Labeling Summary/Package Insert NIOX VERO® (EU)

Product Labeling Summary NIOX VERO®

1. Proprietary and Established Names

NIOX VERO® Airway Inflammation Monitor measures the fraction of exhaled nitric oxide (FeNO) in human exhaled breath.

2. Intended use

NIOX VERO quantitatively measures Nitric Oxide in human breath (Fractional exhaled Nitric Oxide, FeNO) and Nasal Nitric Oxide (nNO) in the aspirated air from the nasal cavity.

FeNO

FeNO is increased in some airway inflammatory processes such as asthma and decreases in response to anti-inflammatory treatment. FeNO measurements with NIOX VERO are quantitative, non-invasive, simple and safe and should be used as part of regular assessment and monitoring of patients with these conditions. NIOX VERO is suitable for patients age 4 and above for FeNO measurements. As measurement requires patient cooperation, some children below the age of 7 may require additional coaching and encouragement. NIOX VERO should be used as directed in the NIOX VERO User Manual.

- **CAUTION!** NIOX VERO for FeNO measurement can be operated with two different exhalation times, 10 seconds and 6 seconds. The 10 second test is the preferred mode. For children who are not able to perform the 10 second test, the 6 second test is an alternative. The 6 second test should be used with caution in patients over the age of 10 years. It should not be used in adult patients. Incorrect use of the 6s exhalation mode may result in falsely low FeNO values, which can lead to incorrect clinical decisions.

nNO

Nasal Nitric Oxide has been shown to be decreased in patients with Primary Ciliary Dyskinesia (PCD), and measurement of nNO can assist in the identification of cases of PCD according to ERS guidelines[1]. Measurement of nNO with the NIOX VERO Nasal Measurement Mode is non-invasive, simple, safe and repeatable in patients age 5 and above when measured according to the NIOX VERO Nasal Measurement Mode User Manual. Suspected cases of PCD following screening with nNO should be confirmed according to published recommendations for PCD diagnosis and management.

3. Summary and Explanation

3.1 Methodology background

Nitric oxide is endogenously produced in the airways [1] and production is increased when inflammation is present [2]. This inflammation is mediated by Th2 cells that can induce the production of nitric oxide from airway epithelial cells [3]. The elevated levels of nitric oxide produced in chronic inflammatory airway conditions, such as asthma, can be measured in exhaled breath. Measurement of exhaled nitric oxide (or fraction of exhaled nitric oxide, FeNO) is an easy, non-invasive procedure that can be performed in adults and children [4].
The Th2-mediated airway inflammation is sensitive to corticosteroids and treatment reduces the levels of exhaled nitric oxide [3]. This means that FeNO can be used for identifying patients who are likely to respond to corticosteroid treatment [5] [6] and also for demonstrating the effects of treatment [7-9].

Clinical studies have shown that FeNO can identify asthmatic patients among undiagnosed individuals with respiratory symptoms [10-14]. In addition, FeNO levels correlate with bronchial hyperresponsiveness evoked by bronchial provocation tests [15, 16].
FeNO measurements in already diagnosed patients can aid in treatment decision making [17]. By including FeNO in asthma management algorithms, reduced exacerbations rates in both children and adults [18-21] have been demonstrated. Also, by measuring FeNO, adherence to anti-inflammatory treatment [22, 23] and exposure to allergens can be monitored [24].
Recommendations for standardised FeNO measurement techniques have been developed [25]. Furthermore, a guideline for the use of FeNO in clinical practice has been published by the American Thoracic Society [26].

1 Lucas JS, Barbato A, Collins SA, et al. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. Eur Respir J 2017; 49: 1601090

3.2 Product characteristics

NIOX VERO® is designed as a hand-held device for measuring FeNO, a marker of airway inflammation, in exhaled breath from humans. NIOX VERO® is suitable for patients age 4 and above. As measurement requires patient cooperation, some children below the age of 7 may require additional coaching and encouragement. NIOX VERO Nasal measurement mode is suitable for patients age 5 and above.

NIOX VERO follows in all essential aspects the recommendations from American Thoracic Society (ATS) and European Respiratory Society (ERS) for standardised measurement procedures of exhaled NO [25]. NIOX VERO uses an electrochemical sensor technology as the analytical method. One vital advantage of this technology is that NIOX VERO requires no calibration. Built-in controls ensure reliability of measured values. NIOX VERO can be used at hospital clinics and in a General Practitioner setting [27].

4. Training requirements

NIOX VERO should only be operated by trained healthcare professionals and only after careful reading of the NIOX VERO User Manual.

5. Clinical Limitations

Elevated FeNO levels are also found in other inflammatory conditions aside from asthma, such as allergic rhinitis and COPD including COPD overlap syndrome [10, 28].

Viral infections might lead to increased FeNO levels. The mechanism behind this increase is however separate from the one causing the increased levels seen in allergic inflammation. Virus related increases in FeNO may be resistant to corticosteroid treatment [3].

Recent intake of nitrate rich food, such as lettuce, can lead to increased FeNO levels [29].

Diseases associated with decreased levels of nitric oxide are for instance cystic fibrosis and primary ciliary dyskinesia [30].

Smoking reduces exhaled NO levels. However, FeNO can still differentiate asthmatics from non-asthmatics among smokers. In a recent study of subjects with respiratory symptoms, those who were diagnosed with asthma and also were current smokers had an increase in FeNO of 60%, compared to current smokers with airway symptoms not diagnosed as asthma [31].

Other factors that may affect FeNO levels are reviewed in section 13, Limitations of the procedure.

In some patients, FeNO is persistently high despite anti-inflammatory treatment. This could be due to several factors, such as non-compliance, poor inhaler technique, inadequate corticosteroid dosage, or continuous allergen exposure [7, 22, 24]. There may also be a small number of patients, especially those with severe asthma, who are unresponsive to steroid treatment or who need additional and other treatments [32-34].

6. Risks to Health

There are no known direct risks to patient health posed by use of NIOX VERO. However, failure of the test to perform as indicated or erroneous interpretation of results may lead to improper patient management. Therefore, use of FeNO measurement results to adjust a treatment regimen without consideration of other clinical factors could pose a risk.

7. Product Description and Operation

For details regarding the parts and accessories, operational and maintenance procedures, refer to NIOX VERO® User Manual.

8. Warnings

The following warnings apply in the handling and operation of NIOX VERO®:

Warning:
NIOX VERO® should only be operated by healthcare professionals.

Warning:
Operate NIOX VERO as stated in the user manual. Circassia accepts no responsibility for damaged equipment or faulty results, if the equipment is not handled according to the manual.

Warning:
Use of substances containing alcohol close to the NIOX VERO instrument may cause erroneous measurement results.

Warning:
DO NOT clean the instrument or handle with alcohol or any spray or wipe containing alcohol!

Warning:
Do not use substances containing alcohol on or close to the NIOX VERO® instrument.
This includes any cleaning agents used to clean the facility, or other equipment in the area, as well as alcohol wipes or sprays used on patients.

Warning:
When selecting an accessory for your NIOX VERO keep in mind that an accessory not recommended by Circassia may result in loss of performance, damage to your NIOX VERO, fire, electric shock, injury or damage to other property. The product warranty does not cover product failure or damage resulting from use with non-approved accessories. Circassia takes no responsibility for health and safety problems or other problems caused by the use of accessories not approved by Circassia.

Warning:
NIOX VERO should not be used adjacent to or stacked with other equipment.

Warning:
Only use the power supply unit provided. Pull the plug when disconnecting NIOX VERO® from the power outlet.

Warning:
Use only the breathing handle supplied by Circassia.

Warning:
No modification of NIOX VERO instrument, handle or sensor is allowed.

Warning:
Do not drop the instrument or subject it to strong impact.

Warning:
Do not use a damaged NIOX VERO instrument or damaged components.

Warning:
Keep the Instrument and sensor out of water. Ensure that no liquid is spilled or dropped on the instrument or the sensor.

Warning:
Do not heat or dispose the instrument or sensor in fire. Refer to the “Disposal of used/ expired products” section of the User Manual.

Warning:
NIOX VERO and the NO scrubber in the breathing handle contain potassium permanganate. Used or expired instruments and breathing handles should be disposed of as hazardous waste in accordance with the local waste disposal regulations.

Warning:
The breathing handle must not be used after expiration date.

Warning:
Patient filters should be used immediately after opening.

Warning:
Always use a new patient filter or nasal kit for each patient. Reuse between patients could increase the risk of cross-contamination or cross-infection. The same filter/nasal kit can be reused in one patient for multiple attempts in the same session.

Warning:
The NIOX VERO Sensor contains chemicals that could be harmful if swallowed.

Warning:
Be careful when opening the sensor can. The inside of the opening may have sharp edges.

Warning:
Do not touch or clean the white sensor membrane.

Warning:
After inserting a new sensor, it is recommended to wait for three hours with the instrument switched on before performing a measurement.

Warning:
Make sure to use the correct measurement mode, otherwise incorrect FeNO results might be obtained.

Warning:
Do not use NIOX VERO in the proximity of areas where volatile substances such as organic fluids or disinfectants are being used. Special attention should be paid to aerosols and disinfection baths (either open vessels or ultrasonic baths). Do not use the instrument in the presence of flammable anaesthetic, vapours or liquids.

9. Cautions

The following cautions apply in the handling and operation of NIOX VERO:

Caution:
Mobile phones, cordless phones and gas emitting appliances might interfere with the instrument and could make it impossible to perform a measurement.

Caution:
The instrument might produce some heat during normal operation. The temperature could increase by up to 5 ºC above the ambient temperature. Make sure that the ventilation slots are not blocked. Do not place the instrument on a bed, sofa, carpet or other soft surface.

Caution:
Keep the sensor out of reach of children.

Caution:
Normally a maximum of 10 measurements per hour can be performed during continuous use. It is possible to perform 20 measurements per hour if the instrument is paused for a minimum of 30 minutes prior to the next session of measurements. The system is not designed for continuous use, due to the risk of water condensation. Typically 30-60 measurements can be made during the course of a working day, depending on the surrounding temperature. An alert will be issued if there is a high risk of condensation due to high use frequency.

Caution:
The sensor shall be kept in its original unopened package before installation. For transportation and storage conditions, refer to the corresponding section in the NIOX VERO User Manual.

Caution:
The sensor is sensitive to changes in ambient temperature and humidity.
The best performance is achieved if the ambient conditions are stable. Refer to the recommended environmental conditions in the NIOX VERO User manual. Keep the unit away from windows, direct sun, radiators, stoves or open fire in order to avoid unstable conditions.

Caution:
When transporting the unit from one location to another, a prolonged stabilisation period before measurement might be required. Refer to the recommended transportation conditions in the “Transport and Storage” in NIOX VERO User Manual. Always use a bag for transportation.

Caution:
The device contains a Lithium-ion Battery which may induce an increased risk of heat, smoke or fire if handled incorrectly; do not open, crush, heat above 60°C or incinerate.

Caution:
Make sure that the gas outlet (four parallel slots to the left of the lid) on the rear side of the device is not covered.

Caution:
Be careful when opening the sensor. The inside of the opening has sharp edges.

Caution:
A PC connected to the USB connector has to be certified for one of the standards IEC-60601-1, IEC 61010-1, IEC 60950 or comparable with safety extra low voltage on the USB ports.

Caution:
The connected PC should be placed out of reach from the patient. Do not, simultaneously, touch the connected PC and the patient.

10. Specimen collection and preparation for analysis

NIOX VERO® provides direct sampling with delayed analysis (65 seconds) of sequentially collected and analysed exhaled air. No subsequent specific specimen collection, specimen preparation or reagents are required.

11. Step by step outline of recommended procedures

For details regarding the operation of the NIOX VERO FeNO measurement mode, read the NIOX VERO User Manual. For details regarding the operation of NIOX VERO nasal mode, refer to the NIOX VERO Nasal User Manual.

12. Results

The FeNO results, expressed as parts per billion (ppb), are presented after a short time (65 seconds) on the display. The instrument automatically calculates the results based on the calibration settings (sensitivity) of the sensor, expressed as nA/ppb.
For details regarding the operation of the NIOX VERO FeNO measurement mode, read the NIOX VERO User Manual. For details regarding the operation of NIOX VERO nasal mode, refer to the NIOX VERO Nasal User Manual.

13. Limitations to the procedure

Biological as well as external factors that could affect FeNO measurements have been described [25]. To assure correct results when performing FeNO measurement with NIOX VERO®, the following cautions apply, according to the ATS/ERS recommendations from 2005 [25]:

Caution:
Food and beverages
Patients should refrain from eating and drinking before NO analysis. An increase in FeNO has been found after the ingestion of nitrate or nitrate-containing foods, such as lettuce (with a maximum effect 2 hours after ingestion) and drinking water and ingestion of caffeine may lead to transiently altered FeNO levels. Until more is known, it is prudent when possible to refrain from eating and drinking for 1 hour before exhaled NO measurement, and to question patients about recent food intake. Alcohol ingestion reduces FeNO in patients with asthma and healthy subjects [25].

Caution:
Respiratory manoeuvres
Because spirometric manoeuvres have been shown to transiently reduce exhaled NO levels, it is recommended that NO measurement be performed before spirometry. The same stipulation applies to other taxing respiratory manoeuvres, unless these can be shown to have no effect on exhaled NO. The FeNO manoeuvre itself and body plethysmography do not appear to affect plateau exhaled NO levels [25].

Caution:
Age/sex
In adults, there is no consistent relationship between exhaled NO level and age, but it has been reported that, in children, FeNO increases with age. In adults, there are conflicting reports regarding the effects of sex, menstrual cycle and pregnancy, so these patient characteristics should be recorded at the time of measurement [25].

Caution:
Airway calibre
It has been demonstrated that FeNO levels may vary with the degree of airway obstruction or after bronchodilatation, perhaps because of a mechanical effect on NO output. Depending on the setting, it may be prudent to record the time of last bronchodilator administration and some measure of airway calibre, such as FEV_1 [25]..

Caution:
Circadian rhythms
Although FeNO levels are higher in nocturnal asthma, there was no circadian rhythm in two studies, but another study did report a circadian pattern, so it is uncertain whether measurements need to be standardised for time of day. It is, however, prudent, where possible, to perform serial NO measurements in the same period of the day and to always record the time [25].

Caution:
Smoking
Chronically reduced levels of FeNO have been demonstrated in cigarette smokers in addition to acute effects immediately after cigarette smoking. Despite the depressant effect of smoking, smokers with asthma still have a raised FeNO. Subjects should not smoke in the hour before measurements, and short- and long-term active and passive smoking history should be recorded [25].

Caution:
Infection
Upper and lower respiratory tract viral infections may lead to increased levels of exhaled NO in asthma. Therefore FeNO measurements should be deferred until recovery if possible or the infection should be recorded in the chart. HIV infection may be associated with reduction in exhaled NO [25].

Caution:
Medications and exhaled NO
The potential effect of drugs on NO cannot be excluded, and so all current medication taken and time administered should be recorded. Exhaled NO falls after treatment with inhaled or oral corticosteroids in subjects with asthma and after inhaled NO synthase inhibitors. Leukotrine-axis modifiers also reduces FeNO. NO donor drugs and oral, inhaled, and intravenous L-arginine increase FeNO and nasal FeNO. Even if a certain medication does not effect NO production, it might affect the apparent level of NO through other mechanisms, such as changes in airway calibre [25].

Caution:
Other factors
The manipulation of physiologic parameters has been shown to affect FeNO. Changing pulmonary blood flow has no effect in humans, but hypoxia decreases exhaled NO and this may occur in subjects at high altitude, particularly those prone to high-altitude pulmonary oedema. The application of positive end-expiratory pressure has been shown to increase FeNO in animals, but airway pressure in humans does not affect exhaled NO plateau levels according to most reports, although one study suggests the opposite. Many studies have examined the effect of exercise on FeNO. During exercise, according to one report, FeNO falls, whereas NO output increases and this effect may last up to 1 hour. Others have reported that FeNO remains stable after exercise. It would seem prudent to avoid strenuous exercise for 1 hour before the measurement [25].

Caution:
Measurement results are to be used as an adjunct to establish clinical and laboratory assessments in asthma.

Caution:
NIOX VERO® has been tested and found to comply with the limits for medical devices according IEC EN 61326-1 "Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 1: General requirements" as well as IEC 60601-1-2 "Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests". These limits are designed to provide protection against harmful interference in a typical medical installation. However, because of the increased use of radio-frequency transmitting equipment and other sources of electrical noise emitters in the healthcare and home environments, such as base stations for radio, cellular/cordless telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast, it is possible that high levels of such interferences due to close proximity or strength of a source, may result in disruption of performance of the instrument. If abnormal performance is observed, it may be necessary to reorient or relocate the NIOX VERO®.

14. Expected Values

Given that physiological and environmental factors can affect FeNO, FeNO levels in clinical practice 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 [35-39].
The lower values reported in children indicate an age dependence of FeNO levels. This has been confirmed in a number of studies, showing that FeNO levels increase with age in children [37, 38, 40]. Furthermore, it has been shown that males have higher FeNO levels than females [12, 36, 39, 41]. There are also studies demonstrating ethnic differences in FeNO levels [42, 43].

It is established that patients with allergic asthma have higher than normal levels of FeNO [2, 12, 13, 15, 44], FeNO levels in asthma patients vary depending upon the extent of their airway inflammation. Literature data suggest that patients with asthma usually have FeNO levels in the range 25–80 ppb although higher levels may occur in some patients [5, 13, 45]. Values at the lower end of the range are usually seen in patients receiving anti-inflammatory treatment [26, 46]. FeNO levels persistently over 50 ppb in adults and over 35 ppb in children are considered to be high [26]. Allergen exposure has been shown to increase FeNO levels in asthmatics [24, 47]. Correlation between symptom improvement and decreasing FeNO has been observed [5, 7, 48, 49].

Monitoring a patient's FeNO levels before and during anti-inflammatory therapy can, therefore, be used for studying the therapeutic effect [5, 50, 51].

Note:
If FeNO levels are high despite medication, this may indicate non-compliance [22, 23], poor inhaler technique or inadequate corticosteroid dosage [7]. Continuous high levels of allergen exposure amplify the inflammatory activity. There may also be a small number of patients, especially those with severe asthma, who are unresponsive to steroid treatment [32-34]. Any change of anti-inflammatory therapy can affect FeNO levels and should be recorded.

Note:
Changes in airway inflammation measured as FeNO levels and lung function parameters may be non-synchronous as they have different response times to anti-inflammatory treatment [52].

15. Clinical data

15.1 Background

NIOX VERO® is a portable device for measurements of exhaled nitric oxide. NIOX VERO is designed to comply fully with the ATS/ERS (American Thoracic Society/European Respiratory Society) guidelines from 2005.
The use of FeNO as a method of monitoring airway inflammation using NIOX VERO is comparable with NIOX MINO (previous device).
Clinical and technical validation studies has been performed to support clinical validation and usability of the NIOX VERO. These studies are described in section 15.2. One clinical validation study (AER-045) has demonstrated substantial equivalence between measurements performed using NIOX VERO and NIOX MINO. An inter-operator variability study (TV-014), investigating the repeatability of FeNO measurements performed by different operators using NIOX VERO demonstrated that FeNO measurements by the NIOX VERO® were repeatable and consistent.
Another study (AER-047) was performed to show equivalence between the six and ten second mode in young children. Moreover the results of this study demonstrate that there is no observable pattern of a training effect or order effect on FeNO results when performed three times by three different operators.
In section 15.3, a clinical study comparing the NIOX MINO and the NIOX is described. Measurements were performed both at baseline and after inhaled corticosteroid treatment.
Finally, in Table 15.6, a number of studies (mostly external) supporting the intended use of NIOX VERO are summarised. NIOX MINO has been used in these studies.

15.2 Clinical studies NIOX VERO

15.2.1 AER-045: Method Comparison Study

AER-045 was a randomised, multi-centre, single-visit, study to determine the agreement between the NIOX MINO® Nitric Oxide Monitoring system and the NIOX VERO® device, using the 10-second exhalation mode, performed in 2013.

Non-diagnosed and diagnosed asthmatic subjects (FeNO between 0-200 ppb), male and female, from 7 years of age, performed a total of two valid FeNO measurements with each device at a flow rate of 50 ml/s (within a maximum of 6 attempts in each device) at the clinic. The order of the devices used was randomised.

In total 81 patients aged 7-78 years, both subjects with physician diagnosed asthma and subjects being evaluated for a diagnosis of asthma were evaluated. Successful performance test rates were similar in both devices for both adults and children. The subjects represented a FeNO range of 5-78ppb.

The mean of the intra-subject FeNO difference is – 2.904 ppb suggesting that FeNO measurements using NIOX VERO on average are lower than FeNO measurements using NIOX MINO. The 95% limits of agreement are -13.40 and 7.59 ppb, indicating that for 95% of all subjects the difference between FeNO measurements using NIOX MINO and NIOX VERO is expected to lie in this interval.

Scatter Plot

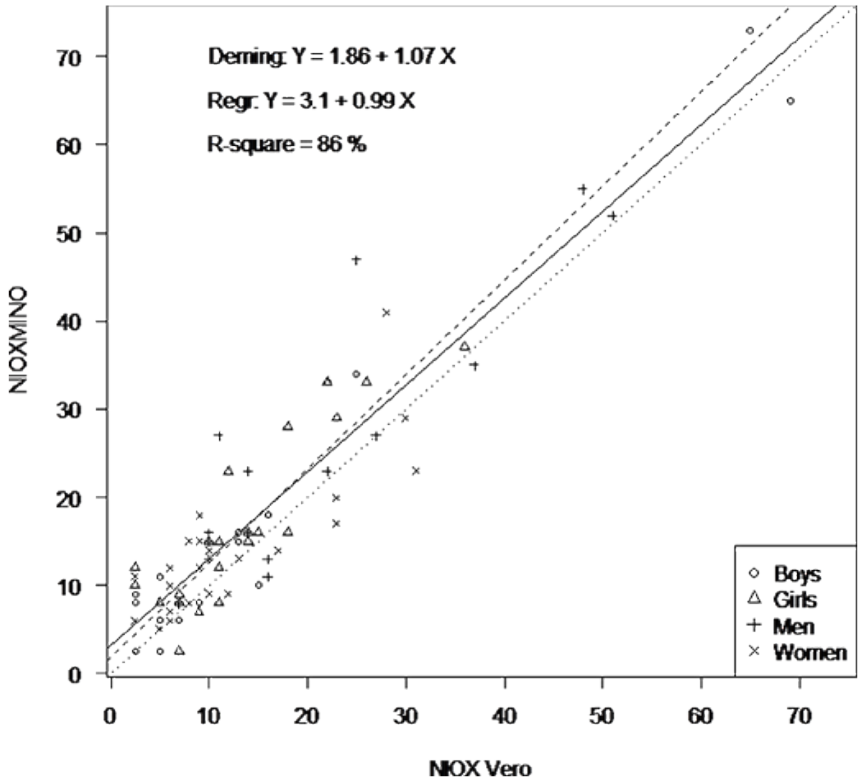


Figure 15.1 Scatterplot on the relationship between NIOX VERO and NIOX MINO. Solid line represents the slope of the linear regression, the dashed line the slope of the Deming regression and dotted line is the line of equality.

Table 15.1.a. Parameter estimates for the linear regression analyses.			
	Estimate	**95 % Confidence Interval**	
Intercept	3.103	(1.286	4.919)
Slope	0.987	(0.896	1.078)

Table 15.1.b. Parameter estimates for the Deming regression analyses			
	Estimate	**95 % Confidence Interval**	
Intercept	1.856	(-0.261	3.382)
Slope	1.070	(0.963	1.240)

Table 15.1.c. Number and proportion of subjects within tolerance limits.	
Number of subjects in analysis	78
Number within tolerance limits	71
Proportion within tolerance limits	0.910
Lower limit of a 95% CI	0.824

FeNO measurements using NIOX MINO are on average slightly higher than FeNO measurements using NIOX VERO. The results were in conformity with the technical specifications for both the NIOX MINO and NIOX VERO devices. Overall there seem to be a slight shift towards higher observed values for NIOX MINO (on average about 3 ppb) at all ppb levels. The repeatability for NIOX VERO seems to be better than repeatability for NIOX MINO.

15.2.2. AER-047 Validation study of the 6 sec mode

This is a randomised, single-center, single visit, point-of-care clinical validation study. A total of 53 subjects were enrolled, including subjects 6-10 years of age.

Results supported the agreement and repeatability of the NIOX VERO® device using the 6-second exhalation mode and the 10-second exhalation mode in subjects 6 to 10 years of age. Observed results were similar between the devices and paired differences in the average FeNO results were centered close to 0 (median = 0.50), further supporting the similarity of the results.

The weighted Deming regression analysis resulted in parameter estimates that were not significantly different from zero and one for the intercept and slope, respectively, further supporting the correspondence of FeNO values. In addition the average bias based on the predicted 6s mode results across the full range of observed 10s mode FeNO results was low (2.7%), and the absolute estimated bias at the 35 ppb cut-off value (1.43) was well below the pre-specified limit of seven ($p<0.0001$). Further, the upper bound on the estimated bias at 35 ppb was 8.7% of the cut-off value, suggesting bias well below 20%.

The Bland-Altman plot (Fig 15.2) revealed an even spread of paired differences in average FeNO results between the modes with larger differences only noted for two subjects with the largest observed FeNO results.

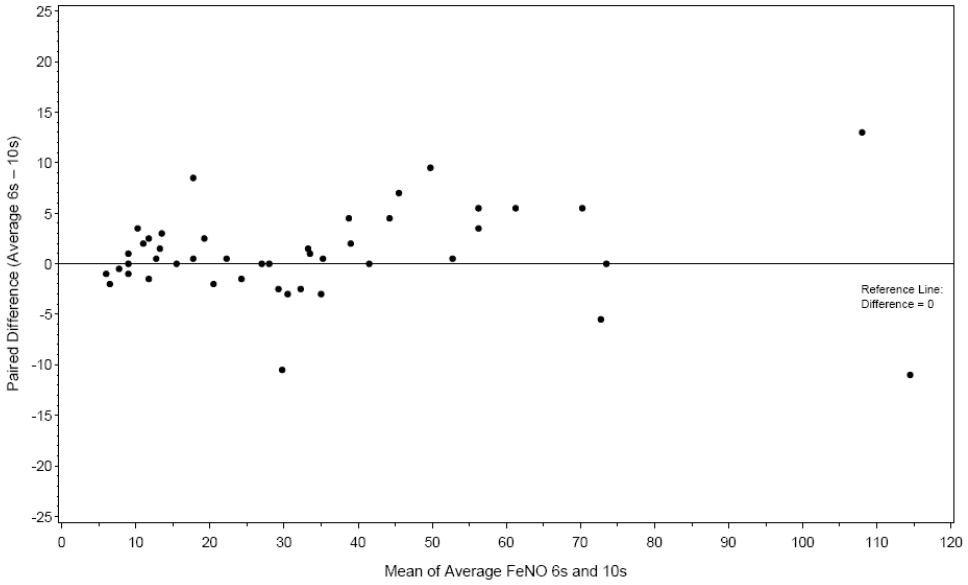


Figure 15.2. Bland-Altman Plot for Average FeNO Results for 6 s and 10 s Mode

In terms of repeatability, intra-subject standard deviations were very similar between the modes with a median paired difference of 0.0 and no statistically significant difference ($p=0.3090$). Finally, a high percentage of subjects (93.8%, 95% Exact CI: 82.8%, 98.7%) were within the tolerance limits.

The similarity of observed results between the modes, the low bias and intra-subject standard deviation, and high percentage of subjects within the tolerance limits provide evidence of a high degree of agreement between the modes and support the viability of the 6s mode as an alternative option in assessing FeNO.

15.2.3 TV-014 : Inter-Operator Variability Study.

The primary objective was to determine the repeatability of FeNO measured with the NIOX VERO® device when three consecutive valid FeNO measurements were obtained in a single subject by three different NIOX VERO® operators using the same NIOX VERO® device.

The primary endpoint was the standard deviation of the intra-subject variance as assessed by the square root of the average variance.

Fractional Exhaled Nitric Oxide (FeNO) levels were assessed for 94 subjects at 3 different sites by a total of 42 different operators and the measurements were found to be consistent and repeatable. There was no evidence that there was an effect on FeNO levels based on order of measurements (p=0.2890). The mean FeNO value was 17.5 ± 16.79 ppb overall and ranged from 5 – 100 ppb. Overall, the mean intra-subject variance was 3.94 (upper 95% CI bound = 6.57), which corresponds to a standard deviation of 1.98 (upper 95% CI bound = 2.56). The overall coefficient of variance (CV) was 0.074 with an upper 95% CI of 0.084 and was obtained by evaluating the CV for each subject. Weighted deming regression was performed between the three possible pairs of measurements and the intercept and slopes were close to 0 and 1, respectively, in all cases without statistical significance noted. Estimated bias was less than 2% for all pairs.

Of the 94 subjects enrolled, 88 (93.6%) had FeNO values < 50 ppb (range 5 – 45 pbb). In these subjects, FeNO values were consistent and repeatable with an intra-subject standard deviation (SD) of 1.17 (upper 95% CI bound = 1.33) and the coefficient of variance was 0.073 (upper 95% CI bound = 0.084). None of the within-subject paired FeNO measurements in this subgroup had a difference > 10 ppb.

In the 6 subjects with FeNO levels ≥ 50 ppb (6.4%), there was greater variability, but the average CV for the triplicates of observations was similar to that of subjects with an average value less than 50 ppb. The intra-subject SD in this subgroup was 6.46 (upper 95% CI bound = 8.30) and the coefficient of variance was 0.081 (upper 95% CI bound = 0.118). Of the 18 within-subject paired differences in this group, 3 pairs (16.7%) were > 20% of the mean FeNO value. However, none of the values were outside of 20% of the overall mean for the triplicates for a given subject. Hence, while variability in intra-subject FeNO values increased with higher values, the CV remained similar.
No adverse events or serious injuries were observed or reported.

Conclusion
The results of this study demonstrated that FeNO measurements by the NIOX VERO® were repeatable and consistent. Moreover the results of this study demonstrate that there is no observable pattern of a training effect or order effect on FeNO results when done three times by three different operators.

15.2.4 NIOX VERO Nasal Measurement Mode

Clinical data

Introduction
A clinical study was completed to assess the ability of the NIOX VERO to differentiate between subjects with Primary Ciliary Dyskinesia (PCD) and healthy subjects (AER-051).

PCD is a genetic disorder that is often under diagnosed or misdiagnosed because symptoms may overlap with other more common respiratory conditions, especially in children. Observational data suggests that early diagnosis and management of patients in a specialised PCD clinic may improve long-term lung function outcomes, therefore making a simple, non-invasive test is a necessity to achieve early diagnosis.

Design
This was a multi-centre, single visit clinical study involving subjects with known PCD [Cohort 1] vs. age matched healthy volunteers [Cohort 2] in subjects aged five years and older. Subjects were asked to perform nNO measurements using the tidal breathing breathing (TB-nNO) method followed by the velum closed with expiration against resistance (ER-nNO) method.

The primary objective was to determine whether subjects with PCD could be differentiated from healthy subjects with measurement of nasal NO using the NIOX VERO. The primary endpoint was the analysis of the means of the successful nNO measurements in subjects with PCD as compared with healthy subjects in those with two measurements.

The secondary objectives were to determine the proportion of subjects able to successfully complete nNO measurements using the TB-nNO method, and the proportion able to successfully complete nNO measurements using the ER-nNO method. The secondary endpoints were observed nNO results (ppb), the proportion able to successfully complete nNO measurements using the TB-nNO method, the proportion able to successfully complete nNO measurements using the ER-nNO method, and the proportion able to successfully complete nNO measurements using both methods.

Results
There were 51 known PCD subjects and 106 age matched healthy subjects that performed nNO measurements using the TB-nNO method for 30 seconds followed by the ER-nNO method for 15-30 seconds (30 seconds preferred). In to-

tal, 154 (98.1%) subjects completed at least one successful nNO measurement in both methods. There were 3 (1.9%) subjects that did not complete a nNO measurement in both breathing methods.

In the PCD cohort, there were 17 subjects in each age group for a total of 51 subjects. The evaluable population for the PCD cohort consisted of 47 subjects (14 5-11 year olds, 16 12-17 year olds and 17 subjects ≥ 18 years old).
In the healthy cohort, there were 42 5-11 year olds, 28 12-17 year olds and 36 subjects ≥18 years old for a total of 106 subjects. The evaluable population for the healthy cohort consisted of 105 subjects (42 5-11 year olds, 27 12-17 year olds and 36 subjects ≥18 years old).

The number of subjects with at least two successful nNO measurements [within 10% or 25 ppb, whichever was greater] from one nostril using either breathing method) was 152 (96.8%) (evaluable population).

- Subjects with two successful measurements [within 10% or 25 ppb, whichever was greater] with TB-nNO method obtained from both nostrils consisted of 121 (77.1%) subjects.
- Subjects with two successful measurements [within 10% or 25 ppb, whichever was greater] with ER-nNO method obtained from both nostrils consisted of 123 (78.3%) subjects.
- Subjects with two successful measurements [within 10% or 25 ppb, whichever was greater] obtained from both nostrils with both breathing methods consisted of 104 (66.2%) subjects.

The means of the successful nNO results for the evaluable population in the PCD cohort for the TB-nNO method was 50.2 (SD = 50.35; median = 36.0) ppb and for the healthy cohort the mean was 587.2 (SD = 242.22; median = 555.5) ppb. Mean nNO in the PCD cohort for the ER nNO method was 82.2 (SD = 105.15; median = 54.0) ppb while mean nNO for the healthy cohort was 917.0 (SD = 373.11; median = 844.6) ppb.

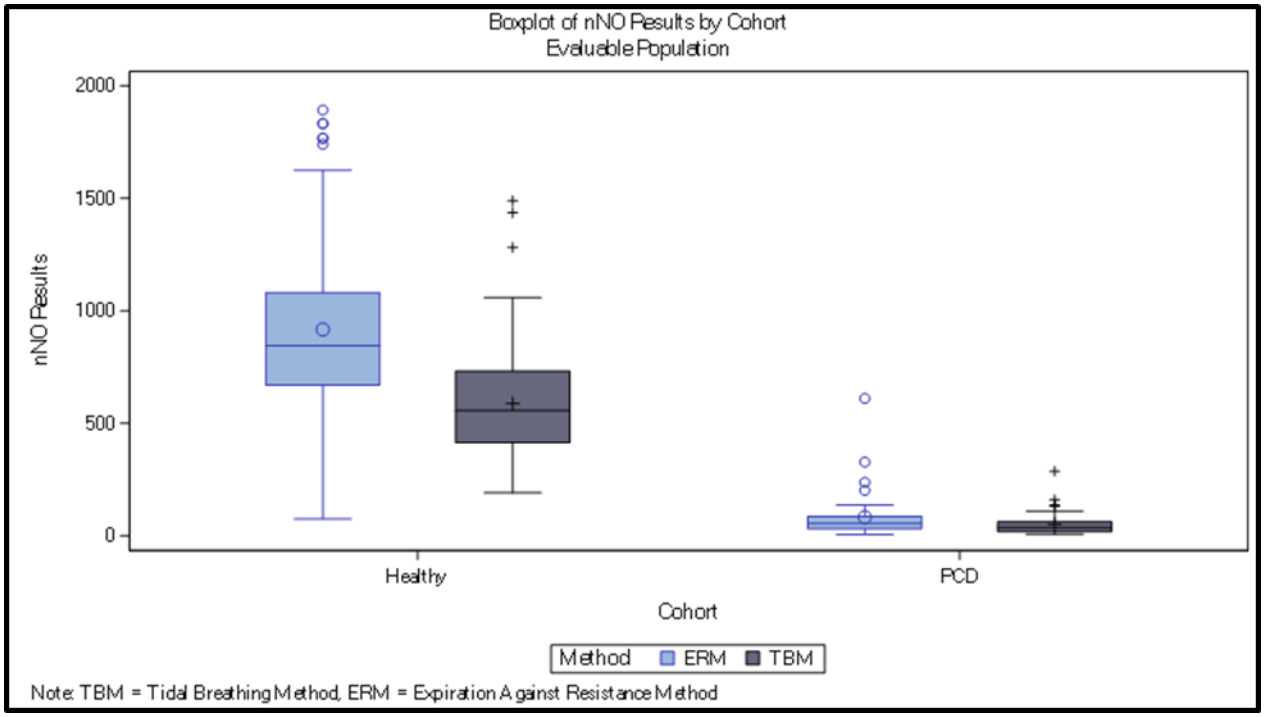
Table 15.2 Means of Successful nNO Results (ppb) by Cohort and Age Group - Evaluable Population \f C \!

1) Means of Successful nNO Results by Cohort for the Evaluable Population

Summary	Cohort		All Subjects
	PCD	Healthy	
Number of Subjects (N)	47	105	152
Number of nNO Measurements (N)	394	772	1166
TB-nNO Overall Measurements (N)			
N	47	99	146
Mean ppb (SD)	50,2 (50,35)	578,2 (242,22)	414,3 (322,24)
Median ppb	36,0	555,5	415,5
Min, Max ppb	6 , 287	190 , 1489	6 , 1489
ER-nNO Overall Results			
N	42	97	139
Mean ppb (SD)	82,2	917,0 (373,11)	664,8 (498,5)
Median ppb	54,0	844,6	682,0
Min, Max ppb	5 , 610	75 , 1893	5 , 1893

Note: Includes all subjects with at least two (2) successful nNO measurements (within 10% or 25 ppb, whichever is greater) from one nostril using either breathing method.

Boxplot of nNO Results by Cohort for the Evaluable Population



Results according to age group and method were as follows:

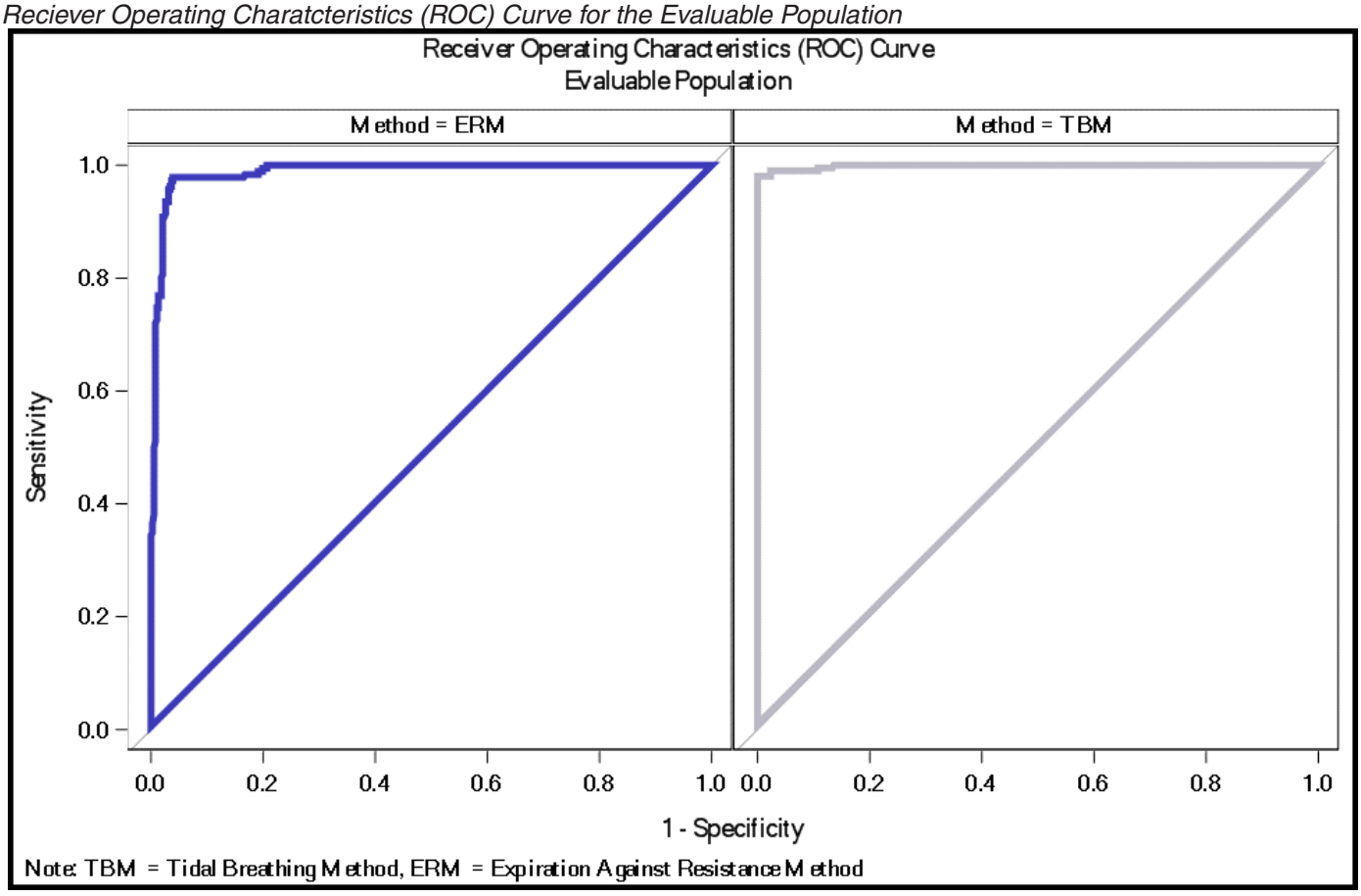
- 5-11 year olds TB-nNO method: mean nNO in the PCD cohort was 60.7 (SD = 72.55; median = 36.0) ppb and for the healthy cohort the mean was 528.3 (SD = 186.78; median = 470.5) ppb.
- 5-11 year olds ER-nNO method: mean nNO in the PCD cohort was 100.2 (SD = 173.71; median = 50.8) ppb while mean nNO for the healthy cohort was 760.4 (SD = 302.36; median = 715.6) ppb.
- 12-17 year olds TB-nNO method: mean nNO in the PCD cohort was 50.3 (SD = 42.95; median = 36.1) ppb and for the healthy cohort the mean was 733.8 (SD = 322.87; median = 638.8) ppb.
- 12-17 year olds ER-nNO method: mean nNO in the PCD cohort was 81.1 (SD = 79.12; median = 57.4) ppb while mean nNO for the healthy cohort was 1085.1 (SD = 402.20; median = 1079.5) ppb.
- > 18 years and older TB-nNO method: mean nNO in the PCD cohort was 41.4 (SD = 33.24; median = 33.3) ppb and for the Healthy cohort the mean was 559.7 (SD = 202.79; median = 508.5) ppb.
- > 18 years and older ER-nNO method: Mean nNO in the PCD cohort was 70.1 (SD = 60.88; median = 46.5) ppb while mean nNO for the healthy cohort was 968.5 (SD = 363.96; median = 846.9) ppb.

An ROC curve analysis was used to determine an optimum nNO cut-off value for both breathing methods.

- TB-nNO method: 121 (43 PCD/78 HC) subjects were analysed. The optimal cut-off was measured at 171 ppb with a specificity of 100% (95% CI: 99.7, 100.0) and a sensitivity of 98% (95% CI: 94.9, 99.4). The AUC was 99.8% (95% CI: 99.7, 100.0), PPV was 100% (95% CI: 98.1, 100.0) and NPV was 98.9% (95% CI: 97.1, 99.7).
- ER-nNO method: 123 (40 PCD/83 HC) subjects were analysed. The optimal cut-off was measured at 356 ppb with a specificity of 96.3% (95% CI: 93.8, 98.0) and a sensitivity of 97.8% (95% CI: 94.4, 99.4). The AUC was 98.7% (95% CI: 98.0, 99.5), PPV was 93.1% (95% CI: 88.5, 96.3) and NPV was 98.8% (95% CI: 97.0, 99.7).

Table 15.3 Receiver Operating Characteristics (ROC) Curve Analysis.		
Summary	**TB-nNO Method [1]**	**ER-nNO Method [2]**
# Subjects (# PCD / # Healthy)	121 (43/78)	123 (40/83)
PCD Cohort Mean nNO +/- SD (median) ppb	49.4 +/- 51.52 (35.3)	85.0 +/- 106.92 (54.9)
HC Cohort Mean nNO +/- SD (median) ppb	570.0 +/- 226.89 (525.8)	948.2 +/- 387.40 (855.3)
Summary	**TB-nNO Method**	**ER-nNO Method**
nNO Cut-off (ppb)	171	356
AUC, % (95% CI)	99.8 (99.7, 100.0)	98.7 (98.0, 99.5)
Specificity, % (95% CI)	100.0 (98.9, 100.0)	96.3 (93.8, 98.0)
Sensitivity, % (95% CI)	98.0 (94.9, 99.4)	97.8 (94.4, 99.4)
PPV, % (95% CI)	100.0 (98.1, 100.0)	93.1 (88.5, 96.3)
NPV, % (95% CI)	98.9 (97.1, 99.7)	98.8 (97.0, 99.7)
Note: AUC= Area under the Curve, NPV=Negative Predictive Value, PPV= Positive Predictive Value. *[1] Additional Evaluable Population 1: For Subjects with two (2) successful measurements (within 10% or 25 ppb, whichever is greater) with Tidal Breathing-nNO Method obtained from the left and right nostril, respectively.* *[2] Additional Evaluable Population 2: For Subjects with two (2) successful measurements (within 10% or 25 ppb, whichever is greater) with Velum Closed ER-nNO Method obtained from the left and right nostril, respectively.*		

Reciever Operating Charatcteristics (ROC) Curve for the Evaluable Population



There was one adverse event where a child was upset about not being able to finish a measurement.

Conclusion

This study showed that the NIOX VERO with its nasal kits and software is capable of measuring nasal NO and that it can be used to help as a screening method for the diagnosis of PCD because it could differentiate subjects with PCD from those that were healthy.

This study showed that the use of the NIOX VERO and its nasal kits is safe and that nasal NO measurements can be performed by children as young as five years of age. This study also showed that a measurement time of 30 seconds could differentiate between those with PCD and those that were healthy.

The results of this study provide an estimate of the optimum nNO cut-off values for the TB-nNO and ER-nNO breathing methods for use in a portable, electrochemical NO analyser.

15.2.5 Conclusions

NIOX VERO® provides a simple, reliable, repeatable and non-invasive method of measuring FeNO according to current ATS/ERS guidelines [25]. Clinical tests in several institutions and also within the manufacturing company have shown that NIOX VERO has substantially equivalent clinical performance characteristics to NIOX MINO®. In addition, clinical tests have shown that the six and ten second exhalation modes are equivalent in young children.

15.3 Clinical correlation and validation study, NIOX MINO

15.3.1 AER-036

AER-036 was a multi-center device randomised open-label prospective single-cohort study aimed at demonstrating substantial equivalence between NIOX MINO® and NIOX® (using the chemiluminescence method). Change in FeNO levels, which often occurs after 2 weeks of corticosteroid therapy, was measured compared to their baseline levels. Symptomatic male and female asthma patients, from 7 years of age performed two valid FeNO measurements during each visit, with NIOX MINO and NIOX respectively, with a limit of six exhalation attempts per subject in each device. The order of the FeNO measurement on NIOX MINO versus NIOX was randomised. During every visit and for every patient, spirometry was performed and asthma symptoms were recorded using Asthma Control Questionnaire® (ACQ) [53]. In total, 156 subjects were included, 105 adults aged 18 - 70 years and 51 children aged 7 - 17 years were recruited. 147 individuals performed valid measurements on both visits and were evaluated per the protocol (see Table 15.4 for demographic data).

Table 15.4 Demographics in Method Comparison Study

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

NIOX MINO and NIOX showed substantially similar performance in FeNO with minor non-significant differences between the devices (37.3% and 35.5% reduction in FeNO, respectively). The reduction in FeNO from visit 1 (V1) to follow-up visit 2 (V2), following corticosteroid treatment, was highly significant for both devices. The patients' asthma symptoms which were followed with the validated ACQ (Asthma Control Questionnaire) also showed a significant improvement in the same range (39.7%) as the improvement of FeNO values. These data (improvement in FeNO 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%).
Table 15.5 below shows a summary of the primary and secondary outcome data.

Table 15.5 Mean change between visit 1 and 2 for the two devices (NIOX MINO® versus NIOX®) and change in clinical well-being and spirometry.

	Mean % change	Standard Error of Mean, %	p-value[1]	n
NIOX MINO	-37.3	2.5	<0.0001	151
NIOX	-35.5	2.7	<0.0001	151
ACQ	-39.7	3.0	<0.0001	151
FEV_1	6.9	1.2	<0.0001	149

[1] p-value for statistical significance of change vs baseline.

The relationship between the percent change in FeNO and the percent change in pre-bronchodilator Forced Expiratory Volume (FEV_1), post-bronchodilator FEV_1 and the total symptom scores; Asthma Control Questionnaire (ACQ®) from V1 to V2 was investigated for the Intent to Treat (ITT) population.

An absolute majority of patients that experienced a reduction of FeNO also had an improvement in asthma symptoms as measured by the ACQ. The magnitude of the FeNO change and degree of improvement in ACQ are different because the scale and precision of these metrics varies. Asthma health status is composed of several distinct components such as social, physical, clinical and occupational, mitigating the likelihood of strong statistical correlation [53].

15.4 Other clinical performance studies

NIOX VERO® follows the 2005 ATS/ERS equipment recommendations for measurement of exhaled NO [25].
The recommendations are based on analysis of FeNO with the chemiluminescence method. However, NIOX VERO, as well as NIOX MINO®, is using a different method (electrochemistry). One benefit of this is that the NIOX VERO sensor does not need any field calibration as it is already calibrated during manufacture. Agreement has been demonstrated for the mean of two valid FeNO measurements in NIOX (using chemiluminescence) and the first valid FeNO measurement in NIOX MINO (using electrochemistry) [4, 54, 55]. Supported by these data, one valid NO measurement should be considered sufficient when using electrochemistry devices, instead of two as recommended in the guideline. While the AER-036 study was performed with the NIOX MINO, given the clinical performance of the two devices, similar results can be expected when monitoring response to therapy with the NIOX VERO.
As described in section 15.4, NIOX VERO has substantially equivalent clinical performance characteristics to NIOX MINO. The NIOX VERO device is hence suitable for clinical evaluation of airway inflammation according to its Intended Use.
Table 15.6 summarises a number of studies supporting the use of NIOX MINO in areas described in the Intended Use and Methodology Background.

Table 15.6 - PUBLISHED STUDIES EVALUATING THE USE OF NIOX MINO®

Reference	Patient group and aim of study	Outcome
Menzies et al [55] (independent study)	101 asthmatic patients and 50 healthy volunteers. Three measurements were performed with NIOX and one with NIOX MINO to study the correlation between the devices.	The values obtained with NIOX MINO are directly comparable with NIOX device. Readings with NIOX MINO were slightly higher, 1.2 ppb.
Khalili et al [54] (Independent study)	110 patients aged 6-86 years, presenting to an allergy and asthma clinic, performed measurements on NIOX and three NIOX MINO instruments	There was a strong correlation between NIOX and NIOX MINO, r=0.98 Intra-subject FeNO difference between the three NIOX MINO instruments revealed no significant difference between measurements, p=0.59 The mean intra subject FeNO difference between NIOX and NIOX MINO was -0.5 ppb
Alving et al [4] (Circassia sponsored study)	71 subjects (healthy controls and atopic patients with and without asthma) performed three exhalations in each device, NIOX® and NIOX MINO®	Median intra-subject difference was 1.2 ppb. NIOX MINO readings were generally higher. The median intra-subject difference between NIOX and the first approved measurement with NIOX MINO was -2.0 ppb. The median repeatability for NIOX and NIOX MINO was 1.1 and 1.2 resp.
Perez-de-Llano et al [48] (Independent study)	102 consecutive asthma patients with suboptimal control were included. The objective was to assess if NIOX MINO could identify patients who would benefit from additional ICS treatment.	53 patients (52%) gained control after a stepwise increase in treatment. A FeNO value ≥30 ppb demonstrated a sensitivity of 87.5% (95% CI 73.9-94.5%) and a specificity of 90.6% (95% CI 79.7-95.9%) for the identification of steroid responsive patients.
Pedrosa et al [15]. (Independent study)	114 consecutive adult patients reporting symptoms consistent with asthma were included. FeNO was measured using NIOX MINO to see if FeNO could aid in the diagnosis of these patients.	Thirty-five out of the 114 patients (30.7%) were diagnosed with asthma. A receiver-operating characteristic curve was constructed for FeNO levels (area under the curve [AUC]: 0.762; 95% confidence interval [CI]: 0.667-0.857; p < .001). The FeNO cut-off point with maximal specificity and sensitivity for asthma diagnosis was 40 ppb.

Table 15.6 - PUBLISHED STUDIES EVALUATING THE USE OF NIOX MINO®		
Koster et al [22] (Independent study)	527 children aged 4-12 years and regular ICS users were included. The outcome, a parent-reported adherence, was assessed by using the Medication Adherence Report Scale.	Increased airway inflammation (a FeNO level of > 25 ppb, using N MINO) was associated with a significantly lower chance of good adherence (OR = 0.25; 95% CI [0.15, 0.41]).
Hewitt et al [56] (Independent study)	78 primary care patients were included. The aim was to evaluate a decision-support algorithm incorporating FeNO measurements.	Well controlled asthma patients increased from 41% at visit 1 to 68% at visit 5 (p=0.001) using a FeNO–based algorithm. The mean fluticasone dose decreased from 312 mcg/day at visit 2 to 211 mcg/day at visit 5 (p=0.022). A FeNO-based algorithm provided for a reduction in ICS doses without compromising asthma control.
Ito et al [57] (Independent study)	The agreement between FeNO 6 sec and 10 sec using NIOX MINO was investigated in 119 children 4-15 years old. Feasibility was assessed in 46 children who had not used NIOX MINO before (4-15 years).	All children successfully performed both exhalation modes. FeNO-6 and FeNO-10 values did not differ significantly (median: 27 ppb, IQR: 16.0-43.5 and median: 29 ppb, IQR: 15.2-42.0, respectively) and there was a good correlation (r=0.984, P>0.001). All children aged 8 years and over succeeded in both FeNO-6 and FeNO-10. For children <8 years, 15/25 children were able to perform FeNO-10 measurements. Two children <8 years did not succeed performing FeNO-6. The 6 sec mode was hence more feasible than the 10 sec mode for measuring FeNO in younger children.

16. Specific Performance Characteristics

The instrument is verified to fulfill the specified performance under the temperature range within +10 to +35 °C, relative humidity range of 20- 80% and pressure range of 700-1060 hPa.

Table 16.1	
Performance Parameter	**NIOX VERO® Limits**
Measurement range	5 - 300 ppb FeNO mode 5 - 2000 ppb Nasal mode
Lowest Detection Limit	5 ppb
Linearity	Squared correlation coefficient r^2 > 0.998, slope 0.95 – 1.05, intercept ±3ppb Determination based on pooled regression analysis from 10 instruments using standard gas reference samples at 7 different concentration levels covering the operating measurement range.
Precision	< 3ppb of measured value for values < 30 ppb < 10% of measured value for values ≥ 30 ppb Expressed as one standard deviation for replicate measurements with the same instrument, using a certified gas concentration of Nitric Oxide reference standard
Accuracy	±5 ppb for measured values ≤ 50 ppb or 10% of measured values > 50 ppb. Expressed as the upper 95% confidence limit, based on absolute mean of differences from certified gas concentration of Nitric Oxide
Method Comparison (FeNO mode)	< 10 ppb for values ≤ 50 ppb, < 20 % for values > 50 ppb Expressed as the difference between a NIOX MINO® FeNO value and the corresponding FeNO value measured with NIOX VERO instrument from Circassia.

Table 16.1	
Inhalation parameters (FeNO mode)	Inhale to TLC (Total Lung Capacity) before start of exhalation. Inhalation in instrument is triggered by a pressure of -3 cm H_20.
Exhalation parameters (FeNO mode)	Exhalation time: Preferred mode: 10 s, Paediatric mode: 6s All exhalations are to be performed at an exhalation pressure of 10 - 20 cm H_2O, to maintain a fixed flow rate of 50 ±5 ml/s. The instrument stops the measurement at pressures outside the interval. Warning alerts sounds at 10 - 12 and 18-20 cm H_2O.

16.1 Interference of analytically determined interfering substances

Sensor interference levels were tested in a laboratory setting, by generating the applicable concentrations of each substance and measuring the sensor signal. Substances were selected based on their oxidising potential, which could interfere with the electrochemical signal for NO detection. The concentrations were in the same range or higher than expected concentration of each substance in exhaled breath [57, 58]. The interference is calculated in relation to the 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 and hydrogen sulfide were the only detected interferents, according to table 16.2 below. When using NIOX VERO, the patient first inhales through a mouthpiece connected to a scrubber that eliminates Nitric Oxide and Nitrogen Dioxide and also other contaminants from the ambient air.

Table 16.2 Interfering substances			
Substance	**Concentration tested**	**Expected concentrations in exhaled breath of healthy subjects**	**Sensor Interference, equivalent to ppb NO**
Acetaldehyde	1000 ppm	100 ppb	Non detectable
Acetone	100 ppm	10 ppm	Non detectable
Acetonitrile	500 ppm	100 ppb	Non detectable
Ammonia	100 ppm, balance air	0.5 ppm	Non detectable
Carbon dioxide (CO_2)	5% Vol, balance air	8%	Non detectable
Carbon monoxide (CO)	250 ppm, balance air	50 ppm	Non detectable
Ethanol	1000 ppm, balance air	165 ppm	Non detectable
Hydrogen (H_2)	500 ppm, balance nitrogen	50 ppm	Non detectable
Hydrogen peroxide (H_2O_2)	500 ppm, balance air	1 ppm	Non detectable
Hydrogen sulfide (H_2S)	1 ppm, balance nitrogen	1 ppm	2.0
Isoprene	1000 ppm, balance air	1 ppm	Non detectable
Nitrogen dioxide (NO_2)	9.2 ppm, balance nitrogen	200 ppb	2.5
Oxygen (O_2)	100% Volume	21%	Non detectable

16.2 Interference of exogenous substances

A clinical validation study was performed to assess the influence of exogenous substances (chewing gum, carbonated beverage and mouthwash) on FeNO measured with NIOX VERO [AER-049]. The subjects were healthy volunteers between 20 and 65 years of age (12 planned, 12 analysed).
The primary endpoint was the difference between baseline FeNO and FeNO measured directly after exposure, in addition to measurements taken at one and two hours after exposure to each exogenous substance.

The results of this study show that there is little or no effect of exogenous substances on the measurement of exhaled nitric oxide. The differences that were seen were all within the performance characteristics of the NIOX VERO.

17. Operating Conditions

Ensure stable operating conditions by avoiding placement of the instrument in direct sunlight, near sources radiating heat, or ventilation. NIOX VERO® operates during the following conditions:
NO in ambient air up to 300 ppb
To verify NO in ambient air, perform an ambient measurement, see NIOX VERO User Manual.
Temperature range of +10 to +35 °C
An atmospheric pressure range of 700 hPa to 1060 hPa
A relative humidity range of 20% to 80%, non-condensing
Performance shall be sustained when measuring continuously at a pace of up to 10 measurements / hour.
Normally a maximum of 10 measurements/ hour can be performed during continuous use. However, it is possible to perform 20 measurements in one hour if the instrument is paused for a minimum of 30 minutes prior to the next session of measurements.

17.1 Calibration

The manufacturer performs calibration for each NIOX VERO® Sensor. No additional calibration is needed during the lifetime of the sensor.

17.2 Quality Control

Built-in quality control functions continuously monitor functionality and detect any potential drift from zero baseline.

18. Routine Maintenance

Please refer to NIOX VERO® User Manual.

19. Periodic Service

No periodic service is performed.

20. Manufacturer Information

Responsible Manufacturer:
Address:
Circassia AB
Hansellisgatan 13
SE-754 50 Uppsala
Sweden

www.circassia.com
www.niox.com

NIOX VERO is CE-marked according to In Vitro Diagnostic Directive IVDD 98/79/EC.
NIOX VERO® is RoHS compliant.

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