Provox® and Provox® Life™ HMEs and HMEFs

Table of Contents

Introduction

This literature review aims to provide an overview of the published work on the different generations of Provox® Heat and Moisture Exchangers (HMEs), Provox® XtraHME, Provox® FreeHands HME, Provox® FreeHands FlexiVoice™, Provox® Micron HME, Provox®® Luna® and Provox® Life™ HMEs, as well as, attachments and accessories developed by Atos Medical.

The searches were conducted using product names and their generic names as keywords in the Pubmed search engine and Cochrane library. Additionally, our company database with publications on these products was screened for relevant publications.

1. Physiological and pulmonary consequences of total laryngectomy

During a total laryngectomy, the entire larynx is irreversibly removed, which leads to a permanent disconnection of the upper and lower airways. The patient breathes in and out through a permanent tracheostoma in the neck, instead of through the nose and mouth (see Figure 1). Therefore, the functions of the upper airways are affected. These include warming, humidifying, and filtering of inhaled air and providing upper airway resistance (1).

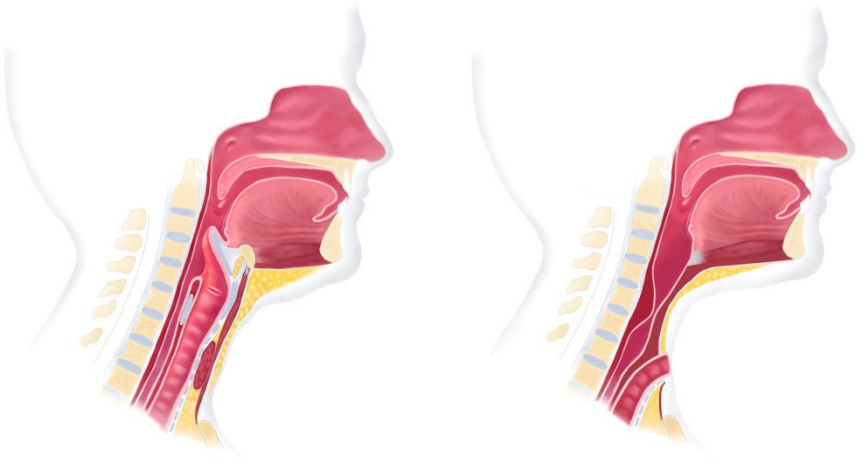

Figure 1 Schematic drawing of normal anatomical situation (left) and the anatomical situation after total laryngectomy (right). In the normal situation the patient can inhale and exhale through the nose and mouth. After total laryngectomy, the upper airways are bypassed and breathing takes place through the tracheostoma in the neck.

In addition, these anatomical changes lead, among other things, to changes in voice production, breathing, and olfaction. In the following sections, clinical evidence pertaining to the impact of breathing through a tracheostoma on tracheal climate, filtration, breathing resistance, pulmonary health and quality of life will be described.

1.1 Tracheal climate (temperature and humidity)

During normal nasal inspiration in a healthy individual with unaltered anatomy, ambient air of, for example, 22°C and 40% Relative Humidity (RH) is conditioned to 29°C and 21 mg H_2O/L (70% RH) in the nose and is further heated to approximately 32°C and 35 mg H_2O/L (98% RH) at the subglottic level(2-5). The point where the inspired gas reaches 44 mg H2O/L (100% RH) at 37°C, is known as the isothermal saturation limit (ISB).

During nasal inspiration the air passes further through the respiratory tract and it reaches these conditions in the small peripheral airways(6). During inspiration through a tracheostoma the ISB moves towards more peripherally located airways and humidification takes place in regions of the airways that only have limited suitability for exchange of heat and moisture leaving a large part of the airways with a humidification deficit(7). Therefore, in patients breathing through a tracheostoma ambient air of, for example, 22°C and 40% RH is only conditioned to 27-28°C and 50% RH at the level of the upper trachea (8), see Figure 2.

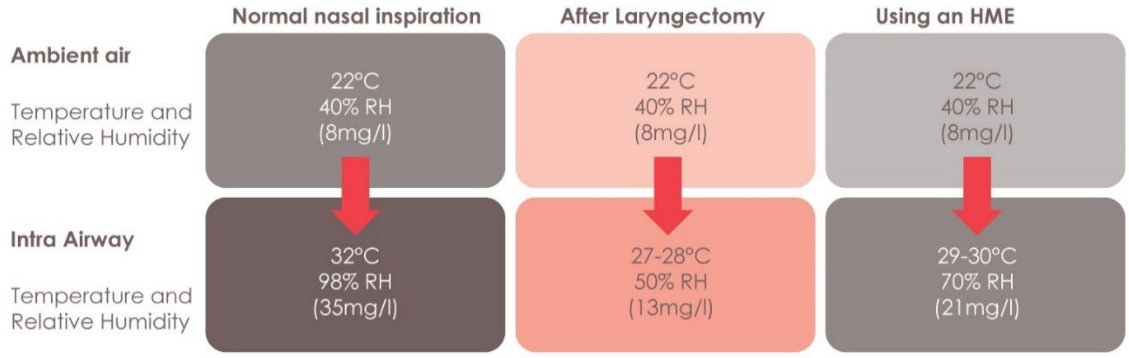

Figure 2 Description of intra-airway tracheal climate in different breathing conditions as measured in different studies (3, 5, 8) . The end-inspiratory relative air humidity (RH) and temperature (C) are given. The measurements were made at room temperature conditions.

Both temperature and humidity have a significant impact on the ciliary activity in the trachea. During normal conditions the cilia move to clear the surface from mucus and impurities or particles that have been deposited in the peripheral regions of the lungs towards the mouth, where the secretion is swallowed, expectorated or aspirated (9, 10). Studies in a rabbit model have shown that at body temperature (37°C) the cilia stop beating when the RH drops below 50%. When RH lowers to 60% there already is a reduction in the mucociliary frequency of 30% (8, 11, 12). The preservation of the mucociliary clearance, together with the filtration function of the nose, as described in the following section, are important for defense against infections.

1.2 Filtration

Apart from warming and humidification, filtration of the air is one of the most important functions of the nose. During normal breathing, the nose not only humidifies and heats the inhaled air but it also filters the air of airborne particles (13). Filtration is important for multiple reasons. One is that the airborne spread of viral and bacterial disease requires, among other things, that infectious particles are inhaled by susceptible individuals and deposited at effective sites within the respiratory system (14). The risk of infection is directly related to the infectious dose of a pathogen, i.e. the number of particles needed to start an infection (15).

Filtration can help prevent the number of particles inhaled, thus reducing the chance the infectious dose is reached. The other reason that filtration by the upper airways is important, is that not only airborne bacteria and viruses are filtered, but also other particles such as allergens, pollen, dust and Particulate Matter (PM)(13). PM refers to small ambient airborne particles from various sources (16-19) and is the pollutant that affects the most people worldwide (20, 21). It is the most harmful fraction of air pollution(21) and has no threshold below which it is not harmful (22). Even exposure at levels below the latest standards contributes to hospital admissions, ER visits, and is linearly associated with all-cause mortality (23-27). Literature suggests that a reduction in exposure to PM can be expected to improve health almost immediately and states that this should be taken into account for cost-benefit analyses, as PM has been shown to place a heavy burden on worldwide healthcare financially (27, 28).

The filtration of air is a complicated subject and depends on tidal volume, breathing pattern, air flow velocity, airway geometry as well as on numerous other parameters including particle mobility, density, hygroscopicity, shape and chemical composition and diameter of particle size (14, 29, 30). The deposition rate and location within the nose depends on the particle diameter. More than 80% of particles of 1-3 µm deposited within the entire nasal airways were held back at the nasal part. About 90% of particles larger than 4 µm were held back in the anterior nasal airways (31).

In laryngectomized patients, the filtration function of the upper airway is entirely lost as the upper airways are completely and permanently bypassed and the patient only breathes through the tracheostoma. Therefore, neck breathers are more susceptible to a much higher deposition of all types of airborne particles in the lower airways. As a result of this lack of filtration as well as the humidification deficit resulting from the loss of the conditioning of the inhaled air in the upper airways, laryngectomized patients experience increased respiratory infections (32-34).

1.3 Breathing resistance

Upper airway resistance accounts for 50-75% of total airway resistance during quiet breathing in normal individuals, of which two thirds is caused by nasal resistance (35, 36). Resistance of the upper airways is an important mechanical respiratory parameter for the optimal alveolar function and gas exchange in the respiratory system. It determines the effort it takes to breathe. Additionally, resistance ensures a difference in pressure between the alveoli and the outside, the transpulmonary pressure that causes the small airways to stay open.

The resistance of the upper airways is dynamic and changes depending on the airflow needs in case of temporary requirement of higher oxygenation. This can be achieved by widening the respiratory tract or switching to oral breathing (37). As a result of a total laryngectomy, this dynamic ability to adapt breathing resistance is lost, since breathing

takes place via the 'resistance-free' tracheostoma. This implies that work of breathing reduces and resistance becomes less dynamic.

It has been hypothesized that the loss of upper airway resistance increases dynamic airway compression by shifting the equal pressure point toward a more peripheral airway region, where the airway has less elasticity and is more easily flattened (38). Because of a decrease in transpulmonary pressure, these airways might then be compressed, which may cause atelectatic collapse of small airways (39).

Furthermore, it has been suggested that a reduced resistance to expiration indirectly decreases arterial oxygen saturation by reduced expiratory lung volumes, resulting in suboptimal pulmonary gas exchange (38, 40, 41).

1.4 Pulmonary health and quality of life

The loss of respiratory conditioning by the upper airways has a negative impact on the tracheobronchial system, which in response to the humidification deficit greatly increases mucus production. The humidification deficit also causes increased viscosity of the mucus. This increased mucus productions leads to symptoms such as increased coughing and forced expectoration which tends to exacerbate during dry and cold season. In patients unable to cough up secretions themselves this may also lead to a need for tracheal suctioning. The combination of increased mucus production and increased viscosity can lead to mucus plugs and the dried secretions can form into crusts. Increased nasal discharge and shortness of breath have also been reported (1, 38, 42-47).

Furthermore, tracheobronchial irritation produces extensive histological changes: squamous metaplasia of the respiratory ciliary epithelium and chronic inflammatory changes of the lamina propria have been observed in the trachea at the level of the carina in laryngectomized and tracheostomized patients (48, 49). This leads to excessive sputum production, frequent involuntary coughing, and repeated forced expectorations to clear the airway (50, 51). These pulmonary symptoms generally develop and increase within the first 6 to 12 months after initial surgery and then tend to stabilize (42, 52).

Laryngectomized patients experience the physical consequences of having a stoma (frequent sputum production from the stoma and its interference with social activities) as the most severe side effect of their surgery (43) (38). The pulmonary symptoms significantly affect the quality of life of the patient; perceived quality of voice, aspects of daily life, anxiety and depression (1, 53)

2. Pulmonary rehabilitation with Heat and Moisture Exchangers

Heat and moisture exchangers (HMEs) compensate for the loss of the natural humidification functions of the nose and are considered standard of care in laryngectomized patients (54, 55). In this section the basic properties and functions of HMEs and HMEFs (Heat and Moisture Exchangers with Filter) are described, followed by a historical overview of HME development and a description of the properties and functions of the HMEs, attachments and accessories in Atos Medical's portfolio.

2.1 HMEs and HMEFs properties and function

Pulmonary rehabilitation seeks to compensate for airway humidification deficits with the ultimate goal of reducing the adverse effects of total laryngectomy on pulmonary health. Heat and Moisture Exchangers (HMEs) are passive humidifiers that were developed to compensate for the loss of heating and humidification by the upper airways in neck breathers. In short, an HME has three physical properties: 1) heat and moisture exchanging capacity; 2) resistance; and to a small extent 3) filtering particles (56). The basic component of a heat and moisture exchanger is foam, paper, or another substance, which acts as a condensation and absorption surface. To enhance the water-retention capacity, the material is often impregnated with hygroscopic salts such as Calcium Chloride (57)(see Figure 3.). The HMEs used for neck breathers are mostly hygroscopic and may also be impregnated with a bactericide solution (e.g. chlorine hexedine) to attempt to control bacterial colonization (58, 59).

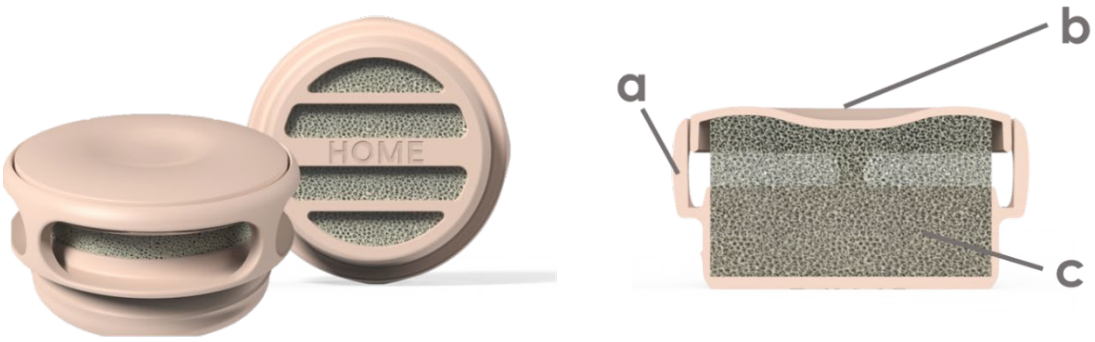

Figure 3 HME (HME pictured: Provox® Life™ Home HME) and its general components. On the left-hand side, an HME for manual occlusion function is shown from the top and bottom side. On the right-hand side, a cross-section of an HME is shown the plastic outside of the HME (a), the plastic lid that is pushed down to close the HME airtight for speaking (b), and the foam on the inside, treated with calcium chloride to retain heat and moisture from exhaled air (c).

An important feature of an HME is a mechanism to facilitate occlusion of the tracheostoma to generate tracheoesophageal speech. This can be accomplished via manual occlusion on the lid of the HME or 'automatically' with a handsfree speaking valve incorporating a membrane that closes automatically when exhaled airflow increases to generate speech (60). The basic functions of an HMEs are illustrated in Figure 4.

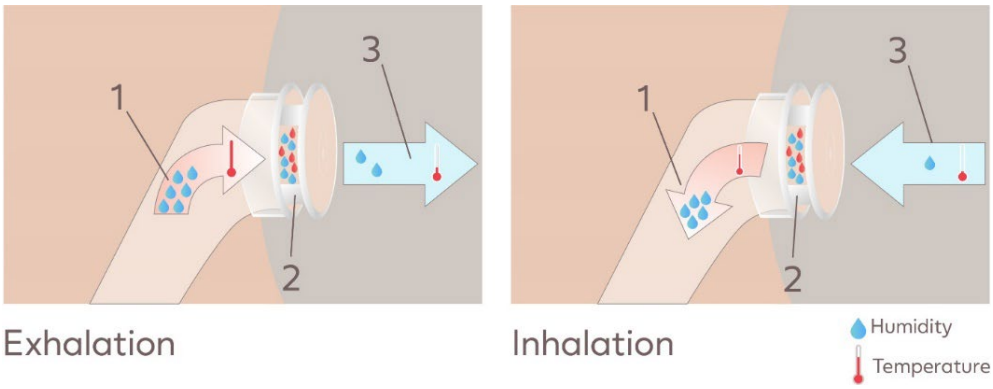

Figure 4 Working principle of an HME. The illustration on the left-hand side shows the mechanism during exhalation (breathing out): Heat and humidity from the exhaled air (1) is being collected in the HME (2). Thus, there is limited loss of heat and moisture into the environment. The illustration on the right-hand side demonstrates how this heat and moisture is returned (1) to the air that passes through the HME (2) on inhalation of cold and dry air (3).

► **Learn more** | **Benefits of Using an HME** video
www.atosmedical.us/professional/videos-and-tutorials **or**
www.youtube.com/watch?v=tCjEBG9rayI

With regards to the filtering function, a standard HME acts as a barrier to larger airborne particles , but, due to their large pore size they do not filter microorganisms, pathogens or other small particles to a significant degree (56). On the other hand, HMEFs combine the humidification properties of an HME with the filtration properties of a highly effective electrostatic filter (>98% bacterial and viral filtration efficiency), which consist of a matt of fibers with electrostatic charges. Any opposing particle with charge is attracted and bound to the material and a hygroscopic layer is added to provided humidification. Electrostatic filters effectively filter small particles such as viruses and bacteria (See Figure 5) (61).

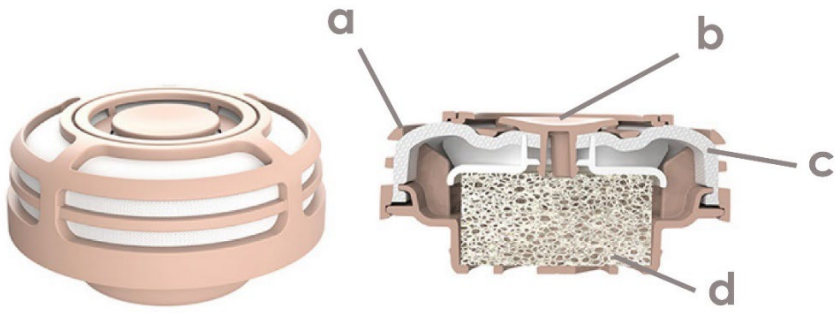

Figure 5 HMEF (HMEF pictured: Provox® Life™ Protect HME) and its general mechanism. On the left-hand side, an HMEF for manual occlusion function is shown from the top. On the right-hand side, a cross-section of an HMEF is shown. The plastic outside of the HMEF (a), the plastic lid that is pushed down to close the HME airtight for speaking (b), and the electrostatic filter inside (c) and the foam, treated with calcium chloride to retain heat and moisture from exhaled air (d).

In addition to heat- and moisture-retaining capabilities, HMEs and HMEFs partially restore the lost breathing resistance. It has been suggested that the breathing resistance provided by HMEs creates a positive end-expiratory pressure and thereby helps to reduce alveolar collapse and improve lung volumes and gas exchange (40, 56, 62).

Another explanation is that HMEs increase extra-thoracic expiratory resistance comparable to the mechanism of purse lip breathing (PLB). This is a phenomenon familiar to patients with COPD, in whom PLB, has been shown to improve arterial oxygenation (63-66). Use of PLB allows a reduction in dynamic airways compression. The positive effects of PLB are mainly attributed to enlarged transpulmonary pressures, reducing the tendency for alveoli to collapse (65-67).

Since a large percentage of laryngectomees present lung disorders in the form of COPD, similar positive effects can be expected by the partial restoration of breathing resistance provide by an HME (8, 38).

However, it is important to bear in mind that an HME also increases inspiratory resistance, in contrast to PLB, which can have clinically relevant effects since too high inspiratory resistance affects may cause patient discomfort and shortness of breath. It may not be tolerated for a longer period of time and can negatively affect adherence to HME use or the ability to use an HME during physical activity/exercise, impacting overall pulmonary rehabilitation (8, 9, 35).

2.2 History of pulmonary rehabilitation in laryngectomy patients

In 1960, Toremalm first described the benefits of HME use for laryngectomized and tracheotomized patients: in comparison to nasal breathing, a person breathing through a tracheostoma loses about 500 ml of water. Their results showed that by using an HME it was possible to retain 250 to 300 ml of this water loss in the respiratory system) (68, 69). Additional studies have shown that the use of an HME reduced water loss of the inhaled air in anaesthetized patients (70, 71).

The use of HME also impacts the temperature in the respiratory system. Evidence shows that the tracheal climate can rapidly change after the application and removal of an HME. The use of an HME increases the temperature in the trachea from 27-28°C to 29-30°C and the relative humidity from 50% to 70% (as shown in Figure 2) after just 10 minutes of HME placement (72).

The temperature of inspired tracheal gases was significantly lower during breathing without an HME compared to breathing with a Hygroscopic Condenser Humidifier (HCH), both at rest and during hyperventilation in tracheostomized patients (73). Furthermore, HMEs showed to provide satisfactory heating and humidification of inspired gases, similar to a heated humidifier in spontaneously breathing tracheotomized patients (74). When comparing the humidification performance of an HME and a heating-and-humidification high-flow device in spontaneously breathing subjects with tracheostomy, the high-flow system achieved higher absolute humidity than the HME, however, both systems supplied an absolute humidity higher than the American Association for Respiratory Care requirements (HME >30 mg/L, heated-and-humidified high flow >33mg/L) (75).

Along with the temperature and humidification, the use of an HME was found to increase the capillary oxygen tension, which indicates the partial pressure of oxygen in the blood – compared to a placebo (62).

In 1990, Ackerstaff and colleagues were the first to publish clinical results on the use of an HME in laryngectomized patients(76). The use of an HME ('StomVent') diminished the frequency of sputum production, forced expectoration and stoma cleaning (76). Additionally, short term effects after only 6 weeks of HME use were a reduction of respiratory symptoms and subsequently improved quality of life; a significantly decrease in symptoms of fatigue and malaise and improved social contacts (77). The HME and baseplate tested in this study ('StomVent') were combined in one piece and could not be separated which resulted in a relatively large number of problems with the adhesive loosening from coughing (77).

A subsequent clinical study tested a newer device where the HME and baseplate could be separated ('Freevent'). The results showed not only a reduction in the incidence of coughing but also the mean daily frequency of sputum production, forced expectoration, and stoma cleaning. The long-term HME user group (3 months of HME use) showed a significant improvement in shortness of breath, fatigue and malaise, sleeping problems, anxiety, depression and perceived voice quality (78). Furthermore, pulmonary function tests showed significant improvements in inspiratory flow and volume values following the use of an HME (78). Despite the fact that the HME and baseplate could be separated, loosening as a result of coughing still occurred frequently because the stoma was still not accessible for cleaning due to two crossed plastic bars blocking the entrance. In addition this device was still difficult to occlude for tracheoesophageal speech as it did not include any mechanism for stoma occlusion. Additionally, the use of the HME ('Freevent') showed significant improvement over time (from baseline to 3 and 6 months) in forced expectorations, perceived voice quality, social anxiety, social interactions and in feelings of anxiety and depression (79).

Respiratory parameters such as coughing, number of chest infections, mucus production and shortness of breath at rest improved in patients using an HME (Trachinaze) compared to a placebo (62). A literature review supports the use of HME devices and concludes they decrease the effect of sputum production, the need for ongoing suctioning, and the formation of stomal crusting as reported (80).

Two other extensive independent reviews (56, 81) concluded that the HME effectiveness on pulmonary rehabilitation is mainly due to the heating and humidification of inhaled air, and that is possibly that the added breathing resistance and slight particle filtration further benefit the respiratory system. However, it is not expected that an HME significantly compensates for the loss of upper airway filtration of smaller particles such as bacteria and viruses; the pores of the HME filter are large and there are no effective mechanisms to help capture and trap particles. Despite the fact that the use of HMEs does not effectively decrease colonization of the lower respiratory tract by pathogenic microorganisms, they do not endanger the health of patients with a tracheostoma through exposure to pathogenic microorganism either (82).

Although an HME cannot completely restore the physiological functions of the upper respiratory tract, depending on their humidification capacity they increase the temperature and humidity level of inspired air, helping to compensate for the humidification deficit in laryngectomized patients (83). Thus, having a positive effect on tracheal epithelium mucosa (83) and overall pulmonary health.

2.3 Provox® HMEs and attachments

The impact of HME use on pulmonary health, humidification and heating of inspired air has been clearly demonstrated in initial clinical research and validated in several studies(78, 79, 84).

In 1995 Atos Medical developed the first generation of Provox® HMEs. These first generation Provox® HMEs were discontinued in 2016. They have been succeeded by the second generation, Provox® XtraHMEs, in 2010 and the third generation, Provox® Life™ HMEs, in 2020 (see Figure 6). The following sections briefly describe the Provox® HMEs and their attachments and include performance characteristics (laboratory data) where relevant.

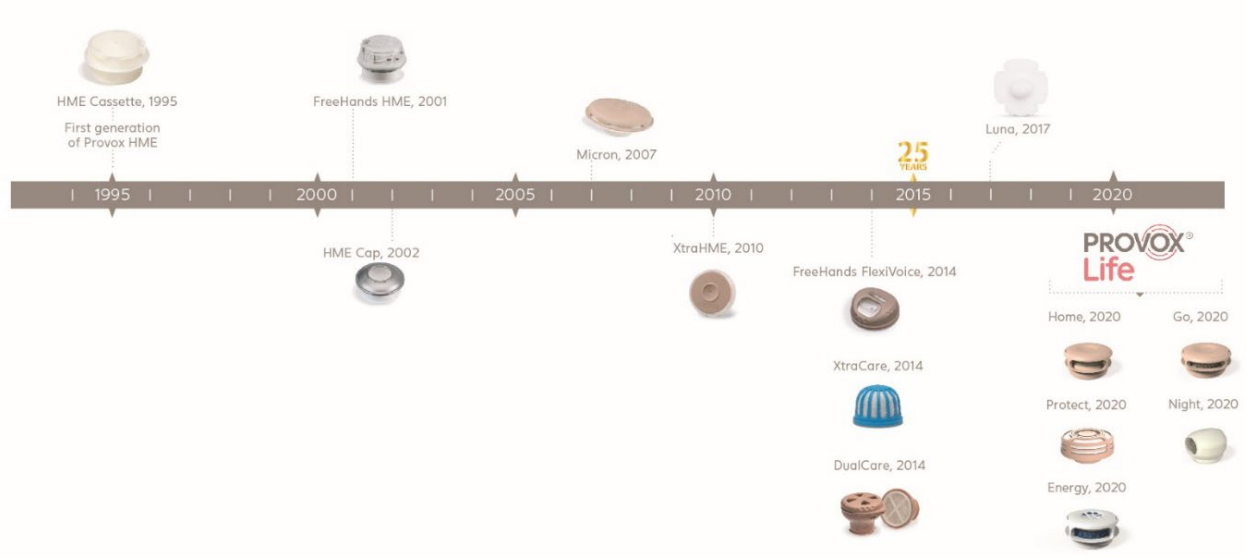

Figure 6 Timeline of the development of different Provox® HMEs and HMEFs.

2.3.1 Provox® HMEs

Provox® HME: Normal and HiFlow

The Provox® HME development and design was guided by the remarks from patients in earlier HME studies (78, 84). The Provox® HME consisted of a separate HME cassette and a self-adhesive baseplate available in two different shapes and four different materials to accommodate different skin types in stoma shapes (see Figure 7).

This first generation of Provox® HMEs was available in Normal and HiFlow and was discontinued in 2016. The HiFlow cassette had a lower resistance than the Normal cassette.

Figure 7 Provox® HME Normal (left) and Provox® HME HiFlow (right).

Provox® XtraHMEs: XtraMoist™ and XtraFlow™

Provox® XtraHMEs were developed to provide improved performance in humidification capacity, an improved humidification capacity/airflow resistance ratio, and new design features to enhance usability, in comparison to the first generation Provox® HMEs. Provox® XtraHMEs were introduced to the market in 2010 and are available in two versions: XtraMoist™ HME and XtraFlow™ HME (See Figure 8).

Figure 8 Provox® XtraHME (XtraFlow™ and XtraMoist™).

The XtraMoist™ HME can be worn day and night under low to normal physical effort, while the XtraFlow™ HME with a lower breathing resistance is designed for use during the day during increased physical effort and to enable adaptation to the increased breathing resistance associated with HME use in relation to open stoma breathing.

Compared to the Provox® HMEs, the XtraHMEs have 50% more HME media (in volume), which acts as a spring. The XtraHME also has a 1.4 mm lower profile than the Provox® HME, and a rim on the lid to guide the correct finger position for occlusion. In Figure 9 the differences between the Provox® HME and the Provox® XtraHME are shown.

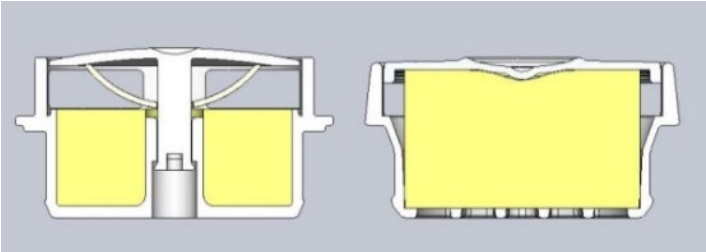

Figure 9 Schematic representation of Provox® HME (left) and Provox® XtraHME (right) in foam is showed in yellow.

The Provox® XtraHMEs (XtraMoist™ and XtraFlow™), which have a higher foam pore density to increase the surface area and binding capacity of hygroscopic salt in a similar size cassette, have been shown to have considerable heating and humidification improvement over Provox® HME (85). Furthermore, Provox® XtraMoist™ HME shows a significantly better water exchange performance than its predecessor according to a feasibility study(86) without decreasing the endotracheal temperature (87). Authors concluded that XtraHMEs show both heating and humidification improvement compared to the Provox® HME.

In an *ex vivo* study comparing humidification performance of 23 commercially available HMEs for laryngectomized patients, Provox® XtraMoist™ HME was shown to have a statistically significantly higher humidification capacity than all other tested HMEs (107). Thus, having a higher reduction of humidification deficit caused by breathing through an open stoma (see Figure 10).

Notably, these results are validated with absolute humidity outcomes. According to this study, humidification capacity correlates well with the end-inspiratory absolute humidity outcome. This means that the wet core weight of an HME is a predictor of its performance(107).

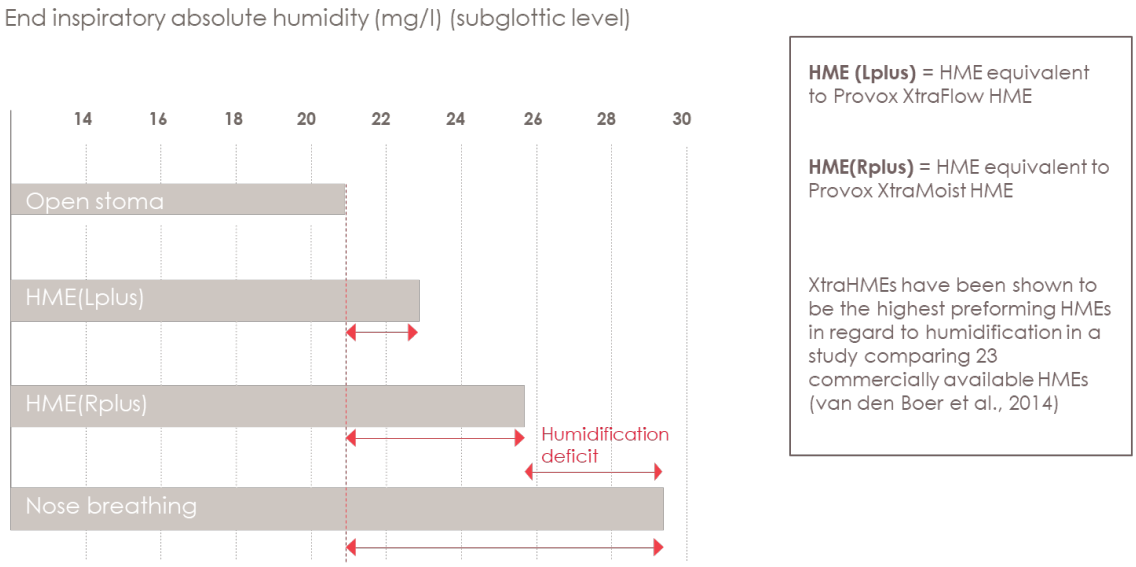

Figure 10 HMEs increase end-inspiratory humidity levels versus open stoma breathing and reduce the humidification deficit versus nose breathing depending on their humidification capacity.

Measuring the difference between wet and dry core weight in two different generations of HMEs (XtraMoist™ , XtraFlow™ , Normal and HiFlow), it has been demonstrated that the water uptake capacity of hygroscopic HMEs is no longer optimal after 24-hours of use due to condensation and secretion build up (88). Thus, from a pure humidification efficiency point of view, an HME should be used for no longer than 24 hours. However, in daily life the HME is replaced more frequently, (studies report 1.1 – 2.8 per day(89-91) [1]), owing to coughing up of secretions and variations in oxygen requirements throughout the day during different activity levels. More recently, COVID-guidelines for the management of laryngectomy care recommend also replacing the HME after community exposure (92).

Provox® Luna®

Launched in February 2017, Provox® Luna® HME and adhesive were developed to improve compliant HME use during the night. An anthropological study conducted by Atos Medical with ReD Associates indicated that as many as 80% of the patients do not use the HME consistently during the night. Reasons cited include discomfort with the current solutions, lack of knowledge regarding the importance of compliant HME use, and the need for intermittent skin rest due to skin irritation. Consequently, compliant 24/7 HME use is not achieved by many patients, which has a negative effect on pulmonary rehabilitation[2].

[1] Post-market surveillance activity conducted by Atos Medical in 2020-2021. Data on File.

[2] Study conducted by Atos Medical with ReD Associates , 2015. Data on file.

Provox® Luna® consists of an adhesive and an HME. Provox® Luna® HME has a superior humidification capacity and comfort compared to other second generation Provox® HMEs. Provox® Luna® Adhesive is made of skin friendly hydrogel material (See Figure 11).

Figure 11 Provox® Luna® HME and adhesive.

Provox® Luna® HME is a soft silicone HME with a pressure drop of 55Pa at 30L/min and a moisture loss of 21.4mg H_2O/L air (according to device specifications). With these values, the humidification properties of the Provox® Luna® HME are similar to Provox® XtraMoist™ , whereas the pressure drop and hence the breathing resistance, is lower than for Provox® XtraMoist™ (with a pressure drop of 70Pa) and slightly higher than that of Provox® XtraFlow™ (with a pressure drop of 40Pa).

Provox® Luna® Adhesive is made of a hydrogel material. Hydrogels are commonly used on a wide variety of wounds, such as skin tears, pressure ulcers, burn wounds and surgical wounds. Hydrogel dressings are water- or glycerine-based products, best suited for dry wounds or those with minimal to moderate exudates(93, 94). Hydrogel sheet dressings are reported to be comfortable and soothing, and to reduce pain because of their cooling effect(95-100).

Provox® Life™ HMEs

Throughout the course of innovation, Provox® HMEs have continuously improved in regards to humidification, breathability and usability. The third generation, Provox® Life™ HMEs, present superior breathability and humidification levels and a wider range of HMEs to improve usability compared to their predecessors.

A higher humidification capacity requires a larger foam volume, or higher foam pore density to increase the surface area and binding capacity of hygroscopic salt. This increases the airflow resistance through the device, which for patients is experienced as a higher breathing resistance (39). Breathing resistance is also increased by the inclusion of an electrostatic filter in HMEFs (39, 101).

An important modification made to achieve the high performance of new Provox® Life™ range of HMEs was to increase the HME diameter by 1 mm (4.5%), from the standard 22 mm to 23 mm. This seemingly small increase in diameter has a considerable impact on both humidification capacity and airflow resistance.

The different HME models are designed to provide the highest humidification while allowing breathability in various situations. Home HME, Go HME, Energy HME and Night HME were developed by optimizing parameters such as foam volume, foam porosity and air inlet/outlet area to accommodate different levels of physical activity (See Figure 12).

Figure 12 (From left to right) Provox® Life™ Home HME, Provox® Life™ Go HME, Provox® Life™ Energy HME and Provox® Life™ Night HME.

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https://youtu.be/CsBR5Sg20cY

The new Provox® Life™ range of HMEs were developed to provide the highest possible humidification while keeping the breathing resistance comfortable. Laboratory measurements of the Provox® Life™ HMEs show a considerably higher humidification capacity (i.e. moisture loss, measured in mg/l) and lower breathing resistance (i.e. air pressure drop, measured in Pascal (Pa) at 30 l/min) in comparison to their functional equivalents in the second generation of Provox® XtraHMEs, see Table 2 in Appendix and Figure 13. As seen in figure 13 the breathing resistance represented by Go HME and Energy HME are 50% and 75% lower respectively compared to Home HME.

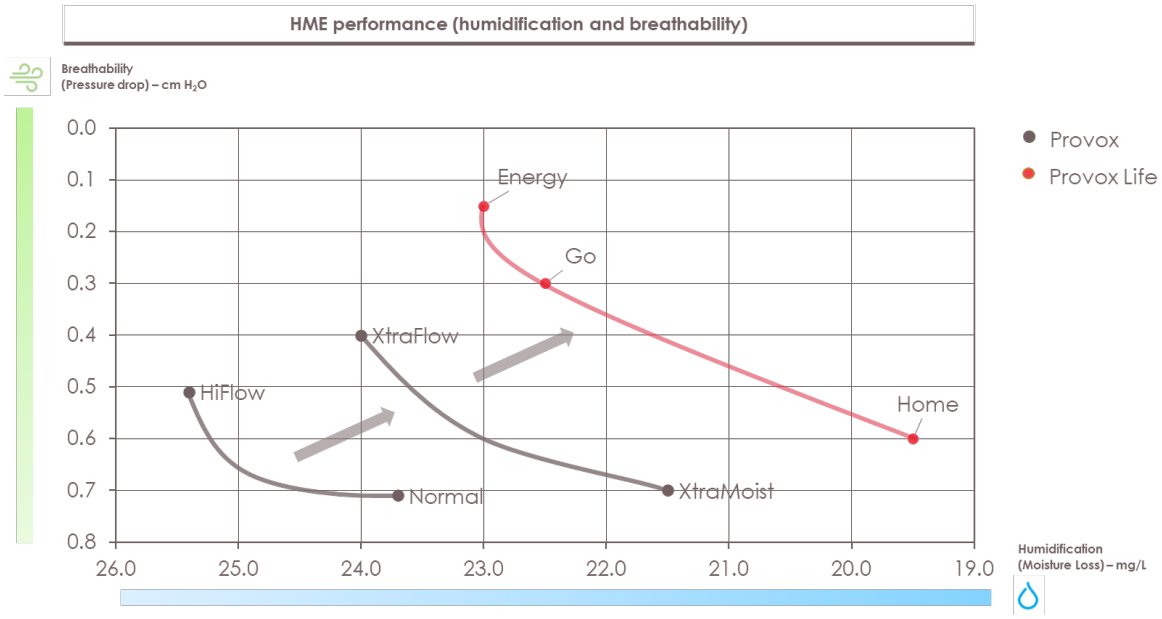

Figure 13 Provox® Life™ optimizes HME performance for everyday situations.

2.3.2 Provox® HMEFs

Provox® Micron HME™

Provox® Micron HME™ is an HMEF that combines a Heat and Moisture Exchanger with a highly effective (>99% Viral and Bacterial Filtration Efficiency)*[3] electrostatic filter (see Figure 14). The electrostatic filter is bidirectional, providing filtration of inhaled and exhaled air.

Figure 14 Provox® Micron HME™.

Provox® Life™ Protect HME

Provox® Life™ Protect HME is an HMEF that combines an HME with a highly effective electrostatic filter (> 98% Viral and Bacterial Filtration Efficiency)*[2] it is part of new Provox® Life™ range of HMEs (See Figure 15). Laboratory measurements demonstrate that Provox® Life™ Protect HME presents 21% more breathability compared to Provox® Micron HME™ and higher humidification capacity (See Table 2 in Appendix).

Figure 15 Provox® Life™ Protect HME.

► **Learn more** | **Provox® Life™ Protect HME** video
https://youtu.be/27ksl-8pfzM

2,3 The VFE (Viral Filtration Efficiency) and BFE (Bacterial Filtration Efficiency) at an increased Challenge Level Test procedure adapted from ASTM F2101, was performed for Provox® Micron HME™ and Provox® Life™ Protect at Nelson Laboratories (US) in accordance with USFDA (21 CFR Parts 58, 210, 211 and 820) regulations. Mean VFE and BFE was >99% for Micron HME™ and >98% for Protect HME. Data on file.

* Since pathogens can enter and leave the human body in other ways (such as the mouth, nose, and eyes), Provox® Micron HME™ and Provox® Life™ Protect HME can never guarantee complete protection. Please read the instructions for use for guidance.

2.3.3 Provox® FreeHands HMEs and Speaking Valves

Provox® FreeHands HME and Provox® FreeHands FlexiVoice™

The legacy Provox® FreeHands HME was developed to enable hands-free speech for tracheoesophageal speakers and was introduced in 2001. In 2014 it was replaced by its successor, Provox® FreeHands FlexiVoice™.

The Provox® FreeHands FlexiVoice™ (see Figure 16 and Figure 17) is a system that combines an automatic speaking valve with the Provox® FreeHands HME cassette.

Upon speech-exhalation, the membrane of the speaking valve closes off automatically, enabling the pulmonary air to be diverted through the voice prosthesis into the esophagus. This system is developed specifically for prosthetic tracheoesophageal speakers.

Although the legacy speaking valve, Provox® FreeHands HME, is a discontinued device, the published literature is still relevant due to the similarity with the Provox® FreeHands FlexiVoice™ speaking valve. Additionally, the evidence for Provox® FreeHands HME is important in showing the developmental history behind Provox® FreeHands FlexiVoice™.

Figure 16 Provox® FreeHands HME cassette.

The Provox® FreeHands FlexiVoice™ speaking valve has two settings. In one setting, the membrane of the speaking valve is always in the opened position, useful during physical activity (locked mode). In the other setting, the speaking valve is bias-open, meaning the membrane is normally in the opened position and only closes upon relatively strong exhalation (automatic speaking mode). The Provox® FreeHands FlexiVoice™ comes in three different strengths to accommodate different speaking pressures (see Figure 17). The membrane also acts as a pressure relief valve, which allows the air to escape when coughing. The design of the speaking valve also allows for speech through manual occlusion, by placing a single finger over the front opening. The speaking valve cannot be used without an HME cassette, meaning the system functions as a full-time HME.

Figure 17 Provox® FreeHands FlexiVoice™ Light, Medium, and Strong.

Provox® Life™ FreeHands HME

The Provox® Life™ FreeHands HME cassette is compatible with Provox® FreeHands FlexiVoice™ and Provox® Life™ adaptors.

2.3.4 Provox® Attachments

Adhesive properties and function

For peristomal attachment, Provox® XtraHMEs and Provox® Micron HME™ can be attached to Provox® Adhesives, which come in different adhesive materials, shapes, and sizes (Provox® OptiDerm™, FlexiDerm™, XtraBase®, StabiliBase™ and StabiliBase™ OptiDerm™). Additionally, some patients may require the use of Provox® Silicone Glue to improve the seal of the adhesive to the skin. Other products that are recommended for proper application of the adhesive are Provox® Cleaning Towel (to prepare and clean the skin) Provox® Adhesive Remove (to remove glue from the skin) and Provox® Skin Barrier (to leave a protective layer on the skin). Using HMEs together with an adhesive provides an airtight seal which makes the conditioning of air more reliable and facilitates tracheoesophageal speech.

OptiDerm™, FlexiDerm™ and XtraBase®

The hydrocolloid Provox® OptiDerm™ is made of a hypoallergenic adhesive material that forms a gel in contact with water. The Provox® OptiDerm™ adhesives are: Provox® OptiDerm™ Round/Oval/Plus (See Figure 18)

Provox® FlexiDerm™ is a very flexible material and has the strongest adhesive properties. It is a sticky, yet soft and flexible adhesive. The Provox® FlexiDerm™ adhesives are: Provox® FlexiDerm™ Round/Oval/Plus (See Figure 18)

Provox® XtraBase® with a concave shaped base was developed especially for hands-free speech. The base of this adhesive is more rigid and gives more support to the peristomal area, both when used during speech with manually occluding HMEs and hands-free speech with an automatic speaking valve (See Figure 18).

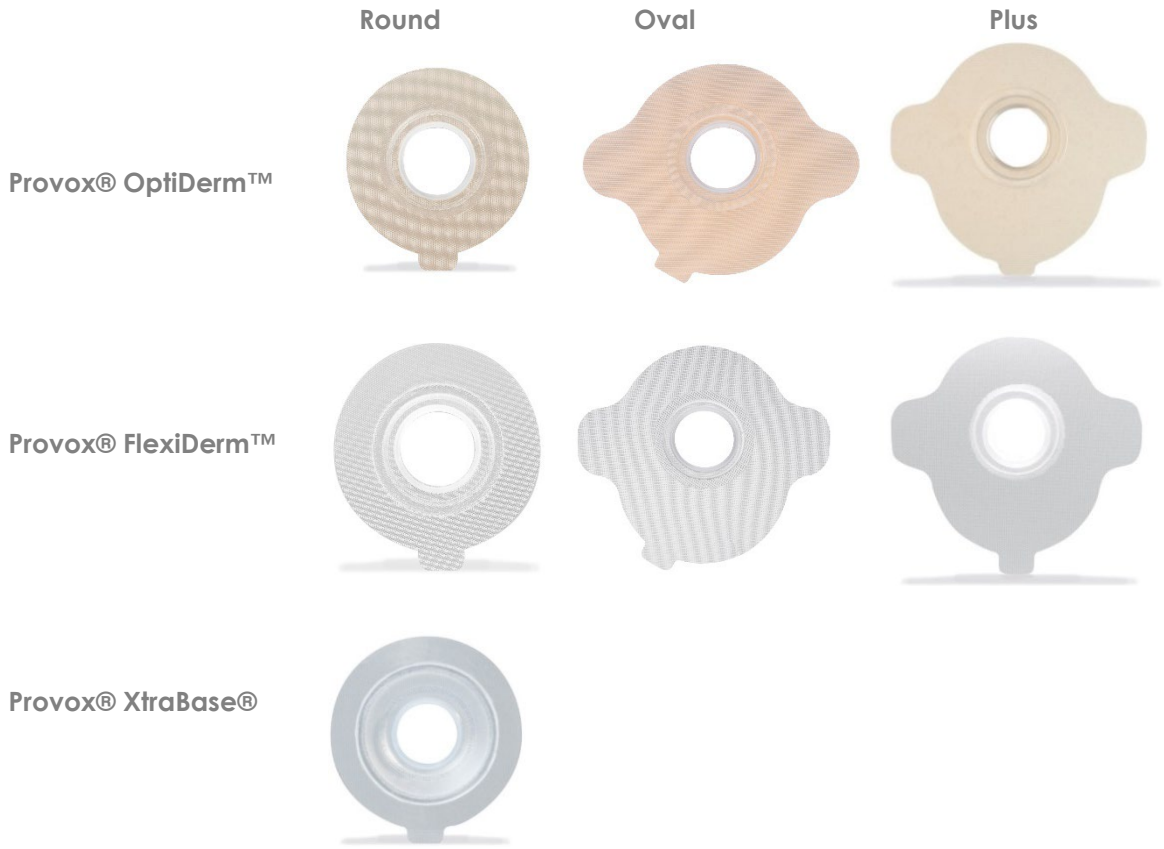

Figure 18 Provox® OptiDerm™, Provox® FlexiDerm™ and Provox® XtraBase® adhesives.

Provox® StabiliBase™ and Provox® StabiliBase™ OptiDerm™

The peristomal adhesive baseplate Provox® StabiliBase™ was introduced in 2012 and consists of a conically shaped, firm plastic base with vertical stabilizing bars to provide support to the tracheostoma during speech (see Figure 19). The base is welded on its outer rim to the adhesive material, which is similar to that of the existing Provox® FlexiDerm™ and Provox® XtraBase® adhesives. The baseplate liner has three removable vertical strips to facilitate application to the skin.

The design of the Provox® StabiliBase™ adapter can be especially suitable for deep tracheostomas.

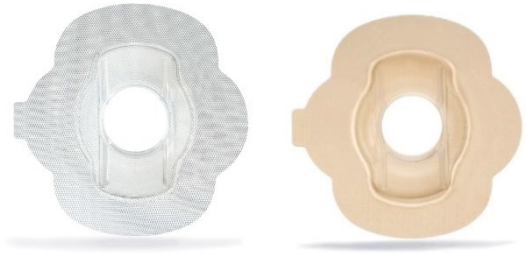

Figure 19 Provox® StabiliBase™ (left) and Provox® StabiliBase™ OptiDerm™ (right).

Provox® Life™ Adhesives

Provox® Life™ Adhesives are designed to be used together with Provox® Life™ HMEs and accessories. Provox® Life™ Standard Adhesives, Provox® Life™ Sensitive Adhesives, Provox® Night Adhesive and Provox® Life™ Stability Adhesive are flexible adhesives suitable for flat to moderately deep stomas. Provox® Life™ Sensitive Adhesives (hydrocolloid) and Provox® Life™ Night Adhesive (hydrogel) have an adhesive material that is hypoallergenic and suitable for sensitive skin (See Figure 20).

The adhesives have been developed to suit different situations and to satisfy patients' individual needs due to differences in skin type and stoma morphology. Parameters such as composition and thickness of the pressure sensitive adhesive material (the material closest to the skin) and the carrier (the outer layer of the adhesive) were optimized to balance adhesion and skin-friendliness for different purposes. For improved fit to a wide range of stoma morphologies, all Provox® Life™ adhesives come in a clover shape. The clover shape was introduced to prevent the occurrence of folds and creases of the adhesive when attached to concave stomas and thereby further contribute to an airtight adhesion.

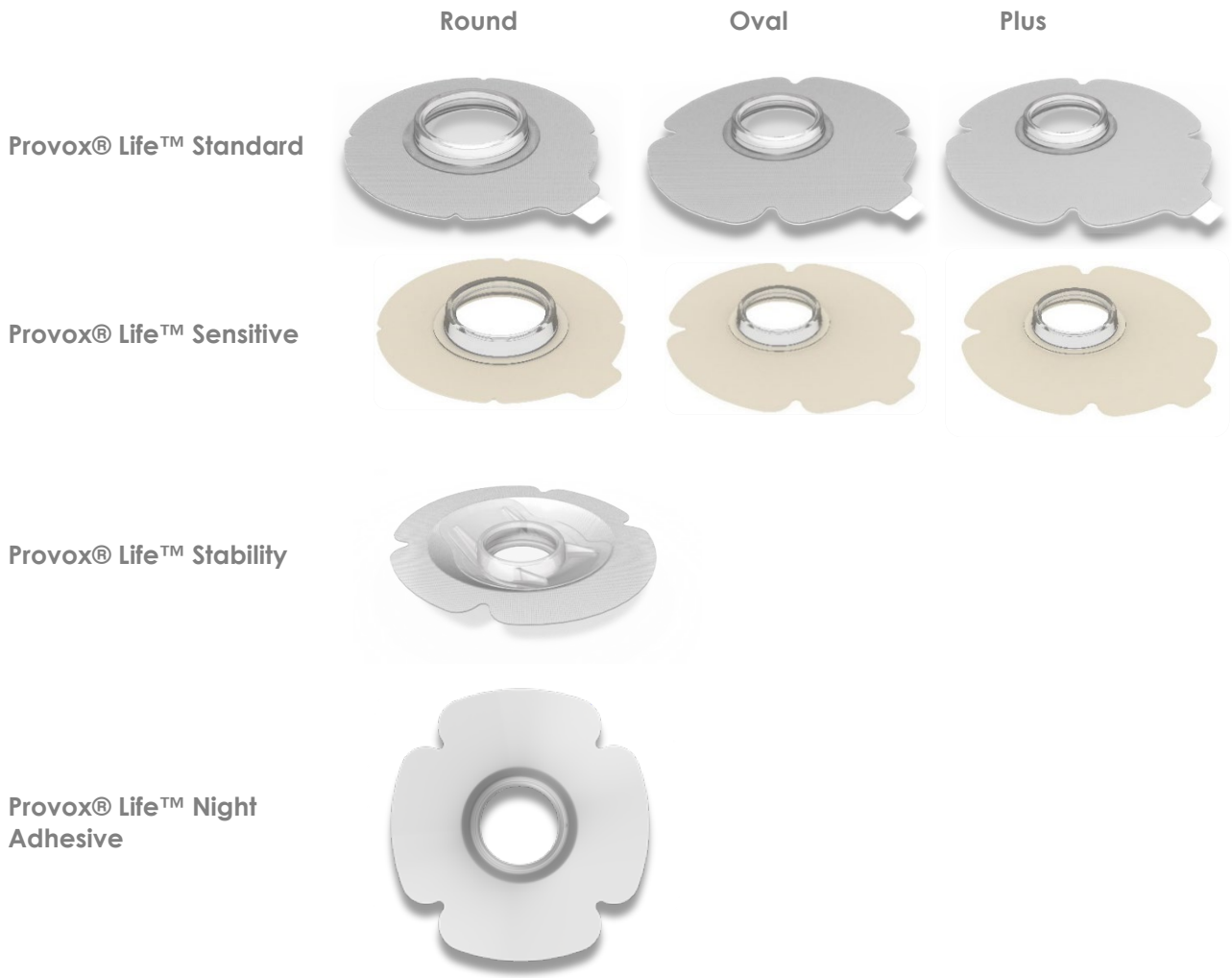

Figure 20 Provox® Life™ Adhesives.

2.3.5 Provox® LaryTubes and LaryButtons properties and function

For intraluminal attachment the Provox® HME can be attached to a Provox® LaryTube™ or a Provox® LaryButton. The primary reason for using a Provox® LaryTube™ or Provox® LaryButton is usually to maintain stoma patency, although a Provox® LaryButton may also be beneficial in combination with a hands-free speaking valve.

Provox® LaryTubes

The Provox® LaryTube™ is a so-called laryngectomy tube (see Figure 21). The Provox® LaryTube™ can be used to attach Provox® HMEs and Provox® FreeHands FlexiVoice™ speaking valve (60, 102-107). The Provox® LaryTube™ is held in place with a Provox® TubeHolder (neck band) and Provox® LaryClip or it can be clicked into a baseplate (model with Blue Ring). For patients using a voice prosthesis, a fenestrated Provox® LaryTube™ is available. The Provox® LaryTube™ is well suited for immediate postoperative Provox® HME use, when a laryngectomy tube is may be needed to maintain stoma patency, HME use during postoperative radiotherapy and HME use in patients with sensitive skin (108). Some patients experience permanent problems with stoma patency, requiring permanent use of a laryngectomy tube (108).

Figure 21 Three different types of Provox® LaryTubes. Top: with blue ring; Middle: standard; Bottom: fenestrated.

Provox® Life™ LaryTube™

Provox® Life™ LaryTube™ can be used to attach Provox® Life™ HMEs and accessories. Provox® Life™ LaryTubes are well suited for patient with a shrinking tracheostoma (See Figure 22). They are available in four types: Standard, Fenestrated Standard, With Ring and Fenestrated with Ring.

Figure 22 Provox® Life™ LaryTubes. (left) standard, (right) fenestrated with Ring.

Provox® LaryButton™

Provox® LaryButton™ is a so-called tracheostoma button (see Figure 23). A tracheostoma button is primarily used in stomas that are shrinking and that have a tight 'lip' or 'rim' that holds the button in place(108)and patients with sensitive skin. Provox® LaryButton™ is a silicone stoma button, that maintains the opening of the stoma. It can be used to attach an HME, also in combination with the Provox® FreeHands FlexiVoice™ speaking valve (90, 102, 103, 109, 110).

Provox® LaryButton™ has a retention collar, but can also be held in place by using a Provox® TubeHolder or Provox® LaryClips (small adhesives combined with Velcro-attached hooks).

Figure 23 Provox® LaryButton with Provox® LaryClips.

Provox® Life™ LaryButton™

Provox® Life™ LaryButton™ is a silicone stoma button that can be used to attach Provox® Life™ HMEs and accessories, similar to the device Provox® LaryButton™ (for attachment of second generation HMEs and HMEF) it can be also used in combination with the Provox® FreeHands FlexiVoice™ HMEs cassettes (See Figure 24).

Figure 24 Provox® Life™ LaryButton™.

2.3.6 Supporting Provox® Accessories

Provox® Accessories were developed to provide protection to the tracheostoma during showering, taking care of the peristomal skin when cleaning, and to help improve the seal of the adhesive to the skin.

Table 1. Provox® accessories.

Product Name	Product Image	Device description	Provox® range compatible	Provox® Life ™ range compatible
Provox® ShowerAid		Provox® ShowerAid is a cover that protects the stoma from water when showering.	✓	
Provox® Adhesive Strip		Provox® Adhesive Strip is a single-use device that provides an additional seal. For use when using Provox® Luna® Adhesive and Provox® Life™ Night Adhesive when showering.	✓	✓
Provox® Adhesive Remover		Provox® Adhesive Remover is a single use wipe that contains a sting free solvent that helps laryngectomized patients remove Provox® Adhesives and Provox® Silicone Glue.	✓	✓
Provox® Skin Barrier		Provox® Skin Barrier contains a sting free solvent that is wiped on skin providing a barrier between Provox® adhesive and the skin.	✓	✓

Product Name	Product Image	Device description	Provox® range compatible	Provox® Life ™ range compatible
Provox® Cleaning Towel		Provox® Cleaning Towel cleans the skin and removes oil from the skin before putting on an adhesive. It is alcohol-based and non-perfumed.	✓	✓
Provox® Silicone Glue		Provox® Silicone Glue is a liquid glue that can be used to improve the adhesion between the skin and the adhesive.	✓	✓
Provox® LaryClip		Provox® LaryClip is an alternative to Provox® TubeHolder (See Figure 23). It consists of a two-piece system that helps to optimise the air-tight attachment of Provox® LaryButtons and Provox® Life™ LaryTubes.	✓	✓

Product Name	Product Image	Device description	Provox® range compatible	Provox® Life ™ range compatible
Provox® FreeHands Support		Provox® FreeHands Support helps reduce stoma movement and improve voice quality when speaking hands-free. It consists of a transparent base with a discrete ring, and a fixation adhesive. The ring is placed over Provox® FreeHands FlexiVoice™. The base and ring support the stoma, and the fixation adhesive attaches the base to the chest.	✓	✓
Provox® Life™ Shower		Provox® Life™ Shower protects the stoma from water when showering. Compatible across the range of Provox® Life™ Adhesives.		✓

3. Provox® HMEs and clinical evidence

Atos Medical's innovations and HMEs development are backed by strong clinical evidence as demonstrated by the amount of clinical and scientific studies conducted on Provox® HMEs during the last 30 years. It can be seen from the amount of 53 clinical studies studies published between 1990 and 2021, 41 (77%) mentioned HMEs manufactured by Atos Medical (See Appendix 2) involving 1801 laryngectomized patients (See Figure 25 and Figure 26).

Clinical Evidence of HMEs use in Laryngectomized patients per manufacturer, based on 53 studies published between 1990 and 2021

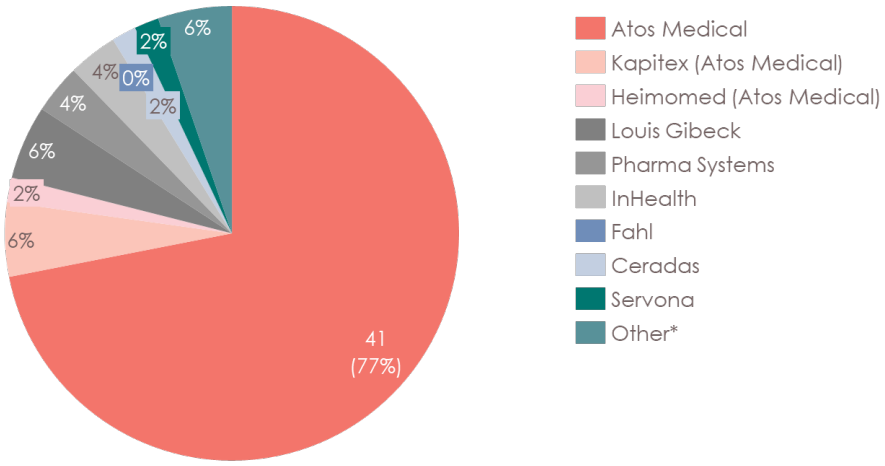

Figure 25 Chart includes only laryngectomy studies published between 1900 and 2021. Clinical evidence: refers to a clinical study where patients were included and an HME from a listed manufacturer has been studied. Some articles mention several brands and are therefore represented multiple times.

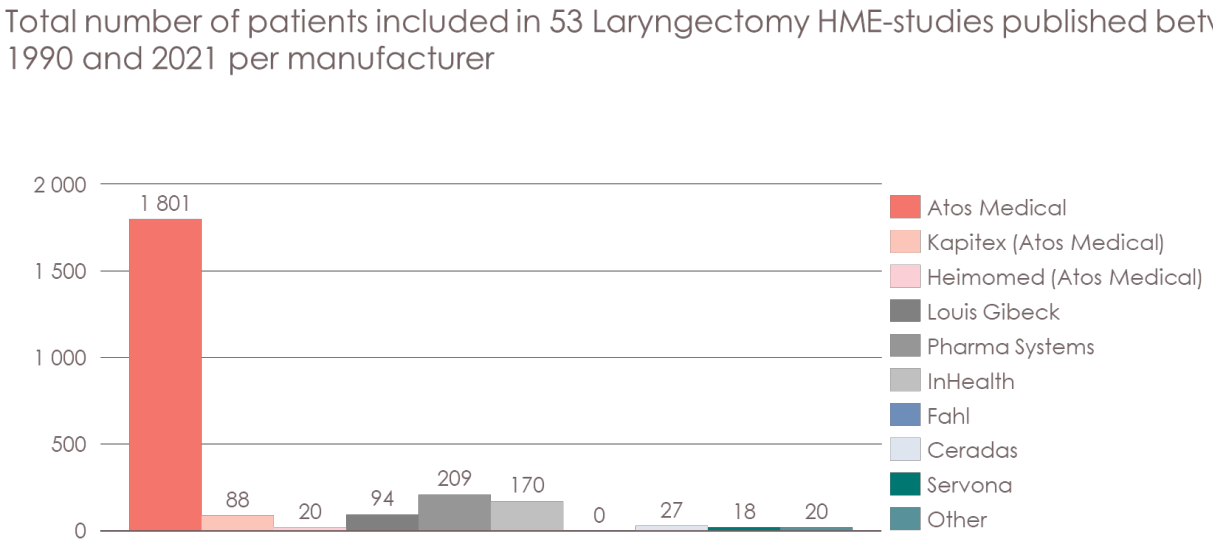

Figure 26 Histogram showing number of patients by manufacturer included in 53 HME studies.

3.1 The impact of HME use on pulmonary physiology and tracheal climate

Since the development of the first HMEs, there has been increasing clinical evidence highlighting the importance of humidification performance and the adherent use of HMEs in pulmonary rehabilitation and related psychosocial aspects.

In the following sections, the clinical data that support the impact on pulmonary rehabilitation and the quality of life of laryngectomized patients with the different generations of Provox® HMEs are presented chronologically.

Measuring intra airway temperature and humidity during breathing is a very complex issue. To determine the effect of HME use in temperature and humidity in laryngectomized patients an Airway Climate Explorer tool was developed at the Netherlands Cancer Institute and validated *in vivo* (111). This tool has allowed to assess the influence of Provox® HME in standard room conditions on tracheal temperature and humidity. In a study including 10 laryngectomized patients it has been shown that the presence of Provox® Normal HME increased the intra-tracheal mean humidity with 3.2 mg H2O/L (95% CI: 1.5–4.8 mg H2O/L; p <0.001), from 21.4 to 24.6 mg H2O/L and decreased the mean intra-tracheal temperature with 1.68C (95% CI: 0.9–2.48C; p <0.001) from 28.58C to 26.98C (112).

Interestingly, in a randomized crossover study conducted in 10 disease-free laryngectomized patients and testing Provox® HMEs in a cold environment, the presence of the Provox® HME significantly increased both inspiratory and expiratory temperature with 3.9C (95% CI: 2.7–5.1C; p <0.001) and 1.2C to 26.98C (95% CI: 0.8–1.2C; p <.001), respectively, and mean humidity minimum and maximum values increased with 4.2 mg H2O/L (95% CI: 3.3–5.0 mg H2O/L; p <0.001) and 2.4 mg H2O/L (95% CI: 1.7–3.1 mg H2O/L; p <0.001), respectively (51) . Additionally, in a warm environment, the presence of an HME has a cooling effect on the temperature while it still humidifies the inspired air (6).

Breathing through an HME increases endotracheal minimum and maximum humidity values. During inhalation the minimum humidity values are dependent on the inhalation breath length (IBL). The lowest humidity values occur at the end of inspiration and decrease when the IBL is lengthened. A study conducted in 13-16 laryngectomized patient show that the presence of Provox® HME cause a significantly shorter inhalation breath length (1.05s) compared to breathing without HME (1.35s, p<0.001) (113). Furthermore, the decay of gradual evaporation of water took longer with the Provox® HME in situ, so the air in the trachea stayed humid longer than without Provox® HME (2.69 vs. 2.19s; P< 0.0001). (113).

The humidification capacity and breathing resistance of an HME are inversely related. When comparing Provox® Normal with Provox® HiFlow (lower breathing resistance) it was shown that even though both HMEs prolonged exhalation breath length (EBL) by approximately +0.5 seconds (p<0.001) ; EBL without HME: 2.19 s, Normal HME: 2.61s, and HiFlow: 2.69s , Provox® Normal had better humidification properties than Provox® HiFlow (+5.8 and 4.7 mg H2O/L, respectively) and showed a small but significant positive effect on tidal volume (0.07 L; p < .05). (39). Therefore, the fact that Provox® HiFlow has 25% lower breathing resistance, means that is a 25% less effective humidifier. However, the use of Provox® Normal and Provox® HiFlow both increased endotracheal humidity significantly compared to no-HME. Thus, an HME with higher humification capacity is the better choice for regular daily use if the breathing resistance is tolerated. In circumstances when a lower breathing resistance is required a lower humidification capacity HME, is an acceptable alternative (39).

Additional efforts have been made to generate *ex vivo* methods to determine HME performance comparable to *in vitro* and *in vivo* results. A study has shown that HME humidification performance could be determined by measuring the weight difference between end-inspiration and end-expiration using a regular balance and a standard spirometer. The results obtained with this method for four Provox® HMEs with known *in vivo* humidity and *in vitro* water loss correlated well with previous *in vivo* measurements (R^2 = 0.98)and *in vitro* values provided by manufacturer (R^2 = 0.77) based on 24-hour ISO 9360-2:2001 assessments(114).

As mentioned before, tracheal mucociliary activity is highly dependent on tracheal humidity. A multi-center case-control study looking at tracheal mucociliary clearance in detail in 3 different groups, 21 long-term HME users, 10 non-HME users and 16 non-HME users before and after 4-9 months HME use. Long-term use of XtraMoist™ and XtraFlow™ HMEs helped to restore tracheal ciliated cells and helped prevent their loss(115). Highlighting the importance of compliant use of HME to have a positive impact on tracheal cilia.

3.2 The impact of HME use on respiratory parameters

The positive impact on pulmonary symptoms resulting from Provox® HME use, were first shown by Hilgers et al. in a prospective non-randomized clinical study (116). This study including 19 patients reports that patients experienced improvement in their respiratory symptoms. The increased breathing resistance caused by Provox® HME did not lead to a discontinuation of the device. However, some patients reported that they sometimes removed the HME during increased physical activity.

Similar results were observed in a short-term study in Denmark in 18 patients, in which 5 patients experienced less coughing and mucus production, 12 reported it was unchanged and 1 patient experienced more coughing after a trial period of 3 weeks. Eleven patients did not experience a change in breathing resistance and 7 found it to be increased (117).

These results were confirmed by similar studies in different countries including: Spain (118), the US (107), Poland(107) and Brazil (119). Thus, indicating that results can be expected to be similar across cultures and climates. For example, the study performed in the US (107) showed that Provox® HME adherence was 73% and that 68% of the patients reported a decrease in coughing, 73% reported decreased mucus production, 60% reported decreased forced expectoration, and 52% reported decreased need for stoma cleaning. The daily cough-expectoration frequency also decreased significantly. The study conducted in Poland by Bien et al. (90) supports these results showing that patients wearing an HME day and night have more significant improvements compared to those who use an HME less consistently, additionally it was shown that sleeping tended to improve. The study conducted in Brazil, showed that the use of Provox® HME over a 6 week time period reduced cough and expectoration of patients (119).

Subsequently, in order to investigate long-term impact of Provox® HME use, 69 patients using Provox® HME were included in a study in The Netherlands. In this study the use of Provox® HME improved respiratory symptoms in 65% of the patients, and 94% of the patients overall benefited of the device. Regarding adherence to HME use 78% of the patients used the device on a regular basis during the night and 53% of the patients also used the device at night, 6% used it irregularly and 16% did not use the device. There was an obvious relationship between the length of use of the device and pulmonary complaints. The longer the device was used, the more the pulmonary complaints (coughing, forced expectoration, sputum production) decreased (120).

In a long term RCT with Provox® HME including 60 patients, a notable improvement with regard to coughing ($p= 0.00174$) and to bronchorrhea ($p= 0.0031$)was reported after 3 months of Provox® HME use compared with the non-HME group. A trend with regard to breathing effort in the Provox® HME group was also reported (91). Provox® HME was used daily by 80% of the patients of whom 42% used it day and night at the end of the 3 months.

The improvement in humidification capacities in Provox® XtraHMEs (XtraMoist™ and XtraFlow™) resulted in a further reduction of mucus production just after three weeks of use in 13 patients in a prospective study (121). During this observation period, 7/13 patients (54%) reported noticeable less mucus production than with their accustomed HME, including one patient who previously did not use an HME at night, but did so during the study period. Interestingly, that patient had the largest reduction in coughing frequency (from 20 times to 5 times daily). Although the appearance of the HMEs used in this study is different from the Provox® XtraHMEs, the HME media used in the HMEs tested in this study is the same as the HME media used in Provox® XtraHMEs.

In line with these results in a RCT, including 45 patients, who were already using an HME showed that the improvement in tracheal climate translated into patients reporting significantly less tracheal dryness with the second generation Provox® XtraHMEs than with the first generation Provox® HMEs ($p = 0.039$) after 6 weeks of use (89). The average daily coughing frequency was lower when using the XtraHME (2.0 vs. 2.59 per day) and the maximum number of forced expectorations was lower using the XtraHME (12 vs. 2.5 per day). Furthermore, Provox® XtraHME use compared to Non-HME use was studied by Parrilla et al., (122). In a multi-center time series study including 30 HME- naïve Italian patients who used Provox® XtraHME for 12 weeks was investigated. Patients using Provox®

XtraHME for more than 20 hours during 12 weeks, already after just 2 weeks there was a significant positive effect of Provox® XtraHME use on pulmonary complaints, with a significant decrease in daily coughs (from 8.8 at baseline to 4.6 with Provox® XtraHME, p<0.0001) and daily forced expectorations (from 6.3 at baseline to 3.0 with Provox® XtraHME, p<0.0001), which further improved after 6 weeks (3.5 and 3.0, respectively) and then stabilized at 12 weeks (2.4 and 1.9, respectively). After 2 weeks of Provox® XtraHME use, 63% of patients reported less coughing and less mucus production.

A parallel study in the previous study population, looked at how laryngectomized patients get accustomed to the use of an HME (both XtraMoist™ and XtraFlow™) and attachments (103). Thirty patients were followed for 12 weeks. In the first 2 weeks, patients reported some discomfort of HME use, such as increased breathing resistance (43.3%) a small proportion of patients experienced problems with increased coughing when starting HME use . However, after 6 weeks patients were generally accustomed to the breathing resistance and just one patient found it more difficult to breathe through the HME after 12 weeks of HME use 72.4% reported that breathing was less difficult and 24.1% found it equal and just 3.4% more strenuous compared to breathing through an open stoma (p=0.002). The number of patients removing their HME due to breathing resistance dropped from 73% to 24.1% (p=0.001) after 12 weeks of HME use.

A retrospective comparative cohort study performed by Ebersole et al., 2020 (123) compared Provox® XtraHME use vs external tracheal humidification (ETH) during post laryngectomy hospitalization in 40 laryngectomized patients. Placement of Provox® XtraMoist™ HME was initiated after medical clearance on postoperative day 1, or when the patient was able to don/doff the HME independently. The rate of mucus plugs −which during post-operatory recovery can be a potentially deadly airway complication− as well as the proportion of patients with one or more mucus plugs events was significantly reduced in the HME group compared with ETH (0.13 and 0.38 per 10 inpatient days, respectively, p=0.02). The proportion of patients with one or more mucus plugs event was also significantly reduced in the HME group (50% ETH and 11% HME, p=0.01).

Early postoperative adoption of Provox® XtraHME helps the patient become accustomed to the device immediately after total laryngectomy which was shown to improve long-term adherence to HME use, thus positive impacting pulmonary health(47).

Another important factor impacting adherence is comfort and skin irritation. The Provox® Luna® system -skin friendly hydrogel adhesive and a soft silicone HME- effect on adherence has been studied in a multicentre, randomized crossover trial conducted in 3 centres in the Netherlands, and including 46 laryngectomized patients. In this study it was shown that the use of the Provox® Luna® HME and adhesive increased the number of adherent patients (96% and 76%, respectively, p=0.02),the average number of hours of daily HME use increased from 21 to 23.2 hours (p=0.003) and frequency of skin improvement overnight increased (3.9 days with Provox® Luna® HME and 8.1 during usual care, p=0.008) (124).

These studies highlight the relevance of adherent use of an HME to increased pulmonary rehabilitation and reduction of pulmonary symptoms. Recently it has been shown that pulmonary problems are an underlying cause of many issues experienced by total laryngectomized patients, including psychosocial and quality of life issues (53). Thus the reduction in pulmonary symptoms is important from a holistic pulmonary rehabilitation point of view. To evaluate the effect of HME use on pulmonary symptoms and their impact on quality of life and daily activities it is a relevant matter.

In this regard a validated instrument commonly use to evaluate cough and sputum symptoms and their impact on daily activities has been developed for patients with COPD (125). As discussed in the introduction of this literature review, a great number of laryngectomized patients present also with COPD and problems such as coughing and sputum are highly prevalent in this patient group. Hence, the Coughing And Sputum Assessment Questionnaire CASA-Q is a relevant tool to determine the impact of pulmonary symptoms and their impact on quality of life in laryngectomized patients. In brief, CASA-Q is a self-administered questionnaire that assesses cough and sputum based on their frequency, severity and impact on daily activities in the previous 7 days. The questionnaire is organized in to four domains: cough symptoms (COUS), cough impact (COUI), sputum symptoms (SPUS) and sputum impact (SPUI) (125).

The introduction of Provox® Life™ HMEs and attachments led to a further optimization of pulmonary rehabilitation after total laryngectomy, as evidenced by Longobardi et al. (126) who compared the Provox® Life™ system with the legacy Provox® XtraHME devices ('Usual Care'). In this randomized, prospective cross-over study 40 patients were included. An increased adherence to HME use was observed when using Provox® Life™, from 22.6 hours per 24 hours during usual care to 23.9 hours when using Provox® Life™ (p=0.011). This corresponded with an increase in HMEs used; an average of 1.7 HMEs was reported during the usual care period, and 2.0 HMEs during Provox® Life™ (p=0.025). A significant reduction in forced expectorations was observed during the Provox® Life™ period (average 4.3 forced expectorations/24 hours) compared to usual care (6.7/24 hours) (p=0.0001), as well as a significant reduction in the frequency of dry coughing, from 4.3 coughs/24 hours in the usual care period and 3.1/24 hours in the Provox® Life™ period (p=0.031). All four domains of the Coughing and Sputum Assessment Questionnaire (CASA-Q) scored significantly higher (i.e. better) during the Provox® Life™ period compared to the usual care period (COUS: p=0.007, COUI: p=0.002, SPUS: p=0.0004, and SPUI: p=0.000003). Breathability through the HME improved when using Provox® Life™, patients reported a statistically significant reduction in shortness of breath when climbing stairs (or physical exercise) (p=0.046) and when walking (on ground level) (p=0.005) with Provox® Life™ compared to usual care.

A mixed-methods study including a rapid literature review, semi-structured expert interviews and an early Health Technology Assessment (HTA) using structured expert elicitation (SEE) with regards to Provox® Life™ was conducted by Panaxea (www.panaxea.eu). The expert interviews and the SEE showed that on average experts expected to see stronger effects in patients using Provox® Life™ HMEs compared to the predecessors, Provox® XtraHME and Provox® HME and/or no HME use regarding improved breathing resistance (53%±28% of patients), decreased shortness of breath (48%±25% of patients), improved tracheal climate (59%±19% of patients), reduced mucus production (53%±22%) and plugging (33%±32%), reduced pulmonary infections (34%±32%), higher number of social contacts (13%±18%), improved overall Quality of Life (QoL) (33%±30%) and improved satisfaction (44%±30%). The average amount of daily coughs was expected to be 2.95 and the number of forced expectorations 2.46. Experts expect that on average less than half of patients would experience sleeping problems (48%±22%) and psychosocial problems (24%±20%).

3.3 The impact of HME use on psychosocial aspects and quality of life

As previously described, pulmonary symptoms significantly affect the well-being and quality of life of the patient; perceived quality of voice, participation in social activities, aspects of daily life, anxiety and depression (1, 53, 78, 127).

In the first Provox® HME study by Hilgers et al, in addition to the pulmonary benefits it was shown that Provox® HME facilitated voicing and improved intelligibility after 3-weeks of Provox® HME use in 9 patients out of 19. Furthermore, patients were positive about the spring valve closure mechanism used for digital occlusion of the Provox® HME (116). Improved speech ability, voice quality, pitch, loudness and intelligibility when using Provox® HME have been reported in several studies (90, 107, 117, 120). It has been shown that maximum phonation time and dynamic loudness range improved when occluding on top of the Provox® HME compared to finger occlusion directly on the stoma (128). This can probably be attributed to better, airtight, occlusion and better distribution of occlusal forces (reducing force on the voice prosthesis and voice producing segment in the esophagus).

Furthermore, most patients found stoma occlusion with Provox® HME easier and more hygienic (117). Patients have also reported that their sleeping improved, from 79% patients reporting to have sleeping problems at baseline, 72% of adherent patients reported sleeping problems after 3 months of Provox® HME use (90).

In a multicenter time series study including 41 patients, it has been shown that the adherent use of Provox® XtraHMEs increased the general quality of life (measured by means of EQ-5D Index) from an average of 0.84 at baseline to 0.90 after 2 weeks of XtraHME use and this improved even further at 12 weeks (0.96, $p<0.0001$)). The EQ-5D VAS scale showed an increase from 61.3 at baseline to 69.8 after 2 weeks and 80.0 after 12 weeks of Provox® XtraHME use ($p<0.0001$). Additionally patients showed a progressive reduction in shortness of breath, fatigue, and psychological stress over time.

Reduced frequency of cleaning of the stoma, improved voice quality, sleeping and a better appearance was also reported after 2 weeks of Provox® XtraHME use (122).

The introduction of Provox® Life™ led to a further improvement in quality of life as evidenced by a significant reduction in in the number of nights sleeping medication was used (219 nights vs 108 nights ($p=0.044$) and a significant reduction in the anxiety/depression domain for the EQ-5D (QoL assessment tool) when using Provox® Life™ HMEs compared to usual care (70% compared to 55% reported "no problems", respectively, $p=0.035$) (126).

3.4 HME use, pulmonary complications and cost-effectiveness

The beneficial physical and psychosocial effects of HMEs for pulmonary rehabilitation have a positive impact on cost-effectiveness during postoperative stages and long-term stages.The immediate postoperative effects on pulmonary rehabilitation and impact in cost-effectiveness after total laryngectomy, were assessed in a study by Merol et al.(104). In this RCT, 53 patients were randomized into the standard external humidifiers (EH) or the experimental Provox® HME arm. Adherence to 24/7 HME use when using Provox® HME (Normal and HiFlow) was 87% (compared to 12% in the EH arm). Adherence and patient satisfaction were significantly higher in the Provox® HME group ($p<0.001$). Additionally the

number of coughing episodes, mucus expectoration for clearing the trachea and sleeping disturbances were significantly less when using Provox® HME (p<0.001). Even though the breathing resistance of the Normal HME is higher than that of the HiFlow none of the patients using the normal HMEs reported shortness of breath. An improved nursing staff satisfaction and preference was also reported. The daily humidification-related costs for the HME system were considerably lower than for the EH system coupled with a reduction for nursing time. Thus, the authors concluded that HMEs can be considered the better and more cost effective option for early postoperative airway humidification after total laryngectomy.

Similarly, a case-control study in Canada including 48 patients in the early post-operative period reported that the use of a Provox® HME reduced the occurrence of post-operative adverse events (mucus plugs) in patients using Provox® XtraHMEs compared to patients using EH. Of those patients who experienced mucus plugs, only 12.5% (3/24) had used a Provox® HME in contrast to 87.5% (21/24) who used EH (p=0.002). The odds ratio (OR) of having an adverse event if not using Provox® HME was 8.27 (CI = 1.94 – 35.71). Provox® XtraHME use significantly reduced the number of days requiring physiotherapy (1.75 days vs. 3.20 days, p = 0.034). days in IC-unit, suctioning per day and in-hospital complications such as mucus plugging and post-operative care requirements compared to EH. In all, these findings would suggest early post-operative HME use to positively impact hospital costs (47).

The effect on cost-effectiveness in long-term laryngectomized patients (average of 274 days after their surgery) when using Provox® HME and Provox® XtraHME have been reported in a survey study that includes answers from 75 patients. More than 85% of the respondents used an HME, of whom 77% were compliant users (use an HME at least 20 hours per day). Compliant HME users presented a reduced use of external humidifiers and vaporizers. Notably HME users also tended to take less sleeping medication, and had better pulmonary status and lower health-care costs. The incidence of pulmonary illnesses (either before or after surgery) was about 25%. More than 90% of the respondents were heavy smokers before laryngectomy. Chronic pulmonary problems were present in a quarter of the participants(129).

In these study it was reported that the main reason for not using an HME 24 hours per day were skin irritation from the adhesive and no use of HME during the night or during physical activity (129). Similarly, another study showed that skin irritation and adhesion problems are the most common reasons for not using the HME in an adherent way (130). Besides, 90% of voice prosthesis users used HME consistently. Authors reported that the use of a voice prosthesis and an early start with HME use after TLE are factors that significantly improve compliant use of Provox® HME (p=0.001) (130).

According to a retrospective study, Provox® HME users have a significant lower incidence of severe tracheobronchitis and pneumonia episodes compared to non-HME users (4.92 vs 6.79, p=0.047), which has an impact on medical costs, quality of life and possibly survival related to tracheobronchitis and/or pneumonia (33).

In a recent study addressing the new generation of Provox® Life™ HMEs, a significant reduction in the frequency of sleeping medication intake (p=0.044) was reported (126).

The cost-effectiveness of HME use in terms of costs per additional quality-adjusted life years (QALYs) has been addressed in a study including in an European setting (Poland). Using a model-based cost-effectiveness analysis of using HMEs versus usual care (UC) (including stoma covers, suction system and/or external humidifier) for patients after laryngectomy has shown that HME use substantially incremented quality-adjusted survival (3.63 QALYs)

compared to UC (2.95 QALYs). The total 10-year health care costs per patient yielded 9,465 Euro for the HME strategy, and 1,168 Euro for the UC strategy. Compared to the UC strategy, the HME strategy resulted in 12,264 Euro/QALY (95 % CI 18,037–51,517) gained, thus HME use was found to be more costly, but more effective. During the immediate postoperative period, the use of HMEs it is more effective and less costly. The cost savings by HME use are resulting from less sleeping problems, less admissions due to tracheobronchitis/pneumonia (pulmonary infections) and no use of external humidifier or saline during hospital admission compared to UC. Additionally HME use resulted in fewer pulmonary infections, and less sleeping problems (34).

From an American perspective (USA), Provox® HME[4] use was more effective and less costly compared with some extent alternative stoma covers (ASCs, e.g., as foam pads or cloth bibs).Provox® HME use resulted in 0.14 QALY gain (5.30 vs 5.15) vs no HME-users. Total costs per patient (lifetime) were $59 362 (HME) and $102 416 (ASC). Provox® HME use cost-effectiveness, expressed in costs was $3770 in total. Patients using Provox® HME reported to have less productivity loss postoperatively and reported fewer occurrences of pulmonary events (airway infections and tracheobronchitis) postoperatively compared with ASC-users (131).

4. Provox® HMEFs and clinical evidence

The clinical effect of the Provox® Micron HME™ with filter (HMEF) in laryngectomized patients was investigated by Scheenstra et al.(132) in a short-term feasibility study. They assessed the Provox® Micron HME™ with filter (HMEF) for short-term endotracheal climate changes and feasibility in daily practice. Compared to open stoma breathing, Provox® Micron HME™ with filter (HMEF) increased endotracheal minimum humidity values (4.7 mgH2O/L, $p < 0.0001$) compared with open stoma. An increased end-inspiratory and end-expiratory temperature values. Patients spontaneously reported a further reduction in pulmonary complaints compared to the use of the normal Provox® HME, 31% of patients reported remarkably decrease sputum production (132).

HMEFs are commonly used in ventilator dependent patients and during anesthesia. Their use has been found to decrease the incidence of Ventilator Associated Pneumonias (VAPs) in ventilated patients on the intensive care unit (ICU) in comparison with Heated Humidifiers(133, 134). Moreover, it has been reviewed that HMEFs decrease the rate of nosocomial pneumonias in comparison with heated humidifiers (135). In a study that was carried out in guinea pigs, a bacterial and viral filter was found to successfully protect the pigs from sensitization to aerosolized Natural Rubber Latex(136). Also, the use of HMEFs during anesthesia prevents bacterial migration from the patient to anesthesia circle systems(137, 138).

[4] Authors have confirmed that majority of patients in the study used Provox® HMEs.

Additionally, patients using Provox® Micron HME™ have reported reduced frequency in common cold symptoms, flu symptoms, asthmatic symptoms and allergy symptoms, and stated that they had a reduction in the amount of secretions and coughing frequency since they started using Provox® Micron HME™. One third of the patients reported to use Provox® Micron HME™ when they were involved in a hobby in a dusty environment, when working in dusty environment, when in a hospital environment, around sick individuals, when flying, when in large crowds and during allergy season. Compliant HME users tended to make less use of external humidifiers, vaporizers, and sleeping medication, and had better pulmonary status and lower health-care costs (129).

The ongoing COVID-19 pandemic has highlighted the need for an HMEF for protection of laryngectomized patients and health care professionals. Clinical guidelines recommended the regular use of a surgical face mask to prevent contact with mouth and nose mucosal surfaces and adhesive stomal support with highly efficient HMEFs such as Provox® Micron HME™ for laryngectomized patients (139-141).

According to laboratory tests* Provox® Micron HME™ has a viral and bacterial filtration efficiency of >99%[5]. A recent study has reported the different filtration efficiency for face masks used during the COVID-19 pandemic, showing that a KN95/FFP2 mask during coughing and exhalation presents a range of filtration efficiency from 83%-99% (142).

These studies illustrate the relevance of Provox® HMEFs in providing the most appropriate protection and humidification of the airways depending on the environment.

5. Provox® FreeHands speaking valves and clinical evidence

One of the most important features of the Provox® FreeHands HME speaking valves is that they provide an automatic mechanism to facilitate occlusion of the tracheostoma to generate tracheoesophageal speech.

A first feasibility study using Provox® Handsfree speaking valve and including 20 patients showed that maximum phonation time using the Provox® FreeHands HME were shorter than with manual occlusion on a regular Provox® HME (15.2 s and 17.9 s, respectively ; p=0.044) but longer than with another hands-free device (11.6, p=0.006). These can be attributed to the fact that when using a hands-free device, some of the speaking air is consumed for closing the valve mechanism, and more air pressure is required to closing the valve. Provox® FreeHands speaking valve showed a larger dynamic loudness range compared to Provox® HME (33.0 dB and 28.2 dB, respectively; p=0.029) and other hands free devices (24.8, p<0.001). The availability of voice with Provox® HME and Provox® FreeHands was always immediate, with no time lag noted, in contrast to other hands free

*The VFE (Viral Filtration Efficiency) and BFE (Bacterial Filtration Efficiency) at an increased Challenge Level Test procedure adapted from ASTM F2101, was performed for Provox® Micron HME™ at Nelson Laboratories (US) in accordance with USFDA (21 CFR Parts 58, 210, 211 and 820) regulations. Mean VFE and BFE was >99%. Data on file.

[5] Since pathogens can enter and leave the human body in other ways (such as the mouth, nose, and eyes), Provox® Micron and Provox® Life™ Protect HME can never guarantee complete protection. Please read the instructions for use for guidance.

devices were there was a time lag of 1-2 s, caused by a difficulty in closing the valve to speak (60).

Similar results in regards to subjective voice quality and loudness range comparing Provox® FreeHands HME with Provox® HME and other hands-free devices have been reported in different studies (143, 144). However, it has been shown that even though speaking characteristics were better with manual occlusion, patients continued to use Provox® FreeHands HME device after the study period. Indicating that they would continue to use it either on a daily basis (average of 5 hours) or for special occasions or a limited number of hours per day (143).

Additional objective perceptual and acoustic analysis of 4 patients comparing Provox® HME with Provox® FreeHands HME have shown higher intensity of read speech (39.1 dB) with Provox® FreeHands HME when compared with Provox® HME (34.5 dB). Decreased pause time (23% vs. 27% respectively ,p=0.033) when using the Provox® FreeHands HME compared to Provox® HME. Additionally reduced maximum phonation time was reported when using Provox® FreeHands vs Provox® HME (8.3 vs 14.3 respectively; p=0.034) (145).

Despite its limitations, the ability to speak hands-free when performing a manual task has been reported as the main advantage of Provox® FreeHands HME and that it is useful and an easy-to-use additional device for special occasions when both hands are needed for tasks other than closing the stoma (driving a car, dining, fishing) (144, 145).

On the other hand fixation of the adhesive to the peristomal skin has been reported as the main disadvantage (145), followed by aspects such as voicing being too tiresome, diminished intelligibility and increased breathing resistance (143), adhesive seal problems (106) have been also been reported as reasons for not using the Provox® FreeHands HME on a daily basis and to discontinue its use.

In a study involving 17 patients who used the Provox® FreeHands HME it was found that phonation time was long, dynamic range wide and a short lag time was needed for closing the valve which enabled patients to produce more natural-sounding speech (according to external phoniatricians). Patients also reported that it was a great advantage to be able to speak hands-free (146).

The possibility to speak hands-free with Provox® FreeHands HME has been shown to allow patients to greater ease in communication, and to have more frequent social contacts (r=0.251, p=0.030), which can impact positively in quality of life (129).

Lansaat et al. (102) evaluated the short- and long-term feasibility of the second generation automatic speaking valve, Provox® FreeHands FlexiVoice™ HME, in a prospective multi-center study including 40 laryngectomized patients. At baseline few patients used the Provox® FreeHands HME daily and a big proportion didn't use handsfree speech. After 6 months patients 37.5% of patients use of the Provox® FreeHands FlexiVoice™ on a daily basis, for a mean of 12.64 h/day. Twenty-five percent were using it on a non- daily basis, for a mean of 3.76 h/day. Patients that stopped using the FlexiVoice™ reported this was due to the unpredictable fixation of the adhesive. The additional manual closure option of the FlexiVoice™ was experienced as beneficial for maintaining the adhesive seal longer. It was concluded that Provox® FreeHands FlexiVoice™ HME allows for hands-free speech in a larger proportion of laryngectomized patients.

6. Provox® attachments and clinical evidence

The most commonly reported problem with the adhesives is that they can cause skin irritation, and that device life is too short, especially when used with a hands-free speaking device. Successful use of the adhesive depends on stoma characteristics, on how the patient uses the adhesive and with what device the adhesive is used. A detailed study of (peri)stomal geometry in relation to adhesive use, revealed a mismatch between patients and adhesives. This data could be used to develop new adhesives that help improve rehabilitation after laryngectomy (147).

Whilst the majority of clinical studies conducted mainly investigate the HMEs and their impact on pulmonary symptoms, outcomes with regards to attachments are often reported as they are considered critical for adherence to HME use. This section provides an overview of results for HME attachments.

In an initial study where Provox® OptiDerm™, Regular and FlexiDerm™ Adhesives were used by 19 patients. Initially patients experienced difficulty with loosening of the baseplate due to phlegm, however this decreased and was resolved after 3 weeks of use. Interestingly, the availability of OptiDerm™, a hydrocolloid plaster, was considered useful for patients who have had recent surgery. Using this adhesive, some patients were able to start speaking within a shorter time limit following total laryngectomy (116).

A prospective non-randomized clinical study where 18 patients participated showed that the majority of patients used one adhesive and 1-2 Provox® HME cassettes per day. Most patients did not experience a change in airway resistance and a small group found it to be increased. Interestingly, less skin irritation and easier removal was reported when using OptiDerm™ adhesive (117).

Subsequent studies have been performed in different countries/climates. A study in Spain has shown that 93% of the patients reported an adhesive removal without pain. Just 10% of the patients reported to have skin irritation, 5% a mild skin irritation and 85% of the patients did not reported skin irritation at all. The possibility of having different adhesives with different shapes was reported as an advantage. Thirty two percent of the patients preferred to use the adhesives in combination (144). In another study conducted in the Netherlands skin irritation problems were resolved by alternating between the OptiDerm™, Regular and FlexiDerm™ adhesive (107). During an clinical study in Poland it was shown that about half of the patients used a round shaped adhesive and the other half an oval shape. Most patients used a combination of various types of adhesives (Regular, FlexiDerm™, OptiDerm™, XtraBase®). Just 6% of the patients reported to have 'very much' skin irritation and 77% 'none' or 'very little'. Removal of the adhesive was not painful in 94% of the patients (90).

In a study performed in Brazil, it was shown that the amount of Provox® HMEs and Provox® adhesives used decreased over time when comparing the first and the sixth weeks of the study. When asked about this decrease, patients pointed to the relation of this fact with the reduction on the frequency of cough and forced expectoration. It is important to mention that during weeks of very hot weather the mean amount of adhesives used was higher due to patients' transpiration that generated troubles with adherence of the adhesives on the skin (148).

Provox® XtraBase® adhesive was developed especially for hands-free speech. The base of this adhesive is more rigid and gives more support to the peristomal area. It was studied in a study including 14 laryngectomized patients who had used the HME successfully

before receiving the FreeHands HME. Both when used with a Provox® HME and with the Provox® FreeHands HME, on average the patients rated by VAS scale that the skin adherence of the XtraBase® was better than that of the 'conventional' (OptiDerm™, Regular, FlexiDerm™) adhesives(144).

In a prospective clinical crossover study including 32 laryngectomized patients using OptiDerm™ and StabiliBase™ OptiDerm™ it was shown that 43% of the users preferred the StabiliBase™ OptiDerm™ over the OptiDerm™ when compared. Therefore, it was concluded that the StabiliBase™ OptiDerm™ is a valuable addition to the existing adhesive range for HME users(149).

Thirty patients, who were at least 3 months post-laryngectomy and previously did not use an HME, were followed for 12 weeks to determine how they adapted to the use of Provox® XtraHME and Provox® attachments. The use of adhesives increased over the time, although over 80% used an adhesive as attachment (Provox® OptiDerm™, Regular, FlexiDerm™, XtraBase® and StabiliBase™), in the first weeks of HME use, patients tended also to use either a LaryTube™ or LaryButton™. The number of patients that used an adhesives to attach the HME increased from 60% to 82% after 12 weeks (p=0.014) (103) .

In a first study, Ratnayake et al. (124) compared the relative compliance and dermatological outcomes in patients using the Provox® Luna® during the night. This multicentre, randomized crossover trial was conducted in 3 centres in the Netherlands, and included 46 laryngectomized patients. The authors found that in the group using the Provox® Luna® during the night, the number of compliant users significant improved and the intervals of daily HME use were longer in comparison to the group that used their 'usual care'. Additionally, there was a significantly increased frequency in self-reported skin improvement overnight when using the Provox® Luna®. At the end of the study, 56% of the patients wanted to continue using the Provox® Luna®.

A randomized cross-over clinical study comparing Provox® Life™ with the legacy Provox® XtraHME devices ('usual care') in 40 laryngectomized patients showed that most patients used Provox® StabiliBase™ during the usual care period, and Provox® Life™ Stability during the Provox® Life™ period. No statistically significant difference was reported regarding adhesive device life between Provox® Life™ (19.3 hours) and usual care (20.3 hours, p=0.456) and patients experienced skin irritation less frequently during the Provox® Life™ period (p=0.013). Based on the diary, patients experienced skin irritation an average on 4.25 days within 14 days with their usual care versus 2.60 days in the Provox® Life™ period (p=0.013) (126).

Studies have shown that the use of a stoma button increases successful use of a hands-free speaking valve(109, 150). A study on the use of the LaryButton™ and LaryClips (109) demonstrated that the system was appreciated by the majority of the patients and that its use led to increased success with usage of hands free speaking valves. It has been described that the LaryButton™ and other stoma buttons have become a preferred method for securing hands-free speaking valves to the stoma (151). These are effective because they eliminate the need for adhesives and glues that are often ineffective in sustaining a peristomal seal during hands-free TE speech production.

7. Perspectives and conclusion

The performance of Provox® HMEs and their impact on tracheal climate and therefore beneficial effect on integrative pulmonary rehabilitation are supported by abundant and

robust clinical and scientific evidence. Continuous innovation has enabled significant improvements in humidification and breathability performance of HMEs and technological advances in adhesives materials. Clinical data demonstrate that these technological improvements further reduce the humidification deficit and improve quality of life.

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9. Appendixes

Appendix 1

Table 2. Humidification capacity and breathability comparison of the different HMEs and HMEFs generations. Moisture loss and Air pressure drop values are according to device specifications, at VT=1000 ml and 30 l/min, respectively (according to ISO 9360) [6].

	Provox® HMEs	Provox® XtraHMEs	Provox® Life™ HMEs
	Normal	XtraMoist™	Home
Moisture loss	24 mg/L	22 mg/L	20 mg/L **9 % higher humidification compared to XtraMoist™**
Air pressure drop	70 Pa	70 Pa	60 Pa

[6] Data on file.

			14% higher breathability compared to XtraMoist™
	HiFlow	**XtraFlow™**	**Go**
Moisture loss	25 mg/L	24 mg/L	23 mg/L **6% higher humidification compared to XtraFlow™**
Air pressure drop	50 Pa	40 Pa	30 Pa **25% higher breathability compared to XtraFlow™**
	HiFlow	**XtraFlow™**	**Energy**
Moisture loss	25 mg/L	24 mg/L	23 mg/L **4% higher humidification compared to XtraFlow™**
Air pressure drop	50 Pa	40 Pa	15 Pa **63% higher breathability compared to XtraFlow™**

	Provox® HMEs	Provox® XtraHMEs	Provox® Life™ HMEs
		Micron HME™	**Protect HME**
Moisture loss		22 mg/L	23 mg/L
Air pressure drop		70 Pa	55 Pa **21% higher breathability compared to Micron HME™**
		FreeHands	**Life FreeHands**
Moisture loss		Moist: 24 mg/L Flow: 25 mg/L	24 mg/L
Air pressure drop		Moist: 70 Pa Flow: 65 Pa	56 Pa **14% breather breathability compared to FreeHands**
		Luna®	**Night**
Moisture loss		22 mg/L	19 mg/L **14% better humidification compared to Luna®**

Air pressure drop		55 Pa	65 Pa

Appendix 2

Reference list used for Clinical Evidence and number of patients graphs:

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Head office:
Atos Medical AB, Hyllie Boulevard 17, SE-215 32 Malmö, Sweden

Manufacturer:
Atos Medical AB, Kraftgatan 8, SE-242 35 Hörby, Sweden Tel: +46 (0) 415 198 00
Email: info@atosmedical.com