Contraception 93 (2016) 310–316

Contraception

Original research article

A prospective, open-label, multicenter study to assess the pharmacodynamics and safety of repeated use of 30 mg ulipristal acetate☆

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Received 18 February 2015; revised 9 November 2015; accepted 21 December 2015

Abstract

Objective: Ulipristal acetate (UPA) 30 mg is safe and effective for emergency contraception (EC). This prospective open-label exploratory study was conducted to obtain additional data on the pharmacodynamic effects of repeated dose of UPA 30 mg during an 8-week period (effects on ovulation inhibition, hormonal levels, endometrium and cervical mucus). Safety and tolerability data of repeated use of UPA EC were also collected.

Study design: A total of 23 healthy female, healthy sterilized women participated in two substudies receiving UPA for 8 consecutive weeks. In substudy 1, UPA 30 mg was administered every 7 days (Q7D $n=12$); while in substudy 2, every 5 days (Q5D $n=11$). Subjects were monitored three times a week in a baseline cycle and during treatment with transvaginal ultrasounds, hormonal measurements and cervical mucus evaluation. Laboratory safety measurements and standard surrogate thrombosis risk markers were measured at baseline and within a few days of the last tablet. A luteal phase endometrial biopsy was taken in the baseline cycle and posttreatment.

Results: A total of 11/12 (91.7%) and 8/11 (72.7%) of the subjects ovulated at least once in substudy Q7D and Q5D, respectively, with similar, normal hormonal profiles. No effect on cervical mucus was observed. All biopsies were classified as benign in both substudies; 5/11 biopsies on Q5D posttreatment were classified as nonphysiological with some of typical progesterone receptor modulator-associated endometrial changes. UPA was well tolerated in both treatment arms while clinical laboratory results and surrogate thrombosis markers were reassuring.

Conclusions: Repeat use of 30 mg oral UPA every 5 or 7 days for 8 weeks initially delays follicular rupture but ovulation eventually occurs with time in most subjects. Safety data indicate that UPA 30 mg could be safely administered if needed more than once for EC in a given menstrual cycle.

Implications: These data demonstrate that repeated use of UPA 30 mg is safe. However, ovulation eventually occurs in a high proportion of women in spite of repeated treatments in both studied regimens. Nevertheless, since the stage of follicular development of women seeking initial or repeat EC use is generally unknown, the repeated use of UPA may still delay follicular rupture and prevent an unintended pregnancy in the event of further unprotected intercourse.

Keywords: Emergency contraception; Ulipristal acetate; Repeated use; Thrombosis risk surrogate markers

1. Introduction

Ulipristal acetate (UPA) is a selective progesterone receptor modulator that blocks the activity of P_4 in target tissues. Single doses of UPA administered in the follicular phase delay ovulation in a dose-dependent manner [10]. A single oral 30 mg dose significantly reduces the risk of pregnancy following unprotected intercourse and is marketed as an emergency contraceptive [2,8,9]. Administration in the advanced follicular phase, with a leading follicle of ≥18 mm, delays ovulation for more than 5 days in 59% of cycles [1]. The 5-day delay is sufficient to allow sperm already present in the female genital tract unviable by the time ovulation occurs [11].

Although product labels caution that emergency contraception (EC) is not to be used as a regular contraceptive method, women may find themselves in need of EC more

☆ Funding: HRA Pharma, Paris, France.

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http://dx.doi.org/10.1016/j.contraception.2015.12.015
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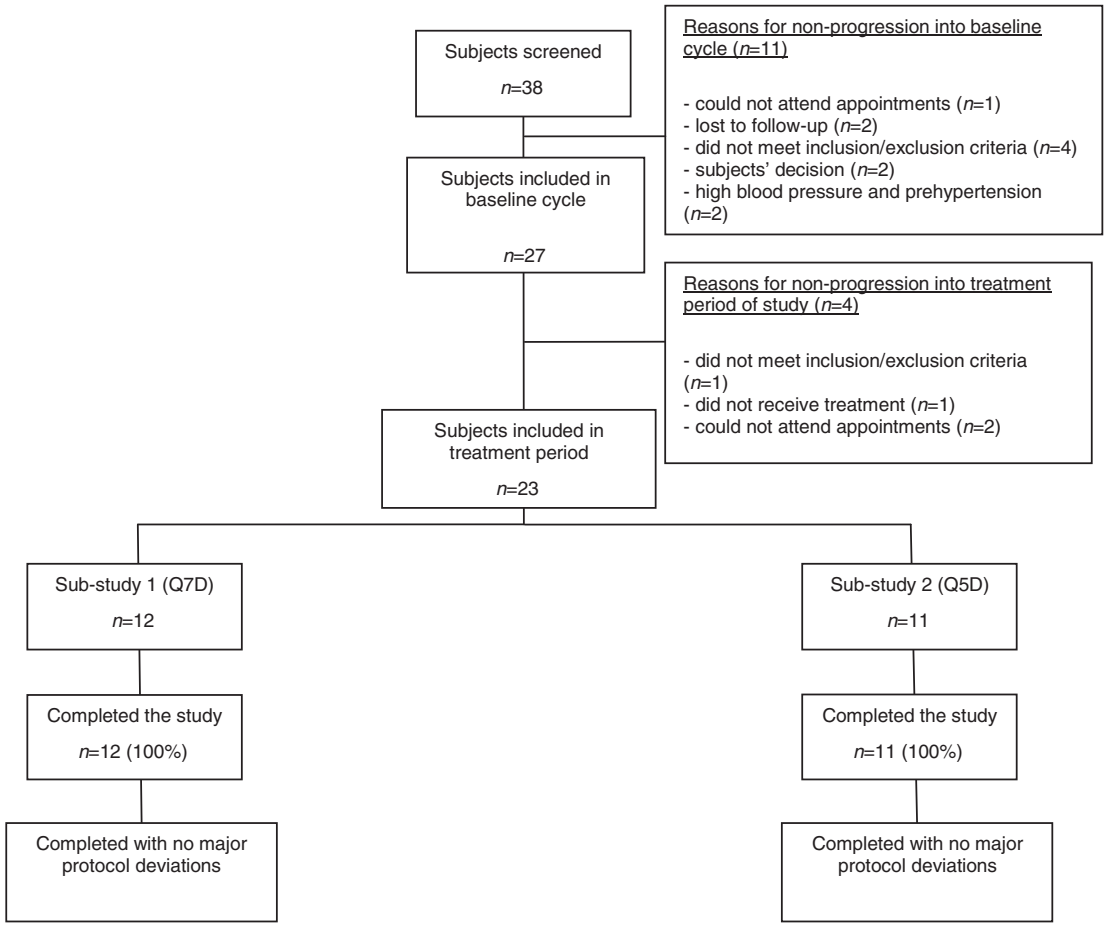

Fig. 1. CONSORT flowchart.

than once in a given cycle. Women who had further unprotected intercourse during the same cycle after using EC were more than four times as likely to get pregnant than those who did not have further unprotected intercourse [12].

The continuous daily oral administration of UPA 5 or 10 mg daily-inhibited ovulation in near 80% of women receiving UPA for a period of 12 weeks [13] as does a 3-month vaginal ring delivering 1.5 or 2.5 mg UPA daily [15].

This prospective, open-label, exploratory study was conducted to obtain additional data on the pharmacodynamic effects of repeated doses of UPA 30 mg during an 8-week period. Specifically, the study explored whether multiple intakes of UPA would inhibit ovulation; affect hormonal levels, endometrium and cervical mucus; and provide safety and tolerability data of repeated use.

2. Materials and methods

2.1. Study design

This was a prospective, phase I, open-label study performed at two sites: Profamilia, Santo Domingo, Dominican Republic, and Instituto Chileno de Medicina Reproductiva, Santiago, Chile. Eligible for enrollment were healthy volunteers, aged 18–35 years, with regular menstrual cycles (24–35 days) and not at risk for pregnancy (tubal ligation).

Local institutional review board approved the protocol at each site. Prior to enrollment, all participants gave written informed consent.

2.2. Treatments

The original protocol was designed to evaluate 30 mg UPA administered once weekly for 8 consecutive weeks, starting 7 days ± 1 day after the onset of menses (substudy 1 Q7D). Due to a several months delay in initiating the study in Chile, the Santo Domingo site completed enrollment and preliminary results indicated high rates of ovulation. Therefore, the protocol was amended with a shorter administrative schedule of every 5 days starting on day 1 (or +1 day) of the menstrual cycle (substudy 2 Q5D) for 8 consecutive weeks.

Research staff administered each UPA tablet after an overnight fast with 240 mL of water. No study medication was given to subjects to take home.

2.3. Study procedures

Study procedures were the same for women in both substudies. Eligible women were followed twice a week