Contraception

Contraception 91 (2015) 211–216

Original research article

New contraceptive patch wearability assessed by investigators and participants in a randomized phase 3 study☆,☆☆,★

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Received 14 July 2014; revised 17 November 2014; accepted 17 November 2014

Abstract

Objective: To evaluate skin irritation and patch adhesiveness of a new weekly low-dose levonorgestrel (LNG) and ethinyl estradiol (EE) contraceptive patch (LNG/EE patch).

Study design: This analysis was part of an open-label, parallel-group, multicenter, phase 3 study that randomized healthy women to the LNG/EE patch (one patch weekly for three consecutive weeks, followed by a patch-free week for 13 cycles) or to an oral contraceptive for six cycles followed by seven LNG/EE patch cycles. Participants selected patch application sites of abdomen, buttock or upper torso. Investigators rated patch adhesiveness and skin irritation using standardized scales. Participants rated skin irritation and itching daily using standardized scales and recorded patch fall-off on daily diary cards.

Results: A total of 32,508 patches were applied (n=1273). At the five clinic visits in which investigators rated the patches, they rated adhesiveness=0 (no lift) for ≥84% of participants and skin irritation=absent/mild for 97% of patches. Participants reported that 2–3.7% of patches fell off and rated skin irritation as absent or mild for 92– 95% of patches, according to site.

Conclusion: Investigator- and participant-rated assessments of LNG/EE patch adhesiveness and irritation demonstrated a low incidence of patch detachment, skin irritation and pruritus.

Implications statement: This secondary analysis of a phase 3 clinical trial of a new weekly low-dose LNG and EE contraceptive patch, which used assessment by both investigators and participants, observed a low incidence of skin irritation, pruritus and patch detachment.

Keywords: Adhesiveness; Ethinyl estradiol; Itching; Levonorgestrel; Transdermal patch

☆ Funding: This study was sponsored by Agile Therapeutics, Inc.

☆☆ Conflicts of interest: Dr. Kaunitz is a consultant to Actavis, Bayer Healthcare, Merck and Teva; his academic department (Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville) receives financial support to conduct clinical trials from Agile Therapeutics, Inc., Bayer Healthcare and Teva. Dr. Portman has received research grants from Agile Therapeutics, Inc., Bayer Healthcare, Teva, Warner Chilcott, Actavis, Merck and the Population Council. He is a consultant to Teva, Actavis and Noven and serves on the speakers bureau for Teva, Warner Chilcott and Noven. Dr. Westhoff is a consultant to Bayer, Merck, Actavis and Agile Therapeutics, Inc. Dr. Mishell is a consultant to Agile Therapeutics, Inc. Dr. Archer is a consultant to Abbott Laboratories, Agile Therapeutics, Inc., Bayer Healthcare, CHEMO, Endoceutics, Ferring Pharmaceuticals, HRA Pharma, Merck, Shionogi Inc., Teva Women's Health, Warner Chilcott and Watson Pharmaceuticals. He has received research support from Abbott Laboratories, Bayer Healthcare, Endoceutics, Merck, Pfizer, Warner Chilcott and Watson Pharmaceuticals and has received industry honoraria from Bayer Healthcare, Besins Healthcare and Merck. Dr. Foegh was formerly an employee of Agile Therapeutics, Inc., and owns stock in the company.

★ Clinical trial registration number: NCT01181479.

Portions of this trial were presented at the American Congress of Obstetricians and Gynecologists Annual Meeting, May 5–9, 2012, San Diego, CA, USA, and May 4–8, 2013, New Orleans, LA, USA; Women's Health 2013: The 21st Annual Congress, March 22–24, 2013, Washington, DC, USA; and the 15th World Congress on Human Reproduction, March 13–16, 2013, Venice, Italy.

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http://dx.doi.org/10.1016/j.contraception.2014.11.013
0010-7824/

1. Introduction

Use of a transdermal hormonal contraceptive patch has been associated with high levels of user satisfaction and compliance compared with daily combination oral contraceptives (COCs) [1,2]. Women using transdermal systems have emphasized the importance of patches that are nonirritating and that adhere well during the entire application time [3]. Hence, comprehensive evaluations of patch adhesiveness and comfort (irritation and itching) are an important part of assessing user acceptability of a new contraceptive patch. In addition, good skin adhesion is necessary and important for efficacy of a contraceptive patch.

Phase 3 clinical studies of a norelgestromin (NGM)/ethinyl estradiol (EE) contraceptive patch [Ortho Evra (NGM/EE transdermal system), Janssen, Titusville, NJ, USA] evaluated patch adhesiveness based on complete detachment reported in participants' diary cards [4,5]. Evaluations of patch-related skin irritation were based on the incidence of spontaneously reported application site-related adverse events (AEs). More extensive evaluations of irritation and adhesiveness were performed in clinical studies of postmenopausal estrogen patches, including periodic investigator assessments of skin irritation, itching (by direct questioning) and adhesiveness using standardized rating scales [6–8]. Such standardized and rigorous evaluation of a contraceptive patch may reveal problems with adhesiveness and irritation that are not severe enough to prompt patch change or to be considered an AE but that may nevertheless lead to dissatisfaction sufficient to reduce compliance to therapy and affect long-term continuation.

We evaluated adhesiveness and irritation in a phase 3 clinical study of a new weekly low-dose levonorgestrel (LNG)/EE contraceptive patch (Twirla, Agile Therapeutics, Inc., Princeton, NJ, USA). The study included standardized assessments of adhesiveness, skin irritation and itching that were completed daily by participants and assessment at five clinic visits by investigators, as well as standard monitoring of application-site AEs and reasons for unscheduled patch changes. Detailed contraceptive efficacy and safety data from this phase 3 clinical study have been published [9]. Patch adhesiveness, skin irritation and itching results are reported here.

2. Materials and methods

2.1. Study design

An open-label, randomized, parallel-group, multicenter phase 3 study (ATI-CL12; clinicaltrials.gov #NCT01181479) evaluated the contraceptive efficacy of an LNG/EE contraceptive patch (Twirla, Agile Therapeutics, Inc., Princeton, NJ, USA) compared with a COC (100 μg LNG and 20 μg EE). Women assigned to the LNG/EE patch group received the patch for thirteen 28-day cycles (21 days with patch+7 days no patch); those assigned to the COC group received the pill for six cycles (21 days active pill+7 days inactive pill) followed by seven additional cycles of treatment with the LNG/EE patch. The study protocol was approved by an institutional review board before recruitment; all participants provided written informed consent before screening.

2.2. Study population

The study enrolled generally healthy, sexually active women aged 17–40 years with regular menses (every 24–35 days) and no body weight restrictions who requested contraception. Smokers 35 years or older and women with uncontrolled hypertension or diabetes mellitus with vascular disease, as well as women with other contraindications to COCs, were excluded.

2.3. LNG/EE contraceptive patch

The LNG/EE contraceptive patch is an adhesive transdermal system that contains LNG and EE in an active matrix core (15.0 cm^2 area) surrounded by a perimeter adhesive system (26.0 cm^2 total area). This patch provides LNG and EE systemic exposure (as measured by area under the curve) comparable to that obtained with a COC containing 120 μg LNG and 30 μg EE [10,11]. The LNG/EE patch was manufactured by Corium International using LNG and EE provided by Schering AG. Patches were applied to abdomen, buttock or upper torso (excluding breasts) according to participant preference but limited to one anatomical site per cycle.

2.4. Study evaluations

2.4.1. Patch adhesiveness

2.4.1.1. Investigator assessment. Investigators rated patch adhesiveness at each of five study visits scheduled during cycles 2, 4, 6, 9 and 13. Adhesiveness was rated using the following five-point standardized adhesiveness scale: 0: ≥90% adhered (no lift); 1: ≥75% adhered but <90% (some edges showing lift); 2: ≥50% adhered but <75% (half of system lifts off); 3: <50% (>half of system lifts off but undetached); 4: patch completely detached.

2.4.1.2. Participant assessment. Women recorded cycle days when patch was worn, days of patch application and removal and reasons for premature patch change (including patch falling off and partial detachment) on daily diary cards completed for each 28-day treatment cycle.

2.4.2. Skin irritation

2.4.2.1. Investigator assessment. Investigators rated skin irritation five times during the study (cycles 2, 4, 6, 9 and 13) using the following criteria: None: no irritation or barely perceptible/spotty erythema; Mild: mild erythema covering most of the application site; Moderate: moderate erythema, possible presence of mild edema; Significant: