PRO E2

Unintended pregnancy in users of nomegestrol acetate and 17β-estradiol compared with levonorgestrel-containing combined oral contraceptives

Real-world efficacy in a post-authorisation safety study of Zoely®[1]

zoely®

nomegestrol acetate 2.5 mg/
estradiol 1.5 mg

Background

Unintended pregnancies may occur even if a woman is on contraception[2]

Some 40% of OC users are non-adherent with their daily pill-taking regimen, which helps to explain a failure rate of up to 9% in the first year of typical use[3]

Tolerance of imperfect use varies between OCs depending on what hormones they contain and in what regimen[4-6]

Zoely® offers practical benefits during real-world use with its unique NOMAC/E2 combination[5-8]

Simple monophasic regimen
Reducing complexity when a pill is missed[5,7]

46-hour half-life
Therapeutic effect is lost less rapidly vs other progestogens with a shorter half-life, giving a 24-hour missed pill window[6,7]

4-day hormone-free interval
Shortening this vulnerable phase supports reliability[8]

Broad error margin
Ovulation takes on average 21 days to return after the last active tablet[8]

PRO-E2

A large, prospective, observational, active surveillance study conducted in 12 countries across Europe and Latin America, and in Australia, PRO-E2 compared users of Zoely® with users of COCs with levonorgestrel[1]

101,498 women were recruited by healthcare professionals under real-life clinical practice conditions, and followed up for up to 2 years between August 2014 and September 2019

101,498

144,901 WY

Baseline characteristics

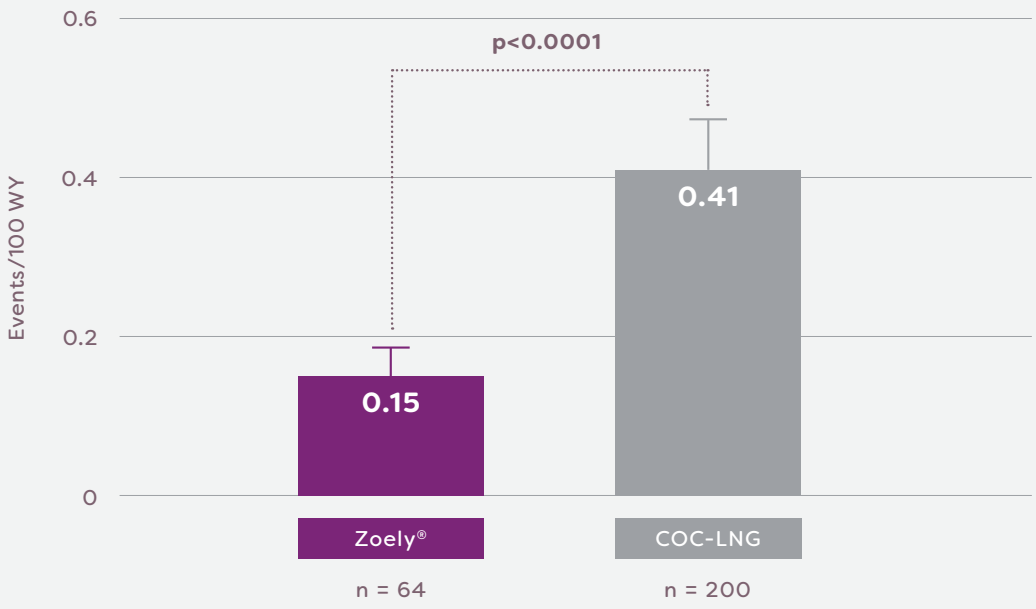
In the actually treated population, Zoely® users had a slightly higher mean age and reported achieving a higher level of education than COC-LNG users[1]

	Zoely®	COC-LNG
Number of users	44,559	46,754
Mean age (years ± SD)	31.0 ±8.63	29.3 ±8.53
Mean weight (kg ± SD)	63.3 ±11.67	63.1 ±12.15
Mean BMI (kg/m² ± SD)	23.2 ±4.07	23.3 ±4.25
Ever been pregnant	57.0%	54.9%
Using COC for non-contraceptive reasons only	9.5%	8.6%
Educated to less than university entrance level	13.6%	20.1%

Results

Zoely® delivered superior contraceptive efficacy to COC-LNGs in the real-world setting[1]

Unintended pregnancy rate

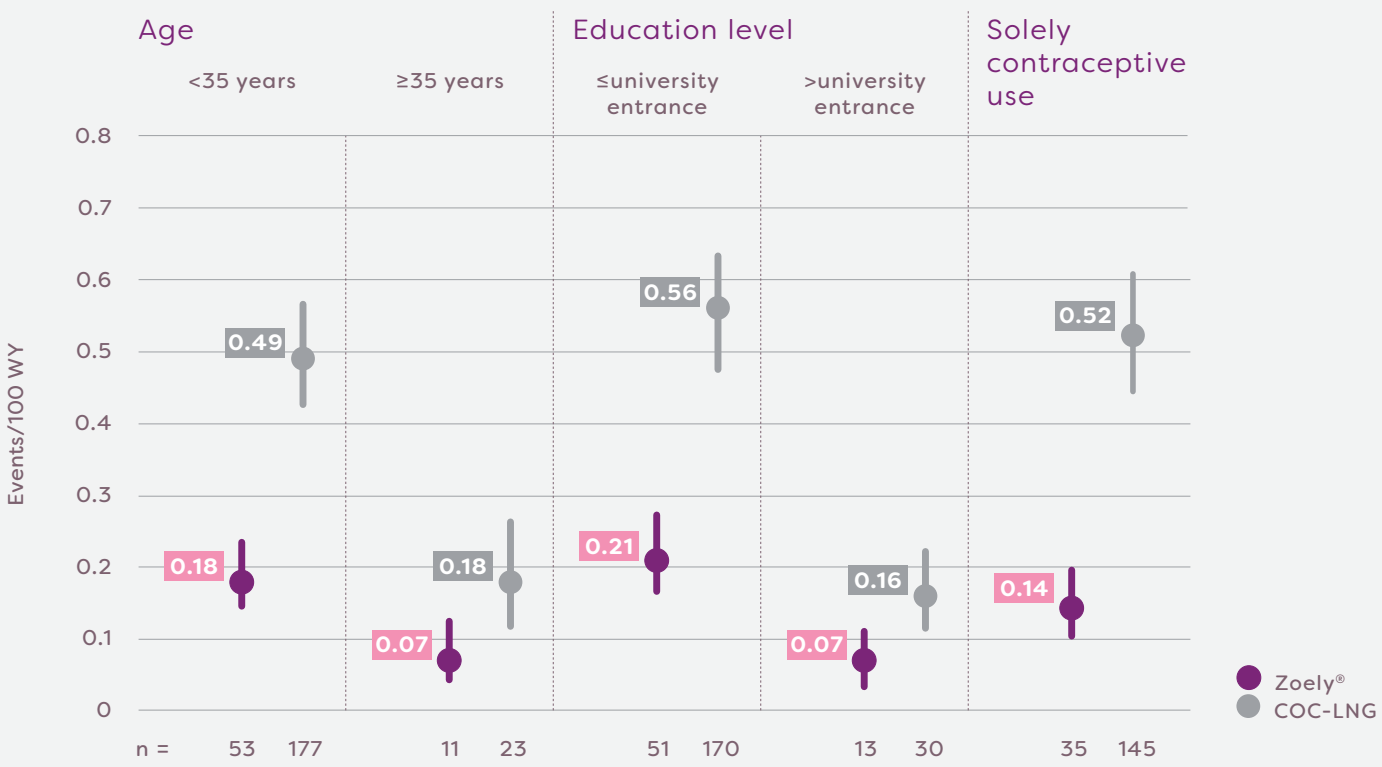


Zoely® vs COC-LNGs
HR: 0.45
95% CI: 0.34 - 0.60

(adjusted for age, BMI, gravidity, COC user status, education level)

The lower rate of contraceptive failure in Zoely® vs COC-LNG users did not appear to be associated with their higher mean age, or their higher educational level (and presumably more compliant use)[1]

Unintended pregnancy rate across stratified groups



Conclusion

The PRO-E2 study found a higher contraceptive effectiveness in Zoely® users compared to COC-LNG users[1]

These results are consistent with the short hormone-free interval of Zoely® and the comparatively long half-life of NOMAC[1]

NOMAC
Nomegestrol acetate

Metabolically **NEUTRAL** without any androgenic, estrogenic or mineralo-glucocorticoid activities[10]

E2
17β-estradiol

NATURAL estrogen with identical structure to the one produced by women[10]

zoely®

nomegestrol acetate 2.5 mg/ estradiol 1.5 mg

For further information see www.zoely.ie

NAME OF THE MEDICINAL PRODUCT: Zoely 2.5 mg/1.5 mg film-coated tablets. Each tablet contains 2.5 mg nomegestrol acetate and 1.5 mg estradiol (as hemihydrate). The Yellow placebo film-coated tablets do not contain active substances. For a full list of excipients see the SPC. **Therapeutic indication:** Oral contraception. **Posology & Method of Administration**: One tablet is to be taken orally daily for 28 consecutive days. Each pack starts with 24 white active tablets, followed by 4 yellow placebo tablets. Special populations: *Renal impairment is* not likely to affect the elimination of nomegestrol acetate and estradiol. *Hepatic impairment* - Since the metabolism of steroid hormones might be impaired in patients with severe hepatic disease, the use of Zoely in these women is not indicated as long as liver function values have not returned to normal. How to take Zoely, to switch from other forms of contraception and in the case of "Missed Pills" see full prescribing information. **Contraindications & Warnings:** Do not use combined hormonal contraceptives (CHCs) in the following conditions: Presence or risk of venous thromboembolism (VTE) or Arterial Thrombosis, pancreatitis, or a history of association of severe hypertriglyceridaemia, severe hepatic disease, liver tumours benign or malignant, known, or suspected sex steroid-influenced malignancies, meningioma, undiagnosed vaginal bleeding, hypersensitivity to the active substances or excipients. **Warnings:** Risk of venous thromboembolism (VTE), Tumours: Cervical cancer in long-term users of COCs (>5 years) has been reported in some epidemiological studies, no epidemiological data on the risk of cervical cancer in users of Zoely are available. The risk of endometrial and ovarian cancer is reduced with COCs containing (50µg ethinylestradiol). In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur. Meningioma (single and multiple) has been reported with prolonged use of nomegestrol monotherapy at doses of 3.75 mg or 5 mg daily and higher. If a meningioma is diagnosed in a patient treated with Zoely, treatment should be stopped. During clinical trials with the Hepatitis C virus (HCV) combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. Additional monitoring of diabetes is advised in the first months of use. Exogenous oestrogens may induce or exacerbate symptoms of angioedema. Crohn's disease, ulcerative colitis, and worsening of depression have been associated and Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use. If any of the conditions or risk factors mentioned below is present, the suitability of Zoely should be discussed with the woman. In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Zoely should be discontinued. Laboratory tests may be influenced, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g., corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. **Interactions:** Ethinylestradiol may decrease the concentrations of lamotrigine by approximately 50%. Interactions between oral contraceptives and enzyme-inducing medicinal products may lead to breakthrough bleeding and/or contraceptive failure. Interactions can occur with substances that induce CYP450 enzymes, resulting in reduced concentrations of sex hormones and decreased effectiveness of combined oral contraceptives. These medicines include anticonvulsants (e.g., carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate); anti-infective drugs (e.g. rifampicin, rifabutin, griseofulvin); St. John's wort; bosentan and HIV or Hepatitis C virus (HCV) protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz). Enzyme induction can occur quickly, and a barrier contraceptive method should also be used during the concomitant use of an enzyme inducer, and for 28 days after its discontinuation. Concomitant administration of ketoconazole, itraconazole, clarithromycin, fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of oestrogens or progestogens. **Fertility, pregnancy and lactation: Z**oely is not indicated during pregnancy and if pregnancy occurs while taking Zoely, further intake should be stopped. The increased risk of VTE during the postpartum period should be considered when re-starting Zoely. Lactation: Breastfeeding may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. *Fertility:* Zoely is indicated for the prevention of pregnancy. **Paediatric population:** Safety and efficacy have not been established in adolescents under 18 years of age. There is no relevant use of Zoely in children and pre-menarchal adolescents. **Effects on ability to drive and use machines:** Zoely has no or negligible influence on the ability to drive and use machines. **Undesirable effects:** Very common (≥1/10): acne, abnormal withdrawal bleeding, Common (≥1/100 to < 1/10): decreased libido, depression/ depressed mood, mood altered, headache, migraine, nausea, metrorrhagia, menorrhagia, breast pain, pelvic pain, weight increased. In addition to these adverse reactions, hypersensitivity reactions have been reported in Zoely users (frequency unknown). For Uncommon and Rare Adverse reactions please see the full SPC. Selected Adverse Reactions: An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis, and pulmonary embolism has been observed in women using CHCs. **Overdose:** Multiple doses up to five times the daily dose of Zoely and single doses up to 40 times the daily dose of nomegestrol acetate alone have been used in women without safety concern. **Shelf life:** 3 years **MARKETING AUTHORISATION HOLDER:** Theramex Ireland Limited 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin D01 YE64 Ireland **MARKETING AUTHORISATION NUMBERS:** EU/1/11/690/001, EU/1/11/690/002, EU/1/11/690/003, EU/1/11/690/004. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:** Date of first authorisation: 27 July 2011, Date of latest renewal: 21 April 2016, **DATE OF REVISION OF THE TEXT:** December 2021 Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu.

IE-OCS-691(1). Date of Preparation: December 2021.

Healthcare professionals should report any suspected adverse events to HPRA Pharmacovigilance, Earlsfort Terrace, Dublin 2. Tel: (01) 6764971 or at www.hpra.ie, email medsafety@hpra.ie. Suspected adverse events should also be reported to Consilient Health Ltd., Tel: (01) 2057766 or email drugsafety@consilienthealth.com.

References

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2. Coombe J *et al.* Aust Fam Physician 2016; 45(11): 842-8.
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7. Christin-Maitre S *et al.* Womens Health (Lond) 2013; 9(1): 13-23.
8. Duijkers IJM *et al.* Eur J Contracept Reprod Health Care 2010; 15(5): 314-25.
9. Chabbert-Buffet N *et al.* Gynecol Endocrinol 2013; 29(10): 891-6.
10. Zoely® Summary of Product Characteristics.

Abbreviations
BMI: body mass index
CI: confidence interval
COC: combined oral contraceptive
COC-LNG: COC with levonorgestrel
E2: 17β-estradiol
HR: hazard ratio
OC: oral contraceptive
NOMAC: nomegestrol acetate
SD: standard deviation
WY: women-years

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