AGILE THERAPEUTICS INC
Form 8-K
January 03, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(D)

of the Securities Exchange Act of 1934

January 3, 2017

Date of report (Date of earliest event reported)

Agile Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**001-36464**	**23-2936302**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

101 Poor Farm Road
Princeton, New Jersey **08540**
(Address of principal executive offices) (Zip Code)

Registrant s telephone number, including area code **(609) 683-1880**

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425).

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12).

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b)).

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01. Other Events.

On January 3, 2017, Agile Therapeutics, Inc. (the Company) issued a press release announcing top-line results from its Phase 3 SECURE clinical trial of Twirla®, its investigational low-dose combined hormonal contraceptive patch. SECURE was a multicenter, single-arm, open-label, 13-cycle trial that evaluated the safety, efficacy and tolerability of Twirla in 2032 healthy women aged 18 and over at 102 experienced investigative sites across the United States. The Company plans to resubmit its new drug application (NDA) for Twirla in the first half of 2017 on the basis of the SECURE results and other information relating to the manufacture of Twirla.

The Company will also host a conference call to discuss the top-line results from the SECURE clinical trial on January 3, 2017. A copy of the conference call presentation materials is also attached hereto as Exhibit 99.2.

Top-line data are based on a preliminary analysis of currently available efficacy and safety data, and therefore the reported results, findings and conclusions related to SECURE are subject to change following a comprehensive review of the complete data related to SECURE.

SECURE was conducted to address issues raised by the U.S. Food and Drug Administration (FDA) in its 2013 Complete Response Letter (CRL) to the Company. The CRL recommended that the Company conduct a new clinical trial and focused on two key elements: improved clinical trial conduct and demonstration of efficacy as measured by an acceptable Pearl Index and related 95% confidence interval in a representative sample of U.S. women who are seeking hormonal contraception, including elements such as contraceptive user status, age, race, ethnicity, and body mass index (BMI). The trial was designed in consultation with the FDA, and comprised a number of stringent trial design elements, including exclusion of treatment cycles not only for use of back-up contraception but also for lack of sexual activity. SECURE had broad entry criteria, placed no limitations on BMI or other demographic factors during enrollment, and enrolled a large and diverse population from the United States in order to allow for efficacy to be assessed across different groups, as requested by the FDA. These entry criteria resulted in the inclusion of a substantial number of women with high BMI, who have frequently been under-represented in past contraceptive studies. The efficacy measure for SECURE was the Pearl Index in an intent to treat population of subjects 35 years of age and under. The FDA also requested inclusion of pre-specified efficacy analyses related to BMI and body weight.

Highlights of the top-line results include:

- Consistent with its broad entry criteria, the SECURE study population was representative of the population of women in the United States with respect to key demographic criteria, including:

- Race (66.9% of subjects were white, 24.3% black and 8.8% other);

- Ethnicity (19.7% were Hispanic, 80.3% non-Hispanic); and

1

- BMI (39.4% of subjects had a normal baseline weight (BMI of under 25 kg/m2), 25.3% of subjects were overweight (BMI of at least 25 kg/m2 but less than 30 kg/m2), and 35.3% were obese (BMI 30 kg/m2 or more). When classified as obese (BMI 30 kg/m2 or more) or non-obese (BMI less than 30 kg/m2), 35.3% of subjects were obese and 64.7% were non-obese).

- Both new and experienced hormonal contraceptive users were enrolled (9.4% of subjects were new users).

- 51.4% of subjects discontinued prematurely from the study and the loss to follow-up rate was 11.3%, which is in line with loss to follow-up rates observed in previous clinical trials of combined hormonal products and substantially better than the 20% loss to follow-up rate observed in the Company s previous Phase 3 trial.

- The Pearl Index for the overall intent to treat population of subjects 35 years of age and under was 4.80 with an upper-bound of the 95% confidence interval of 6.06. As with all hormonal contraceptive trials, the number of pregnancies included in the Company s calculation of the Pearl Index is subject to review by the FDA as part of its overall review of the NDA for Twirla.

- Consistent with other recent hormonal contraceptive clinical trials, including Ortho Evra® and Quartette®, and the FDA s 2015 meta-analysis on the effect of obesity on the effectiveness of hormonal contraceptives, a relationship between obesity and efficacy was observed among subjects 35 years of age and under:

BMI Category	BMI (kg/m2)	% of Trial Population	Pearl Index	Upper Bound of 95% CI
Normal	< 25	39%	3.03	4.62
Overweight	25 - < 30	25%	5.36	7.98
Obese*	≥ 30	35%	6.42	8.88
Non-Obese*	< 30	65%	3.94	5.35
Obese*	≥ 30	35%	6.42	8.88

*In its 2015 meta-analysis, the FDA examined the effect of obesity on two populations: non-obese (< 30 kg/m2) and obese (≥ 30 kg/m2). Non-obese includes subjects in the normal and overweight categories.

- The highest Pearl Index for a hormonal contraceptive product approved by the FDA was 3.19 with an upper-bound of the 95% confidence interval of 5.03. As with all products, ultimate approvability of a hormonal contraceptive is based on a risk/benefit assessment of the overall safety and efficacy profile of a product, not only a specific Pearl Index. For hormonal contraceptive trials, the FDA generally evaluates efficacy results of each individual study in the unique context of the study population and trial design.

- Twirla was generally well tolerated and had an overall favorable safety profile, consistent with publicly available information relating to other low-dose combined hormonal products. The most frequent hormone-related adverse events, none of which were experienced by more than 5% of subjects, were generally in line with those events observed in other low dose combined hormonal products and included:

Adverse Event	SECURE (n=2032)
Headache	4.3%
Nausea	4.1%
Breast tenderness/pain/discomfort	2.0%
Mood swings/changes/depression	2.7%
Heavy/irregular vaginal bleeding	1.8%

- The percent of subjects reporting bleeding-related adverse events was low, 1.8%, and only 1.4% of women discontinued for bleeding issues.

- Serious adverse events were observed in 1.7% of subjects. The most common serious adverse events included deep vein thrombosis, pulmonary embolism, gallbladder disease, ectopic pregnancy and depression.

- Overall, patch-related irritation and itching rates were low. Of reported patches worn, 83% had no patch site irritation and 65% had no itching. Generally, reported irritation and itching was mild. Severe itching or irritation were observed in 2.3% and 1.5% of patches worn, respectively.

- The patch adhesion profile was favorable with a low rate of detachment. Of reported patches worn, the range of detachments was 10% in cycle 1 and reduced to 2% by cycle 13.

The Company will also host a conference call to discuss the top-line results from the SECURE clinical trial on January 3, 2017.

Copies of the Company s press release and the conference call presentation materials are attached hereto as Exhibits 99.1 and 99.2, respectively, and are hereby incorporated by reference herein.

Risks Related to the Reported Results of SECURE

The reported results of SECURE are based on top-line data and may ultimately differ from actual results once additional data are received and fully evaluated.

The reported results of SECURE that we have publicly disclosed, and that are discussed herein, consist of top-line data. Top-line data are based on a preliminary analysis of currently available efficacy and safety data, and therefore the reported results, findings and conclusions related to SECURE are subject to change following a comprehensive review of the more extensive data that

we expect to receive related to SECURE. Top-line data are based on important assumptions, estimations, calculations and information currently available to us, and we have not received or had an opportunity to fully and carefully evaluate all of the data related to SECURE. As a result, the top-line results of SECURE that we have reported may differ from future results, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. In addition, third parties, including regulatory agencies, may not accept or agree with our assumptions, estimations, calculations or analyses or may interpret or weigh the importance of data differently, which could impact the potential for approval of Twirla, or if approved, the labeling and commercial value of Twirla and our business in general. If the top-line data that we have reported related to SECURE differ from actual results, our ability to obtain approval for, and commercialize, our products may be harmed, which could harm our business, financial condition, operating results or prospects.

The FDA may disagree with our interpretation of clinical results obtained from SECURE, our results do not guarantee support for a resubmission of our NDA or for regulatory approval, and, even if the SECURE data are deemed to be positive by the FDA, the FDA may disagree with other aspects of the SECURE study and decline to approve Twirla for the proposed indication.

We have reported positive top-line data from SECURE. However, even if we believe that the data from SECURE are positive, the FDA could determine that the data from SECURE were negative or inconclusive or could reach a different conclusion than we did on that same data. Negative or inconclusive results of a clinical trial or difference of opinion could cause the FDA to decline to approve our application or require us to repeat the trial or conduct additional clinical trials prior to obtaining approval for commercialization, and there is no guarantee that additional trials would achieve positive results to the satisfaction of the FDA or that the FDA will agree with our interpretation of the results. Any such determination by the FDA would delay the timing of our commercialization plan for Twirla or prevent its further development, or the further development of our other product candidates, and adversely affect our business operations. Additionally, the FDA may provide review commentary at any time during the resubmission and review process which could delay the review timeline, adversely affect the review process, or even prevent the approval of Twirla, any of which would adversely affect our business. We may not be able to appropriately remedy issues that the FDA may raise in its review of our NDA resubmission, and we may not have sufficient time or financial resources to conduct future activities to remediate issues raised by the FDA.

There is no guarantee that the data obtained from SECURE will be supportive of, or guarantee, an NDA resubmission, or result in our successfully obtaining FDA approval of Twirla in a timely fashion and for a commercially viable indication, if at all. For example, the FDA could determine that the trial did not meet its objectives or the FDA could still have concerns regarding the conduct of the SECURE study, including regarding discontinuance of subjects from the trial. At any future point in time, the FDA could require us to complete further clinical or preclinical trials, or take other actions which could delay or preclude any NDA resubmission or approval of the NDA and could require us to obtain significant additional funding. There is no guarantee such funding would be available to us on favorable terms, if at all, nor is there any guarantee that FDA would consider any additional information complete or sufficient to support approval. If the Twirla NDA is resubmitted, the FDA may hold an advisory committee meeting to obtain committee input on the

safety and efficacy of Twirla. Typically, advisory committees will provide responses to specific questions asked by the FDA, including the committee s view on the approvability of the product candidate under review. Advisory committee decisions are not binding but an adverse decision at the advisory committee may have a negative impact on the regulatory review of Twirla. Additionally, we may choose to engage in the dispute resolution process with the FDA if we do not receive approval, which could extend the timeline for any potential approval.

Further, if we are able to resubmit an NDA for Twirla with the clinical data from SECURE, there is no guarantee that such data will be deemed sufficient by the FDA. While we designed the protocols for SECURE to address the issues raised in the CRL, there is no guarantee that the FDA will deem such protocols or results from the study sufficient to address those issues when they are formally reviewed as a part of an NDA resubmission or to demonstrate safety and efficacy to the satisfaction of the FDA. The FDA has significant discretion in the review process, and we cannot predict whether the FDA will agree with our conclusions regarding the results of the SECURE trial, including whether our data are reliable and generalizable. For example, the FDA may disagree with our calculations relating to the number of pregnancies occurring on study, or may view the SECURE data as insufficient to demonstrate a favorable benefit/risk profile for approval for the proposed indication. In addition, based on top-line data, the Pearl Index for the overall intent to treat population of subjects 35 years of age and under was 4.80 with an upper-bound of the 95% confidence interval of 6.06, but in the obese subpopulation of subjects 35 years of age and under, the Pearl Index was 6.42 with an upper-bound of the 95% confidence interval of 8.88. If we were to exclude the top-line data on the obese subpopulation, our Pearl Index for non-obese patients was 3.94 with an upper-bound of the 95% confidence interval of 5.35. The highest Pearl Index for a hormonal contraceptive product approved by the FDA was 3.19 with an upper-bound of the 95% confidence interval of 5.03. Although ultimate approvability of a hormonal contraceptive is based on a risk/benefit assessment of the overall safety and efficacy profile of a product, not only a specific Pearl Index, the FDA could conclude that our Pearl Index for either the overall study population or only the non-obese study population is too high to demonstrate efficacy and an adequate risk/benefit profile, and as such, the FDA could decline to approve Twirla on this or any other basis. Further, the FDA may not agree with our analysis of the relationship between obesity and efficacy for Twirla and the FDA may interpret our overall data differently than we do and may decline to approve Twirla on this or any other basis.

Moreover, even if we obtain approval of Twirla, any such approval might significantly limit the approved indications for use, including by limiting the approved label for use by more limited patient populations than we propose, require that precautions, contraindications or warnings be included on the product labeling, including black box warnings, require expensive and time-consuming post-approval clinical studies, risk evaluation and mitigation strategies, or REMS, or surveillance as conditions of approval, or, through the product label, the approval may limit the claims that we may make, which may impede the successful commercialization of Twirla. For example, the FDA may deem the higher Pearl Index in the obese subpopulation to warrant a labeling limitation or warning for such subpopulation, which could limit the commercial potential of the product, if approved. Moreover, because we did not conduct any head-to-head studies of Twirla against Ortho Evra®, we will not be able to make direct comparative claims regarding the safety, efficacy or pharmacokinetics of Twirla and Ortho Evra or its generic version, Xulane®.

We are substantially dependent on the commercial success of Twirla.

If we obtain FDA approval of Twirla, Twirla will be the first product that we commercialize. The rest of our pipeline of products are in earlier stages of clinical development and will require additional clinical and product development and funding in order to advance towards commercialization, which could take considerable time. If Twirla is not approved, our ability to advance our pipeline would be significantly adversely affected. Our ability to generate revenues

and become profitable will depend in large part on the commercial success of Twirla. If Twirla or any other product that we commercialize in the future does not gain an adequate level of acceptance among physicians, patients and third parties, we may not generate significant product revenues or become profitable. Market acceptance of Twirla, and any other product that we commercialize, by physicians, patients and third party payors will depend on a number of factors, some of which are beyond our control, including:

- Efficacy, safety and other potential advantages of our product candidates in relation to alternative treatments;

- Relative convenience and ease of administration of our product candidates;

- Availability of adequate coverage or reimbursement of our product candidates by third parties, such as insurance companies and other payors, and by government healthcare programs, including Medicare, Medicaid and state health insurance exchanges;

- Prevalence and severity of adverse events associated with our product candidates;

- Cost of our product candidates in relation to alternative treatments, including generic products;

- Extent and strength of our third-party manufacturer and supplier support;

- Extent and strength of our marketing and distribution support;

- Limitations or warnings contained in our product s FDA approved labeling; and

- Distribution and use restrictions imposed by the FDA or to which we agree as part of a mandatory REMS or voluntary risk management plan.

For example, if Twirla is approved by the FDA, physicians and patients may not be immediately receptive to a transdermal contraceptive system, as opposed to a pill or any other method, and may be slow to adopt it as an accepted treatment for the prevention of pregnancy. In addition, even though we believe Twirla has the potential to offer significant advantages over other treatment options, because no head-to-head trials comparing Twirla to the competing approved patch product have been conducted, the prescribing information approved by the FDA may

not contain claims that Twirla is safer or more effective than the currently approved patch product, or other claims that may be necessary for successful marketing of Twirla. Accordingly, we will not be permitted to promote Twirla, if approved, for any comparative advantages to the currently marketed contraceptive patch. The availability of numerous inexpensive generic forms of contraceptive products may also limit acceptance of Twirla among physicians, patients and third party payors. If Twirla does not achieve an adequate level of acceptance among physicians, patients and third party payors, we may not generate significant product revenues or become profitable.

Even if we obtain marketing approval for Twirla or other product candidates, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, Twirla or other product candidates could be subject to labeling and other restrictions, including withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems.

Even if we obtain U.S. regulatory approval of Twirla or other product candidates, the FDA may still impose significant restrictions on their indicated uses, including more limited patient populations, require that precautions, contraindications, or warnings be included on the product labeling, including black box warnings, or impose ongoing requirements for potentially costly and time-consuming post-approval studies, including Phase 4 clinical trials, and post-market surveillance to monitor safety and efficacy. Claims that we may make may also be restricted through our approved labeling. For example, based on the SECURE top-line data, the Pearl Index for the overall intent to treat population of subjects 35 years of age and under was 4.80 with an upper-bound of the 95% confidence interval of 6.06, but in the obese subpopulation of subjects 35 years of age and under, the Pearl Index was 6.42 with an upper-bound of the 95% confidence interval of 8.88. The highest Pearl Index for a hormonal contraceptive product approved by the FDA was 3.19 with an upper-bound of the 95% confidence interval of 5.03. Although ultimate approvability of a hormonal contraceptive is based on a risk/benefit assessment of the overall safety and efficacy profile of a product, not only a specific Pearl Index, the FDA could conclude that the Pearl Index in the obese subpopulation is too high to demonstrate efficacy and an adequate risk/benefit profile. As such, even if we receive approval of Twirla, the FDA could impose restrictions on use by the obese subpopulation or otherwise require labeling limitations or warnings for such subpopulation, which could limit the commercial potential of the product, if approved.

If approved, Twirla and our other product candidates will also be subject to ongoing regulatory requirements governing the manufacturing, labeling, packaging, storage, distribution, import, export, safety surveillance, advertising, marketing promotion, recordkeeping, reporting of adverse events and other post-market information, and further development. These requirements include registration with the FDA, listing of our drug products, payment of annual fees, as well as continued compliance with current Good Clinical Practices (cGCPs) for any clinical trials that we conduct post approval. Application holders must notify the FDA, and depending on the nature of the change, obtain FDA pre-approval for product manufacturing changes. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current Good Manufacturing Practices (cGMP) requirements relating to quality control, quality assurance and corresponding maintenance of records and documents. If we are found to be noncompliant with applicable requirements, the FDA and other government authorities may issue a Warning Letter or Untitled Letter, or take other regulatory action such as a product seizure and detention, withdrawal of product approval, request for a recall, refusal to allow the import or export of the product, criminal or civil penalties, injunction against or restriction of manufacture or distribution, consent decrees, disgorgement, restitution, clinical holds or terminations, exclusion from federal healthcare programs, corporate integrity agreements, or imprisonment.

Forward-Looking Statements

This Current Report contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this Current Report that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation, expectations regarding the clinical significance and regulatory review of top-line data from our Phase 3 SECURE study and the timing of resubmission of our NDA for Twirla.

The Company may, in some cases use terms such as predicts, believes, potential, continue, anticipates, estimates, expects, plans, i could, might, will, should or other words that convey uncertainty of the future events or outcomes to identify these forward-looking statements. Our forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions and uncertainties. Any or all of the forward-looking statements may turn out to be wrong, or be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Our statements about the results and conduct of our clinical trial could be affected by the potential that there are changes in the data or interpretation of the data by the FDA (for example, the FDA may include additional pregnancies in its calculation of the Pearl Index, which would increase the Pearl Index), whether the results will be deemed satisfactory by the FDA (for example, we describe the results of the SECURE trial as positive, the FDA may disagree with that characterization), and whether additional studies will be required or other issues will arise that will delay resubmission of our NDA or negatively impact acceptance, review and approval of Twirla by the FDA; our statements about the potential commercial opportunity could be affected by the potential that our product does not receive regulatory approval, does not receive reimbursement by third party payors, or a commercial market for the product does not develop because of any of the risks inherent in the commercialization of contraceptive products. For all these reasons, actual results and developments could be materially different from those expressed in or implied by our forward-looking statements. All forward looking statements are subject to risks detailed in our filings with the U.S. Securities and Exchange Commission, including the Company s Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q. You are cautioned not to place undue reliance on these forward-looking statements, which are made only as of the date of this Current Report on Form 8-K. We undertake no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstances.

Item 9.01. **Financial Statements and Exhibits.**

(d) **Exhibits.**

Exhibit Number	Description
99.1	Agile Therapeutics, Inc. Press Release dated January 3, 2017.
99.2	Agile Therapeutics, Inc. Presentation on SECURE Top-Line Results

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Agile Therapeutics, Inc.

Dated: January 3, 2017	By:	/s/ Alfred Altomari
	Name:	Alfred Altomari
	Title:	President and Chief Executive Officer