Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 30, 2019

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland.

Topic: The committee discussed new drug application (NDA) 204017 (levonorgestrel and ethinyl estradiol) transdermal system, submitted by Agile Therapeutics, Inc., for the prevention of pregnancy in women of reproductive potential.

These summary minutes for the Ocotber 30, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration were approved on November 26, 2019.

I certify that I attended the November 26, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/

Kalyani Bhatt, BS, MS
Designated Federal Officer, BRUDAC

/S/

Vivian Lewis, MD
Chairperson, BRUDAC

Summary Minutes of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 30, 2019

The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 30, 2019, at the FDA White Oak Campus, Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Agile Therapeutics, Inc. The meeting was called to order by Vivian Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately 150 people in attendance. There were nine (9) Open Public Hearing (OPH) presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed new drug application (NDA) 204017 (levonorgestrel and ethinyl estradiol) transdermal system, submitted by Agile Therapeutics, Inc., for the prevention of pregnancy in women of reproductive potential.

Attendance:
Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Douglas C. Bauer, MD; Matthew T. Drake, MD, PhD; Vivian Lewis, MD (Chairperson); Pamela A. Shaw, PhD

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): Toby Chai, MD; James Q. Clemens, MD, FACS, MSCI**;** Beatrice Edwards, MD, MPH, FACP; Margery Gass, MD; Christian P. Pavlovich, MD; Gloria Richard Davis, MD, MBA, NCMP, FACOG

Bone, Reproductive and Urologic Drugs Advisory Committee Member Not Present (Non-Voting): Gerard G. Nahum, MD, FACOG (Industry Representative)

Temporary Members (Voting): Abbey Berenson MD, MMS, PhD; Monica M. Christmas, MD, FACOG, NCMP; Kathryn M. Curtis, PhD; David L. Eisenberg, MD, MPH, FACOG; Esther Eisenberg, MD, MPH; Carol Gagliardi, MD; Sadia Haider, MD, MPH; Sally Ann Hunsberger, PhD; Virginia (Jennie) C. Leslie, MD; David J. Margolis MD, PhD; Sabrina Miller (Patient Representative); Thomas Ortel, MD, PhD

Acting Industry Representative to the Committee (Non-voting): Venkateswar Jarugula, PhD (Acting Industry Representative)

FDA Participants (Non-Voting): Audrey Gassman, MD; Jerry Willett, MD; Nneka McNeal Jackson, MD; Laura Lee Johnson, PhD; Rita Ouellet-Hellstrom, PhD, MPH

Open Public Hearing Speakers: Sarah Christopherson (National Women's Health Network); Claudia Nunez-Eddy, MS (National Center for Health Research); Vanessa Lukas; Arthur Waldbaum, MD (Downtown Women's Health Care); Jan Erickson (National Organization for Women); Marta Hill Gray (Gray Matter Group); Rebecca Thimmesch (Adolescent for Youth); Nico Osier, PhD, RN; Deborah Arrindell (American Sexual Health Association)

The agenda was as follows:

Call to Order and Introduction of Committee	**Vivian Lewis, MD** Chairperson, BRUDAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, BRUDAC
FDA Opening Remarks	**Audrey Gassman, MD** Deputy Director Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Agile Therapeutics, Inc.**
Introduction	**Geoffrey Gilmore** Senior Vice President Agile Therapeutics, Inc.
Need for More Contraceptive Options and Evolving Clinical Trial Environment	**David Portman, MD** CEO and Chief Medical Officer Sermonix Pharmaceuticals Founder, Director Emeritus, and Principal Investigator The Columbus Center for Women's Health Research Adjunct Instructor Department of Obstetrics and Gynecology Wexner Medical Center at The Ohio State University
Study Design, Efficacy and Safety	**Elizabeth Garner, MD, MPH** Chief Medical Officer ObsEva SA Consultant, Former Chief Medical Officer Agile Therapeutics, Inc.

Clinical Perspective	**David Portman, MD**

Clarifying Questions to Applicant

BREAK

FDA PRESENTATIONS

Background	**Jerry Willett, MD** Clinical Team Leader DBRUP, ODE III, OND, CDER, FDA
Effectiveness Considerations	**Yun Tang, PhD** Statistical Reviewer Division of Biometrics III Office of Biostatistics Office of Translational Sciences, CDER, FDA
Safety Profile and Benefit-Risk Considerations	**Nneka McNeal-Jackson, MD** Clinical Reviewer DBRUP, ODE III, OND, CDER, FDA

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions to Applicant or FDA

BREAK

Questions to the Committee/Committee Discussion and Voting

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION**: Discuss the effectiveness of AG200-15, including:
    a. Interpretation of efficacy results from Study 23 as they relate to study design and enrolled patient population
    b. Interpretation of subgroup analyses by body mass index, weight, and race/ethnicity

Committee Discussion: *The committee members agreed that AG 200-15 does not meet the past product expectations for the upper bound of the 95% confidence interval of a Pearl Index (PI) of less than 5.0. Further, members raised questions as to what should be the standard for an acceptable PI for new contraceptives. Committee members addressed a concern for associating PI with efficacy since the patient population of a study can influence PI values. There was further discussion about reassessing the traditional PI limit versus identifying more appropriate efficacy endpoints.*

The subgroup analysis based on body mass index (BMI) was useful for committee members, but it was noted that the product's efficacy is reduced in patients with higher BMI. There was little discussion about race/ethnicity factors, except as related to association with differences in range of BMI.

Please see the transcript for details of the committee discussion.

2. **DISCUSSION**: Discuss the safety profile of AG200-15, including:
    a. Interpretation of the venous thromboembolism (VTE) safety signal as it relates to weight and body mass index (BMI)

    b. Interpretation of the product tolerability (e.g., cycle control)

Committee Discussion*: The committee members agreed that risk of VTE is a serious safety concern with hormonal contraceptives, such as AG 200-15. The committee members recommended labeling should be clear about the risk of VTE for obese women. Although there weren't enough events to quantify the risk for non-obese women, the committee members also recommended the potential risk to be conveyed to prescribing providers and patients. Product tolerability was not a big concern for the panel since spotting and bleeding are common adverse events and that there was a favorable lower incidence of headache. Some members stated they would have preferred that the cycle control data was separated into bleeding events and spotting. Please see the transcript for details of the committee discussion.*

3. **VOTE**: Do the benefits of AG200-15 outweigh its risks to support the drug's approval for the prevention of pregnancy?

   If you vote YES, explain the rationale for your vote and address the following:
   - Whether this product should be approved for use in the general population or a more narrowly defined patient population
   - How this product should be used within the context of available contraceptive therapies

   If you vote NO, explain the rationale for your vote and provide any recommendations.

   Vote Results: Yes: 14 No: 1 Abstain: 1

   Committee Discussion*: The majority of the committee members agreed that the benefits of AG200-15 outweigh its risks to support the drug's approval for the prevention of pregnancy. Members who voted "Yes" noted this product's convenience including patients who would prefer AG200-15 than a more invasive methods (e.g. long acting reversible contraceptions (LARCs) and injections) despite apparent lower efficacy. Some committee members stated that there is an unmet need for a lower dose transdermal hormonal method. Most of these members recommended a limitation of use based on BMI because of the data presented for efficacy and safety. Some members stated the importance of communicating the BMI associated concerns as a continuum with confidence bands and not an absolute cut-off (e.g. greater risk and lower efficacy with greater BMI over 25) and agreed this information would be useful to prescribers in counseling patients and to patients in making their choice. Some members also recommended the FDA conduct research to find out what women's preferences were regarding contraceptive choice.*

   Members who voted "No"and "Abstain" noted their concerns. The member who voted no raised concerns about the product's effectiveness. The member who voted "Abstain" further stated that the data was not focused on effectiveness and that the endpoints needed to be reassessed.

   Please see the transcript for details of the committee discussion.