GYNECOLOGY

Safety and tolerability of a new low-dose contraceptive patch in obese and nonobese women

Andrew M. Kaunitz, MD; David F. Archer, MD; Daniel R. Mishell Jr, MD; Marie Foegh, MD, DrSc

OBJECTIVE: The safety and tolerability of a new low-dose levonorgestrel/ethinyl estradiol (LNG/EE) contraceptive patch was compared with 2 combination oral contraceptives in 2 clinical studies in which approximately 30% of enrolled participants were obese.

STUDY DESIGN: Two phase 3, open-label, randomized, parallel-group, multicenter trials compared the LNG/EE contraceptive patch (n = 1579) with combination oral contraceptives (n = 581) in healthy women 17–40 years of age. Combination oral contraceptives were LNG 100 μg per EE 20 μg (combination oral contraceptive 20; n = 375) or LNG 150 μg per EE 30 μg (combination oral contraceptive 30; n = 206). Safety and tolerability data from the 2 trials were evaluated in integrated safety analyses.

RESULTS: Treatment-emergent adverse events of 2% or greater in the LNG/EE contraceptive patch were nasopharyngitis (5.2%), nausea (4.1%), upper respiratory infection (3.5%), headache (3.4%), sinusitis (2.9%), cervical dysplasia (2.3%), and urinary tract infection (2.1%). Including skin reaction–related treatment-emergent adverse events, the proportion of women who experienced any treatment-emergent adverse event was similar among women randomized to the contraceptive patch (47.5%), the combination oral contraceptive 20 (47.4%), or the combination oral contraceptive 30 (46.8%). The incidence of treatment-emergent adverse events was similar in obese vs nonobese participants in all groups. Serious adverse events occurred in less than 1% of participants in any of the treatment groups.

CONCLUSION: The LNG/EE contraceptive patch and combination oral contraceptives were well tolerated and associated with similar treatment-emergent adverse event incidences in obese and nonobese women.

Key words: combination oral contraceptive, contraceptive patch, obese, Ortho Evra, Twirla

Cite this article as: Kaunitz AM, Archer DF, Mishell DR, et al. Safety and tolerability of a new low-dose contraceptive patch in obese and nonobese women. Am J Obstet Gynecol 2015;212:318.e1-8.

Combination oral contraceptives (COCs) represent an effective and safe means of contraception.[1] Nevertheless, inadequate compliance with daily COCs among some women can reduce their ability to effectively prevent pregnancy.[2-4] The transdermal contraceptive patch (CP), applied weekly in clinical trials, has been associated with improved compliance compared with COCs.[5]

The only transdermal contraceptive approved by the US Food and Drug Administration is the norelgestromin (NGMN)/ethinyl estradiol (EE) patch, Ortho Evra. Although the initial package

From the Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville, Jacksonville, FL (Dr Kaunitz); Department of Obstetrics and Gynecology, Clinical Research Center, Eastern Virginia Medical School, Norfolk, VA (Dr Archer); Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, CA (Dr Mishell); and Agile Therapeutics, Inc, Princeton, NJ (Dr Foegh).

Received April 9, 2014; revised Aug. 19, 2014; accepted Sept. 10, 2014.

This study was supported by Agile Therapeutics, Inc, Princeton, NJ.

A.M.K. is a consultant to Actavis, Bayer HealthCare, Merck, and Teva; his academic department receives financial support to conduct clinical trials from Agile Therapeutics, Inc, Bayer HealthCare, and Teva. D.F.A. is a consultant to Abbott Laboratories, Agile Therapeutics, Inc, Bayer HealthCare, CHEMO, Endoceutics, Ferring Pharmaceuticals, HRA Pharma, Merck, Shionogi, Teva Women's Healthcare, Warner Chilcott, and Watson Pharmaceuticals; he has received research support from Abbott Laboratories, Bayer HealthCare, Endoceutics, Merck, Pfizer, Warner Chilcott, and Watson Pharmaceuticals and industry honoraria from Bayer HealthCare, Besins, and Merck. D.R.M. is a consultant to Agile Therapeutics, Inc. M.F. is a former employee of Agile Therapeutics, Inc, and has stock holdings in the company.

Dr Foegh is currently with the Department of Pharmacology, New York Medical College, Valhalla, NY.

Presented, in part, in poster format at the 61st Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, May 4-8, 2013, New Orleans, LA.

Corresponding author: Andrew M. Kaunitz, MD. andrew.kaunitz@jax.ufl.edu

0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2014.09.014

label claimed this patch delivered a low dose of EE (the equivalent of a 20 μg COC),[6,7] the NGMN patch actually produces EE levels (area under the curve) that are approximately 60% higher than those of a COC containing EE 35 μg.[8] Increased estrogen exposure may increase the risk of serious adverse events (SAEs; eg, venous thromboembolism [VTE])[9] as well as other hormone-related treatment-emergent adverse events (TEAEs; eg, breast symptoms).[10] Three phase 3 clinical trials found that approximately 1 in 5 women treated with Ortho Evra (Janssen Pharmaceuticals, Inc, Titusville, NJ) experienced hormone-related TEAEs such as breast symptoms and/or headache and/or nausea.[8]

The risk of VTE among women without risk factors using COCs is 3-9 per 10,000 woman-years.[11,12] The risk of VTE associated with contraceptive estrogen exposure may be increased in women with higher body mass index (BMI). For example, in a study of 3834 patients with VTE, obese women (BMI of ≥30 kg/m^2) not using COCs had a 2.4-fold higher risk of VTE compared with normal-weight women (BMI <25 kg/m^2) not using COCs.[13] However, among obese women using COCs, the risk of VTE was 24-fold higher than that for normal-weight women who did not use COCs. Whether obese women may be at increased risk of other TEAEs related to hormonal contraception is largely unknown because obese women have previously been excluded from clinical studies of contraceptives.[14]

Twirla (Agile Therapeutics, Inc, Princeton, NJ) is an investigational CP developed with the goal of delivering a dose of levonorgestrel (LNG) and EE that is effective and maintains serum EE exposure similar to that attained with low-dose COCs (ie, EE dose of 35 μg/d or less). This 7 day LNG/EE CP consistently produced LNG and EE levels under the curve equivalent to those associated with the use of an LNG 120 μg/EE 30 μg COC in phase 1 and 2 trials.[15,16]

A report summarizing the findings of the phase 3 trial comparing the LNG/EE CP with a COC containing 100 μg of LNG and 20 μg of EE (COC20) and focusing on compliance and contraceptive efficacy has been published.[17] Here we present integrated safety and tolerability data from the previously reported trial and a second phase 3 clinical trial that compared the efficacy and safety of the LNG/EE CP with a COC containing LNG 150 μg and EE 30 μg (COC30). Safety and tolerability were assessed based on the incidence of TEAEs, SAEs, discontinuation rates, and changes in physical examinations, vital signs, and clinical laboratory tests.

Because the 2 studies were conducted using similar protocols and during the same time period, data from the 2 studies were pooled to add increased numbers of participants to the safety analyses. These phase 3 studies were designed to enroll a population of women with BMIs representative of the US population; approximately 33% of the participants were to be obese (BMI of ≥30 kg/m^2) and approximately 50% of obese women were to have a BMI of 35 kg/m^2 or greater, permitting a comparison of the safety profiles of patch and COC in obese vs nonobese women.[18]

Materials and Methods

Study design

Two phase 3, open-label, randomized, multicenter, parallel-group clinical studies were conducted to evaluate the safety and efficacy of the LNG/EE CP. Eligible participants in study CL12[17] were randomized in a 3:1 ratio to treatment with LNG/EE CP for 13 cycles or to treatment with COC20 for 6 cycles followed by LNG/EE CP for 7 cycles (Figure 1, A).

Participants in study CL13[19] were randomized in a 1:1 ratio to LNG/EE CP for 6 cycles or to COC30 for 6 cycles (Figure 1, B). A cycle was defined as a 28 day period with 21 days on treatment (consecutive administration of three 7 day patches or 21 days of active pill taking) followed by 7 days off treatment (ie, no patch applied or no active pills taken) in both studies. All patches were applied to the abdomen, buttock, or upper torso (excluding the breasts) according to participant preference.

Participants

Both studies enrolled sexually active women aged 17-40 years of any body weight with regular menses (every 24-35 days) who were requesting contraception. All participants were in good general health, as confirmed by medical history, physical and gynecologic examinations, and screening laboratory values and were appropriate candidates for combination estrogen/progestin contraception.

Any healthy woman with any BMI was included. Smokers were permitted if they were younger than 35 years of age. Women with well-controlled hypertension or diabetes mellitus without vascular disease were enrolled if their BMI was less than 32 kg/m^2 and they were 17-40 years of age. The BMI cutoff of 32 for women with hypertension or diabetes mellitus was selected to avoid compounding VTE risk among these at-risk populations.

Centralized stratified randomization was used to achieve high BMI enrollment targets (approximately 33% with BMI of ≥30 kg/m^2; approximately 50% of obese participants with BMI of ≥35 kg/m^2).[17] The study protocols were approved by applicable institutional review boards (New England Institutional Review Board, Newton, MA; Schulman Associates, Cincinnati, OH; Crescent City Institutional Review Board, New Orleans, LA; Western Institutional Review Board, Olympia, WA), received ethics committee approval, and all participants provided written informed consent before screening.

New users of hormonal contraceptives were defined as women with no exposure to hormonal contraceptives within 6 months prior to the start of the study medication; current users were those who stopped a hormonal contraceptive within 7 days of starting study treatment; recent users were those who had used a hormonal contraceptive within the previous 6 months (but not within 7 days of study start).

Study drugs

Patch

Adhesive patches contained LNG and EE in a 15.0 cm^2 active matrix core surrounded by a perimeter adhesive system (26.0 cm^2 total area). The LNG/EE CP is manufactured by Corium International (Grand Rapids, MI).