CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213388Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 19, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213388
Product Name and Strength:	Oriahnn [a] (elagolix, estradiol, and norethindrone acetate and elagolix) capsules, 300 mg/1 mg/0.5 mg and 300 mg
Applicant/Sponsor Name:	ABBVIE INC
OSE RCM #:	2019-1690-2
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 14, 2020 for Oriahnn. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label and carton labeling for Oriahnn (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised container label and carton labeling are acceptable from a medication error perspective. We have no further recommendations.

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[a] The proposed proprietary name Oriahnn was found conditionally acceptable on December 26, 2019.
[b] Whaley E. Human Factors Study Results and Label and Labeling Review for Oriahnn (NDA 213388). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 29. RCM No.: 2019-1690-1.

Reference ID: 4610926

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 29, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213388
Product Name and Strength:	Oriahnn [a] (elagolix, estradiol, and norethindrone acetate and elagolix) capsules, 300 mg/1 mg/0.5 mg and 300 mg
Applicant/Sponsor Name:	ABBVIE INC
OSE RCM #:	2019-1690-1
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label and carton labeling received on April 24, 2020 for Oriahnn. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label and carton labeling for Oriahnn (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised carton labeling is acceptable from a medication error perspective. However, the revised container label is unacceptable from a medication error perspective. Specifically, the strength statement on the weekly blister pack container label lacks prominence. Additionally, the net quantity statement is more prominent than key labeling information, including the strength statement.

[a] The proposed proprietary name Oriahnn was found conditionally acceptable on December 26, 2019.
[b] Whaley E. Human Factors Study Results and Label and Labeling Review for Oriahnn (NDA 213388). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 5. RCM No.: 2019-1690 and 2019-2033.

Reference ID: 4619006

3 RECOMMENDATIONS FOR ABBVIE INC

We recommend the following be implemented for this NDA 213388:

A. Container label – weekly blister pack

1. The strength statement lacks prominence. As such, we recommend the prominence of the strength statement is increased per 21 CFR 201.15(a)(6).
2. The net quantity statement is more prominent than the product strength and also competes in prominence with the proprietary name and established name. This increased prominence may decrease readability of other important product information. As such, we recommend the net quantity statement is revised to be less prominent.[c]

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[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Reference ID: 4599996

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LOLITA G WHITE
04/29/2020 12:00:18 PM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 28, 2020

To: Hylton V. Joffe, M.D., M.M.Sc., Director
Division of Bone, Reproductive and Urologic Products

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

Subject: **NDA**: 213388
Product name: Oriahnn (elagolix sodium plus estradiol/ norethindrone acetate) oral capsules
Dosages, formulations, routes: 300 mg elagolix sodium plus estradiol/norethindrone acetate [E2/NETA 1 mg/0.5 mg])
Indication(s): Management of heavy menstrual bleeding associated with uterine fibroids
Sponsor: Abbvie
PDUFA Goal Date: July 7, 2020

Materials Reviewed:

Placebo controlled safety and efficacy study adverse event data, NDA 213388 submission dated July 31, 2019.

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I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Bone, Reproductive and Urologic Products (DBRUP) to evaluate an abuse liability statement submitted by Abbvie Pharmaceutical in (NDA 213388) for Oriahnn (elagolix sodium plus estradiol/norethindrone acetate) capsules. The proposed trade name, Oriahnn, was conditionally accepted by OSE in January 2020.

The proposed product is indicated for the reduction of heavy menstrual bleeding associated with uterine fibroids. The drug is a film-coated, oral capsule taken twice a day (BID). The proposed dose is a combination of 300 mg elagolix sodium plus 1 mg/0.5 mg of estradiol/norethindrone acetate (E2/NETA). CSS previously reviewed one of the components of the drug (single-entity elagolix sodium) and concluded that the drug did not have an abuse potential and should not be scheduled under the Controlled Substances Act (CSA) (May 2, 2018 review by Katherine Bonson for NDA 210,450). The second FDA-approved component of the drug (estradiol and norethindrone acetate) (Activella® NDA 20907), was not reviewed by CSS, is not scheduled under the CSA, and does not contain a section 9.0 (Drug Abuse and Dependence) in the drug label.

2. Conclusions

- Oriahnn does not appear to have a potential for abuse and does not warrant scheduling under the CSA at this time.
- A prior abuse liability assessment of single-entity elagolix sodium concluded that the drug did not produce signals suggestive of abuse and should not be scheduled under the CSA.
- Estradiol and norethindrone acetate combination products (e.g., Activella®) do not appear to have an abuse liability and are not scheduled under the CSA.
- Clinical trials with Oriahnn did not produce adverse events (AEs) suggestive of abuse potential.

Reference ID: 4599696

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. The combination drug product Oriahnn does not warrant scheduling under the CSA at this time.
2. Unless a signal for abuse is identified via postmarketing surveillance, no additional abuse liability assessments of Oriahnn are required.

II. DISCUSSION

1. Chemistry

1.1 Product Information

The proposed drug product consists of three previously approved drug substances: elagolix sodium, estradiol, and norethindrone acetate. The formulation uses elagolix sodium, previously approved as Orlissa®, under NDA 210450, and estradiol and norethindrone acetate, (approved as Activella®, under NDA 20907. Neither drug product is scheduled under the CSA.

According to the Sponsor: "Elagolix is a novel, oral, short-acting, nonpeptide gonadotropin releasing hormone receptor antagonist that dose-dependently suppresses follicle stimulating hormone and luteinizing hormone levels, which leads to decreased blood levels of the ovarian sex hormones estradiol and progesterone. E2/NETA is an orally administered estrogen/progestin compound that has been combined with elagolix as hormonal add-back therapy to reduce the hypoestrogenic effects of elagolix."

2. Nonclinical Studies

No new abuse-related nonclinical studies were required to support the NDA submission for Oriahnn. Review of nonclinical studies of previously reviewed NDAs for elagolix sodium did not identify a signal of abuse potential.

3. Clinical Pharmacology

The Sponsor asserts that pharmacokinetic properties of Oriahnn do not differ from the approved products for the active ingredients contained in Oriahnn (elagolix and estradiol/norethindrone acetate). These pharmacokinetic properties will be reviewed and addressed by the Office of Clinical Pharmacology.

Reference ID: 4519096

4. Clinical Studies

4.1 Adverse Event Profile in Phase 2 and 3 Clinical Studies

The Sponsor completed a total of 12 clinical studies, including one bioavailability study (M15-872), two bioequivalence studies (M16-856, and M19-648), four drug-drug interaction studies (M13-757, M14-708, M16-855, and M16-85), and five safety and efficacy studies, including long term safety and efficacy studies (M12-663, M12-813, M12-815, M12-817, and M12-816). Most of the studies were open-label, non-placebo controlled studies of short duration (e.g., single dose). Because the design of these studies was not amenable for AE analyses of abuse liability, only the safety and efficacy studies were assessed for abuse-related AEs (i.e., studies M12-663, M12-813, M12-815, M12-817, and M12-816). A short description of each of these studies followed by an abuse-related AE analysis appears below:

Study M12-663: A Phase 2a Proof of Concept Study to Evaluate the Safety and Efficacy of Elagolix in Pre-Menopausal Women with Heavy Uterine Bleeding and Uterine Fibroids

This was a Phase 2a, proof-of-concept study evaluating the efficacy of Elagolix in controlling heavy menstrual bleeding associated with uterine fibroids. Elagolix was administered in total daily doses of 200-600 mg under BID or QD dosing regimens. To accommodate multiple dosing paradigms, study participants were enrolled into six separate cohorts as outlined in Table 1, taken from the Sponsor's study report:

Table 1. Cohort Design

Cohort	Approximate No. of Subjects	Treatment	Design
1	45	Elagolix 200 mg BID Placebo	Randomized, double-blind, placebo-controlled
2	45	Elagolix 300 mg BID Placebo	Randomized, double-blind, placebo-controlled
3	30	Elagolix 200 mg BID + low-dose Activella	Open-label
4	75	Elagolix 100 mg BID Elagolix 400 mg QD Placebo	Randomized, double-blind, placebo-controlled
5	30	Elagolix 600 mg QD	Open-label
6	30	Elagolix 300 mg BID + cyclical EP	Open-label

Table 1. Cohort design for study Study M12-663. Participants were enrolled in one of six separate dosing regimens

Reference ID: 4599696

Subjects were dosed for three months followed by a three-month, post-treatment, follow-up period. Treatment-emergent adverse events (TEAEs) were examined for abuse-related signals. According to the Sponsor, approximately 70-80% of study subjects experienced a TEAE, and AEs did not appear to be dose-related. A display of abuse-related TEAEs appears below in Table 2:

COHORT	Preferred Term	TREATMENT			
COHORT 1					
		Placebo	Elagolix 200 mg BID (N=35) n (%)		
	mood swings	1 (5.6%)	2 (5.7)		
	amnesia	0	1 (2.9)		
	depression	2 (11.1)	1 (2.9)		
COHORT 2					
		Placebo	Elagolix 300 mg BID (N=30) n (%)		
	mood swings	0	1 (3.3)		
COHORT 3					
			Elagolix 200 mg BID + Activella (N=34) n (%)		
	depression		1 (2.9)		
	mood swings		1 (2.9)		
COHORT 4					
		Placebo	Elagolix 100 mg BID (N=33) n (%)	Elagolix 400 mg BID (N=32) n (%)	TOTAL (N=65) n (%)
	anxiety	0	2 (6.1)	0	2 (3.1)
	depression	0	1 (3.0)	0	1 (1.5)
	mood swings	0		1 (3.1)	1 (1.5)
COHORT 5					
			Elagolix 600 mg QD (N=30) n (%)		
	mood swings		1 (3.3)		
COHORT 6					
			Elagolix 300 mg BID + Cyclical EP (N=27) n (%)		
	somnolence		1 (3.7)		
	anxiety		1 (3.7)		
	depression		1 (3.7)		

Reference ID: 4619096

As seen in Table 2, abuse-related AEs were minimal, occurring in a maximum of two subjects, with no reports of euphoria.

Study M12-813: A Phase 2b Study to Evaluate the Safety and Efficacy of Elagolix in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

According to the Sponsor, the objectives of the study were to assess the safety, tolerability, and efficacy of elagolix alone (300 mg BID and 600 mg QD) and in combination with two different strengths of estradiol (E2)(0.5 mg and 1.0 mg) and northindrone acetate (NETA) (0.1 and 0.5 mg) as add-back therapy to reduce heavy menstrual bleeding (HMB). The treatment parameters and cohorts of the study appear below:

Table 2. Dosing/treatment regimens for study M12-813

Cohort	Treatment	Randomized and Treated	Study Drug Completion
1	Placebo	65	50
	Elagolix 300 mg BID alone	65	52
	Elagolix 300 mg BID + LD E2/NETA QD	64	53
	Elagolix 300 mg BID + SD E2/NETA QD	65	52
2	Placebo	78	67
	Elagolix 600 mg QD alone	77	58
	Elagolix 600 mg QD + LD E2/NETA QD	76	53
	Elagolix 600 mg QD + SD E2/NETA QD	77	53

LD E2/NETA = estradiol 0.5 mg/norethindrone acetate 0.1 mg,

SD E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg

Hot flush, headache, and nausea were the most common AEs and the majority of TEAEs were mild or moderate in severity. No abuse-related AEs occurred at a rate of ≥5% or in more than n=2 subjects (data not shown).

Study M12-815: A Phase 3 Study to Evaluate the Efficacy and Safety of Elagolix in Combination with Estradiol/Norethindrone Acetate for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women

According to the Sponsor, the goal of this Phase 3, randomized, double-blind study was to assess the efficacy, safety, and tolerability of elagolix (300 mg BID) alone, and in combination with once a day (QD) estradiol 1 mg/norethindrone acetate 0.5 mg (E2/NETA) in premenopausal women aged 18-51. The study consisted of a screening period, six-month treatment period, and 12-month post-treatment follow-up period. The primary outcome measure was the percentage of subjects with menstrual blood

Reference ID: 4619696

loss (MBL) <80 mL during the last 28 days of the study and the percentage of subjects with ≥50% reduction in MBL. 412 subjects (n=412) completed the study.

"Mood Swings" occurred in seven (6.7%) subjects that received elagolix alone, and in eight (3.9%) subjects that received elagolix plus E2/NETA. In comparison, only two (2%) subjects receiving placebo reported AEs of "Mood Swings." No other abuse-related AEs occurred in more than 5% of study participants. Depression was the only abuse-related AE that occurred in greater than two subjects with one instance occurring in a subject receiving placebo and another in a subject receiving elagolix plus E2/NETA.

Study M12-817: A Phase 3 Study to Evaluate the Efficacy and Safety of Elagolix in Combination with Estradiol/Norethindrone Acetate for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women

According to the Sponsor, the objectives of this study were to assess the efficacy, safety, and tolerability of elagolix 300 mg (BID) alone, and in combination with estradiol 1 mg/norethindrone acetate 0.5 mg (E2/NETA) once a day (QD) versus placebo to reduce heavy menstrual bleeding (HMB) associated with uterine fibroids. A second study objective was to characterize the impact of E2/NETA on the safety/tolerability (including bone mineral density [BMD] and other hypoestrogenic side effects) and efficacy of elagolix.

This double blind, randomized, multisite trial was performed in premenopausal women 18-51 years old. The study consisted of a screening period of 2.5 to 3.5 months prior to administration of drugs, a six-month treatment period, and a 12-month follow-up period. A total of 378 (n=378) subjects completed the study across the three treatment conditions. As was the case with study M12-815 (discussed above) the only abuse-related AEs that occurred in ≥5% of study subjects was "mood swings." No other abuse-related AEs occurred in ≥2 study participants.

Study M12-816 Extension Study to Evaluate the Efficacy and Safety of Oriahnn in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

The objective of this study was to evaluate the long-term efficacy and safety of elagolix alone and in combination with estradiol 1 mg/norethindrone acetate 0.5 mg (E2/NETA) once a day (QD) versus placebo to reduce heavy menstrual bleeding (HMB) associated with uterine fibroids. The Sponsor also evaluated the effect of elagolix on hypoestrogenic side effects and changes in bone density. This was an extension study for studies M12-815 and M12-817 described above. However, subjects that received placebo in studies M12-815 and M12-817 were switched to one of the elagolix groups (i.e., elagolix 300 mg BID or elagolix 300 mg BID + E2/NETA).

Similar to the initial studies (M12-815 and M12-817) abuse-related AEs were minimal, with only "anxiety" and "mood swings" occurring in ≥5% of study subjects. See table 3 below.

Reference ID: 4599096

Table 3. Abuse-related AEs for study M12-816

AEs That Occurred in ≥ 5% of Subjects in Any Treatment Group

System Organ Class Preferred Term	Number (%) of Subjects PBO/ ELA[a] N = 59	 PBO/ ELA+AB[a] N = 58	 ELA/ ELA[a] N = 98	 ELA+AB/ ELA+AB[a] N = 218
Psychiatric disorders				
Anxiety	1 (1.7)	3 (5.2)	1 (1.0)	3 (1.4)
Mood swings	3 (5.1)	2 (3.4)	1 (1.0)	2 (0.9)

Overall, the profile of abuse-related adverse events does not suggest a signal for abuse potential following Oriahnn administration.

4.2 Human Abuse Potential Studies

A human abuse potential (HAP) study was not performed.

Reference ID: 4699096

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 20, 2020
To:	Maria Wasilik Senior Health Regulatory Project Manager **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Jina Kwak, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide
Drug Name (established name):	ORIAHNN (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules)
Dosage Form and Route:	co-packaged for oral use
Application Type/Number:	NDA 213388
Applicant:	AbbVie Inc.

1 INTRODUCTION

On July 31, 2019, AbbVie Inc. submitted for the Agency's review a New Drug Application (NDA) for elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules, co-packaged for oral use. This NDA proposes an indication for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. On January 7, 2020 the proprietary name ORIAHNN was granted.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on October 4, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ORIAHNN (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules) co-packaged for oral use tablets.

2 MATERIAL REVIEWED

- Draft ORIAHNN (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules) MG received on July 31, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 13, 2020.
- Draft ORIAHNN (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules) Prescribing Information (PI) received on July 31, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 13, 2020.
- Approved ORILISSA (elagolix) tablets, for oral use comparator labeling dated July 23, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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JINA KWAK
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LASHAWN M GRIFFITHS
04/20/2020 04:24:59 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: April 20, 2020

To: Maria Wasilik
Regulatory Project Manager
Division of Urology, Obstetrics and Gynecology (DUOG)

From: Jina Kwak
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter
Team Leader, OPDP

Subject: **NDA 213388**
OPDP labeling comments for TRADENAME (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use

---

In response to DUOG consult request dated October 4, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG) and carton and container labeling for TRADENAME (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use.

PI and MG: OPDP's comments on the proposed labeling are based on the draft PI and MG received by electronic mail from DUOG (Maria Wasilik) on April 13, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed and comments on the proposed MG will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 31, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

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JINA KWAK
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Clinical Inspection Summary

Date	March 05, 2020
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Christina Chang, M.D., Team Leader Linda Jaffe, M.D./Marcea Whitaker, M.D., Clinical Reviewer Maria Wasilik, Regulatory Project Manager Division of Bone, Reproductive, and Urology Products (DBRUP)
NDA #	213388
Applicant	AbbVie Inc.
Drug	Orianne (elagolix plus estradiol/norethindrone acetate)
NME (Yes/No)	No
Review Priority	Standard
Proposed Indication(s)	Management of heavy menstrual bleeding (HMB) associated with uterine leiomyomas (fibroids)
Consultation Request Date	September 27, 2019
Summary Goal Date	March 19, 2020
Action Goal Date	May 21, 2020
PDUFA Date	May 31, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two identical phase 3 studies (Protocols MI2-815 and MI2-817) were submitted to the Agency in support of this New Drug Application (NDA) for Orianne (elagolix plus estradiol/norethindrone acetate) for the proposed indication. Four clinical investigators (CIs), Drs. Simha (Site 21939), Hatch (Site 79936), Gee (Site 45766), and Sekine (Site 101861) were selected for clinical inspections.

The inspections verified the sponsor (AbbVie Inc.) submitted clinical data with source records at the CI sites. Based on the results of these CI inspections, study protocols MI2-815 and MI2 817 appear to have been conducted adequately, and clinical data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

AbbVie Inc. submitted NDA 213388 to support the use of Orianne (elagolix plus estradiol/ norethindrone acetate) for the management of heavy menstrual bleeding (HMB) associated with uterine leiomyomas (fibroids). To support the application, the sponsor submitted clinical data from two identical studies (Protocols MI2-815 and MI2-817), titled "A Phase 3 Study to Evaluate the Efficacy and Safety of Elagolix in Combination with Estradiol/ Norethindrone Acetate for the

Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women".

The study objectives were:

- To assess the efficacy, safety and tolerability of elagolix 300 mg twice a day (BID) in combination with E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg) once a day (QD), versus placebo to reduce HMB associated with uterine fibroids in premenopausal women 18 to 51 years of age.
- To characterize the impact of E2/NETA on the safety/tolerability [including bone mineral density (BMD) and other hypoestrogenic side effects] and efficacy of elagolix.

These phase 3, randomized, double-blind, multicenter, placebo-controlled studies consisted of 4 periods: 1) a Washout Period (if applicable); 2) a Screening Period of approximately 2.5 to 3.5 months prior to the first dose of study drug; 3) a 6-month Treatment Period; and 4) a 12-month Post-Treatment Follow-Up (PTFU) Period for subjects who either prematurely discontinued from the Treatment Period or completed the Treatment Period, but did not enroll in the extension study (Study M12-816). After meeting eligibility criteria and providing informed consent, subjects were randomized in a 1:1:2 ratio to 1 of 3 treatment groups: placebo, elagolix 300 mg BID, or elagolix 300 mg BID + E2/NETA QD.

The primary efficacy endpoint was the percentage of subjects meeting a composite endpoint consisting of the following two bleeding assessments:

- Menstrual Blood Loss (MBL) volume < 80 mL during the Final Month (the last 28 days of treatment), AND
- 50% or greater reduction in MBL volume from baseline to the Final Month

Quantitative measurement of the volume of MBL was performed using the alkaline hematin method by (b) (4). Study subjects were dispensed sanitary collection kits to collect their sanitary products starting in Screening and throughout the 6-month Treatment Period to determine the change from baseline in MBL volume. The study sites were responsible to collect and submit the subjects' used sanitary products to (b) (4) for analysis.

Study MI2-815 screened a total of 3613 subjects, randomized 413 subjects in 76 study centers in the US, including Puerto Rico. The first subject was enrolled on December 22, 2015 and the last subject was completed on December 12, 2019.

Study MI2-817 screened a total of 3263 subjects, randomized 378 subjects in 77 study centers in the US and Canada. The first subject was enrolled on February 03, 2016 and the last subject was completed on January 23, 2019.

Four clinical investigators, Dr. Samuel Simha (Site 21939; Protocol MI2-815), Dr. Amber Hatch (Site 79936; Protocol MI2-815), Dr. Phyllis Gee (Site 45766; Protocol MI2-817), and Dr. Kenneth Sekine (Site 101861; Protocol MI2-817) were requested for clinical inspection in support of the application. These sites were selected because of their relatively high subject enrollments, above-average site-specific efficacy results, and lack of recent inspections.

III. RESULTS

1. Dr. Samuel Simha, Site #21939 (Protocol M12-815)

Research Memphis Associates, LLC
1028 Cresthaven Road
Memphis, TN 38119-3895
Dates of inspection: November 18-21, 2019

This clinical investigator was inspected on November 18-21, 2019 as a data audit for Study M12-815. This was the initial inspection for Dr. Simha. The study site screened 79 subjects and enrolled 12 subjects. All 12 subjects completed the study. The first subject was enrolled on 02/09/2016 and the last subject's last visit was on 02/22/2017. At the end of the six months, the protocol allowed subjects to transition to an open-label extension study or continue on the 12-month post-treatment follow-up period. Two (2) subjects ((b) (6)) entered into the 12-month follow-up period and the other ten (10) subjects were enrolled in the extension study. All of the 12 enrolled subjects' records for protocol-required procedures were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, informed consent forms (ICF), documentation of eligibility criteria, medical records, adverse events (AEs), the investigational product (IP) accountability records, visit data, laboratory results, ultrasound and MRI reports, collection of used sanitary products, electronic case report forms (eCRF), monitoring log and reports, and related regulatory documents [e.g., institutional review board (IRB) approvals and communications, training on the trial, financial disclosures, and delegation of authority].

The inspection found adequate source documentation for all study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. There was no evidence of underreporting of AEs. There was one reported major protocol deviation: Subject (b) (6) was randomized prior to having all of the eligibility requirement reviewed. This subject was later determined to be eligible for the study. The sponsor decided that the subject could continue the study. This protocol deviation was included in the study report. At the end of the inspection, no Form 483 (Inspectional Observations) was issued.

2. Dr. Amber Hatch, Site #79936 (Protocol M12-815)

Unified Women's Clinical Research, Suite 151
111 Hanestown Court
Winston-Salem, NC 27103
Dates of inspection: November 25-26, and December 3, 2019

This clinical investigator was inspected on November 25-26, and December 3, 2019 as a data audit for Study M12-815. This was the initial inspection for Dr. Hatch. The study site screened a total of 83 subjects and enrolled 18 subjects. Sixteen (16) subjects completed the study and two subjects withdrew due to relocation and time constraints. The first subject was enrolled on 08/22/2016 and the last subject's last visit was on 11/09/2017. An audit of the 18 enrolled subjects' records was conducted.

Source records reviewed during the inspection included the study protocol and amendments; ICFs; subject records included inclusion/exclusion criteria; adherence to protocol; AE reporting, lab results, ultrasound and MRI reports; and comparison of source records to data listings; control of the IPs; and related regulatory documents (e.g., IRB approvals and communications, training on the trial and financial disclosures).

The inspection found adequate source documentation for all 18 enrolled study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The site was blinded to the blood volume and submitted the used sanitary products collected from subjects to (b) (4) labs. There was no evidence of underreporting of AEs. Seven instances were noted in which subjects signed the incorrect ICF. However, only one of the seven subjects were enrolled in the study (Subject (b) (6)). This deviation was promptly corrected and reported to the IRB and the sponsor. At the end of the inspection, no Form 483 was issued.

3. Dr. Phyllis Gee, Site #45766 (Protocol M12-817)
Willowbend Health & Wellness
4401 Coit Road, Suite 205
Frisco, TX 75035
Dates of inspection: December 9-17, 2019

This clinical investigator was inspected on December 9-17, 2019 as a data audit for Study M12-817. This was the initial inspection for Dr. Gee. The study site screened a total of 64 subjects and enrolled 11 subjects. Ten (10) subjects completed the study and one (1) subject (Subject (b) (6)) lost to follow up. The first subject was enrolled on 05/23/2016 and the last subject's last visit was on 11/28/2017. Subject records for all of the 11 randomized subjects were reviewed.

Source records reviewed during the inspection included all sponsor correspondence e-mails, financial disclosure, IP accountability and administration, subject case histories, AEs, concomitant medications, eCRF, monitoring visit log and correspondence, and reported minor and major protocol deviations. ICF was obtained appropriately for all subjects. Documentation of IP accountability was verifiable. Randomization and test article allocation appeared adequate.

At the end of the inspection, a Form FDA 483 was issued with the following observations:

1. An investigation was not conducted in accordance with the investigational plan.

   Specifically,
   1) Subject eligibility: Subject (b) (6) was randomized on 05/31/2017 despite an exclusionary QTcB of 453 ms on ECG (a corrected QT interval of < 450 ms was allowed) at screening.

Reviewer's Comments:
The CI responded that the subject was randomized in error because the QTc values were not included on the prequalification checklist in error. This problem was identified by the sponsor and a deviation report was sent to the IRB and the sponsor. This appears to be an isolated event and was included in the study report.

2) Adverse event collection:
- Subject (b) (6), with documented medical history of hypertension, experienced worsening hypertension (118/82 mm Hg at screening on 6/1/2016, 143/88 at randomization on 9/19/2016, and 150/96 mm Hg at Month 6 on 3/9/2017) that was not reported to the sponsor.
- Subject (b) (6) experienced worsening anemia by Month 6 that was not reported to the sponsor.

Reviewer's Comments:
The CI responded that the documentation of elevated blood pressure for Subject (b) (6) was not done timely and was deleted due to confusion; and the delay in Subject (b) (6)'s AE completion was due to the subject being lost to follow up. The two underreported AEs were considered to be non-serious adverse events and may not change the safety profile of the study drug.

3) Treatment compliance: Subjec (b) (6) was not in compliance with directions to remove study drug from blister packs at the time of dosing. Scanned blister packs indicated that the subject removed multiple doses of the IP/placebo or hormones/placebo from the blister packs on the day of or just hours prior to a study visit at Months 5, 6, and at completion of the study. The reason for the removal of multiple study medications from the blister cards was not addressed in the subject's records.

Reviewer's Comment:
The subject was assigned to the elagolix 300 mg BID + E2/NETA QD treatment cohort and this protocol deviation was not reported. However, this noncompliance appears to be an isolated incidence.

4) Study procedures for informed consent: Subject (b) (6) had blood samples drawn for pharmacogenetic analysis without signing a separate ICF

Reviewer's Comment:
The CI responded that the incidence for Subject (b) (6) was reported to the IRB and the specimen was destructed.

In general, this clinical site appeared to be in compliance with Good Clinical Practices except the observations noted above. These observations appear unlikely to have significant impact on overall efficacy and safety results. Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Dr. Kenneth Sekine, Site #101861 (Protocol M12-817)
Solutions Through Advanced Research
11945 San Jose Blvd. Suite 400
Jacksonville, FL 32223
Dates of inspection: November 18-21, 2019

This clinical investigator was inspected on Nov 18-21, 2019 as a data audit for Study M12-817. This was the initial inspection for Dr. Sekine. The study site screened a total of 57 subjects and enrolled 10 subjects. The first subject was screened on 06/23/2016 and the last subject was screened on 04/20/2017. All randomized 10 subjects' records were reviewed.

Source records reviewed during the inspection included screening, ICF process, CRFs/EDC, case history files, source documentation, investigator responsibilities, AE reporting, IP accountability, dosing, randomization procedures, monitoring visit log, and protocol deviations.

The inspection found adequate source documentation for all study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. There was no evidence of underreporting of AEs. At the end of the inspection, no Form 483 was issued.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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CC:
Central Doc. Rm.\NDA 213388
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DBRUP\CDTL\Christina Chang
DTOP\Reviewer\Linda Jaffe/Marcea Whitaker
DTOP\Project Manager\Maria Wasilik
OSI\DCCE\Division Director\Ni Aye Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Min Lu
OSI\DCCE\GCPAB\Reviewers\Ling Yang\Roy Blay
OSI\DCCE\Program Analysts\Yolanda Patague

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: Feb 21, 2020

TO: Hylton Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic/New Drug Study Integrity
Office of Study Integrity and Surveillance

SUBJECT: Routine inspection of AbbVie Clinical Pharmacology Research Unit, Grayslake, IL

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of studies M16-856 and M19-648(NDA 213388) conducted at AbbVie Clinical Pharmacology Research Unit (ACPRU), Grayslake, IL.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

After reviewing the inspectional finding, I conclude the clinical data from the audited studies are reliable to support a regulatory decision.

2 Inspected Studies:

NDA 213388

Study Number: M16-856

Reference ID: 4659000

Study Title: "A bioequivalence and food effect study of elagolix/estradiol/norethindrone acetate capsules in healthy postmenopausal female subjects"
Dates of conduct: 01/07/2019 – 03/22/2019

Study Number: M19-648
Study Title: "A bioequivalence and food effect study of elagolix capsules in healthy premenopausal female subjects"
Dates of conduct: 01/02/2019 – 04/16/2019

Clinical site: AbbVie Clinical Pharmacology Research Unit
480 South US Highway 45
Grayslake, IL

ORA investigators Jeanne J Thai and Ruth A. Williams inspected ACPRU, Grayslake, IL from Jan 06-10, 2020.

The inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

At the conclusion of the inspection, investigators Thai and Williams did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, investigators Thai and Williams discussed one item at the closeout meeting. The discussion item and my evaluation are presented below:

Discussion Item 1: 15 out of 39 subjects were initially consented with an outdated informed consent form (ICF) for study M16-856. The aforementioned subjects were ultimately reconsented with the updated ICFs prior to randomization and prior to study drug administration.

OSIS Evaluation: All 15 subjects who were initially consented with an outdated ICF version were immediately reconsented on the same day with the most up to date ICF version. Because these subjects were reconsented prior to randomization and drug administration, this finding does not impact on subject safety or data reliability.

Reference ID: 4669000

4. Conclusion:

After reviewing the inspectional finding, I conclude the clinical data from the audited studies are reliable.

Based on the inspectional finding, studies of similar design conducted between the previous inspection (Dec 2017) and the end of the current surveillance interval should be considered reliable without an inspection.

Xiaohan Cai, Ph.D.
Senior Staff Fellow

Final Classification:

NAI- AbbVie Clinical Pharmacology Research Unit,
Grayslake, IL
FEI#: 3013956469

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OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Cai
ORA/OMPTO/OBIMO/ ORABIMOW.Correspondence@fda.hhs.gov

Draft: XHC 2/21/2020
Edit: YMC 2/21/2020

ECMS: Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/AbbVie Clinical Pharmacology, Grayslake, IL, USA

OSIS File #: BE 8686

FACTS: 11956017

Reference ID: 4569000

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: Jan 30, 2020

TO: Hylton Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic/New Drug Study Integrity
Office of Study Integrity and Surveillance

SUBJECT: Routine inspection of Anaheim Clinical Trials, LLC, Anaheim, CA

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study M16-856 (NDA 213388) conducted at Anaheim Clinical Trials, LLC (ACT), Anaheim, CA.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

After reviewing the inspectional findings, I conclude the clinical data from study M16-856 conducted at ACT, Anaheim, CA are reliable to support a regulatory decision. Another inspection of studies M16-856 and M19-648 (NDA 213388) conducted at AbbVie Clinical Pharmacology Research Unit, Grayslake, IL, is currently pending.

2 Inspected Study:

NDA 213388

Study Number: M16-856

Study Title: "A bioequivalence and food effect study of elagolix/estradiol/norethindrone acetate capsules in healthy postmenopausal female subjects"

Dates of conduct: 01/07/2019 – 03/22/2019

Clinical site: Anaheim Clinical Trials, LLC
1085 N. Harbor Bl.
Anaheim, CA

ORA investigator Angela Shepas inspected ACT, Anaheim, CA from Dec 12-13 and 16-18, 2019.

The inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

At the conclusion of the inspection, investigator Shepas did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, investigator Shepas presented four discussion items at the closeout meeting. The discussion items and my evaluation are presented below:

Discussion Item 1: Subject (b) (6) did not meet protocol eligibility criterion 10 requiring no history of the surgical procedure cholecystectomy. The subject previously underwent a cholecystectomy in August 2001 but was dosed on 1/31/2019.

OSIS Evaluation: The site acknowledged the protocol deviation as an oversight and reported this deviation. Although subject (b) (6) did not meet the protocol eligibility criteria, it is unlikely to impact data reliability, considering the surgery occurred 18 years ago. However, the protocol deviation is already included in the report and I recommend the review division evaluate its impact on the study results.

Discussion Item 2: The reference statement to clinicaltrials.gov was included in the informed consent form (ICF), though this study was not registered on clinicaltrials.gov.

OSIS Evaluation: The site erroneously included the reference statement to clinicaltrials.gov in the ICF. The site promised to correct the issue with better review process on ICF for future studies. Because the study is not required to be registered in clinicaltrials.gov, this finding does not impact data reliability.

Reference ID: 4659096

Discussion Item 3: The clinical investigator (CI)'s curriculum vitae in the background material did not accurately reflect that the CI no longer worked at three other listed sites.

OSIS Evaluation: The CV from the CI was not timely updated to reflect his current working locations. This finding also applied to two sub-investigators for the inspected study. Although the CVs of the CI and sub-investigators were not timely updated for other sites, this finding does not impact data reliability because there is no concern on the qualification of investigators participating the inspected study.

Discussion Item 4: Eligibility criterion 8 required no history of clinically significant allergies. There was no statement of clinical significance for the allergy histories of subjects (b) (6) and (b) (6).

OSIS Evaluation: The study CI stated that the allergy condition for subjects (b) (6) and (b) (6) was not clinically significant and occurred in year of 1962 and 1983, respectively. In addition, this finding was reported as protocol deviation for both subjects. Therefore, this finding does not impact on the data reliability.

4. Conclusion:

After reviewing the inspectional findings, I conclude the clinical data from study M16-856 conducted at ACT, Anaheim, CA are reliable.

Based on the inspectional findings, studies of similar design conducted between the previous inspection (May 2016) and the end of the current surveillance interval should be considered reliable without an inspection.

Xiaohan Cai, Ph.D.
Senior Staff Fellow

Final Classification:

NAI- Anaheim Clinical Trials, LLC
Anaheim, CA
FEI#: 3010306410

cc:

Reference ID: 4659096

OTS/OSIS/Kassim/ Fenty-Stewart/Johnson/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Cai
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Draft: XHC 1/23/2020; 1/29/20; 1/30/20
Edit: YMC 1/23/2020; JC 1/24/2020; 1/30/2020

ECMS: Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Anaheim Clinical Trials, (1211 West La Palma), Anaheim, CA, USA

OSIS File #: BE 8686

FACTS: 11972170

Reference ID: 4659096

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