ppb	15	75	213	15	75	213
Limits	< 3 ppb	< 10 %	< 10%	< 3 ppb	< 10%	< 10%
NIOX MINO #						
1	0.9 ppb	2.3 %	3.9 %	1.9 ppb	4.0 %	3.3 %
2	1.1 ppb	2.3 %	2.5 %	1.7 ppb	4.0 %	2.3 %
3	1.0 ppb	2.8 %	2.4 %	1.6 ppb	4.1 %	2.1 %
4	0.7 ppb	2.3 %	2.4 %	1.4 ppb	4.0 %	2.2 %
5	0.7 ppb	2.3 %	2.3 %	1.7 ppb	4.0 %	2.2 %
6	0.8 ppb	2.1 %	1.9 %	1.7 ppb	3.3 %	2.1 %
7	0.6 ppb	2.3 %	2.5 %	1.4 ppb	4.1 %	2.3 %
8	1.3 ppb	2.7 %	2.3 %	2.0 ppb	4.4 %	2.2 %
9	0.8 ppb	2.5 %	2.5 %	1.4 ppb	4.1 %	2.2 %
10	0.8 ppb	2.1 %	2.1 %	1.7 ppb	3.7 %	2.0 %

### Clinical Precision

Reproducibility was assessed in a clinical setting, evaluating the variability between measurements performed in the same patient by different operators. Total 62 subjects were assessed. Three operators each took two completed measurements in the same subject in a point of care setting. The order of the three operators used was randomized and the subject was to attempt to perform two completed measurement with each operator; i.e. a total of six completed FE<sub>NO</sub> measurements per subject with the NIOX MINO<sup>®</sup>, within a maximum of 18 attempts per subject.

The table below shows the agreement among operators for first NIOX MINO measurement at six different measurement ranges. The standard deviation was based on the individual FE<sub>NO</sub> values.

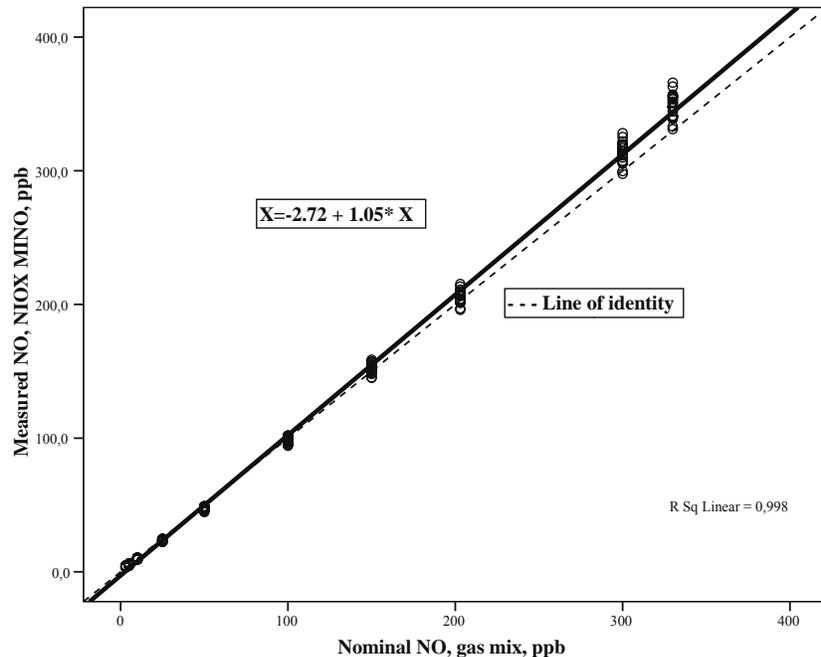
	N	Within sd	95 % CI for sd	Within CV	95 % CI for CV
Median 0-10	1	0.58 ppb	Not possible to calculate	5.59 %	Not possible to calculate
Median 10-20	6	1 ppb	( 0.61 ppb : 1.39 ppb )	6.06 %	( 3.78 % : 15.02 % )
Median 20-30	16	1.98 ppb	( 1.27 ppb : 2.7 ppb )	7.91 %	( 5.83 % : 12.3 % )
Median 30-40	20	1.95 ppb	( 1.37 ppb : 2.52 ppb )	5.4 %	( 4.1 % : 7.89 % )
Median 40-50	5	2.43 ppb	( 1 ppb : 3.85 ppb )	5.51 %	( 3.3 % : 16.02 % )
Median 50+*	12	3.74 ppb	( 2.45 ppb : 5.03 ppb )	6.26 %	( 4.43 % : 10.67 % )

\*Within the patients with a median of 50+ there were two subjects who had a very large variation. One had a CV of 75% and one had 38 %. This row presents data excluding these two subjects.

b. *Linearity/assay reportable range:*

Linearity was evaluated using 10 concentration levels within the range 3-330 ppb (3, 5, 10, 25, 50, 100, 150, 200, 300 and 330 ppb), with 3 replicates at each level. All NIOX MINO systems were scheduled for testing after keeping them continuously powered up for 0, 6, 12 and 18 months respectively, at ambient conditions, i.e. at room temperature, between 16°C and 30°C, and a relative humidity (RH) between 20% and 60% (non-condensing). The mean NO concentration for each set of replicates was plotted against the nominal NO concentration and the data subjected to regression analysis, applying option confidence intervals for slope.

The total regression analysis gave a slope of 1.03 and intercept 2.8 and the squared correlation coefficient  $r^2$  was  $\geq 0.998$  for all the 20 devices tested. Results in NIOX MINO at 3 and 5 ppb are displayed as <5 ppb, and results at 300 and 330 ppb are displayed as >300 ppb, and therefore these levels are not included in the plot. The results show that NIOX MINO<sup>®</sup> is linear within the measuring range of 5 – 300 ppb.



Linearity determination, plotted data from 20 NIOX MINO units

The combined effects of temperature and relative humidity (RH) were measured at 60°F, 72°F and 85 °F (16°C, 22°C and 30 °C) and 20%, 40% 60% RH. This covers all the conditions within the low and high temperature and humidity ranges. Measures were taken at 15 ppb, and at 75 ppb, with standard reference gas mixtures of NO in N<sub>2</sub> as nominal values for 15 ppb and 75 ppb. The data are presented in the tables below as the mean deviation from the nominal values 15 ppb and 75 ppb, respectively. The deviations are within the sponsor's technical specifications, i.e.  $\pm 5$  ppb for the level 15 ppb and max 15 % for the level 75 ppb.

Effect of temperature and humidity measured at 15 ppb					
Temp °C	RH %	Mean deviation, ppb	n	Standard Error of Mean, ppb	Upper 95% confidence limit, ppb
20-25	35-45	1.36	38	0.135	1.6
20-25	55, 60	1.09	18	0.145	1.4
16	20	1.25	10	0.301	1.9
15	35-45	0.78	10	0.176	1.2
32	35-45	1.61	9	0.548	2.9
30	60	1.84	10	0.284	2.5
20-25	15, 20	0.90	20	0.130	1.2

Effect of temperature and humidity measured at 75 ppb					
Temp °C	RH %	Mean deviation, %	n	Standard Error of Mean, ppb	Upper 95% confidence limit, %
20-25	35-45	5.2	38	0.66	6.3
20-25	55, 60	4.1	18	0.69	5.2
16	20	5.0	10	0.90	6.6
15	35-45	13.1	10	1.10	15.1
32	35-45	4.8	9	1.35	7.3
30	60	13.0	10	0.87	14.6
20-25	15, 20	5.6	20	0.92	7.2

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*  
The NIOX MINO Sensor is an electrochemical sensor pre-calibrated and pre-programmed by the manufacturer for a defined number of tests (50, 100 or 300 tests). The instrument is calibrated using certified gas concentrations of nitric oxide and prompts the user for upcoming exchange prior to sensor expiration and does not allow for measurements with an expired sensor.

The shelf life is 3.5 years from the manufacturing date of the NIOX MINO unit or 1500 measurements, whichever comes first. The sensor has a shelf life of 12 months from the manufacturing date, stored in unopened primary package.

The sensor expires after 4 months once opened and mounted in NIOX MINO instrument or after the specified number of measurements. When there is less than 10% of the number of the measurements left, or less than 2 weeks of use remaining, a message is shown on the display. The shelf life for NIOX Filter in unopened primary package is 3 years. NIOX Filter is for single use and must be replaced for every new patient and measurement occasion.

d. *Detection limit:*

Lowest detection limit was determined in a laboratory setting, using mixtures of standard reference NO gas and N<sub>2</sub> gas below and above the detection limit, at 3 and 5 ppb. Three replicate determinations of each concentration were made at each occasion. 20 NIOX MINO sensors, continually mounted in 20 NIOX MINO instruments, respectively, were used in these tests. The resulting data at 3 ppb and 5 ppb are presented in the table below.

Measured data at 3 ppb and 5 ppb for 20 NIOX MINO units

NIOX MINO NO		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Nominal 3	replicate 1	3,3	4,7	4,4	3,6	4,3	4,1	4	4,1	3,2	4,1	4,5	2,3	4,7	3,5	3,7	3,6	4,8	3,4	5,5	4,4
	2	4,4	3,4	4,7	3,8	5	3,6	4,5	2,7	2,9	3,9	4,2	4,4	3,8	4	4,9	4,3	4,6	4,2	3,7	3,6
	3	3,3	3,3	4,8	4	5	3,9	3,7	4,6	3,4	3,6	3,3	3,8	3,9	4,5	3,3	4	3,3	3,1	4,2	3,4
	Average	3,7	3,8	4,6	3,8	4,8	3,9	4,1	3,8	3,2	3,9	4,0	3,5	4,1	4,0	4,0	4,0	4,2	3,6	4,5	3,8
Nominal 5	replicate 1	6,8	5,6	6,1	5,3	5,6	5,3	6,4	4,6	4,1	6,8	5	6,2	4,9	5	5,4	5,3	6,5	5,8	6,6	4,8
	2	5,9	5,2	6,8	4,8	4,8	5,3	5,6	5,7	4,1	5	5,2	4,4	5,2	4,4	5,2	5,5	5,2	6,2	6,5	5,7
	3	5,1	5,3	5,8	4,3	7,1	6,1	5,7	6,1	5	5,2	4,7	4	6,5	5,9	6,6	5,8	5,8	5,3	6	5,2
	Average	5,9	5,4	6,2	4,8	5,8	5,6	5,9	5,5	4,4	5,7	5,0	4,9	5,5	5,1	5,7	5,5	5,8	5,8	6,4	5,2

At the nominal value of 3 ppb, the overall mean measured value was 3.95 ppb (95%CI 3.79;4.12). At the nominal value of 5 ppb, the overall mean measured value was 5.50 ppb (95%CI 5.31;5.70).

The manufacturer chose the specification limit for lowest detectable level at 5 ppb.

e. *Analytical specificity:*

Sensor interference levels were tested in a laboratory setting. The substances and concentrations tested are summarized in the table below. Substances were selected based on their oxidizing potential, which could interfere with the electrochemical signal from NO detection. The concentrations were in the same range or higher than expected concentration of each substance in exhaled breath. The interference is calculated in relation to highest NO level in the measurement range, i.e. 300 ppb. The applicable concentration of each substance was generated, the gas stream was fed to the sensor by a gas-mixer, and the sensor signal was measured. All tests were performed at normal ambient conditions; Temperature between 20 and 24 °C, relative humidity between 45 and 55%.

Nitrogen Dioxide was the only detected significant interferent. The NIOX MINO<sup>®</sup> is designed to use a scrubber to eliminate Nitric Oxide and Nitrogen Dioxide and also other contaminants from the ambient air.

Interfering substances (calculated at 300 ppb NO)			
Substance	Concentration	Expected concentrations in exhaled breath of healthy subjects	Sensor Interference, equivalent to ppb NO
CO <sub>2</sub>	≤ 8 %	< 4-5 %	< 3 ppb
Ethanol	≤ 165 ppm	13 - 1000 ppb	< 3 ppb
NH <sub>3</sub> (Ammonia)	≤ 0.5 ppm	50 - 500 ppb	< 3 ppb
CO	≤ 50 ppm	0.5 - 15 ppm	< 3 ppb
Isoprene	≤ 1 ppm	5 - 580 ppb	< 3 ppb
H <sub>2</sub> O <sub>2</sub>	≤ 1 ppm	< 1 ppb	< 3 ppb
O <sub>2</sub>	≤ 21 %	< 17 %	< 3 ppb
H <sub>2</sub>	≤ 50 ppm	< 20 ppm	< 3 ppb
H <sub>2</sub> S	≤ 1 ppm	300 - 500 ppb	< 3 ppb
Acetone	≤ 10 ppm	1.2 - 1880 ppb	< 3 ppb
Acetonitrile	≤ 100 ppb	< 100 ppb	< 3 ppb
Acetaldehyde	≤ 100 ppb	< 50 ppb	< 3 ppb
NO <sub>2</sub>	≤ 200 ppb	Below detectable level	< 10 ppb*

\*The gas scrubber in the instrument is designed to eliminate interference of Nitrogen Dioxide (NO<sub>2</sub>).

#### Interference of exogenous substances

A clinical study was performed to investigate the influence of exogenous substances (chewing gum, carbonated beverage and mouthwash) on FE<sub>NO</sub> measured with NIOX MINO. The primary endpoint was the difference between baseline FE<sub>NO</sub> and FE<sub>NO</sub> measured directly after, one and two hours after exposure to each exogenous substance. Results were obtained from 11 apparently healthy subjects between 20 and 65 years of age

The result showed that there are no statistically detectable changes in the FE<sub>NO</sub> levels from baseline to 0 minutes, 1 or 2 hours assessments for chewing gum, carbonated beverage and mouth wash. The student's T-test for the difference between baseline FE<sub>NO</sub> and FE<sub>NO</sub> measured one and two hours after exposure to each exogenous substance was calculated. The largest systematic change was observed for chewing gum, which demonstrated a decrease in the clinically observed difference with less than one ppb. The results for chewing gum are presented in the table below.

Student's t-test of difference between baseline FE <sub>NO</sub> and FE <sub>NO</sub> measured immediately after, 1 and 2 hours after exposure to chewing gum.					
Difference	No. of observations	Mean	Standard deviation	t-value	p-value
immediately after vs baseline	11	0.36	1.86	0.65	0.5310
1 hour vs baseline	11	-0.91	1.51	-1.99	0.0744
2 hour vs baseline	11	-0.18	2.18	-0.28	0.7880

f. *Assay cutoff:*  
Not Applicable

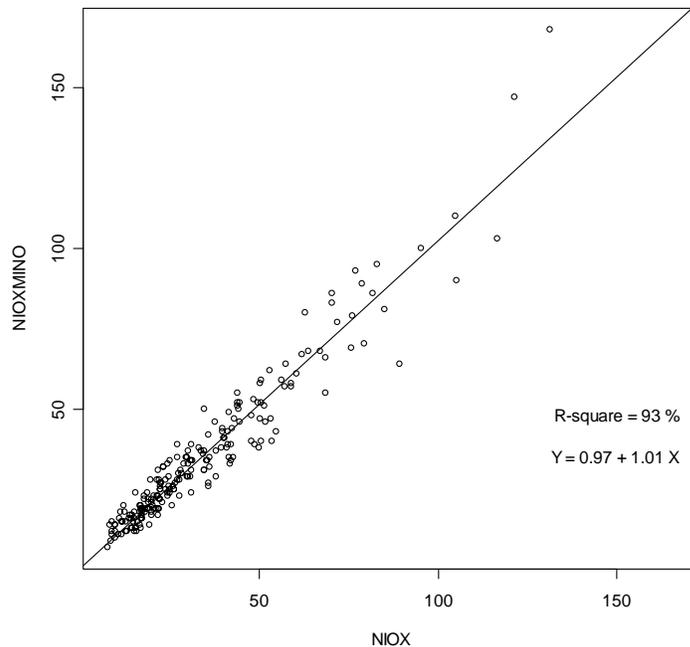
2. Comparison studies:

a. *Method comparison with predicate device:*

A method comparison between NIOX MINO<sup>®</sup> and predicated device NIOX<sup>®</sup> in FE<sub>NO</sub> values using the same subjects was performed. Data from the clinical study and the published study by Alving et al (Alving, K., C. Janson, and L. Nordvall, Performance of a new hand-held device for exhaled nitric oxide measurement in adults and children. *Respir Res*, 2006. 7: p. 67) were analyzed. The first reading in NIOX MINO was compared with the mean of readings in NIOX for each subject. Pooling the data yielded an N of 208 subjects and a regression analysis resulted in an intercept of 0.97 (95% CI - 0.65; 2.59) and a slope of 1.01 (95% CI 0.98; 1.05). The results are presented in the table below.

Percentage of patients within sponsor's tolerance limits			
	First NIOXMINO		
	Total	Subset <30 ppb	Subset >30ppb
	N=209	N=111	N=98
Proportion of patients within limits	94.2%	100%	87.7%
Lower limit of 95 % CI	91.6%	100%	82.3%

\* For subjects with a FE<sub>NO</sub> value below 50 ppb (mean of NIOX and NIOX MINO) the sponsor's tolerance limit was defined as ±10 ppb. For subjects with a FE<sub>NO</sub> above 50 ppb the tolerance limit was defined as ±20 %.



A scatter plot comparing the mean of two measurements with predicate, NIOX<sup>®</sup> with the first measurement in NIOX MINO<sup>®</sup> and the associated regression line

The scatter plot showed that the deviation is increased at higher FE<sub>NO</sub> values compared to values in the lower range. When divided in measurement ranges > 50 ppb, 50 – 100 ppb and > 100 ppb, the Mean Difference in ppb, for one standard deviation is shown in table below:

Method Comparison	
Mean Range ppb	Standard Deviation
<50 ppb	4.81 ppb
50 – 100 ppb	9.23 ppb
>100 ppb	21.94 ppb

- b. *Matrix comparison:*  
Not applicable.
3. Clinical studies:
- a. *Clinical Sensitivity:*  
Not applicable.
  - b. *Clinical specificity:*  
Not applicable.
  - c. Other clinical supportive data (when a. and b. are not applicable):  
A multi-center device randomized open-label prospective single-cohort study aimed at demonstrating substantial equivalence between NIOX MINO<sup>®</sup> and predicate device (NIOX<sup>®</sup>) when measuring the change of FE<sub>NO</sub> that often occurs after 2 weeks of corticosteroid therapy compared to their baseline levels was conducted. Symptomatic asthmatic males and females, from 7 years of age performed two valid FE<sub>NO</sub> measurements at each visit, with NIOX MINO and NIOX respectively, with a limit of six exhalation attempts per subject in each device. The order of the FE<sub>NO</sub> measurement on NIOX MINO versus NIOX was randomized. At every visit and for every patient, spirometry was performed and asthma symptoms were recorded using Asthma Control Questionnaire<sup>®</sup> (ACQ). In total, 156 subjects were included, 105 adults 18 - 70 years old and 51 children 7 - 17 years old. 147 individuals performed valid measurements on both visits and were evaluated per protocol. The demographics of the subjects are presented in the table below.

		Adults (N=105)	Children (N=51)	Total (N=156)
<b>Gender</b>	<b>n (%)</b>			
<b>Male</b>		53 (50.5)	31 (60.8)	84 (53.8)
<b>Female</b>		52 (49.5)	20 (39.2)	72 (46.2)
<b>Ethnic origin</b>	<b>n (%)</b>			
<b>Caucasian</b>		100 (95.2)	42 (82.4)	142 (91.0)
<b>African</b>		2 (1.9)	2 (3.9)	4 (2.6)
<b>Hispanic</b>		-	1 (2.0)	1 (0.6)
<b>Asian</b>		2 (1.9)	4 (7.8)	6 (3.8)
<b>Other</b>		1 (1.0)	2 (3.9)	3 (1.9)
<b>Age (years)</b>				
	<b>Mean (SD)</b>	42.9 (14.9)	12.3 (2.9)	32.9 (19.0)
	<b>Median</b>	42.0	13.0	30.0
	<b>Range</b>	18 to 70	7 to 17	7 to 70
	<b>n</b>	105	51	156

NIOX MINO<sup>®</sup> and the predicate, NIOX<sup>®</sup>, showed similar performance in FE<sub>NO</sub> with minor non-significant differences between the types of device used (37.1% and 35.5% reduction in FE<sub>NO</sub>, respectively). The reduction in FE<sub>NO</sub> from visit 1 to follow-up visit 2, following corticosteroid treatment was significant for both devices. The patients' well-being which was followed with the validated ACQ (Asthma Control Questionnaire) also showed a significant improvement in the same range (39.7%) as the improvement of FE<sub>NO</sub> values. These data (improvement in FE<sub>NO</sub> and ACQ) were in accordance with the spirometry that also showed a significant improvement although the magnitude of the improvement using this method was less obvious (+6.9%).

The table below shows a summary of the primary and secondary outcome data for the Intent to Treat (ITT) population. The following two tables show the subgroup analyses for children and adults, respectively.

Mean change between visit 1 and 2 for the two devices (NIOX MINO <sup>®</sup> versus predicate NIOX <sup>®</sup> ) and change in clinical well being and spirometry.				
	Mean % change	Standard Error of Mean, %	p-value <sup>1</sup>	N
NIOX MINO	-37.1	±3.02	<0.0001	151
NIOX	-35.5	±2.89	<0.0001	151
ACQ	-39.7	±3.23	<0.0001	151
FEV <sub>1</sub>	6.9	±0.57	<0.0001	149

<sup>1</sup>= p-value for statistical significance of change vs baseline.

Subset analysis for children, first attempt NIOX MINO				
	Mean % change	Standard Error of Mean, %	p-value <sup>1</sup>	n
NIOX MINO (first reading)	-41.1	+/-4.39	<0.0001	49
NIOX	-42.0	+/-4.63	<0.0001	49
ACQ	-35.8	+/-6.50	<0.0001	49
FEV <sub>1</sub>	8.3	+/-2.20	0.0005	48

<sup>1</sup>= p-value for statistical significance of change vs baseline.

Subset analysis for adults, first attempt NIOX MINO				
	Mean % change	Standard Error of Mean, %	p-value <sup>1</sup>	n
NIOX MINO (first reading)	-35.9	+/-3.06	<0.0001	102
NIOX	-32.3	+/-3.33	<0.0001	102
ACQ	-41.6	+/-3.27	<0.0001	102
FEV <sub>1</sub>	6.3	+/-1.35	<0.0001	101

<sup>1</sup>= p-value for statistical significance of change vs baseline.

The relationship between the percent change in FE<sub>NO</sub> and the percent change in pre-bronchodilator FEV<sub>1</sub>, post-bronchodilator Forced Expiratory Volume (FEV<sub>1</sub>) and the total symptom scores; Asthma Control Questionnaire (ACQ) from V1 to V2 was investigated for the ITT population per the tables above.

118 out of 133 (89%) patients experienced a reduction of FE<sub>NO</sub> had also an improvement in symptom score as measured by the ACQ. The magnitude of the FE<sub>NO</sub> change and degree of improvement in ACQ are different because the scale and precision of these metrics varies. The data presented in the table below indicate that FEV<sub>1</sub> (spirometry) and symptom score (ACQ) are different metrics and are not directly correlated with FE<sub>NO</sub> in both NIOX MINO and the predicate, NIOX.

Correlation between change in FE <sub>NO</sub> and change in FEV <sub>1</sub> and ACQ for NIOX and NIOX MINO in the ITT population (adults and children combined)			
		NIOX	NIOX MINO
Change in FEV <sub>1</sub>	R-square correlation	-0.213	-0.208
	P-value	0.0100	0.0120
Change in asthma symptom score (ACQ)	R-square correlation	0.274	0.244
	P-value	0.0008	0.0029

### Subgroup analysis, gender/sex

A significant difference between males and females for the proportion of patients within the sponsor's tolerance limits was observed (see the table below). This indicates that sex could be a confounder when comparing measurements with NIOX MINO<sup>®</sup> and the predicate, NIOX<sup>®</sup>. As between men and women, in this study, 92 % of the men and 77% of the women were within the sponsor's tolerance limits. For subjects with a FE<sub>NO</sub> value below 50 ppb (mean of NIOX and NIOX MINO) the sponsor's tolerance limit was defined as ±10 ppb. For subjects with a FE<sub>NO</sub> above 50 ppb the sponsor's tolerance limit was defined as ±20 %.

Tolerance limit percentages for individual sexes		
	Number of Subjects PP	First NIOX MINO trial
	Total	n (%) within limits*
Females	70	54 (77)
Males	77	71 (92)

\* Fishers exact test: p=0.01

### **Ethnicity**

Another clinical study has been performed, comparing NIOX MINO<sup>®</sup> and the predicate, NIOX<sup>®</sup>, by Khalili et al (Khalili B, Boggs PB, Bahna SL. Reliability of a new hand-held device for the measurement of exhaled nitric oxide. *Allergy* 2007;62(10):1171-4), with 110 subjects wherein 32% were African Americans. A subgroup analysis comparing Caucasians and African Americans was performed on data from this study, and no statistical significant difference was observed between Caucasians and African Americans with respect to correlation coefficients (r=0.975 vs r=0.982, p=0.378 [Significance test based on Fisher Z-transform]). See the table below.

Subgroup analysis comparing Caucasians and African Americans			
Parameter	African Americans (n=33)	Caucasians (n=76)	Entire group (n=109)
<u>Correlation analysis</u>			
R	0.97	0.98	0.98
p-value	< 0.0001	< 0.0001	< 0.0001
<u>Regression analysis</u>			
Slope (95% CI)	1.09 (1.00; 1.18)	1.02 (0.97;1.06)	1.05 (1.01; 1.09)
Intercept (95% CI)	-2.06 (-5.83; 1.70)	-0.48 (-1.83; 0.87)	-1.09 (-2.50; 0.31)
<u>Tolerance limit analysis</u>			
Proportion of patients within tolerance limits	0.97	0.99	0.98
Lower limit of 95% CI	0.92	0.96	0.96

4. Clinical cut-off:  
Not applicable.

5. Expected values/Reference range:

The expected values are provided from the literature. In the labeling the sponsor states, "Given that physiological and environmental factors can affect FE<sub>NO</sub> levels, in clinical practice, 'healthy' FE<sub>NO</sub> levels need to be established on an individual basis. However, most healthy individuals will have NO levels in the range 5-35 ppb (children slightly lower 5-25 ppb) when measured at 50 mL/s. (ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. Am J Respir Crit Care Med. 2005;171:912-930)."

**N. Instrument Name:**

NIOX MINO Breath Nitric Oxide Test System

**O. System Descriptions:**

1. Modes of Operation:

NIOX MINO System is a hand-held, portable system for the non-invasive, on-line, quantitative measurement of the fractional nitric oxide (NO) concentration in expires human breath (FE<sub>NO</sub>) measured in parts per billion (ppb).

The NIOX MINO system is comprised of the NIOX MINO unit with AC/DC adapter, an electrochemical sensor, disposable patient filter, a QC sensor, a QC filter, test card for storage of patient data, and an optional printer.

The NIOX MINO system includes a sampling and gas conditioning system and a man-machine interface (MMI). The user is guided on the built-in touch-screen display through the breathing maneuver by use of the interactive MMI. The valves and pumps of the instrument are automatically controlled to handle the inhaled samples appropriately via the instrument electronics and software program. Filtering of inhaled air eliminates contamination from ambient NO levels. A built-in flow control keeps exhalation at 50 ml/s so that it is standardized for all patients. The NO concentration is detected by an electrochemical sensor. Results are processed using dedicated software and are expressed as the NO concentration in parts per billion (ppb).

NIOX MINO utilizes analytical electrochemical sensor. The test procedure starts with the patient emptying the lungs and then inhaling N)-free air to total lung capacity (TLC) in order to trigger the 10-second exhalation standard mode, through the mouthpiece.

2. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this product:

Yes X or No \_\_\_\_\_

3. Specimen Identification:

There is no mechanism to identify the specimen.

4. Specimen Sampling and Handling:

The user obtains a breath sample by exhaling into the device.

5. Calibration:

The manufacturer performs the calibration for each NIOX MINO<sup>®</sup> Sensor. *NIOX MINO Sensor* is an electrochemical sensor pre-calibrated and pre-programmed for a defined number of tests (50, 100 or 300 tests). The user easily exchanges it upon expiration. The instrument prompts the user for upcoming exchange prior to sensor expiration and does not allow for measurements with an expired sensor.

6. Quality Control:

NIOX MINO<sup>®</sup> provides internal controls as well as an External Quality Control program for the user to verify the reliability of measurements.

The External Quality Control consists of a daily and a weekly control procedure. When the weekly quality control procedure is not performed successfully, the instrument's Lock-Out function is activated and the text "LOCK-OUT" is displayed. It is not possible to perform any FE<sub>NO</sub> measurements in the instrument when in Lock-Out mode. Once lock-out occurs, the mandatory Weekly Quality Control procedure must be immediately performed. The instrument cannot be used until this has been performed successfully.

Daily Quality Control Procedure consists of a biological control test of a human breath sample:

An exhaled breath sample from one or more qualified staff members is used. The staff member conducts a standard exhalation test, and the instrument is expected to display a result that is within the staff members moving average  $\pm 10$  ppb, which average must remain within 10 - 40 ppb. Values should be logged in a log book. See NIOX MINO<sup>®</sup> Quality Control Test User Manual.

Weekly Quality Control Procedure is mandatory and prompted for:

- Every time a new instrument is used for the first time.
- Every time a new NIOX MINO<sup>®</sup> Sensor has been mounted.
- After 45 measurements or 7 days, whichever comes first.

Weekly Quality Control tests consist of three sequentially performed tests, for details on the procedure; see NIOX MINO Quality Control Test User Manual.

1. The first test is performed using exhaled breath samples from one or more

qualified staff members. The staff member conducts a standard exhalation test, and the instrument is expected to display a result that is within the staff members moving average  $\pm 10$  ppb which average must remain within 10 - 40 ppb. Values should be logged in a log book. Values are logged in a log-book.

2. The second test is performed with the NIOX MINO<sup>®</sup> QC Filter, specially designed to present a sample which should be free of NO. When the instrument completes its analysis of this sample, it should present a result below the detection limit.
3. The third test uses a NIOX MINO<sup>®</sup> QC Sensor, specially designed to provide electronic signals to the NIOX MINO, simulating exhaled breath samples containing Nitric Oxide (NO) of 15 ppb and 75 ppb. These levels are in the clinical “normal” and the clinical “high” range.

There is also a possibility to manually prompt for this QC sequence, using a QC Test card.

**P. Other Supportive Instrument Performance Characteristics Data Not Covered In The “Performance Characteristics” Section above:**

**Q. Proposed Labeling:**

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

**R. Conclusion:**

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