A new monophasic combined oral contraceptive (COC) has been developed containing nomegestrol acetate (NOMAC) and the naturally occurring estrogen 17β-estradiol (E2). NOMAC/E2 was approved by the European Medicines Agency in 2011.

NOMAC/E2 provides robust contraceptive efficacy and is associated with shorter and lighter withdrawal bleeding episodes compared with an established COC containing drospirenone/ethinyl estradiol (DROSPE).1

The objective of this study (www.ClinicalTrials.gov identifier: NCT00779332) was to investigate the effect of multiple oral doses of NOMAC/E2 on the QTcF interval.

The study was designed to investigate whether once-daily multiple therapeutic and supra-therapeutic doses of NOMAC/E2 prolong the mean QTcF interval in ECG recordings at steady-state conditions of NOMAC/E2 compared with placebo.

**STUDY DESIGN AND POPULATION**

This was a randomised, double-blind, double-dummy, parallel-group trial comparing 2.5/1.5 mg of NOMAC/E2 (therapeutic dose), 12.5/7.5 mg of NOMAC/E2 (supra-therapeutic dose) placebo; and moxifloxacin 400 mg.

Moxifloxacin is known to prolong the QTc interval and was included in this trial as a positive control.

The study was conducted between May and October 2008.

Healthy women aged 18–50 years at the day of the first pill intake were randomised to the four treatment groups.

Study medication was administered from Day -1 to 14.

Moxifloxacin was administered double-dummy with placebo on Day 14 after placebo dosing on Day -1 to 13 (Figure 1).

The primary variable for the NOMAC/E2 comparison with placebo was the time-matched QTcF interval from baseline at time point 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 23.5 h after dosing on Day 14.

Triplicate intervals were extracted from the continuous 12-lead ECG recordings at these timepoints.

**STATISTICAL ANALYSIS**

For the primary variable, per time point, an analysis of covariance (ANCOVA) was conducted with treatment as fixed effect and baseline QTcF interval at time point t as covariate.

This analysis was conducted for all randomised subjects who received at least one dose of study medication, had no major protocol violation and for whom at least one QTcF interval was available.

A safety analysis was also conducted for all randomised subjects who received at least one dose of study medication.

**RESULTS**

**STUDY POPULATION**

189 women were randomised to 1 of the 4 treatment groups:

- NOMAC/E2 2.5/1.5 mg, n = 42; NOMAC/E2 12.5/7.5 mg, n = 42; moxifloxacin, n = 42; placebo, n = 63 (Figure 2).

The mean ± SD age of the total study population at screening was 34.7±9.0 years; the mean (± SD) systolic/diastolic blood pressure was 103.5±6.7/65.2±7.3 mm Hg; and the mean (± SD) body mass index was 23.2±2.7 kg/m².

**TIME-MATCHED QTcF DIFFERENCES**

The largest time-matched QTcF differences compared with placebo were 1.6 ms for the therapeutic dose (2.5/1.5 mg) and 3.1 ms for the supra-therapeutic dose (12.5/7.5 mg) (Table 2), with estimated time-matched mean QTcF differences to placebo below 5 ms for each time point (Figure 3).

The upper limit of the one-sided 95% confidence interval for the time-matched QTcF difference compared with placebo for both therapeutic and supra-therapeutic doses were below the 10 ms threshold of regulatory concern defined in the ICH-E14 guideline for all time points (Figure 3).

For the moxifloxacin group, assay sensitivity was demonstrated (based on six time points) the maximum mean QTcF prolongation was 19.1 ms, with a lower limit of the one-sided 95% confidence interval of 15.2 ms (Table 2).

**CONCLUSIONS**

This thorough QTcF study showed that NOMAC/E2 was not associated with clinically relevant QTc interval prolongation in healthy women, even after dosing at five times the therapeutic dose.

NOMAC/E2 was well tolerated, both at the therapeutic dose and at five times the therapeutic dose.

**ACKNOWLEDGMENTS**

This study was funded by Merck & Schöna, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA. Medical writing and editorial assistance was provided by Rona Hitchcox, PhD, of Evidence Scientific Solutions, London, UK. This assistance was funded by Merck & Co., Inc., Whitehouse Station, NJ, USA.

**REFERENCES**