

AGILE THERAPEUTICS INC  
Form 10-K  
March 26, 2015

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**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549

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**FORM 10-K**

ý ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the year ended December 31, 2014

OR

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from \_\_\_\_\_ to \_\_\_\_\_  
Commission File Number 001-36464

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**Agile Therapeutics, Inc.**

(Exact name of registrant as specified in its charter)

**Delaware**

(State or other jurisdiction of incorporation or organization)

**23-2936302**

(I.R.S. Employer Identification No.)

**101 Poor Farm Road**

**Princeton, New Jersey 08540**

(Address including zip code of principal executive offices)

**(609) 683-1880**

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

**Title of each class**

Common stock, par value \$0.0001 per share

**Name of exchange on which registered:**

The NASDAQ Global Market

Securities registered pursuant to Section 12(g) of the Act: **None**

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Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes  No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes  No

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes  No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes  No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definition of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer       Accelerated filer       Non-accelerated filer       Smaller reporting company   
(Do not check if smaller reporting company)

Indicate by checkmark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes  No

The aggregate market value of the voting stock held by non-affiliates of the registrant as of June 30, 2014 was approximately \$78.7 million.

As of March 16, 2015 there were 22,154,365 shares of the registrant's common stock outstanding.

### DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2015 Annual Meeting of Stockholders (the "Proxy Statement"), to be filed within 120 days of the registrant's year ended December 31, 2014, are incorporated by reference in Part II and Part III of this Report on Form 10-K. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K

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**Agile Therapeutics, Inc.  
Annual Report on Form 10-K  
For The Year Ended December 31, 2014**

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**SPECIAL CAUTIONARY NOTICE REGARDING FORWARD-LOOKING STATEMENTS**

This annual report on Form 10-K includes statements that are, or may be deemed, "forward-looking statements." In some cases, these forward-looking statements can be identified by the use of forward-looking terminology, including the terms "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately" or, in each case, their negative or other variations thereon or comparable terminology, although not all forward-looking statements contain these words. They appear in a number of places throughout this Form 10-K and include statements regarding our current intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned development of Twirla and our other product candidates, the strength and breadth of our intellectual property, our ongoing and planned clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates, the degree of clinical utility of our products, particularly in specific patient populations, expectations regarding clinical trial data, our development and validation of manufacturing capabilities, our results of operations, financial condition, liquidity, prospects, growth and strategies, the length of time that we will be able to continue to fund our operating expenses and capital expenditures, our expected financing needs and sources of financing, the industry in which we operate and the trends that may affect the industry or us.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics, and healthcare, regulatory and scientific developments and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Form 10-K, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this Form 10-K. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this Form 10-K, they may not be predictive of results or developments in future periods.

Some of the factors that we believe could cause actual results to differ from those anticipated or predicted include:

the success and timing of our clinical trials;

our inability to timely obtain from our third party manufacturer, Corium, sufficient quantities or quality of our product candidates or other materials required for a clinical trial;

our ability along with Corium to complete successfully the qualification and validation of equipment related to the expansion of Corium's manufacturing facility;

our ability to obtain and maintain regulatory approval of our product candidates, and the labeling under any approval we may obtain;

our plans to develop and commercialize our product candidates;

the size and growth of the potential markets for our product candidates and our ability to serve those markets;

regulatory developments in the United States and foreign countries;

the rate and degree of market acceptance of any of our product candidates;

our available cash;



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the accuracy of our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;

our ability to obtain additional funding;

our ability to obtain and maintain intellectual property protection for our product candidates;

the successful development of our sales and marketing capabilities;

the performance of third-party manufacturers; and

our ability to successfully implement our strategy.

Any forward-looking statements that we make in this Form 10-K speak only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this Form 10-K. You should also read carefully the factors described in the "Risk Factors" section of this Form 10-K to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Form 10-K will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

This Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third party research, surveys and studies are reliable, we have not independently verified such data.

We qualify all of our forward-looking statements by these cautionary statements. In addition, with respect to all of our forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

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**Item 1. Business**

**Overview**

We are a women's health specialty pharmaceutical company focused on the development and commercialization of new prescription contraceptive products. Our product candidates are designed to provide women with contraceptive options that offer greater convenience and facilitate compliance. We have developed a proprietary transdermal patch technology, called Skinfusion®, which is designed to provide advantages over currently available patches and is intended to optimize patch adherence and stability and patient comfort. Our lead product candidate, Twirla®, also known as AG200-15, is a once-weekly prescription contraceptive patch currently in Phase 3 clinical development. The U.S. hormonal contraceptive market, with total market sales of \$5.3 billion in 2014, represents the greatest opportunity for Twirla. Over half of those sales were generated by branded products. Currently, there is only one other contraceptive patch available in the United States which is available in branded and generic versions, and we believe it has limitations due to its dose and physical characteristics. Twirla is designed to address these limitations. We believe there is an unmet market need for a low-dose contraceptive patch, which is designed to increase patient convenience and compliance in a non-invasive fashion.

Twirla is a combined hormonal contraceptive, or CHC, patch that contains the active ingredients ethinyl estradiol, or EE, which is a synthetic estrogen, and levonorgestrel, or LNG, which is a type of progestin, a synthetic steroid hormone, both of which have an established history of efficacy and safety in currently marketed combination low-dose, oral contraceptives. Twirla is designed using our proprietary Skinfusion technology to consistently deliver both hormones over a seven-day period at levels comparable to currently marketed low-dose oral contraceptives. By delivering these active ingredients over seven days, in a comfortable, convenient and easy-to-use weekly patch, Twirla is designed to promote enhanced patient compliance. The patch is applied once weekly for three weeks, followed by a week without a patch. If approved, Twirla will be packaged with three patches per carton to provide for one 28-day cycle of therapy.

We have conducted a comprehensive clinical program, with completed Phase 1, Phase 2, and Phase 3 trials enrolling over 2,100 women, over 1,500 of whom received Twirla. We are currently conducting an additional Phase 3 trial, the SECURE study, in which we plan to enroll approximately 2,100 women for up to one year of treatment. In Phase 1 and Phase 2 clinical trials, we demonstrated that Twirla delivers levels of both EE and LNG to the blood stream that are consistent with current low-dose oral contraceptives. In our two completed Phase 3 clinical trials that enrolled over 1,900 women in the aggregate for up to 12 months, we demonstrated that Twirla generally had comparable efficacy and tolerability to an approved low-dose oral contraceptive. In our completed Phase 3 trials to date, 485 women received Twirla for 12 months. Across all completed clinical trials, Twirla was generally well tolerated and had a favorable safety profile.

We have filed a Section 505(b)(2) New Drug Application, or NDA, for approval of Twirla by the U.S. Food and Drug Administration, or FDA, which is required before marketing a new drug in the United States. Our 505(b)(2) NDA relies in part on clinical trials that we conducted and in part on the FDA's findings of safety and efficacy from investigations for approved products containing the active ingredients and published scientific literature for which we have not obtained a right of reference. The FDA has indicated in a Complete Response Letter, or CRL, that our NDA was not sufficient for approval as originally submitted. After multiple communications with the FDA, we have received significant guidance as to what additional clinical development and other activities need to be completed prior to approval. In accordance with the FDA's advice and comments, we are conducting an additional Phase 3 clinical trial which was initiated in 2014 and is currently enrolling subjects. Based on the guidance that we received from the FDA, we believe that this additional trial will address all of the

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clinical issues raised in the CRL. Following completion of this additional Phase 3 clinical trial, we will respond to the CRL and supplement our NDA with the results of the trial.

We intend to commercialize Twirla in the United States, if approved, through a direct sales force. Obstetricians and gynecologists, or ObGyns, contribute nearly 45% of the U.S. contraception prescription volume, and Nurse Practitioners and Physician Assistants, or NP/PAs, who are often affiliated with an ObGyn practice, contribute an additional 25% of the U.S. prescriptions. We believe that we can address this market with a specialty sales force of approximately 70 to 100 representatives. We also intend to augment our sales force through digital marketing and other techniques to market directly to patients.

Our Skinfusion technology makes Twirla the first patch capable of delivering a contraceptive dose of LNG across the skin, allowing weekly application using a patch that is soft and flexible and is designed to adhere well with low levels of skin irritation. We, along with Corium International, Inc., or Corium, our manufacturing partner, have made a significant investment in a proprietary process to manufacture Twirla. We believe we have developed a robust process to reliably manufacture Twirla on a commercial scale. The materials produced for our clinical trials were manufactured using the same process that we expect will be used for our commercial-scale manufacturing, and we have made a significant investment in equipment for commercial-scale manufacturing if Twirla is approved. We believe that the technical challenges and know-how involved in manufacturing, including proprietary chemistry, production to scale and use of custom equipment and reproducibility, present significant barriers to entry for other pharmaceutical companies who might potentially want to replicate our Skinfusion technology.

Our intellectual property represents an additional barrier to potential competitors. We have seven issued U.S. patents which cover Twirla that we intend to list in the Orange Book, the last of which expires in 2028. The Orange Book lists drug products, including related patent and exclusivity information, approved by the FDA under the Federal Food, Drug, and Cosmetic Act. If a patent is listed in the Orange Book, potential competitors seeking approval of drug products under an Abbreviated New Drug Application, which provides for the marketing of a generic drug product that has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics and intended use, among other things, of a previously approved product, or a 505(b)(2) application, for which the listed drug is a reference product, must provide a patent certification in their application stating either that (1) no patent information on the drug product has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. In addition, we continue to prosecute additional patent applications relating to Twirla, as well as our other product candidates, both in the United States and internationally. The intellectual property behind all of our product candidates in the pipeline and our Skinfusion technology consists of patent families developed and wholly-owned by us. There are no royalties or payments owed to third parties on our Skinfusion technology or any of our product candidates.

In addition to Twirla, we are developing a pipeline of other new transdermal contraceptive products, including AG200-ER, which is a regimen designed to allow a woman to extend the length of her cycle, AG200-SP, which is a regimen designed to provide a shortened hormone-free interval, and AG890, which is a progestin-only contraceptive patch intended for use by women who are unable or unwilling to take estrogen.

**Background**

*Hormonal Contraception Overview*

A woman is biologically capable of pregnancy from the time of her first menstrual cycle, at the average age of 12.6 years, to natural menopause, at the average age of 51.3 years. This is nearly half of



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a typical woman's lifespan and, for the typical woman, the majority of this time frame is spent trying to avoid pregnancy or is characterized by no desire to become pregnant. Nearly half of the pregnancies that occur each year in the United States are unplanned. The United States was the first country to approve a hormonal contraceptive, with the approval of the first contraceptive pill in 1960. The latest data from 2011 to 2013 from the Centers for Disease Control, or CDC, indicate that approximately 28% of women aged 15 to 44 use some form of hormonal contraception, which amounts to approximately 17 million U.S. women.

Hormonal contraceptives are composed of synthetic estrogens and progestins. Contraceptives containing both estrogen and a progestin are referred to as CHCs, and contraceptives containing only progestin are referred to as P-only. There are three synthetic estrogens approved for use in contraceptive products: EE, mestranol and estradiol valerate. EE has been available for over 40 years and is the estrogen component in nearly all CHCs today. There are 10 different progestins that have been used in contraceptives sold in the United States. The progestin component provides most of the contraceptive effect, while the estrogen component primarily provides cycle control, for example, minimizing bleeding or spotting between cycles. The progestin exerts its contraceptive effect by inhibiting ovulation, or release of an egg from the ovary, and by thickening cervical mucus. Thickening cervical mucus helps to prevent sperm entry into the upper genital tract. The estrogen component, in addition to providing cycle control, makes a small contribution to contraception by decreasing the maturation of the egg in the ovary.

Hormonal contraceptives are generally well-tolerated and are generally safer than pregnancy. A risk associated with hormonal contraceptives is a rare but serious adverse event called venous thromboembolism, or VTE, which involves the formation of a blood clot in a vein. VTEs can be life-threatening, and typically present as either deep vein thrombosis or pulmonary embolism. Evidence supports that the increased risk of VTE in CHC users is dependent upon the estrogen dose and duration of use. Estrogen increases formation of clotting factors in the liver and decreases production of elements that promote breakdown of blood clots. Most experts believe that progestins on their own have minimal to no impact on the clotting system, but some progestins, when combined with estrogen, can increase estrogen's effect on the clotting system.

The likelihood of a woman spontaneously developing a VTE is extremely low and the use of combination oral contraceptives, or COCs, increases the incidence only slightly, and less than pregnancy. Epidemiologic studies evaluated by the FDA have demonstrated the incidence of VTE in women based on pregnancy or use of COCs as follows:

**Incidence of VTE Based on Pregnancy Status or use of COCs**

<b>Population</b>	<b>VTE incidence (cases per 10,000 woman years*)</b>
Non-pregnant woman who does not use a COC	1 to 5
COC users	3 to 12
Pregnant women	5 to 20
Postpartum women (in the 12 weeks following delivery)	40 to 65

\* One woman year is one woman using a contraceptive for one year, which is either 12 months or 13 cycles

The available progestins are commonly categorized into generations, based on their history of introduction in the United States. The first and second generation progestins, including LNG, have been available in contraceptive formulations in the United States for over 25 years. The third and fourth generation progestins, for example desogestrel and drospirinone, respectively, were introduced to reduce androgenic side effects, such as oily skin and acne. Epidemiologic data suggest that CHCs

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containing third and fourth generation progestins are associated with an increased risk of VTE as compared to those containing the second generation progestin, LNG.

*Effectiveness of Hormonal Contraceptives*

For the purpose of FDA approval, contraceptive effectiveness is measured by a calculation called the Pearl Index, or PI. The PI is a measure of the rate of pregnancies over a specific period of time in a clinical trial, and is expressed as the number of pregnancies per 100 WY of use. Each cycle lasts 28 days, so there are approximately 13 cycles in one year. According to FDA guidance, the PI calculation includes all pregnancies, but only includes cycles where the woman indicates that she engaged in sexual activity and did not use backup contraception, such as a condom, and where she has completed a study diary. The PI values from clinical trials are affected by several factors, including differences in study design, increased sensitivity of early pregnancy tests, weight and body mass index, or BMI, of the study population, user experience and inconsistent or incorrect use of the contraceptive method.

The contraceptive failure rates in clinical trials are generally lower than those seen once a CHC is approved and in use by a broad population, referred to as typical use, without the close monitoring of a clinical trial setting. There is a large difference in pregnancy rates under conditions of perfect use, where the method is used following the directions exactly, and typical use. For example, for CHCs, including oral contraceptives, the vaginal ring and the transdermal patch, the percent of women experiencing an unintended pregnancy during the first year of use is 0.3% for perfect use and 9.0% for typical use.

*U.S. Hormonal Contraceptive Market Background*

Contraceptive methods, other than sterilization, can be divided into non-hormonal and hormonal alternatives. Non-hormonal products available in the United States include the diaphragm, male condom and female condom. There are several categories of hormonal contraception products available in the United States, including:

oral contraceptive;

vaginal ring;

transdermal patch;

intrauterine contraceptive device, or IUD;

subcutaneous implant; and

injectable.

The U.S. hormonal contraceptive market recorded annual sales in 2014 of \$5.3 billion, according to IMS Health. The CHC portion of the market, consisting of pills, a transdermal patch and a vaginal ring, generates significantly greater prescription volume and sales compared to the P-only portion of the market, consisting of IUDs, injectables, implants, and P-only pills. In 2014, IMS Health reported total U.S. sales of \$4.0 billion for the CHC market and \$1.3 billion for the P-only market. Twirla is a CHC and, if approved, we believe it will compete primarily with products in the CHC market.

The U.S. hormonal contraceptive market is a mature market, with many branded and generic products available. In the past 10 years, the market growth was flat to declining as measured by prescription volume, with the exception of a 4.8% increase in 2013 compared to 2012. The average annual growth rate in dollar sales for the five years ended December 31, 2014 was 2.9% for the total hormonal contraceptive market and 0.7% for the CHC market. Market growth in gross sales is primarily due to price increases amongst branded products.

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We believe there are two possible factors primarily affecting prescription volume growth in the contraceptive market. First, according to U.S. Census Bureau data and projections, the population of women aged 15 to 44 years has been growing at a rate of approximately 0.4% to 0.5% per year since 2011, increasing this population by 250,000 to 300,000 women per year.

**Contraceptive Population  
(Total women aged 15-44 yrs)**

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Source: U.S. Census Bureau, National projections released 2008 based on 2000 census data.

Second, in 2010, the Patient Protection and Affordable Care Act, as amended by the Healthcare and Education Reconciliation Act, or collectively, the ACA, was signed into law, which, among other things, requires all health plans, with limited exceptions, to cover certain preventive services for women with no cost sharing, which means no deductible, no co-insurance and no co-payments by the patient, effective August 1, 2012. These services include those set forth in the Guidelines for Women's Preventive Services, or HRSA Guidelines, and adopted by the U.S. Department of Health and Human Services Health Resources and Services Administration. Contraceptive methods and counseling, including all FDA approved contraceptive methods as prescribed, are included in the HRSA Guidelines. Since these new ACA provisions went into effect in August 2012, quarterly prescription volume growth for the CHC market rose from negative growth year-on-year to positive growth between 4.0% and 5.0% for each of the six quarters following implementation. However, this appears to be a temporary phenomenon, as the market volume growth in 2014 fell to 0.8%, a rate closer to population growth.

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**Effect of the ACA on CHC Market Growth**

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Source: IMS National Prescription Audit, IMS Health

During the period following enactment of the ACA, generic oral contraceptives have shown the greatest growth, primarily at the expense of branded oral contraceptives. This is likely due to the policies that have been implemented by many managed care plans, which are generally only providing generic oral contraceptives with no cost-sharing to the patient. The effect on non-oral products is less clear, but prescription volume for the vaginal ring showed a 5.9% decline from 2013 to 2014, while the prescription volume for the patch increased by 2.1% over the same time period. As interpreted by the applicable governmental agencies, health plans are only required to cover one product for each contraceptive "method" without cost-sharing by the patient. For other products that fall within the same "method" that are not the preferred product, payors are allowed to use reasonable medical management techniques, such as applying cost-sharing obligations. We therefore cannot be sure that the growth in the CHC market is due entirely to the new coverage and ACA requirements, and it is too early to determine the full effect of the ACA on our business. We believe the CHC market will maintain a long-term positive annual growth rate in line with contraceptive population growth.

In spite of the availability of generic contraceptives for over 25 years, branded products have maintained a significant share of the CHC market, with 58% of dollar sales and 22% of prescriptions for the 12 months ended September 2014. Branded contraceptives in the CHC market have driven significant increases in the value of branded total prescriptions, or TRx. In the five years ended December 2014, the average annual price increase among the top branded products was 10.4%. The average price per cycle, referred to as the wholesale acquisition cost, or WAC, for a single 28-day cycle of the top branded products was \$41.53 in 2006 and rose to \$108.61 by January 2015. The branded and generic forms of the CHC transdermal patch are currently priced at \$110.22 and \$95.12 per cycle, respectively. The other non-oral form of CHC, the vaginal ring, is currently priced at \$105.81 per cycle. We cannot predict whether the manufacturers of branded products will continue to increase prices going forward, but we believe we will be able to set a WAC price for Twirla, if approved, that is comparable to other branded CHC products at the time of launch. Based on IMS Health data, we estimate that each percentage point of market share of CHC total prescriptions in the United States currently represents approximately \$136 million of annual gross sales potential for Twirla, if approved.

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*Contraceptive Pills*

Based on data from the CDC, of women who choose to use a hormonal contraceptive, approximately 64% use the contraceptive pill, vaginal ring or patch, the majority of which use the contraceptive pill. We believe that contraceptive pills are the most popular choice because:

patients and physicians are familiar with pills;

pills were the first to market and have been aggressively promoted for a long period of time;

historically, pills have been a covered benefit with good reimbursement in private and public healthcare plans; and

pills are a non-invasive option.

However, compliance remains a significant draw-back with pills. Published studies have shown that the average woman who uses oral contraceptives misses approximately two to four pills per month, which increases the potential for unintended pregnancies. We believe that a patch can offer greater convenience than a pill, as it does not require daily administration and, for certain women, could lead to greater compliance and ease of use.

*Contraceptive Patch Market Experience*

The Ortho Evra® contraceptive patch, or Evra, was introduced in early 2002 and was the first FDA-approved contraceptive patch. The initial approved labeling for Evra indicated that it delivered a daily EE dose of 20 micrograms. Evra had rapid uptake in the contraceptive market, and achieved a 10% share of the CHC market by September 2003. Following FDA approval of Evra, users of Evra began to report thrombotic and thromboembolic events to the FDA. Johnson & Johnson, the manufacturer of Evra, revised the Evra labeling in November 2005 to include information that EE exposure with Evra is 60% higher than that of an oral contraceptive containing EE of 35 micrograms, based on area under the curve, a commonly-used metric for measuring EE exposure in contraceptives. This information was ultimately included in a black box warning and bolded warnings unique to the Evra label. The Evra market share declined rapidly following the labeling changes, from a peak share of 11% in 2005, to 4% by the end of 2006, to 1.4% by the end of 2013, where it appears to have stabilized, with a 1.5% share of the market based on combined prescriptions for Evra and its generic equivalent in 2014.

In April 2014, Mylan Inc. announced the launch of Xulane, a generic version of Evra. Generic pharmaceutical products are the chemical and pharmaceutical equivalents of the brand or a reference listed drug, or RLD. Generic drugs are bioequivalent to their reference brand name counterparts. Bioequivalence studies compare the bioavailability of the proposed drug product with that of the RLD product containing the same active ingredients. Bioavailability is a measure of the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action. Under pharmacy dispensing rules governed by state law, depending on the state, if an automatic generic substitute is introduced, the pharmacist may dispense either the prescribed product, or they may replace it with an equivalent generic without being required to inform the patient or healthcare professional. In addition, the FDA offers a 180-day exclusivity period for generic products in specific cases. The first generic applicants to submit a substantially complete Abbreviated New Drug Application containing a paragraph IV certification to a listed patent are protected from competition from other generic versions of the same drug for the 180 days. As of March 2015, no other generic equivalents to Evra have been introduced.

The FDA has maintained, in spite of the wording in the labeling for Evra and its approved generic, that none of the epidemiologic studies to date provides a definitive answer regarding the relative risk of VTE with Evra compared to combined oral contraceptive use or whether the increased

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risk that some studies demonstrated is directly attributable to Evra. An advisory committee for the FDA stated that the benefits of Evra outweigh the risks. In its denial of a Citizen's Petition calling for the withdrawal of Evra, the FDA followed the committee's recommendations stating that the increased VTE risk does not warrant removal from the market, and that the labeling revisions to the Evra label provide an update and guidance on the interpretation of the epidemiologic data about the risk of VTE with Evra. In spite of the labeling changes, and Johnson & Johnson ceasing promotion of Evra in 2007, Evra and its generic equivalent generated \$153 million in gross sales in 2014.

We believe that the rapid uptake and acceptance of Evra upon its introduction demonstrates that there is an unmet market need for a transdermal patch as a contraceptive option. Also, the epidemiologic data on VTE risk suggest that there is a need for a contraceptive patch that delivers both a low dose of EE similar to oral contraceptives and a first or second generation progestin.

**Our Product Candidates**

Each of our product candidates utilizes our proprietary Skinfusion technology, which is designed to provide advantages over the currently available patch. Skinfusion is designed to deliver contraceptive-levels of hormones to the blood stream through the skin over a seven-day period. It is also designed to optimize patch adherence and stability and patient comfort. Our lead product candidate is Twirla, a prescription CHC patch which contains both EE and LNG and is designed to deliver a low dose of EE and LNG comparable to the total dose delivered with low-dose oral contraceptives. In addition to Twirla, we are developing a pipeline of other new transdermal contraceptive products, including AG200-ER, which is a regimen designed to allow a woman to extend the length of her cycle and AG200-SP, which is a regimen designed to provide shorter, lighter monthly withdrawal bleeding. We are also developing AG890, which is a P-only prescription contraceptive patch intended for use by women who are unable or unwilling to take estrogen.

Our current product candidate pipeline is summarized in the graphic below:

**Agile Therapeutics Pipeline**

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*Twirla Product Overview*

Twirla is a CHC patch which contains both EE and LNG. Twirla is designed to address an unmet medical need for increased compliance and improved ease of use as compared to oral contraceptives. A single Twirla patch delivers the active ingredients LNG and EE over a seven-day dosing interval, and thereby eliminates the need to take a daily pill as is necessary with an oral contraceptive. Twirla uses a traditional 28-day contraceptive regimen, where one patch is applied weekly for three consecutive weeks and then there is a fourth patch-free week in each 28-day time period. Twirla may be applied to the buttock, abdomen or upper torso, but not the breast. In clinical trials to date, women most frequently chose the buttock and abdomen for patch placement. The exact patch location needs to be rotated with each patch change. Twirla has demonstrated a therapeutically equivalent pharmacokinetic profile when worn on the buttock, abdomen or upper torso. A drug's pharmacokinetic profile refers to the specific way in which a given drug is handled by the body over time, reflecting the particular patterns of absorption, distribution and elimination of the drug in the body.

Twirla is designed to be highly appealing to patients as a method of contraception. The patch is round and made of a soft, flexible, silky fabric, designed to flex with the movement of a woman's body. Twirla is a matrix patch consisting of several layers of material that contain the active ingredients EE and LNG, as well as the inactive ingredients Dimethylsulfoxide, Ethyl Lactate, Capric Acid and Lauryl Lactate, which are ingredients to assist in the transport of EE and LNG across the skin, and adhesives that enable adherence to the skin. The final top layer is the one seen on the skin, and consists of a thin, silky material consisting of only adhesive. There is a barrier formed between the inner portion of the patch, which contains the active ingredients, and the outer portion of the patch, which only contains the adhesive. This barrier is intended to prevent the active and inactive ingredients from migrating to the peripheral portion of the patch, and from breaking down the adhesive in that portion of the patch. Twirla is also designed to help prevent seepage of the adhesives from around the edge of the patch where it could collect dirt and leave a sticky black ring on the skin. The six layers of the patch are integrated to create a patch which has a slim profile, and is unobtrusive when applied. The results of

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multiple clinical trials suggest that Twirla delivers the active ingredients needed for contraception over a seven-day period and that it remains adhered to the skin of most subjects for the full seven-day period, even under conditions of heat, humidity, showering, exposure to water and vigorous exercise.



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*Twirla Patch Profile*

The following table compares Twirla with the currently marketed Evra product as stated in its label, based upon publicly-available information regarding Evra and the characteristics of Twirla and other Twirla attributes observed in our completed Phase 3 clinical trials. We have not performed a head-to-head comparison of Twirla to Evra.

<b>Characteristic</b>	<b>Twirla</b>	<b>Ortho Evra*</b>
Form of product	Transdermal patch Round, approximately 28 square centimeters Soft, silky, stretchy fabric	Transdermal patch Square, approximately 20 square centimeters Smooth, plastic film
Active ingredients	EE, LNG	EE, norelgestromin
Pharmacokinetic profile of EE per day	~30 micrograms	60% higher than that of an oral contraceptive containing 35 micrograms (~56 micrograms)**
Regimen	One patch weekly 21 days active / 7 days patch-free	Same as Twirla
Package configurations	1 box of 3 patches = 1 cycle 1 box with 1 patch = replacement	Same as Twirla
Top four adverse events/reactions in clinical trials	Nausea 3.0% Application site irritation 2.4% Breast tenderness 2.1% Headache 2.0%***	Breast symptoms 22.4% Headache 21.0% Application site disorders 17.1% Nausea 16.6%

\* Source of Ortho Evra data is U.S. prescribing information or package insert.

\*\* The Ortho Evra package insert indicates a strength of 35 micrograms of EE per day.

\*\*\* Adverse events deemed definitely, probably or possibly related to Twirla in completed Phase 3 clinical trials.

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**Twirla**

**Evra**

Twirla employs our Skinfusion patch technology, resulting in a unique appearance and feel of the patch. Evra does not utilize our Skinfusion technology; its active ingredients and adhesives are dispersed to its edges. One frequent complaint about patches that do not utilize Skinfusion is that they collect dirt and lint and may leave a sticky black ring of residue on the skin which can be difficult to remove. We do not have any direct comparison of the appearance of the patch on the skin at the end of seven days between Twirla and Evra, but we believe, based on anecdotal feedback from our clinical trial investigators, as well as based upon the differences in the design of the two patches, that Twirla may have an advantage in this regard.

We have not performed a head-to-head comparison of Twirla to Evra, however, a pharmacokinetic study that we conducted with Twirla was similar in design to the pharmacokinetic study conducted with Evra that provided the information regarding the daily amount of EE delivered that is currently in the Evra package insert. The figure below combines the results for average EE concentrations from these two studies, and suggests a comparison of the observed blood concentration of EE for Twirla versus Evra versus observed and estimated data for the pill. The lower amount of EE delivered from Twirla as compared to Evra can be observed. If Twirla is approved by the FDA, we will not be able to make direct comparative claims regarding the safety, efficacy or pharmacokinetics of Twirla and Evra, since none of our completed clinical trials studied, nor does our contemplated additional Phase 3 clinical trial expect to study, Twirla in a head-to-head comparison with Evra.

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**EE Concentrations (pg/ml)**

The Evra curve presented in the graphic above was estimated based on the graph provided in the Evra label. In the legend to the figure above, "OC" refers to an oral contraceptive containing 35 micrograms of EE. The OC data prior to Day 21 are estimated steady-state data based on Day 21 EE concentrations observed during our pharmacokinetic study.

Twirla contains LNG, which is the progestin used as the reference standard when comparing risk of VTE between progestins. Evra contains the progestin norelgestromin, which is a prodrug of norgestimate, a second generation progestin that has not demonstrated an increased risk of VTE independent of EE. We do not expect any meaningful clinical differences between Twirla and Evra based on the progestin component, but our market research with ObGyns has demonstrated that they perceive LNG to be one of the safest progestins available.

*Twirla Product Profile*

Assuming completion of a successful additional Phase 3 clinical trial and approval of our marketing application by the FDA, we believe the clinical trial data from the ongoing Phase 3 trial (SECURE) for Twirla will support our future marketing of Twirla as follows:

Twirla is a weekly contraceptive patch, designed to offer convenience and compliance.

Twirla is designed to meet the contraceptive needs and the busy lifestyle of today's women.

Twirla contains the active ingredients EE and LNG, both of which have been used in contraceptives for over 25 years.

Twirla delivers the low daily dose of EE of approximately 30 micrograms, comparable to low-dose oral contraceptives.

Twirla is designed to demonstrate efficacy comparable to other approved prescription contraceptives.

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Twirla has a favorable safety and tolerability profile.

Twirla was designed with Skinfusion technology, which has demonstrated adhesion over the seven-day wear period, even under conditions of heat, humidity, showering, exposure to water and vigorous exercise.

Because Twirla contains the progestin LNG, we believe that the final approved label for Twirla will be consistent with the class labeling for other contraceptives containing EE and LNG, including the class black box warning.

**Twirla Clinical Development Program**

*Completed Clinical Trials*

Our clinical program includes three Phase 1 studies, one Phase 2 study, and three Phase 3 studies, as well as other supporting studies. We are currently conducting the third Phase 3 study in response to FDA comments and guidance. In Phase 1 and Phase 2 clinical trials, we demonstrated that Twirla delivers levels of both EE and LNG to the blood stream that are consistent with currently marketed low-dose oral contraceptives. In our completed Phase 3 clinical trials, we demonstrated that Twirla was comparable to an approved low-dose oral contraceptive in two randomized studies, one that enrolled over 1,500 women over 12 months and the other that enrolled over 400 women over six months. Across all completed clinical trials, Twirla was generally well-tolerated and had a favorable safety profile. Because we relied, in part, on the FDA's findings of safety and efficacy from investigations for approved products containing EE and LNG and published scientific literature for which we have not obtained a right of reference, we were not required to conduct preclinical studies. In the pharmacokinetic study comparing Twirla to an approved low-dose oral contraceptive, results demonstrated that Twirla delivers a daily dose of EE that results in estrogen exposure similar to low-dose oral contraceptives containing approximately 30 micrograms.

Our two completed Phase 3 trials enrolled over 1,900 subjects to evaluate the safety and efficacy of Twirla. Each of these studies included an active comparator arm with an approved low-dose oral contraceptive. The results of these studies demonstrated that Twirla was generally well-tolerated, with levels of adverse events generally comparable to those of low-dose oral contraceptives. In these studies, subjects had a higher rate of self-reported compliance when using the patch as compared with the group using oral contraceptives. However, as discussed further below, the FDA issued a CRL in response to our marketing application for Twirla and requested an additional Phase 3 study and additional chemistry manufacturing and control, or CMC, information. The results of the larger of our Phase 3 clinical trials demonstrated that approximately only 3% of patches became completely detached from the skin of subjects during the seven-day period, and that the patch generally remained adhered to the skin even when exposed to normal daily activities and conditions such as showering, swimming and other forms of exercise, heat and humidity.

More specifically, our safety population included subjects who received at least one dose of Twirla or COC. In the combined safety population of our completed Phase 3 trials, there were a total of 22 serious adverse events, or SAEs, of which 16 were from the Twirla cohort, which had approximately 2.3 times as many subjects as the oral contraceptive comparator cohort. Three of these SAEs (0.2% of the overall Twirla safety population) were considered to be possibly related to the study drug and included one drug overdose with Benadryl®, one case of uncontrollable nausea and vomiting and one instance of deep vein thrombosis. In addition to the SAEs described above, some subjects taking Twirla experienced non-serious adverse events, such as nausea, headache, application site irritation and breast tenderness. Subjects receiving the oral contraceptive comparator also generally experienced similar non-serious adverse events such as nausea, headache, and breast tenderness, though at different rates. We believe that Twirla will have a label consistent with all marketed low-dose CHC products, which include class labeling that warns of risks of certain serious conditions, including venous and arterial

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blood clots, such as heart attacks, thromboembolism and stroke, as well as liver tumors, gallbladder disease and hypertension, and a black box warning regarding risks of smoking and CHC use and particularly in women over 35 years old that smoke.

In our Phase 3 trials, the primary measure of efficacy is the Pearl Index, or PI, which is calculated based on the number of observed on-treatment pregnancies and total number of on-treatment cycles during the study. Specifically, the PI is expressed as the number of pregnancies per 100 WY of use. The pooled PI value in the completed Phase 3 trials for the Twirla patch was 5.76 and for the combined oral contraceptive control arms was 6.72, which were higher than the range of 1.34 to 3.19 in pivotal studies conducted on products approved by the FDA in the previous ten years.

We believe that the results for both the patch and oral contraceptive control arms in the completed Phase 3 trials were affected primarily by issues with study conduct at several study sites, including rapid enrollment which led to inability to manage the study population, poor subject compliance, and high rates of loss to follow-up. In the larger of our completed Phase 3 clinical trials, 96 sites enrolled subjects, 60 of which had no on-treatment pregnancies. Nineteen percent of the on-treatment pregnancies reported during this trial came from one site. This site represented approximately 8% of the randomized subject population. Thirty six percent of on-treatment pregnancies were reported at four of the 96 sites. These four sites represented approximately 15% of the randomized subject population.

Experts agree that the characteristic most likely to impact contraceptive failure and pregnancy rates is the subject's likelihood of using a method inconsistently or incorrectly. Consistent with expert opinions, our analyses have suggested that the results for both the patch and oral contraceptive control arms in the completed Phase 3 trials were also affected in part by the study population, which comprised a disproportionately high number of new users and minority subjects, known to be at higher risk of noncompliance and pregnancy, as compared to the majority of other recent CHC clinical trials which have gained approval in the United States.

Individuals who immediately switch from one hormonal contraception method to another, referred to as current users, or who have recently used another method of hormonal contraception, are less likely to experience contraceptive failure than a new user because they are less likely to have inconsistent or incorrect use. These experienced subjects are often selected for trial participation because their inclusion will lower failure rates. Indeed, many contraceptive trials have enrolled a high proportion of these subjects. Direct comparisons across multiple trials are limited by differences in study design and population, as well as differences in definitions of user status; however, as shown in the table below, some comparisons are possible. For example, when compared against trials that captured current hormonal contraceptive use, in the larger of our completed Phase 3 trials, we had a lower proportion of subjects randomized to receive Twirla that were current users, only 17.8%, reflecting a population with less experience using hormonal contraception, compared to two recently approved hormonal contraceptives. When compared against trials that categorized subject experience more broadly by their use of hormonal contraception within the 6 months prior to enrollment, our trial also had a lower proportion of experienced subjects, only 44%. In both the COC and Twirla groups, new users had approximately three times the rate of noncompliance compared to experienced users, as verified through blood tests revealing non-detectable blood levels of EE and LNG. Similarly, the pooled PI values from our completed Phase 3 clinical trials were more than twice as high among new users compared to experienced users, and in the primary efficacy analysis population there were no pregnancies observed in current users of other hormonal contraception who immediately switched to the patch upon entry into the trial.

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In addition, our completed Phase 3 clinical trials also included a higher proportion of black and Hispanic subjects than most recent hormonal contraceptive trials. Although the underlying reasons are not well-understood, several articles in medical journals, such as *Contraception* and the *American Journal of Obstetrics & Gynecology*, and in at least one report by the U.S. Department of Health and Human Services, state that contraceptive failure rates are highest in black and Hispanic subjects. In our completed Phase 3 trials, rates of laboratory-verified noncompliance were substantially higher in blacks and Hispanics compared to non-Hispanic white subjects in the larger of our Phase 3 trials, and as shown in the table below, there were substantially higher PI values in the black and Hispanic subpopulations than in non-Hispanic white subjects. Additionally, as shown in the table the observed PI values were more dramatically increased for new users who were also black or Hispanic.

**Study Population Demographics in Selected Contraception Trials**

Parameter		Contraceptive Product (Year of Approval) % of subjects in category*					
		Twirla	Seasonique (2006)	Yaz (2006)	Lo-Seasonique (2008)	Natazia (2010)	Quartette (2013)
Hormonal contraception use							
Current Users		18(a)		60(b)		59(c)	
Within 6m of enrollment	Yes(d)	44	68		61	44	
	No(e)	56	32		39	56	
Race/ethnicity	Hispanic	15	5	5	10	13	11
	Black	22	11	4	12	7	18

\*

Table includes subjects randomized to Twirla in our larger Phase 3 clinical trial. The data pertaining to the approved drug products were derived from multiple studies, with differing study designs, as reported in the FDA medical review documents for each product.

Current user definitions (extrapolated for approved products):

- (a) Used a hormonal contraceptive within 7 days of enrollment.
- (b) Using an oral contraceptive at screening, just prior to study start.
- (c) Using oral contraceptives prior to study start.
- Use within 6 months of enrollment definitions:
- (d) Twirla: recent and current users; Quartette/Seasonique/Lo-Seasonique: continuous users.
- (e) Twirla: new users; Seasonique/LoSeasonique: fresh start and prior users; Quartette: new start and prior user.

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<b>Parameter</b>	<b>Demographic</b>	<b>Pearl Index*</b>
Race/ethnicity	White (not Hispanic)	3.6
	Hispanic	5.0
	Black	15.1
Previous contraceptive use status	New users(a)	8.7
	Experienced users(b)	3.0
	Current users(c)	0.0
Race/ethnicity and Previous contraceptive use status	Hispanic subjects who were new users	7.5
	Black subjects who were new users	16.0

\*

Table includes the pooled PI values for subjects in the primary efficacy analysis population randomized to Twirla.

- (a) New users = never used hormonal contraception or had not used hormonal contraception in the 6 months prior to enrollment.
- (b) Experienced users = recent (used a hormonal contraceptive within 6 months of enrollment) and current users.
- (c) Current users = subjects who used a hormonal contraceptive within seven days of enrollment.

*CRL and FDA Interactions*

In February 2013, we received a CRL from the FDA indicating that the results from our completed Phase 3 trials would not be sufficient for approval, and the FDA proposed that we conduct an additional Phase 3 trial. Among the comments expressed in the letter were some regarding the PI values seen in the studies. Specifically, the FDA indicated that the PI values in the studies, in both the subjects using the Twirla patch and the control arm using oral contraceptives, were higher than seen in clinical trials used for registration of other approved hormonal contraceptives. The FDA recommended that we conduct an additional Phase 3 trial with a simplified clinical trial design and improved study conduct, including site monitoring and data collection procedures. The FDA also required additional information relating to the laser etching of label information on each patch and required that the patch used in the new trial utilize the same etching as will be used for the commercial product, in order to demonstrate that it does not adversely affect the performance of the patch. Furthermore, the FDA also requested in the CRL additional information on controls and release specifications related to the patch, and manufacturing and control information related to the Drug Master File of one of the raw materials in Twirla.

In October 2013, we met with the FDA and received further guidance on requirements for our planned Phase 3 trial. In addition, we had a follow-up written interaction with the FDA in February 2014 and have received substantial written comments from the FDA in subsequent interactions. We enrolled the first subject in the SECURE study in the third quarter of 2014, and expect to complete enrollment in the third quarter of 2015. The patches being studied in the SECURE study are laser etched using the same process as we anticipate for commercialization of Twirla, if approved. We will continue additional supportive testing in order to respond to the FDA's CMC questions.



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*The SECURE study, our third Phase 3 Clinical Trial*

Our third Phase 3 clinical trial is intended to address a number of issues identified in the CRL, including but not limited to, a simplified trial design, study conduct, recruitment of study population and compliance. We have designed the SECURE study as follows:

Single-arm study;

Approximately 2,100 female subjects will receive Twirla for up to one year;

Approximately 80 sites located in the United States with experience in conducting contraceptive studies;

The subjects are using an electronic diary to record the data that are critical to the calculation of the PI, such as sexual activity, back-up contraception use, and patch usage and adhesion; and

We will assess patch adhesion based on a quantifiable daily subject assessment of percent adherence of the patch to the skin.

By not having a comparator, we will increase the number of cycles collected for the primary efficacy analysis. The single-arm design will also substantially reduce the complexity of statistical analyses required to interpret the results of the trial and will reduce uncertainty around interpretation of any unexpected differences in observed PI values between Twirla and a comparator arm that could occur. Importantly, the simplified protocol design should also be easier for clinical sites to understand and implement. In addition, we believe that having no oral contraceptive comparator will attract subjects who are interested in participating in the transdermal method as opposed to subjects who may be at higher risk for early discontinuation from the study if randomized to the patch. We believe this phenomenon occurred in the larger of our completed Phase 3 clinical trials and may have contributed to the early observed discontinuation rate.

The SECURE study is employing several measures designed to improve upon one aspect of prior study conduct: loss to follow-up. First, the SECURE study is being conducted in approximately 80 sites in the United States that have experience conducting contraceptive trials and experienced study coordinators. Study sites have been evaluated extensively for their prior hormonal birth control trial experience through a data-driven approach assessing performance on previous clinical studies, staffing of experienced study coordinators with longevity at the site, demographics of potential study subjects, and audit history. Fewer sites will enable more focused oversight of participating sites and facilitate more individualized attention to enrolled study subjects, as compared to our previous Phase 3 study which was conducted at 96 sites. Training of study coordinators at the investigator meeting, at study initiation visits, and through ongoing communication should also reduce loss to follow-up. In addition, study sites that are showing early trends toward higher rates of loss to follow-up or overall poor study management will be re-trained and, if necessary, discontinued. Upon subject enrollment, sites will also ask for multiple methods of contact for each subject, and will obtain permission to contact family members and utilize public records to locate subjects who are lost to follow-up.

After site selection, recruitment of the study population is the next crucial step toward achievement of a population that will provide reliable and generalizable data in the SECURE study. We have trained our sites to provide individualized attention to recruitment of subjects who are most likely to adhere to the study protocol with respect to compliance, including correct patch application, timing of patch removal and replacement, electronic diary, or e-diary, completion and study visits. Potential subjects are carefully screened for ability, motivation and willingness to comply with all of the study visits and other requirements. Study coordinators and investigators have received in-depth training on selection of appropriate subjects prior to beginning subject enrollment, and these criteria are being reviewed throughout the study enrollment period. Subjects are also advised through the informed consent process that noncompliance with study procedures may lead to discontinuation from

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the trial. In addition, each site is providing real-time recruitment information to the CRO throughout the recruitment process, which facilitates enrollment of the appropriate subject population. We continue to expect that enrollment of the SECURE study will be completed in the third quarter of 2015.

A number of measures have been put in place in order to facilitate compliance with study procedures. To ensure subjects are adequately educated regarding their responsibilities during the trial, a detailed subject teaching plan has been developed and implemented, and subject education regarding the importance of compliance, including videos, brochures and one-to-one education with study coordinators, is provided at repeated intervals throughout the study. A number of measures have been put in place to support and monitor compliance through the study. One key measure is the use of e-diary and text message technology, which provides personalized reminders to subjects for patch application, diary completion and study visits, measures we believe will improve overall subject compliance. Phone contact with subjects between visits is part of the study protocol, which will increase the frequency of contact with subjects throughout the study.

The electronic diary platform being utilized in the SECURE study is PHT's LogPad® system, a handheld device specifically designed for subject-entered data capture. In addition to contributing to improved compliance, the use of e-diary technology may also contribute to improved data quality and completeness in the SECURE study. Subjects use their e-diaries to record the data that are critical to the calculation of the PI, including sexual activity and use of back-up contraception. Subjects also record their bleeding patterns and patch adherence using a new, more precise scale. During the study screening period, subjects receive comprehensive training on use of the e-diaries and are required to demonstrate both appropriate use and ability to comply with the study protocol during a two-week run-in period in order to be enrolled in the study. The diaries are designed to be simple and easy-to-use, and to enhance data quality, and have built-in prompts to avoid subject error in data entry. As the subjects enter data into the e-diaries, information is transmitted to the vendor database and is available for real-time review by the Agile team, the CRO and our study monitors. The CRO and our study monitors analyze individual subject and site data and can immediately implement additional training or intervention with study site coordinators and subjects as needed, including potentially discontinuing noncompliant sites or subjects. Real-time e-diary and study visit data also potentially minimize the number of subjects lost to follow-up. By selecting an appropriate subject population and implementing the compliance measures described above, we anticipate that the number of pregnancies will be reduced as compared to the previous Phase 3 studies. None of these real-time measures were utilized in our previous clinical trials. We believe we have designed and are implementing a clinical trial that addresses the feedback provided by the FDA in the CRL and additional guidance we have received in subsequent interactions with the FDA.

An independent Pregnancy Review Committee comprised of experts has been selected to review all pregnancies and determine on or off-treatment status, which will affect the numerator of the PI calculation. Accurate and timely pregnancy adjudication is critically important in order to reduce the likelihood that pregnancies which occur during these time periods will be included by the FDA during the review process. In order to avoid pre- or post-treatment pregnancies being included, every pregnancy will be assessed via ultrasound as soon as possible and full data will be collected regarding the relationship of the pregnancy to the subject's use of Twirla. Based on the observations regarding the clustering of pregnancies at a few sites during our completed Phase 3 trials, we believe that focused attention to ensuring full implementation of the compliance measures at every site will substantially reduce the overall incidence of pregnancies during the SECURE study. We did not have an independent Pregnancy Review Committee for our previous clinical trials.

The observed PI values will not only be impacted by the number of pregnancies that occur in the study, but also by the number of cycles that are included in the analysis, which affects the denominator of the PI calculation. Cycles in which a subject is not sexually active, has incomplete diary information or uses a back-up method of contraception will not be counted toward the number of cycles included in

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the calculation of the PI. Indicators of subjects who are likely to exhibit the behaviors listed above are being carefully assessed during the recruitment process so as to reduce the number of cycles discarded from the analysis.

We have engaged Parexel International Corporation, or Parexel, a CRO with substantial experience in contraception studies and excellent site monitoring capabilities. We actively participated in site selection, and actively participate in monitoring subject recruitment, site monitoring and oversight of Parexel's activities, and will continue to do so throughout the length of the trial. Our CRO was selected based not only on the above criteria, but on a clear track record of responding to trends and information through early intervention in order to assure compliance with trial procedures at both the subject and site levels.

Assuming successful completion of the SECURE study by the second half of 2016, we plan to submit a complete response that includes the additional clinical trial results to the FDA in the first half of 2017.

**Twirla Line Extensions and Other Product Candidates**

In addition to Twirla, our product pipeline consists of two classes of product candidates: Twirla line extensions and other transdermal contraceptive product candidates. These product candidates are designed to address market needs and offer additional non-daily contraceptive options. Based on the results of our market research on line extension regimen concepts, we believe that our line extension product candidates are commercially viable and could garner a share of the contraceptive market.

The hormonal contraceptive market has a long history of manufacturers successfully using line extensions to extend the lifecycle of a brand, often by gaining additional exclusivity periods for the product extension under the provisions of the Hatch-Waxman Act or with additional patents. Our lifecycle strategy with Twirla is to introduce line extensions that will have exclusivity for some time period, either due to our intellectual property estate, or due to Hatch-Waxman exclusivity. The line extensions in our pipeline include using our Skinfusion technology to allow a 28-day regimen where women will experience shorter, lighter withdrawal bleeding, as well as extending the cycle beyond the typical 28-day regimen to allow women to experience fewer withdrawal bleeds each year.

Our Twirla line extensions include the following:

AG200-ER is an extended cycle regimen utilizing our current patch product designed to allow a woman to extend the time between her episodes of withdrawal bleeding. There are several currently approved oral contraceptives that provide an 84 or 91-day extended cycle regimen. However, there is no approved contraceptive patch product offering an extended cycle regimen. AG200-ER is a contraceptive patch which is designed to address the limitations of the currently approved extended regimen oral contraceptives by providing a more convenient, weekly dosing schedule. By adjusting the length of the cycle, AG200-ER is designed to potentially minimize breakthrough bleeding and spotting, which is a commonly-reported concern with patients using an extended regimen contraceptive product. AG200-ER utilizes the same drug product as Twirla, and therefore requires no further patch development. We are currently evaluating the optimal cycle length to advance into clinical development.

AG200-SP is a 28-day regimen designed to provide users with shorter, lighter withdrawal bleeds and potentially improve contraceptive efficacy. AG200-SP may also provide benefit in patients with sensitivity to abrupt changes in hormone levels. Oral contraceptives that use a shortened hormone-free interval, or SHFI, by delivering hormones beyond 21 days currently comprise 43% of U.S. branded TRx volume, demonstrating high acceptability among patients and providers. AG200-SP is designed to provide a simplified 28-day regimen through use of a smaller, lower-dose patch in the fourth week, which will allow patients to continuously apply patches

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without interruption. AG200-SP requires additional patch development work prior to potentially conducting Phase 1 studies.

Our other product candidate is a P-only contraceptive patch described below:

AG890 is an LNG-only contraceptive patch, intended for use by women who are unable or unwilling to take estrogen, including those who are breastfeeding or who are at greater risk of VTE, such as women who smoke, are over 35 years of age, or who are obese. Currently, the P-only market consists of pills and several non-oral options, including IUDs, implants and injections. AG890 is intended to fulfill an unmet medical need for a non-daily, easily reversible form of contraception in the P-only market. We have conducted a Phase 1 clinical trial with AG890. In addition, the National Institutes of Health, through a clinical trial agreement with us, conducted a Phase 1/2 trial with AG890. The Phase 1/2 study was a multicenter study to evaluate the pharmacokinetics, safety and mechanisms of potential contraceptive efficacy of AG890. The trial is complete and findings indicate that additional patch development work for dose selection will be required, including additional Phase 1 and Phase 2 studies to determine the optimal formulation and dose to advance to Phase 3.

We do not expect to be required to conduct preclinical studies for any of these product candidates. Based upon a number of factors, including, but not limited to, our available capital resources and feedback from the FDA, we intend to review the clinical path for each of these three product candidates in 2015.

**Sales and Marketing**

*Twirla Commercialization Strategy*

We expect to build a sales and marketing infrastructure in the United States to support the launch of Twirla for contraception, if approved. We anticipate that a targeted sales force focused initially on ObGyns, NPs, PAs and primary care providers who comprise the top prescribers of contraceptives will be highly effective. Outside the United States, in the future we may decide to commercialize Twirla, if approved, by entering into third-party collaboration agreements with pharmaceutical partners.

*Twirla Promotion Strategy*

We have employed several key strategies during the development of Twirla to prepare us for the launch of Twirla. These include:

Seeking advice and input from key opinion leaders, or KOLs, in women's health and contraception;

Sponsoring continuing medical education, or CME, programs at key congresses and symposia around the country;

Establishing relationships with women's health advocacy groups;

Conducting extensive market research to better understand the market dynamics and identify product positioning and messages for Twirla with prescribers and consumers;

Assuring that data from our clinical trials are presented in a timely manner at clinical congresses and published in appropriate peer-reviewed medical journals; and

Developing and registering the trademark Twirla and developing key branding elements, including packaging design for submission with the NDA.

Prescribing in the CHC category is primarily driven by ObGyns, who write nearly 45% of the total prescriptions. In addition, NPs and PAs, who are often affiliated with an ObGyn practice but can also



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be in a primary care setting, also write contraceptive prescriptions. The ObGyns, NPs and PAs combine to write nearly 70% of total CHC prescriptions. In addition, 34% of all prescriptions written by ObGyns are for contraceptives. We plan to focus the promotion of Twirla on these key prescribers and other key customer groups, including consumers and commercial managed care plans. We believe that we can deploy a focused sales force effort targeting the approximately 22,000 prescribers responsible for 80% of branded CHC prescriptions. We believe that this universe of branded prescribers can be covered adequately by a specialty sales force of between 70 and 100 total representatives. In areas of the country where it is not efficient to deploy a sales representative, remote promotion can be used to reach these prescribers.

We plan to deploy patient promotion at the launch of Twirla, both in the physician's office, and through targeted media campaigns. We plan to use both branded and unbranded campaigns to create awareness of Twirla among consumers. We believe there are cost-effective means to reach our target demographic of females aged 18 to 34 years, the so-called Millennials, who are more likely to seek health information online and through social networks. Traditional mass-market direct-to-consumer advertising on television may not be required to reach these consumers. Marketing tactics aimed at today's female consumer need to be optimized for mobile technology, because smartphones and text messaging are the preferred means of communication. Millennials also engage in online activities to a high degree. For example, approximately 80% use a social network and approximately 40% read blogs. We believe that a focused consumer promotion plan that uses digital media and other mass-market advertising vehicles will generate consumer awareness and demand for Twirla if approved.

Managed care plans have traditionally used differential co-pays to attempt to drive patients to use either generic products or products for which they have a contract with the manufacturer. Many plans encourage patients to obtain their branded contraceptives through mail-order, incentivizing them with a 90-day co-pay that is often less on a per-month basis than that for a 30-day supply. Most manufacturers of contraceptive brands offer a coupon to patients covered by non-governmental payors to offset the difference in co-pay between a generic and Tier 2 or Tier 3 for their promoted brands. These co-pay coupons are a useful tactic to overcome barriers to initiating therapy in such patients. When used in conjunction with product samples given out by the physician, a co-pay coupon often allows the patient to then fill their first prescription for free or at a steep discount, and limits the out of pocket expenditure for the patient for several months. This co-pay assistance creates brand loyalty, particularly for a brand where there is no generic alternative. We believe that we will be able to use free product samples and co-pay coupons or vouchers at the time of Twirla's launch to gain use of the product by patients covered by non-governmental payors while we are negotiating contracts with select commercial health plans and awaiting formulary review.

***Market Research***

We have conducted market research with healthcare professionals, consumers and managed care decision-makers to determine market drivers, unmet needs and the reaction to the Twirla product profile. A total of nearly 650 healthcare professionals and over 3,000 consumers have participated in our market research on Twirla and the contraceptive market. The main findings of the market research are discussed below.

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*Topline Summary of Our ObGyn/NP Market Research:*

Compliance is a substantial problem with oral contraceptives, and many women are not comfortable with the "invasiveness" of a vaginal ring, IUD or implant.

The daily dose of estrogen delivered is the most important information requested by ObGyns and NPs in order for them to prescribe Twirla, if approved.

Prescribers need assurance that what happened with Evra will not occur with Twirla, although they are generally unable to state the actual EE dose delivered by Evra.

ObGyns are not familiar with the PI calculation, and generally assume all FDA-approved contraceptives are about equally effective.

Two of our market research studies have included an allocation exercise to estimate the potential uptake of Twirla and peak market share. In both of these studies, ObGyns and NPs indicated their allocation of contraceptive prescriptions before and after reviewing a product profile like Twirla. In the first study, ObGyns estimated use of a product like Twirla in 17% of their CHC patients and in the second study, ObGyns and NPs estimated use of a product like Twirla in 18% of their contraceptive patients. A proprietary calibration model developed by Kantar Health was applied to the peak share estimate, to adjust for physician overstatement, resulting in an estimated peak market share of 9% of the CHC market. We believe a peak CHC market share of 9% can be achieved with Twirla within seven years of launch, allowing us time to establish a presence in the CHC market and to overcome any perceptions or barriers among prescribers due to the past history of Evra.

*Topline Summary of Our Consumer Market Research:*

The most important benefit to consumers is the ability for Twirla to "make their life easier" and "take birth control off their minds."

All women are "busy" and most women admit to missing at least one or more birth control pills every month.

There is little to no awareness of Evra among consumers, and no pre-existing safety hangover to overcome.

The fact that Twirla may minimize the 'black ring' effect is important.

Among women who are currently considering starting prescription contraception, nearly half would be interested in using Twirla, and over 90% of those interested said they would discuss Twirla with their doctor.

*Topline Summary of Our Managed Care Market Research:*

Contraceptives are not among the top categories affecting health plan budgets. New contraceptives will likely be subject to 'hands off' management by payors.

Prior to formulary review, most commercial plans will add Twirla, if approved, to their system and reimburse the product as a non-preferred agent.

## Edgar Filing: AGILE THERAPEUTICS INC - Form 10-K

Contracting is a critical driver to gain preferred formulary placement.

The managed care research summarized above was conducted prior to the implementation of the contraceptive mandate in the ACA. We have reviewed the latest policies released in 2014 for several major managed care plans and these reveal that the various plans have interpreted the requirement for coverage of contraceptives under the ACA differently. Some plans have designated that all contraceptives containing the same progestin are equivalent, and therefore only cover a select few products containing each progestin, usually the least expensive generics, with no co-pay. Other plans



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have defined contraceptive methods into categories such as "hormonal", "emergency contraception", and "barrier methods", and they cover just one product for each method with no co-pay. Generally, it appears that most plans are only offering generic oral contraceptives at a zero co-pay and that branded or non-oral CHC products are often available only with cost-sharing by the patient, usually in the form of a Tier 3 co-pay, or at no cost with prior authorization from the prescriber. IUDs and implants can usually be obtained at no cost to the patient only if they are purchased by the physician, rather than by the patient at a pharmacy.

**Competition**

The industry for contraceptive products is characterized by intense competition and strong promotion of proprietary products. While we believe that our Skinfusion technology provides us with a competitive advantage, we face potential competition from many different sources, including large pharmaceutical companies, specialty pharmaceutical and generic drug companies, and medical device companies. Any product candidates that we successfully develop and commercialize will compete with existing products and new products that may become available in the future.

We face competition from a variety of non-permanent birth control products. There are barrier methods, such as the contraceptive sponge, diaphragm, cervical cap or shield and condoms. Then, there are hormonal methods, which is the category for our product candidates, such as oral contraceptives, injections, implants, IUDs and vaginal ring and transdermal contraceptive products.

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The following table compares the effectiveness of birth control methods. We adapted the table from the World Health Organization, 2011 Family Planning Wall Chart.

Although there are over 180 CHC products, including branded and generics, available on the market today, approximately 50% of the total market sales, or \$2.1 billion in 2014, consisted of sales of just eight branded products. Our potential competitors include large, well-established pharmaceutical companies, and specialty pharmaceutical sales and marketing companies. The product with the highest dollar sales in the CHC market for the 12 months ending December 2014 was Nuvaring®, marketed by Merck, the only contraceptive vaginal ring available on the market, with over \$650 million in sales for 2014. The Loestrin® franchise, marketed by Allergan (formerly known as Actavis), consisting of two oral contraceptives, Minastrin® 24 and LoLoestrin®, also totaled over \$550 million in sales in 2014. Other competing products include: Gianvi® and Quartette®, marketed by Teva, Beyaz® and Yaz®, which totaled over \$160 million in sales in 2014, and Mirena®, marketed by Bayer, Generess®, which had over \$110 million in sales in 2014, marketed by Allergan, and Alesse®, marketed by Pfizer. Additionally, several generics manufacturers currently market and continue to introduce new generic contraceptives, including Sandoz, Glenmark, Lupin, Amneal and Mylan. Ortho Tri-Cyclen® Lo, also an oral contraceptive, had \$480 million in sales in 2014, in spite of no promotion by Johnson & Johnson. Ortho Evra® achieved \$150 million in sales in 2013, but faced competition from a generic version introduced in April 2014 by Mylan called Xulane®. Xulane captured \$77 million in sales in 2014, but the total combined patch sales of Evra plus Xulane were \$153 million. Based on the market experience of other non-oral dosage forms, including the Evra product, we believe there is a continuing demand for an

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innovative transdermal contraceptive patch that can provide convenience in a low-dose transdermal format.

There are other contraceptive products in development that, if approved, will compete with Twirla and our other product candidates. Companies that have new contraceptive products in various stages of development include Bayer's contraceptive patch and an oral contraceptive, each in Phase 3 development and Teva's oral contraceptive in Phase 3 development. Allergan has a vaginal ring which is a generic equivalent to Nuvaring and an IUD that is similar to Mirena awaiting approval, a P-only patch for which they received a CRL from the FDA, and an oral contraceptive and an additional vaginal ring in Phase 2 development. However, in the past few years, some of the large pharmaceutical companies such as Johnson & Johnson and Pfizer have dissolved their women's health specialty marketing and sales teams, and Bayer has shifted their focus away from their CHC products to their IUD franchise.

We are aware of only one other CHC transdermal patch in development. This patch is being developed by Bayer, and contains the active ingredients EE and gestodene, a third generation progestin. Bayer has stated that their gestodene patch is small, round, and transparent, and delivers a daily EE dose comparable to a 20 microgram EE oral contraceptive. Phase 3 studies of the Bayer gestodene patch began in 2004, and they completed a Phase 3 efficacy trial in the United States in December 2010. Bayer also completed Phase 3 efficacy trials in the European Union, or E.U., and Latin America in September 2011, submitted a marketing application to the E.U. in September 2012, and received approval to market the gestodene patch in the E.U. in February 2014. At the time of the E.U. submission, Bayer reported that they were in talks with the FDA regarding a U.S. submission, but there has been no further public information regarding a U.S. submission or approval, and the most recent Bayer pipeline information does not list the gestodene patch.

To date, there are no contraceptives containing gestodene available in the United States. We are aware that Wyeth was developing oral contraceptives containing gestodene in the late 1980s, with an NDA filed for an oral contraceptive containing gestodene and EE in 1988, and Wyeth planned filing an NDA for a second oral contraceptive containing gestodene in 1991. These products were never approved, and in a Wyeth pipeline report from 1996, there was no mention of any gestodene-containing product candidates among its contraceptives in development. Although not available in the United States, gestodene has been widely used outside the United States for a number of years. As with other third generation progestins, epidemiologic studies have reported a two-fold increase in risk of VTE with contraceptives containing gestodene compared to those containing LNG. We believe that if Bayer were to obtain FDA approval for the gestodene patch, the approved labeling may contain the same language that products containing third generation progestins have, which states that these contraceptives have a two-fold increase in risk of VTE as compared with contraceptives containing second generation progestins.

**Manufacturing**

We do not own any manufacturing facilities. We currently rely, and expect to continue to rely, on a third party for the manufacture of our product candidates for clinical trials, as well as for commercial manufacture if any of our product candidates receive marketing approval. In 2006, we entered into an exclusive agreement with Corium International, Inc., or Corium, to develop Twirla using our Skinfusion technology, and also for AG890, which is a P-only contraceptive patch in Phase 1/2 of clinical development. Our Corium agreement is an exclusive arrangement until Corium has commercially produced a significant, agreed-upon quantity of patches, currently projected to occur no earlier than five years following commercial launch of Twirla. Pursuant to the terms of our agreement, Corium is required to use commercially reasonable efforts to maintain sufficient manufacturing capabilities to supply the quantities of Twirla required for its initial commercial launch and commercial sales thereafter. We believe that our current manufacturing capacity at Corium should be able to meet all of

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the current Phase 3 clinical trial (the SECURE study) needs. Corium needs to conduct the equipment and facility validation and expansion of its manufacturing capabilities in order to be capable of supplying projected commercial quantities of Twirla, if approved. We expect the validation and expansion to be completed in coordination with our planned commercialization activities. Corium is responsible for all aspects of Twirla manufacturing.

**Strategic Agreements**

*Agreement with Corium*

Pursuant to our manufacturing agreement, Corium's exclusive right to manufacture Twirla and AG890 extends until Corium has commercially produced a significant, agreed-upon quantity of patches, currently projected to occur no earlier than five years following commercial launch of Twirla, at which point the agreement will expire. Under the terms of our agreement, we will pay Corium a defined price per finished patch, whether used for samples or commercial sale. We will owe no royalties to Corium in connection with the production of finished patches. The contract may be terminated by either party for the other party's uncured material breach. Following the end of the exclusivity period, if we were to seek a second source of supply, we would be required to obtain FDA approval through an NDA supplement for an additional manufacturing sites. The process of acquiring a second source of supply and obtaining FDA approval generally takes two years or more, and would require us to make substantial investments in new facilities and equipment.

Under our agreement, Corium has performed process development and manufacturing of Twirla for each of our clinical trials. For the development work performed, we paid Corium for time and materials related to the achievement of certain development goals. To date, we have made approximately \$1.7 million of milestone payments to Corium, all of which were paid between the years 2006 and 2009. Corium is not eligible for any milestone payments in the future. During 2012, we paid Corium an aggregate of \$3.5 million towards leasehold improvements incurred by Corium to its facilities to provide for adequate manufacturing space for our product candidates.

In order to accommodate our anticipated commercial launch of Twirla, if approved, Corium has completed a substantial build-out of its facilities in Grand Rapids, Michigan, and it has installed over \$10.0 million of equipment we purchased. This additional equipment and these facilities may require FDA pre-notification, pre-approval or inspection; however, we believe we can accomplish this expansion through an Annual Report filing to the Twirla NDA.

**Reimbursement**

Managed care plans have traditionally used differential co-pays to attempt to drive patients to use either generic products or products for which they have a contract with the manufacturer. Typically, a managed care plan's formulary is organized into between three and six tiers. Each tier is then associated with a set range of co-pay amounts, with products in the lower tiers having a lower co-pay. Many plans encourage patients to obtain their branded contraceptives through mail-order, incentivizing them with a 90-day co-pay that may be less on a per-month basis than that for a 30-day supply. Contraceptive brands are generally placed on Tier 2 only if there is a contract with the plan, although there are a few plans that place several branded products on Tier 2.

Managed care plans have individually interpreted the requirement for coverage of contraceptives under the ACA. Some plans have designated that all contraceptives containing the same progestin are equivalent, and therefore only cover a select few products containing each progestin, usually the least expensive generics, with no co-pay. Other plans have defined contraceptive methods into categories such as "hormonal", "emergency contraception", and "barrier methods", and they cover just one product for each method with no co-pay. Generally, it appears that most plans are only offering generic oral contraceptives at a zero co-pay and that branded or non-oral CHC products are often available

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only with cost-sharing to the patient, usually in the form of a Tier 3 co-pay, or at no cost with prior authorization from the prescriber. IUDs and implants can usually be obtained at no cost to the patient only if they are purchased by the physician, rather than by the patient at a pharmacy.

**Government Regulation**

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

*FDA Regulation*

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending NDAs, withdrawal of an approval, imposition of a clinical hold or termination, issuance of Warning, Untitled, or Cyber Letters, requests for product recalls, product seizures or detention, total or partial suspension or restriction of production, marketing or distribution, injunctions, fines, debarment, refusal to allow the import or export of product, adverse publicity, modification of promotional materials or labeling, refusals of government contracts, exclusion from participation in federal and state healthcare programs, restitution, disgorgement, imprisonment, consent decrees and corporate integrity agreements, or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

Completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's Good Laboratory Practice, or GLP, regulations;

Submission to the FDA of an Investigational New Drug Application, or IND, which must become effective before human clinical trials may begin;

Approval by an independent Institutional Review Board, or IRB, for each clinical site before each trial may be initiated;

Performance of human clinical trials, including adequate and well- controlled clinical trials, in accordance with cGCPs to establish the safety and efficacy of the proposed drug product for each indication;

Submission to the FDA of an NDA;

Satisfactory completion of an FDA advisory committee review, if applicable;

Satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity, as well as the potential for completion of an FDA inspection of selected clinical sites to determine cGCP compliance; and

FDA review and approval of the NDA.



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*Preclinical Studies and IND Submission*

Preclinical studies include laboratory evaluation of drug substance chemistry, pharmacology, toxicity and drug product formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests and preclinical literature, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND, unless the sponsor is relying on prior FDA findings of safety or efficacy of the drug product, in which case, some of the above information may be omitted. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

*Clinical Trials*

Clinical trials involve the administration of an investigational new drug to human subjects under the supervision of qualified investigators in accordance with cGCP requirements, which includes the requirements that all research subjects provide their informed consent in writing for their participation in any clinical trial, and the review and approval of the study by an IRB. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the trial procedures, the parameters to be used in monitoring safety and the efficacy criteria to be evaluated and a statistical analysis plan. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB for each clinical trial site participating in the clinical trial must review and approve the plan for any clinical trial before it commences, and the IRB must continue to oversee the clinical trial while it is being conducted, including any changes. Information about certain clinical trials, including a description of the study and study results, must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or subjects with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically is administered through controlled studies to a limited subject population with the target disease or condition to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the drug for specific targeted diseases and to determine dosage tolerance and optimal dosage. In Phase 3, the drug is administered to an expanded subject population, generally at geographically dispersed clinical trial sites, in two adequate and well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product candidate for approval, to establish the overall risk-benefit profile of the product candidate and to provide adequate information for the labeling of the product candidate. In the case of a 505(b)(2) NDA, which is a marketing application in which sponsors may rely on investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted, some of the above-described studies and preclinical studies may not be required or may be abbreviated. Bridging studies may be needed, however, to demonstrate the applicability of the studies that were previously conducted by other sponsors to the drug that is the subject of the marketing application.

The manufacture of investigational drugs for the conduct of human clinical trials is subject to cGMP requirements. Investigational drugs and active pharmaceutical ingredients imported into the United States are also subject to regulation by the FDA relating to their labeling and distribution.

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Further, the export of investigational drug products outside of the United States is subject to regulatory requirements of the receiving country as well as U.S. export requirements under the FDCA.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and the IRB and more frequently if serious adverse events occur. Information about certain clinical trials, including a description of the study and study results, must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website. Marketing application applicants must also report certain investigator financial interests to FDA.

Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to subjects. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group regularly reviews accumulated data and advises the study sponsor regarding the continuing safety of trial subjects, potential trial subjects, and the continuing validity and scientific merit of the clinical trial. We may also suspend or terminate a clinical trial based on evolving business objectives or competitive climate.

*U.S. Marketing Approval*

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. These user fees must be filed at the time of the first submission of the application, even if the application is being submitted on a rolling basis. A user fee for the Twirla contraceptive patch was submitted with the original NDA. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has agreed to certain performance goals regarding the timing of its review of an application. The FDA's standard review goal is to act on 90% of all Non-New Molecular Entity applications within ten months of FDA receipt of the application. This time period may be extended by FDA should an applicant submit new information to the agency during the course of FDA's review of the marketing application. The time period is also only a goal and may not be met by FDA. We expect that our products, if and when approved, will be subject to a standard review goal.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA for a new active ingredient, indication, dosage form, dosage regimen or route of administration must contain data that are adequate to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. We believe that we may be able to obtain a waiver from the conduct of a PREA study as, historically, waivers have been granted for other contraceptive applicants.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted



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application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held, as well as the manufacturing processes and controls, meet standards designed to ensure the product's continued safety, quality and purity.

The FDA may refer a marketing application to an external advisory committee for questions pertaining to issues such as clinical trial design, safety and efficacy, and public health questions. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it typically follows such recommendations and considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA will inspect the facility or facilities where the product is manufactured, referred to as a Pre-Approval Inspection. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications by the manufacturer and all of its subcontractors and contract manufacturers. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with cGCP. Also, as part of its regulatory review, the FDA verifies the data contained in the NDA.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and may take several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a CRL. A CRL indicates that the review cycle of the application is complete and the application is not ready for approval. A CRL generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing, or other information in order for the FDA to reconsider the application. We received a CRL for Twirla. We expect the FDA's CRL review timeline for Twirla to be approximately six months after submission of our response to the existing CRL. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product candidate, it may limit the approved indications for use of the product candidate and require that contraindications, warnings or precautions be included in the product labeling, including a black box warning. The FDA also may not approve the inclusion of labeling claims necessary for successful marketing. Moreover, the FDA may require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms. For example, the FDA may require a risk evaluation and mitigation strategy, or REMS, as a condition of approval or following approval to mitigate any identified or suspected serious risks and ensure safe use of the drug. The REMS plan could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools. A REMS could materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements, FDA notification, and FDA review and approval. Further, should new safety information arise, additional testing, product labeling or FDA notification may be required.

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*Hatch-Waxman Act*

Section 505 of the FDCA describes three types of marketing applications that may be submitted to the FDA to request marketing authorization for a new drug. A Section 505(b)(1) NDA is an application that contains full reports of investigations of safety and efficacy. A 505(b)(2) NDA is an application that contains full reports of investigations of safety and efficacy but where at least some of the information required for approval comes from investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. This regulatory pathway enables the applicant to rely, in part, on the FDA's prior findings of safety and efficacy for an existing product, or published literature, in support of its application. Section 505(j) establishes an abbreviated approval process for a generic version of approved drug products through the submission of an Abbreviated New Drug Application, or ANDA. An ANDA provides for marketing of a generic drug product that has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics and intended use, among other things, to a previously approved product. ANDAs are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and efficacy. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to, or performs in the same manner as, the innovator drug through *in vitro*, *in vivo*, or other testing. The generic version must deliver the same amount of active ingredients into a subject's bloodstream in the same amount of time as the innovator drug and can often be substituted by pharmacists under prescriptions written for the reference listed drug. In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the applicant's drug or a method of using the drug. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an ANDA or 505(b)(2) NDA.

Upon submission of an ANDA or a 505(b)(2) NDA, an applicant must certify to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. Generally, the ANDA or 505(b)(2) NDA cannot be approved until all listed patents have expired, except where the ANDA or 505(b)(2) NDA applicant challenges a listed patent through the last type of certification, also known as a paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application will not be approved until all of the listed patents claiming the referenced product have expired.

If the ANDA or 505(b)(2) NDA applicant has provided a Paragraph IV certification to the FDA, the applicant must send notice of the Paragraph IV certification to the NDA and patent holders once the application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the paragraph IV certification. If the paragraph IV certification is challenged by an NDA holder or the patent owner(s) asserts a patent challenge to the paragraph IV certification, the FDA may not approve that application until the earlier of 30 months from the receipt of the notice of the paragraph IV certification, the expiration of the patent, when the infringement case concerning each such patent was favorably decided in the applicant's favor or settled, or such shorter or longer period as may be ordered by a court. This prohibition is generally referred to as the 30-month stay. In instances where an ANDA or 505(b)(2) NDA applicant files a paragraph IV certification, the NDA holder or patent owner(s) regularly take action to trigger the 30-month stay, recognizing that the related patent litigation may take many months or years to resolve. Thus, approval of an ANDA or 505(b)(2) NDA could be delayed for a significant

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period of time depending on the patent certification the applicant makes and the reference drug sponsor's decision to initiate patent litigation.

The Hatch-Waxman Act establishes periods of regulatory exclusivity for certain approved drug products, during which the FDA cannot approve (or in some cases accept) an ANDA or 505(b)(2) application that relies on the branded reference drug. For example, the holder of an NDA, including a 505(b)(2) NDA, may obtain five years of exclusivity upon approval of a new drug containing new chemical entities, or NCEs, that have not been previously approved by the FDA. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the therapeutic activity of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company that contains the previously approved active moiety. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

The Hatch-Waxman Act also provides three years of marketing exclusivity to the holder of an NDA (including a 505(b)(2) NDA) for a particular condition of approval, or change to a marketed product, such as a new formulation for a previously approved product, if one or more new clinical studies (other than bioavailability or bioequivalence studies) was essential to the approval of the application and was conducted/sponsored by the applicant. This three-year exclusivity period protects against FDA approval of ANDAs and 505(b)(2) NDAs for the condition of the new drug's approval. As a general matter, the three year exclusivity does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy.

Our NDA for Twirla was submitted under Section 505(b)(2), and we expect that some of our other drug candidates will utilize the Section 505(b)(2) regulatory pathway. Even though several of our drug products utilize active drug ingredients that are commercially marketed in the United States in other dosage forms, we need to establish safety and efficacy of those active ingredients in the formulation and dosage forms that we are developing. All approved products, both innovator and generic, are listed in the FDA's Orange Book.

*U.S. Post-Approval Requirements*

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to manufacturing recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion, reporting of adverse experiences with the product and drug shortages, and compliance with any post-approval requirements imposed as a condition of approval, such as Phase 4 clinical trials, REMS and surveillance to assess safety and efficacy after commercialization. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any approved products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data other than bioavailability or bioequivalence studies. In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, list drugs manufactured at their facilities with the FDA, and are subject to periodic announced and unannounced inspections by the FDA and these state agencies for compliance with cGMP and other requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented, or FDA notification. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and

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documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

Restrictions on the marketing, distribution or manufacturing of the product, complete withdrawal of the product from the market or requests for product recalls;

Fines, or Untitled, Cyber or Warning Letters or holds on or termination of post-approval clinical trials;

Refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;

Product seizure or detention, or refusal to permit the import or export of products;

Injunctions or the imposition of civil or criminal penalties including disgorgement, restitution, fines and imprisonment;

Consent decrees, corporate integrity agreements or exclusion from federal healthcare programs;

Debarment;

Mandated modification of promotional materials and labeling and the issuance of corrective information; or

The FDA or other regulatory authorities may issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies are prohibited from marketing or promoting their drug products for uses outside the approved label, a practice known as off-label promotion. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability, including criminal and civil penalties under the FDCA and False Claims Act, exclusion from participation in federal healthcare programs, mandatory compliance programs under corporate integrity agreements, debarment and refusal of government contracts.

In addition, the distribution of prescription pharmaceutical products, including samples, is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Moreover, the recently enacted Drug Quality and Security Act imposes new obligations on manufacturers of pharmaceutical products related to product tracking and tracing. Among the



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requirements of this new legislation, manufacturers will be required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, label drug product with a product identifier and keep certain records regarding the drug product. The transfer of information to subsequent product owners by manufacturers will eventually be required to be done electronically. Manufacturers will also be required to verify that purchasers of the manufacturers' products are appropriately licensed. Further, under this new legislation, manufacturers will have drug product investigation, quarantine, disposition, and FDA and trading partner notification responsibilities related to counterfeit, diverted, stolen and intentionally adulterated products, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

*U.S. Fraud and Abuse, Data Privacy and Security and Transparency Laws and Regulations*

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state fraud and abuse laws restrict business practices in the biopharmaceutical industry. These laws include, among other things, anti-kickback, physician payment transparency and false claims laws and regulations as well as data privacy and security laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances.

Additionally, the intent standard under the Anti-Kickback Statute and criminal healthcare fraud statutes was also amended by the ACA to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provided that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

The federal civil False Claims Act prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment to, or approval by, the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. The civil False Claims Act has been used to assert liability on the basis of kickbacks and other improper referrals, improperly reported government pricing metrics such as Best Price or Average Manufacturer Price, improper promotion of off-label uses not expressly approved by the FDA in a drug's label, and allegations as to misrepresentations with respect to the services rendered. Additionally, the civil monetary penalties statute, which, among other things, imposes fines against any person who is determined to have presented, or caused to be presented, claims to a federal healthcare program that the person knows, or should know, is for an item or service that was not provided as claimed or is false or fraudulent. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also

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created federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, including private third party payors and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services relating to healthcare matters. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, that apply regardless of the payor.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes security standards and certain privacy standards directly applicable to business associates. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, state laws may govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Additionally, federal physician payment transparency laws, including the federal Physician Payment Sunshine Act created under Section 6002 of the ACA and its implementing regulations, require that manufacturers of drugs for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with certain exceptions, report annually to the government information related to payments or other "transfers of value" made or distributed to physicians, which is defined to include doctors of medicine, dentists, optometrists, podiatrists and chiropractors, generally, with some exceptions, and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, physicians and teaching hospitals. Additionally, applicable manufacturers and group purchasing organizations are required to report annually to the government certain ownership and investment interests held by physicians and their immediate family members. , Manufacturers must submit reports by the 90th day of each calendar year. Disclosure of such information is made on a publicly available website.

There are also an increasing number of analogous state laws that require manufacturers to file reports with states on pricing and marketing information, and to track and report gifts, compensation, other remuneration and items of value provided to healthcare professionals and healthcare entities. Many of these laws contain ambiguities as to what is required in order to comply with such laws. For example, several states have enacted legislation requiring pharmaceutical companies to, among other things, establish and implement commercial compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, or register their sales representatives. Certain state laws also regulate manufacturers' use of prescriber-identifiable data. These laws may affect our future sales, marketing and other promotional activities by imposing administrative and compliance burdens. In addition, given the lack of clarity with respect to these laws and their implementation, our reporting actions once we commercialize could be subject to the penalty provisions of the pertinent state and federal authorities.

If our operations are found to be in violation of any of the laws or regulations described above or any other laws that apply to us, we may be subject to a variety of penalties, depending upon the law found to have been violated, potentially including criminal and significant civil monetary penalties,

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damages, fines, imprisonment, exclusion from participation in government healthcare programs, corporate integrity agreements, refusal of government contracts, contract debarment and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

*Coverage and Reimbursement Generally*

The commercial success of our product candidates and our ability to commercialize any approved product candidates successfully will depend in part on the extent to which governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payors provide coverage for and establish adequate coverage of and reimbursement levels for our product candidates. Government authorities, private health insurers and other organizations generally decide which drugs they will pay for and establish reimbursement levels for healthcare. In particular, in the United States, private health insurers and other third-party payors often provide reimbursement for products and services based on the level at which the government provides reimbursement through the Medicare or Medicaid programs for such products and services. In the United States, the European Union an