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Daré Bioscience, Inc. (DARE-NASDAQ)

Compelling PCT Data Bolsters Ovaprene's Chances of Success. BV-1, Topical Sildenafil Also Progressing. Acquisition Adds Novel Contraceptive-Focused Tech

We use 5.0x sales and discount revenue at 20%, 15% and 10% reflecting bear, base and bull cases, respectively. Base case puts fair value of DARE at approximately $5.80/share.

Current Price (12/06/19)	$0.82
Valuation	**$5.80**

OUTLOOK

Operational highlights: compelling topline data from the Ovaprene PCT study (to support petition of FDA for approval of a pivotal registrational study), acquisition of Microchips Biotech, which brings a novel drug-delivery technology being developed for wireless admin of levonorgestrel aimed at large women's contraceptive market, anticipated design of a pivotal FDA trial of BV-1, and continued regulatory progress of Topical Sildenafil, including conclusion of content validity study in Q3'19.
As it relates to Ovaprene: compelling topline PCT announced in November, indicates near-perfect efficacy in preventing pregnancy. Barring any major surprises in the full dataset, we think these PCT Study results (in addition to prior positive human clinical data) provide substantive support for approval of pivotal study IDE and meaningfully bolsters the chances of eventual FDA approval of Ovaprene. Also, as Ovaprene represents a new class of contraception with attributes that score high on consumer surveys, it has the potential to be particularly influential at attracting (previous) non-users of contraception and increasing the proportion of people that use some form of pregnancy prevention. Regulators undoubtedly understand this, which is another reason why we like the chances of eventual FDA approval of Ovaprene.

SUMMARY DATA

52-Week High	**$3.25**
52-Week Low	**$0.60**
One-Year Return (%)	**-4.81**
Beta	**1.83**
Average Daily Volume (sh)	**235,944**
Shares Outstanding (mil)	**17**
Market Capitalization ($mil)	**$16**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**8**
Insider Ownership (%)	**17**
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 2019 Estimate	**N/A**
P/E using 2020 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in '000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2019	0.0 A	0.0 A	0.0 A	0.0 E	0.0 E
2020					0.0 E
2021					0.0 E

Earnings Per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	-$0.88 A	-$0.32 A	-$0.23 A	-$0.26 A	-$1.57 A
2019	-$0.27 A	-$0.29 A	-$0.20 A	-$0.27 E	-$1.04 E
2020					-$1.12 E
2021					-$0.94 E

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

Q3 2019 Pipeline and Financials Update

DARE has been extremely busy lately as their acquisition strategy continues in parallel with their organic product and pipeline development. They continue to make seemingly unimpeded progress on almost all of their top development programs and could have several operationally meaningful and potentially value-additive milestones upcoming. We will be eagerly awaiting updates on Ovaprene, BV-1, Topical Sildenafil, the Microchips Biotech drug delivery technology, VVA1 and the earlier stage assets and activities.

Highlights on the operational front include compelling topline data from the Ovaprene PCT study (which is expected to be used to petition FDA for approval of a pivotal registrational study), the acquisition of Microchips Biotech, which brings a novel drug-delivery technology being developed for wireless, patient operated delivery of levonorgestrel (a synthetic progestogen commonly used in IUDs and other implanted women's contraceptives) aimed at the $6B women's contraceptive market, the announced anticipated design of a pivotal FDA trial of BV-1 (DARE's bacterial vaginosis candidate), and continued progress of Topical Sildenafil through the FDA regulatory process including conclusion of content validity study in Q3'19.

Q3 2019 Financial Update

Daré (DARE) reported financial results for their third quarter and provided an operational update. Relative to the financials, operating expenses were $3.4M, slightly better than our $3.2M estimate and while up 30% from the comparable period in 2018, this is down 14% sequentially (from $4.0M in Q2'19).

R&D expense, including license fees, was $2.1M, compared to $1.5M and $2.5M in the prior-year and three-month periods, respectively. This was about 7% higher than our $1.8M estimate. We note that Q3 expenses included $113k accrual associated with the license fees related to DARE-BV1, DARE's new bacterial vaginosis candidate, and another $21k related to ($50k annual) accrual of the Juniper license fee (associated with some of DARE's earlier-stage hormone-replacement therapy programs). The year-earlier period did not include any license-related expenses while the quarter-earlier period did include $163k in license fees (as we note below, Q3'19 GAAP R&D expense also benefitted from an offset related to recent grant funding). Meanwhile, SG&A expense was $1.3M, up slightly from $1.2M in Q3'18 but flat from Q2 of this year and a hair better than our estimate.

While we continue to expect R&D expense and opex as a whole to increase with further progression of DARE's lead development programs, grant income should offset some of the anticipated near-term growth. In March DARE received Notice of Award of $983k (of an anticipated $1.9M total) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The grant is recognized as an (accrued) offset to development expenses of Ovaprene. In Q3 $231k was offset against gross R&D expense.

Cash balance was $2.4M at quarter-end – but, subsequent to quarter-end, DARE acquired Microchips Biotech Inc (which closed on or about November 11, 2019), which (among other material changes) substantially increases the (combined companies') cash position. DARE used $3.2M (or $2.3M ex-changes in working capital) of cash for operating activities in Q3'19 and $9.5M ($10.0M ex-changes in working capital) through the first nine months of the year.

Pipeline timetable snapshots and recent highlights (each program discussed in detail later in report)

>> Ovaprene timetable

- Post-coital test (PCT) commenced in May 2018
- Positive data from PCT announced in November 2019
- PCT study data expected to support IDE seeking FDA approval to conduct a pivotal randomized controlled study
- Per Q3 2019 conf call, DARE hopes to initiate Ovaprene pivotal study in 2H'20 (inline with our prior expectations)

Ovaprene recent highlights: compelling topline PCT study data was announced in November and indicates near-perfect efficacy in preventing pregnancy. Comments re: safety are somewhat ambiguous although do not suggest any significant issues. Barring any major surprises in the full dataset, we think these PCT Study results (in addition to prior positive human clinical data) provide substantive support for approval of pivotal study IDE and meaningfully bolsters the chances of eventual FDA approval of Ovaprene.

We also note that Ovaprene would represent a new class of contraception with attributes that score high on consumer surveys. As such, it has the potential to be particularly influential at attracting (previous) non-users of contraception and increasing the proportion of people that use some form of pregnancy prevention. Regulators

undoubtedly understand this, which is another reason why we like the chances of eventual FDA approval of Ovaprene.

>> Topical Sildenafil timetable

- Had Type C meeting with FDA in Q3'18 regarding development program including design of Ph2b clinical trial
- Content validity study completed in Sept 2019 (inline with expectations), setting stage for commencement of Ph2b at-home, product dosing portion
- Next step is requesting another Type C meeting with FDA for additional guidance prior to commencing at-home portion of Ph2b study
    - Type C meeting expected to happen by end of 2019
    - Ph2b study at-home portion is now not likely to begin before early 2020
- Topline data from the Phase 2b study might be available by Q4 2020

Topical Sildenafil recent highlights: content validity / patient reported outcomes study completed in Q3'19. CVS/PRO study conducted to further understand / identify the most important aspects associated with women's arousal and to help refine design of subsequent-stage trials, including choice of optimal outcome measures and how best to assess those. With CVS completed, next step is Type C meeting with FDA to discuss results for additional guidance on Ph2b at-home portion. DARE still shooting for FDA Type C meeting by 2019 YE. Study start and topline data could happen by Q1'20 and Q4'20, respectively.

A somewhat milestone-type event happened in June 2019 when FDA approved Vyleesi (bremelanotide), an injectable drug developed by Amag Pharmaceuticals (AMAG), for the treatment of HSDD in premenopausal women (Vyleesi is only the second drug approved to treat female HSDD). This is significant in our opinion and may be another sign that FDA is taking a more proactive-type approach than they might on most therapies, especially those that address non life-threatening indications (such as sexual function disorders) – we think this could bode well for DARE and Topical Sildenafil.

>> DARE-BV1 timetable

- Expect to follow 505(b)2) FDA pathway
- Submit documentation seeking FDA approval to commence Ph3 study - while had been expected in 2H'19, we think it is more likely a 2020 event
- Commence Phase 3 portion if / following IND approval – possibly a 1H'20 event
- Phase 3 study read-out in 2020
- If Phase 3 is successful, file NDA in 2020 / 2021 (we think 2021 is reasonably possible but 2020 is highly unlikely). We continue to model initial BV-1 revenue in 2022
- Extension study: if pivotal study progresses well, plan to conduct extension (i.e. marketing) study which will evaluate subjects for an additional 60 -90 days post BV1 treatment

BV-1 recent highlights: DARE outlined their anticipated regulatory pathway and provided details of the late-stage clinical strategy for their bacterial vaginosis candidate, BV-1. In addition to a pivotal (n=250) Ph3 FDA registrational study, DARE hopes to also conduct an extension study. The single Ph3 pivotal study will be used to support an eventual 505(b)(2) filing while the extension study (see pivotal and extension study designs below) is essentially to bolster the competitive proposition of BV-1 and will presumably be used for marketing (and, perhaps, reimbursement) purposes. Importantly, pivotal study design appears consistent with FDA's BV-related Draft Guidance (2016). DARE also indicated that some non-clinical studies will also be conducted in parallel with these clinical trials.

We view the pivotal + extension study strategy as a welcome surprise as while placebo design likely enhances the chances of successfully demonstrating effectiveness, it does not provide much insight into the commercial competitiveness or performance against other BV therapies. DARE's pivotal / extension study strategy provides them with the benefits of a potentially easy hurdle (i.e. vs placebo) in the pivotal FDA study and the extension study could provide some substantive insight as to how BV-1's performance stacks up against competing (and already commercially available) bacterial vaginosis treatments.

>> Microchips Biotech snapshot:

acquired in November, brings novel wireless user-controlled drug delivery technology, nearly $6M in net cash and potentially valuable intangibles. Technology has been validated in humans in osteoporosis patients and being developed for wireless delivery of levonorgestrel aimed at the women's contraceptive segment. Microchips' technology is designed to provide the unique combination of long duration (implanted for two or more years), precise dosing and ability to wirelessly turn on or turn off dosing based on an individuals' specific needs. These are potentially significant advantages, offering most of the specific benefits of each of the current class of contraceptives and little or none of the disadvantages. While DARE has yet to provide product and indication-

specific development results or anticipated milestones or related timelines, we expect some will be forthcoming now that the merger has closed.

Positive Ovaprene Topline PCT Data, Anticipating Near-Term IDE Filing

On November 12th DARE announced topline results from their post-coital test clinical study of Ovaprene, their novel non-hormonal monthly vaginal ring. While we will wait for additional details of the full study results to be released before we take a more definitive position on the strength of the data, we are encouraged by the data as well as DARE's unambiguous language in the PR related to achievement on the primary endpoint.

Per the study listing on clinicaltrials.gov (ID: NCT03598088), "The purpose of this clinical trial is to assess the ability of Ovaprene™ to prevent sperm from penetrating midcycle cervical mucus. In addition, safety, release of ingredients, acceptability and fit will be assessed." The primary outcome (i.e. endpoint) measure is, "To evaluate changes from baseline in the Post Coital Test Results (PCT) due to device use. [Time Frame: 175 Days]".

PCT studies are commonly used to evaluate contraceptive effectiveness. Finding five or fewer motile sperm per high powered field in the cervical mucus is considered demonstration of effectiveness in PCT studies as it relates to preventing pregnancy. So, five or fewer motile sperm in the cervical mucus was a goal of DARE's study as well.

Ovaprene PCT Study Design: the study compared the number of progressively motile sperm (PMS) per high powered field (HPF) found when no contraception was used (i.e. baseline) versus the number of motile sperm per HPF when Ovaprene was used. PCT tests were taken at mid-cycle (with participants completing a full menstrual cycle before progressing to the subsequent intervention). Caya diaphragm (which uses spermicide) was used as contraception in cycle 2 (i.e. following baseline cycle) of the study. In cycle 3 participants wore Ovaprene and were evaluated for safety but refrained from intercourse and in cycles 4 and 5 Ovaprene was used following intercourse.

Results: DARE notes that the PCT study met its primary endpoint with an average of less than five progressively motile sperm per high powered field found in the midcycle cervical mucus of subjects using Ovaprene collected two to three hours after intercourse. While we hope to hear additional details when the full data is released, DARE does provide some highly encouraging supporting data in the November press release which we include below.

Ovaprene PCT Study Topline Data (Nov 2019)

	Mean	Median	Standard Deviation	Interquartile Range
Baseline PCT's	27.21	23.2	17.88	24.8
Ovaprene PCT's	0.48	0	1.18	0.1

Source: data sourced from DARE 11/12/19 press release

Of the 38 women that qualified for baseline (i.e. were found to have more than five motile sperm following post-enrollment intercourse), 26 completed at least one Ovaprene PCT. Mean / median PMS/HPF of these 26 participants was 27.21 / 23.20 at baseline versus 0.48 / 0.00 following intercourse with Ovaprene. DARE also notes that mean PMS/HPF among these 26 women after intercourse with the diaphragm was 0.22 (median not disclosed).

Safety: while DARE did not provide much in the way of details on the safety assessments, they do note on the November press release that no serious or adverse events were observed. However, also mentioned was that "The safety findings in the PCT clinical study are also reassuring in that they are typical of what we would expect in a standard diaphragm study. Notably, while a diaphragm is worn only during intercourse in a standard diaphragm study, Ovaprene was worn by participants in this study continuously for about three weeks in each of three cycles"[1].

No SAEs is clearly good news but we find the other language somewhat peculiar, particularly given the lack of any further details about safety results of Ovaprene. While we think it comes across as somewhat oddly ambiguous, this part…"safety findings in the PCT clinical study are also reassuring"…certainly strongly suggests that DARE is at least satisfied with the safety results. Along with the full effectiveness data, we hope to hear more details on the safety portion as well.

[1] Christine Mauck, MD Dare Biosciences Medical Director. Dare Bio PR 11/12/19

Our take on the topline PCT data: we reiterate that will reserve more definitive judgment of the outcomes of this PCT study when we know more about the full results. That said and while only so much can be drawn from small PCT studies, we are encouraged by the data as we think it clearly shows that Ovaprene is demonstrating effectiveness in preventing pregnancy.

DARE notes that data of some currently marketed contraceptives that showed no motile sperm in their respective PCT studies have typical use (i.e. real-world use) effectiveness of 86% - 91% -- perhaps with the implication being that Ovaprene's results from this study (0.48 mean / 0.00 median PMS/HPF) might suggest that it (Ovaprene) may eventually prove to be similarly effective as those currently marketed contraceptives.

If that is indeed the implication, it's a bit premature in our opinion – although not necessarily unreasonable. More importantly, we think the key takeaways are that this topline data suggests overwhelming effectiveness of Ovaprene and implies a sizeable safety margin (for error). Average of just PMS/HPF of 0.48 is as much as 9x better than Ovaprene might presumably need to perform in a pivotal study to demonstrate that it is an effective means of pregnancy prevention – a big margin that helps to bolster our confidence of the eventual approvability of Ovaprene.

Barring any significant surprises in the full data, we think these results do add substantive support as to the effectiveness of Ovaprene and increase the likelihood of eventual FDA approval. And not withstanding our opinions about the safety related language, there has been little (from this and prior studies) that suggests any potential serious issues with Ovaprene's safety / tolerability. And as a reminder, this PCT study data builds on an earlier clinical study, which was used as further support in demonstrating human proof-of-concept. Results of that PCT study (n=20) also showed no viable sperm in the cervical mucus and that the device was well tolerated.

We also note that Ovaprene (if approved) represents a new class of contraception that unlike anything currently available, is hormone-free and provides monthly protection - attributes that score high on consumer surveys. As such, Ovaprene has the potential to be particularly influential in attracting (previous) non-users of contraception and increasing the proportion of people that use some form of pregnancy prevention. Development of new and alternative methods of contraception can be a means to reduce the number of unintended pregnancies, which account for 45% (or 2.8M) of all pregnancies in the U.S. every year. Regulators undoubtedly understand this, which is another reason why we like the chances of eventual FDA approval of Ovaprene.

So, despite some lingering questions that we have, we view these (new PCT study) results as meaningfully net positive for the eventual chances of U.S. regulatory approval of Ovaprene. And, in the meantime, we think FDA approval of an IDE for a pivotal study of Ovaprene became even more likely. In fact, barring any surprises on effectiveness or safety that confounds these topline results, we see no reasons why FDA would not approve an IDE.

If all goes well, a pivotal study for Ovaprene could be underway in 2H'20 (inline with our prior and current expectations). Pivotal study, as envisioned today, is expected to include ~250 (evaluable) participants with evaluation over 6 months (management estimates that the study may need to enroll 450 to 500 subjects to have n=250 evaluable through 6 months). Primary endpoint would be pregnancy probability as well as safety. Secondaries are likely to include user-type feedback such as ease of use, fit, comfort, etc. As noted, assuming no surprises in the full data set (we have no reason to expect that there will be), DARE hopes to initiate a pivotal study for Ovaprene in 2H 2020 (inline with our prior thinking). If all goes well, we believe an FDA PMA filing could happen in 2022/2023 and that it is possible Ovaprene could launch in the U.S. by sometime in 2023/2024.

Microchips Biotech merger (i.e. acquisition)

In November DARE closed what is effectively an acquisition of Microchips Biotech Inc., which brings that company's novel wireless user-controlled drug delivery technology, adds nearly $6M in net cash and brings other potentially valuable intangibles. The technology has been validated in humans in osteoporosis patients and is currently being developed for wireless delivery of levonorgestrel aimed at the women's contraceptive segment – an annual global market worth over $6B.

Per terms of the transaction, DARE issued three million shares of its common stock to Microchips' shareholders and is subject to paying up to $46.5M in contingent consideration related to product development, regulatory and funding milestones and another (up to) $55.0M of contingent consideration based on certain commercial development milestones. Per DARE's press release announcing the deal, they anticipate less than $1.3M of the contingent consideration will be due through 2021.

In addition to the drug delivery technology and intangible assets, Microchips brings an expected post-close net cash balance of ~$5.7M, net (i.e. $6.9M less anticipated closing costs) and assumes any liabilities. As it relates to intangibles – in addition to the more tangible intangibles such as 98 patents and 19 patent applications associated with the drug delivery technology – these include Microchips' history of scoring significant grant funding (including almost $18M from the Gates Foundation), relationships with founders of the technology and R&D history (which includes initial human testing) and experience related to development of the technology for contraceptive and osteoporosis applications. Microchips' current development programs are eligible for an additional $2.5M of Gates Foundation funding, which is expected to cover ongoing preclinical development. Microchips' President and CEO, Cheryl Blanchard, will join DARE's board of directors.

Microchips' wireless user-controlled drug delivery technology is designed to be implanted in and operated by patients, allowing for the precise delivery of hundreds of doses of medication for up to two years or more. In addition to the benefits of precision dosing, the technology is also designed to allow for automated delivery based on a preset schedule, functionality that could eliminate the guesswork associated with (and in many cases, fear of) self-administered injections. As non-compliance due to patient-related dosing errors (i.e. misdosing, failing to take medication at recommended intervals, etc) is relatively common and typically associated with poorer outcomes, Microchips' delivery technology represents a potentially significant value-add to patient health in our opinion.

The technology, which was initially developed at the Massachusetts Institute of Technology (by Robert Langer and Michael Cima), already underwent in-human proof-of-concept clinical testing in patients with osteoporosis. Current development (currently in pre-clinical stage) is focused on women's contraception, specifically delivery of (the synthetic progestogen) levonorgestrel. In contrast to current levonorgestrel-based contraceptives such as 'Plan B' (i.e. 'the day after pill') and long-lasting implants (which can remain implanted for up to five years) including (levonorgestrel-containing) IUD's and Jadelle / Implanon (levonorgestrel-releasing devices implanted under the skin on the upper arm) Microchips' technology is designed to provide the unique combination of long duration (implanted for two or more years), precise dosing and ability to wirelessly turn on/off dosing based on an individuals' specific needs.

These are potentially significant advantages, offering most of the specific benefits of each of the current class of levonorgestrel-based contraceptives and little or none of the disadvantages. These include offering the relative flexibility of Plan B (dose only when needed, potential lower exposure to and associated side effects of levonorgestrel) without the downsides of the 'day after pill' – such as risk of not taking it in time and cost / inconvenience of regular (e.g. daily) use. And while Microchips' levonorgestrel delivery solution also offers the long-duration convenience associated with IUD's and arm implants, the wireless on/off functionality means that (in addition to the flexibility it affords to family planning) users can minimize or eliminate levonorgestrel exposure and the potential for associated risks.

While DARE has yet to provide product and indication-specific development results or anticipated milestones or related timelines, we expect some will be forthcoming now that the merger has closed.

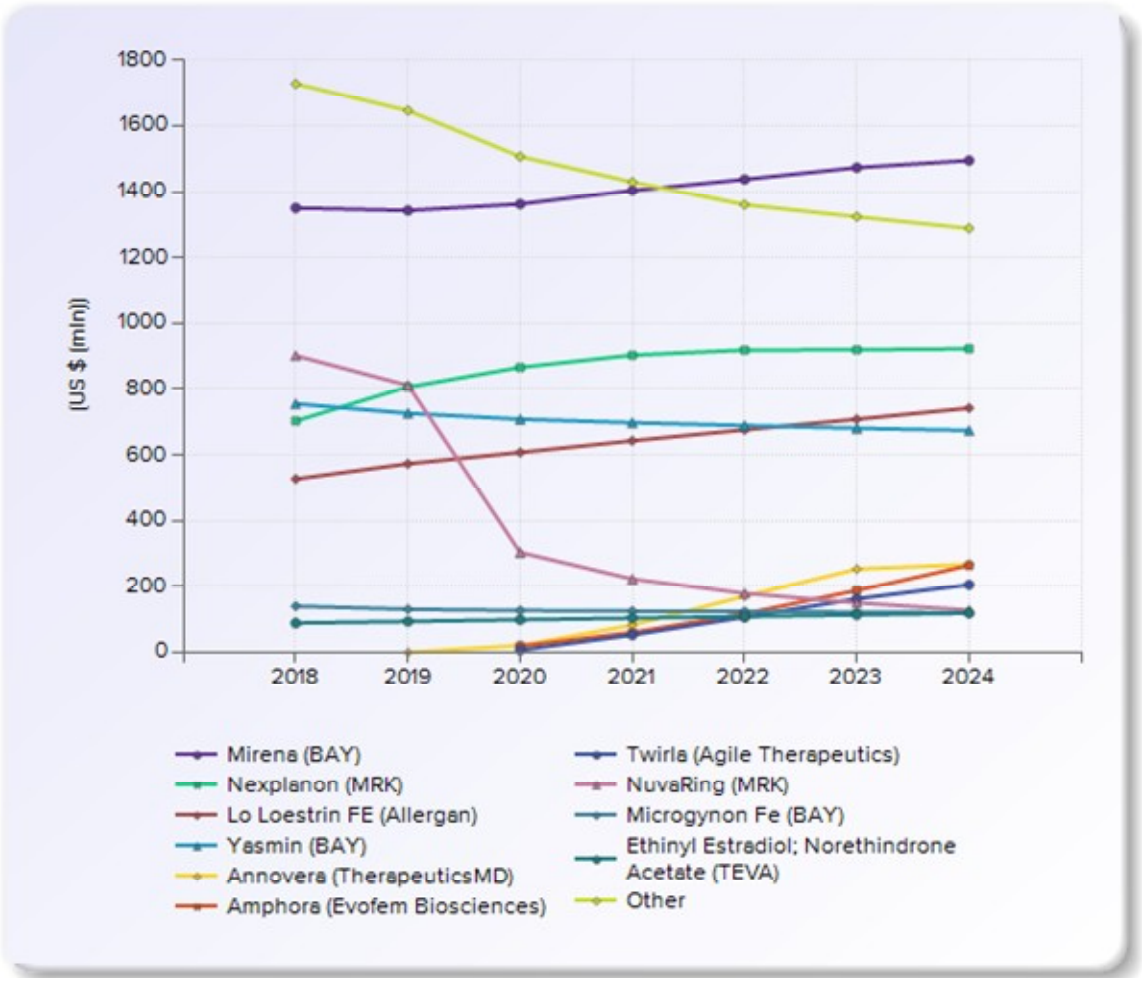
Market for implanted, patient controlled levonorgestrel delivery…

If successfully developed as currently envisioned for wireless, patient controlled levonorgestrel delivery, the technology would compete within the prescription contraceptives market, which generates more than $6B of global sales each year.[2,3] We discuss details about the composition of this broad women's contraceptive market to (hopefully) provide some context of how and where Microchips' contraceptive product might fit within it.

The top 10 highest selling products accounted for $4.5B, or 72% of total ($6.2B) Rx contraceptive global revenue in 2018 and are forecast to account for nearly 80% of forecasted total sales in the year 2024. The majority of the remaining $1.7B (28% of $6.2B) relates to hormonal birth control pills. Mirena (levonorgestrel-based IUD), with worldwide sales of $1.35B in 2018, is currently the best-selling Rx contraceptive (and with forecasted revenue of almost $1.5B in 2024, is expected to continue to be for at least the next five years).

[2] Evaluate Pharma: Rx contraceptives $6.2B global sales in 2018.
[3] Excludes revenue related to non-Rx products and procedures such as condoms and surgical sterilization

Women's Rx Contraceptives WW Sales 2018 - 2024



EvaluatePharma® [December 2019], Evaluate Ltd.

Combined global sales of all contraceptives (including IUD's, patches and implants) that contained levonorgestrel were approximately $1.6B in 2018 and forecasted to grow to $1.7B in 2024. We note that while sales of Plan B (discussed above), is not included in these figures as it is sold without prescription, they are likely not significant enough to make any meaningful difference.

As it relates to levonorgestrel-based IUD's and specifically to the U.S. market, these products currently generate almost $900M in annual sales in the U.S. and this is expected to continue to grow. Bayer, which owns the Mirena, Kyleena (which can remain implanted for up to five years) and Skyla (implanted for up to three years) brands, currently dominates the U.S. levonorgestrel IUD space.

However, new products represent much of the anticipated near-term market tailwind, which could also have some effect in altering the competitive landscape of this category. LILETTA 52mg levonorgestrel-releasing intrauterine system is the most recent addition and is expected to help catalyze the branded segment of this product category. LILETTA, developed through a collaboration between the global non-profit Medicines360 and Allergan (AGN), was originally approved in the U.S. in 2015 for up to three years protection. In October 2019 FDA approved LILETTA 52mg, which provides the benefits of one-handed insertion and extends duration to six years, the longest pregnancy protection of any hormonal IUD.

Refresher on DARE-BV1

In late 2018 DARE acquired worldwide rights to a late-stage hydrogel-based treatment for bacterial vaginosis (BV) as well as the underlying proprietary hydrogel drug delivery technology that it is built upon. DARE received exclusive global rights to MP-101 (clindamycin phosphate 2%), subsequently renamed DARE-BV1, as well as to the hydrogel delivery technology for any vaginal or urological application in humans. Current patents extend through 2028 while patents pending, when effective, would have terms through 2035.

Bacterial Vaginosis, What It Is, How Prevalent and How Is it Treated?
Different kinds of bacteria are present in the vagina and when the bad kind aren't well controlled, bacterial vaginosis can occur. Specifically, lactobacillus, a friendly bacterium typically keeps unfriendly bacteria at bay. But, if that balance is disrupted and lactobacillus levels fall, bad bacteria can proliferate and result in BV. While not all cases of bacterial vaginosis (which is different from a yeast infection) are symptomatic, in those that are, typical symptoms include vaginal discharge, fishy odor and pain when urinating.

As BV is caused by adverse disruption in vaginal bacteria (i.e. microflora), it can increase the risk of acquiring other, serious health problems. This includes HIV, sexually transmitted diseases and, among women that are pregnant, increases the risk of miscarriage, preterm delivery and endometriosis. As such, treatment, particular among pregnant women or those that plan on becoming pregnant, effective treatment is important.

According to results of a large study that surveyed more than 4,600 women aged 14 to 49 years, it is estimated that 29% of American women, or approximately 21M, have bacterial vaginosis at any particular time. The study also found that among those that have the condition, there were no symptoms reported by 84% - which suggests that the U.S. symptomatic population is approximately 3.3M.[4]

First-line treatment of bacterial vaginosis is antibiotics, namely clindamycin, metronidazole or tinidazole – either orally or locally (probiotics are also sometimes used as an adjunct to antibiotics). As the CDC guidelines illustrate (below), these medications must be taken for at least two days and at most for five to seven days. History as shown that compliance wanes with longer or otherwise more burdensome dosing regimens – which results in lower effectiveness of the drug regimen. For example, of the estimated 4M women that are treated for BV each year, only roughly one-half are believed to finish a five to seven-day treatment course.

Solosec (secnidazole), approved in September 2017 and the newest entry into the antibiotic BV space, is dosed just once and could draw appeal for its lower dosing requirement. DARE's DARE-BV1 is clindamycin engineered in a way to increase exposure to the drug, thereby presumably increasing its effectiveness and/or reducing the dosing burden.

While we discuss effectiveness of antibiotics in more detail below, in general it is estimated that up to 15% of patients are not cured with the first round of treatment and, of those that are, as many as 80% will experience recurrence of the condition. This means that any treatment that can either increase the first-course cure rate, reduce the recurrence rate and/or reduce the treatment burden (without compromise to efficacy), and do so with an acceptable safety and tolerability profile, is likely to experience meaningful adoption.

CDC <u>recommends</u> use of one of the following treatment regimens to address BV;

- Metronidazole 500 mg orally twice a day for 7 days
- Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days
- Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days
- Tinidazole 2 g orally once daily for 2 days
- Tinidazole 1 g orally once daily for 5 days
- Clindamycin 300 mg orally twice daily for 7 days
- Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days

As it relates to clindamycin ovules, CDC notes that since they can weaken latex and rubber containing birth control products such as condoms and diaphragms, that they recommend against use of these within 72 hours of using clindamycin ovules

Gel Drug Delivery Technology and DARE-BV1…
DARE-BV1 is designed to increase exposure to clindamycin as compared to other topically delivered antibiotics– and, if it can actually do that, could presumably increase cure rates, decrease recurrence rates and require a less burdensome dosing regimen. Per DARE's public filings describing it;

- the proprietary gel drug-delivery technology…"The proprietary in-situ gel system we licensed is designed to undergo transition from a viscous liquid to a bioadhesive gel, or solution-to-gel (sol-to-gel) transition, at the site of application using body temperature as the trigger, and release the incorporated active drug over multiple days, enabling single treatment products."

[4] Koumans, Emilia H. et al. The Prevalence of Bacterial Vaginosis in the United States, 2001–2004; Associations With Symptoms, Sexual Behaviors, and Reproductive Health. Sexually Transmitted Diseases: November 2007 - Volume 34 - Issue 11 - p 864-869

- DARE-BV1…"this proprietary technology is formulated with clindamycin, an antibiotic used to treat certain bacterial infections including BV, and is designed to produce a dual release pattern after vaginal application (an initial burst with approximately 50% of the active ingredient released in three days, followed by a slow release of the second 50% over the following four days), providing prolonged duration of exposure to clindamycin at the site of infection."

BV-1 Pilot Study Data supported human proof-of-concept…
Per DARE, an n=30 pilot study demonstrated an 86% cure rate with one administration of DARE-BV1. It is our understanding that this is the totality of the human clinical data supporting the effectiveness of the compound. The data has not been formally published but is summarized in DARE's recent investor presentations.

Per DARE the pilot study showed a better clinical cure rate as compared to Solosec (more detail below), Clindesse (branded clindamycin) and metronidazole. Note, however, that this pilot study is much too small to draw any concrete conclusions relative to efficacy (or safety). But it does suggest potentially compelling competitiveness (if replicated in larger studies).

A single dose of DARE-BV1 demonstrated **high clinical cure rate** compared to other approved products

Product	Clinical (Amsel) Cure	Bacteriologic (Nugent) Cure	Therapeutic Cure
DARE-BV1 *novel gel (clindamycin)*	86%	57%*	57%*
Solesec®[1] *(secnidazole 2g oral granules)*	53-68%	40-46%	35-40%
Clindesse®[2] *clindamycin phosphate Vaginal Cream, 2%*	41-64%	45-57%	30-42%
Metrogel, 1.3% [3]	37%	20%	17%

* Based on data from 9 evaluable patients

- 28 of 30 women completed the study
- Test-of-Cure Visit (Day 7 – 14)
  - **24 of 28 (86%) women achieved clinical cure based on Amsel criteria**
  - 4 of 7 (57%) women had bacteriologic cure and 4 of 7 (57%) had therapeutic cure
- Continued clinical response visit (Day 21 – 30)
  - **22 of 24 (92%) women showed continued clinical cure**
  - 7 of 9 women had bacteriologic cure and 6 of 9 had therapeutic cure

/dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=551e43d5-f700-4d6e-8029-026f8a8932ff&type=display. Cure rate range reflects low and high cure rates across multiple studies.
www.clindesse.com/pdf/PI.pdf. Cure rate range reflects low and high cure rates across multiple studies
www.accessdata.fda.gov/drugsatfda_docs/label/2014/205223s000lbl.pdf

Source: Dare Biosciences Investor Presentation 2019

BV-1 FDA Strategy: 505(b)(2) FDA NDA Pathway, Single Ph3 Pivotal Study
DARE has previously mentioned that, based on discussions between MilanaPharm and FDA, that they believe that they can move directly to Phase 3 and that a single study will be sufficient to support a U.S. regulatory filing. Given that clindamycin is generic with a well-established safety profile (spanning over 50 years of use) and, presumably prior discussions with FDA, DARE anticipates being able to follow a 505(b)(2) U.S. regulatory pathway.

Based on our background work, we did not find precedent of another sponsor using the 505(b)(2) pathway for a topical clindamycin-based compound in a bacterial vaginosis indication. Although we did find some for other indications, such as Almirall's Veltin (clindamycin phosphate 1.2% and tretinoin 0.025%) for acne. So, while are far from certain that such a pathway will be deemed appropriate by FDA for DARE-BV1, we do think there are reasonable reasons to believe that it could be.

As it relates to potential timing of a Phase 3 study, DARE commented on their Q3'19 earnings call in November that they are working on startup activities and hope to be in a position to commence the study in early 2020 (pushed

back from prior expectations of late-2019). If all goes well, they believe an NDA filing could happen by late-2020 or early-2021.

BV studies are, fortunately, relatively short. Treatment over ~30 days followed by evaluation periods of between one and four weeks means these pivotal studies can move pretty quickly. But while we continue to think that this program could move along relatively swiftly, we think it is now unlikely that an NDA filing would happen before 2021.

In addition to a pivotal (n=250) Ph3 FDA registrational study, DARE hopes to also conduct an extension study. The single Ph3 pivotal study will be used to support an eventual 505(b)(2) filing while the extension study (see pivotal and extension study designs below) is essentially to bolster the competitive proposition of BV-1 and will presumably be used for marketing (and, perhaps, reimbursement) purposes. DARE also indicated that some non-clinical studies will also be conducted in parallel with these clinical trials.

BV-1 Pivotal Ph3 Study Design [DARE-BV-001] (anticipated)….
DARE currently expects this to be a randomized, double-blind, placebo-controlled study at multiple U.S. sites. Anticipated enrollment is ~250 women which will be randomized as; 2 BV-1 patients to every 1 placebo patient (i.e. total enrollment should be approximately 167 BV patients and 83 placebo). Primary efficacy endpoint is clinical cure at Day 21 – 30 visits. Definitions of "cure" as it relates to both the primary and secondary endpoints appear to be consistent with those used in pivotal studies of other bacterial vaginosis drugs as well as FDA's Draft Guidance specific to BV pivotal study design (FDA's Draft Guidance for Industry (published in July 2016 and available here http://bit.ly/2K86qxf) for sponsors developing drugs for the treatment of bacterial vaginosis provides guidelines for appropriate pivotal study design). Metronidazole gel will be used as rescue therapy for any patient that does not meet the 'clinical cure' definition at the Days 7-14 or Days 21-30 evaluation periods.

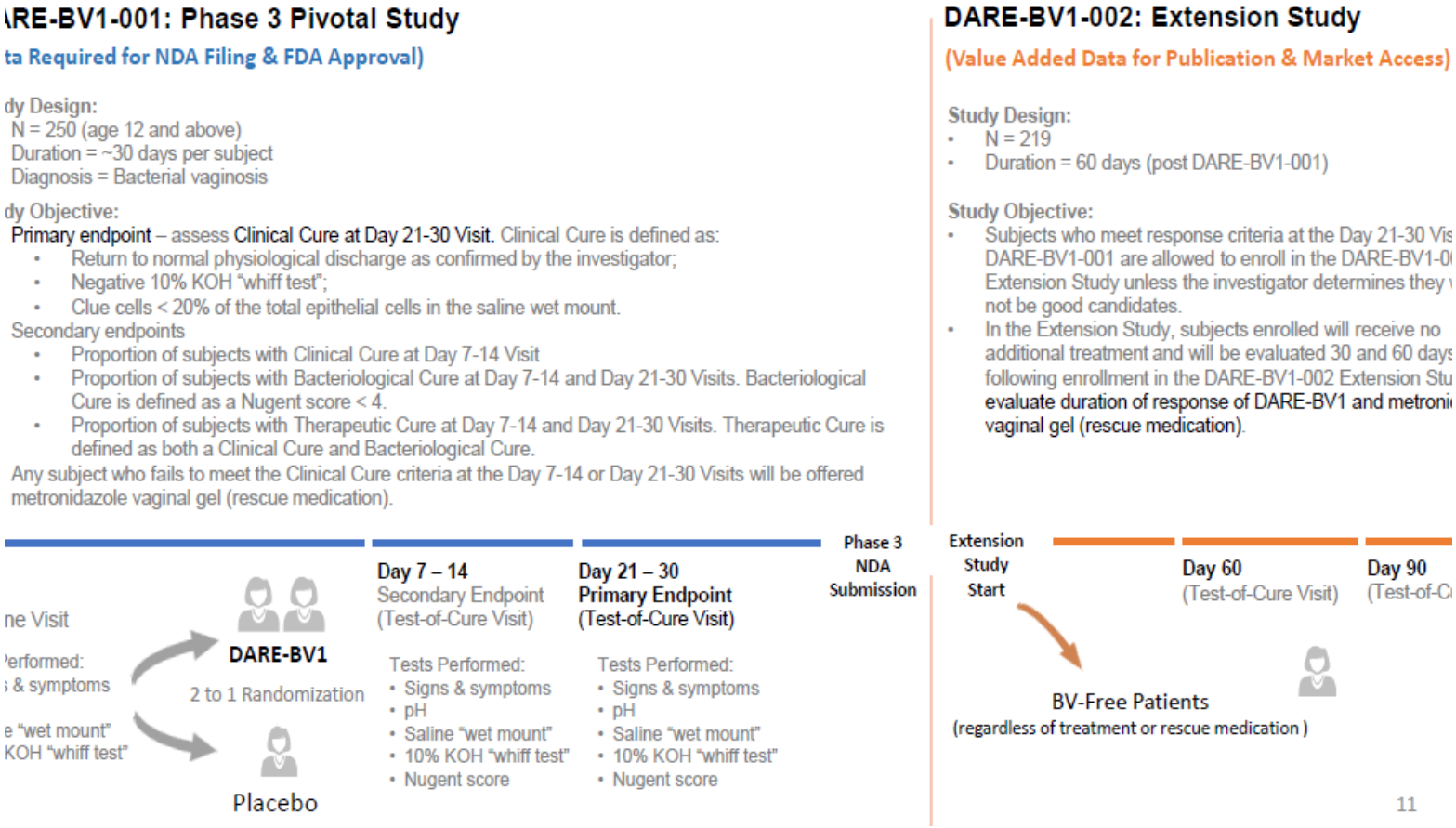
BV-1 Extension (non-FDA) Study Design [DARE-BV1-002] (anticipated)…
Patients, including BV-1 patients and those that receive metronidazole gel rescue therapy and which meet the response criteria from Day 21-30 visits in the Phb3 pivotal study will be eligible to enter this extension study. Extension study patients will not receive treatment and will be evaluated at 30 and 60 days following enrollment (into the extension study).

This study extends the evaluation period in order to better determine just how long the duration of effect is of BV-1. And, given that metronidazole gel (i.e. currently marketed BV therapy) is being used as rescue, this extension study should provide additional insight into the relative performance (such as duration, overall efficacy and tolerability) and competitiveness of BV-1 as compared to current treatments for bacterial vaginosis.

BV-1 Pivotal + Extension Study Strategy is a welcome surprise…
Management had previously mentioned that they were leaning towards a pivotal study design using placebo (as opposed to an active BV therapy) as the comparator. While placebo design likely increases the chances of successfully demonstrating effectiveness, it may not provide as much insight into the commercial competitiveness or performance against other BV therapies. As such, we are pleasantly surprised by the pivotal / extension study strategy as results from the 'easier' comparable (i.e. vs placebo) in the pivotal FDA study could be enhanced (from a competitive, not necessarily regulatory, standpoint) by data from the extension study - which hopefully will provide additional and substantive insight as to how BV-1's performance stacks up against competing (and already commercially available) bacterial vaginosis treatments.

So, while this pivotal + extension (i.e. marketing) study strategy may not be quite as robust from a competitive positioning standpoint as would a BV-1 vs active comparator pivotal study (of course, assuming BV-1 was superior), it should maximize chances of success in the pivotal while not sacrificing the ability to generate potentially valuable head-to-head data for their commercialization (and reimbursement?) efforts (if and when approved for sale). We also continue to think that if and when DARE-BV1 is approved for sale by FDA, it is conceivable that the company would conduct a post-marketing head-to-head study versus other BV therapies with the aim of demonstrating superiority.

BV-1 Ph3 FDA Pivotal Study and 60-Day Extension (Marketing) Study (anticipated designs)



Source: Dare Biosciences Investor Presentation 2019

Bacterial Vaginosis Competitive Landscape, Market

Effectiveness of current BV therapies is difficult to quantify…

DARE notes that the (n=30) pilot study demonstrated a cure rate of 88% with just one administration of DARE-BV1 and that current BV therapies typically have a success rate of less than 70%. Based on our, admittedly somewhat limited literature review, it appears an 88% cure rate, if confirmed in a larger RCT, could be highly competitive to that of current BV therapies including all of those listed above (as CDC recommended regimens).

Jeane-Pierre Menard complied an excellent review[5] of clinical studies of BV therapies, which included a general comparison of their effectiveness in curing the condition. While somewhat dated (2011), we think it remains wholly relevant given that his review focuses on all of the current CDC recommended treatments as well as therapies that were novel at the time. Among his comments are that it is problematic to compare different BV studies of different BV therapies due to lack of consistent design (including endpoint methodologies) among the various clinical trials.

Nonetheless, his review of results of head-to-head clinical studies does provide some context as to what "competitive" cure rates may constitute. Among some of his findings are (reference his full review for more information);

- **Metronidazole**: cure rates after four weeks of treatment of metronidazole ranged from 58% to 100% vs 5% to 29% for placebo. These results encompass a number of different clinical studies including those that looked at oral and vaginal metronidazole and at various dosing regimens. One or more studies found cure rates as high as 87% following a single 2g oral dose with no difference in duration of effect between the single 2g dose and multiple doses over two or more days. But, another study found a single 2g dose was only associated with a 62% cure rate. Another study found 7-day metronidazole regimen is superior to that of a single-dose regimen.

[5] Jeanne-Pierre Menard. Antibacterial treatment of bacterial vaginosis: current and emerging therapies. International Journal of Women's Health 2011:3 295–305

Metronidazole is associated with more side effects than some other BV therapies including metallic taste and (in some cases) candida infection

- **Clindamycin**: one study which evaluated oral versus intravaginal administration found oral at 450mg 3x/day and 2% clindamycin cream 5g once daily for 7 days had similar cure rates. A study comparing clindamycin ovules (for 3 days) with clindamycin cream (for 7 days) found cure rates of 54% and 48%, respectively (not significantly different). A single dose of vaginal clindamycin cream was found to have similar effectiveness and safety to that of a 7-dose regimen of the same. Clindamycin appears to have the most favorable side effect profile of all other standard-of-care BV antibiotics
- **Metronidazole vs clindamycin**: topical clindamycin (2% clindamycin cream 5 g at bedtime for 7 days; ovule 100 mg daily for 3 days) or oral clindamycin (500 mg twice daily for 7 days) appeared to be equivalent to oral (500 mg twice daily for 7 days) or topical metronidazole (0.75% gel 5 g daily for 7 days). Clindamycin appeared to be associated with lower rates of adverse effects such as nausea and metallic taste as compared to oral metronidazole
- **Tinidazole vs metronidazole**: similar effectiveness (~74% tinidazole vs 82% metronidazole) at 14-days as well as similar short-term recurrence rates. Tinidazole has been associated with side effects similar to those of metronidazole including metallic taste, nausea, vomiting, etc.

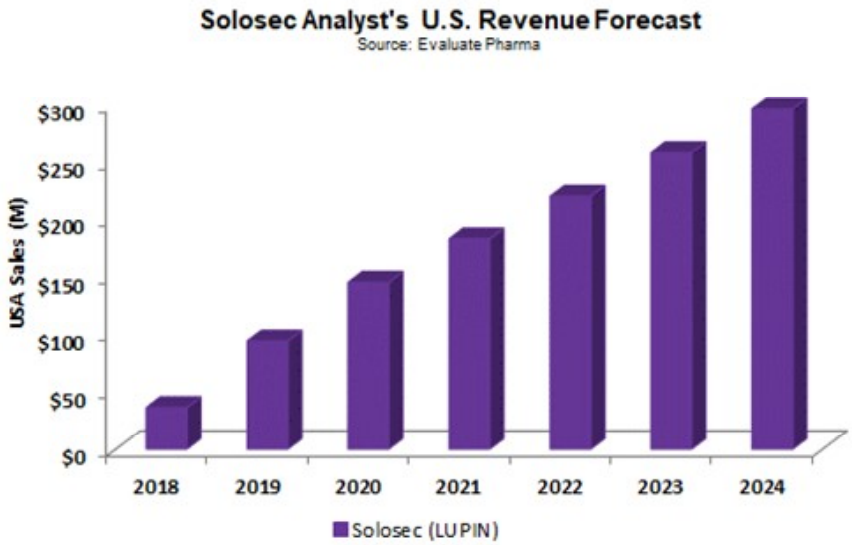
This is not meant to be an exhaustive list nor necessarily provide any sort of benchmark for what DARE-BV1 would need to meet to be considered competitive as a BV treatment. It should, however, provide some context for not only what it is considered a general level of effectiveness as well as illustrate the futility of trying to make sense out of comparing outcomes of different clinical studies.

Market Potential of DARE-BV1…

Market research firm Global Info Research pegs the total current U.S. BV drug market at about $160M – which supports IMS data from 2016 showing that BV-related clindamycin and metronidazole sales were approximately $30M and $125M, respectively (tinidazole sales were negligible). So, we think we can estimate with reasonable confidence that the U.S. market for BV antibiotics is worth just north of $150M today. And, with ~4M women treated annually for the condition (out of ~21M total that are afflicted at any one time), that means each patient represents, on average, ~$40 of revenue.

Given that longer and more burdensome dosing regimens can result in lower rates of compliance and higher rates of discontinuation, and even less incentive to start therapy altogether, we think a single-dose therapy could have the effect of significantly expanding the overall treated population – perhaps by as much as 50% (i.e. to a total of 6M women).

Solosec appears to be priced at approximately 4x that of clindamycin, which may reflect its convenient single-dose regimen. Lupin's May 2018 press release announcing launch of Solosec mentions that they expect peak sales of their drug to reach $100M - $150M over the next three to four years – which, based on our calculations (including total treated population increasing from 4M to 6M), implies that they believe their more convenient dosing therapy will claim between 7% and 10% market share. Current consensus analyst forecasts are more optimistic than Lupin, projecting that Solosec will generate about $93M in sales in 2019 and grow to more than $280M by the year 2024.



EvaluatePharma® [December 2019], Evaluate Ltd.

Topical Sildenafil

DARE, which licensed rights to Topical Sildenafil (TS) in February, plans to develop TS for Female Sexual Arousal Disorder (FSAD), a condition characterized by the inability to attain and/or maintain sufficient physical sexual arousal and also characterized by stress. While FSAD is estimated to affect approximately 13M women in the U.S., no products currently exist that are indicated to treat the condition. While FDA does recognize FSAD as a distinct condition, the agency has never explicitly defined the specific symptoms or physiological traits of what constitutes FSAD. But, that's mostly because an FSAD pivotal study has not yet been successful.

The safety and tolerability profile of sildenafil, which is the active ingredient in Viagra (pill), has been well-established in men. Unlike Viagra, Topical Sildenafil is a cream and designed for local administration. This is expected to provide much more targeted therapeutic effect on the genitalia and mitigate the risk profile as compared to oral Viagra (which has been associated with some elevated cardiovascular risks in men). Topical Sildenafil has already been evaluated in a phase 1 (n=21) and phase 2b study (n=31), which demonstrated that it was well tolerated and resulted in increased blood flow to the vaginal tissue in both pre- and post-menopausal women. IP includes six issued U.S. patents related to topical delivery. Given sildenafil's (i.e. Viagra's) known safety profile, a 505(b)(2) FDA NDA pathway may apply.

DARE has had several interactions with FDA focused on defining FSAD in the context of clinically meaningful endpoints and related design of their ongoing content validity study. This includes a Type C meeting with FDA in Q3'18. Another meeting is anticipated following conclusion of the content validity study, which finished in Q3 2019. The follow-up FDA meeting, which will focus on additional guidance prior to the commencement of the at-home portion of the Phase 2b study, could possibly happen before 2019 year-end. Ph2b at-home portion could begin in early 2020 with topline data in Q4 of that year.

Given the current ambiguity of what defines "FSAD", and the sizeable boneyard from failed attempts by others at designing a 'female Viagra', we are glad to see that DARE is taking a very pragmatic approach – as anything else could be a big mistake and waste of time and money. And while there is no precedent for what an appropriately-designed FSAD clinical study would like, FDA's Draft Guidance for *Low Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs for Treatment*, published in October 2016, provides at least a starting point to work from.

We also think it is important to keep in mind that while there remains ambiguity in terms of how to define and measure clinically meaningful "arousal", that the lack of complete clarity is not FDA's intention – in fact, we think recent history shows that FDA's goal is to facilitate industry's development of novel drugs to treat women's sexual function disorders – and part of that is working with companies like DARE to design feasible clinical trials (including defining and measuring endpoints). We think this is a critical point and is one of the reasons why we have provided additional detail on this topic in prior reports.

Increasing awareness of FSD has potential to meaningfully benefit uptake of TS, if and when approved…

Awareness of the existence and prevalence of female sexual dysfunction appears to be on the increase, which we think could ultimately significantly benefit uptake of Topical Sildenafil, if when approved for sale. While an estimated one-third of all sexually active women are believed to experience sexual dysfunction such as Female Sexual Arousal Disorder, it had been largely ignored from the standpoint of regulators and pharmaceutical development. That has started to change.

Publishing of FDA's Draft Guidance in 2016 was somewhat of a seminal moment in bringing awareness of the unmet need for female sexual disorder therapies. FDA did significant work in compiling their industry guidance for female sexual dysfunction which we think speaks to the agency's motivation to facilitate drug development for these conditions.

Following publishing of DSM-V (i.e. the Diagnostic and Statistical Manual of Mental Disorders, published in 2013, which modified the characterization of arousal and desire disorders stating that they could not be reliably distinguished and, therefore, combined FSAD and hypoactive sexual desire disorder (HSDD) into a new category called Female Sexual Interest/Arousal Disorder (FSIAD), FDA held separate patient-focused public meetings and an industry-focused meeting with the respective goals of hearing perspectives from women with female sexual dysfunction on their condition and on currently available therapies and to discuss several scientific challenges associated with drug development, including diagnostic criteria, endpoints, and patient-reported outcome instruments. Results of these meetings (and related public workshops) highlighted the need for effective pharmaceutical therapies to treat female sexual dysfunction and were used to compile FDA's Industry Guidance to help facilitate development of new drugs that specifically address FSIAD, HSDD and FSAD.

Results were also used for the basis of FDA's decision to not combine FSAD and HSDD into a single disorder of FSIAD (as DSM-V had), but to instead recognize all three (i.e. FSAD, HSDD and FSIAD) as potential targeted primary indications. FDA specifically notes that FSAD and HSDD should remain characterized as distinct disorders given that the DSM revision (combining HSDD and FSAD into FSIAD) have not been universally accepted by the scientific community (including the International Society for the Study of Women s Sexual Health).

Vyleesi FDA Approval (June 2019) May Be Good Omen for DARE / Topical Sildenafil…

The effort that FDA put into compiling their 2016 Draft Guidance is clearly indicative of their recognition that there is an unmet need for more effective therapies to treat FSD. A somewhat milestone-type event happened in June 2019 when FDA approved Vyleesi (bremelanotide), an injectable drug developed by Amag Pharmaceuticals (AMAG), for the treatment of HSDD in premenopausal women. This is significant in our opinion and may be another sign that FDA is taking a more proactive-type approach than they might on most therapies, especially those that address non life-threatening indications (such as sexual function disorders). This potentially bodes well for DARE and Topical Sildenafil. FDA approval makes Vyleesi just the second drug approved to treat female sexual dysfunction.

The first, Addyi (flibanserin), was approved by FDA for HSDD in August 2015. While Addyi has been a commercial flop (generating revenue of just ~$55M in 2016 and $80M in 2017), which has largely been blamed on a black box warning about the risk of low blood pressure when taking the drug while using alcohol, FDA recently agreed to soften that language. In April 2019 FDA allowed (manufacturer) Sprout Pharmaceuticals to mitigate the risk warning on Addyi's label – from (previously) stating that alcohol should be completely avoided when using the drug to (now) stating that alcohol should be avoided within two hours of taking Addyi.

To be clear (as discussed above) HSDD is a different disorder than is FSAD (i.e. the indication that DARE intends to pursue with Topical Sildenafil) and therefore will not necessarily compete with DARE's candidate. But they both fall under the broader category of female sexual dysfunction. The more awareness that is brought about the existence and prevalence of these conditions, the better the likelihood of eventual uptake of Topical Sildenafil, in our opinion. And headlines such as Addyi's black box warning being softened and FDA approval of Vyleesi should help in that regard.

Valuation

Ovaprene

Based on our estimates and assumptions (below), Ovaprene represents more than 60% of DARE's current total value. We believe, if successfully developed and eventually approved for sale, that Ovaprene's attributes could position it as competitive to most contraceptive products – both hormonal and non-hormonal. And while overall use of contraception in the U.S. has remained largely steady (at ~62% of women of reproductive age) over the last two decades, it is possible that perceived advantages of Ovaprene (and the fact that it would represent a new class of contraception) could attract (previous) non-users of contraception and effectively result in expansion of the overall U.S. market. Market expansion may also be facilitated by public and non-profit initiatives aimed at increasing contraceptive use as a whole, as well as by the (relatively recent) mandated insurance coverage. And while the original mandate has recently been slightly watered down and is potentially at-risk of partial or complete repeal, we think at least a portion of any total market size expansion is likely to be sustained over time (regardless of reimbursement status).

However, we feel that Ovaprene is too early in development to reasonably estimate how demand may differ based on individual segments within the larger women's contraceptive market. For example, while we think Ovaprene may provide an attractive alternative to users of short-acting hormonal contraceptives, estimating proportional switching-based demand from users of the pill versus that of the patch or vaginal rings is too granular of an exercise at this stage. Similarly, we have little confidence in accurately forecasting potential differences in the rate or level of uptake as a result of switching (or supplemental use) from condom users versus that from couples that primarily practice withdrawal.

Instead, we think (at this stage) that given the similarity in class (i.e. monthly vaginal rings), that NuvaRing's commercial history provides a better basis for estimating what potential demand for Ovaprene may look like. To be clear, we acknowledge that significant differences exist between NuvaRing and Ovaprene (as envisioned). Similarly, we think that by the time that Ovaprene would potentially launch, the competitive landscape of the U.S. contraceptives market may be meaningfully different as compared to during much of NuvaRing's commercial history (for context, NuvaRing launched in the U.S. in 2002). Some of the differences between Ovaprene and NuvaRing and the dynamics of the markets during the respective periods of commercialization should play in Ovaprene's favor, while others, we think, are/were likely to have been more a benefit to NuvaRing. While not an exhaustive list, some of the more significant factors (favorable and unfavorable) that have been incorporated into our modeling methodology include;

Contextual product-specific considerations

- Women like features of vaginal rings, just not necessarily all the hormones:
    - 50% of women that try hormonal methods discontinue use and of those that do, side effects are the overwhelming reason why
    - most commonly cited specific reasons for discontinuation were; side effects, worried about side effects and did not like changes to menstrual cycle
    - a recent study found a potential association between use of hormonal contraception and depression
- NuvaRing risks (almost all of which are relate to hormones):
    - NuvaRing is contraindicated for women at risk of arterial or venous thrombotic diseases. Study of 1.6M women found users of NuvaRing had a greater than 6x times increased risk of blood clots as compared to non-users
    - FDA's Adverse Events Reporting System (FAERS) lists 8,710 reports of 'serious' events attributable to NuvaRing, including 240 deaths. Of the serious events, ~36% related to blood clots (in either the lung or the leg)
    - $100M judgement: in 2014 Merck paid $100M to settle a liability lawsuit which claimed NuvaRing caused blood clots
- Interestingly, despite the negative publicity of the lawsuit, NuvaRing's revenue continued to grow. By contrast, liability-related lawsuits against the makers of certain other hormonal contraceptives such as Yaz (oral progestin), Norplant (levonorgestrel implant) and Depo-Provera (norelgestromin/ethinyl estradiol injection) negatively affected sales. This may suggest that many NuvaRing users believe the convenience-related benefits of vaginal rings (i.e. effectiveness, reversibility and convenience of monthly use) outweigh the risks – which may also suggest that a non-hormonal vaginal ring (i.e. Ovaprene) would be a particularly appealing option

- For much of its commercial life, NuvaRing has had significant sales/marketing support, which undoubtedly aided uptake and sales. Schering-Plough acquired it via its purchase of Organon in 2007 then in 2009, SGP and Merck merged
- NuvaRing patent expiration: NuvaRing's patent expired in April 2018. Mithra Pharma/Mayne Pharma, Teva and Dr. Reddy's Labs expect to launch a generic version of NuvaRing in 2020. Others could follow. Lower generic pricing and tier 1 formulary coverage could catalyze uptake of that contraceptive method and take share of others. This, in our opinion, will be an interesting dynamic to keep an eye on as while, intuitively, we might expect NuvaRing generics to represent direct competition to Ovaprene, they may in fact prove a (net) catalyst to driving demand for it. Our reasoning is that friendlier pricing of the generics may promote switching from other methods and result in sustainably-higher market share of vaginal rings (as a class). If that happens, by the time Ovaprene could come to market, more women would be vaginal ring-experienced and looking for a non-hormonal option.
- New vaginal ring: the competitive landscape is soon to include ANNOVERA, a one-year Nestorone (segesterone acetate, a progestin) /ethinyl estradiol vaginal ring, which received FDA approval in August 2018. The ring is left in place for 21 days and then removed for 7 days. ANNOVERA has a Pearl Index (i.e. average rate of pregnancy when used by 100 women for 1 year) of 2.98, just slightly higher (i.e. worse) than that of NuvaRing (between 1.3 and 2.0). Therapeutics MD, which licensed the technology from Population Council, expects to launch ANNOVERA in any day now. Pre-marketing studies (per Pop Council) indicated 89% of women surveyed were 'satisfied' with the ring as a contraceptive method. Analysts currently forecast ANNOVERA to generate $21M of revenue in 2020 and for that to grow to almost $270M in 2024

Contextual market considerations

- Women want more contraceptive options, which is evidenced by one survey (n=2k) that showed 70% of women have quit or are considering quitting use of the pill. Top reasons for quitting the pill include that they want a more convenient method that does not require daily administration and one with no hormones
- Contraceptive reimbursement: the Affordable Care Act of 2010 mandated that all health insurance plans (aside from self-insured employer plans or grandfathered plans) provide no-out-of-pocket coverage of contraceptives. Specifically, the ACA requires coverage of 18 distinct methods of contraception (reimbursement is subject to updating, revision and potentially, complete repeal)
- Recent public and non-profit initiatives aimed at increasing contraceptive use

Sum-of-the-Parts

Given the likelihood that initial commercialization related to any of DARE's various development programs is at least four years away, we think price-to-sales, based on sum-of-the-parts, is the most appropriate valuation methodology. Additionally, while we think the earlier-stage programs currently represent option-like value, based on our background work, their intrinsic worth (at this point) is too difficult to quantify within a reasonable-enough range to warrant inclusion in our (risk-adjusted) valuation model.

We also note that we do not currently model any implied contribution related to the Microchips drug delivery technology as we feel it is not at a mature enough stage and lacks substantive supporting evidence as to reasonably judge eventual chance of regulatory success. This is subject to updating depending on progress of development of the technology.

Our forecasts and assumptions are based solely on our research and experience and should not be interpreted to reflect those of management. We model Ovaprene, Topical Sildenafil, and VVA1 based on commercialization histories of NuvaRing, Addyi and Osphena, respectively, as proxy-like guides. While we are not suggesting that commercialization experience of DARE's candidates will necessarily mirror that of these three products, we do think this is an appropriate and reasonable approach given indication-based and (in some cases,) other similarities and, simply, due to the fact that there is just not enough information (at this point) to confidently model uptake-curves using an alternative method.

Some of the key assumptions in our model related to Ovaprene, TS and VVA1 include:

Ovaprene

- launches late-2023
- achieves nearly 25% share of NuvaRing's peak penetration by 2026 and 30% by 2028. These equate to ~1.9% and 2.6%, respectively, penetration of the estimated total U.S. contraceptive market
- U.S. annual revenue per user averages $300 initially and grows with inflation (for context NuvaRing averaged ~$424 from 2011 through 2017)
- OUS revenue equal to 85% of U.S. (similar to NuvaRing)

- royalties average 12%
- additional 5% OUS haircut
- 60% risk-adjustment haircut reflects risk of regulatory failure. Clinical trial successes would likely positively influence (i.e. reduce) our risk adjustment

Topical Sildenafil
- launches 2022
- achieves 25% share of Addyi's peak penetration by 2025 and 70% by 2028. These equate to less than 1% penetration of the estimated total U.S. FSAD market in those years
- U.S. revenue per user averages ~$1.5k initially and grows with inflation. This assumes $30/dose and 52 doses per year
- OUS revenue equals 30% of U.S.
- royalties average 12%
- additional 5% OUS haircut
- 70% risk-adjustment haircut reflects risk of regulatory failure – a significant portion of this risk-adjustment reflects current ambiguity over regulatory "FSAD definition" in the context of designing and successfully executing a clinical program for Topical Sildenafil – depending on outcomes of meetings with FDA, our risk-adjustment could come down

DARE-VVA1
- launches 2023
- achieves 27% share of Osphena's peak penetration by 2026 and 30% by 2028 (which we also assume represents DARE-VVA1 peak). These equate to less than 1% penetration of the estimated U.S. hormone receptor positive breast cancer VVA+ market in those years
- U.S. revenue per user averages $2.2k initially (similar to Osphena historical) and grows with inflation
- OUS revenue equals 30% of U.S.
- royalties average 12%
- additional 5% OUS haircut
- 35% risk-adjustment haircut reflects risk of regulatory failure – we base our risk adjustment on Osphena's history and regulatory successes in U.S. and OUS

P/S Values Ovaprene, TS and VVA1 at ~$4.90/share
We use 5.0x sales and discount revenue at 20%, 15% and 10% reflecting bear, base and bull cases, respectively. Given assumed commercial acceleration for each of the therapies not occurring until at least 2025, we think 2025, 2026 and 2027 are 'usable' out-years in the valuation waterfall (see below) and still reflect growth potential implied by a 5x sales multiple. Based on an estimated (post-Microchips acquisition) fully-diluted share count of approximately 25M, base case values these three therapies at approximately $4.90/share – which we add to our calculated value of BV1 (below). [Note that the o/s share count reflects basic shares, option/warrants share equivalents and 3M shares issued to Microchips shareholders].

Initial Modeling of DARE-BV1 values it at ~$0.90/share
Market research firm Global Info Research pegs the total current U.S. BV drug market at about $160M – which supports IMS data from 2016 showing that BV-related clindamycin and metronidazole sales were approximately $30M and $125M, respectively (tinidazole sales were negligible). So, we think we can estimate with reasonable confidence that the U.S. market for BV antibiotics is worth just north of $150M today.

For initial modeling purposes of DARE-BV1, we think 10% - 15% peak market share is a reasonable assumed starting point. While significantly superior efficacy or easier dosing regimen (which could also benefit the tolerability profile) to topical clindamycin could quickly promote it to first-in-class status, it is too early to estimate with any reasonable degree of confidence how DARE-BV1 will compare to its generic counterpart (or other antibiotics).

Other assumptions include initial revenue from DARE-BV1 in 2022 (more conservative than management's estimated launch in 2020/2021) and single-digit market share penetration over the first 4 – 5 years after launch, initial double-digit share at year 5 – 6 and peak share of 15%. We assume 60% chance of regulatory success, OUS sales equal to 30% of that of the U.S. and licensing/milestone/royalties payments aggregating to 25% of gross revenue. Based on an estimated fully-diluted share count of approximately 25M, base case values DARE-BV1 at approximately ~$0.90/share.

Sum-of-the-parts values the combined company at $4.90/share + $0.90/share = ~$5.80/share. This is adjusted from $6.50/share previously, largely as a result of the increase in shares outstanding

VALUATION WATERFALL

Risk-Adjusted Forecasted Revenue

	2020	2021	2022	2023	2024	2025	2026	2027	2029
Ovaprene	$0	$0	$0	$5,291	$22,667	$50,315	$73,489	$85,088	$127,987
%of total		-	*0%*	*50%*	*69%*	*72%*	*68%*	*67%*	*69%*
PT-101 (VVA)	$0	$0	$0	$1,430	$3,484	$8,840	$16,150	$18,214	$18,764
%of total		-	*0%*	*14%*	*11%*	*13%*	*15%*	*14%*	*10%*
Topical Sildenafil (FSAD)	$0	$0	$814	$2,203	$4,192	$7,092	$10,941	$14,612	$25,591
%of total		-	*50%*	*21%*	*13%*	*10%*	*10%*	*12%*	*14%*
MP-101 (BV)	$0	$0	$818	$1,661	$2,529	$3,423	$6,948	$8,816	$13,623
%of total		-	*50%*	*16%*	*8%*	*5%*	*6%*	*7%*	*7%*
TOTAL Risk-adj Revenue	**$0**	**$0**	**$1,632**	**$10,585**	**$32,871**	**$69,669**	**$107,528**	**$126,729**	**$185,964**

Risk-Adjusted Market djusted Market Value

Present Value based on 2029 out-year:	Per-share value	2019	2020	2021	2022	2023	2024	2025	2026	2027	2029
20% discount rate	$2.56	$64,412	$80,515	$100,644	$125,805	$157,256	$196,570	$245,713	$307,141	$383,926	$599,885
15% discount rate	$5.29	$133,326	$156,854	$184,534	$217,099	$255,411	$300,483	$353,510	$415,894	$489,287	$677,214
10% discount rate	$10.51	$264,727	$294,141	$326,823	$363,137	$403,486	$448,317	$498,130	$553,478	$614,976	$759,229
Present Value based on 2028 out-year:											
20% discount rate	$3.17	$79,871	$99,839	$124,799	$155,998	$194,998	$243,747	$304,684	$380,855	$476,069	$743,857
15% discount rate	$6.17	$155,599	$183,058	$215,362	$253,368	$298,079	$350,682	$412,567	$485,373	$571,027	$790,348
10% discount rate	$11.58	$291,788	$324,209	$360,232	$400,258	$444,731	$494,145	$549,050	$610,056	$677,840	$836,839
Present Value based on 2027 out-year:											
20% discount rate	$3.18	$80,251	$100,313	$125,392	$156,740	$195,925	$244,906	$306,132	$382,665	$478,331	
15% discount rate	**$5.84**	$147,143	$173,109	$203,657	$239,597	$281,879	$331,622	$390,144	$458,993	$539,991	
10% discount rate	$10.34	$260,600	$289,555	$321,728	$357,476	$397,195	$441,328	$490,365	$544,849	$605,388	
Present Value based on 2026 out-year:											
20% discount rate	$3.37	$85,046	$106,308	$132,885	$166,106	$207,632	$259,540	$324,426	$405,532	$506,915	
15% discount rate	**$5.82**	$146,763	$172,662	$203,132	$238,978	$281,151	$330,766	$389,136	$457,808	$538,597	
10% discount rate	$9.74	$245,487	$272,763	$303,070	$336,744	$374,160	$415,734	$461,926	$513,251	$570,279	
Present Value based on 2025 out-year:											
20% discount rate	$3.58	$90,201	$112,752	$140,940	$176,174	$220,218	$275,272	$344,091	$430,113		
15% discount rate	**$5.81**	$146,502	$172,356	$202,771	$238,554	$280,652	$330,179	$388,446	$456,995		
10% discount rate	$9.18	$231,437	$257,152	$285,725	$317,472	$352,747	$391,941	$435,490	$483,877		
Present Value based on 2024 out-year:											
20% discount rate	$2.90	$73,053	$91,316	$114,145	$142,681	$178,352	$222,940	$278,675			
15% discount rate	$4.43	$111,671	$131,378	$154,562	$181,837	$213,926	$251,678	$296,092			
10% discount rate	$6.61	$166,612	$185,124	$205,693	$228,548	$253,942	$282,158	$313,509			
Present Value based on 2023 out-year:											
20% discount rate	$1.71	$43,085	$53,857	$67,321	$84,151	$105,189	$131,486				
15% discount rate	$2.46	$61,987	$72,926	$85,795	$100,936	$118,748	$139,704				
10% discount rate	$3.47	$87,346	$97,051	$107,835	$119,816	$133,129	$147,921				

FINANCIAL MODEL

DARE	2018 A	Q1A	Q2A	Q3A	Q4E	2019 E	2020 E	2021 E
Ovaprene U.S. Mkt Assumptions								
Net annual revenue per patient	$300					$300	$300	$315
NuvaRing Avg Annual Patients	1,106,000					1,117,060	1,128,231	1,150,795
NuvaRing Peak US Revenue	564,000,000					$572,460,000	$581,046,900	$593,762,604
U.S. Contracep Product Patient Mkt	$23,000,000					23,000,000	23,460,000	23,929,200
U.S. Contraceptives Mkt Value	$5,500,000,000					5,500,000,000	$5,610,000,000	5,722,200,000
Ovaprene U.S. Penetration Assumptions								
Penetration of US contraceptives $ valu	0.0%					0.0%	0.0%	0.0%
Penetration of NuvaRing's Peak US pati	0.0%					0.0%	0.0%	0.0%
Number of Annual U.S. Ovaprene patient	0					0	0	0
OVAPRENE U.S. REVENUE ($'	**$0**					**$0**	**$0**	**$0**
OVAPRENE OUS REVENUE	**$0**					**$0**	**$0**	**$0**
Ovaprene OUS as % of U.S.	35.0%					35.0%	35.0%	35.0%
TOTAL OVAPRENE REVENUE	**$0**					**$0**	**$0**	**$0**
yoy growth						-	-	-
PT-101 U.S. Mkt Assumptions								
Net annual revenue per patient	$2,160					$2,182	$2,203	$2,225
PT-101 Total Patient Market	1,400,000					1,414,000	1,428,140	1,442,421
Osphena Peak US Revenue	$43,000,000					$43,645,000	$44,293,675	$44,364,170
PT-101 Patient Market Value	$3,024,000,000					$3,084,782,400	$3,146,786,526	$3,210,036,935
PT-101 U.S. Penetration Assump	0.0%					0.0%	0.0%	0.0%
Penetration' of Osphena's Peak Revenue	0.0%					0.0%	0.0%	0.0%
Penetration of US HRP+ VVA	0.00%					0.00%	0.00%	0.00%
U.S. PT-101 REVENUE ($000s)	**$0**					**$0**	**$0**	**$0**
PT-101 OUS REVENUE	**$0**					**$0**	**$0**	**$0**
PT-101 OUS as % of U.S.	20.0%					20.0%	20.0%	20.0%
TOTAL PT-101 REVENUE	**$0**					**$0**	**$0**	**$0**
yoy growth						-	-	
Topical Sildenafil US Mkt Assumptions								
TS Net Annual revenue per patient	$1,560					$1,576	$1,591	$1,607
TS Total US Patient Market	13,000,000					13,195,000	13,392,925	13,593,819
Addyi Peak Revenue	$78,000,000					$79,170,000	$80,357,550	$81,562,313
TS Patient Market Value	$20,280,000,000					$20,790,042,000	$21,312,911,556	$21,848,931,282
TS U.S. Penetration Assumptions								
Penetration' of Addyi's Peak Revenue	0.00%					0.00%	0.00%	0.00%
Penetration' of FSAD	0.00%					0.00%	0.00%	0.00%
Total TS REVENUE ($000s)	**$0**					**$0**	**$0**	**$0**
TS OUS REVENUE	**$0**					**$0**	**$0**	**$0**
TS OUS as % of U.S.	20.0%					20.0%	20.0%	20.0%
TOTAL TS REVENUE	**$0**					**$0**	**$0**	**$0**
yoy growth	-					-	-	-
BV1 US Mkt Assumptions								
BV Net Annual revenue per patient	$150					$152	$153	$155
BV Total US Patient Market	6,000,000					6,090,000	6,181,350	6,274,070
BV Antibiotics Peak Revenue	$160,000,000					$162,400,000	$164,836,000	$167,308,540
BV Patient Market Value	$900,000,000					$922,635,000	$945,839,270	$969,627,128
BV U.S. Penetration Assumptions								
Penetration of BV Antibiotics' Peak Re	0.00%					0.00%	0.00%	0.00%
Penetration of BV	0.00%					0.00%	0.00%	0.00%
Total BV1 REVENUE ($000s)	**$0**					**$0**	**$0**	**$0**
BV1 OUS REVENUE	**$0**					**$0**	**$0**	**$0**
BV1 OUS as % of U.S.	20.0%					20.0%	20.0%	20.0%
TOTAL BV1 REVENUE	**$0**					**$0**	**$0**	**$0**
yoy growth	-					-	-	-
Total Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-
Cost of Goods Sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Margin	-	-	-	-	-	-	-	-
SG&A	$4,655.8	$1,277.2	$1,307.4	$1,319.0	$1,451.3	$5,354.8	$8,641.7	$9,263.8
%SG&A	-	-	-	-	-	-	-	-
R&D	$7,039.0	$1,805.9	$2,675.1	$2,099.6	$3,166.7	$9,747.2	$13,036.5	$13,701.7
%R&D	-	-	-	-	-	-	-	-
Impairment of Goodwill	$5,187.5	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
TOTAL OpEx	**$16,882.3**	**$3,083.1**	**$3,982.5**	**$3,418.5**	**$4,618.0**	**$15,102.1**	**$21,678.2**	**$22,965.5**
% Total OpEx	-	-	-	-	-	-	-	-
Operating Income	($16,882.3)	($3,083.1)	($3,982.5)	($3,418.5)	($4,618.0)	($15,102.1)	($21,678.2)	($22,965.5)
Operating Margin	-	-	-	-	-	-	-	-
Total Other Income (Expense)	$64.9	$38.9	($767.5)	$10.1	$18.7	($699.9)	$84.5	$112.2
Pre-Tax Income	($16,817.4)	($3,044.2)	($4,750.0)	($3,408.5)	($4,599.3)	($15,801.9)	($21,593.7)	($22,853.3)
Tax expense (benefit)	$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%*
Net Income	($16,817.4)	($3,044.2)	($4,750.0)	($3,408.5)	($4,599.3)	($15,801.9)	($21,593.7)	($22,853.3)
YOY Growth	*46.0%*	*-60.4%*	*51.6%*	*51.4%*	*56.7%*	*-6.0%*	*36.7%*	*5.8%*
Net Margin	-	-	-	-	-	-	-	-
EPS (GAAP)	($1.57)	($0.27)	($0.29)	($0.20)	($0.27)	($1.04)	($1.12)	($0.94)
YOY Growth	*-56.0%*	*-69.9%*	*-6.7%*	*-10.0%*	*6.7%*	*-33.8%*	*8.2%*	*-16.0%*
Shares O/S	10,732	11,422	16,105	16,683	16,750	15,240	19,250	24,250

APPENDIX

Earlier-stage programs, some background

Earlier stage programs

In May 2018 DARE announced a merger agreement with (privately-held) Pear Tree Pharmaceuticals that added a **novel, vaginally-delivered treatment for VVA in women with hormone-receptor-positive (including ER-positive and PR-positive) breast cancer**. DARE-VVA1 is a proprietary vaginal formulation of oral tamoxifen, a selective estrogen-receptor modulator (SERM) which, along with aromatase inhibitors (AIs), are the most widely used drugs to treat hormone-receptor-positive (HRP) breast cancer. VVA, characterized by vaginal dryness and pain during intercourse (i.e. dyspareunia), is caused by low estrogen levels associated with menopause. Localized estrogen therapy is typically used to treat VVA but, since it can interfere with action of AIs/oral tamoxifen and increase the risk of cancer recurrence, it is often contraindicated for women with (or at risk of) HRP breast cancer as well as those taking AIs, the use of which has been shown to further exacerbate VVA symptoms. Approximately 600k post-menopausal women in the U.S. take AIs to treat or mitigate risk of HRP breast cancer and an estimated 2M women in the U.S. with breast cancer suffer from VVA, the majority of which do not receive treatment. DARE intends to develop DARE-VVA1 for the treatment of VVA in women with (or at risk of recurrence of) hormone-receptor positive breast cancer, including those undergoing therapy – an indication for which there is no currently approved treatment.

A four-subject proof-of-concept study indicated DARE-VVA1 was associated with improvement in vaginal dryness and decreased vaginal pH (see table below). Moreover, systemic absorption of tamoxifen was not significant – and less than one-twentieth the concentration of oral tamoxifen. Following eight weeks of treatment with DARE-VVA1 (20mg), median plasma concentration of tamoxifen was 5.8 ng/m (1.0 – 10.0 ng/ml) which compares to 122 ng/ml (71 – 183 ng/ml) average steady-state plasma concentration following three months of treatment with oral tamoxifen (20mg). This is an important finding as it suggests that DARE-VVA1 (i.e. topical tamoxifen) could safely be used (to treat VVA symptoms) in patients undergoing treatment with oral tamoxifen (for the treatment of HRP+ breast cancer). These results were published in the journal Clinical and Experimental Obstetrics and Gynecology in 2019.

Results of the n=4 POC study published in Clinical and Experimental Obstetrics and Gynecology

Vaginal Tamoxifen	Enrollment (Baseline)	On Treatment (Month 3)	Paired Difference (Baseline vs. Month 3)
Median Vaginal pH Lower pH value is a measure of symptom relief *Normal vaginal pH is usually less than 4.5.*[2]	**7.1** range 6.5 to 7.5	**5.0** range 5.0 to 5.2	**-2.0 median** range -2.5 to -1.5
Vaginal Dryness Rated using a visual analogue scale (VAS) that ranged from: **0** = Not bothered by dryness **10** = Extremely bothered by dryness Decreased vaginal dryness is a measure of symptom relief	**8.0** range of 7.5 to 9.0	**3.0** range 2.0 to 3.0	**-5.5 median** range -6.0 to -4.5

Source: DARE Bioscience. Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663 XLVI, n. 2, 2019

Interestingly, Ospemifene (marketed as Osphena), also a SERM, acts as an estrogen agonist in the endometrium and works similar to the way that estrogen does in reducing VVA symptoms. Osphena (taken orally) is the only FDA-approved (since February 2013) product for the treatment of VVA that can claim it does not raise estrogen levels. It, however, is not indicated specifically for women with (or at risk of) HRP breast cancer (i.e. the claim that DARE expects to pursue). Presumably the method-of-action of DARE-VVA1 would prove similar to that of Osphena. Next steps in development of DARE-VVA1 are to optimize the vaginal formulation before moving to larger clinical trials.

In April 2018 DARE secured exclusive worldwide rights to a **novel intravaginal ring (IVR) drug-delivery platform technology** from Juniper Pharmaceuticals. DARE obtained rights to three pre-clinical candidates; OAB1 (fka JNP-

101) oxybutynin for overactive bladder, HRT1 (fka JNP-201) natural progesterone and estradiol hormone replacement therapy (for menopause) and FRT1 (fka JNP-301) natural progesterone for the prevention of preterm birth. By using a solid ethylene vinyl acetate (EVA) polymer matrix to release drugs, the novel drug-delivery technology is expected to allow for delivery of multiple drugs at multiple release rates and provide longer duration of efficacy as compared to current methods. Initial human proof-of-concept was established in a six-subject clinical trial whereby their IVR delivered leuprolide (a hormone which is used for the treatment of prostate and breast cancers as well as endometriosis and other conditions). Development for all indications is expected to follow 505(b)(2) pathways which would include a phase 2 bioavailability and dose-finding study followed by a pivotal phase 3 clinical trial.

Preclinical study results of HRT1 and FRT1 were recently published online. In April 2019 results of a pharmacokinetics (PK) study of HRT1 evaluating it as a potential hormone replacement therapy (in sheep) was published online in the Journal of Pharmaceutical Sciences. Then, in May 2019, a PK sheep study of FRT1, evaluating it as a potential therapy for preterm birth and fertility, was published online in the journal Drug Delivery and Translational Research. Commencement of a phase 1 (PK/safety) human study has been mentioned as expected to happen in the near-term. The study (n=30) will evaluate two doses of HRT1 to determine steady-state over 28 days. The study will be conducted in Australia (and led by DARE's Australian subsidiary) to take advantage of government incentives.

In March 2018 DARE announced an agreement with (privately-held) Orbis Biosciences related to the development of **two long-acting injectable contraceptives**. Development work to-date (pre-clinical) has been through a subcontracted program funded by FHI 360, which was sponsored by the Bill & Melinda Gates Foundation. Built on Orbis' controlled-release technology, ORB-204 and ORB-214 are pre-clinical stage etonogestrel injectable contraceptives being developed for (relatively long) pregnancy-protection durations of six and twelve months, respectively. Currently available injectables have a duration of only three months. While specifics were not publicly disclosed, per terms of the agreement with Orbis, if "upcoming development efforts [are] successful" DARE has the option to license rights to ORB-204 and ORB-214. Etonogestrel is currently used in FDA-approved contraceptive implants as well as in vaginal rings including NuvaRing. We expect we will hear development-related status updates in the near-future.

In July 2018 DARE announced an asset transfer agreement with Hydra Biosciences for their CatSper ion channel intellectual property. Ion channels are membrane proteins that allow for the flow of ions, and therefore the transmission of information, into cells. Backed by some of the largest global life sciences-focused venture capital funds, Hydra's main focus is the Transient Receptor Potential (TRP) ion channel and the development of drugs for diseases that may respond to modulation of the TRP channel.

While CatSper, or Cation Channel of Sperm, is distantly related to TRP, it is unique to sperm. The CatSper channel is essential for male fertility, controlling entry of calcium (Ca^{2+}) into the sperm cells, which is necessary for hyperactivation (i.e. swimming) to occur. Significant preclinical work has already been done that indicates CatSper may be a viable target for contraception. The CatSper family consists of four members, CatSper1 through CatSper 4, all of which are required for fertility. CatSper 1 and 2 have been established as critical for hyperactivity and motility while CatSper 3 and 4 are believed to play a role in the acrosome reaction (i.e. a process as the sperm approaches the egg). Studies on mice have shown that disruption of one or more of these channels resulted in immotile sperm but did not affect sperm production.

A drug that could temporarily block or disable CatSper could serve as a novel contraceptive option and could, at least theoretically, be taken by men and women. And, given that CatSper is unique only to sperm presents the possibility that a highly CatSper-targeted therapy could be virtually side-effect free.

The novelty of the target, non-hormonal nature and the potential that a CatSper-targeted contraceptive could be side-effect free and used by both men and women would put it in a class of its own. It also lends itself to increasing contraceptive use and, therefore, fits perfectly within the mandates of the NIH, the Bill & Melinda Gates Foundation, FHI 360 and other agencies and organizations which have provided funding for the development of novel modes of contraception which can help to reduce the rates of unintended pregnancies.

HISTORICAL STOCK PRICE

Source: Zacks Investment Research

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