A Randomised, Double-Blind, Placebo- and Positive-Controlled, Parallel-Group Trial to Investigate the Effect of Multiple Oral Doses of NOMAC/E2 on QTcF Intervals in Healthy Women

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INTRODUCTION

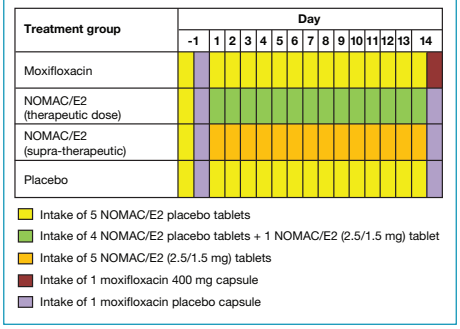
- A new monophasic combined oral contraceptive (COC) has been developed containing nomegestrol acetate (NOMAC) and the naturally occurring estrogen 17β-estradiol (E2).
  - NOMAC/E2 was approved by the European Medicines Agency in 2011.
- NOMAC/E2 provides robust contraceptive efficacy and is associated with shorter and lighter withdrawal bleeding episodes compared with an established COC containing drospirenone/ethinyl-estradiol (DRSP/EE).[1,2]
- Female sex hormones may affect ventricular repolarisation.[3]
- The objective of this study (www.ClinicalTrials.gov identifier: NCT00779532) was to investigate the effect of multiple oral doses of NOMAC/E2 on the QT/QTc interval.
  - The primary parameter was the Fridericia-corrected QT (QTcF) interval of the electrocardiogram (ECG).
  - Prolongation of the QT/QTc interval (defined as the interval between the start of cardiac ventricular depolarisation and the end of ventricular repolarisation) on ECG recordings is commonly used as a measure of the potential for a drug to induce cardiac arrhythmias, such as torsades de pointes (TdP).
- 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 concentrations of NOMAC/E2 compared with placebo.

MATERIALS AND METHODS

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 used 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 dosing 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**).

Figure 1. Clinical trial design.



- The primary variable for the NOMAC/E2 comparison with placebo was the time-matched change in the QTcF interval from baseline at time points 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

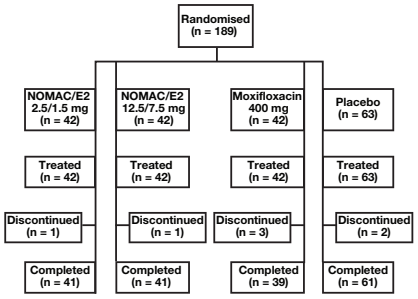
- For the primary variable, per time point *t*, an analysis of covariance (ANCOVA) was conducted with treatment as fixed effect and baseline QTcF interval at time point *t* as covariable.
  - This analysis was conducted for all randomised subjects who received at least one dose of study medication, had no major protocol violation and for whom at least one QT 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 measurements were 106.2±9.2/67.2±8.4 mm Hg (**Table 1**).

Figure 2. Flow chart of study participants.



E2, 17β-estradiol; NOMAC, nomegestrol acetate

Table 1. Demographic data at screening.

	NOMAC/E2 2.5/1.5 mg (n = 42)	NOMAC/E2 12.5/7.5 mg (n = 42)	Moxifloxacin (n = 42)	Placebo (n = 63)	Total (n = 189)
Age, years, mean (± SD)	34.3±8.5	36.4±9.1	33.3±9.2	34.9±9.1	34.7±9.0
Race, n (%)					
White	42 (100)	42 (100)	40 (95.2)	60 (95.2)	184 (97.4)
Black/African American	–	–	–	1 (1.6)	1 (0.5)
Asian	–	–	1 (2.4)	1 (1.6)	2 (1.1)
Other	–	–	1 (2.4)	1 (1.6)	2 (1.1)
Body mass index, kg/m², mean (± SD)	23.2±2.7	23.8±2.8	22.4±2.5	23.9±3.0	23.4±2.8
Systolic BP, mm Hg, mean (± SD)	103.5±6.7	107.6±11.3	107.2±8.8	106.3±9.2	106.2±9.2
Diastolic BP, mm Hg, mean (± SD)	65.2±7.3	67.0±9.3	67.8±7.9	68.4±8.5	67.2±8.4
Heart rate, bpm, mean (± SD)	59.4±7.2	62.7±9.9	64.2±10.0	61.5±8.7	61.9±9.1

BP, blood pressure; E2, 17β-estradiol; NOMAC, nomegestrol acetate

TIME-MATCHED QTCF DIFFERENCES

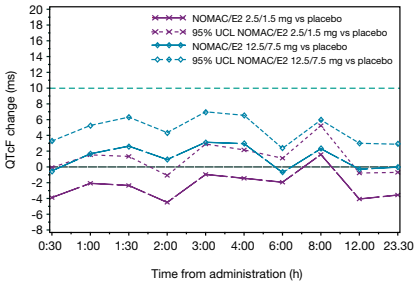
- The largest time-matched QTcF differences compared with placebo were 1.6 ms for the therapeutic dose (2.5/1.5 mg); and 3.1 ms for the supra-therapeutic dose (12.5/7.5 mg) (**Table 2**), with estimated time-matched mean QTcF differences to placebo below 5 ms for each time point (**Figure 3**).
- The 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[4] 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**).

Table 2. Largest time-matched difference to placebo for the time-matched QTcF change with corresponding one-sided 95% confidence limit by treatment group.

	NOMAC/E2 2.5/1.5 mg (n = 41)	NOMAC/E2 12.5/7.5 mg (n = 41)	Moxifloxacin (n=37)
Time after dosing for largest mean difference (h)	8	3	3
Largest difference to placebo for the time-matched QTcF change (ms)	1.6	3.1	19.1
One-sided 95% upper confidence limit (ms)	5.2	7.0	15.2[a]

[a]One-sided 95% lower confidence limit (ms)

Figure 3. Estimated mean difference to placebo for the time-matched QTcF change with corresponding one-sided 95% upper confidence limit by treatment group.



The green dotted line represents the 10 ms threshold of regulatory concern defined in the ICH-E14 guideline.[4]
E2, 17β-estradiol; NOMAC, nomegestrol acetate; QTcF, Fridericia-corrected QT interval; UCL, upper confidence limit

ADVERSE EVENTS

- The incidence of adverse events (AEs) was comparable between treatment groups, with headache (10.6%), breast discomfort (7.9%), acne (5.8%) and lower abdominal pain (5.3%) being most frequently reported as drug-related AEs in the total population (**Table 3**).
- There were slight increases in breast discomfort (16.7% vs 7.1%), lower abdominal pain (7.1% vs 0.0%) and mood swings (7.1% vs 0.0%) in women receiving the supra-therapeutic dose of NOMAC/E2 compared with those receiving the therapeutic dose (**Table 3**).
- The incidence of acne, lower abdominal pain and increased appetite in women receiving five times the therapeutic dose were similar or lower compared with those in the placebo group (acne, 4.8% vs 6.3%; lower abdominal pain, 7.1% vs 7.9%; increased appetite, 2.4% vs 1.6%; **Table 3**).
- None of the women experienced events that were part of the standardised MedDRA query 'Torsade de pointes'/ QT prolongation' (broad and narrow definition).
- There were no subjects with clinically significant abnormal safety ECG results.
- Moreover, no clinically significant vital signs values were observed and there were no remarkable differences between treatment groups in the mean and median vital signs values.
- None of the AEs were of severe intensity and none of the women experienced a serious AE.

Table 3. Number (%) of subjects with at least one AE starting during the in-treatment period (with incidence of >5% in at least one treatment group), by MedDRA preferred term, treatment group and relationship to study drug.

Adverse event	NOMAC/E2 2.5/1.5 mg (n = 42)		NOMAC/E2 12.5/7.5 mg (n = 42)		Moxifloxacin (n = 42)		Placebo (n = 63)		Total (n = 189)	
	Related n (%)	Total n (%)	Related n (%)	Total n (%)	Related n (%)	Total n (%)	Related n (%)	Total n (%)	Related n (%)	Total n (%)
Headache	3 (7.1)	3 (7.1)	3 (7.1)	5 (11.9)	7 (16.7)	7 (16.7)	7 (11.1)	8 (12.7)	20 (10.6)	23 (12.2)
Breast discomfort	3 (7.1)	3 (7.1)	7 (16.7)	7 (16.7)	1 (2.4)	1 (2.4)	4 (6.3)	4 (6.3)	15 (7.9)	15 (7.9)
Acne	4 (9.5)	4 (9.5)	2 (4.8)	2 (4.8)	1 (2.4)	1 (2.4)	4 (6.3)	4 (6.3)	11 (5.8)	11 (5.8)
Abdominal pain, lower	0 (0.0)	0 (0.0)	3 (7.1)	3 (7.1)	2 (4.8)	2 (4.8)	5 (7.9)	5 (7.9)	10 (5.3)	10 (5.3)
Increased appetite	3 (7.1)	3 (7.1)	1 (2.4)	1 (2.4)	4 (9.5)	4 (9.5)	1 (1.6)	1 (1.6)	9 (4.8)	9 (4.8)
Pelvic pain	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.4)	0 (0.0)	0 (0.0)	6 (9.5)	6 (9.5)	7 (3.7)	7 (3.7)
Fatigue	2 (4.8)	3 (7.1)	1 (2.4)	1 (2.4)	0 (0.0)	1 (2.4)	3 (4.8)	3 (4.8)	6 (3.2)	8 (4.2)
Mood swings	0 (0.0)	0 (0.0)	3 (7.1)	3 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.6)	3 (1.6)
Nausea	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0 (0.0)	5 (11.9)	0 (0.0)	1 (1.6)	2 (1.1)	8 (4.2)
Leukocyturia	0 (0.0)	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.1)	0 (0.0)	2 (3.2)	0 (0.0)	7 (3.7)
Naso-pharyngitis	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.1)	0 (0.0)	3 (4.8)	0 (0.0)	7 (3.7)

CONCLUSIONS

- This thorough QT/QTc 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.

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