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Zacks Small-Cap Research

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NanoVibronix Inc (NAOV-NASDAQ)

Initiation Coverage: *technology represents a potential paradigm shift in the treatment of chronic pain, difficult-to-heal wounds and biofilm eradication*

We value NAOV using P/S multiple methodology applied to our forecasted revenue in 2024, representing a five-year growth runway from today. Based on the assumptions outlined in our valuation section, we look for revenue of approximately $105M in 2024. We apply a 3.5x multiple and discount back at a risk-adjusted 30% per year to arrive at calculated current fair market value of ~$62M, or $9.00/share. Our risk-adjusted discount rate is subject to change and could narrow with substantive operational and product development progress or could widen with operational and product development delays or failures.

Current Price (01/17/19)	$3.33
Valuation	**$9.00**

OUTLOOK

NanoVibronix develops, manufactures and commercializes proprietary low intensity low frequency wearable ultrasound medical devices for the treatment of pain, reduction in bacterial colonization and for wound healing. Their specific focus within each of these applications represents current unmet clinical needs and substantial commercial markets. The safety of low intensity, low frequency ultrasound and compact size and simple operation of NAOV's technology lend themselves to at-home use. This not only eliminates the inconvenience and cost of treatment at a hospital or clinic, but also provides the opportunity for longer duration and more frequent treatment sessions.

While we think the initial rather narrowly-focused market segments such as Trigeminal Neuralgia for PainShield and chronic wounds for WoundShield represent some of the low-hanging fruit and where initial adoption may be the most brisk, eventual use among the more general respective populations could represent relatively massive upside. As the 'general pain' market is hundreds of times the size of the TN population and the CLI population is ~20x the size of the DFU market, even 1% adoption among these broader segments would represent significant revenue. Nonetheless, even the relatively narrowly-focused markets are substantial in size, with single-digit penetration in this populations potentially representing tens of millions of dollars of revenue for NAOV.

SUMMARY DATA

52-Week High	**$5.00**
52-Week Low	**$3.05**
One-Year Return (%)	**-23.60**
Beta	**-0.05**
Average Daily Volume (sh)	**3,782**
Shares Outstanding (mil)	**6**
Market Capitalization ($mil)	**$22**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**14**
Insider Ownership (%)	**19**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**22.0**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Growth**
Industry	**Med-Tech Devices**

ZACKS ESTIMATES

Revenue
(in '000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	0.6 A	0.6 A	0.6 A	0.5 A	2.2 A
2017	0.5 A	0.5 A	0.6 A	0.7 A	2.3 A
2018	0.8 A	1.3 A	0.5 A	0.8 E	3.5 E
2019					5.8 E

Earnings Per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.19 A	-$0.13 A	-$0.13 A	-$0.24 A	-$0.62 A
2017	-$0.37 A	-$0.19 A	-$0.35 A	-$0.26 A	-$1.17 A
2018	-$0.12 A	-$0.13 A	-$0.21 A	-$0.19 E	-$0.65 E
2019					-$0.74 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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SNAPSHOT

NanoVibronix, Inc. (NASDAQ: NAOV), develops, manufactures and commercializes proprietary low intensity low frequency wearable ultrasound medical devices for the treatment of pain, reduction in bacterial colonization and biofilm disruption, and for wound healing. Their specific focus within each of these applications represents current unmet clinical needs and substantial commercial markets. NAOV employs a razor/razor blade revenue model.

Built on surface acoustic wave (SAW) technology, NAOV's products utilize a small, thin (3mm) proprietary transducer to transmit low intensity low frequency (~100 kHz) ultrasound (LILFU) over a relatively large area and up to 10cm beyond the footprint of the transducer. The relative safety of low intensity, low frequency ultrasound and compact size and simple operation of NAOV's technology lend themselves to at-home use. This not only eliminates the inconvenience and cost of treatment at a hospital or clinic, but also provides the opportunity for longer duration and/or more frequent treatment sessions.

With the vast majority of therapeutic ultrasound consisting of high frequency (i.e. 1 MHz and above), relatively large devices which require a trip to the hospital or clinic and a trained technician to operate, NanoVibronix's technology represents a potential paradigm shift in the treatment of chronic pain, difficult-to-heal wounds and biofilm eradication. The safety profile and lack of invasiveness of NAOV's products also means that they can be used as a complement to or in conjunction with existing therapies, thereby mitigating competitive headwind risk and potentially affording opportunities to partner and collaborate with already established industry players.

NanoVibronix has been active in conducting clinical studies and compiling additional clinical data demonstrating the effectiveness of their products in each of their respective indications. They have also been busy in driving awareness, regulatory activities and in building out their distribution capabilities.

NanoVibronix's low intensity low frequency ultrasound technology consists of a small, handheld reusable driver unit which is connected to their relatively tiny proprietary disposable transducer. This transducer is connected to either a clip (UroShield) or patch (PainShield and WoundShield) which attaches to the area to be treated. The company's current product suite includes;

- **UroShield**: for the prevention of bacterial colonization and biofilm in urinary catheters. Currently CE Marked, an FDA De Novo filing for UroShield is anticipated in 1H 2019. If all goes to plan, the device could make its U.S. introduction later this year. The target market is big (24M indwelling catheters sold in the U.S. each year) and largely underserved (antibiotics are first-line treatment yet "…often prove to be ineffective…")[1]. Indwelling catheter induced urinary tract infections are commonplace and, given that they cost the healthcare system billions of dollars each year, hospitals have an economic interest to adopt novel technologies (potentially such as UroShield) that can prevent them.

UroShield



Source: NanoVibronix

- **PainShield**: for the treatment of pain, muscle spasms and tendon diseases. The product has U.S. 510(k) clearance, CE Marking and Health Canada regulatory approval. At-home use for trigeminal neuralgia (TN), a neurological condition characterized by extreme pain along the trigeminal nerve in the face, is the main focused market for PainShield. First-line treatment of trigeminal neuralgia, which causes such severe pain that it has been called the "suicide disease", are anticonvulsants. Surgery and opioids may also be used. While medications can be initially effective, their ability to control the disease usually wanes over time. Estimated U.S. incidence of TN is between ~40k and 140k. General soft tissue pain represents a less-defined but relatively enormous market and potent opportunity for PainShield, as does the recent crackdown on opioid overprescribing.

PainShield



Source: NanoVibronix

WoundShield



Source: NanoVibronix

- **WoundShield**: to speed the healing of hard-to-treat wounds. WoundShield is CE Marked and has Health Canada approval. The chronic wound market is large and encompasses diabetic foot ulcers (U.S. prevalence is ~5.5M with recurrence rate of 66%), venous leg ulcers (U.S. prevalence is ~600k with one-third recurring four or more times) and pressure ulcers (U.S. incidence of ~2.5M). An estimated $25B or more is spent each year on treating chronic wounds. While there are several modalities of advanced wound therapies available with varying degrees of effectiveness, almost all require operation by a trained clinician and a trip to the hospital. By contrast, WoundShield is designed for at-home use by an individual patient. Another potentially potent, and largely unique, advantage of WoundShield is the ability to use it as an adjunct, or complement, to existing advanced wound care modalities.

[1] Roger C. L. Feneley, Ian B. Hopley, Peter N. T. Wells. J Med Eng Technol. 2015 Nov 17; 39(8): 459–470. Urinary catheters: history, current status, adverse events and research agenda

- Earlier stage pipeline, which is also built on the SAW technology, includes LungShield and RenooSkin;
  - **LungShield**: similar in form to UroShield but different in its application, LungShield is designed to reduce the risk of endotracheal infection in a hospital setting. It is currently being evaluated in a human pilot study in patients undergoing mechanical ventilation to determine its effect on development of bacterial colonies on endotracheal tubes
  - **RenooSkin**: to facilitate rejuvenation of facial skin. Unlike the NAOV's other products in which the transducer is enclosed in a patch or clip, RenooSkin consists of a head band-like applicator which houses two transducers near each ear. In vitro studies have indicated RenooSkin may be as effective as Retin-A (tretinoin, which generates ~$300M in annual sales) in its ability to rejuvenate skin. Target market is the non-prescription skincare space. Skin care is a very large market, generating ~$8B in annual sales in the U.S. Facial skin care is the fastest growing subcategory within skin care with sales of products such as face masks, facial moisturizers and facial sprays increasing by as much as 39% annually

While sales have been largely immaterial to-date, that could soon change as new management has been busy implementing a multi-pronged strategy aimed at accelerating revenue growth. We believe the key components of this include;

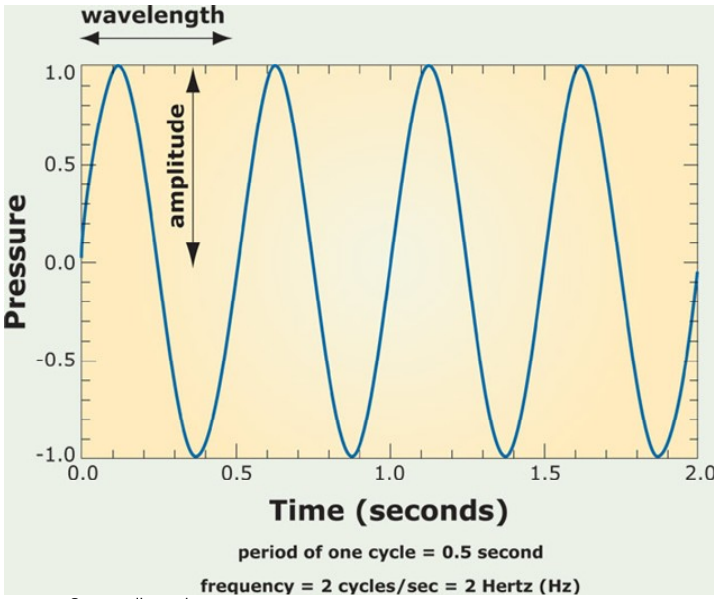
- a focus on leveraging clinical evidence to facilitate awareness-building, sales and marketing, and regulatory efforts
- publishing existing clinical data and generating new data through commencement of additional clinical studies
- expanding the distribution footprint and overall sales capabilities
- label expansion (including OTC use for PainShield) and additional regulatory clearances for their existing product suite and initial approvals for their product pipeline
- optimize manufacturing to increase production efficiencies and scalability
- obtaining reimbursement
- licensing to category-specific companies with significant distribution

BACKGROUND

Sound: wavelength, frequency and energy

Soundwaves travel in longitudinal waves. Different sounds have different frequencies, the wavelengths of which are measured in hertz. Hertz is a measure of cycles per second – which is simply the number soundwaves that pass a certain point each second (or, more technically, the number of times a particle completes one compression and rarefaction in one second). All sounds travel at the same speed, regardless of their frequency. This means that sounds' wavelength and frequency are inversely correlated – so, lower frequency sound has a relatively greater wavelength (i.e. lower hertz) than does higher frequency sound and vice versa.

Inverse relationship between wavelength and frequency

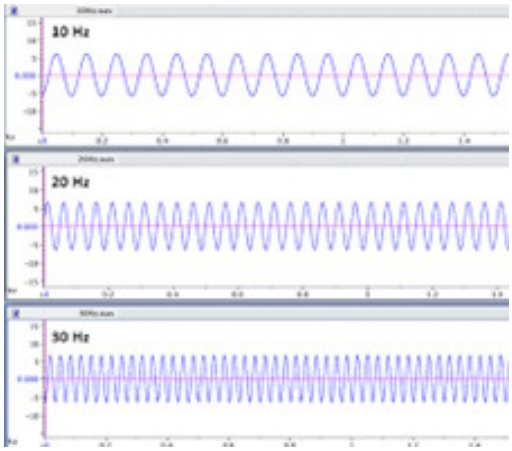


Source: albany.edu

Sound is a physical, mechanical wave that is created through vibrations. The energy of a particular (mechanical) sound wave is determined by two factors; amplitude and frequency. Amplitude, which is depicted (in the illustration above) by the distance of the peak (and trough) of the wave from its midline (or resting position), is analogous to volume. So, all else equal (including frequency), a louder sound will have more energy. The other component to a sound's energy, frequency, is, as explained, the number of times its wave (measured in hertz) passes a certain point. So, all else equal (including amplitude), a higher frequency wave will have more energy due simply to it passing more frequently.

Therapeutic ultrasound creates thermal and cavitational effects…

Ultrasound is sound waves that are at frequencies greater than that audible by the human ear, which is generally considered to be between 20 and 20,000 hertz (i.e. 20 kilohertz or 20 kHz). As such, ultrasound is defined as sound waves of frequencies greater than 20,000 hertz, or 20 kilohertz (i.e. 20 kHz).



Infrasound (below audible range)

Audible sound

Ultrasound (above audible range)

Source: Cornell University

While the use of ultrasound for therapeutic purposes is not new (with published evidence of its utility for medical benefits going back as early as the 1930s), the use of low frequency ultrasound is still in its relative infancy. Unlike NanoVibronix's devices, which utilize low frequency ultrasound (i.e. 20 – 100 kHz), to-date 'therapeutic ultrasound' has been almost exclusively defined as frequencies between 200 kHz and 20MHz (with the vast majority of ultrasound devices using 0.7 – 3 MHz). Ultrasound's healing and pain reduction benefits are believed to result from several effects including promotion of blood flow, fibroblast proliferation, formation of new blood vessels, protein secretion and enzymatic reactions as well as by increasing permeability of vascular walls and nitric oxide production, among others.

Therapeutic ultrasound is created through the transfer of electrical energy into mechanical vibrations in the form of sound waves, which produce certain biological effects through both thermal and cavitational means. Absorption of ultrasound in biological tissue results in the transformation of the acoustical energy into heat (energy). All else equal, the greater amount of ultrasound absorbed, the greater the heat that is produced.

Meanwhile, cavitation, which results from alternating positive and negative pressure of the ultrasound wave, refers to the formation, growth and, in some cases, the collapse of gas-filled bubbles. Formation and growth of these bubbles (i.e. 'stable cavitation') has been shown to be therapeutically beneficial to certain cell processes including protein synthesis. By contrast, however, collapse of these bubbles ('unstable/transient cavitation') releases a large amount of energy which can cause 'microjets' which can damage tissue (and therefore should be avoided if possible).

Ultrasound effects are frequency and wavelength-dependent

Thermal and cavitational effects of ultrasound have been shown to be frequency-dependent, which is largely associated with the difference in wave parameters. While these effects are also dependent on the medium in which ultrasound travels (e.g. human tissue versus blood), we confine our discussion to the frequency relationship in order to delineate the differences between low frequency (LF) and high frequency (HF) ultrasound.

As higher frequency soundwaves have more energy, thermal effects increase with a rise in ultrasound frequencies. Kenneth, et al.[2,3] found that ultrasounds' bio-effects occur with thermal exposures equivalent to 41 – 45^{0} C for at least five minutes. At these temperatures and exposure times, the therapeutic effects of ultrasound can include

[2] Kenneth, A., Knight, L. and Draper, D.O., 2007. Therapeutic modalities: the art and the science, Lippincott Williams & Wilkins, United States
[3] Ahmadi, F. et al (2012). "Bio-effects and safety of low-intensity, low-frequency ultrasonic exposure." Prog Biophys Mol Biol 108(3): 119-138.

increased blood flow, reduction in muscle spasm, pain reduction, increased tissue extensibility (i.e. stretch-ability) and reduction in inflammation. However, high frequency ultrasound can also generate significant heat at the transducer surface and result skin burns if not operated properly.

Low frequency ultrasound, on the other hand, will not generate enough heat to damage the skin – this is one of the advantages of NanoVibronix's (low frequency) devices and one of the particularly important characteristics that make the devices practical for at-home use and over-the-counter (OTC) regulatory approval. NAOV is currently pursuing FDA approval of PainShield for use without a prescription.

NAOV's technology eliminates risk of low frequency transient cavitation…

Cavitational, including both stable (i.e. beneficial) and unstable (i.e. detrimental), effects of ultrasound are similarly dependent on frequency, intensity and exposure time. However, unlike thermal effects which increase at higher frequencies, cavitational effects are more pronounced at lower frequencies and, per findings by Ueda et al.[4], transient cavitation formed in the coupling medium (i.e. gel or aqueous solution used to optimize contact between an ultrasound transducer and the skin) is particularly prone to increasing with a decrease in frequency. In fact, cavitation effect in coupling media has been cited as one of the most significant differences between high and low frequency therapeutic ultrasound. Due to the potential for serious adverse cavitation effects (such as tissue injury), experts recommend that certain coupling media-related protocols are followed when using low frequency ultrasound – these include degassing the coupling media, use of a high viscosity coupling media or doing away with the coupling media altogether. Given that NanoVibronix's Surface Acoustic Wave low frequency ultrasound technology does not require a coupling medium, there is no associated risk of transient cavitation.

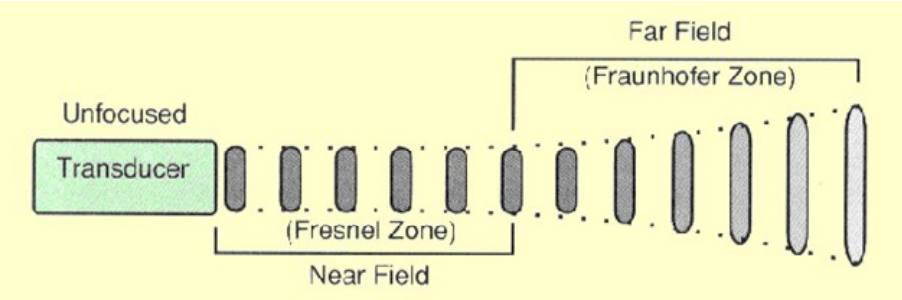
Therapeutic depth of ultrasound…

The therapeutic depth, or maximum depth at which there is a positive bio-effect, of ultrasound depends on several factors, including wavelength, frequency and the medium through which the waves are passing. "Velocity' of ultrasound is defined as the speed that it travels through a medium. It is calculated as velocity (v) = frequency (f) x wavelength (λ) and measured in meters per second. As the velocity of sound in any homogenous material (such as tissue, water, air, etc) is constant, lower frequency sound waves (i.e. greater wavelength) should penetrate deeper into a given substance than those of higher frequencies. But, the depth of penetration also depends on the amount of attenuation and absorption of ultrasound waves – which largely depends on the characteristics of the medium.

The therapeutic depth of ultrasound is also determined by the depth of its 'near field'. An ultrasound beam produces a beam into two distinct areas, a 'near field' (aka Fresnel zone) and a 'far field' (aka Fraunhofer zone). The former, which represents the portion of the beam immediately in front of the transducer, has characteristically significant fluctuations in sound intensity while the latter, which extends from beyond the near field, is much uniform. Intensity in the near field oscillates between zero and maximum while the beam diverges and weakens in the far field.

The significance of this in relation to the therapeutic depth of LF versus that of HF ultrasound is that the depth of the near field (and, therefore the depth of the area where the sound is at its maximum strength) decreases with a similar decrease in frequency. So, while LF ultrasound can penetrate much further than HF ultrasound[5], its therapeutic depth is compromised by its relatively shallow near field and high proportion of its energy that is absorbed in superficial tissue.

Far and Near Fields



Source: Perry Sprawls. Ultrasound Production and Interactions

[4] Ueda, H., Mutoh, M., Seki, T., Kobayashi, D. and Morimoto, Y., 2009. Acoustic cavitation as an enhancing mechanism of low-frequency sonophoresis for transdermal drug delivery, Biological and Pharmaceutical Bulletin. 32 (5), 916-920

[5] "The penetration depth of kilohertz US is expected to be in excess of 20 times greater than MHz ultrasound." Tim Watson, Professor of Physiotherapy at the University of Hertfordshire (UK). Longwave (Kilohertz) Ultrasound Therapy. www.electrotherapy.org

Evidence Indicates LF May Be As-Effective as HF Ultrasound in Certain Therapeutic Applications
While we were unable to find robust head-to-head studies with definitive results comparing LF and HF ultrasound in the context of therapeutic efficacy, Tim Watson, professor of physiology at the University of Hertfordshire (UK), has done a fairly extensive literary search and analysis on the subject. He comments on the dearth of compelling evidence comparing the two modalities but also cites results of several preclinical and clinical studies that (at least) suggest LF may be as effective, or even more effective, than HF ultrasound in certain therapeutic applications. This includes localized therapy for the improvement of joint mobility. While these studies relate to applications outside of NanoVibronix's current areas of focus (i.e. pain, wound healing and biofilm eradication), we offer a summary discussion to provide context of both the therapeutic potential of LF ultrasound as well as the broad scope of possible medical applications of the modality. We discuss evidence supporting NAOV's specific technology and for their targeted applications later in this report.

Among the clinical studies cited are;

- kHz vs. MHz in treatment of ankle injuries (i.e. Bradnock 1995): patients with inversion ankle injuries were treated for five minutes with either low frequency or high frequency ultrasound. Results, as determined by pre to post-treatment improvement in gait and pain, showed statistically significant greater improvement among the kHz-treated group (immediately following treatment). Longer-term follow-up was part of the study protocol.
- LF ultrasound vs. sham in rehab of wrist fracture (i.e. Basso and Pike, 1998): n=38 with wrist fracture received either LF ultrasound (46KHz at 74 W/cm^2) (n=19) or sham (n=19) immediately following removal of cast to assess improvement in wrist motion and duration. Results (at weeks two and eight) showed no statistically significant difference between sham and LF treatment on these parameters.
- LF ultrasound vs. hot water bottle on ankle mobility of non-injured Achilles tendon (i.e. Meakins and Watson, 2006): designed to compare a home-remedy heat treatment (i.e. hot water bottle) to kHz ultrasound. Crossover design (n=18) with each therapy compared with its own control. Results showed that both LF ultrasound and hot water bottle treatment statistically significantly (both p-values <0.0005) improved ankle mobility versus their respective controls. There was no statistically significant difference in treatment effect between LF US and HWB.

NanoVibronix's Wearable LILFU Technology
Per patent filings, NanoVibronix's technology has shown promise in the following, "inhibiting adhesion, micro-massage, healing processes, tissue fluid interchange, increased growth of capillary, increased pH of tissue liquids, lowered pain syndrome, resistance of thrombus formation, better drug administering, reduced friction, the cleansing of tissue, the removal of necrotic debris, disinfection, the "biostimulation' of cells, blood flow, micromassaging, drying, intensity of drug diffusion, activeness of the coating agents, and wound healing."[6]

NanoVibronix's wearable low intensity low frequency ultrasound technology consists of a small, handheld reusable (~3-year life) driver unit connected to a proprietary disposable (1-month life) transducer. The small, thin (3mm) transducer, which is connected to either a clip (UroShield) or patch (PainShield and WoundShield) which attaches to the area to be treated, delivers low frequency ultrasonic waves over a relatively large area and up to 10cm beyond the footprint of the transducer.

The relative safety of low intensity, low frequency ultrasound and compact size and simple operation of NAOV's technology lend themselves to at-home use by the individual patient. This not only eliminates the inconvenience and cost of treatment at a hospital or clinic, but also provides the opportunity for longer duration and/or more frequent treatment sessions.

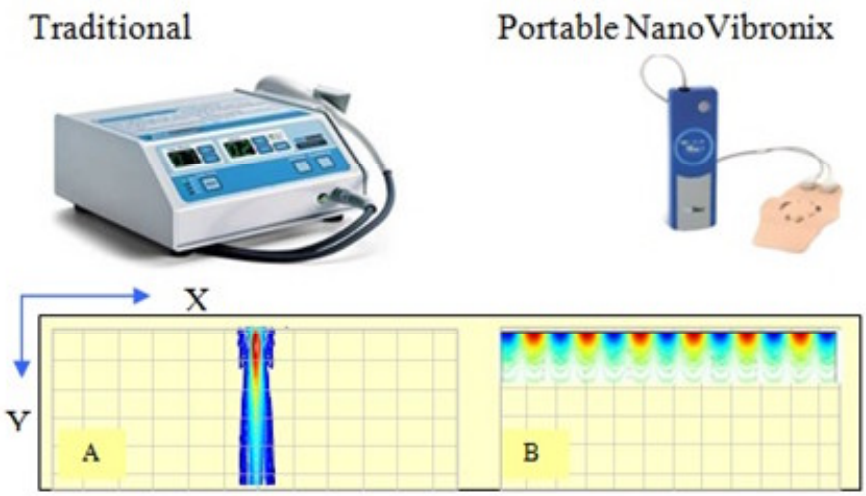
As discussed, the benefits of low frequency ultrasound include less heat production and, therefore, less potential for safety risks such as skin burns and other tissue damage. We think that this also means that regulatory approval for at-home use and over-the-counter (OTC) sale is a reasonable pursuit. Another potentially significant advantage of NAOV's technology is that it does not require use of a coupling medium – the benefits of which we further elucidate below.

Proprietary transducer sets NAOV's technology apart…
Unlike traditional ultrasound, which delivers sound waves along a narrow beam and relatively deeply into the body, NanoVibronix's proprietary transducer transmits surface acoustic waves at a wider footprint and at a much shallower depth. In fact, the vast majority of SAW transmitted ultrasound is absorbed in the surface of the tissue with maximum depth of only about 40% as deep as traditional ultrasound.

[6] Zumeris et al. US 9,585,977 B2. March 7, 2017

NAOV's transducer also spreads the SAW across a relatively wide area – about 10cm from the treatment head, while the beam of almost all other ultrasound technologies is confined to the width of the transducer. It accomplishes this through the production of certain specific surface acoustic waves, namely Rayleigh, Lamb, Plate, Stoneley and Sezawa waves. As the name implies, these waves travel across the surface of a substance (such as skin) and between the boundary of two different media. The low intensity nature limits penetration to approximately 1 to 2 wavelengths. Penetration of the therapeutic ultrasound wave can be managed by varying the frequency (as noted earlier, penetration will increase with a decrease in frequency).

NanoVibronix's Relatively Wide and Shallow Energy Distribution



Source: NanoVibronix, SEC 10-K filed 3/29/2018

Another benefit and advantage of NanoVibronix's products is that they do not require a coupling gel which, as noted, have certain characteristics which make them particularly prone to (adverse) transient cavitation – which is itself more problematic at lower frequencies. And it's not just transient cavitation that can pose problems with coupling media. Spratt et al. (2014) found that 35% of ultrasound gels and more than 50% of gel bottles in the U.S. were infected with one or more forms of contamination, some of which tested positive for MRSA[7].

Convenience and ease of use is also arguably enhanced when a gel is not required. This may be particularly true for at-home use and even more so in the case of wearable ultrasound – which can be 'messy' if transmission gel was required. Wearability of NAOV's products further benefits from the slimness of the transducer – at just ~3mm it's about 1/5th the width of ZetrOZ's sam Sport, the only other FDA-cleared wearable ultrasound device that uses similar technology.

NanoVibronix's PainShield



Source: nanovibronix.com

ZetrOZ Systems' sam® Sport



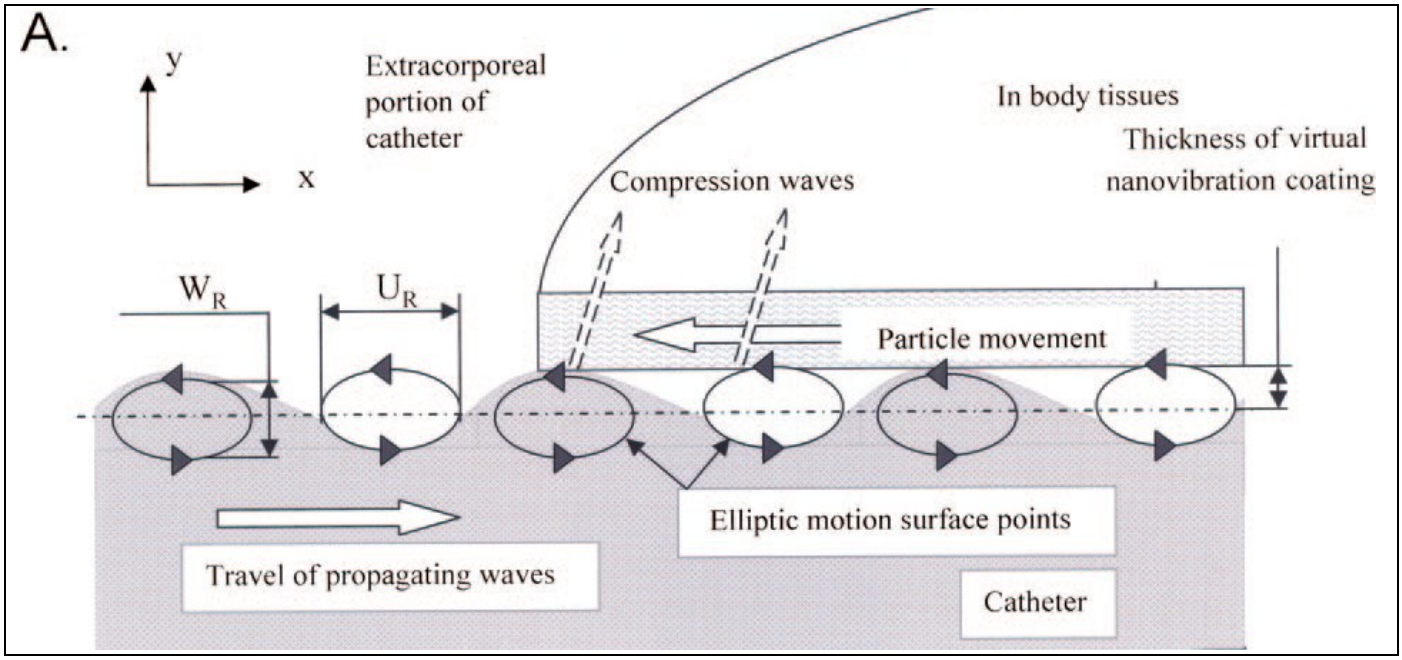
Source: zetroz.com

[7] Spratt, H. et al. (2014). "Physical therapy clinic therapeutic ultrasound equipment as a source for bacterial contamination." Physiother Theory Pract 30(7): 507-511

UroShield

UroShield is designed to prevent bacterial colonization and formation of biofilm in urinary catheters as well as reduce pain associated with urinary catheter use. It does this by sending low frequency SAW along the outside and inside surfaces of urinary catheters, thereby preventing bacteria from adhering to the tube and deterring formation of biofilm.

As the diagram below illustrates, UroShield was developed to spread low-frequency surface acoustic waves across all surfaces of a catheter and surrounding tissue. The waves travel in longitudinal direction, parallel to the propagation of the wave and across the catheter surface, which in-turn triggers horizontal particle displacement. This results in transversal compression waves which travel over the tissue and fluid surrounding the catheter, thereby ensuring all surfaces, including the catheter and adjacent biological material are affected by the SAW.



(A) Schematic illustration of the modes of dispersion of surface acoustic waves on solid surfaces. Horizontal particle displacement (UR) and another transversal compression wave component (WR) are indicated.
Source: Hazan, Z. et al. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2006, p. 4144–4152

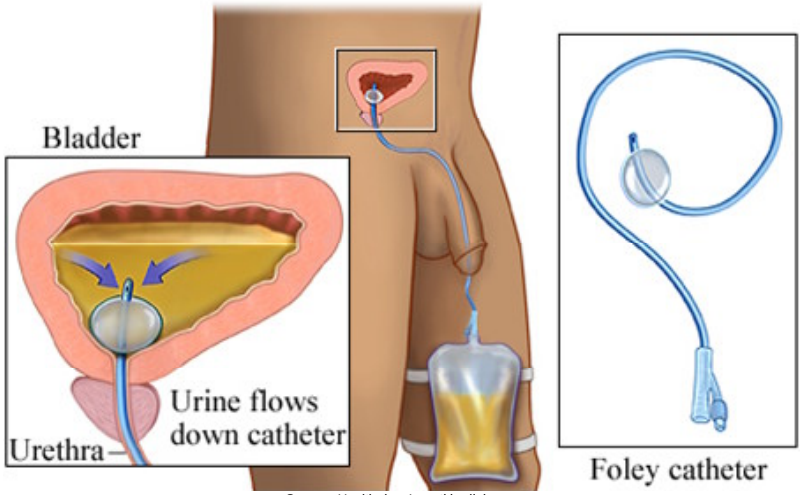
The target market, represented by 24M indwelling catheters sold each year in the U.S. (and, to a lesser extent, the 72M sold OUS), is large and underserved. Current annual U.S. sales of indwelling catheters are estimated to be ~$400M, representing approximately 35% of the larger urinary catheter market.[8] GrandView Research forecasts the global urinary catheter market to expand at a 5.4% CAGR through 2024 and be catalyzed by aging of the worldwide population as well as from increasing incidence of certain conditions and diseases including urinary incontinence, benign prostate hyperplasia (BPH), bladder cancer and neurological conditions that affect bladder functioning.

Catheter associated urinary tract infections (CAUTI) are a significant problem with studies showing that all catheterized bladders become colonized with bacteria within 24 hours. Moreover, daily and monthly infection rates are 5% and 95%, respectively[9]. In other words, almost all patients that are catheterized for 30 consecutive days will acquire a urinary tract infection and the risk increases by at least 3% every day.

Indwelling urinary catheters are used for individuals with impaired bladder function. Specifically, they are used to reestablish more normal functioning among those that suffer from either incontinence or urine retention - which affects between ~15% and 45% of people over the age of 65 and is commonly associated with BPH. They are also commonly used for individuals undergoing chemotherapy, under anesthesia, those that are comatose, paralyzed or are recovering from injuries or surgery that affect their bladder function.

[8] GrandView Research, Urinary Catheter Market Analysis
[9] Maki D.G., Tambyah P.A. Engineering out the risk for infection with urinary catheters. Emerging Infectious Diseases. 2001;7:342–347

Approximately 15% - 25% of all patients admitted to acute care hospitals receive a urinary catheter. The most commonly used indwelling catheter, called the Foley catheter, consists of two channels that run the length of a flexible tube, which is inserted into the urethra (or, in some cases, through an incision directly into the bladder). One channel drains urine from the bladder while the other is used to inflate a balloon (via sterile water pumped through the channel) at the end of the tube, which helps to anchor the catheter inside the bladder.



Source: Healthwise Inc., thinglink.com

Indwelling catheters become infected from bacteria moving along both the inside and outside of the tube and into the urinary tract and bladder. Biofilm accumulation can also cause blockage of the catheter, a potentially very serious complication that can result in death if not cleared. **If not effectively addressed**, CAUTI can result in severe pain and eventual damage to the bladder and kidneys. Bladder and kidney damage can have very serious consequences, including resulting in death. As of 2002 (the most recent year of available statistics), catheter-induced infections were believed to have caused more than 10k deaths in the U.S.

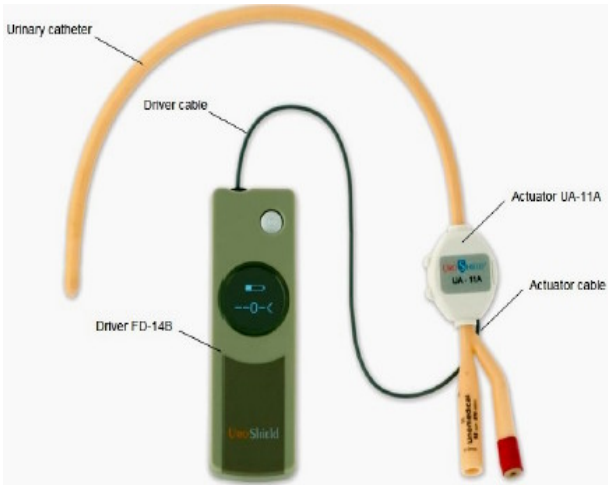
Indwelling catheter induced urinary tract infections are also extremely costly to treat, with an estimated $36B (or 90x the annual U.S. market for indwelling catheters) spent in the U.S. in 2015 to address the problem.[10] They are also one of the most problematic infections for medical facilities to deal with, accounting for approximately 40% of all hospital-acquired infections. Given the enormous financial burden of addressing CAUTI and the fact that (since the implementation of the Affordable Care Act) hospitals are no longer reimbursed by Medicare for the cost of treating urinary tract infections, medical facilities have an economic interest to adopt novel technologies (potentially such as UroShield) that can prevent them. While antibiotics are first-line treatment for catheter-induced infections, their overuse has been a major contributor to the development of resistant bacterial strains and, per estimates by the World Health Organization, resulted in antibiotic failure-to-cure rates of 50% or more. Noteworthy is that clinical studies have shown that UroShield may be more effective than antibiotics and have also shown that UroShield, when used in conjunction with antibiotics, can enhance their effectiveness.

In fact, **as it relates to enhancing the effects of antibiotics**, a study found that when UroShield was used in conjunction with antibiotics against E. coli, Staphylococcus epidermidis and Pseudomonas aeruginosa, the surface acoustic waves generated by the device were able to eradicate more than 85% of the bacteria. In addition, the study showed that SAW may actually trigger a cellular response of some strains of bacteria, thereby increasing their susceptibility to antibiotics and reducing their virulence.[11]

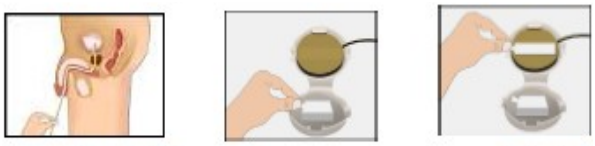
[10] Roger C. L. Feneley, Ian B. Hopley, Peter N. T. Wells. J Med Eng Technol. 2015 Nov 17; 39(8): 459–470. Urinary catheters: history, current status, adverse events and research agenda

[11] Kopel M. et al. Surface acoustic waves increase the susceptibility of Pseudomonas aeruginosa biofilms to antibiotic treatment. Biofouling. Vol 27, No 7, August 2011, 701-710

UroShield, Directions for Use



1. Once the urinary catheter is inserted, peel off the protective strips from both sides of the clip-on while it is open.



2. Place the actuator over the catheter 3 cm away from the point the catheter entry to the body in females and about 5 - 10 cm in males, so that the catheter fits the actuator in the semi-circular grooves at each clip-on end.



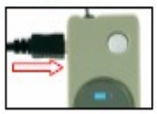
3. Once the clip-on is in place, close the actuator carefully, until the two sides snap together. **Ensure that the catheter has not been deformed or pinched at either ends of the clip-on.**



4. Plug the actuator cable connector into the driver cable connector. **Ensure that it is fully inserted and secured.**



5. Connect the driver to mains adaptor and plug it to the mains. Now the device is in charging mode.



6. Press the ON/OFF button for 2-3 sec to turn the device ON. After about 30 seconds, the LCD screen will indicate battery and activity status.

The UroShield is working.



7. Screen server mode that displays a scrolling message, starts after 3 minutes.



8. Check activity status by a short push of the ON/OFF button.

9. to the UroShield can be shut down at any time by pressing the ON/OFF button and hold it for 2-3 seconds.



UroShield should be used continuously while connected to wall mains. While the patient is moving around, the UroShield can be operated out of the built-in battery for up to 8 hours. A visual and audible alerts will indicate when battery capacity falls below 0.5 hour of work.

UroShield is CE Marked (as of 2007), allowing it to be sold in Europe as well as other areas of the world that accept that regulatory designation. It is also approved for sale in Israel (2008) and Canada (September 2016). NAOV has been busy recently beefing up distribution of UroShield, signing agreements covering Canada (Instrumed Surgical signed in April 2018), India (Cnergy Group signed in December 2018), Israel (MDS Pharma signed in December 2018) and Switzerland (Stöckli Medical AG signed in December 2018). This is in addition to already established distribution in the U.K.

U.S. regulatory clearance of UroShield, along with accelerating OUS sales, are primary goals of NAOV's. While NAOV's public statements (including in SEC filings, press releases and investor presentations) have indicated that they have recently considered both 510(k) and De Novo FDA pathways, it is our understanding that they are committed to the latter.

De Novo entails requesting that FDA classify UroShield as a Class II device – which is reserved for low-to-moderate risk devices. If granted, this is analogous to 510(k) clearance but without the requirement for existence of an already-cleared substantially equivalent predicate device. It also avoids the much more rigorous, time-consuming and costly PMA pathway. Key for successful De Novo Class II designation is sufficient evidence of safety (as well as demonstrated efficacy) of the device – which, along with earlier studies, was likely bolstered by positive efficacy and safety outcomes of the latest randomized controlled study, data from which was published in November 2018. If all goes to plan, NAOV hopes to have U.S. marketing clearance for UroShield in 2H 2019.

In July 2017 NanoVibronix hired Idonea Solutions, Inc, a U.S. regulatory consulting firm, to advise them on an FDA strategy for UroShield. While we have not done an exhaustive review of Idonea, we did find that they successfully petitioned for De Novo Class II designation of a seizure monitoring device (unrelated to NAOV or any of their products) in February 2017. While the specific game-plan for a De Novo submission for UroShield has not been announced, we think management was waiting for results of their latest UroShield clinical study before committing to a specific strategy. So, as those results, announced in November 2018, appear to be highly positive (discussed below), we may hear more about NAOV's U.S. regulatory plans for UroShield in the near future.

Reimbursement should not necessarily play a significant role in determining the ultimate success of UroShield given that we anticipate use of it would largely be for indwelling catheter procedures at hospitals and other healthcare facilities. As we anticipate that UroShield would be used in place of or in conjunction with antibiotics as a measure to reduce rates of CAUTI, we think it should be a seamless fit within healthcare facilities' already established procedures and protocols. Nonetheless, NanoVibronix has indicated that securing reimbursement for UroShield is a near-term goal and one that may be attainable following successful completion of additional clinical studies demonstrating the efficacy of UroShield in CAUTI.

Clinical data…

Clinical trials have shown that UroShield is effective in the prevention of biofilm and reduction of medication use, urinary tract infections and pain, burning and itching associated with use of urinary catheters. Low-frequency surface acoustic waves accomplish this by interfering with cell-to-cell communication, repelling bacteria and preventing them from adhering to and accumulating on the outside and inside surfaces of indwelling catheters. This prevention of biofilm also reduces risk of blockage of the catheter. Clinical studies have shown that UroShield is effective at reducing or completely eliminating all of the most common bacterial strains[12] associated with CAUTI including Proteus mirabilis, which produces more biofilm than any other bacteria and is isolated from ~40% of CAUTI urine samples and associated with ~80%[13] of catheter blockages. Studies have also shown that SAW can enhance efficacy of antibiotics by increasing their penetration into biofilm.

Clinical evidence of UroShield's effectiveness (and safety) encompasses six case studies and randomized controlled trials which evaluated an aggregate of 190 patients. Among these (all of which are listed below), is an n=55 double-blinded randomized controlled trial, results of which were published in a November 2018 issue of Medical & Surgical Urology and which showed use of UroShield was associated with significantly less biofilm formation as compared to control.

This latest study[14] evaluated UroShield versus a sham device in the reduction of bacterial load on indwelling catheters as well as in the prevention of CAUTI among patients in a network of skilled nursing homes in the U.S. UroShield and sham devices were connected to indwelling catheters (~3 inches from insertion point) for a period of 30 days, which is when the catheter was removed and a new catheter inserted. Catheters of 51 patients were evaluable at the end of the study, including 26 and 25 treated with UroShield and sham devices, respectively. Patients were evaluated for an additional 60 days, encompassing another two catheter changes (neither of which were attached to devices), and tracked for microbial counts in the catheters and in urine. Treated infections were also monitored.

Results showed a statistically and clinically significant reduction in the number of colony forming units (CFUs) among the UroShield patient group as compared to those receiving sham (control). **The difference was dramatic** with CFU counts remaining constant in the sham arm while falling nearly 90% in the UroShield arm. While sham CFU counts remained at baseline levels (i.e. 100k or greater) through 30, 60 and 90 days, the UroShield arm experienced mean improvement (versus control) of 87.2k at 30 days, 87.5k at 60 days and 79.3k at 90 days. **All differences were highly statistically significant** with p-values<0.001 at each 30-day period. **Efficacy of UroShield also appeared to be durable**, with no significant change in CFU counts from 30 to 60 days and only incremental increase from 60 to 90 days (p=0.09). The efficacy in reducing CFU counts appears to be directly related to reduced CAUTI incidence.

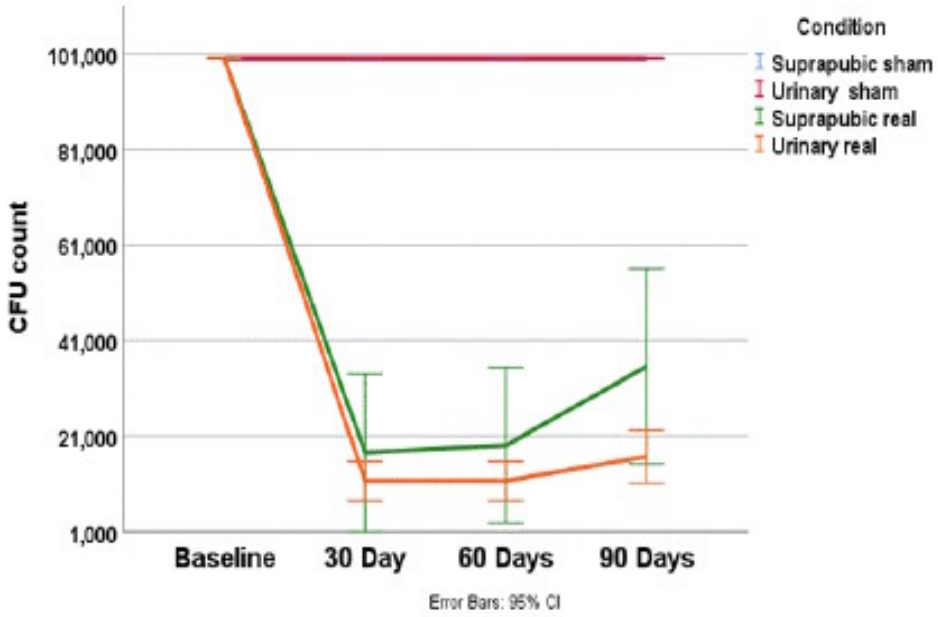
As it relates to CAUTI rates, UroShield again significantly outperformed sham. While every enrolled patient had been treated for CAUTI prior to the initiation of SAW and sham treatment, patients in the UroShield group experienced significantly fewer catheter-induced infections that those in the sham arm. At 30 days, 100% of UroShield patients were infection-free, compared to 73% of sham control patients – the difference (i.e. 0 versus 7 infections) was statistically and clinically significant. While the published manuscript does not report on infection rates at 60 days, it does for 90 days. At 90 days, three patients (i.e. 10.3%) in the UroShield arm had acquired an infection, compared to 14 (i.e. 53.8%) in the sham group – the difference was, again, statistically significant (p=0.001).

[12] Includes Proteus mirabilis, E. coli, Providencia rettgeri, Candida albicans, Pseudomonas aeruginosa, Klebsiella pneumoniae, Serratia marcescens, Morganella morganii, Alcaligenes faecalis, Staphylococcus aureus, Citrobacter freundii, Acinetobacter baumanii, Providencia stuartii, Klebsiella ornithinolytica, Enterococcus faecalis and Aerococcus urinae

[13] Lindsay E. Nicolle. Antimicrob Resist Infect Control. 2014; 3: 23. Catheter associated urinary tract infections

[14] Markowitz et al., Med Sur Urol 2018, 7:4. The Effect of Surface Acoustic Waves on Bacterial Load and Preventing Catheter- associated Urinary Tract Infections (CAUTI) in Long Term Indwelling Catheters

While Sham CFU Counts Remained at ~100k, UroShield Counts Fell Nearly 90%

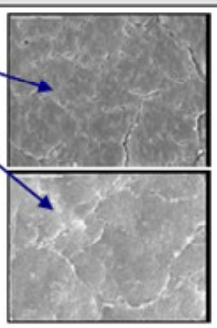


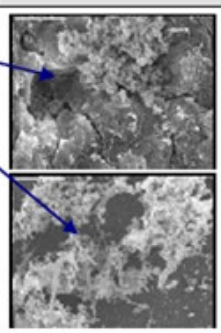
Source: Markowitz S, et al 2018

Prior UroShield clinical studies include;

- **2006-2006, Univ of Heidleberg, Germany: n=22 (11 per arm), double-blinded, sham-controlled RCT** evaluating UroShield in prevention of biofilm on patients with indwelling Foley catheter. Primary endpoints included both efficacy (prevention of biofilm, reduction in pain medication) and safety/tolerability (lack of adverse/serious events, lack of device-associated complaints) measures. Average catheter days (i.e. from insertion until withdrawal) were 8.8 and 9.2 in the UroShield and sham groups, respectively. Results showed that no biofilm was present on the UroShield catheters as compared to seven of the sham catheters which had biofilm present. In addition, UroShield patients used statistically significant (p=0.003) less analgesics; a total of 4 pills were prescribed for UroShield patients, compared to 18 pills for the sham group. Moreover, UroShield patients received medication during just 4% of days, compared to 17% of days for sham patients. In terms of safety, one UroShield patient suffered a stroke, although it was deemed to be not likely related to the device (the patient had a history of heart disease and also had a prior stroke). There were two additional adverse events in the UroShield group and three adverse events in the control group – but none were attributed to the devices.

Biofilm: no presence in UroShield group (L), observed on 7 catheters in sham group (R)

Active group (A)	Subject	Biofilm presence	SEM
N = 11	3	-	
	4	-	
	5	-	
	6	-	
	10	-	
	12	-	
	13	-	
	15	-	
	17	-	
	20	-	
	22	-	
Total Biofilm Presence		N = 0	

Control group (B)	Subject	Biofilm presence	SEM
N = 11	1	+	
	2	+	
	7	-	
	8	-	
	9	+	
	11	-	
	14	-	
	16	+	
	18	+	
	19	+	
	21	+	
Total Biofilm Presence		N = 7	

Source: Zillich S. et al., NanoVibronix

- **2007, Univ of Heidelberg, Germany: n=40 (20 per arm), double-blinded, RCT** evaluating UroShield in the prevention of bacteruria (i.e. harmful bacteria in the urine) as compared to antibiotics in patients undergoing radical prostatectomies (i.e. surgical removal of the prostate). Patients were randomized to either one

intraoperative dose of antibiotics and UroShield (i.e. treatment) or one intraoperative dose of antibiotics, followed by five doses over the subsequent five days (i.e. control). Results, per NOAV's most recent 10-K, showed that the UroShield group had only one case of bateruria (i.e. 5% of patients), compared to four cases in the control arm (i.e. 16% of patients).

- **2007, Shaare Zedek Medical Center, Jerusalem: n=10, open label trial** evaluating UroShield for the improvement of pain, discomfort, spasms and overall well-being in patients receiving emergency placement of a urinary catheter due to acute obstruction. Results, per NAOV's most recent 10-K, showed that within 24 hours, all patients showed an improvement in pain, itching, burning and spasm levels. Moreover, patients experienced an increase in well-being.

- **2007-2009, Shaare Zedek Medical Center, Jerusalem: n=40, open label, randomized trial** evaluating UroShield in the reduction of postoperative catheter related pain and spasms. Results, per NAOV's most recent 10-K, showed that UroShield device was effective in reducing postoperative catheter related pain discomfort and bladder spasms and that there was also a notable trend towards reduction of bacteriuria.

- **2010-2011, Hungary: n=27, physician-initiated study** evaluating UroShield in reduction of bacteruria. Results, per NAOV's 10-K, showed a reduction in pain and significant decrease in bacteruria rate

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PainShield

PainShield is used for the treatment of pain, muscle spasms and tendon diseases. Use of it currently requires a physician's prescription. Other than contraindications for patients with cancer or for placing the patch directly over ischemic tissue in patients with ischemic disease, PainShield can be used for just about any indication that a doctor believes that it may effectively address.

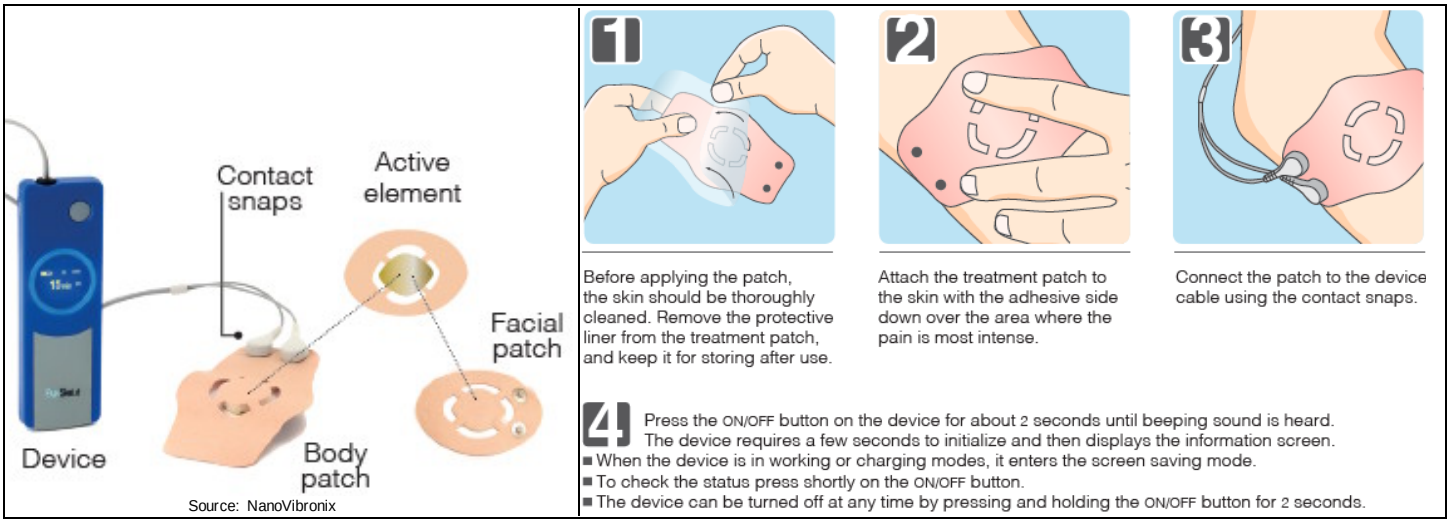
Along with the microprocessor-controlled driver unit, PainShield consists of a transducer and two different types of treatment patches; one for the face and one for general areas of the body. PainShield operates at a power of 0.4 W and 90 kHz frequency. PainShield allows for six treatment cycles with each cycle consisting of 30 minutes on-time, followed by 30 minutes off. The device automatically shuts off after the final cycle (i.e. 6.5 hours) or can be turned off at any time by holding down the power button. The driver unit displays treatment cycle (1 through 6), battery life and treatment time (0 – 30 minutes).

This intermittent (on-off action) and extended treatment time over six hours, which NAOV refers to as 'targeted slow-release', is believed to support healing as a result of relative long-duration stimulation of blood-flow to the site of interest. This also differs from other low-frequency ultrasound devices which provide a shorter treatment duration and continuous, as opposed to intermittent, therapy.

PainShield is classified as a Class II device by FDA and received 510(k) regulatory clearance in the U.S. in August 2008 with an indicated use "to apply ultrasonic energy to generate deep heat within body tissues for the treatment of selected medical conditions such as relief of pain, muscle spasms and joint contractures."[15] While sale of it currently requires a prescription, a major operational focus of NAOV's is to gain FDA approval for over-the-counter sale – the company has outlined a game plan aimed at that pursuit.

PainShield is also CE Marked (as of July 2008), allowing for sale in Europe and other areas of the world that accept that regulatory designation, including Ecuador and India. It is also approved for sale in Canada and was cleared for marketing in Israel in 2010. NAOV has indicated that they are evaluating other geographic markets, including Southeast Asia and if they secure distribution agreements in those parts of the world, will then pursue requisite regulatory approvals.

PainShield, Directions for Use



NAOV has signed distribution agreements for PainShield in North America, Europe, Asia and India. The company sells all of their products direct through their own website and in May 2018 penned a distribution agreement with Fabrication Enterprises, Inc. for the U.S. with a focus on sports medicine and the physical therapy markets. The product is also carried by Golfballs.com (a golf-oriented online retailer), is marketed by IMS Medical in the U.K., Morulaa HealthTech in India and MDS Pharma Ltd in Israel (MDS Pharma also handles distribution of WoundShield and UroShield in Israel).

Fritz Clinic, which runs seven health wellness clinics in Alabama focused on non-opioid pain treatment, became NAOV's **first facility-based collaborative partner for PainShield**. The press release announcing the agreement, which was penned earlier this month, notes that Fritz Clinic is one of the largest specialized opioid addiction centers in the southeast and currently treats several thousands of patients each month by helping them overcome opioid dependence and misuse. As many of these patients began using prescription opioid pills to address chronic pain, PainShield is expected to be an integral part of Fritz Clinic's therapeutic protocol.

Sales to-date have not been overly significant. PainShield launched in 2009 and through the end of 2017, approximately 1,700 units and 15,000 treatment patches had been sold. While NAOV does not disclose revenue per product, annual sales have averaged less than $275k since 2015 (and, through Q3 2018, are at an annualized run-rate of ~$350k). While reimbursement for PainShield is available, it only covers use in a clinic, which has likely inhibited at-home use (which also requires a prescription). Management has indicated that they believe the prescription requirement in the U.S. has also been an impediment to sales growth.

U.S. OTC Strategy…

Much of NAOV's growth strategy for PainShield hinges on driving sales through generation and publication of additional clinical data and, as it relates specifically to the U.S. market, removing the prescription requirement. Per the company's most recent investor presentation, they anticipate making a U.S. regulatory filing for that purpose following completion of;

- Usability Study-User-View, a well-respected company is performing the required "Usability" or "Human Factor" study
- Redesign Product Packaging-Packaging must be aligned with OTC products and FDA requirements Users Manuals-Users manuals were redesigned, written, and now comply with FDA OTC requirements Quick Reference Guides
- Redevelopment of Quick reference guides to comply with FDA OTC requirements
- Product Redesign-In order to meet OTC electrostatic emissions standards

Clinical Data Strategy…

While PainShield can be prescribed for just about any ailment that a doctor deems it appropriate to treat, it is common that novel medical devices, particularly those without dedicated insurance reimbursement such as is the case with PainShield (and most new, non-replacement medical devices), may experience rather lackluster uptake and utilization. That certainly has been the case with PainShield. While OTC approval in the U.S., if that eventually

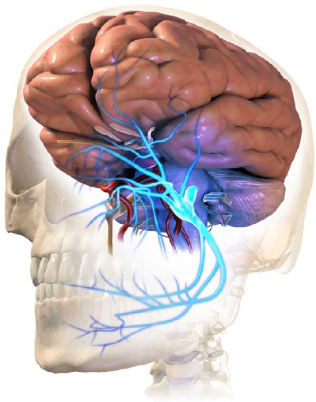
[15] FDA 510(k) Summary K081075 February 5, 2014

happens, will open up a potentially important sales channel, we think physicians will continue to represent the majority of the upside with PainShield, particularly as it relates to potential use in place of opioids.

Based on our experience, there are typically two ways that companies will address weak sales – one is by increasing sales, marketing and distribution resources and the other is through the generation of compelling clinical evidence. The former often requires a significant capital outlay and while relatively simple to implement, if it is not supported by the latter it often results in a poor return on investment. The latter, by contrast, is often a more involved undertaking but, if 'successful' (i.e. the clinical evidence is indeed compelling), has a much better chance of generating positive ROI – particularly when also used to petition for reimbursement. We think NAOV's strategy of educating providers and consumers with an evidence-based approach (which applies to all of their products) and not one that solely relies on selling to them through a beefed-up sales effort has the best chance of ultimately succeeding.

Trigeminal neuralgia (TN), a neurological condition that affects the trigeminal nerve (in the face), is NAOV's main focused market for PainShield. First-line treatment of TN, which is characterized by such extreme pain that it is commonly referred to as the "suicide disease", are anticonvulsants. While medications can often initially control the disease, their effectiveness falls to 50% or less over time. Surgery and opioids may also be used – both of which come with major drawbacks. While surgery is also usually effective (~90% of the time), the pain often returns. Studies show that as few as 68% of patients are pain-free one-year following surgery and pain has returned in 50% of cases within five years. Moreover, surgery comes with compromises (in addition to recovery time and cost) and can include sensory loss (~50% of cases), numbness (up to 37% of cases), tingling (up to 13% of cases) and hearing loss (10%), among other side effects.[16] Meanwhile, opioids only mask the pain, lose effectiveness over time and put the patient at significant risk of developing addiction to the medication.

Trigeminal Neuralgia



Source: Blausen Medical, Wikipedia

An estimated 40k and 140k new cases of TN occur in the U.S. each year and as many as 200k or more Americans may be suffering from the disease at any given time.[17] As studies have indicated no clear geographical differences in TN prevalence, we estimate that as many as 1M people in the developed world may have the condition.

In July 2018 NAOV announced positive final results from an n=59 double-blinded, cross-over trial conducted in the U.S. among patients with unilateral trigeminal neuralgia. While the disclosed results were not overly detailed, NAOV's July 24th press release notes that patients in the PainShield group (n=30) experienced a significant difference in the outcomes of pain (as assessed by Visual Analog Scale, or VAS), quality of life and breakthrough medications taken. The announcement notes that PainShield patients experienced a 55.2% improvement from baseline scores versus 2.3% improvement in the control cohort. In addition, while control saw a 1.5% decrease in breakthrough pain medication use (including opioids), PainShield patients used 46.4% less. Moreover, there was an improvement in uninterrupted sleep favoring the PainShield group. NAOV expects to submit the data for publication, which may provide some more detail about the results.

General soft tissue pain represents a less-defined but relatively enormous market. Given the diversity of pain symptoms and areas of the body (such as sprains, ligament strains and tears, contusions, tendinitis, bursitis, etc) that could potentially fall into this category it is difficult to quantify the scope or size of this market. While it may be easier to narrow the general pain market into likelihood of addressability by PainShield (i.e. type of soft tissue pain that the device could effectively treat) with clinical trials in specific indications, we think a reasonable current approach is to use 'myofascial pain syndrome' as a proxy estimate for the potential overall soft-tissue injuries market size.

Myofascial pain syndrome refers to inflammation of soft tissues of the body which results in pressure on particularly sensitive parts of muscles – commonly referred to as 'trigger points'. It is a broad category encompassing a large variety of symptoms and causes including muscle, ligament and tendon injury, tenderness and persistent pain. Myofascial pain is estimated to account for approximately 30% of pain-related general physician visits.[18] It is also relatively common following certain surgeries, including after breast cancer surgery, myofascial pain incidence of

[16] Mark Oberman. Treatment options in trigeminal neuralgia. Ther Adv Neurol Disord. 2010 Mar; 3(2): 107–115
[17] Reinard, K. et al. Racial disparities in the diagnosis and management of trigeminal neuralgia. J Neurosurg Volume 126 • February 2017. Published online March 11, 2016; DOI: 10.3171/2015.11.JNS151177
[18] Skootsky SA, et al. Prevalence of myofascial pain in general internal medicine practice. West J Med. 1989 Aug; 151(2): 157–160.

which is nearly 50%.[19] Overall, it is estimated that ~85% of people will experience myofascial pain at least once in their lifetime with 27% of the population experiencing it at any given time (i.e. annual incidence).[20]

Myofascial pain is often treated with medication including NSAIDs, opioids, antidepressants and anticonvulsants and, less commonly, muscle relaxants and flupirtine. Physical therapy which can include the use of TENS, acupuncture and high-frequency ultrasound (among other modalities) may also be prescribed. As the chart below illustrates, both drugs and physical therapy are often lacking in effectiveness – in fact a study found that approximately 50% of all surveyed physicians reported that current symptom-based treatment options are lacking. This, we believe, represents a potentially significant opportunity for PainShield.

So, while PainShield is potentially appropriate to treat a host of non-myofascial classified pains, given the difficulty in quantifying each of these potential specific markets, we think ~27% is a reasonable proxy for estimating incidence of the 'general pain' market potentially applicable to PainShield. As such, we estimate the annual size of this market represents approximately 85M Americans and roughly 150M people residing in developed European countries.

Current Myofascial Pain Treatment Options Are Insufficient

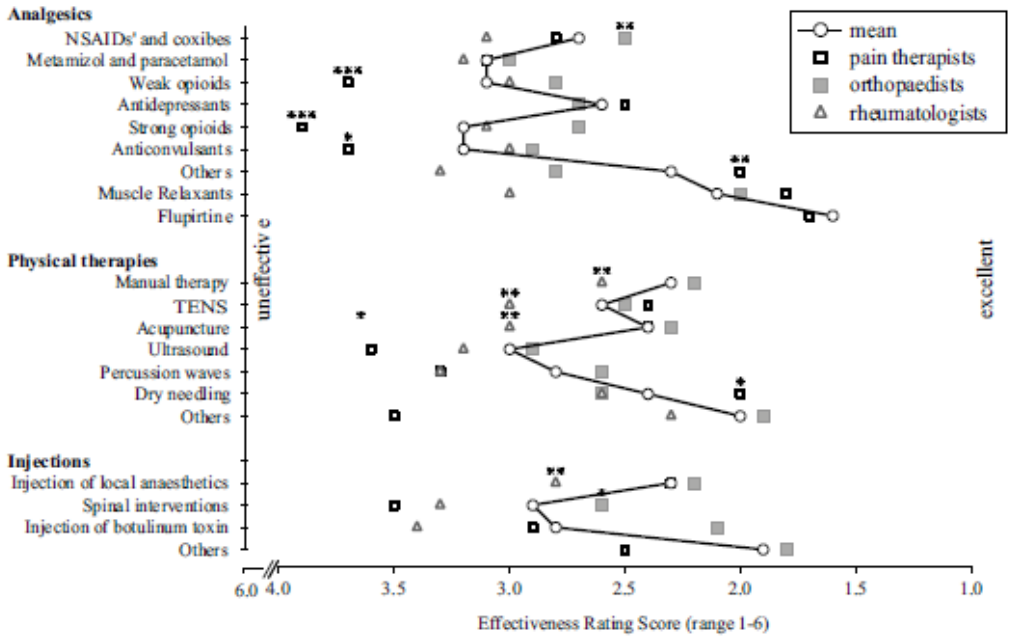


Figure 2 Ratings of Treatment Options. demonstrates the physician estimated efficacy of different therapeutic options in the treatment of myofascial pain on a 6-fold scale (with 1 being "excellently effective" and 6 being "ineffective"). Ratings towards the lower ranks on the value axis indicate a higher estimated effectiveness. Data are expressed as mean ± SD. (*), (**) and (***) express the different levels of significance $p < 0.05$, 0.01 and 0.001. Between-group differences were examined with Kruskal-Wallis tests, using the Mann-Whitney U tests for post-hoc two-group comparisons. Stars are placed upon the confirmed group, respectively. TENS: transcutaneous electrical stimulation.

Source: Fleckenstein et al. BMC Musculoskeletal Disorders 2010, 11:32

Additional trials of PainShield…

While NAOV has not provided detailed results or designs of the following PainShield studies (in various pain related indications), they are listed in their 2017 10-K as trials that have been completed and are supported of the efficacy of PainShield. In addition to these, they list a larger, n=200, study in patients with chronic pelvic pain as a potential future endeavor

[19] Lacomba T., et al. Incidence of myofascial pain syndrome in breast cancer surgery: a prospective study. Clin J Pain. 2010 May;26(4):320-5. doi: 10.1097/AJP.0b013e3181c4904a.

[20] Fleckstein J., et al., Discrepancy between prevalence and perceived effectiveness of treatment methods in myofascial pain syndrome: Results of a cross-sectional, nationwide survey. BMC Musculoskeletal Disorders 2010, 11:32

Purpose	Doctor/Location	Time, subjects	Objectives	Results
A sound solution for Trigerminal Neuralgia Physician initiated	Dr. Ch. Adahan Sheba Medical Center	2009 15 patients	●Reduction in pain ●Reduction in disability ●Improvement of function and quality of life ●Accelerating of healing	73% of the subjects experienced complete or near complete relief.
Randomized control trial examining the efficacy of low intensity low frequency Surface Acoustic wave ultrasound in trigerminal neuralgia pain For Ph.D., Funded by Israeli Ministry of Health	Dr. M. Zwecker Chaim Sheba Medical Center, Tel Hashomer, Israel	2012-2012 16 patients	●Reduction in pain ●Reduction in disability ●Improvement of function and quality of life ●Accelerating of healing	In conclusion this study supports the hypothesis that the application of Low Intensity Low Frequency Surface Acoustic Wave Ultrasound (LILF/SAW) may be associated with a clinically significant reduction of pain severity among patients suffering from trigeminal neuralgia disease.
Treating Rutgers university athletic injuries with bandaid sized ultrasound unit PainShield	R. Monaco, G. Sherman, Rutgers University Athletic, Rutgers, New Jersey	2011 35 patients	●To assess the pain, functional capacity and discomfort of the subject ●To assess the subject's quality of life ●To assess the injury status ●To assess the efficacy of the treatment ●To assess compliance factors	Active group: 74% had improvement, 26% no change Sham group: 56% no change, 44% had improvement This is an indication of the effectiveness of the device. Lack of funding for statistical analysis has stopped this trial prior to fulfillment.
Reduction of chronic abdominal and pelvic pain, urological and GI symptoms using wearable device delivering low frequency ultrasound	D. Wiseman, Synechion Institute for Pelvic Pain	2011 19 patients	●To assess the efficacy of PainShield for pelvic and related pain	Improvement in pain related symptoms noted for all symptoms.
PainShield for Trigeminal Neuralgia	Shira Markowitz, MD, New York, NY	Early 2018 60 patients	●To assess the efficacy of PainShield for treating trigeminal nerualgia	Interim results released in the fourth quarter of 2017, which reported improvement in pain and quality of life; final results expected to be reported in the second quarter of 2018

Testimonials and Endorsements…

In addition to the growing database of clinical evidence supporting the efficacy and safety of PainShield, the ability of the device to substantially reduce or eliminate pain is further backed by patient testimonials as well as endorsements from high-profile professional athletes. While we acknowledge that, as compared to clinical evidence of robustly-designed clinical trials, these represent more subjective support of PainShield's effectiveness, we also think it would be remiss to dismiss these as completely meaningless. In addition, while endorsements and testimonials may have little influence in regulatory-related matters, they certainly can influence patient, and even physician, adoption and utilization (as the age of online product reviews has proven). As such, we believe these are relevant in the context of building awareness and marketing of the product.

Patient testimonials can be found on NAOV's website, their Facebook page as well as distributors' websites. We acknowledge the potential for weeding out any negative reviews and only posting positive ones but also note that in reading some of these reviews, we think a reasonable judgment can be made that (at least some of) these reviewers experienced real pain relief with PainShield – including some which indicate they had exhausted other options. Additionally, several of these reviews relate to effective relief of Trigeminal Neuralgia (i.e. suicide-inducing) pain with PainShield.

Randall Rysedorph, President of the Fritz Clinic, also endorses PainShield, noting in NAOV's January 11, 2019 press release that he had a personal experience with severe pain that he had been unable to effectively address (for two years) until finally trying PainShield – which, he notes, has changed his life.

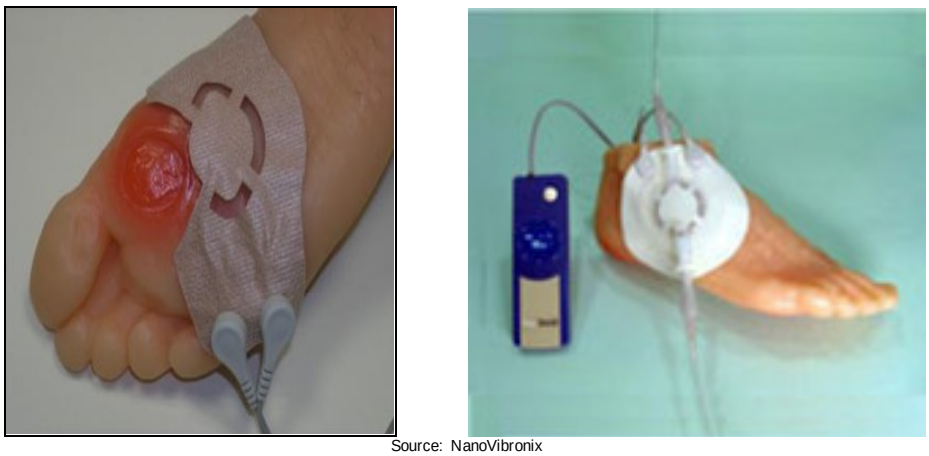
In addition to patient testimonials, Mariano Rivera (Yankees pitcher for 19 years), Bret Saberhagen (pitched for 15 years with various MLB teams) and Vinny Testaverde (quarterback for 21 seasons for various NFL teams) have all **endorsed PainShield** over the last three years for its ability to reduce or eliminate chronic pain.

WoundShield

WoundShield is designed to facilitate healing of chronic and otherwise hard-to-treat wounds such as diabetic foot ulcers and severe burns. Similar to the PainShield and UroShield configurations, WoundShield consists of a reusable driver unit and a disposable patch.

WoundShield's use of surface acoustic waves allows for its placement adjacent to the wound as ultrasound waves move laterally from the transducer to facilitate healing through promotion of local perfusion and tissue oxygenation – which have been shown to be critical for healing chronic wounds. The use of low intensity, low frequency surface acoustic waves means the therapeutic ultrasound reaches the entire wound surface and can be used for a relatively long duration – both of which are believed to result in more complete and rapid wound healing. An instillation patch also allows WoundShield to be applied directly to the wound – in this configuration it facilitates oxygenation and absorption of topical medications through sonophoresis.

WoundShield applied adjacent (L) and directly (R) to wounds



Source: NanoVibronix

WoundShield's simple, safe and non-invasive operation separates it from other wound care methods…
Another benefit of WoundShield is that its relatively simple operation and the established safety profile of low frequency ultrasound means that it can conceivably be operated by the patient and in the convenience of their own home. Simplicity, safety and at-home, patient-use have other benefits as well – namely that they provide the opportunity for relatively long treatment durations and, specifically as it relates to WoundShield, at a relatively low cost (as compared to other advanced wound therapies – as discussed below). Low and long treatment, which in the case of WoundShield, represents a frequency of <100 kHz and a duration of potentially several 6.5-hour cycles per day. These are major and significant distinctions as it relates to almost all other advanced wound care therapeutics – the use and application of which require a trained technician and a trip to the hospital or clinic – which also comes with a relatively short treatment duration and high cost.

The low-intensity, non-invasive nature of WoundShield and the ability to place the treatment patch adjacent to the wound also lend **use of it as an adjunct to various other advanced wound care therapies**. This flexibility is rather unique as most advanced wound care modalities have a degree of invasiveness and are therefore largely precluded from being used together. As such, we believe this advantage could prove to be of significant value given that the advanced wound care device market is highly concentrated among a small handful of modalities and manufacturers. This potentially affords NAOV options to partner with already-established wound care device manufacturers – which, given the enormous size of the market, may provide de-risked yet attractive commercialization opportunities.

WoundShield is CE Marked (November 2012), allowing for sale in Europe, India and Ecuador, and has Canadian License approval (November 2016). The device, per disclosures in recent public filings, has generated only minimal sales to-date. NAOV is focused on changing that, however, and is in the midst of implementing a growth strategy. Part of that includes broadening their distribution capabilities and geographic footprint – the other part, which may be a somewhat longer-term goal, is to obtain U.S. regulatory clearance for the device (the strategy around which we

hope to hear more about in the near future). If and when approved for sale in the U.S., it is anticipated that use of WoundShield will require a prescription.

As it relates to distribution, in June 2018 NAOV announced that that they granted exclusive rights to MDS Pharma to market WoundShield in Israel (MDS also distributes PainShield and UroShield in that country). NAOV's press release announcing the agreement notes that MDS has an established distribution network that includes health insurance providers, private pharmacies, health stores, beautician centers, private clinics, and leading health websites.

Diabetic foot ulcers largely define chronic wound market…

The chronic wound care market is big and growing. While it also includes venous and pressure ulcers, the vast majority of the chronic wound market is defined by diabetic foot ulcers. Approximately 30M Americans and 415M people worldwide have diabetes and prevalence is on the rise, with almost 2M new cases diagnosed each year in the U.S. An estimated 9.5% of Americans currently have diabetes – this is expected to grow to as much as 33% by the year 2050.

Foot ulcers are relatively common among diabetics as a result of nerve damage and vascular complications caused by the disease. Nerve damage can cause peripheral neuropathy, or loss of feeling in the foot which means injuries such as cuts or bruises may go undetected (especially to the underside of the foot) which can quickly worsen. Vascular disease and poor blood flow (especially to the skin) is another common symptom of diabetes which can in itself cause ulcers and impair the body's ability to heal wounds. Chronic wounds are typically characterized by constant excessive inflammation, infections, formation of biofilm, impaired proliferative and secretory cell capacities (i.e. cells do not respond to healing stimuli) and lack of sufficient oxygenation.[21]

Diabetic foot ulcers afflict roughly 15% - 25% of all diabetics within their lifetimes. Approximately 1.5 million diabetic foot ulcers occur every year in the United States, with an estimated 6.5M Americans suffering from the condition at any given time. DFU precedes over 80% of all non-traumatic lower-limb amputations among diabetics, leading to more than 80k amputations annually. Clinical studies have shown that comprehensive foot programs (including advanced therapies) can reduce amputation rates by 45% to 85%.

DFU is usually a progressive condition and can worsen very rapidly over time. If the wound is not controlled within a short period (~ 4 weeks), the risk of infection, hospitalization, amputation and death escalates. This not only puts the patients' health at risk, it can also dramatically increase the cost of treatment. As such, effective and timely therapy that closes the wound and facilitates complete healing is critical in order to avoid long-term complications, potentially including amputation.

The cost of addressing diabetic foot ulcers can also be very costly. Depending on the source, the cost of care of diabetic foot ulcers can vary significantly, but generally falls somewhere between $7k and $60k per ulcer (the discrepancy largely due to whether amputation is required) and $25B in aggregate in the U.S. The annual direct cost of care of DFU to Medicare alone could be as much as $2.2B. When considering private payers and ancillary costs such as lost work time, the total cost of DFU in the U.S. is likely in the many tens of billions of dollars. As such, payers and providers, in addition to patients, have an economic interest in effective DFU therapy.

Standard of care for treating chronic wounds is often less than completely effective. Standard of care, which typically includes dressing the wound (which usually involves a moist wound dressing, covered in dry gauze and secured with tape or elastic bandage) and possibly the use of a walking boot, remains the most commonly prescribed first-line therapy and can be effective for early-onset (i.e. - acute) ulcers. However, a considerable amount of clinical trial data from over the last 20 years has proven that standard of care is significantly less effective in healing more severe (i.e. - older, larger) wounds and earlier intervention is positively correlated with improved patient outcomes.

The body of evidence strongly supports the use of more effective (i.e. - advanced) therapies at an earlier stage of treatment in order to reduce the risk of acute wounds becoming chronic and increase the likelihood of chronic wounds fully healing. A retrospective analysis of clinical trial data of 622 patients with chronic DFUs prescribed standard of care showed 31% (139 of 450) of patients achieved complete healing after 12 weeks. This fell to 24% (41 of 172) of patients where standard of care was continued for 20 weeks.[22] Current widely-accepted protocol is to employ advanced wound therapies and techniques if, after a period of four weeks of standard of care, a wound has not reduced in size by 50% or more.

[21] Frykberg R. and Banks J. Challenges in the Treatment of Chronic Wounds. ADVANCES IN WOUND CARE, VOLUME 4, NUMBER 9, 2015
[22] Margolis D, et al. Healing of neuropathic ulcers receiving standard treatment: a meta-analysis. Diabetes Care 1999;22(5):692-695

The advanced wound care product market is represented by various devices, wound matrices, dressings, skin substitutes and other therapies which, in aggregate, generate revenue of more than $15B per year in the U.S. While the availability of advanced wound care products is large and diverse, share of the commercial market is largely concentrated among only a few select modalities. Among the most commonly used are advanced dressings, negative pressure wound therapy (NPWT), bio-engineered skin (i.e. skin substitutes), growth factors and hyperbaric oxygen therapy (HBOT). While, combined, these therapies account for over 90% of the advanced wound care market, none are considered a 'silver bullet' when it comes to healing DFUs (66% of which recur and 12% of which result in eventual amputation) and other chronic wounds and all suffer from one or drawbacks.[23]

There is little evidence supporting the effectiveness of most advanced wound dressings in the healing of chronic wounds. NPWT, while popular and supported by clinical data, is mildly invasiveness, can be painful and is relatively costly. NPWT is estimated to have garnered between 20% and 50% share of the advanced wound care market. Bio-engineered skin substitutes are invasive, can be painful and are also costly relative to WoundShield. Growth factors, as a class, have less-than compelling evidence of effectiveness, are invasive and also relatively costly. HBOT, which involves the administration of oxygen into the wound over several sessions, is supported by some (although far from a compelling amount of) clinical evidence, although it is relatively expensive.

The other drawback, as we noted above, is that all of these modalities, with the exception of HBOT, can largely only be used in isolation. This mostly relates to their invasiveness but also due to their high cost. By contrast, as WoundShield can be applied adjacent to the wound and is relatively inexpensive, it is practical for it to be used as a complement or supplement to any of these other advanced wound care therapies.

In terms of expense, a typical course of DFU treatment can vary widely depending on the severity of the wound and advanced treatment modality chosen. A six to eight-week regimen of NPWT, skin substitutes or growth factors can range between $5k and $15k. HBOT therapy is generally the most expensive advanced modality, with a typical full treatment regimen costing $30k or more. Expense of advanced wound dressings are likely to be significantly less than that, although their use is not recommended for particularly difficult to heal wounds.

The high cost and lack of consistent effectiveness of current advanced wound therapies[24], leaves what we believe is ample room in the market for a novel, relatively low-cost device such as WoundShield. While NAOV has not disclosed pricing, using publicly available retail pricing information of PainShield as a guide, we estimate total cost of up to eight weeks' worth of WoundShield therapy (including the cost of the reusable driver unit) could reasonably be expected to be less than $2,500.[25]

Evidence supporting effectiveness of WoundShield in chronic wound healing…
The effectiveness of WoundShield in improving localized blood flow, oxygenation, epidermal growth and ischemia of chronic wounds was the subject of several preclinical studies and two published clinical studies (while we focus our discussion on the two published clinical studies, details of the preclinical studies are accessible on the 'publications' section of NAOV's website).

These published studies, one of which used WoundShield in an instillation configuration while the other used a patch proximal to the wound bed, showed the device was able to significantly increase oxygenation of foot ulcers among patients with severe cardiovascular (i.e. PAD, CLI, hypertension) and metabolic (i.e. diabetes) disease. And, as the level of oxygenation of ischemic tissue has been found to be positively correlated to wound healing (and inversely correlated to risk of lower limb amputation), these studies further suggest that WoundShield may be able to (significantly and clinically meaningfully) improve patient outcomes.

- **Covington, et al.*, Ultrasound-Mediated Oxygen Delivery to Lower Extremity Wounds***
  Among the published clinical studies was a single-arm trial of seven patients with critical limb ischemia (CLI) and full-thickness wounds which were treated with WoundShield with an instillation patch (i.e. via sonication), which used hyper-oxygenated saline to deliver oxygen to the wound bed. CLI is defined by a severe blockage of blood flow in the legs and/or feet and generally has a poor prognosis with a five-year all-cause mortality rate of 70% (for context, five-year all-cause mortality of colorectal cancer is ~36%).[26] As lack of blood flow deprives tissue of oxygen, CLI significantly hinders wound healing (particularly on the lower legs and feet) and often results in

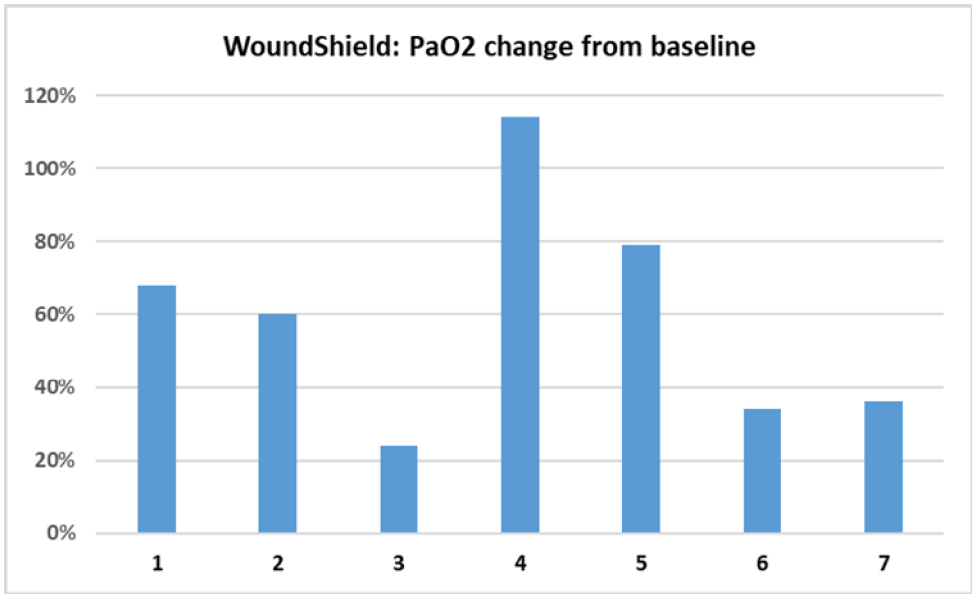
[23] Sen CK, et al. Human Skin Wounds: A Major and Snowballing Threat to Public Health and the Economy. Wound Repair Regen. 2009 Nov–Dec; 17(6): 763–771.
[24] Greer N, Foman N, Dorrian J, et al., Advanced Wound Care Therapies for Non-Healing Diabetic, Venous, and Arterial Ulcers: A Systematic Review. Washington (DC): Department of Veterans Affairs (US); 2012 Nov.
[25] Calculated as; $500 driver unit + (60 days x $30 patch) = $2,300. This assumes one patch is used per day, which be highly conservative given that PainShield's patches can be used for up to 1 month
[26] Powell R. et al. Interim analysis results from the RESTORE-CLI, a randomized, double-blind multicenter phase II trial comparing expanded autologous bone marrow-derived tissue repair cells and placebo in patients with critical limb ischemia. Journal of Vascular Surgery. Volume 54, Issue 4, October 2011, Pages 1032-1041

amputation. As such, facilitating healing in these patients is critical. An estimated 12% of adults in the U.S. suffer from CLI.

The purpose of the study, which was led by researchers at Duke Raleigh Wound Clinic at Duke University and published in the journal, Wounds in 2012, was to evaluate the ability of WoundShield to increase oxygenation of the wound bed of full thickness (in depth) wounds measuring between 2.0 and 20.0 cm^2. Primary endpoint was the change from baseline in P_aO_2 (i.e. partial pressure of oxygen in arterial blood) levels.

Of the nine enrolled patients, results were obtainable for seven. P_aO_2 oxygen levels were measured at three time points; baseline, following 20 minutes of control drip-delivered (i.e. non-sonicated) hyper-oxygenated saline and finally, following 25 minutes of sonicated hyper-oxygenated saline (via WoundShield). Baseline measurements revealed that they wound bed was hypoxic (i.e. deprived of adequate oxygen supply).

Results showed no change in P_aO_2 baseline levels following the 20 minutes of non-sonicated hyper-oxygenated saline drip (i.e. wound bed remained hypoxic) but did show a significant change from baseline after the 25 minutes of WoundShield hyper-oxygenated saline sonication. WoundShield sonication increased P_aO_2 levels by a minimum of 24% and by as much as 116%, with a median increase of 60%. The change from baseline, based on Wilcoxon signed rank test, was statistically significant (p=0.018). This study not only indicated that WoundShield can significantly increase oxygenation of the wound bed but also demonstrated that administration of hyper-oxygenated saline alone (i.e. without the use of WoundShield) results in no discernable increase in oxygenation. As clinical studies have proven that topical wound oxygenation is a key determinant in healing outcomes, this study also indicates that WoundShield can increase the rate of healing and improve CLI outcomes.[27]



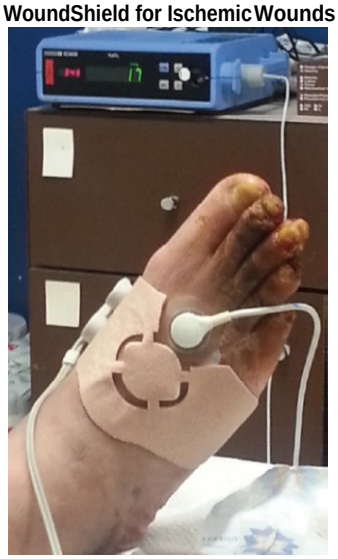
Source: Covington, S., et al.

- **Rosenblum, et al., *Surface Acoustic Wave Patch Therapy Affects Tissue Oxygenation In Ischemic Feet***

WoundShield/PainShield was evaluated in a single-arm study for its ability to improve local tissue oxygenation among a group of ten patients suffering from CLI. The study, conducted at a vascular surgery center located at Shaarei Zedek Medical Center in Jerusalem, Israel, was published in Wounds in 2014.

All patients had an ankle brachial index (ABI) of <0.4mm Hg, consistent with a diagnosis of severe peripheral artery disease (PAD). The severity of this diagnosis is associated with relatively high risk of amputation, gangrene, ulceration and delayed wound healing.[28] Additionally, two of the ten patients had necrosis of at least two toes and were provided use of the WoundShield device for nightly use over the course of one month.

WoundShield for Ischemic Wounds


Source: Rosenblum et al.

[27] Chandan Sen. Wound Healing Essentials: Let There Be Oxygen. Wound Repair Regen. 2009; 17(1): 1–18.
[28] Khan T., et al. Critical Review of the Ankle Brachial Index. Curr Cardiol Rev. 2008 May; 4(2): 101–106.

Tissue oxygenation, as determined by transcutaneous tissue oxygen tension ($TcPO_2$), was measured at baseline, during WoundShield/PainShield treatment and then 15 minutes following conclusion of treatment. After baseline $TcPO_2$ levels were established, each patient received SAW therapy delivered at 96 kHz and applied via a patch proximal to the $TcPO_2$ lead. SAW therapy was administered for 30 minutes and then turned off, at which point $TcPO_2$ drop-off levels were recorded for 15 minutes.

As noted, two patients with necrosis also used the device overnight (i.e. for 6.5 hours, cycling on and off for 30 minutes each) for 30 days. For these patients, oxygenation was measured at baseline, during 30-day treatment, again for baseline after 30-day treatment and finally, after 30 minutes in-clinic treatment.

Results (table below) showed a significant increase in oxygen saturation among all patients following SAW therapy. And while oxygen levels fell when the device was turned off, all levels remained greater than their respective baseline values.

Table 1. Results of oxygen saturation during treatment with a surface acoustic wave device.

Patient number (Age)	Baseline (mmHg)	High during treatment (mmHg)	Percent change during treatment	Value after rest (mmHg)
1 (65)	19	31	63.15	30
2 (40)	43	57	32.56	53
3 (73)	36	56	55.56	55
4 (68)	31	36	16.12	36
5 (70)	11	19	72.72	17
6 (75)	16	43	168.75	43
7 (71)	49	56	14.29	54
8 (71)	23	33	43.47	31
9 (68)	40	55	37.5	54
10 (62)	28	37	32.14	34

As it relates to the two patients that used the device overnight for 30 days, oxygen levels more than doubled in one patient and nearly doubled in the other from initial baseline to during overnight treatment. Additionally, oxygenation further increased from the second baseline to following final (in-clinic) 30-minute treatment (table below).

Table 2. Results after 1 month of use of the surface acoustic wave device.

Patient	Original baseline (mmHg)	End of treatment (mmHg)	1-month baseline (mmHg)	End of treatment (mmHg)
1	16	43	34	49
2	23	33	40	50

Given the positive correlation between transcutaneous tissue oxygen tension and healing of ischemic tissue, results of this study further support the hypothesis of the effectiveness of WoundShield (which, in this case was used with a proximal patch) in facilitating wound healing among patients with severe cardiovascular and metabolic disease states.

OUTLOOK, MODEL ASSUMPTIONS and VALUATION

New management was recently brought on board in order to accelerate growth and while revenue has been largely immaterial to-date, we think that soon changes as a result of the effects of one or more potential near-term catalysts and other recent events aimed at facilitating growth. Included among these are;

- **Prescription opioid crackdown**: U.S. state and federal regulators recently announced new measures aimed at stemming the oversubscribing of opioid pain medication. This includes a goal of the Trump administration to reduce opioid prescriptions by one-third over the next three years and more than 30 states enacting legislation limiting the number of opioid prescriptions for all conditions except cancer and palliative care. Insurers, both private and Medicare, have also placed limits on the number of prescriptions that they will now cover. These measures, coupled with a reaction by some doctors to do away with prescribing opioids altogether, has not only resulted in a significant decrease in the availability of these drugs for recreational purposes (and solely to feed addictions), but has also reduced access for patients that rely on them to control chronic pain.

  This, we think, has created a potentially potent opportunity for NAOV with PainShield, particularly given that, in the face of the crackdown on opioids, the U.S. government is encouraging (and in some cases sponsoring) the development and use of alternative pain therapies (in fact, Mariano Rivera, per NAOV's March 21, 2018 press release, recently approached President Trump about PainShield). Fritz Clinic, which treats thousands of patients per month and will use PainShield as an alternative to opioids, is the first of potentially more collaborations which could expand use and build awareness of the utility of the device to reduce reliance of these highly addictive medications.

- **OTC approval of PainShield**: NAOV has pointed to the prescription requirement as an impediment to adoption, use and overall availability of PainShield. Given the documented safety of low intensity low frequency ultrasound and simplicity of use of PainShield – which minimize potential safety risks – we think it is reasonable to assume that NanoVibronix can and will attain OTC approval. Based on feedback from FDA, the company has implemented a multi-step plan (including conducting usability study, redesign of product, manuals and users guide, and more) to precede an expected eventual regulatory filing seeking OTC FDA approval. We would view completion of each of these steps as positive tangible progress towards that goal and, given that retail access to the device would significantly increase the available target market, believe market value of the company should benefit from incremental progress in this regard.

- **Expanding distribution**: along with working to expand regulatory-related availability of their devices, NAOV has also been busy expanding geographical reach – and we think this will continue. Distribution agreements were recently signed for UroShield covering Canada (April 2018), India (December 2018), Israel (December 2018) and Switzerland (December 2018).

  Beefing up U.S. distribution for PainShield has been a recent priority and now includes Fritz Clinic (as of January 2019), Golfballs.com (Q3 2018) and Fabrication Enterprises, Inc (May 2019). We expect further expansion of PainShield's U.S. footprint will remain a priority. OUS sales of PainShield should benefit from recently penned distribution agreements in the U.K. (December 2017), India (December 2017) and Israel (June 2018).

  Similar to PainShield, WoundShield is also distributed via MDS Pharma in Israel (as of June 2018). While management has indicated that they are focused on broadening their distribution capabilities and footprint of WoundShield, we think the device also lends itself to partnership/collaborations opportunities. U.S. regulatory clearance could open up significant opportunity for WoundShield. The low-intensity, non-invasive nature of WoundShield and the ability to place the treatment patch adjacent to the wound also lend use of it as an adjunct to various other advanced wound care therapies (which is a novelty for advanced wound care devices).

- **Clinical data**: given the proven ability of compelling clinical data to generate positive ROI, we are encouraged that NAOV's growth strategy also relies on an evidence-based approach. We think NAOV's strategy of educating providers and consumers through clinical data (which applies to all of their products) and not one that solely relies on selling to them through a beefed-up sales effort has the best chance of ultimately succeeding. Expanding their clinical trial database and growing the list of published clinical studies is among the most potent influences to drive awareness and accelerate physician adoption and utilization.

- **Exploit unmet needs**: we think NAOV has ripe opportunities to exploit unmet therapeutic needs as it relates to CAUTI, chronic pain and chronic wounds with UroShield, PainShield and WoundShield, respectively. Competition to UroShield is represented by antibiotics, which are considered first-line therapy for CAUTI yet often prove ineffective, the overuse of which has been a major contributor to the emergence of resistant bacterial strains and resulted in antibiotic failure-to-cure rates of 50% or more.

While medications can often initially control Trigeminal Neuralgia, their effectiveness falls to 50% or less over time. Surgery and opioids may also be used – both of which come with major drawbacks. While surgery is also usually effective (~90% of the time), the pain often returns. Opioids often results in long-term addiction. And it is not just TN that represents unmet need for pain relief. Soft tissue pain is often addressed with NSAIDs, opioids, antidepressants and anticonvulsants – yet physicians report that available options are insufficient in about 50% of cases.

Chronic wounds are a costly financial burden to the U.S. healthcare system and current treatment options are often less than completely effective. With roughly two-thirds of chronic wounds recurring and ~12% of DFUs ending in amputation, there is an obvious unmet need for more effective options.

- **Adjunctive, not necessarily competitive, use**: the safety of LILFU affords the use it as an adjunct to existing therapies. This, we believe, is of significant benefit to NAOV as their products are not necessarily competitive threats to already established players and products. This means that larger industry participants such as CAUTI antibiotics or silver alloy (bacteria-resistant) catheter manufacturers may not view UroShield as a threat. Similarly, opioid, anticonvulsant and NSAID drug manufacturers (which includes many of the 'Big Pharma') may not need to worry about PainShield being positioned as a replacement for their products. And, WoundShield, being that it might be used in conjunction with NPWT, bio-engineered skin (i.e. skin substitutes), growth factors and hyperbaric oxygen therapy (HBOT), is not necessarily competing with ~90% or more of the advanced wound care market.

  And it's not just the lack of risk of competitive retaliation that adjunctive-use affords. It also potentially offers the opportunity to partner with others in the industry. So, if for example, WoundShield reduces healing time of DFU's when used in conjunction with V.A.C, there may be an opportunity to license NAOV's product to Kinetic Concepts (or KCI, which generates billions in U.S. sales of their V.A.C. NPWT device). Management's prior experience at the likes of KCI, ConvaTec and MiMedx may help in this regard. Similar opportunities might present themselves for UroShield and PainShield as it relates to the CAUTI and pain markets, respectively.

- **Pay-for-performance vs Fee-for-service reimbursement**: more payers are moving away from a fee-for-service reimbursement model to one where they pay-for-performance. While fee-for-service financially incentivizes providers to have a revolving door of patients which are never fully cured – which essentially defines "chronic" conditions, pay-for-performance does just the opposite. Pay-for-performance reimburses healthcare facilities a set amount to address a particular condition and therefore incentivizes them to provide more efficient, more effective and less costly care. So, for chronic conditions such as DFUs, providers may find the relatively low cost of WoundShield (whether used in isolation or to complement other advanced wound therapies) particularly attractive. Similarly, with insurers no longer reimbursing for hospital-acquired infections, including CAUTI (which cost the U.S. healthcare system tens of billions of dollars annually), healthcare facilities and providers have an economic interest to use the most efficacious and cost-effective means to prevent them – potentially including UroShield (either alone or in conjunction with antibiotics).

- **Pipeline product candidates**: while we believe most of the near-term growth opportunity lies with UroShield, PainShield and WoundShield, NAOV's earlier-stage pipeline, namely LungShield and RenooSkin, offer potential incremental long-term upside to both revenue and market value of the company. Given the difficulty in valuing these relatively early-stage assets, they are not included in our initial (i.e. current) valuation – but that could change with substantive development progress of either.

- **Leadership with relevant experience**: Brian Murphy was brought on as CEO in October 2016 and tasked with accelerating revenue growth. He comes with a 25-year background in sales and management at medical technology companies, largely with a focus on the advanced wound care market. This includes his most recent prior position where he was in charge of the commercial sales efforts at MiMedx Group, Inc. an innovative advanced wound care company. Earlier in his career Mr. Murphy worked at KCI and ConvaTec – both major players in the advanced wound care space.

  Chairman of the Board, Chris Fashek was former Vice Chairman and President of KCI and is credited with leading the introduction of their NPWT technology (which proved to be wildly successful). Mr. Fashek also has prior experience at other wound care focused healthcare companies including as CEO at Atteris Healthcare, Chairman at Systagenix and President/Chairman at Spiracur.

  Harold Jacob, NAOV's Chief Medical Officer (and Director and prior Chairman), is board-certified in internal medicine and gastroenterology and was also a former director at Given Imaging.

- **Manufacturing optimization and scale-up**: NAOV recently brought on Quasar, a China-based contract manufacturer of medical devices and electronics, to facilitate its expected commercial ramp-up. Quasar will manufacture PainShield, UroShield and WoundShield at its Shenzhen, China facility. We anticipate this will be

bring down production costs, enhance gross margins and afford NAOV the ability to rapidly build inventory as demand dictates.

- **Reimbursement**: NanoVibronix has indicated that securing reimbursement for UroShield, PainShield and WoundShield is a near-term goal and one that we think that, if successful, could be a significant catalyst to both generating awareness and facilitating adoption of these products. We think dedicated reimbursement could be particularly beneficial for uptake of PainShield and WoundShield given the reliance on insurance in these treatment categories.

- **Target markets are massive**: while we think the initial rather narrowly-focused market segments such as Trigeminal Neuralgia for PainShield and chronic wounds such as DFUs for WoundShield represent some of the low-hanging fruit and where initial adoption may be the most brisk, eventual use among the more general respective patient populations could represent relatively massive upside. As the 'general pain' (such as myofascial pain) market is hundreds of times the size of the TN population and the CLI population is ~20x the size of the DFU market, even 1% adoption among these broader segments would represent significant revenue for NAOV. Nonetheless, even the relatively narrowly-focused markets are substantial in size, with single-digit penetration in these populations potentially representing tens of millions of dollars of revenue for NAOV.

Model Assumptions

Our model assumptions include:

- Average selling price of the hardware and disposables of approximately $300 and $50, respectively
- Market sizes represent North America, developed Europe and, in some cases, Israel and other countries
- PainShield
    - TN
        - Target market size of ~400k people
        - Target market worth an estimated $130M
        - Once adopted, use is indefinite and each patient uses 12 patches per year
        - One percent penetration by year 2020, 2.5% penetration by 2024
    - "General pain'
        - Market size is ~235M people
        - Target market worth an estimated $30B
        - Much more sporadic use relative to TN
        - Less than 1% penetration through 2024
- WoundShield
    - Chronic wounds/DFU
        - Market size ~3M people
        - Target market worth an estimated $500M
        - Each patient requires 12 weeks of treatment and uses 3 patches
        - One-half of one percent penetration by 2022, 2.5% penetration by 2024
    - CLI / other wounds
        - Market size ~60M people
        - Target market worth an estimated $7.5B
        - Each patient requires 1 month of treatment and uses 1 patch
        - One-half of one percent penetration by 2022, less than 1% penetration by 2024
- UroShield
    - CAUTI market size of ~50k catheters
    - Target market worth an estimated $1.4B
    - One-half of one percent penetration by 2022, 2.5% penetration by 2024

Valuation

We think our above assumptions are reasonable and, arguably, conservative. We value NAOV using P/S multiple methodology applied to our forecasted revenue in 2024, representing a five-year growth runway from today. Based on the above assumptions, we look for revenue of approximately $105M in 2024. We apply a 3.5x multiple and discount back at a risk-adjusted 30% per year to arrive at **calculated current fair market value of ~$62M, or $9.00/share**. Our risk-adjusted discount rate is subject to change and could narrow with substantive operational and product development progress or could widen with operational and product development delays or failures.

FINANCIAL MODEL

NanoVibronix, Inc

	2017 A	Q1A	Q2A	Q3A	Q4A	2018 A	2019 E	2020 E	2021 E
Total Revenues	$239.0	$77.0	$132.0	$54.0	$82.0	$345.0	$581.2	$1,578.8	$5,177.0
YOY Growth	*4.4%*	*48.1%*	*153.8%*	*-16.9%*	*17.1%*	*44.4%*	*68.5%*	*171.7%*	*227.9%*
Cost of Goods Sold	$88.0	$22.0	$55.0	$46.0	$51.0	$174.0	$488.2	$607.9	$1,667.0
Gross Income	$151.0	$55.0	$77.0	$8.0	$31.0	$171.0	$93.0	$971.0	$3,510.0
Gross Margin	*63.2%*	*71.4%*	*58.3%*	*14.8%*	*37.8%*	*49.6%*	*55.2%*	*61.5%*	*67.8%*
SG&A	$2,549.0	$709.0	$751.0	$1,213.0	$1,102.0	$3,775.0	$4,652.0	$5,241.0	$6,874.0
% SG&A	*1066.5%*	*920.8%*	*568.9%*	*2246.3%*	*1343.9%*	*1094.2%*	*800.5%*	*332.0%*	*132.8%*
R&D	$693.0	$136.0	$151.0	$121.0	$131.0	$539.0	$861.0	$1,341.0	$1,587.0
% R&D	*290.0%*	*176.6%*	*114.4%*	*224.1%*	*159.8%*	*156.2%*	*148.2%*	*84.9%*	*30.7%*
Operating Income	($3,091.0)	($790.0)	($825.0)	($1,326.0)	($1,202.0)	($4,143.0)	($5,420.0)	($5,611.0)	($4,951.0)
Operating Margin	*-1293.3%*	*-1026.0%*	*-625.0%*	*-2455.6%*	*-1465.9%*	*-1200.9%*	*-932.6%*	*-355.4%*	*-95.6%*
Total Other Income (Expense)	($2,677.0)	$13.0	$11.0	($7.0)	$2.2	$19.2	$41.0	$37.2	$0.0
Pre-Tax Income	($5,768.0)	($777.0)	($814.0)	($1,333.0)	($1,199.8)	($4,123.8)	($5,379.0)	($5,573.8)	($4,951.0)
Tax expense (benefit)	$38.0	$12.0	$10.0	$11.0	$10.0	$43.0	$53.8	$78.0	$89.1
Tax Rate	*-0.7%*	*-1.5%*	*-1.2%*	*-0.8%*	*-0.8%*	*-1.0%*	*-1.0%*	*-1.4%*	*-1.8%*
Net Income	($5,806.0)	($789.0)	($824.0)	($1,344.0)	($1,209.8)	($4,166.8)	($5,432.8)	($5,651.9)	($5,040.1)
YOY Growth	*105.1%*	*-109.3%*	*-1.6%*	*-15.5%*	*-7.4%*	*-28.2%*	*30.4%*	*4.0%*	*-10.8%*
Net Margin	*-2429.3%*	*-1024.7%*	*-624.2%*	*-2488.9%*	*-1475.4%*	*-1207.8%*	*-934.8%*	*-358.0%*	*-97.4%*
EPS	($1.17)	($0.12)	($0.13)	($0.21)	($0.19)	($0.65)	($0.74)	($0.66)	($0.55)
YOY Growth	*89.1%*	*-136.2%*	*-16.2%*	*-52.0%*	*-7.0%*	*-44.6%*	*14.3%*	*-10.2%*	*-17.6%*
Diluted Shares O/S	4,964	6,419	6,429	6,438	6,440	6,432	7,335	8,500	9,200

Brian Marckx, CFA

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LEADERSHIP

Management –

Brian Murphy
Chief Executive Officer and Director
Mr. Murphy has served as NAOV's chief executive officer and director since October 2016. Mr. Murphy has over 25 years of senior sales, operations and general management experience in medical device and medical technology companies, including ATI Medical Equipment Corporation, Mountain Medical Equipment Inc. and Healthdyne Technologies Inc. From 2012 to 2016, Mr. Murphy served in various roles at MiMedx Group, Inc., where he initiated and managed the commercial sales and national accounts efforts within the advanced wound care segment. From 2010 to 2012, Mr. Murphy was the chief executive officer of O2 Insights, Inc., a start-up wound care diagnostics company, and led the sale of the company to Systagenix Ltd. in June 2012. From 2008 to 2010, Mr. Murphy served as vice president of sales for ConvaTec and led the negative pressure wound therapy business. From 1992 to 2008, Mr. Murphy served a total of 17 years at Kinetic Concepts, Inc. (KCI) in various positions overseeing sales, operations and general management. Mr. Murphy holds a Bachelor of Arts degree in communications from Southern Illinois University.

Harold Jacob, M.D.
Chief Medical Officer and Director
Dr. Jacob has served as NAOV's chief medical officer since March 1, 2014, and as their director since September 2003. From September 2003 to February 4, 2014, Dr. Jacob served as chairman of NAOVs board of directors and from September 2003 to March 1, 2014, Dr. Jacob served as their chief executive officer. Dr. Jacob also performed the functions of a principal financial officer until April 1, 2014. Dr. Jacob is NAOV's co-founder and has worked extensively in medical device development. Dr. Jacob also served part-time as an attending gastroenterologist at Shaare Zedek Medical Center in Jerusalem, Israel from 2004 to March 2011. Since April 2011, he has been an attending physician in Gastroenterology at Hadassah University Hospital in Jerusalem, Israel. From 1999 to the present, Dr. Jacob has served as the president of Medical Instrument Development Inc., which provides consulting services to start-up and early stage companies and patents its own proprietary medical devices. From 1997 to 2003, Dr. Jacob served as director of medical affairs at Given Imaging Ltd., a company that developed the first swallowable wireless pill camera for inspection of the intestines. Dr. Jacob also formerly served as a director for Oramed Pharmaceuticals Inc., a pharmaceutical company focused on the development of innovative orally ingestible capsule medication.

Steve Brown, CPA
Chief Financial Officer
Steve Brown has served as NAOV's chief financial officer since February 2015. He is also currently serving on the Board of Directors of IDW Media Group Holdings ("IDW"), a publishing and entertainment company. Mr Brown has previously served as several executive positions including as Chief Financial Officer for IDT Corporation (NYSE "IDT") from April 1995 to January 2009 in which he oversaw the financial end of taking a start-up telecommunications company public and guided it through the spin-offs of two subsidiaries, various public offerings and bank facilities. During his tenure, Mr. Brown also served on IDT's Boards of Directors for six years, and on the Board of Net2Phone Inc. for five years. Mr. Brown was also the founder and chairman of IDT Entertainment Inc., a movie studio and media subsidiary that IDT eventually sold for a profit in excess of $225M. From 2009 to present, Steve is also a managing partner of The Mcguffin Group Financial, a financial consulting firm concentrating on advising early stage companies. He is also currently serving on the Board of Directors of IDW Media Group Holdings ("IDW") as Vice-Chairman, a publishing and entertainment company. Steve also is a partner in an accounting and tax practice, Brown, Brown and Associates. Steve received his certified public accountant license from the State of New York and is a member of the Academy of Television Arts and Sciences and serves on the Board of Directors for several educational institutions including serving on the Board of Governors for Touro College.

Itai Levinson
General Manager & Vice President, International Sales and Global Marketing
Itai Levinson joined NAOV in April 2018. Prior to joining NanoVibronix, he served as director of business development for ReWalk Robotics Ltd. (formally Argo Medical Technologies), a medical device company developing technologies to improve the quality of life for people living with lower limb disability, via the creation of market leading robotic technology. Within this role he oversaw commercial activities including leading efforts to establish and manage strategic alliances and distribution partnerships, initially in Japan, Taiwan, South Korea, and China. This was followed by the identification and contracting of new European distribution partners. His responsibilities included educating the marketplace and working closely with global key opinion leaders to increase brand and product awareness, subsequently working towards regulatory approvals in the Asian territories, defining and creating the required marketing and support tools to provide clinical training, pre-sale and post-sale support to distribution partners around the globe. Previously, he held the role of director of operations at ReWalk, where he helped build the operational infrastructure, turning a conceptual prototype into a commercially viable, regulatory approved medical device. Together with his team, he established the supply chain and defined the processes needed to prepare the device for sustainable and scalable contract manufacturing. He holds a BSc. degree in Industrial Engineering and Management from the Technion, Israel Institute of Technology and a MBA from the University of Haifa.

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