PRO E2

Prospective Controlled Cohort Study on the Safety of a Monophasic Oral Contraceptive containing Nomegestrol Acetate (2.5mg) and 17β-estradiol (1.5mg) (PRO-E2 Study): Risk of venous and arterial thromboembolism[1]

A post-authorisation safety study of Zoely®[1]

zoely®

nomegestrol acetate 2.5 mg/
estradiol 1.5 mg

Background

Combined oral contraceptives are associated with an increased risk of venous thromboembolism compared with non-use[2]

While the risk is smaller than the risk in pregnancy, VTE is one of the most serious adverse events linked to the use of COCs[2,3]

There is, however, uncertainty surrounding the actual risk associated with various different formulations of COCs, particularly regarding the type of progestin[2]

Risk of developing a VTE in a year according to progestin component[4]	Risk per 10,000 women
Not using a COC	2
Levonorgestrel, norethisterone or norgestimate	5-7
Etonogestrel or norelgestromin	6-12
Drospirenone, gestodene or desogestrel	9-12
Chlormadinone, dienogest or nomegestrol	not yet known*

*studies were ongoing or planned when the EMA compiled this table

Theramex
For Women, For Health

PRO E2

The use of COCs can affect haemostasis in a number of ways, increasing the activity of some coagulation factors by up to 30-50% and decreasing the activity of some naturally occurring anticoagulants by 30-40%[5,6]

Design

PRO-E2 is a 'real-world' study comparing users of Zoely® and users of combined oral contraceptives with levonorgestrel (COC-LNG):[1]

Design

Multinational, large, prospective, observational active surveillance study using a non-inferiority design

Countries

Australia, Europe and Latin America

Cohorts

Zoely® and COCs with levonorgestrel

Users

"Starters" (first-ever users of a COC) and "Restarters" (use of the same or a different COC after a break of ≥2 months)

Sample size

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

101,498

144,901 WY

Outcome measures[1]

Primary outcome

VTE (specifically deep venous thrombosis of the lower extremities and pulmonary embolism)

Secondary outcomes

- All VTE
- Arterial thromboembolisms
- Depressive disorders
- Cholelithiasis
- Inflammatory bowel disease
- Short- and long-term fertility
- Pregnancy outcomes
- Weight change
- Hepatobiliary disorders
- Acne

Baseline characteristics

Baseline characteristics of the actually treated population were largely similar for Zoely® and COC-LNG users[1]

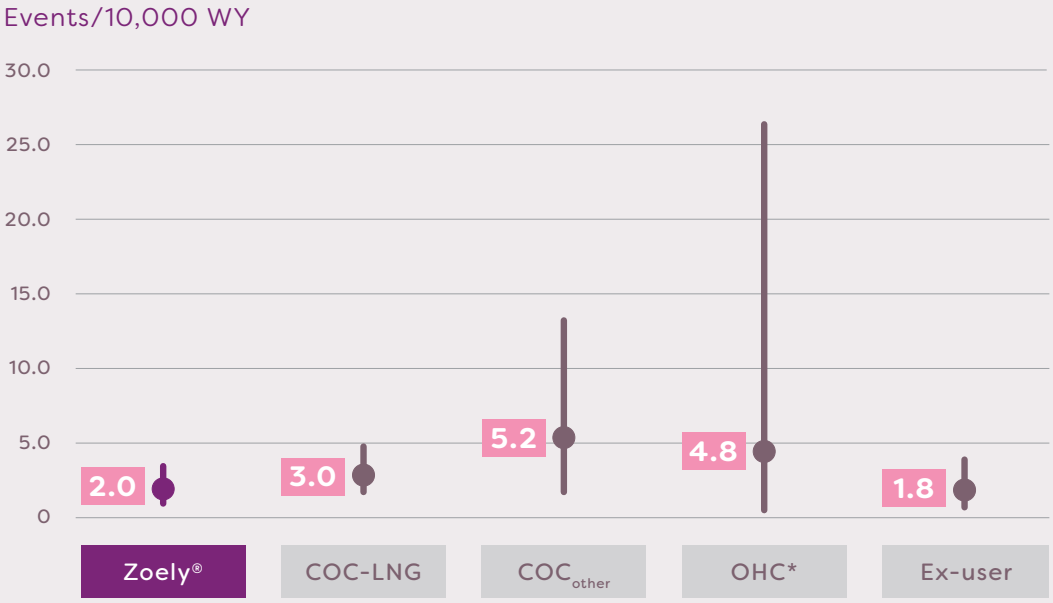
	Zoely®	COC-LNG
Number of users	44,559	46,754
Mean age (years ± SD)	31.0 ±8.63	29.3 ±8.53
Mean weight (kg ± SD)	63.3 ±11.67	63.1 ±12.15
Mean BMI (kg/m^2 ± SD)	23.2 ±4.07	23.3 ±4.25
BMI ≥ 30 (%)	6.3%	7.1%
Heavy smoker [>15 cigarettes/day] (%)	3.4%	3.0%
High blood pressure [treated] (%)	1.0%	0.8%
Family history of VTE (%)	2.5%	2.4%
Family history of ATE (%)	2.0%	1.8%

Zoely® users had a higher mean age than COC-LNG users ($p<0.0001$), but they were similar with regard to cardiovascular risk factors[1]

Overall, 63.5% of users were starters and 36.5% restarters[1]

Results

Zoely® was not associated with a higher risk of VTE compared with COC-LNGs[1]

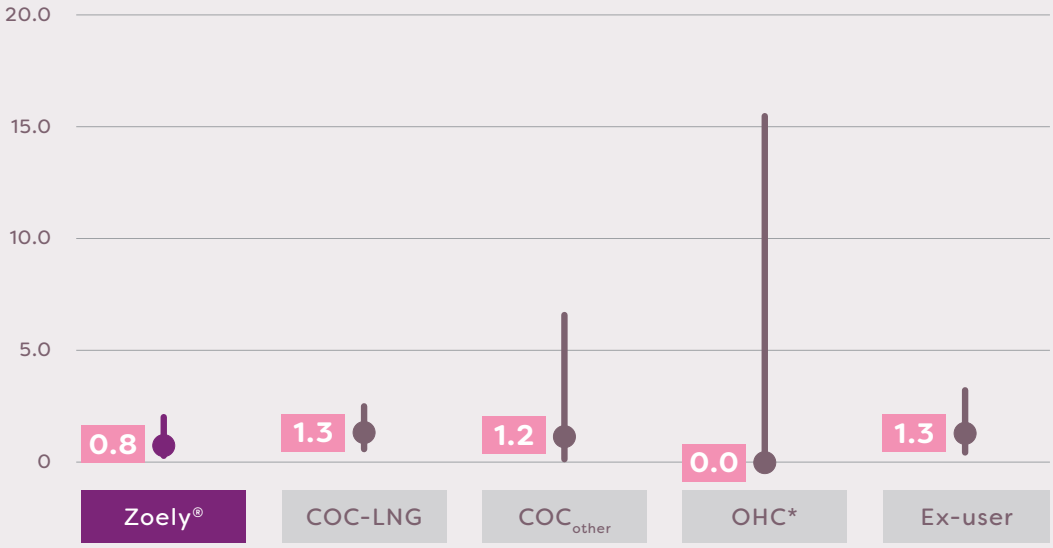


	Zoely®	COC-LNG	COC other	OHC*	Ex-user
n=	9	15	4	1	5
WY=	45,750	49,729	7,620	2,073	28,372

Zoely® vs COC-LNGs
HR: 0.59
95% CI: 0.25 - 1.35

(adjusted for age, BMI, current duration of HC use, family history of VTE)

Zoely® was not associated with a higher risk of ATE compared with COC-LNGs[1]



	Zoely®	COC-LNG	COC other	OHC*	Ex-user
n=	4	7	1	0	4
WY=	48,846	54,037	8,300	2,364	31,354

*OHC: other hormonal contraceptive

Conclusions

The PRO-E2 study has shown that the VTE and ATE risk associated with Zoely® use is no higher than with COC-LNG use[1]

The low risk observed in Zoely® users is not unexpected[1]

- previous studies have demonstrated that it has fewer adverse effects on coagulation and fibrinolysis parameters than COC-LNGs

These results for NOMAC containing Zoely® show that an assumption that all newer generation COCs will have a higher VTE risk than those containing LNG may not be valid[1]

Differences between the estrogen components (E2 vs EE) should also be considered when comparing the risk of VTE among COC users[1]

NOMAC
Nomegestrol acetate

Metabolically **NEUTRAL** without any androgenic, estrogenic or mineralo-glucocorticoid activities[8]

E2
17β-estradiol

NATURAL estrogen with identical structure to the one produced by women[8]

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. The occurrence of meningiomas (single and multiple) has been reported in association with use of nomegestrol acetate, especially at high doses and for prolonged use (several years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any nomegestrol acetate-containing treatment, must be stopped, as a precautionary measure. There is some evidence that the meningioma risk may decrease after treatment discontinuation of nomegestrol acetate. 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:** Zoely 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. **Pack Size and Cost:** 28, GMS reimbursable price €8.35. **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: November 2022.** Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu.

IE-ZOE-146

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

1. Reed S *et al.* Eur J Contracept Reprod Health Care 2021; 26(6): 439-46.
2. Practice Committee of the ASRM. Fertil Steril 2017; 107(1): 43-51.
3. European Medicines Agency. Available at: www.encepp.eu/encepp/viewResource.htm;jsessionid=Vkvfa8OriTVttmNTmv252UKpO_HvfmKH-ASfQnlCh8Qw3X9FRd-n!463752572?id=7157 Accessed on: 18.11.22.
4. European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/referral/benefits-combined-hormonal-contraceptives-chcs-continue-outweigh-risks_en.pdf Accessed on: 18.11.22.
5. de Bastos M *et al.* Cochrane Database Syst Rev 2014; (3): CD010813.
6. Del Savio MC *et al.* Expert Rev Clin Pharmacol 2020; 13(7): 685-94.
7. Chabbert-Buffet N *et al.* Gynecol Endocrinol 2013; 29(10): 891-6.
8. Zoely® Summary of Product Characteristics.

Abbreviations

ASRM: American Society for Reproductive Medicine
ATE: arterial thromboembolism
BMI: body mass index
CI: confidence interval
COC: combined oral contraceptive
COC-LNG: COC with levonorgestrel
E2: 17β-estradiol
EE: ethinylestradiol
EMA: European Medicines Agency
HC: hormonal contraceptive
HR: hazard ratio
OHC: other hormonal contraceptive
NOMAC: nomegestrol acetate
SD: standard deviation
VTE: venous thromboembolism
WY: women-years

IE-ZOE-61(1)
Date of preparation: November 2022

Consilient Health

Theramex
For Women, For Health