FINDINGS FROM THE PRO-E2 STUDY

PRO-E2

Largest combined oral contraceptive safety study yet conducted

Australian health professionals with an interest in women's health attended a livestream webinar with Obstetrician and Gynaecologist, A/Prof. Gino Pecoraro, who translated the findings of the post authorisation safety study, PRO-E2, to everyday clinical practice. Real-world evidence and ongoing safety monitoring are increasingly important to the decisions clinicians make for their patients on a daily basis. To access the presentation recording, please visit https://theramex.com.au/hcp-resources/#proe2 or scan

POST-AUTHORISATION SAFETY STUDY: PRO-E2

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Zoely® (NOMAC-E2) is unique in containing a fixed combined dose of nomegestrol acetate and 17β-estradiol which is taken for 24 days followed by 4 days of placebo. It is the only monophasic regimen combined oral contraceptive (COC) currently available combining 17β-estradiol, an oestrogen with an identical structure to the one naturally produced by women, with nomegestrol acetate, a highly selective progestogen derived from the naturally occurring hormone, progesterone.

The most relevant adverse clinical outcome linked to COC use is venous thromboembolism (VTE), specifically deep venous thrombosis of the lower extremities and pulmonary embolism, a serious but uncommon event. COCs that contain the progestogens levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of venous thromboembolism (VTE), both deep vein thrombosis (DVT) and pulmonary embolism (PE).[1,2] Studies have shown an association between the use of COCs containing ethinylestradiol and an increased risk of VTE.[1] As there were no large, prospective randomised studies comparing the risk of VTE with various doses of oestrogen and types of progestin, the European Medicines Agency which conditionally authorised Zoely® mandated a post-authorisation safety study. The results reflect real world practice in over 100 000 women from Australia, Europe and Latin America who were followed for up to 2 years.

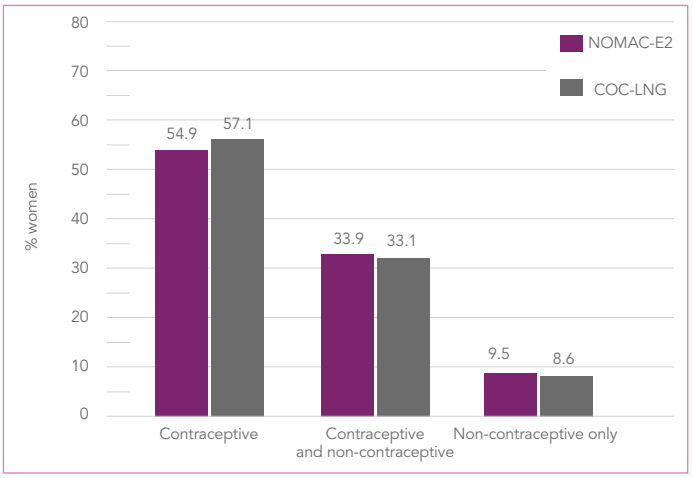
Study overview

PRO-E2 is a mandated safety study providing real-world evidence to inform real-world practice. It is a large, international, prospective, non-interventional, active surveillance, cohort study conducted in 12 countries in a study population representing actual oral contraceptive users. The study compares 101 498 women who were newly prescribed Zoely® or a levonorgestrel-containing combined oral contraceptive pill (COC-LNG) including women who restarted a COC after a break of at least 2 months.[3]

The majority of women in the study were first-time users of any COC and were taking the pill for contraceptive reasons: fewer than one in 10 participants reported non-contraceptive reasons as their only motivation for COC use, for example, bleeding-related issues and cycle control were common non-contraceptive reasons for use.

The study investigates the safety of NOMAC-E2 with respect to the main outcome, the risk of VTE (specifically DVT of the lower extremities and PE). The secondary outcomes were all VTE, arterial thromboembolisms, depressive disorders, cholelithiasis, inflammatory bowel disease, effect on fertility (contraceptive failure and return to fertility), pregnancy outcomes, weight change, hepatobiliary disorders and acne.[3]

Reasons for seeking an oral contraceptive



COC-LNG: levonorgestrel-containing combined oral contraceptive pill
NOMAC-E2: nomegestrol acetate combined with 17β-estradiol

Summary of study findings

- The PRO-E2 study was designed to reflect real-life clinical use of COCs; the generalisability of the results is high
  - There was no increase in the risk of DVT of the lower extremities and PE in the NOMAC-E2 cohort above that found in COC-LNG
  - Hazard ratio (HR) adjusted for age, BMI, current duration of COC use and family history of VTE was 0.59 (95% 0.25 – 1.35)
- NOMAC-E2 use is not associated with a higher risk of VTE compared with the use of other COCs
- NOMAC-E2 users are not at higher risk of serious adverse events depressive disorders, weight changes or acne changes compared to COC-LNG users
- The risk of unintended pregnancy was statistically significantly lower in those taking NOMAC-E2 compared to COC-LNG.

Study findings

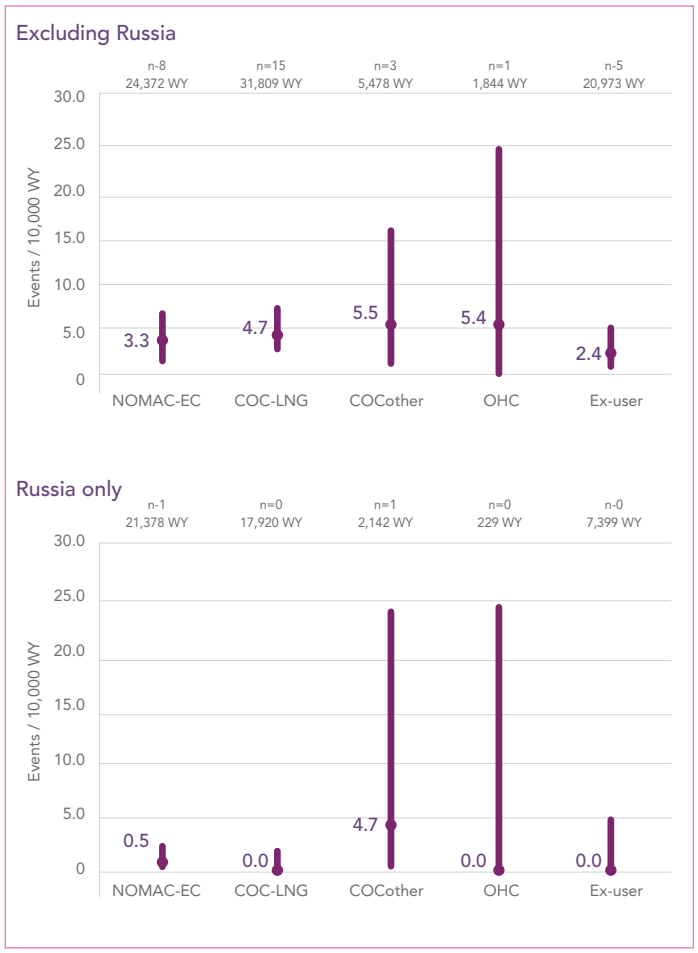
The PRO-E2 safety study of over 101 000 women conducted in 12 countries has confirmed that the risk of VTE (DVT of the lower extremities and PE) is at least as low with NOMAC-E2 (Zoely®) as with COC-LNG. The main outcome of the study was comparable in NOMAC-E2 users and in those taking a COC-LNG: there was no statistical difference between the two treatment groups. The lower VTE rate observed in this study compared to previously published data may have stemmed from the very low incidence rate reported in the Russian study participants: however, when excluding the Russian participants from the analysis, data show the incidence rate of VTE in the COC-LNG group (5.8 per 10 000 women years) close to the expected rate currently reported of 5-7 per 10 000 women years.[3]

The PRO-E2 study, which reflects the lived experience of women, confirms that NOMAC-E2 offers efficacy against unintended pregnancy. The study demonstrated a statistically significantly lower risk of unintended pregnancy compared with those taking a COC-LNG ($p < 0.0001$) and the lower rate of unintended pregnancy was more evident in women younger than 35 years of age.

These data allow women together with their clinicians to make informed decisions about their choice of contraception, and other added benefits such as improvement of acne and low impact on body weight.

A/Prof. Gino Pecoraro

All 14 secondary outcomes of the study were recorded, with the risk of depressive disorders or changes in weight or acne score with NOMAC-E2 use comparable to that of COC-LNG use. There was no evidence that NOMAC-E2 users were at higher risk of serious adverse events than COC-LNG users.



NOMAC: nomegestrol acetate; E2: 17βestradiol; COC: combined oral contraceptive; LNG: levonorgestrel; OHC: oral hormonal contraceptive; WY: woman years - a woman taking an oral contraceptive for one year; DVT: deep vein thrombosis; PE: pulmonary embolism

PRO-E2 study report available at:

http://www.encepp.eu/encepp/openAttachment/studyResult/41498

References

1. Theramex Australia Pty Ltd. Australian Product Information ZOELY. Date of revision: 19 March 2021. 2. van Hylckama Vlieg A, et al. BMJ 2009;339:b2921. 3. Reed S, et al. Eur J Contracept Reprod Health Care 2021;26:439-46.

Please review the Product Information before prescribing.

Full Product Information is available from Medical Information: 1800 THERAMEX (1800 843 726)

ZOELY® 2.5mg Nomegestrol acetate / 1.5mg estradiol (as hemihydrate).

INDICATION: Oral contraception. **CONTRAINDICATIONS**: Presence or risk of the following: venous thromboembolism (VTE); arterial thromboembolism (ATE); severe hepatic disease as long as liver function values have not returned to normal; liver tumours (benign or malignant); meningioma. History of migraine with focal neurological symptoms, pancreatitis or a history thereof if associated with severe hypertriglyceridaemia. Known or suspected: sex steroid-influenced malignancies (e.g., of the genital organs or the breasts); pregnancy; hypersensitivity to any of the active substances of ZOELY or to any of the excipients. **PRECAUTIONS**: A medical history/ examination prior to initiation. Exclude pregnancy before use. Medical check-ups during use. If any of conditions/risk factors below is present, benefits of the use of ZOELY should be weighed against possible risks and discussed before using ZOELY. Risk of VTE, risk of ATE, neoplasms, meningioma, hepatitis C, hypertriglyceridaemia, hypertension, jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham chorea; herpes gestationis; otosclerosis related hearing loss; (hereditary) angioedema, acute or chronic disturbances of liver function, diabetes, Crohn disease, chloasma and galactose intolerance. **INTERACTIONS**: Hepatic metabolism, antibiotics, others: ombitasvir/paritaprevir/ritonavir. **ADVERSE EVENTS**: Acne, abnormal withdrawal bleeding, decreased libido, depression, migraine, nausea, metrorrhagia, menorrhagia, breast pain, pelvic pain, weight increase, see PI for others. **DOSAGE**: One tablet daily at about the same time. Take with some liquid as needed, and in the order as directed on the package. Based on product information last amended 19 March 2021.

Theramex

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