Zacks Small-Cap Research

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SANUWAVE Health (SNWV-OTC)

SNWV: Record Revenue As International Strategy Builds Momentum

We have used P/S comp as our valuation methodology – for consistency, we continue to use that. Smith & Nephew currently trades at approximately 3.5x analyst's 2019 forecasted revenue. We have SNWV generating approximately $8.5M in revenue in 2019 - based on the SNN comp 2019 P/S multiple, this values SNWV at about $0.25/share.

Current Price (04/06/17)	$0.13
Valuation	**$0.25**

OUTLOOK

Newly implemented international strategy bearing fruit and gaining momentum. Q4 2016 and FY both set new revenue records. Indications are that momentum is carrying into 2017. Entry into additional countries, relaunch in others and additional clinical evidence supporting the efficacy of dermaPACE all expected to further catalyze international sales growth.

Relative to the pursuit of FDA clearance of dermaPACE, on the Q4 '16 earnings call in early April '17 management mentioned that their most recent interaction with the U.S. regulatory agency was in late-January/early-February of this year and consisted of responding to questions and clarifications related to the filing, clinical trial data and "technical performance and labeling."

So while management did not provide specifics of the questions or other inquiries from FDA, we interpreted their message to be that the process continues to move along with no particular surprises. Management did specifically mention that they have been promptly replying to all of FDA's inquiries and that they (i.e. SNWV) expect a final decision from the agency later this year.

SUMMARY DATA

52-Week High	**$0.20**
52-Week Low	**$0.03**
One-Year Return (%)	**139.22**
Beta	**0.30**
Average Daily Volume (sh)	**208,761**
Shares Outstanding (mil)	**139**
Market Capitalization ($mil)	**$18**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**23**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**N/A**
Industry	**Med Products**

ZACKS ESTIMATES

Revenue
(in 000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	269 A	203 A	256 A	648 A	1,376 A
2017	185 E	244 E	482 E	637 E	1,548 E
2018					3,924 E
2019					8,421 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.02 A	-$0.01 A	-$0.01 A	-$0.02 A	-$0.06 A
2017	-$0.01 E	-$0.01 E	-$0.01 E	-$0.01 E	-$0.03 E
2018					-$0.02 E
2019					-$0.02 E

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

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Q4 Results, Operational Update: *Re-Igniting International Biz As Await FDA Decision on De Novo…*

SANUWAVE announced fourth quarter financial results and provided a business update. **On the financial side**, revenue set a new record - as expected following the company's January preannouncement. While we continue to expect revenue in the near-term to be susceptible to lumpiness as the company further broadens its international footprint – which could encompass adding up to ten new regions/distributors throughout 2017 – we also think that annualized revenue will continue to march higher.

On the operational front – management talked about several new or expanded initiatives on the call aimed at both broadening the potential market for dermaPACE as well as promoting adoption of their flagship device. In addition to expanding their international presence, this includes the initiation of additional clinical studies in non-DFU related medical indications. Management also provided an update to the de novo filing seeking Class II classification of dermaPACE by FDA – while SNWV is keeping details tight to the chest, they did indicate that they process remains on-track, that interaction between them and the agency (including recent requests for additional information) is fluid and that they continue to expect to hear a final decision sometime this year.

Record Revenue…
Q4 2016 revenue was $648k, representing sequential and yoy growth of 153% and 74%, respectively, and setting a new record. For the full year, revenue was $1.38M, also a record and up 43% from 2015. Management noted on the call that they sold twice the number of machines in 2016 as they did the prior year. Much of the growth is related to an increase in sales of orthoPACE devices in S. Korea – management outlined their focus to further build on their momentum in that country and expects sales there to again steepen later this year.

The uptick in international orders appears to be coming from the fruits of SNWV's recently implemented higher-touch strategy with their third-party distributors. As a reminder, the company recently adopted a more interactive role with their distribution partners in order to better understand and respond to the dynamics and intricacies of each of their OUS markets with the ultimate goal of growing international revenue.

They are further building on this strategy, which included the recent (February) hiring of Andre Mouton, an experienced sales director to lead their international sales efforts. Mr. Mouton has apparently been busy as the company is aiming to add an additional 7 – 10 distributors in the course of 2017, 3 – 5 of which he thinks will be on board by late Q2. We discuss the company's re-ignited international strategy in more detail below.

Q4 OpEx was $1.0M, roughly inline with our estimate. And while G&A jumped about 45% sequentially from Q3 '16, all and more of the increase looks to be related to (non-cash) stock compensation.

Cash…
Cash used in operating activities was $490k ($196k ex-changes in working capital) and $3.2M ($2.7 ex-changes in wc) in the three and twelve months ending December 31, 2016. Cash balance was $134k at year-end. Subsequently the company received approximately $77k from warrant exercises. SNWV expects monthly cash burn in to average $175k - $225k in 2017. We continue to expect the company to look to raise additional cash via the sale of equity or debt or potentially through one or more partnering arrangements.

FDA Pathway Update…
While management noted that they will continue to follow their policy of disseminating any material news as it relates to their quest towards FDA clearance of dermaPACE via press releases, they did provide a brief update on the status of their de novo filing with FDA on the Q4 call. As a reminder SNWV filed their de novo application on July 23, 2016 requesting that dermaPACE be classified as a Class II device. On the earnings call earlier this week management mentioned that their most recent interaction with the U.S. regulatory agency was in late-January/early-February of this year and consisted of responding to questions and clarifications related to the filing, clinical trial data and "technical performance and labeling."

So while management did not provide specifics of the questions or other inquiries from FDA, we interpreted their message to be that the process continues to move along with no particular surprises. Management did specifically mention that they have been promptly replying to all of FDA's inquiries and that they (i.e. SNWV) expect a final decision from the agency later this year.

Recall that during SNWV's Q3 '16 earnings call (November '16) that management noted that they expected to hear from FDA by the end of January '17 in the form of additional questions (which occurred as expected). As we noted since SNWV's announced de novo filing, it is not uncommon that FDA's response to de novo filings happens much later than their intended goal of 120 days - in fact average review time for de novo applications in 2014 and 2015 was almost 400 days. So, applying that ~400-day average to SNWV's filing, would put a final FDA decision somewhere around the end of August 2017 – while that timeline is just a hypothetical at this point, it provides some context around intended versus actual decision timelines.

See our Appendix for refresher on dermaPACE U.S. pivotal studies as well as the de novo filing.

In The Meantime….
In the meantime SNWV is powering ahead with its newly revamped and again recently updated strategy aimed at growing international sales. As noted, most recently this included the hiring of Mr. Mouton to lead their international efforts who expects to bring on an additional 7 – 10 international distributors/territories over the course of 2017, including 3 – 5 by the end of Q2. S. Korea has recently developed into a more substantial territory for the company and while SNWV does not break out revenue by geography, the implication is that S. Korea was likely the most significant catalyst to 2016 revenue growth. Reimbursement in S. Korea, which management indicated could materialize later in 2017, could provide another boost to adoption in that country.

International strategy involves targeting key opinion leaders to help drive adoption. Management noted that it typically takes about 3 – 9 months after a new distributor/territory comes online to be able to assess the potential of the launch and before any significant related revenue may be generated. As such, assuming SNWV does bring on the number of new territories that they hope to during the current year, much of the revenue benefit may not be realized until 2018. Nonetheless, management noted on the Q4 call that they expect revenue to begin to pick up towards the end of Q2 of this year and expect 2017 to set a new record in total revenue.

In Parallel…
In parallel to broadening their geographic footprint SNWV will also look to expand the indicated uses for their device. In that vein they have several clinical studies that have either recently initiated or are expected to do so in the near-term. One or more of these studies could have results published by the end of 2017. These include:

- **Belgium DFU Home Care study**: SNWV has partnered with Ortho-Medico, their distribution partner for the Benelux region, in sponsoring a clinical trial evaluating dermaPACE in the treatment of diabetic foot ulcers in the home-care setting. The trial, which recently commenced enrollment, is being conducted by the Free University of Brussels and UZ Brussel (University Hospital) and is expected to include ~100 DFU patients randomized to either dermaPACE or standard-of-care. As all patients will be treated in-home (i.e. outside the clinic/hospital), results of the study are expected to help broaden the potential international customer base to users such as home-health professionals and organizations. As DFU patients often have significant mobility limitations and challenges, trips to the hospital for treatment can present substantial hardship. As such, we think home-health could be a particularly attractive segment for dermaPACE and one that results of this study, assuming positive, could help SNWV to exploit.
- **Australian Venous Leg Ulcer studies**: SNWV's Australian distributor, in collaboration with researchers in Melbourne, has participated in several case studies using dermaPACE in venous leg ulcers. Management noted on the Q4 call that they expect feedback from these studies by the end of 1H '17.
- **U.S. studies**: In addition to DFU, SNWV is investigating the use of their technology in the healing of post-operative scars and in improving vascularization – both of which lend themselves to the dermaPACE's method of action – that is promotion of blood flow and related healing. While these studies are still in the early planning stages, management did offer some general information on the Q4 call - including that the post-op scarring program may initially involve patients undergoing elective cosmetic surgery (such as tummy-tucks) with each patient representing both treatment and control arms (e.g. one incision scar would be treated with dermaPACE, while the other would receive standard-of-care). If deemed successful, larger studies could follow – including potentially overseas.

  While SNWV did not specifically mention that cosmetic surgery would be their intended end-market for such a potential post-op scarring indication, we think that it could represent a significant market. We note that the aesthetic/cosmetic medical device space has been particularly hot as of late – evidenced in part by the February 2017 announcements that Allergan (AGN) will acquire ZELTIQ Aesthetics (ZLTQ) and Hologic (HOLX) will acquire Cynosure (CYNO). Based on our research (we cover VIVE and MRLB, both aesthetic medical device companies) much of the growth of the aesthetic space (according to the American Society of Plastic Surgeons, the number of cosmetic procedures performed in the U.S. has grown 115% since the year 2000) relates to the fact that aesthetic procedures are largely patient-pay, non-reimbursable which affords clinics the benefit of virtually no exposure to denied insurance claims or otherwise uncollectable or aged

accounts receivables. It can also provide a supplemental source of revenue for healthcare providers. And it is not just the U.S. that is seeing an increase in these types of procedures. In fact, according to ISAPS, S. Korea (i.e. SNWV's most important international territory) ranks 3rd (behind only the U.S. and Brazil) in the total number of cosmetic/aesthetic procedures performed each year.

Model update:

While FDA's target turn-around for a de novo decision is 120 days, history suggests it may not be until late this Summer (or even later) until SNWV hears a final decision. As such we assume dermaPACE receives FDA clearance in late 2017. We now assume it launches in the U.S. in 1H 2018. And while we think the de novo pathway makes sense based on the reasons we cite, given the ambiguity in terms of FDA's decision-making process along with other unknowns including anything that may be unique to the switch from PMA to de novo, we are maintaining a high (i.e. 70% sales haircut) revenue discount.

We believe that our assumed, yet risk-adjusted, eventual FDA clearance/approval is a reasonable assumption given FDA's continued engagement with SNWV, strong safety profile of dermaPACE, significant efficacy on 100% wound closure in the combined data as well as efficacy in sub-groups (even at 12 weeks), on secondary measures and less invasive nature of dermaPACE compared to other DFU therapies.

Our 70% haircut represents risk that dermaPACE fails to gain regulatory approval as well as certain operational risks including failure to raise additional capital, slow adoption of dermaPACE upon launch and insufficient sales/marketing capabilities (whether that be in-house or via 3rd party distribution), among others. **Additional positive and tangible headway towards approval as well as mitigation of other operational risks would likely warrant a reduction in this risk discount (and would likely benefit our price target).** We have dermPACE launching in the U.S. in 1H 2018. We model 2019 (the first full year that dermaPACE is in U.S. market) U.S. revenue of $16.8 – which equates to $5.0M with the risk discount.

We had not previously and still do not incorporate any potential contribution from non-medical applications or expansion of the U.S. label in additional indications including (for example) post-op scarring. This is also subject to updating and is contingent upon further development progress, solidifying proof-of-concept and additional progress towards eventual commercialization – whether organically or via licensing / partnering. It is also possible SNWV looks to just monetize the related IP – which also holds potential promise for revenue, or at least financing upside. To be clear, we think certain of these non-medical applications and expansion of the medical-related label may have real and, potentially significant value and we continue to remain encouraged by the recent development and validation progress – but we still feel it is too early to assign an estimated value – whether on a related-revenue or related-monetization basis.

Our modeled revenue also consists of OUS sales of ortho/dermaPACE. We think it is reasonable to assume that management's recent efforts to grow ex-U.S. sales via new distribution agreements and entry into new geographically territories can pay additional dividends in the form of a steepening of the overseas revenue curve. We have OUS sales growing from about $1.4M in 2016 to approximately $3.4M in 2019.

We have used P/S comp as our valuation methodology – for consistency, we continue to use that. Smith & Nephew currently trades at approximately 3.5x analyst's 2019 forecasted revenue. We have SNWV generating approximately $8.5M in revenue in 2019 - based on the SNN comp 2019 P/S multiple, this values SNWV at about $0.25/share.

FINANCIAL MODEL

SANUWAVE Health, Inc.

	2015 A	Q1A	Q2A	Q3A	Q4A	2016 A	Q1E	Q2E	Q3E	Q4E	2017 E	2018 E	2019 E
Total Revenues	$965.5	$269.3	$203.4	$255.7	$647.7	$1,376.1	$184.7	$244.0	$482.0	$637.0	$1,547.7	$3,924.0	$8,421.0
YOY Growth	*13.3%*	*26.0%*	*-15.2%*	*78.0%*	*74.3%*	*42.5%*	*-31.4%*	*20.0%*	*88.5%*	*-1.6%*	*12.5%*	*153.5%*	*114.6%*
Cost of Revenues	$285.0	$73.2	$78.0	$98.7	$315.3	$565.1	$74.99	$92.7	$180.3	$235.1	$583.0	$1,393.0	$2,795.8
Gross Income	$680.5	$196.1	$125.4	$157.0	$332.4	$810.9	$109.7	$151.3	$301.7	$401.9	$964.7	$2,531.0	$5,625.2
Gross Margin	*70.5%*	*72.8%*	*61.7%*	*61.4%*	*51.3%*	*58.9%*	*59.4%*	*62.0%*	*62.6%*	*63.1%*	*62.3%*	*64.5%*	*66.8%*
R&D	$2,172.9	$310.0	$476.2	$266.5	$76.0	$1,128.6	$218.0	$244.0	$218.0	$297.0	$977.0	$1,854.0	$2,026.0
% R&D	*225.0%*	*115.1%*	*234.1%*	*104.2%*	*11.7%*	*82.0%*	*118.0%*	*100.0%*	*45.2%*	*46.6%*	*63.1%*	*47.2%*	*24.1%*
SG&A	$2,735.1	$499.1	$589.9	$645.9	$938.9	$2,673.8	$624.0	$632.0	$784.0	$821.0	$2,861.0	$3,421.7	$5,936.8
% G&A	*283.3%*	*185.3%*	*290.0%*	*252.6%*	*145.0%*	*194.3%*	*337.8%*	*259.0%*	*162.7%*	*128.9%*	*128.0%*	*87.2%*	*70.5%*
Depreciation	$3.6	$0.8	$0.8	$1.6	$16.6	$19.9	$16.6	$16.6	$16.6	$16.6	$66.4	$75.0	$75.0
Amortization	$306.7	$76.7	$76.7	$76.7	$76.7	$306.8	$76.7	$76.7	$76.7	$76.7	$306.8	$40.0	$45.0
Write down of assets	($100.0)	$0.0	$0.0	$0.0	($1.6)	($1.6)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($4,437.8)	($690.5)	($1,018.2)	($833.6)	($774.3)	($3,316.5)	($825.6)	($818.0)	($793.6)	($809.4)	($3,246.5)	($2,859.7)	($2,457.6)
Operating Margin	*-459.6%*	*-256.4%*	*-500.6%*	*-326.1%*	*-119.5%*	*-241.0%*	*-447.0%*	*-335.3%*	*-164.6%*	*-127.1%*	*-209.8%*	*-72.9%*	*-29.2%*
Total Other Expense	($372.5)	($1,034.1)	($104.0)	($306.2)	($1,677.3)	($3,121.5)	($234.0)	($275.0)	($313.0)	($355.0)	($1,177.0)	($1,275.0)	($1,300.0)
Pre-Tax Income	($4,810.2)	($1,724.6)	($1,122.1)	($1,139.8)	($2,451.5)	($6,438.0)	($1,059.6)	($1,093.0)	($1,106.6)	($1,164.4)	($4,423.5)	($4,134.7)	($3,757.6)
Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	($4,823.7)	($1,721.6)	($1,127.8)	($1,142.1)	($2,465.5)	($6,456.9)	($1,059.6)	($1,093.0)	($1,106.6)	($1,164.4)	($4,423.5)	($4,134.7)	($3,757.6)
YOY Growth	*-19.5%*	*46.9%*	*-25.9%*	*1.4%*	*145.9%*	*33.9%*	*-38.5%*	*-3.1%*	*-3.1%*	*-52.8%*	*-31.5%*	*-6.5%*	*-9.1%*
Net Margin	*-499.6%*	*-639.2%*	*-554.5%*	*-446.7%*	*-380.7%*	*-469.2%*	*-573.7%*	*-448.0%*	*-229.6%*	*-182.8%*	*-285.8%*	*-105.4%*	*-44.6%*
EPS (continuing ops)	($0.08)	($0.02)	($0.01)	($0.01)	($0.02)	($0.06)	($0.01)	($0.01)	($0.01)	($0.01)	($0.03)	($0.02)	($0.02)
Diluted Shares O/S	63,025	75,220	102,646	115,529	137,084	107,620	138,700	145,000	167,000	194,000	161,175	195,000	220,000

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APPENDIX

De Novo Refresher

Pursuing De Novo U.S. Regulatory Pathway, Filing Made July 2016, Responded to Questions Jan 2017 …
On the Q1 '16 call in May 2016 management noted that, following their meeting with FDA, that they were in the process of putting together a PMA filing and at that time were anticipating the submission would be made in June or July. Clearly SNWV decided to consider alternative options and, apparently after additional consultation with MCRA, abandoned the PMA route in favor of the de novo pathway. On August 11th 2016 they announced that they submitted a de novo filing to FDA (on July 23rd) requesting that dermaPACE be classified as a Class II device. SNWV had noted previously that they were expecting a response from the agency in Q4 2016 but on the Q3 call (on November 10th) mentioned that they expected to hear back from FDA in January 2017 – also noting that they expected FDA's response would be in the form of additional questions.

On the Q4 '16 earnings call in early April 2017 management mentioned that their most recent interaction with the U.S. regulatory agency was in late-January/early-February of this year and consisted of responding to questions and clarifications related to the filing, clinical trial data and "technical performance and labeling."

So while management did not provide specifics of the questions or other inquiries from FDA, we interpreted their April 2017 message to be that the process continues to move along with no particular surprises. Management did specifically mention that they have been promptly replying to all of FDA's inquiries and that they (i.e. SNWV) expects a final decision from the agency later this year.

Our Comments:

De Novo primer: FDA created the de novo pathway in an effort to help streamline approval of novel, low-to-moderate risk medical devices. Prior to de novo the only route for new devices and for which there was not an acceptable predicate, regardless of their risk profile, was the relatively long, arduous and costly PMA process. In other words, novel, low risk devices were, by default, considered Class III, or high risk, medical devices if a similar device had not already been approved by FDA (i.e. lack of predicate excluded 510(k) route).

The 510(k) de novo pathway was created as part of the FDA Modernization Act of 1997 which was meant to streamline the review and approval process for novel, low-risk devices but was so cumbersome (and nonsensically requires the petitioner to first file a 510(k) then for FDA to respond with a 'Not Substantially Equivalent" (i.e. no predicate) letter before it can be refiled as a straight de novo) and time consuming that it was hardly ever used.

The FDA Safety and Innovation Act of 2012 brought a significant change by creating the direct de novo pathway which does not require an initial 510(k) filing. Instead an applicant can directly apply for their device to be considered a Class I or Class II device (with general or general and special controls).

Why SNWV's pivot from PMA to de novo? FDA has some discretion in the criteria and information that they use and how they apply that in determining whether a particular device should be cleared for sale. While this creates some ambiguity in terms of their decision-making process, there is no question that an acceptable benefit-risk profile is of paramount importance. The following document sheds some light on how FDA applies the risk-benefit tradeoff for the PMA pathway and for the de novo pathway.

Per FDA's, "Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications",

> *FDA determines whether PMA applications provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors. To aid in this process, PMA applicants submit valid scientific evidence, including one or more clinical investigations where appropriate, which FDA reviews to determine whether "the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device." FDA staff review the data submitted as part of the PMA application and determine – based on a number of factors – if the data support the claims made by the sponsor concerning clinically significant results from the device, i.e., intended use and indications for use, and if the data analysis demonstrates that the probable benefits of the device outweigh its probable risks.*

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A balanced consideration of probable benefits and probable risks is an essential part of FDA's determination that there are reasonable assurances of safety and effectiveness.

Regarding the de novo pathway it goes on to say,

Because devices classified under this pathway (de novo devices) are low to moderate risk devices, they may not need to confer as substantial a benefit to patients in order to have a favorable benefit-risk profile. Devices granted marketing authority under de novo petitions should be sufficiently understood to explain all the risks and benefits of the device such that all risks can be appropriately mitigated through the application of general and/or special controls to provide reasonable assurance of safety and effectiveness.

If the primary endpoint (statistically superior difference in 100% wound closure at 12 weeks) had been met using the combined (pivotal plus supplemental clinical trials) study data, SNWV would have filed a PMA application. But the primary endpoint was not met. While the clinical data shows an efficacy signal, including significance on 100% wound closure at 20 weeks and, with certain sub-groups (such as high BMI patients), at 12 weeks, we think SNWV concluded (based on advice from MCRA, and potentially from feedback from FDA) that the benefit (i.e. efficacy), as interpreted by FDA under the PMA pathway, was not strong enough to support PMA approval. Or at least, not strong enough for approval without first going through a panel review – a process which would be drawn out and which could still result in a not approvable response.

By pursuing the de novo pathway, SNWV shifts more of the emphasis to the strong safety profile of dermaPACE, essentially lowering the approval hurdle given that, per FDA's guidance above, Class II devices "may not need to confer as substantial a benefit to patients in order to have a favorable benefit-risk profile".

As a reminder safety has been a non-issue. There was not a statistically significant difference in safety between the dermaPACE and control arms in the pivotal or supplemental study or when the data was combined with Bayesian analysis. In the combined data, 73.2% of dermaPACE subjects reported adverse events compared to the control's 68.9% (p=0.338). 55.8% of subjects saw treatment-emergent adverse events versus the control's 51.2% (p=0.444). Differences were not statistically significant.

We think the de novo pathway makes sense given dermaPACE's strong safety profile and the fact that FDA had previously communicated to SNWV that they will consider the totality of the efficacy data. As we have outlined in our discussion of the combined studies' results, there is an obvious efficacy signal. Another point in dermaPACE's favor, which relates to safety and lack of adverse events, is the non-invasive nature of the device – which would provide an alternative to other relatively invasive DFU therapies including negative pressure and skin substitutes.

Other considerations of de novo pathway:

- Review Time: For PMA's FDA's stated goal is to review and make an approval decision within 180 days. For direct de novo applications their stated goal is to make a determination within 120 days. In reality, however, FDA's turnaround time for both pathways is typically much longer than their cited respective timeline goals. PMA applications over the last few years have, on average, taken 15 – 18 months for the FDA to make a decision. And while one of the potential benefits that FDA has cited for the creation of the de novo pathway was reduced review and approval times, according to a study[1] by Hogan Lovells U.S. LLP, average review time for de novo applications in 2014 and 2015 was almost 400 days – while better than average PMA review time, this suggests SNWV may not hear a final decision until late Summer 2017.

- Competitive considerations: assuming dermaPACE is cleared for sale as a Class II device, it potentially opens the door for competitors to cite it as a predicate device under a 501(k) clearance pathway. However, in reality it may not be that straightforward given the proprietary nature of SNWV's technology, the relative robustness of the randomized clinical trial design and supporting clinical data (notwithstanding the missed primary endpoint) and the special controls (required for a Class II submission) which may provide enough differentiation to thwart any competitors' attempts to claim "substantial equivalence" to dermaPACE. In addition, if SNWV were to successfully expand the label (for example to include other types of chronic wounds), precedent has suggested that FDA may disallow the 510(k) pathway for any competitors (that

[1] http://www.meddeviceonline.com/doc/the-de-novo-classification-process-a-work-in-progress-0001

were successful in citing dermaPACE as a predicate for chronic DFU) seeking the same indication to follow de novo.

- Wasn't an option until 2012: SNWV's pivotal dermaPACE study commenced in 2007 and the third and final module of the PMA filing was made in July 2011. The direct de novo pathway was not an option until July 2012. It's possible that SNWV would have initially chosen the direct de novo route had it been available.

- Switching from PMA to de novo: given the uniqueness of the situation, we do not know if the late-hour switch from PMA to de novo presents the potential for any distinct administrative or regulatory issues with FDA. We assume, however, that MCRA has already addressed anything that may relate to this and has enough comfort of the viability of switching to the de novo pathway

- Lower regulatory burden, cost: the de novo route may provide some relief to the regulatory burden as compared to PMA. While panel review was a real possibility with PMA, there is less likelihood that FDA will convene a panel with de novo. De novo submissions do not require the applicant to pay a user fee and typically will not require post-marketing studies (although the latter can be on a case-by-case basis). And, perhaps, most significant as it relates to regulatory burden is that if SNWV seeks in the future to expand the dermaPACE label, de novo clearance is much more streamlined than if PMA was pursued

Trial Data Refresher

U.S. dermaPACE Update: Combined data hit 100% closure @ 20, 24 weeks but supplemental trial missed on these measures. Promising sub-group and secondary data…

Additional supplemental clinical study and combined data (i.e. when the pivotal and supplemental data were combined using FDA-agreed Bayesian analysis) were announced in March 2016. As a reminder, 100% wound closure at the 12-week follow-up was the primary endpoint in both the pivotal and supplemental studies. Both studies failed to meet this. A subsequent meeting with FDA revealed that the agency was open to considering the totality of the data to support an efficacy claim in a future regulatory filing. As the pivotal study had shown statistical significance of 100% wound closure at 20 weeks, SNWV analyzed the combined data using that timepoint, as well as at 24 weeks, as a proxy for the primary endpoint.

In October 2015 the company announced that while the supplemental study did not hit statistical significance of 100% wound closure at 20 weeks, the combined data did. We noted that that was a highly promising development as had the combined data not shown statistically superior efficacy of dermaPACE over sham at the 20-week mark, that it was our opinion that the device would have had little to no chance of eventually gaining FDA approval/clearance. And, importantly, safety has not been an issue in either of the studies or when the studies were analyzed together.

On March 24th SNWV announced additional clinical data, through 24 weeks, related to both 100% wound closure as well as secondary endpoints and other potentially relevant results. Particular points of interest in the most recent announcement include;

100% wound closure:

- on combined analysis (i.e. data from both studies analyzed together) dermaPACE showed statistically significant superior efficacy over sham control in 100% wound closure at 24 weeks (in addition to the prior data which showed the same at 20 weeks)
    - 20 weeks: 35.5% dermaPACE vs. 24.4% control, p=0.027
    - 24 weeks: 37.8% dermaPACE vs. 26.2% control, p=0.023
    - In addition, management noted that there was a trend of superior efficacy of dermaPACE in wound closure beginning around week 14
    - 12 weeks: while more dermaPACE patients achieved 100% wound closure at 12 weeks as compared to sham control (22.7% vs. 18.3%), the difference was not statistically significant (p=0.32)
- supplemental study: dermaPACE was not statistically different than that of sham control in 100% wound closure at 20 weeks (p=0.339) or 24 weeks (35.4% vs 26.2%, p=0.254)

Secondary endpoints and other relevant analysis:

- Rate of healing: combined data showed approximately 25% of dermaPACE patients reached wound closure by week 12 (i.e. final follow-up of primary endpoint). The same percentage (25%) in the sham control group did not reach wound closure until day 112 (i.e. end of week 16)
    - combined data showed a statistically significant difference (p=0.0346) through 24 weeks favoring dermaPACE in the time to wound closure
- Wound area reduction: combined data showed statistically significant reduction in wound area favoring dermaPACE. The average wound area reduction in dermaPACE subjects was 1.92cm2 compared to 0.16cm2 in the control group at 24 weeks (p=0.047)
    - combined data showed a statistically significant difference in wound area reduction favoring dermaPACE from the week-six follow up through the end of the study
    - achievement of 50% wound area reduction also favored dermaPACE, although this just missed statistical significance at both 12 and 24 weeks
        - 66.9% of dermaPACE patients achieved at least a 50% decrease in wound size at 12 weeks compared to 60.4% in the control group (p=0.0554)
        - 70.4% of dermaPACE patients achieved at least a 50% decrease in wound size at 24 weeks compared to 61.6% in the control group (p=0.0899)
- Wound expansion: combined data showed statistically significant superior efficacy of dermaPACE compared to control in prevention of wound expansion. dermaPACE demonstrated superior results in the prevention of wound expansion (≥ 10% increase in wound size) over the course of the study at 12 weeks (18.0% versus 31.1%; p=0.005, respectively). While this trend continued through 24 weeks, the difference did not remain statistically significant
- Amputations: at 24 weeks, the limb amputation rate of the target ulcer was 2.3% for dermaPACE versus 3.0% in the control group. While the difference was not statistically different (p=0.745), the trend did favor dermaPACE and, given that amputations are relatively rare, the study would have needed to be much larger to demonstrate statistical difference in amputations
- Recurrence rates: combined data showed that at 24 weeks 92.3% of dermaPACE subjects who demonstrated wound closure did not have a recurrence of DFU versus 88.4% in the control group. Again, while not statistically different (p-value=0.490), the trend in recurrence rate did favor dermaPACE. But, perhaps more important is that this 92.3% non-recurrence rate (which is similar to the 95.5% non-recurrence rate of the pivotal dermaPACE study) compares very favorably to recurrence rates in clinical studies as high as 19% and 40% of Dermagraft and Apligraf, respectively. These are (relatively invasive and costly) skin substitutes used to treat DFU and potential competitors to dermaPACE.

Demographic sub-group analysis: a deeper dive was done to flesh out any differences-of-interest in results based on patient demographics. This could be relevant to design of potential follow-up studies

- **Height:** combined data showed statistically significant superior efficacy of dermaPACE compared to sham control (30.0% vs 14.1%) in 100% wound closure at 12 weeks with patients measuring 70 inches and taller
- **Age, BMI, height, sex:** while the combined data did show statistically superior efficacy of dermaPACE over sham control at 24 weeks, there were sub-populations in which efficacy of dermaPACE was even more pronounced. Patients younger than 65 years, body mass index (BMI) less than 32, height greater than or equal to 70 inches, and male subjects all had success rates statistically significantly higher than the control group (p = ≤ 0.050).

Safety remains a non-issue: there was not a statistically significant difference in safety between the dermaPACE and control arms in the pivotal or supplemental study or when the data was combined with Bayesian analysis. In the combined data, 73.2% of dermaPACE subjects reported adverse events compared to the control's 68.9% (p=0.338). 55.8% of subjects saw treatment-emergent adverse events versus the control's 51.2% (p=0.444). Differences were not statistically significant.

Assuming FDA does consider the totality of the data, there is reason to be hopeful that there is a pathway towards eventual U.S. marketing approval…

- while the supplemental study did not demonstrate an efficacy difference of dermaPACE versus sham control (i.e. standard of care) on the 100% wound closure measure for the entire trial population, it did show a statistically superior difference on this measure in those patients with a BMI of less than 32 (i.e. – less obese patients)

- the pivotal study as well as the combined data showed statistically superior efficacy of dermaPACE compared to sham control at both 20 and 24 weeks.
- combined data showed statistically significant superior efficacy of dermaPACE compared to sham control (30.0% vs 14.1%) in 100% wound closure at 12 weeks with patients measuring 70 inches and taller
- there were sub-populations in which efficacy of dermaPACE was even more pronounced at 24 weeks. Patients younger than 65 years, body mass index (BMI) less than 32, height greater than or equal to 70 inches, and male subjects all had success rates statistically significantly higher than the control group ($p = \leq 0.050$).
- there was also statistically significant differences or at least trends favoring dermaPACE over control in rates of healing, wound area reduction, prevention of wound expansion, amputations and recurrence rates. Recurrence rates of both dermaPACE studies also compare favorably to clinical studies of Dermagraft and Apligraf
- safety has consistently been a non-issue with dermaPACE. All other leading DFU therapies (skin substitutes, gels and VAC) are more invasive and susceptible to greater safety risks. As FDA must weigh risk and reward when considering approval of a novel therapy, dermaPACE's relatively low risk profile could work to lower its respective efficacy hurdle. By pursuing the de novo pathway, SNWV shifts more of the emphasis to the strong safety profile of dermaPACE, essentially lowering the approval hurdle given that, per FDA's guidance, Class II devices "may not need to confer as substantial a benefit to patients in order to have a favorable benefit-risk profile"
- one-size may not have to fit all with FDA. While 100% wound closure at 12 weeks has been the recent historical standard by which FDA has judged efficacy of DFU therapies, the fact that the agency continues to entertain the possibility of a pathway of approval for dermaPACE may mean they are open to other considerations. Given the strong safety profile of dermaPACE and less invasive nature as compared to other DFU therapies, coupled with efficacy signals in wound area reduction, rate of healing and lower recurrence, we think the de novo pathway makes sense.

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