As combined oral contraceptives (COCs) have been further developed over the past decades, their ethinylestradiol (EE) content has been reduced. However, reducing the EE dose also led to a less favourable control of bleeding.

Based on the lower impact of estradiol (E2) and estradiol valerate (EV) on the hepatic system and subsequently on haemostatic parameters compared to ethinyl estradiol it is assumed that E2 and E2V are associated with a similar or even lower risk of cardiovascular events, including venous (VTE) and arterial thromboembolism.

In 2012, an E2V-based COC was introduced to the market that appears to combine both reliable contraception and an acceptable bleeding profile.

This regimen consists of a dynamic dosing regimen with a 26-day active tablet phase followed by two placebos. Two tablets with 3mg EV, five tablets with 2mg DNG and 2mg EV, 17 tablets with 3mg DNG and 2mg EV, and two tablets with 1mg EV, and two placebos. The dynamic dosing regimen aims to ensure that sufficient oestrogen levels are available during the first half of the cycle in which endometrial proliferation is promoted under the influence of estradiol. Shortening the hormone-free interval from the conventional seven days to only two days and extending the oestrogen phase at the end of the progestogen phase are expected to be beneficial for cycle control, tolerability and effectiveness.

The INAS-SCORE study was conducted as a phase IV commitment to European regulatory authorities. The study design was transatlantic, prospective, noninterventional cohort study conducted in the US and seven European countries with three exposure groups: New users of DNG/EV, other oCOC users, and levonorgestrel-containing COC users. All self-reported clinical outcomes of interest (OoI) were validated via attending physicians and relevant source documents. The primary objective was to evaluate the serious cardiovascular events (SCE), particularly venous thromboembolic (VTEs) events. The secondary objectives were to evaluate effectiveness of oxilation prevention, as well as return to fertility after stopping contraception. Comprehensive follow-up procedures were implemented. Statistical analyses were based on Cox regression models. Real-world evidence is important to connect clinical trial data to routine clinical practice settings; it helps reflect priorities to ensure a well-rounded clinical development and market access plan that includes not only RCTs but also more pragmatic research in real clinical practice. These aspects are well recognised by the pharmaceutical industry, reflecting the need for a change in focus toward demonstrating the value of a new medicine in routine clinical practice settings.

Study design

The INAS-SCORE trial was a large, real-world study (also referred to as a real-life study) designed to fill this gap and provide real-world data comparing dienogest/estradiol valerate (DNG/EV) with other COCs in a representative population. The INAS-SCORE study was conducted as a phase IV commitment to European regulatory authorities and was funded with an unconditional grant from Bayer AG. A robust study of more than 50 000 new COC users was actively monitored for up to five years for the occurrence of rare or unexpected adverse outcomes possibly related to COC exposure.

The population of the INAS-SCORE study is representative of real-world clinical practice. It enrolled all consenting women who required a new prescription for a COC, and could be attributed to one of the following groups: Comprehensive data collection and quality control. Base line data were recorded via self-administered questionnaires:

1. Information was collected:
   - State of health
   - Medical history
   - Medication history
   - History of COC use
   - Potential prognostic factors for serious diseases, particularly cardiovascular disease.

To prevent loss to follow up, participants provided their addresses and phone numbers, as well as back-up contacts and contact information for their primary care physicians and/or gynaecologists.

Baseline questionnaires were completed in the physicians’ offices and checked by the physicians or their co-workers.

Follow-up assessments for each woman were scheduled every six months for the first two years and annually thereafter.

• Follow-up questionnaires addressed occurrence of adverse events
   - In particular serious adverse events
   - Cardiovascular events
   - Reasons for discontinuing OC use or for switching to another hormonal contraceptive were requested if applicable.

4. Questionnaires were collected in each country by local study teams
   • These teams reviewed the questionnaires for completeness, plausibility and consistency of responses.
   • Missing or inconsistent information was clarified with women by phone

5. In a second quality control step, the central study team at ZEG (Berlin)
Finding the right pill can take longer than finding the right man

For many women, finding the right pill can be a long journey. Qlaira® delivers a derivative of natural estradiol in unique combination with dienogest.1-3,4

Suitable for women 18-50 years of age,5 Qlaira® offers benefits beyond contraception:

- The shortest hormone free interval6 - improvement of HWaS including pelvic pain and headache6
- First oral contraceptive that delivers 17β-estradiol7
- Lowest impact on haemostatic markers and liver metabolism8,9
- Good cycle control, with short and light menstrual bleeding8,10
- Improved sexual functioning10

STRENGTHS OF THE STUDY
1. A large, international, real-world, prospective, comparative cohort study
2. Availability of important confounder information (e.g. BMI and family history of cardiovascular outcomes)
3. Validation of outcomes of interest and exposure of relevant cases
4. Comprehensive follow-up procedure and very low loss to follow-up
5. Independent blinded adjudication of critical outcomes
6. Relevant statistical analyses
7. Study population with baseline characteristics similar to OC users under routine clinical conditions
8. Reproducibility of typical time pattern of VTE risk
9. Supervision by an independent Safety Monitoring and Advisory Council
10. Scientific independence from study funder.

WEAKNESSES OF THE STUDY
1. Observational studies are associated with a potential for bias, and residual confounding can never be entirely eliminated - therefore the ability to infer causation is limited.
2. Risk estimates close to unity may not allow differentiation between causation, bias and confounding.

HOW CAN THE METHODOLOGY FROM THE INAS-Score STUDY HELP INFORM CLINICAL PRACTICE?
1. The INAS-Score study provides comparative data showing the short- and long-term cardiovascular risks associated with COCs in a real-world setting.
2. The real-world nature of this study means clinicians can be confident that these data reflect routine clinical practice, adding important information to that derived from clinical studies

RESULTS
To date, there were no studies available investigating the cardiovascular safety of combined oral contraceptives not containing ethinylestradiol.

PRIMARY OBJECTIVE
To assess cardiovascular risks of short- and long-term use of DNG/EV and of other COCs in a study population that is representative of actual users of individual preparations. The following outcomes were assessed:

- Venous thromboembolism e.g. (deep venous thrombosis & pulmonary embolism)
- Arterial thromboembolism (acute myocardial infarction and cerebrovascular accidents).

All other serious cardiovascular events were also analysed.

In a real-world study, the treatment cohorts are usually not comparable due to selected prescribing based on patient characteristics. Therefore, the cohorts need to be adjusted for potential risk factors at baseline to allow a valid comparison (compare like with like). The hazard ratios without adjustments are called ‘crude hazard ratios’, those with these adjustments are called ‘adjusted hazard ratios. In total, 47 venous thrombotic events (European study population) were confirmed in the study. The risk seen in the primary data set, as defined by the European Medicines Agency (EMA), found no indication that there was an increased risk of dienogest/estradiol valerate compared to other COCs (combined oral contraceptives) or to levonorgestrel-containing combined oral contraceptives. In contrast, a decrease in risk was found, which was statistically significant when compared to all other combined oral contraceptives. Also, when the venous thromboembolic risk of dienogest/estradiol valerate was compared to levonorgestrel-containing COCs, a decrease in risk was found, which was not statistically significant. Arterial events were also investigated in our study. Lower incidences of arterial events in the dienogest/estradiol valerate group was found when compared to levonorgestrel-containing COCs.
compared to other combined oral contraceptives, including the direct comparison of dienogest/estradiol valerate to levonorgestrel-containing COCs. Based on the data from this very large and robust dataset, it can be stated that the cardiovascular risk of dienogest/estradiol valerate is similar if not even lower compared to other combined oral contraceptives, including levonorgestrel-containing oral contraceptives.

Results: Contraceptive effectiveness

As a secondary objective the INAS-SCORE study also investigated the effectiveness of dienogest/estradiol valerate on ovulation inhibition, and return to fertility compared to other combined oral contraceptives under routine clinical practice. Based on the primary dataset, as defined by the European Medicines Agency (EMA), it was found that all combined oral contraceptives are efficacious. However, the contraceptive effectiveness of dienogest/estradiol valerate seems to be even better than other combined oral contraceptives, including levonorgestrel-containing combined oral contraceptives.

The results found a reduction of contraceptive failure compared to levonorgestrel-containing COCs (combined oral contraceptives) of almost two, which was also statistically significant. When compared to all other COCs, a borderline statistically significant decrease in contraceptive failure was found. In summary dienogest/estradiol valerate is at least as efficacious as other combined oral contraceptives on the market.

RETURN TO FERTILITY

Barnett et al. (2016) sought to estimate the real-use contraceptive effectiveness of the DNG/EV combined oral contraceptive compared to others were slightly lower compared to other COCs. This was to be expected due to the different age profiles of the cohorts and because fecundity decreases with age.

Crude pregnancy rates for DNG/EV users overall was slightly lower compared to other COC cohorts. This difference disappeared after age-adjustment. Accordingly, no difference was seen when analysis was limited to women aged 25-34 years. Likewise, no significant difference in pregnancy rates was seen between contraceptive types when results were stratified for parity.

CARDIOVASCULAR OUTCOMES AND SAFETY

The incidence rates for VTE, ATE and serious cardiovascular events were lower for DNG/E2V compared to oCOC and LNG. The primary statistical analysis (European data set) of these outcomes yielded HR adj of 0.4 for VTE and 0.6 for serious cardiovascular events for the comparison of DNG/EV vs oCOC.

The primary analysis was based on the European population. The European regulatory authorities requested that an additional analyses be based on the European cohort alone (primary analysis), since uptake of DNG/EV was low in the US. To compensate, follow up in Europe was extended.

Incidence rate for confirmed VTE was observed with DNG/EV compared to LNG-containing COCs or other COCs.

Incidence rate for ATE was lower for DNG/EV compared to other COCs, including LNG-containing COCs.

CONCLUSIONS

The INAS-SCORE study provides comparative data showing the short- and long-term cardiovascular risks associated with COCs in a real-world setting. The real-world nature of this study means clinicians can be confident that these data reflect routine clinical practice, adding important information to that derived from clinical studies.

The INAS-SCORE study tells us that:

• COCs have excellent contraceptive effectiveness with typical use.
• DNG/EV is associated with a similar or even lower risk of contraceptive failure compared to oCOC or LNG-containing COCs (European cohort).
• Pregnancy rates after cessation of COC use with the intention of becoming pregnant are high.

The study results tell us that a COC containing DNG/EV is associated with a similar or even lower cardiovascular risk compared to LNG-containing COCs in routine clinical practice.

REFERENCES

