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Daré Bioscience, Inc. (DARE-NASDAQ)

DARE: Upcoming Milestones Inc FDA Feedback on Topical Sildenafil FSAD Program

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 $6.75/share.

Current Price (09/18/18)	$1.00
Valuation	**$6.75**

OUTLOOK

Daré continues to not only move their various development programs forward, but also continues to add promising candidates to their high-potential women's health-focused pipeline. Relative to the former, DARE provided development updates during recent presentations at two of the most highly anticipated annual small-cap conferences; Canaccord Genuity's Annual Growth Conference (August 9th) in Boston and H.C. Wainwright's Annual Global Investment Conference (September 6th) in NYC. Relative to the latter, DARE's most recent pipeline addition, CatSper, a potential first-in-kind contraceptive for both men and women, was announced in mid-July.

Given progress with Topical Sildenafil in FSAD, we cover this topic in detail. Discussions with FDA are ongoing and apparently fruitful. Current timeline is to complete a content validity study – essentially a market research study which, along with further consultation with FDA (a type C meeting with FDA is anticipated later this year), will be used to further refine design of their phase 2b clinical study. So, while a lot of important questions remain, if all goes well, many of those could be answered by year-end. We think agreement with FDA on design of phase 2b clinical trial protocol would me a major milestone and, potentially, a value inflection point. As such, we will be eager to hear updates.

SUMMARY DATA

52-Week High	**$3.59**
52-Week Low	**$0.74**
One-Year Return (%)	**-69.83**
Beta	**2.67**
Average Daily Volume (sh)	**186,453**
Shares Outstanding (mil)	**11**
Market Capitalization ($mil)	**$11**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**7**
Insider Ownership (%)	**19**
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 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Value**
Industry	**Med-Biomed**

ZACKS ESTIMATES

Revenue
(in '000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2018	0.0 A	0.0 A	0.0 E	0.0 E	0.0 E
2019					
2020					

Earnings Per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.27 A	-$1.42 A	-$0.33 A	-$1.48 A	-$3.56 A
2018	-$0.88 A	-$0.32 A	-$0.26 E	-$0.27 E	-$1.61 E
2019					-$0.91 E
2020					-$0.74 E

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

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WHAT'S NEW

Q2 / Pipeline Update

Daré (DARE) continues to not only move their various development programs forward, but also continues to add promising candidates to their high-potential women's health-focused pipeline. Relative to the former, DARE provided development updates during recent presentations at two of the most highly anticipated annual small-cap conferences; Canaccord Genuity's Annual Growth Conference (August 9th) in Boston and H.C. Wainwright's Annual Global Investment Conference (September 6th) in NYC. Relative to the latter, DARE's most recent pipeline addition, CatSper, a potential first-in-kind contraceptive for both men and women, was announced in mid-July. We cover DARE's pipeline-related updates below.

The Q2 10-Q was filed in early August. As anticipated, operating expenses climbed from the previous quarter, reflecting personnel additions, Ovaprene development-related costs, expenses related to the (May) acquisition of Pear Tree Pharmaceuticals and an increase in licensing fees related to Juniper's intravaginal ring technology (which DARE secured in April).

Cash balance was a healthy $12.5M at Q2 quarter-end and the balance sheet remains debt-free. Cash balance should further benefit from ~$1.7M that remains under the NIH grant related to development of Ovaprene. Securing non-dilutive funding, such as this recent award, is an ongoing goal for DARE. Given that their focus on developing novel contraceptives aligns with the goals of foundations and certain government initiatives aimed at reducing unwanted pregnancies through increasing the use of birth control (which includes providing new contraceptive options), we anticipate further success in securing non-dilutive funds.

DARE Adds Novel Preclinical Contraceptive Candidate for Men and Women

In mid-July 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 (Ca2+) 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.

Ovaprene update

Ovaprene is DARE's lead development program with a post-coital trial (PCT) ongoing and currently anticipated to have topline data in Q2 2019. (For reference, the clinicaltrials.org posting is here: NCT03598088). As a reminder, DARE plans to use results (assuming positive) of this trial to petition FDA for IDE approval of a pivotal randomized controlled study. Importantly, current anticipated timelines are unchanged (i.e. not delayed) from prior expectations.

The PCT is a single-arm, 25-participant trial assessing the ability of Ovaprene to prevent sperm from penetrating the cervical mucus. Secondary measure is the change in ferrous gluconate (i.e. Ovaprene's spermiostasis agent) in the cervicovaginal fluid from pre to post-coital. Inclusion criteria requires participants to have previous had tubal sterilization.

Each participant will be followed over the course of five menstrual cycles and cervical mucus will be evaluated as follows; baseline at cycle 1 with use of no contraception, cycle 2 with use of Caya diaphragm, and cycles 3 through 5 with use of Ovaprene. The purpose of the Caya diaphragm (in cycle 2) is just to validate that the study conditions do not influence results as compared to what would be expected in the real world. 'Success' of effectiveness, which will be defined as finding five or fewer sperm per high-powered field in the cervical mucus, means that DARE would expect to move immediately towards an IDE package for approval to conduct a pivotal study.

Pivotal study, as envisioned today, is expected to include ~250 participants with evaluation over 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. So, assuming success on efficacy and in hitting their timelines in the PCT, a pivotal study is still realistic to commence in 2020/2021. If all goes well, an FDA PMA filing could happen in 2021/2022 and it is possible that Ovaprene could launch in the U.S. by sometime in 2022/2023. All these timelines are unchanged from our previous estimates.

Topical Sildenafil

Topical Sildenafil (TS) is DARE's deputy-lead program, rights to which they licensed in February. DARE 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. 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 indicated that initial discussions with FDA, mostly focused on defining FSAD in the context of clinically meaningful endpoints, have been fruitful. 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 sizeable 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 are spending so much time on this topic.

Sexual arousal and desire are more complicated in women: with men, an erection is correlated to arousal and arousal is correlated to desire to have sex – which means defining 'arousal' and 'desire' (and the connection between the two) in men is straightforward, as is designing clinical trials for novel ED drugs. With women, the connection between desire and arousal, appears to be more complicated – which complicates (or, at least increases the challenge of) designing female sexual dysfunction related clinical trials.

Pfizer (PFE) hoped to show that oral sildenafil (Viagra) would be effective at increasing women's sexual arousal and desire to have sex as it has done so successfully in men. While studies showed that it was effective at increasing physiological arousal[1,2,3,4] (i.e. genital stimulation, blood flow/clitoral engorgement) in women, that was not

[1] Caruso S, Rugolo S, Agnello C et al. Sildenafil improves sexual functioning in premenopausal women with type 1 diabetes who are affected by sexual arousal disorder: a double-blind, crossover, placebo-controlled pilot study. Fertil Steril. 2006; 85:1496-501.

significantly correlated to an increase in their (psychological) desire for sex. Following "inconclusive results" from several large scale, placebo-controlled studies with over 3,000 women, PFE subsequently dropped their female Viagra program[5].

Sildenafil increased arousal but trial design was flawed: Interestingly, PFE's thesis that oral Viagra could increase women's sexual arousal actually appears to have merit. We think that where Pfizer may have failed was in trial design, which appears to have been influenced by the assumption that arousal correlates to desire. Instead of focusing only (or mostly) on 'arousal', it appears they used a variety of female sexual dysfunction endpoints. There are only two PFE sildenafil FSD-related studies still listed on clinicaltrials.gov. The largest of which (n=267) is an open label study which used the Sexual Quality of Life-Female (SQOL-F) questionnaire as a substantial basis for the outcome measures. SQOL-F, an 18-item self-reported outcome instrument designed by Pfizer, focuses on measuring 'sexual confidence', 'emotional well-being' and 'relationship issues' – clearly not indicative of an arousal focus.

Our thesis that failure in proper clinical trial design as a result of incorrectly assuming correlation between arousal and desire seems particularly plausible given that at that time, there was virtually no reliable evidence for basing FSD-related clinical trial decisions. If PFE had focused solely on 'arousal' and in designing an appropriate clinical program around efficacy on FSAD, efficacy may have been much more favorable.

DSM: FDA considers guidance from the Diagnostic and Statistical Manual of Mental Disorders (DSM) in their industry guidance related to clinical trials for women with disorders related to sexual desire and/or sexual arousal. DSM, published by the American Psychiatric Association, is periodically updated. DSM-IV (published 1994, revised 2000) categorized FSAD and hypoactive sexual desire disorder (HSDD) as separate conditions. Under DSM-IV;

- FSAD is defined as "persistent or recurrent inability to attain or maintain until completion of the sexual activity an adequate lubrication-swelling response to sexual excitement, the disturbance causes marked distress or interpersonal difficulty and is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition"
- HSDD is defined as "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity, the disturbance causes marked distress or interpersonal difficulty and is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition"

DSM-V was published in 2013 and modified the characterization of arousal and desire disorders – stating that they could not be reliably distinguished and, therefore, combined FSAD and HSDD into a new category called Female Sexual Interest/Arousal Disorder (FSIAD). FSIAD is defined as;

- lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following; absent/reduced interest in sexual activity, absent/reduced sexual/erotic thoughts or fantasies, no/reduced initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate, absent/reduced sexual excitement/pleasure during sexual activity in almost all or all sexual encounters, absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues, absent/reduced genital or non-genital sensations during sexual activity in almost all or all sexual encounters
    - these symptoms must have persisted for a minimum of 6 months
    - these symptoms must cause clinically significant distress
    - these symptoms must not be better explained by a non-sexual mental disorder, consequence of relationship distress or other significant stressors and not attributable to substances or medication

FDA Recognizes FSAD, HSDD and FSIAD: 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 female sexual dysfunction. Following publishing of DSM-V, FDA held separate patient-focused public meetings and an industry-focused meeting with the respective goals of hearing "perspectives from women with female sexual

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[2] Erkan Alataş, MD; A. Baki Yağci, MD. The Effect of Sildenafil Citrate on Uterine and Clitoral Arterial Blood Flow in Postmenopausal Women. MedGenMed Ob/Gyn & Women's Health, 2004

[3] Laan, E et al. The Enhancement of Vaginal Vasocongestion by Sildenafil in Healthy Premenopausal Women. Journal of Women's Health & Gender-Based MedicineVol. 11, No. 4. Jul 2004

[4] Berman J. et al. Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal disorder: a double-blind, placebo controlled study. J Urol. 2003 Dec;170(6 Pt 1):2333-8.

[5] Susan Mayor. Pfizer will not apply for a licence for sildenafil for women. BMJ. 2004 Mar 6; 328(7439): 542.

dysfunction (FSD) 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).

Given significant disagreement regarding the change from various groups, including International Society for the Study of Women's Sexual Health (ISSWSH), FDA chose to not adopt DSM-V definition and instead continues to recognize (i.e. as of their 2016 Draft Guidance) 'desire' and 'arousal' as separate and distinct conditions.

2016 Draft Guidance: *Low Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs for Treatment Guidance for Industry DRAFT GUIDANCE*. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Published October 2016. The purpose of the Draft Guidance is to aid sponsors in developing drugs for FSD-related indications, specifically FSIAD, HSDD and FSAD.

The Guidance document is 12 pages long and can be found here (http://bit.ly/2OtqpnS). As is the case with all of FDA's topical industry draft guidance, it is non-binding and while providing recommendations, allows sponsors to use an alternative approach as long as it "satisfies the requirements of the applicable statues and regulations." It is also not 'finalized' – meaning (or at least implying) that FDA believes that there is more to learn about FSD-related diagnosis and how best to evaluate the safety and efficacy of therapies targeting these conditions.

While FDA's Guidance provides recommendations, it does not provide specific direction on choosing, constructing and validating patient-reported outcomes (PROs), nor does it offer a template for clinical trial design. Key points include that, "It is essential that sponsors use well-defined and reliable PRO instruments" and "For any PRO instrument proposed as a key study endpoint to support labeling claims, the sponsor should provide supportive information for FDA review (e.g., a copy of the assessment, the instrument's conceptual framework and scoring, evidence of the instrument's content validity and other measurement properties including reliability, construct validity, and ability to detect change)."

FSFI: While a validated PRO for 'low arousal' does not exist, FDA's Guidance suggests that the arousal domain of the Female Sexual Function Index (FSFI) may be a good place to start. It also suggests that, if used, FSFI-arousal should be supplemented by additional validated 'low arousal' measures. FSFI is a 19-question PRO that a clinical trial participant completes monthly. Questions relate to six domains (desire, arousal, lubrication, orgasm, satisfaction and pain) as a measure for overall sexual function. It has a history of use as a primary endpoint in both drug (see Addyi, below) and device studies (including as the primary endpoint in Viveve Medical's ongoing U.S. pivotal phase 3 study for 'improvement in sexual function').

It is important that whatever DARE uses for a primary endpoint, that it is clinically meaningful and validated. We note that two studies are widely cited as validation for FSFI in female arousal, desire and orgasmic disorders;

- Rosen, R, et al[6]. administered it to 128 subjects with FSAD (and a similar number of age-matched controls) and concluded that the "results support the reliability and psychometric (as well as clinical) validity of the Female Sexual Function Index (FSFI) in the assessment of key dimensions of female sexual function in clinical and nonclinical samples." Additionally, individual domain scores as well as the total FSFI score "showed good ability to differentiate between FSAD and non-FSAD subjects." The study was published in 2000 in the Journal of Sex & Marital Therapy.
- Meston, CM[7] extended FSFI validation with women diagnosed with female orgasm disorder (FOD) and HSDD. Results showed that each of the FSFI domains as well as the total FSFI score differentiated (significantly) between HSDD subjects (n=44) and controls as well as FOD subjects (n=71) and controls. The authors concluded that the "ability of FSFI to differentiate between clinical and nonclinical groups of women lends

[6] Rosen R, et al. The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function, 26:191–208, 2000
[7] MEston CM, (2003) Validation of the Female Sexual Function Index (FSFI) in Women with Female Orgasmic Disorder and in Women with Hypoactive Sexual Desire Disorder, Journal of Sex & Marital Therapy, 29:1, 39-46,

support for the discriminant validity of the FSFI among these groups [i.e. those diagnosed with HSDD and FOD] of women". The study was published in 2003 in the Journal of Sex & Marital Therapy

The 'arousal' domain consists of FSFI questions three through six and asks the respondent to rate their feelings of arousal in the context of frequency, level, confidence and satisfaction:

FSFI-arousal

Q3) ***Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?***

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

Q4) ***Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?***

- No sexual activity
- Very high
- High
- Moderate
- Low
- Very low or none at al

Q5) ***Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?***

- No sexual activity
- Very high confidence
- High confidence
- Moderate confidence
- Low confidence
- Very low or no confidence

Q6) ***Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?***

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

SOURCE fsfiquestionnaire.com

FDA encourages use of co-primaries and secondaries…

FDA encourages the use of co-primary and secondary endpoints to further support demonstration of treatment benefit. FSFI-arousal is presumably an option for DARE as a primary or secondary endpoint, although their September investor presentation indicates their first choice for primaries may be a 'genital sensation' measure and 'distress'. FSFI (i.e. the full 19-item questionnaire) may also be under consideration (as a secondary). Others potentially under consideration, we think, could be PROs related to 'satisfying sexual events' (SSEs), a short-recall period (e.g. daily) arousal diary, lubrication and associated distress.

However, FDA's Draft Guidance is less than clear in certain areas as it relates to endpoints. For example, while it states that change in the number SSEs can be used as a primary endpoint in FSD trials (for indications such as low desire, interest and/or arousal), a few paragraphs later they suggest against use of SSE as a primary as; DSM does not include it as a definition for low interest, desire and/or arousal and comments from the October 2014 public meetings recommended against its use as a primary.

As such and coupled with the lack of industry-wide acceptance of SSEs as a valid proxy for desire or arousal (along with its controversy as an endpoint in Addyi trials- see below), we don't expect it to be on DARE's short list of primary endpoints (although, perhaps as a secondary). In fact, DARE's September 2018 investor presentation indicates that they proposed to FDA to not include SSE as a primary and that the agency was receptive.

We do think a short-recall arousal diary, lubrication and distress could be viable coprimaries and/or secondaries. FDA's Draft Guidance recommends using a short-recall measure, especially for drugs dosed daily or on an as-

needed basis (as Topical Sildenafil is being designed) – while we are not aware of a validated short-term/daily arousal measure, we think it is likely to be addressed with FDA.

It seems clear that FDA embraces the DSM-IV definition of FSAD – which hinges the inability to maintain adequate lubrication as a response to sexual excitement and which causes marked distress and which cannot be better explained by other causes. DARE indicated that they are interested in a 'genital sensation' related measure (which could encompass lubrication) as a primary – although we do not yet know specifics.

As it relates to 'lubrication', we think one possibility is the FSFI-lubrication domain (below), which consists of four questions (#s 7 – 9) related to lubrication in the context of; frequency, ability to achieve, frequency in maintaining and ability to maintain.

FSFI-lubrication

Q7) Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

Q8) Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

Q9) Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

Q10) Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

SOURCE: fsfiquestionnaire.com

As it relates to 'distress', FDA's Guidance provides little direction as to an appropriate PRO for distress associated with low arousal. The Female Sexual Function Index (FSDS), a validated[8] 12-question PRO, was designed to measure sexually-related personal distress in women. It was subsequently modified, adding a 13th question; *bothered by low sexual desire*, to customize it specifically for distress associated with low desire. This modified (and validated[9]) version, FSDS-R, is cited in FDA's Draft Guidance as potentially useful for 'desire' related programs and was used as a secondary endpoint in all three of Addyi's phase 3 FDA trials (for HSDD). It also received (largely) strong support from panelists during the October 2014 industry-focused workshops as an appropriate measure of distress associated with HSDD.

We are not aware of a validated PRO for distress associated with low arousal. This may be a case where DARE will need to design their own PRO – which presumably might include using FSDS as a guide and modifying it so as to be suitable for measuring arousal related distress (similar to how FSDS was modified for HSDD).

[8] DeRogatis L, et al. J Sex Med. 2008;5:357-364.
[9] DeRogatis L, et al. *J Sex Marital Ther*. 2002;28:317-330.

FSDS-R (validated for 'desire')

The Female Sexual Distress Scale-Revised (FSDS-R; revised 2005): Screening Questionnaire for Measuring Sexually Related Personal Distress in Women With Female Sexual Dysfunction (FSD)

Name: Date:

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST 30 DAYS INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: **Personal responsibility for your sexual problems.**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

How often did you feel

1. Distressed about your sex life	0	1	2	3	4
2. Unhappy about your sexual relationship	0	1	2	3	4
3. Guilty about sexual difficulties	0	1	2	3	4
4. Frustrated by your sexual problems	0	1	2	3	4
5. Stressed about sex	0	1	2	3	4
6. Inferior because of sexual problems	0	1	2	3	4
7. Worried about sex	0	1	2	3	4
8. Sexually inadequate	0	1	2	3	4
9. Regrets about your sexuality	0	1	2	3	4
10. Embarrassed about sexual problems	0	1	2	3	4
11. Dissatisfied with your sex life	0	1	2	3	4
12. Angry about your sex life	0	1	2	3	4
13. Bothered by low sexual desire	0	1	2	3	4

A score of ≥11 effectively discriminates between women with FSD and no FSD.*

Total

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* DeRogatis L, et al. *J Sex Med*. 2008;5:357-364.

SOURCE: obgynalliance.com

Addyi's experience provides insight and may prove beneficial to DARE: While FDA has little experience with FSFI-arousal, they do have some experience with FSFI-desire as it served as an endpoint in Addyi's (Flibanserin) U.S. phase 3 studies. Flibanserin was initially developed as an SSRI but after failing anti-depression trials, Boehringer Ingelheim switched to HSDD.

Addyi was evaluated in three U.S. phase 3 clinical trials for HSDD, the first two used 'satisfying sexual events' (SSEs) and a 'daily desire diary' as co-primary endpoints and FSFI-desire and FSDS-R (a distress-related PRO) as secondaries, while the third study used FSFI-desire and SSEs as co-primaries and FSDS-R as a secondary. All three studies showed statistically significant improvement in SSE's as well as on FSFI-desire and reduction of stress (as measured by FSDS-R) but 'desire' as measured by the daily diary was not statistically significant in either of the two studies in which it was included.

While Addyi was eventually approved in August 2015 for the treatment of HSDD, questionable efficacy and safety concerns resulted in it being a commercial flop (generating revenue of just ~$55M in 2016 and $80M in 2017). Much of the questions relative to efficacy appeared to relate to questions about the validity of the studies' endpoints – including criticism that the number of SSEs is not a reliable proxy for determining 'desire'.

Addyi was a disappointment for Boehringer Ingelheim and Sprout (Sprout acquired rights following Boehringer's initial attempt at an HSDD indication which an FDA panel voted 10-1 against on efficacy and 11-0 against on safety) but also likely served as somewhat of an embarrassment, and learning experience, for FDA. It may have also been a catalyst towards publishing of their revised guidance (in 2016). Important to note is that FDA draft guidance for FSD-related studies during much of the time of Addyi's development for HSDD was relatively scant – in fact FDA's 2000 FSD Draft Guidance, which provided little in the way of actual 'guidance' of validated PROs, was withdrawn in 2010.

The reason for our discussion about Addyi is because we think it illustrates the potential complexity of designing an appropriate FSD-related study and the potential for poor outcomes of failing to do so. FDA's FSD-related guidance at that time was significantly lacking, which may have contributed to Addyi's ultimate commercial failure. We also find it interesting that FDA eventually approved Addyi despite the advisory panels' near-unanimous vote against doing so in 2010 and lack of much additional evidence of efficacy and safety supporting Sprout's refilling of the NDA in 2013.

Public pressure to approve a drug that could address low sexual desire in women (similar to what Viagra had done for men), as well as potentially, motivation within FDA to do the same, may have played a part. Either way, we think the high-profile failure of what was expected to be the first 'female Viagra' may have been a real motivating moment for FDA in building a better framework for the evaluation of novel FSD drugs and in having a proactive approach towards working with sponsors in trial design and endpoint selection. So, Addyi's failure may be an indirect benefit to DARE.

Considerations:

Others have attempted FSD-related (i.e. HSDD, FSAD) U.S. clinical programs and most have failed. Addyi is the only drug to be approved for an FSD indication but it is largely viewed as a commercial failure. Vivus' FSAD program for their alprostadil (Alista) is an example of another failure. Alprostadil injection is FDA approved for ED but, alprostadil (cream) failed to demonstrate efficacy in a phase 2 study in FSAD with a primary endpoint of female sexual encounter profile (FSEP). Apricus, similarly attempted and failed at a U.S. FSAD indication for alprostadil cream (under Femprox name).

DARE's goals will need to focus on 'arousal' – including a clinically relevant definition, how to measure it, how to identify the appropriate trial population and making sure it is delineated from 'desire'. They will also need to have agreement with FDA. Learning from the mistakes of other FSD-related programs, including those of PFE, Sprout/Boehringer and Vivus, and working with a receptive and motivated FDA means DARE could be starting from a much more favorable position than others that have attempted an FSD clinical program. A lot of questions remain unanswered, however.

While FDA recognizes female low sexual arousal as distinct from 'desire', there is lack of agreement that the two can be distinguished. DSM-IV defined female low arousal separately from female low desire but DSM as-updated (in 2013) modified the characterization of arousal and desire disorders – stating that they could not be reliably distinguished and, therefore, combined FSAD and HSDD into a new category, FSIAD. There is also disagreement as to the validity of specific FSD-related symptoms. For example, given lack of expert consensus that lubrication correlates to arousal, 'lubrication' was absent in DSM-V as symptomatic of FSIAD despite being included in the 'arousal' definition in DSM-IV.

Given ambiguity over whether clinical FSAD even exists and if it does, uncertainty about how to properly define it, means DARE faces challenges not typical of most (non-FSD) drug developers. "Correctly' defining symptomatic female low sexual arousal and using that to successfully identify an appropriate FSAD target population (including, potentially delineating from comorbid arousal-desire) will be critical for DARE to be successful in demonstrating efficacy of Topical Sildenafil in FSAD.

Eligibility and inclusion/exclusion criteria are considerations in identifying the appropriate target population. Sprout used what some claimed was too restrictive inclusion/exclusion enrollment criteria in order to cherry-pick a population that would respond to Addyi. Specifically, that one of their pivotal phase 3 trials was restricted to only women that were; pre-menopausal, in stable heterosexual relationships, without existing psychiatric or other medical conditions and absent use of medications. Eligibility criteria were less strict in Sprout's other phase 3 trials.

FDA's Draft Guidance addresses eligibility – while noting that exclusion criteria should be limited to ensure the trial population is representative of women that would likely use the drug, also recommending that eligibility be confined only to those most likely to respond to the drug. The only specifics on this topic in the Draft Guidance is that trial subjects should have a history of low arousal and associated distress, sexually active and in stable relationships. It further recommends including subjects with a broad range of severity of sexual dysfunction (with associated distress) and considering including both pre and post-menopausal women in the same trial or in separate trials (DARE recently noted that they expect Topical Sildenafil's target population to include both pre and post-menopausal women). Further, exclusion/inclusion criteria can be modified in subsequent phase 3 trials so as to evaluate the drug in a less restrictive patient population.

Safety has been a topic of some concern with oral sildenafil for ED (as well as for Addyi for female HSDD). FDA inherently has a higher safety hurdle for drugs that treat non-life threatening conditions, particularly those with daily or on-demand dosing. While generally considered safe, Viagra has been associated with certain cardiovascular and other risks, such as hearing and vision loss. 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 potentially mitigate the risk profile as compared to oral Viagra.

Timelines…

Management noted in their recent presentations that they have been in contact with FDA in order to get clarity on many of the topics we have covered – including defining and measuring 'arousal' and identifying the most appropriate endpoints and PROs. DARE's current timeline is to complete a content validity study – essentially a market research study which, along with further consultation with FDA (a type C meeting with FDA is anticipated later this year), will be used to further refine design of their phase 2b clinical study. So, while a lot of important questions remain, if all goes well, many of those could be answered by year-end. We think agreement with FDA on design of phase 2b clinical trial protocol would me a major milestone and, potentially, a value inflection point. As such, we will be eager to hear any additional feedback from FDA.

BACKGROUND

DARE is a pre-revenue, clinical-stage company engaged in the development of novel therapeutic technologies targeting unmet needs in women's health. The company, which went public through a reverse-merger in July 2017**,** currently has two core programs in phase 2 development; **Ovaprene**®, a novel non-hormonal monthly intravaginal ring contraceptive, and **Topical Sildenafil**, a proprietary cream incorporating the active ingredient in Viagra, for the treatment of female sexual arousal disorder.

Looking to further expand their women's reproductive health pipeline, in just the last several months DARE added a number of earlier-stage opportunities. Recent additions to their pipeline include;

- VVA1 (fka PT-101): DARE added VVA1 through their May acquisition of Pear Tree Pharmaceuticals. VVA1 is a proprietary formula of the drug tamoxifen, one of the most widely used treatments for hormone-receptor positive (HRP) breast cancer. DARE intends to develop VVA1 for the treatment of vaginal atrophy in women with, or at risk of developing, HRP breast cancer – an indication for which it has shown early promise
- Novel intravaginal ring technology: in April DARE secured exclusive rights (from Juniper Pharmaceuticals) to a novel intravaginal ring drug-delivery platform technology, including its use in three pre-clinical candidates for; overactive bladder, hormone replacement therapy and for the prevention of preterm birth
- Novel long-acting injectable contraceptives: in March DARE penned an agreement with Orbis Biosciences which gives them the option to license rights to two (pre-clinical stage) novel long-acting injectable contraceptives
- CatSper contraceptive for men/women: In mid-July DARE acquired rights to Hydra Biosciences' CatSper ion channel intellectual property. As Cation Channel of Sperm (CatSper) is unique to sperm, a drug that could temporarily block or disable it could serve as a novel contraceptive option for both men and women

Ovaprene



SOURCE: Dare Bioscience

Core Programs

In July 2017 DARE obtained worldwide rights (licensed from ADVA-Tec) to **Ovaprene**, the company's lead development program. Ovaprene, a monthly non-hormonal intravaginal ring, represents a new class of women's contraception. Unlike all other current non-coital methods, Ovaprene is hormone-free. Instead of hormones it uses a mesh barrier to physically block sperm while non-hormonal ingredients (ferrous gluconate), which are released from the silicone ring, induce spermiostasis. While certain features of vaginal rings (including effectiveness, reversibility and convenience of monthly use) score high in consumer surveys and studies, hormone-related side-effects (including risk of serious cardiovascular events) are an oft-cited drawback of currently available options, such as NuvaRing (etonogestrel/ethinyl estradiol). Hormonal contraceptive methods, which (in addition to the vaginal ring) also come in the form of the pill, implant, patch, IUD and injection, account for approximately 74% of U.S. contraceptive product use (condoms account for another 25%). But while hormonal contraceptives remain popular, 50% of women that try them discontinue use and of those that do, side effects are the overwhelming reason why.

Approximately 40M women in the U.S. currently use some form of birth control, 23M of which use one or more contraceptive products, including ~17M which use hormonal methods. The unmet need for an effective monthly contraceptive option which is free of hormone-related side effects (and related concerns) has created an opportunity for DARE. Development of new and alternative methods of contraception is also recognized as 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. Of the unintended pregnancies, 41% (~1.2M) are attributed to inconsistent or incorrect use of contraception and 54% (~1.5M) result from the lack of contraceptive use (or month+ gap of use). Reducing unwanted pregnancies and increasing contraceptive access and use are the subject of grants from the National Institute of Health (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. In April DARE received (an initial) $225k of an anticipated $1.9M grant from a division of NIH - this provides DARE with non-dilutive funding for development of Ovaprene.

Human proof-of-concept of Ovaprene was demonstrated in a small (n=20) post-coital test (PCT) study which showed no viable sperm in the cervical mucus and that the device was well tolerated. Ovaprene is a combination product (device/drug), U.S. regulatory oversight of which will be the responsibility of FDA's (CDRH) medical device branch and which will follow a PMA pathway. DARE's U.S. regulatory strategy and anticipated timelines are similar to that followed by other approved barrier methods including the Caya diaphragm. Specifically, DARE plans to use results (assuming positive) of their recently-initiated post-coital trial (n=25) to petition FDA for IDE approval of a pivotal randomized controlled study. DARE's anticipated timelines are to complete the PCT (data expected Q2 2019) and file for IDE approval in 2019 and start/finish a pivotal study (n=~250) in 2020/2021. If all goes well, an FDA PMA filing could happen in 2021/2022 and it is possible that Ovaprene could launch in the U.S. by sometime in 2022/2023.

In February 2018 DARE in-licensed rights to **Topical Sildenafil** (SST-6007) for any indications related to female sexual dysfunction and female reproductive health. DARE plans to develop Topical Sildenafil for Female Sexual Arousal Disorder (FSAD), a condition characterized by the inability to attain and/or maintain sufficient physical sexual arousal. While FSAD is estimated to affect approximately 13M women in the U.S., no products currently exist that are indicated to treat the condition (importantly, FDA does recognize FSAD as a distinct condition). 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. Contingent on pathway and trial design-related feedback from FDA (a meeting with which is anticipated in the near-term), DARE's estimated development timelines include start/complete a phase 2b study in 2018/2020 and commence a phase 3 study in 2H 2020.

Management noted in their recent presentations that they have been in contact with FDA in order to get clarity on critical topics such as defining and measuring 'arousal' and identifying the most appropriate endpoints and PROs. DARE's current timeline is to complete a content validity study – essentially a market research study which, along with further consultation with FDA (a type C meeting with FDA is anticipated later this year), will be used to further refine design of their phase 2b clinical study. So, while a lot of important questions remain, if all goes well, many of those could be answered by year-end. We think agreement with FDA on design of phase 2b clinical trial protocol would me a major milestone and, potentially, a value inflection point. As such, we will be eager to hear any additional feedback from FDA.

Strategic Pipeline: *VVA therapy, intravaginal ring technology, longer-acting injectable contraceptive, men/women contraceptive …*

In May 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**. PT-101 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 PT-101 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 PT-101 was associated with improvement in vaginal dryness and decreased vaginal pH. 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 PT-101 would prove similar to that of Osphena. Next steps in development of PT-101, per DARE's May 7th press release announcing the merger, are to optimize the vaginal formulation before moving to larger clinical trials.

In April 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. DARE noted in September that a phase 1 (PK/safety) study is starting for HRT1 which will evaluate two doses to determine steady-state over 28 days.

In March 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.

DARE Adds Novel Preclinical Contraceptive Candidate for Men and Women

In mid-July 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 (Ca2+) 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.

Valuation

Ovaprene

Based on our estimates and assumptions (below), Ovaprene represents more than 70% 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 8,281 reports of 'serious' events attributable to NuvaRing, including 233 deaths. Of the serious events, 38% 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 and Dr. Reddy's Labs both expect to launch a generic version of NuvaRing in 2019. 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 could soon include a one-year Nestorone (a progestin) /ethinyl estradiol vaginal ring, an NDA for which Population Council filed in January 2018. Pre-marketing studies (per Pop Council) indicated 89% of women surveyed were 'satisfied' with the ring as a contraceptive method

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.

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 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

PT-101

- launches 2023
- achieves 27% share of Osphena's peak penetration by 2026 and 30% by 2028 (which we also assume represents PT-101 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 DARE at $6.75/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 a current fully-diluted share count of approximately 15.7M, base case puts fair value of DARE at approximately $6.75/share.

VALUATION WATERFALL

Risk-Adjusted Forecasted Revenue

	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
Ovaprene	$0	$0	$0	$5,187	$22,220	$49,323	$72,041	$83,411	$97,531	$125,465
%of total		-	*0%*	*59%*	*74%*	*76%*	*73%*	*72%*	*71%*	*74%*
PT-101 (VVA)	$0	$0	$0	$1,430	$3,484	$8,840	$16,150	$18,214	$18,487	$18,764
%of total		-	*0%*	*16%*	*12%*	*14%*	*16%*	*16%*	*14%*	*11%*
Topical Sildenafil (FSAD)	$0	$0	$814	$2,203	$4,192	$7,092	$10,941	$14,612	$20,763	$25,591
%of total		-	*100%*	*25%*	*14%*	*11%*	*11%*	*13%*	*15%*	*15%*
TOTAL Risk-adj Revenue	**$0**	**$0**	**$814**	**$8,820**	**$29,896**	**$65,255**	**$99,132**	**$116,237**	**$136,781**	**$169,819**

Risk-Adjusted Market Value

Present Value based on 2029 out-year:	Per-share value	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
20% discount rate	$3.23	$50,783	$63,479	$79,349	$99,186	$123,982	$154,978	$193,722	$242,152	$302,691	$378,363	$472,954	$591,192
15% discount rate	$7.10	$111,685	$131,394	$154,581	$181,860	$213,953	$251,710	$296,129	$348,387	$409,868	$482,197	$567,291	$667,401
10% discount rate	$14.93	$234,802	$260,891	$289,879	$322,088	$357,875	$397,639	$441,821	$490,912	$545,458	$606,065	$673,405	$748,228
Present Value based on 2028 out-year:													
20% discount rate	$3.74	$58,747	$73,434	$91,792	$114,740	$143,425	$179,281	$224,102	$280,127	$350,159	$437,699	$547,124	
15% discount rate	$7.28	$114,447	$134,643	$158,404	$186,357	$219,244	$257,934	$303,452	$357,002	$420,003	$494,121	$581,319	
10% discount rate	$13.65	$214,616	$238,463	$264,959	$294,398	$327,109	$363,455	$403,839	$448,710	$498,566	$553,963	$615,514	
Present Value based on 2027 out-year:													
20% discount rate	$3.97	$62,404	$78,005	$97,506	$121,883	$152,354	$190,442	$238,053	$297,566	$371,957	$464,946		
15% discount rate	**$7.28**	$114,420	$134,612	$158,367	$186,314	$219,193	$257,874	$303,381	$356,919	$419,905	$494,006		
10% discount rate	$12.89	$202,646	$225,162	$250,180	$277,978	$308,865	$343,183	$381,314	$423,682	$470,758	$523,065		
Present Value based on 2026 out-year:													
20% discount rate	$4.23	$66,526	$83,158	$103,948	$129,934	$162,418	$203,022	$253,778	$317,223	$396,528			
15% discount rate	**$7.30**	$114,803	$135,063	$158,897	$186,938	$219,927	$258,738	$304,397	$358,115	$421,311			
10% discount rate	$12.21	$192,029	$213,366	$237,073	$263,414	$292,682	$325,203	$361,336	$401,485	$446,094			
Present Value based on 2025 out-year:													
20% discount rate	$3.48	$54,739	$68,424	$85,530	$106,913	$133,641	$167,052	$208,815	$261,018				
15% discount rate	**$5.65**	$88,906	$104,596	$123,054	$144,769	$170,316	$200,372	$235,732	$277,332				
10% discount rate	$8.93	$140,450	$156,055	$173,395	$192,661	$214,067	$237,853	$264,281	$293,645				
Present Value based on 2024 out-year:													
20% discount rate	$1.99	$31,348	$39,185	$48,981	$61,226	$76,533	$95,666	$119,583					
15% discount rate	$3.05	$47,919	$56,376	$66,324	$78,029	$91,798	$107,998	$127,057					
10% discount rate	$4.55	$71,495	$79,439	$88,265	$98,073	$108,970	$121,078	$134,531					
Present Value based on 2023 out-year:													
20% discount rate	$0.74	$11,560	$14,450	$18,062	$22,578	$28,222	$35,278						
15% discount rate	$1.06	$16,631	$19,566	$23,019	$27,081	$31,860	$37,483						
10% discount rate	$1.49	$23,435	$26,039	$28,932	$32,147	$35,719	$39,688						

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FINANCIAL MODEL

DARE	2017 A	Q1A	Q2A	Q3E	Q4E	2018 E	2019 E	2020 E
updated rows are green highlight								
Ovaprene U.S. Mkt Assumptions								
Net annual revenue per patient	$200					$300	$300	$300
NuvaRing Avg Annual Patients	1,106,000					1,106,000	1,117,060	1,128,231
NuvaRing Peak US Revenue	$564,000,000					564,000,000	$572,460,000	$581,046,900
U.S. Contracep Product Patient Mkt	23,000,000					$23,000,000	23,000,000	23,460,000
U.S. Contraceptives Mkt Value	$5,500,000,000					$5,500,000,000	5,500,000,000	$5,610,000,000
Ovaprene U.S. Penetration Assmptions								
Penetration of US contraceptives $ value						0.0%	0.0%	0.0%
Penetration of NuvaRing's Peak US patients						0.0%	0.0%	0.0%
Number of Annual U.S. Ovaprene patients						0	0	0
OVAPRENE U.S. REVENUE ($'000)	**$0**					**$0**	**$0**	**$0**
OVAPRENE OUS REVENUE						**$0**	**$0**	**$0**
Ovaprene OUS as % of U.S.						85.0%	85.0%	85.0%
TOTAL OVAPRENE REVENUE						**$0**	**$0**	**$0**
yoy growth							-	-
PT-101 U.S. Mkt Assumptions								
Net annual revenue per patient	$2,160					$2,160	$2,182	$2,203
PT-101 Total Patient Market	1,400,000					1,400,000	1,414,000	1,428,140
Osphena Peak US Revenue	$43,000,000					$43,000,000	$43,645,000	$44,299,675
PT-101 Patient Market Value	$3,024,000,000					$3,024,000,000	$3,084,782,400	$3,146,786,526
PT-101 U.S. Penetration Assumptions						0.0%	0.0%	0.0%
Penetration' of Osphena's Peak Revenue						0.0%	0.0%	0.0%
Penetration of US HRP+ VVA						0.00%	0.00%	0.00%
U.S. PT-101 REVENUE ($000s)						**$0**	**$0**	**$0**
PT-101 OUS REVENUE						**$0**	**$0**	**$0**
PT-101 OUS as % of U.S.						30.0%	30.0%	30.0%
TOTAL PT-101 REVENUE						**$0**	**$0**	**$0**
yoy growth							-	-
Topical Sildenafil US Mkt Assumptions								
TS Net Annual revenue per patient	$1,560					$1,560	$1,576	$1,591
TS Total US Patient Market	13,000,000					$13,000,000	13,195,000	13,392,925
Addyi Peak Revenue	$78,000,000					$78,000,000	$79,170,000	$80,357,550
TS Patient Market Value	20,280,000,000					20,280,000,000	20,790,042,000	21,312,911,556
TS U.S. Penetration Assumptions								
Penetration' of Addyi's Peak Revenue						0.00%	0.00%	0.00%
Penetration' of FSAD						0.00%	0.00%	0.00%
Total TS REVENUE ($000s)						**$0**	**$0**	**$0**
TS OUS REVENUE						**$0**	**$0**	**$0**
TS OUS as % of U.S.						30.0%	30.0%	30.0%
TOTAL TS REVENUE						**$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	-	-	-	-	-	-	-	-
SG&A	$2,704.9	$1,303.2	$1,157.2	$1,461.0	$1,551.0	$5,472.4	$6,450.0	$6,856.0
% SG&A	-	-	-	-	-	-	-	-
R&D	$984.7	$1,186.7	$2,467.6	$1,514.0	$1,542.0	$6,710.3	$7,455.0	$8,142.0
%R&D	-	-	-	-	-	-	-	-
Impairment of Goodwill	$7,490.9	$5,187.5	$0.0	$0.0	$0.0	$5,187.5	$0.0	$0.0
TOTAL OpEx	**$11,180.5**	**$7,677.4**	**$3,624.8**	**$2,975.0**	**$3,093.0**	**$17,370.2**	**$13,905.0**	**$14,998.0**
% Total OpEx	-	-	-	-	-	-	-	-
Operating Income	($11,180.5)	($7,677.4)	($3,624.8)	($2,975.0)	($3,093.0)	($17,370.2)	($13,905.0)	($14,998.0)
Operating Margin	-	-	-	-	-	-	-	-
Total Other Income (Expense)	($340.7)	($2.0)	$15.1	$6.0	$5.1	$65.5	$28.2	$16.7
Pre-Tax Income	($11,521.2)	($7,679.3)	($3,609.7)	($2,969.0)	($3,087.9)	($17,304.7)	($13,876.8)	($14,981.3)
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	($11,521.2)	($7,679.3)	($3,609.7)	($2,969.0)	($3,087.9)	($17,304.7)	($13,876.8)	($14,981.3)
YOY Growth	*1612.7%*	*3049.0%*	*624.5%*	*81.1%*	*-69.7%*	*50.2%*	*-19.8%*	*8.0%*
Net Margin	-	-	-	-	-	-	-	-
EPS (GAAP)	($3.56)	($0.88)	($0.32)	($0.26)	($0.27)	($1.61)	($0.91)	($0.74)
YOY Growth	*342.4%*	*230.0%*	*-42.3%*	*-21.1%*	*-89.1%*	*-54.9%*	*-43.5%*	*-18.9%*
Shares O/ S	3,232	8,685	11,422	11,450	11,455	10,753	15,250	20,300

Brian Marckx, CFA

HISTORICAL STOCK PRICE

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DARE BIOSCIENCE (W)
Price ($)
55
50
45
40
35
30
25
20
15
10
5
0
11/2/15
1/25/16
4/18/16
7/11/16
10/3/16
12/26/16
3/20/17
6/12/17
9/4/17
11/27/17
2/19/18
5/14/18
8/6/18
<< 10/6/06
9/17/18 >>

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