Zacks Small-Cap Research

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Agile Therapeutics Inc. (AGRX-NASDAQ)

AGRX: Initiating Coverage of Agile Therapeutics; NDA for Weekly Contraceptive Patch Set to Be Filed…

Based on our probability adjusted DCF model that takes into account potential future revenues from Twirla®, AGRX is valued at $7/share. This model is highly dependent upon Twirla® attaining regulatory approval and its commercial success and will be adjusted accordingly based upon regulatory and commercial outcomes.

Current Price (05/15/17)	$3.51
Valuation	**$7.00**

INITIATION

Agile Therapeutics, Inc. (AGRX) is a specialty healthcare company developing products to fulfill the unmet needs of women. The company is developing hormonal contraceptives that offer greater convenience than what is currently offered by the once-daily contraceptive pill. The company's lead product, Twirla® (AG200-15), is a once-weekly low–dose combination hormonal contraceptive patch that has completed three Phase 3 clinical trials. Agile will be resubmitting the new drug application (NDA) for Twirla® in the first half of 2017.

Twirla® is set to enter a hormonal contraceptive market in the U.S. that had total market sales of approximately $3.7 billion in 2016. With only one other contraceptive patch on the market, which has limitations due to a higher level of hormones and negative physical characteristics, we believe Twirla® could attain significant market share. With a current valuation of only $101 million, Agile may offer investors the chance for outsized returns.

SUMMARY DATA

52-Week High	**$8.27**
52-Week Low	**$2.04**
One-Year Return (%)	**-44.64**
Beta	**1.83**
Average Daily Volume (sh)	**177,752**
Shares Outstanding (mil)	**29**
Market Capitalization ($mil)	**$101**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**81**
Insider Ownership (%)	**4**
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 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**

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

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	0 A	0 A	0 A	0 A	0 A
2017	0 A	0 E	0 E	0 E	0 E
2018					18.5 E
2019					38.9 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.27 A	-$0.29 A	-$0.27 A	-$0.19 A	-$1.02 A
2017	-$0.26 A	-$0.25 E	-$0.25 E	-$0.26 E	-$1.03 E
2018					-$0.72 E
2019					-$0.30 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of Agile Therapeutics, Inc. (AGRX) with a $7.00 valuation. Agile is a women's specialty healthcare company developing products to fulfill the unmet contraceptive needs of women. The company's lead product, Twirla® (AG200-15), is a once-weekly low-dose combination hormonal contraceptive patch. Agile has conducted a comprehensive development program for Twirla® that includes three Phase 3 clinical trials, and the company will be resubmitting the new drug application (NDA) during the first half of 2017. We believe Twirla® has a number of positive attributes that are likely to lead to commercial success, including:

- **Convenient Once-Weekly Application**: The market leader for female hormonal contraception is the once-daily pill. The reason for its popularity has more to do with familiarity than with any significant advantage it has in terms of potency or superior safety profile. While effective, there are significant drawbacks regarding compliance associated with oral contraceptives, with studies showing that the average woman misses approximately two to four pills per month. Twirla® is a patch that is applied three times per month (once per week), thus instead of needing to remember to take a daily pill every day for three weeks, users of Twirla® need to just remember to apply a new patch once a week.

- **Superior Tolerability Profile**: Twirla® is a low-dose contraceptive patch, which translates into fewer adverse side effects as compared to hormonal contraceptive products that deliver higher doses of estrogen. The recently completed Phase 3 SECURE trial, which included 2032 women, showed the highest percent of adverse events were associated with headache (4.3%), nausea (4.1%), and breast tenderness (2.0%). In contrast, in the clinical trials for the Ortho Evra® patch, those same adverse events were experienced but a much higher percentage of subjects (headache = 21.0%; nausea = 16.6%; breast tenderness = 22.4%).

- **Real-World Efficacy Shown in Diverse Population**: For the SECURE trial, the FDA requested that Agile have limited exclusion criteria and include women of all ethnicities, races, and body types. Previous contraceptive studies were typically conducted in a female population that was heavily skewed toward Caucasians with normal body mass indexes (BMIs). The SECURE trial population included a high percentage of subjects that were overweight (25%) or obese (35%). Results showed that the Pearl Index (PI), which is a measurement of the rate of pregnancies over a specific period of time in a clinical trial, was highly correlated with BMI. Those with a normal BMI (<25) had a PI of 3.03, while those that were overweight (BMI ≥ 25 - < 30) and obese (BM ≥ 30) had PIs of 5.36 and 6.42, respectively.

- **Skinfusion Technology Superior to Other Patches**: Agile has developed a proprietary patch technology, termed Skinfusion, that optimizes adhesion while delivering a steady stream of contraceptive hormones through the skin. The outer surface of the patch is made of a soft fabric, while the inner portion consists of several layers of material that contain the active ingredients ethinyl estradiol and levonorgestrel. The patch is designed to prevent seepage of the adhesive from around the edge, where it could collect dirt and leave a "black ring" on the skin, a frequent complaint from users of patches that do not utilize the Skinfusion technology. No royalties are owed to any third parties for the Skinfusion technology.

Agile reported $41.7 million in cash and cash equivalents at the end of the first quarter of 2017, which we believe is sufficient to fund operations into the second quarter of 2018. Assuming the NDA is resubmitted in the first half of 2017, with a six-month review Twirla® could be approved by the end of 2017. Agile will require additional capital for the commercial launch of Twirla®, which could be acquired through a number of different means, including a commercial partnership, the sale of equity, debt financing (Agile recently amended its loan and security agreement with Hercules Capital, Inc. that allows the company the opportunity to draw an additional $8.5 million until January 31, 2018), or royalty monetization.

INVESTMENT THESIS

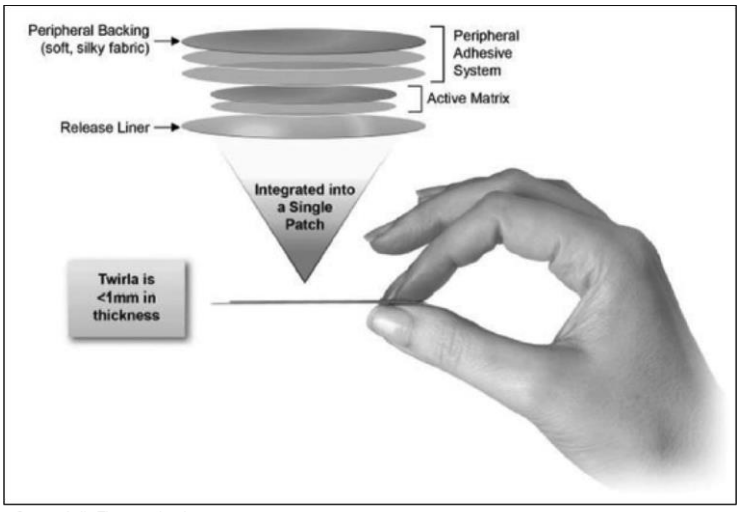
Agile Therapeutics, Inc. (AGRX) is a women's healthcare company focused on developing healthcare products to fulfill the unmet contraceptive needs of women. The company's lead candidate product, Twirla®, is a once-weekly low-dose hormonal contraceptive patch that contains the active ingredients ethinyl estradiol (EE, a synthetic estrogen) and levonorgestrel (LNG, a type of progestin). The patch utilizes the company's Skinfusion technology, which allows Twirla® to be the first contraceptive patch capable of delivering LNG across the skin in a reliable manner. The company has conducted a comprehensive development program for Twirla® that includes three Phase 3 clinical trials. Results from the latest Phase 3 trial were released in January 2017 and showed Twirla® to be effective, with a favorable safety profile in a highly diverse patient population. We anticipate the company resubmitting the new drug application (NDA) for Twirla® in the first half of 2017, with potential approval before the end of 2017.

Twirla®

Twirla® is a combination hormonal contraceptive (CHC) product that contains both EE and LNG. It is a patch that is applied once-weekly for three weeks, with no patch applied during the fourth week of a 28-day cycle. As a patch, Twirla® is designed to eliminate the need to take a daily pill, which is necessary with oral contraceptive products. It may be applied to the upper torso (excluding the breasts), abdomen, or buttock.



The patch is made of a soft, flexible fabric that is designed to move with the woman's body. It is a matrix composed of multiple layers that contain the active ingredients EE and LNG along with inactive ingredients intended to aid in transport of the active ingredients across the skin. The adhesive is separated from the active ingredients by a barrier layer, which prevents their dispersal to the periphery of the patch and interfering with adhesion. Lastly, the patch is designed to prevent adhesive material from collecting along the edge of the patch, where it could collect dirt and leave behind a "black ring", a common complaint from users of other contraceptive patches.

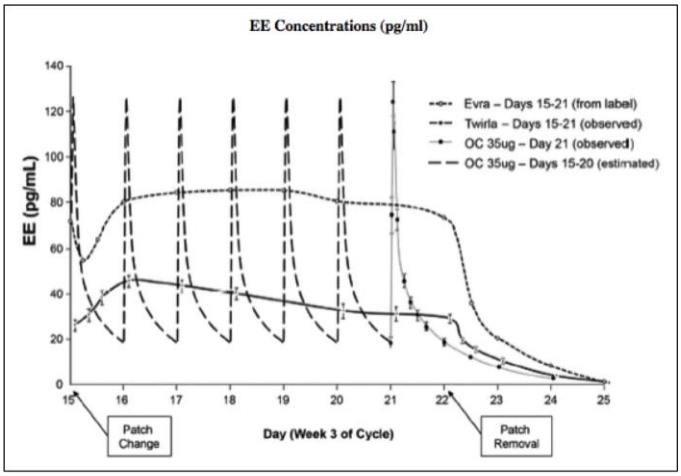


Source: Agile Therapeutics, Inc.

Twirla® Development Program

Agile has conducted a comprehensive development program that consisted of three Phase 1, one Phase 2, and three Phase 3 clinical trials.

Pharmacokinetic Data: While the company has not performed a head-to-head comparison of Twirla® to Xulane®, the generic version of the first ever approved contraceptive patch Ortho Evra® (which was discontinued in the U.S. in 2015), a pharmacokinetic (PK) study conducted with Twirla® was similar in design to one conducted with Ortho Evra®. The following graph shows the PK data for Twirla® compared to oral contraceptives (OC) containing 35 µg of EE and the Ortho Evra® patch. The Ortho Evra® data was estimated based on the graph provided in that products label. The OC data prior to day 21 was estimated steady-state data based on Day 21 EE concentrations observed during the PK study. The data shows that the level of EE administered from Twirla® leads to a lower EE plasma concentration, which likely contributes to the decreased side effect profile of Twirla® compared to Ortho Evra® or daily contraceptive pills.



Source: Agile Therapeutics, Inc.

First Two Phase 3 Trials: The two Phase 3 trials completed prior to the more recent Phase 3 SECURE trial enrolled over 1,900 subjects. Each of those trials included an active comparator arm with an approved low-dose oral contraceptive. The results showed that Twirla® was generally well tolerated and adverse events were comparable to those seen with low-dose oral contraceptives. In addition, subjects using the patch self-reported a higher level of compliance than those using oral contraceptives. The primary measure of efficacy was the Pearl Index (PI), which is a measurement of the rate of pregnancies over a specific period of time in a clinical trial and corresponds to the number of unintended pregnancies that would be expected in 100 woman-years of exposure. The pooled PI value for the first two Phase 3 clinical trials was 5.76 for those using Twirla® and 6.72 for those using oral contraceptives. These values were much higher than the range for PI values seen in other pivotal studies for products approved by the FDA in the last 10 years (1.34 to 3.19). One possible explanation for the unusually high PI numbers could be due to the relatively high percentage of new users and minority subjects compared to studies for other approved products, as shown in the following table. While the underlying reasons are not well understood, multiple reports in the literature state that contraceptive failure rates are highest in black and Hispanic subjects (Sundaram *et al*., 2017; Dehlendorf *et al*., 2014).

		Product (Year Approved) % of Subjects*					
Parameter		Twirla	Seasonique (2006)	Yaz (2006)	Lo-seasonique (2008)	Natazia (2010)	Quartette (2013)
Hormonal Contraception Use							
Current Users		18	-	60	-	59	-
Within 6 Months of Enrollment	Yes	44	68	-	61	-	44
	No	56	32	-	39	-	56
Race/Ethnicity	Hispanic	15	5	5	10	13	11
	Black	22	11	4	12	7	18

*Data derived from two Phase 3 clinical trials for Twirla prior to SECURE and from FDA medical review documents for each product

Source: Agile Therapeutics, Inc. / Zacks SCR

In February 2013, Agile received a complete response letter (CRL) from the FDA that indicated approval of Twirla® would not be possible at that time and that data from an additional Phase 3 clinical trial would be necessary. In

addition, the FDA wished to see improved study conduct, including additional site monitoring and data collection procedures. The FDA requested that Twirla® be studied in a representative sample of U.S. women, with no enrollment restrictions based on demographic characteristics such as, race, ethnicity, or body mass index (BMI). Weight and/or BMI exclusion criteria have been employed in most contraceptive clinical trials in the past.

SECURE Trial: Agile's third Phase 3 clinical trial for Twirla® was a multicenter, single-arm, open-label, 13-cycle trial that enrolled 2,032 women aged 18 and over at 102 experienced investigative sites in the U.S. The trial was designed in consultation with the FDA and included a number of stringent trial design elements, such as exclusion of treatment cycles for both use of back-up contraception and lack of sexual activity. The broad enrollment criteria led to the inclusion of a large proportion of subjects with high BMI, a group that had typically been excluded from prior contraceptive studies. Demographic data from the SECURE trial, as well as from other contraceptive studies for Ortho Evra® and Quartette®, is shown in the table below.

Study	SECURE	Ortho Evra Trials	Quartette Trial
Race			
White	67%	91%	64%
Black	24%	5%	19%
Asian	3%	2%	2%
Other	6%	2%	14%
Ethnicity			
Hispanic	20%	Not available	11%
Non-Hispanic	80%		89%
Hormonal Contraception Use			
Current user	35%	Not available	44%
Recent user	13%		
Former user	43%		39%
New user	9%		17%

Study	SECURE	Ortho Evra Trials	Quartette Trial
Age			
Mean age	28 years	28 years	27 years
≤ 35 years	90%	83%	90%
> 35	10%	17%	10%
Body Mass Index			
Mean BMI*	28.3 kg/m^2	23.6 kg/m^2	27.4 kg/m^2
< 25 (normal)	39%	Not available	47%
25 - < 30 (overweight)	25%		25%
≥ 30 (obese)	35%		28%

Source: Agile Therapeutics, Inc.

A number of measures were utilized in the SECURE trial to improve overall study conduct, and in particular to improve upon the 'lost to follow-up' rate. These measures included working with a highly experienced contract research organization, selecting experienced sites based on assessing performance in previous clinical trials, increasing and improving monitoring and training (including the use of text messaging to provide reminders to subjects for patch application), and the use of electronic diaries for subjects.

The following table shows that discontinuation rates due to 'lost to follow-up' were much lower for the SECURE trial than for the previous Phase 3 clinical trials of Twirla® and slightly better than for the Quartette® trial. The discontinuation rates for SECURE are also in line with several previously conducted contraceptive trials leading to FDA approvals.

	SECURE		Agile Prior Phase 3*		Quartette†	
Metric	**n**	**%**	**n**	**%**	**n**	**%**
Enrolled	2032	100.0	1129	100.0	3597	100.0
Discontinued**	1043	51.4	644	57.0	1453	40.3
Lost to Follow-up	229	11.3	229	20.3	480	13.3
Completed	988	48.6	485	43.0	2144	59.6

**Main reasons for subject discontinuation from SECURE trial: subject decision, adverse event, loss to follow-up

Source: Agile Therapeutics, Inc.

The primary outcome of the SECURE trial was the PI in an intent-to-treat (ITT) population of subjects 35 years of age and under. The FDA also requested a pre-specified efficacy analysis regarding BMI, body weight, and the PI. The overall PI for the ITT population was 4.80 with an upper bound of 6.06. An effect on the PI by both BMI and weight was observed, as shown in the following table and graphs.

BMI Category	BMI (kg/m^2)	% of Study Population	Pearl Index	UB 95% CI
Normal*	< 25	39%	3.03	4.62
Overweight	≥ 25 - < 30	25%	5.36	7.98
Obese	≥ 30	35%	6.42	8.88
Non-Obese*	< 30	65%	3.94	5.35
Obese	≥ 30	35%	6.42	8.88

ITT = Intent to Treat; all results shown are based on ITT subjects ≤ 35 years of age
UB 95% CI = upper bound of the 95% confidence interval

Source: Agile Therapeutics, Inc.

Figure 2: % Pregnancy vs. Weight categories

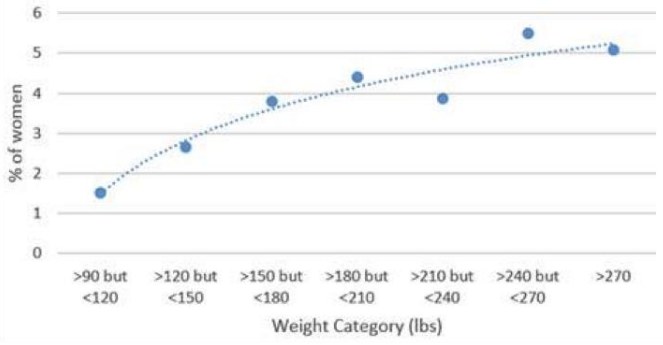
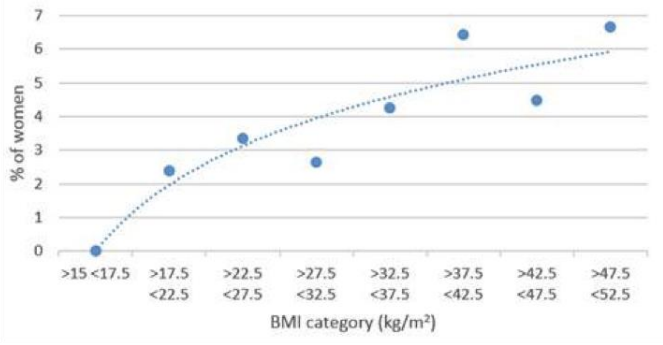


Figure 3: % Pregnancy vs. BMI categories



Source: Nelson et al., 2017

Twirla® was very well tolerated with rates of adverse events that were in line with previous clinical trials and much lower than for trials of other low-dose combination hormonal products, as shown in the following table. The company recently reported that unscheduled bleeding/spotting days per month decreased from a mean of 3.1 day in cycle 1 to 1.6 days in cycle 13. In addition, patch related irritation and itching rates were low (83% had no patch site irritation; 65% had no itching) and while patch detachment was reported by 10% of subjects in cycle 1, this was reduced to 2% by cycle 13.

Adverse Event	SECURE Trial	Prior Agile Phase 3 Trials	Ortho Evra Trials*	Quartette Trial*
Total in Safety Population	2032	1043	3322	3597
Headache	4.3%	3.7%	21.0%	12.2%
Nausea	4.1%	4.3%	16.6%	6.7%
Breast tenderness/pain/discomfort	2.0%	1.8%	22.4%	2.2%
Mood swings/changes/depression	2.7%	2.8%	6.3%	2.9%
Heavy/irregular vaginal bleeding**	1.8%	2.1%	6.4%	9.7%

**1.4% of subjects in the SECURE trial discontinued due to a bleeding-related adverse event

Source: Agile Therapeutics, Inc.

With a robust data package in hand, we anticipate Agile resubmitting the new drug application (NDA) for Twirla® before the end of the second quarter of 2017. In April 2017, the company held a pre-submission meeting with the FDA, and based on the preliminary information provided, the FDA indicated that the SECURE trial results appear acceptable for resubmission, however there was no discussion on whether the results would be sufficient for approval. Based upon the data showing an increased PI in women with higher BMI, we believe there is a possibility for there to be language in the final approved label regarding the use of Twirla® in women based on weight.

Contraceptive Effectiveness and Obesity

The results obtained by Agile showing an increased PI with increased BMI are not unprecedented, but instead likely represent the inclusion of a diverse group of subjects in the SECURE trial that was not true in most prior contraceptive clinical trials. A number of studies have been published that show how obesity can affect the metabolism of combined hormonal contraceptives, including the patch, and their effectiveness:

Zieman *et al*., 2002: This was an analysis of pooled data from three pivotal studies of the contraceptive patch Ortho Evra®. The contraceptive failure rate was found to be low and uniformly distributed across the weight range for women <90 kg, however for women who were ≥90 kg, there appeared to be an increased risk of pregnancy. While those ≥90 kg made up only 3% of the study population they accounted for 33% (5/15) of the reported pregnancies. In addition, 20% of the study population was ≥74 kg and this cohort accounted for 60% (9/15) of the reported pregnancies. Body weight was a significant risk factor for pregnancy in a proportional hazards model ($P < 0.001$).

Holt *et al*., 2005: This was a case-control study that investigated the pregnancy rate among (combination oral contraceptives (COC) users and found a 60% increased risk of unintended pregnancy in COC users with BMI >27.3 kg/m^2. Among women who were consistent users (they missed no pills in the reference month), the risk of pregnancy doubled in women with BMI >27.3 kg/m^2 or >32.2 kg/m^2. Weight was also a factor, as women weighing >74.8 kg had a 70% higher risk of pregnancy compared to women weighing 74.8 kg or less.

Edelman *et al*., 2009: This study compared the effects of a COC on the hypothalamic-pituitary-ovarian axis in obese and non-obese women. Obese women were found to have a significantly larger mean area under the curve (AUC), longer LNG half-life (and thus a lower maximal LNG concentration on Cycle 2, Day 1), and a longer time to reach steady state. These factors potentially lead to a time after the placebo week when obese women would not be adequately protected from pregnancy.

Lopez *et al*., 2010: This was a Cochrane Review of 11 studies that used pregnancy as an outcome and found that women with a BMI >25 kg/m^2 were almost twice as likely to become pregnant when on COCs than normal-weight women. In addition, they found that for those using a patch contraceptive there was a significant association of pregnancy with body weight, but not with BMI, although the authors stipulate that "the field could use trials of contraceptive methods stratified by BMI" due to limited data being available.

Dinger *et al*., 2011: This study examined outcome data from over 50,000 U.S. women from a prospective, non-interventional long-term cohort study and found that women with higher BMI were more likely to get pregnant when on oral contraceptives, even after adjusting for age, parity, and education level.

Yamazaki *et al*., 2015: This was a meta-analysis conducted using individual participant data directly from Phase 3 clinical trial data of COCs and published by current and former FDA reviewers. The trials were reviewed by the FDA between 2002 and 2012 and all measured effectiveness using the PI. The pooled PI from seven clinical trials was 3.14 for obese and 2.53 for non-obese women. The overall hazard ratio for unintended pregnancy in obese women compared to non-obese women was 1.44, presenting a 44% higher pregnancy rate for obese women using COCs after adjusting for age and race.

The takeaway from all of these studies is that there does appear to be a correlation between BMI (and/or body weight) and PI for women on hormonal contraceptives, and that the results seen in the SECURE trial are not unique to Twirla® and do not represent any type of patch-specific negative attributes.

Contraceptive Market

Competition in the contraceptive market is intense as there are a large number of pharmaceutical, specialty pharmaceutical, generic, and medical device companies that produce a wide range of products. If approved, Twirla® will face competition from both non-hormonal products (e.g., diaphragm, cervical cap, condom) as well as hormonal products (e.g., oral contraceptives, injections, implants, intrauterine devices, vaginal rings). According to the 2016 FDA Birth Control Chart, there are 18 unique forms of birth control, each of which could be considered a competitor to Twirla®, however the main competition will be in the hormonal contraceptive market.

According to EvaluatePharma, the worldwide hormonal contraceptive market (including both combination and progestin-only products) totaled approximately $6.5 billion in 2016, while the U.S. market totaled approximately $3.7 billion. The top selling products are shown in the following table.

Product	Type	Active Ingredient(s)	Company	2016 WW Sales ($millions)	2016 US Sales ($millions)
Mirena	IUD	levonorgestrel	Bayer	$1,154	$776
Nuvaring	Vaginal ring	ethinyl estradiol; etonogestrel	Merck	$777	$576
Yasmin	Combination Pill	drospirenone; ethinyl estadiol	Bayer	$750	$142
Nexplanon	Implant	etonogestrel	Merck	$606	$420
Lo Loestrin	Combination Pill	ethinyl estradiol; norethindrone acetate	Allergan	$404	$404
			Total	$3,691	$2,318

Source: EvaluatePharma / Zacks SCR

There has been little to no growth as measured by prescription volume over the past ten years in the hormonal contraceptive market, except for a 4.8% increase in 2013 compared to 2012. This was a one-time boost in prescriptions due to the enactment of the Patient Protection and Affordable Care Act (ACA), which required all health care plans to offer preventative services to women with no deductible, co-insurance, or co-payments. The preventative services include all FDA approved contraceptive methods.

Following enactment of the ACA, generic oral contraceptives showed the highest growth, likely due to the fact that most health insurance companies were offering generics as a no cost-sharing option (i.e., no deductible, co-pay, or co-insurance). In May 2015, several U.S. government agencies clarified the requirements for the contraceptive coverage under the ACA. These requirements include at least one form of contraception in each of the 18 current methods the FDA lists in the Birth Control Chart must be offered with no cost-sharing. Since the patch is listed among the 18 current contraceptive methods, at least one patch product must be offered to patients with no cost-sharing. Recently, there has been much talk about repealing certain parts of the ACA, however at this point nothing has occurred and the requirements in regards to contraceptive coverage are still in effect.

Contraceptive Patch Experience

Ortho Evra® was the first contraceptive patch approved by the FDA in 2002. It was an immediate commercial success and achieved a 10% share of the combined hormonal contraceptive market within two years of launch. However, in November 2005 Johnson and Johnson revised the label of Ortho Evra® to indicate that the amount of EE a patient was exposed to was approximately 60% higher than that from an oral contraceptive containing 35 µg of EE. The labeling change included a black box warning on an increased risk of venous thromboembolism and the pharmacokinetic profile of EE. Following the label change, the market share for Ortho Evra® declined rapidly, from a peak of 11% in 2005 to 1.4% in 2013. A generic version of Ortho Evra® (Xulane®) was introduced by Mylan in April 2014, and in early 2015 Johnson and Johnson discontinued production of Ortho Evra® in the U.S. Thus far, no other generic equivalents of Ortho Evra® have been introduced in the U.S. Total revenues for Xulane® in 2016 were $211 million.

Bayer is developing what we believe to be the only other combined hormonal contraceptive patch, which uses EE and a third generation progestin (gestodene, which has not been approved by the U.S. FDA). Bayer completed a Phase 3 efficacy trial in the U.S. in 2011, however the company never submitted a NDA to the FDA for the gestodene patch and no longer lists it with the pipeline.

Twirla® Commercialization Plan and Market Research

It approved, Agile plans on building a sales and marketing force for Twirla® that will initially focus on OBGyns, Nurse Practitioners, Physician Assistants, and Primary Care Physicians who are the top prescribers of contraceptives in the U.S. The company plans to utilize a sales force of 70-100 representatives that could reach the approximately 22,000 prescribers responsible for 80% of branded CHC products.

As opposed to a traditional direct-to-consumer advertising campaign that includes television ads, Agile plans to rely mostly on social media to reach its target demographic of women age 18-34 years. Most women of that age get their information through social networks, with text messaging being the preferred method of communication. A targeted advertising campaign that utilizes social media and blogs, combined with some traditional outlets such as magazines, are likely to create sufficient brand awareness of Twirla® while at the same time being a cost-effective approach.

Agile has performed market research with over 800 healthcare professionals and 3,300 consumers to gain insight into Twirla® and the contraceptive market. Some important points from this data include:

- Healthcare practitioners have a large influence on which hormonal contraceptive their patients ultimately choose. Most present oral contraceptives first due to its long history and familiarity.

- The PI is not an important factor given that most consumers are not going to understand it, thus healthcare practitioners place very little emphasis on it. Given a choice between products with comparable PIs, which product has the lower PI is not going to be a deciding factor as efficacy is assumed for all approved CHC products.

- Many consumers lose excitement for oral contraceptives after realizing the difficulty of remembering to take one every day.

- Approximately 15% of women surveyed indicated they would be "extremely likely" to ask their doctor for a prescription for Twirla®.

- The prescription contraceptive market is not a high priority for payers and knowledge of individual products is low. Payers indicated a willingness to work with a manufacturer to make one product preferred (i.e., $0 co-pay) in a contraceptive category, although preferred status may not preclude other products in that category from having a $0 co-pay.

Currently, the company does not have plans to commercialize Twirla® outside the U.S., however if that were to occur it would be through a partnership with another pharmaceutical company.

Background Material

Hormonal Contraception

Beginning with the first menstrual cycle (average age of 12.6 years) and continuing through natural menopause (average age of 51.3 years), a woman is biologically capable of becoming pregnant. A woman typically does not wish to be pregnant during the majority of her childbearing years, and thus must use some form of birth control in order to prevent pregnancy.

The U.S. was the first country in the world to approve the use of contraceptive pills in 1960. Contraceptive pills are composed of synthetic estrogens and progestins, which are known as combination hormone contraceptives (CHCs), or progestin only, which are referred to as P-only. Currently, there are three synthetic estrogens approved in the U.S.: EE, mestranol, and estradiol valerate. EE was first approved over 40 years ago and is utilized in most CHCs sold currently. There are 10 different progestins that have been used at one time or another in the U.S. and include three generations of molecules. First and second generation progestins, such as LNG, have been available in the U.S. for over 25 years. Third and fourth generation progestins (e.g., desogestrel and drospirenone) were developed to prevent common side effects such as acne, however data suggests they carry an increased risk of venous thromboembolism (VTE) compared to first and second generation products.

The estrogen component of CHCs is mainly responsible for cycle control and helps to minimize or prevent bleeding and spotting between cycles. It also results in decreased maturation of the egg in the ovary. The progestin portion inhibits ovulation and thickens cervical mucus, thus helping to prevent sperm from entering the uterus.

The most serious potential risk associated with the use of hormonal contraceptives is the development of VTE, which results in the formation of a clot in a vein. The reason for this is that estrogen increases expression of clotting factors in the liver and decreases production of factors that breakdown blood clots. VTE can be life threatening if the clot breaks off and moves to the lung and causes a pulmonary embolism. While the risk for developing VTE is greater for a woman taking hormonal contraception compared to those that are not, the risk is not as high as in a pregnant woman, as shown in the following chart.

Population	VTE Incidence (cases per 10,000 woman years)
Non-pregnant woman not on hormonal contraception	1 to 5
Woman on hormonal contraception	3 to 12
Pregnant woman	5 to 20
Postpartum woman (12 weeks following delivery)	40 to 65

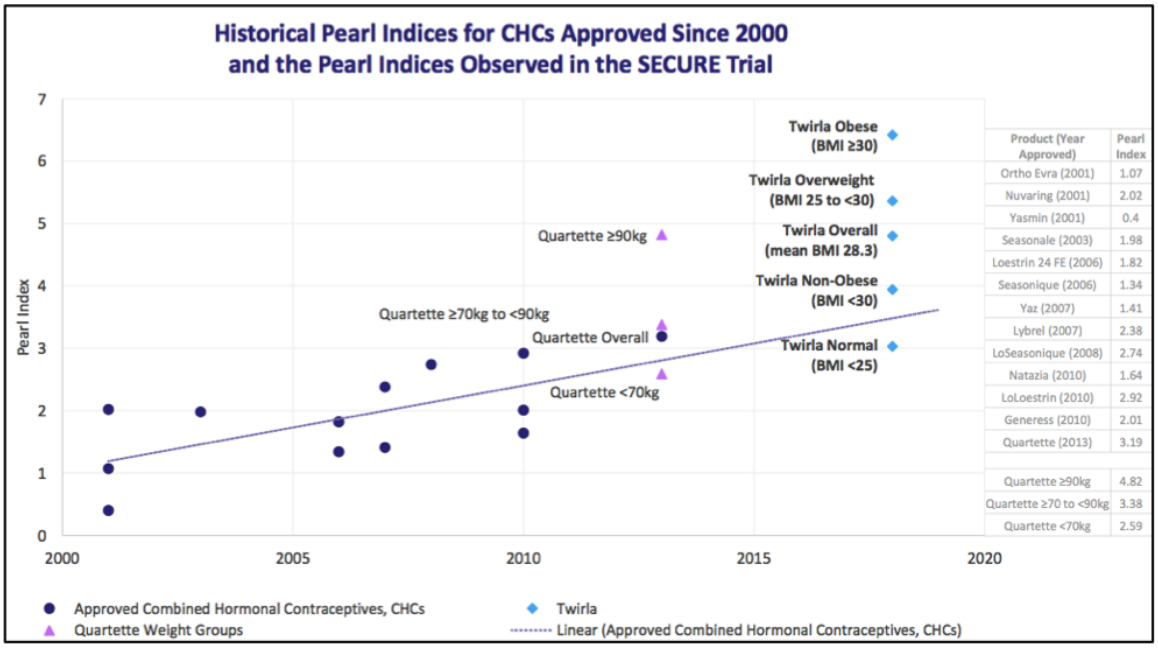
Source: U.S. FDA

Contraceptive Effectiveness

The Pearl Index (PI) is the most common way of expressing the effectiveness of different types of birth control (Pearl, 1933). It represents the number of pregnancies per 100 women-years of exposure, or how many pregnancies will occur in 100 sexually active women in one year. The formula to calculate the PI is:

$$\frac{\text{Total \# pregnancies x 13 x 100}}{\text{Total \# of cycles}}$$

Recent FDA guidance has indicated that the PI is calculated based on all pregnancies that occurred while the subject was on treatment, but only includes cycles where the women indicates she was sexually active and did not use a backup form of birth control. Exclusion of cycles where a woman was not sexually active, which were typically included in contraceptive studies in the past, could lead to a higher PI. There has been a trend of increasing PI values for the past 15 years in clinical trials, however the exact reasons for this are not entirely clear.



Source: Agile Therapeutics, Inc.

Additional Product Candidates

In addition to Twirla®, Agile has additional product candidates that fall into two classes: Twirla® line extensions and other transdermal contraceptive product candidates. At the moment, essentially all of the company's resources are directed toward developing and seeking regulatory approval for Twirla®, and the company will require additional capital in order to advance any of the following candidates through clinical testing.

AG200-ER: This is an extended cycle regimen of the current patch product that is designed to allow an extended period of time between withdrawal bleeding (e.g., fewer periods per year). There are multiple oral contraceptives that offer 84 and 91-day extended cycle regimens, however there is no approved contraceptive patch offering the same. AG200-ER uses the same drug product as Twirla®, and the company is currently evaluating the optimal cycle length to advance into Phase 3 clinical testing.

AG200-SP: This is a modified 28-day regimen designed to provide users with shorter, lighter periods and potentially improve contraceptive efficacy. Users would use the same drug product as Twirla® for the first three weeks of the cycle and then a smaller, lower dose patch (SmP) during the fourth week. The company will need to perform additional development work on the SmP before conducting a pharmacodynamics/pharmacokinetics study.

AG200-ER (SmP): This is an extended cycle regimen of the current patch product and the SmP that is designed to allow an extended time between periods and potentially minimize breakthrough bleeding and spotting, something

that is commonly reported for women on extended regimen oral contraceptives. The company will need to perform additional development work on the SmP before conducting a pharmacodynamics/pharmacokinetics study.

AG890: This is an LNG-only contraceptive patch that is intended for women who are unable or unwilling to take estrogen. It could potentially be used by those who are breastfeeding, at greater risk for VTE, smokers, those over the age of 35, or who are obese. The company has performed a Phase 1 clinical trial and the NIH has conducted a Phase 1/2 clinical trial with AG890. Data analysis is ongoing and once complete the company will be able to determine which formulation and dose to move into Phase 3 testing.

Intellectual Property

Agile currently has 13 issued U.S. patents, eight of which that cover Twirla® and will be listed in the FDA Orange Book. The patents for Twirla® have varying expiration dates, the last of which is in 2028. The company also has five patents that cover other product candidates in the pipeline. All of the patents are wholly owned by Agile, with no royalties or payments owed to a third party. A list of the patents that cover Twirla is provided in the following table.

Twirla® Patents

U.S. Patent Number	Claims	Expiry Date
7,045,145	Adhesive matrix of transdermal delivery system	March 2021
7,384,650	Dry product formulation of transdermal delivery system	March 2021
8,221,784	Dry product formulation of transdermal delivery system	March 2021
8,221,785	Dry product formulation of transdermal delivery system	March 2021
8,883,196	Method of controlling fertility	November 2020
8,246,978	Structural features of transdermal delivery system	July 2028
8,747,888	Structural features of transdermal delivery system	July 2028
9,050,348	Structural features of transdermal delivery system	August 2028

Source: Agile Therapeutics, Inc. / Zacks SCR

Financials and Capital Structure

On May 8, 2017, Agile released financial results for the first quarter of 2017. As expected, the company did not report any revenues. Net loss for the quarter was $7.5 million, or $0.26 per share. R&D expenses for the first quarter of 2017 totaled $4.7 million, compared to $4.9 million for the first quarter of 2016. The decrease was due to a decrease in clinical development expenses partially offset by increases in manufacturing, regulatory, and personnel expenses. G&A expenses for the first quarter of 2017 were $2.4 million, compared to $2.1 million for the first quarter of 2016. The increase was due to increased commercial development expenses and professional fees.

Cash burn for the first quarter of 2017 totaled approximately $6.0 million, and the company exited the first quarter of 2017 with approximately $41.7 million in cash and cash equivalents. We believe this is sufficient to fund operations into the second quarter of 2018, however the company will require additional capital for the commercial launch of Twirla®.

In February 2015, the company entered into a loan and security agreement with Hercules Capital, Inc. for a term loan of up to $25.0 million. A first tranche of $16.5 million was funded upon execution of the loan, and the company recently extended the period during which it may draw an additional tranche of $8.5 million until January 31, 2018. The loan accrues interest at a rate of the greater of 9.0% or 9.0% plus Prime minus 4.25%. Principal is due in 23 consecutive monthly installments beginning on February 1, 2017 and ending on Dec. 1, 2018.

As of May 5, 2017, Agile had approximately 28.8 million shares of common stock outstanding. In addition, the company has approximately 3.7 million stock options, 0.2 million warrants, and 0.2 million unvested restricted stock units for a fully diluted share count of approximately 32.9 million.

Risks to Consider

There is no guarantee Twirla® will be approved. Agile has put together a comprehensive data packet for the resubmission of the Twirla® NDA, however there is no guarantee that the FDA will deem the study results from the SECURE trial as positive and may require additional data or other information in order for Agile to gain approval for Twirla®. If the FDA requires additional clinical or preclinical trials, it would require the company to obtain significant additional funding to conduct that testing. The PI for the overall intent to treat population in the SECURE trial was 4.80 with an upper bound of the 95% confidence interval of 6.06. If obese patients are excluded, the PI for non-obese patients was 3.94 with an upper-bound of the 95% confidence interval of 5.35. Thus far, the highest PI for a hormonal contraceptive product approved by the FDA to date is 3.19 and the highest upper-bound of the 95% confidence interval was 5.03.

Even If approved, Twirla® could have certain restrictions. Based on the increased PI seen in the obese population in the SECURE trial, even if approved Twirla® could have restrictions on the label limiting the patient population that is approved to use the product. In addition, there may be precautions, contraindications, or warnings included on the product label that could ultimately limit its commercial appeal. Due to the fact that no head-to-head studies of Twirla® and Ortho Evra® were performed, the company won't be able to make direct comparative claims regarding the safety, efficacy, or pharmacokinetics between Twirla® and Ortho Evra® or its generic version, Xulane®.

Agile will require significant additional funding to launch Twirla®. As of now, Agile is planning on building a sales force with approximately 70-100 individuals to market Twirla®. This will require significant additional capital, and the company could raise this additional capital through a number of different means, including issuing equity, debt, through a royalty monetization, or a strategic collaboration. The sale of equity or convertible debt securities could result in significant shareholder dilution.

MANAGEMENT PROFILE

Alfred Altomari – Chairman and Chief Executive Officer

Alfred Altomari has served as the Chairman of the Board, President and Chief Executive Officer of Agile since October 2016 and has been a member of the Board of Director's since February 2004. Mr. Altomari was appointed President and Chief Executive Officer in 2010. Previously, Mr. Altomari served as Agile's Executive Chairman from 2004 to 2010. From 2008 to September 2010, Mr. Altomari was also a consultant. From 2003 to 2008, Mr. Altomari held multiple senior management positions at Barrier Therapeutics, Inc., including Chief Commercial Officer, Chief Operating Officer, and Chief Executive Officer. In 2008, in his role as Chief Executive Officer and as a member of Barrier's board of directors, Mr. Altomari completed the successful sale of Barrier to Stiefel Laboratories, which was subsequently acquired by GlaxoSmithKline plc. From 1982 to 2003, Mr. Altomari held numerous executive roles in general management, commercial operations, business development, product launch preparation, and finance with Johnson & Johnson. Mr. Altomari also serves on the board of directors of Insmed Inc. and Recro Pharma, Inc. Mr. Altomari received an M.B.A. from Rider University and his B.S. from Drexel University. He currently serves on LeBow College of Business Advisory Board and the Board of the Charles D. Close School of Entrepreneurship at Drexel University. He currently is a member of the Board of Directors for TASK (Trenton Area Soup Kitchen).

Scott Coiante – Chief Financial Officer and Senior Vice President

Scott Coiante has served as Vice President and Chief Financial Officer of Agile since June 2011. He joined the company in December 2010 and served as the Vice President of Finance between then and June 2011. Beginning in 2005, he served as Vice President Finance, Treasurer, Principal Accounting Officer at Medarex, Inc., a publicly listed biopharmaceutical company, which Bristol-Myers Squibb Co. acquired in September 2009. From 2002 through 2005 he served as Director of Finance. While at Medarex, he was responsible for corporate financial functions including treasury, accounting, SEC reporting, tax and assurance. From 1989 to 2002, he held management positions of increasing responsibilities at Ernst & Young LLP, which included managing audit engagements, financial preparation, and financial reporting for client public offerings, both initial and follow-on, and SEC registration filing statements for both public and private companies, predominantly within the life science and pharmaceutical industries. He holds a B.S. in accounting from Villanova University.

Elizabeth Garner, M.D., M.P.H. – Chief Medical Officer and Senior Vice President

Elizabeth Garner, M.D., M.P.H. has served as Chief Medical Officer of Agile since January 2014. Previously, she served as Vice President, Medical Affairs, Women's Health and Preventive Care at Myriad Genetics Laboratories from 2012 to 2014. From 2011 to 2012, she was Senior Medical Director, Women's Health at Abbott Laboratories where she served as the Clinical Lead, Endometriosis Program. Prior to that, Dr. Garner served as Associate Director and then Director, Vaccines Clinical Research at Merck Research Laboratories from 2007 to 2011. Dr. Garner received joint M.D. and M.P.H degrees from Harvard Medical School and the School of Public Health. She completed her residency in obstetrics and gynecology at Brigham and Women's/Massachusetts General Hospitals; her subspecialty fellowship in gynecologic oncology at Brigham and Women's and the Dana Farber Cancer Institute; and received board certification in both general Obstetrics and Gynecology and Gynecologic Oncology. Prior to entering the pharmaceutical industry, she had several years of experience in academic clinical practice, research, and teaching at Harvard Medical School.

Renee Selman – Chief Commercial Officer

Renee E. Selman has served as Chief Commercial Officer of Agile since July 2016. Most recently, Ms. Selman served as President of Adheris Health, a business unit of inVentiv Health, from 2010 until 2015. Adheris Health is one of the nation's largest providers of targeted patient acquisition and adherence programs. Their evidence-based behavioral interventions help patients stay on their prescribed therapy. Ms. Selman spent 20 years at Johnson & Johnson where she held senior executive roles including Worldwide President, Ethicon Women's Health and Urology from 2005 to 2010, and Vice President U.S. Sales and Marketing Wound Management from 2003 to 2005. While at J&J, she held roles of increasing responsibility at Ortho McNeil Pharmaceutical, including Group Director ORTHO EVRA® from 1999 to 2003, where she led a cross functional team that launched the first ever contraceptive patch. Ms. Selman serves on the boards of the Hunterdon County Medical Center, the Drug Information Association, and the Purdue University Krannert School of Management Alumni Board. She is a graduate of Purdue University with a B.S.I.M (Bachelor Science Industrial Management) in Business and a minor in Chemistry.

VALUATION

We are initiating coverage of Agile Therapeutics, Inc. (AGRX) with a $7.00 valuation. Agile Therapeutics, Inc. (AGRX) is a women's healthcare company focused on developing products to fulfill the unmet contraceptive needs of women. The company's lead candidate product, Twirla®, is a once-weekly low-dose hormonal contraceptive patch that contains the active ingredients ethinyl estradiol (EE, a synthetic estrogen) and levonorgestrel (LNG, a type of progestin). We anticipate the company resubmitting the new drug application (NDA) for Twirla® in the first half of 2017, with potential approval before the end of 2017.

Twirla®

Twirla® is a combination hormonal contraceptive product that contains both EE and LNG. It is a patch that is applied once-weekly for three weeks, with no patch applied during the fourth week of a 28-day cycle. As a patch, Twirla® is designed to eliminate the need to take a daily pill, which is necessary with oral contraceptive products. The patch utilizes the company's Skinfusion technology, which allows Twirla® to be the first contraceptive patch capable of delivering LNG across the skin in a reliable manner. The company has conducted a comprehensive development program for Twirla® that includes three Phase 3 clinical trials. Results from the latest Phase 3 trial (SECURE) were released in January 2017 and showed Twirla® to be effective, with a favorable safety profile in a highly diverse patient population.

The primary outcome of the SECURE trial was the Pearl Index (PI) in an intent-to-treat (ITT) population of subjects 35 years of age and under. The FDA also requested a pre-specified efficacy analysis regarding BMI, body weight, and the PI. The overall PI for the ITT population was 4.80 with an upper bound of 6.06. An effect on the PI by both BMI and weight was observed,

We believe Twirla® has a number of advantages over oral contraceptives, which are the current market leader for female hormonal contraception. The most important advantage has to do with compliance, since Twirla® only needs to be applied once per week while oral contraceptives must be taken every day. In addition, since Twirla® is a low-dose hormonal contraceptive product it has a favorable tolerability profile, as exhibited by the much lower incidence of a wide range of side effects compared to higher-dose oral contraceptives.

Valuation

We value Agile using a probability adjusted discounted cash flow model that takes into account potential future revenues for Twirla®. We anticipate Agile refiling the NDA before the end of the second quarter of 2017 and that the FDA will perform a 6-month review, which should lead to a PDUFA date before the end of 2017.

Even with a PI that is slightly higher than has previously been seen in other approved hormonal contraceptive products, we do not believe this is a reason for the FDA not to approve Twirla®. The company has done a good job of showing why the PI is higher than previously seen in other hormonal contraceptive trials based on a correlation between BMI and the PI. Trials for previous hormonal contraceptive products typically had an upper limit for BMI to be included in the trial, thus it is not surprising those trials would show a lower PI than the SECURE trial. Once approved, we don't believe the slightly higher PI will have an adverse impact on peak revenues. We base this on market research presented by the company showing that clinicians do not discuss PI values with their patients and instead focus on the characteristics of each product that may fit best with a particular patients lifestyle while assuming that if approved by the FDA the product is effective at preventing pregnancy. Lastly, we believe the SECURE trial adequately addressed all the concerns the FDA had when the CRL for Twirla® was issued, thus we anticipate the product being approved in late 2017.

According to EvaluatePharma, the U.S. hormonal contraceptive market (including both combination and progestin-only products) totaled $3.7 billion. We forecast for Agile to attain 9% market share 7 years after launch in 2018. This leads to peak revenues of approximately $400 million. After accounting for operating expenses, an estimated 35% tax rate, a 12% discount rate, and an 80% probability of approval we value Twirla® at $258 million. When taking into account estimated capital requirements for the launch of Twirla® of $35 million, and dividing by the fully diluted share count of 32.9 million share, this leads to a valuation of approximately $7.00 per share.

PROJECTED FINANCIALS

Agile Therapeutics, Inc.
Income Statement

Agile Therapeutics, Inc.	2016 A	Q1 A	Q2 E	Q3 E	Q4 E	2017 E	2018 E	2019 E
Twirla	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$18.9**	**$38.5**
YOY Growth	-	-	-	-	-	-	*#DIV/0!*	*103.7%*
Licensing / Development	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
Total Revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$18.9	$38.5
YOY Growth	-	*#REF!*	*#REF!*	*#REF!*	*#REF!*	*-100.0%*	*#DIV/0!*	*103.7%*
Cost of Goods Sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$3.0	$6.0
Product Gross Margin	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*84.1%*	*84.4%*
SG&A	$8.8	$2.4	$2.3	$2.3	$2.4	$9.4	$25.0	$30.0
% SG&A	*137310.6%*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*132.3%*	*77.9%*
R&D	$20.9	$4.7	$4.5	$4.5	$4.6	$18.3	$18.0	$17.0
% R&D	*326862.4%*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*95.2%*	*44.2%*
Operating Income	($29.7)	($7.1)	($6.8)	($6.8)	($7.0)	($27.7)	($27.1)	($14.5)
Operating Margin	*-464073.0%*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*-143.4%*	*-37.7%*
Interest Income / Net	($2.1)	($0.4)	($0.5)	($0.5)	($0.5)	($1.9)	($1.6)	($0.5)
Pre-Tax Income	($31.8)	($7.5)	($7.3)	($7.3)	($7.5)	($29.6)	($28.7)	($15.0)
Taxes	($3)	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($28.7)	($7.5)	($7.3)	($7.3)	($7.5)	($29.6)	($28.7)	($15.0)
YOY Growth	*#REF!*	-	-	-	-	*3.1%*	*-3.1%*	*-47.7%*
Net Margin	*-448767.7%*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*-151.9%*	*-39.0%*
Reported EPS	($1.02)	($0.26)	($0.25)	($0.25)	($0.26)	($1.03)	($0.72)	($0.30)
Fully Diluted Shares	28.3	28.8	28.8	28.9	29.0	28.9	40.0	50.0

Source: David Bautz, PhD - Zacks Investment Research, Inc.

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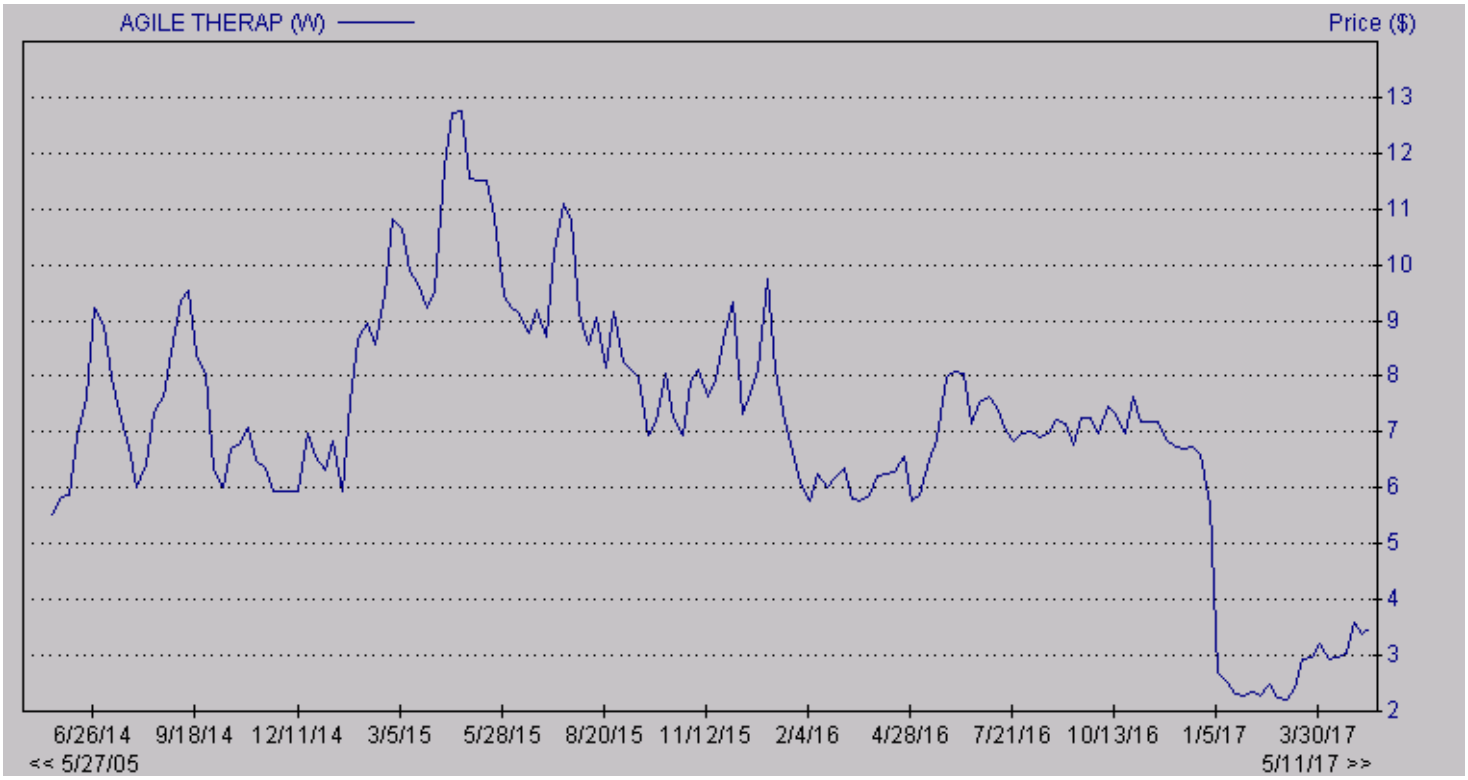
HISTORICAL STOCK PRICE



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