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Effect of mavoglurant (AFQ056) on the pharmacokinetics of a combined oral contraceptive containing ethinyl estradiol and levonorgestrel in healthy women

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Introduction

- Mavoglurant (AFQ056) is a structurally novel, selective metabotropic glutamate receptor 5 antagonist currently under clinical development. It is expected to normalise excessive glutamatergic signalling that is believed to be associated with a variety of neurological and psychiatric diseases[1]
- Mavoglurant is metabolised by multiple cytochrome P450 (CYP) enzymes including CYP1A1, CYP2C9, CYP2C19 and CYP3A4 and is not a strong inhibitor or inducer of drug metabolising enzymes or transporters
- Given the early stage of clinical development, treatment with mavoglurant currently requires the use of contraceptive measures in women of childbearing potential
- Contraception may additionally be required as a consequence of other medicines used concomitantly in the envisioned target patient populations, e.g. anti-depressants, neuroleptics and anti-epileptics, some of which exhibit teratogenic potential[2]
- This study investigated the effect of concomitant administration of mavoglurant on the single-dose pharmacokinetics (PKs) of a commonly used low-dose combination oral contraceptive (OC) containing ethinyl estradiol (EE) and levonorgestrel (LNG)

Methods

Study design

- This was a phase I, open-label, two-period, fixed-sequence, drug–drug interaction study[2,3] (**Figure 1**)

Figure 1. Study design

Combination OC was administered as a single dose of EE 30 µg/LNG 150 µg. Mavoglurant was administered at a clinically relevant multiple dose of 100 mg b.i.d. In the context of a study protocol amendment, an up-titration with a starting dose of mavoglurant 25 mg b.i.d. and daily increment of 25 mg was implemented aimed at improving the tolerability of mavoglurant in this population of young female participants.
EE, ethinyl estradiol; LNG, levonorgestrel; OC, oral contraceptive.

Study population

- A total of 30 healthy, non-smoking women aged 18–40 years with body mass index (BMI) of 18–30 kg/m^2 and body weight of ≥50 kg were enrolled
- Participants were required to use double-barrier methods of contraception until study completion and not to use any OC for at least 28 days prior to first dosing
- Key exclusion criteria were the use of concomitant medications within 4 weeks before the first dosing until study completion or any relevant disease history of any major system organ class

Bioanalytical methods

- A validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method was used for quantification of mavoglurant and EE/LNG in plasma[3,4]

PK parameters

- C_{max}, t_{max} and AUC_{last}
- PK parameters were derived by non-compartmental analysis method using WinNonlin Pro® version 5.2 (Pharsight Corporation, Mountain View, CA, USA) software

Statistical analysis

- C_{max} and AUC_{last} of EE and LNG were analysed separately on the logarithmic scale using a mixed effect model adjusted for treatment as fixed effect and for participants as a random effect
- Estimates were back-transformed to the original scale and the geometric mean treatment ratios (OC+mavoglurant/OC alone) were reported along with their 90% confidence intervals (CIs)

Safety assessments

- Safety and tolerability of the study medications were assessed by adverse event (AE) monitoring, assessment of vital signs, ECG and laboratory data

Results

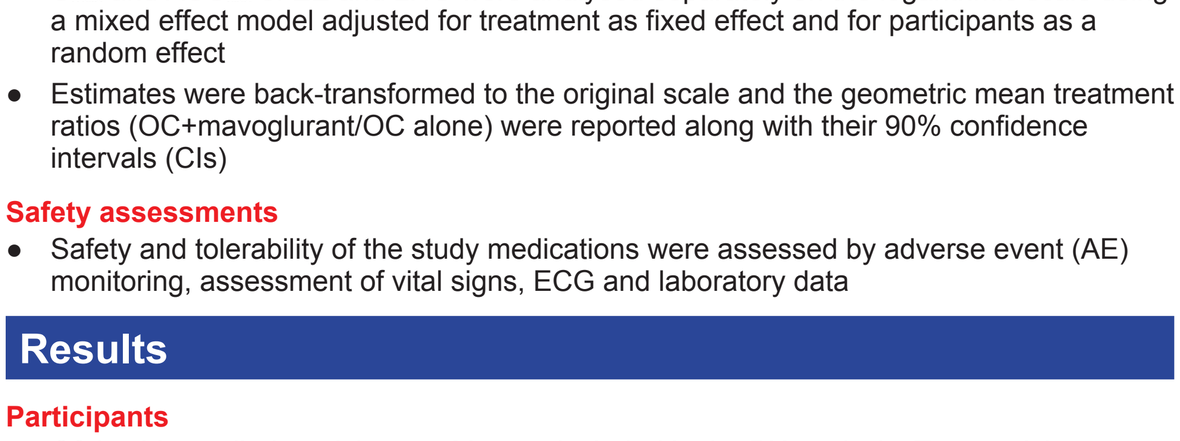
Participants

- Of the 30 enrolled participants, 28 were included in the PK analysis. Two participants were excluded from PK analysis, one due to a protocol deviation (pregnancy reported) and the other withdrawn consent for personal reasons. All the enrolled participants were included in the safety data analysis
- The study population was predominantly Caucasian (n=24; 80%), with a mean (±standard deviation [SD]) age of 24.2 (±4.5) years, a mean BMI of 23.1 (range: 19.2–29.2) kg/m^2 and a mean (±SD) bodyweight of 66.5 (±10.5) kg

Plasma pharmacokinetics

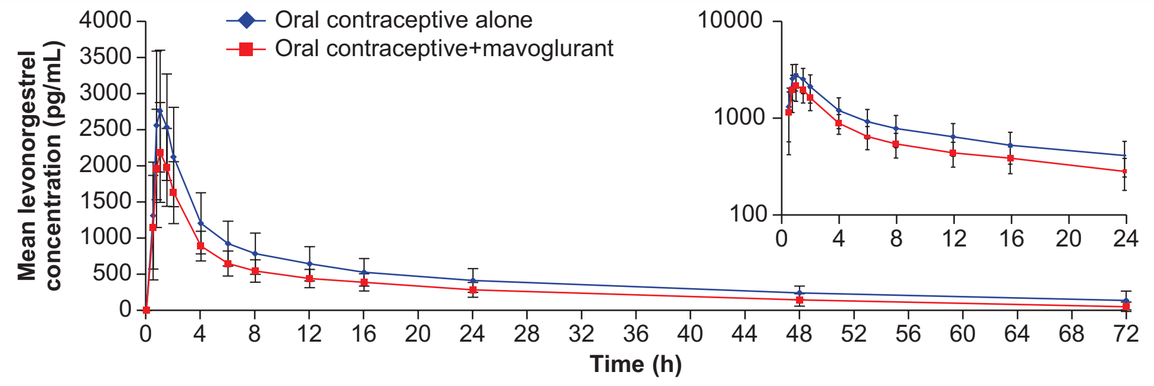
- Mean plasma concentration-time curves for EE and LNG following single oral dose administration of OC alone or with mavoglurant 100 mg b.i.d. are illustrated in **Figures 2** and **3**, respectively

Figure 2. Plasma concentration-time profile of ethinyl estradiol when oral contraceptive was administered alone or with mavoglurant



Data is displayed as arithmetic mean±SD.
SD, standard deviation.

Figure 3. Plasma concentration-time profile of levonorgestrel when oral contraceptive was administered alone or with mavoglurant



Data is displayed as arithmetic mean±SD.
SD, standard deviation.

- The adjusted geometric mean ratio of LNG when OC given in combination with mavoglurant versus OC given alone was 0.81 (90% CI, 0.75–0.87) and 0.68 (90% CI, 0.63–0.73) for C_{max} and AUC_{last}, respectively. Therefore, a significantly lower LNG exposure was observed when administered concomitantly with mavoglurant **(Table 1)**
- The adjusted geometric mean ratio of EE C_{max} and AUC_{last} were entirely contained within the bioequivalence range of 0.80–1.25 (as defined in the FDA Drug Interaction Guidance). Hence, there was no effect of mavoglurant on EE pharmacokinetics **(Table 1)**

Table 1. Pharmacokinetic parameters for ethinyl estradiol and levonorgestrel following single oral dose administration of oral contraceptive alone or with mavoglurant

Analyte	Treatment	C_{max}, pg/mL	AUC_{last}, h×pg/mL	t_{max}, h[a]
EE	OC alone[b]	68±23.6 (34.8%) n=28	506±194 (38.4%) n=28	1 (0.75–2.00) n=28
	OC+mavoglurant	63.1±18.7 (29.7%) n=24	450±116 (25.8%) n=24	1.5 (0.52–2.02) n=24
	GMR (90% CI)	0.97 (0.90–1.06)	0.94 (0.86–1.03)	-
LNG	OC alone[b]	2940±913 (31.1%) n=27	31200±10800 (34.7%) n=27	1 (0.75–2.00) n=27
	OC+mavoglurant	2340±690 (29.5%) n=24	20800±7630 (36.6%) n=24	1 (0.50–2.02) n=24
	GMR (90% CI)	0.81 (0.75–0.87)	0.68 (0.63–0.73)	-

[a]t_{max} reported as median (minimum, maximum).
[b]n is different for EE and LNG, as one participant was excluded from LNG PK data estimations in Period 1 because the pre-dose concentrations were >5% C_{max} for this participant.
Data is presented as arithmetic mean±SD (CV%) unless specified otherwise. PK analysis was performed for all participants who completed at least one treatment.
AUC_{last}, area under the plasma concentration-time curve from time 0. to the time of the last measurable concentration; C_{max}, maximum plasma concentration; CI, confidence interval; CV, coefficient of variance; EE, ethinyl estradiol; GMR, estimated geometric mean ratio; h, hour; LNG, levonorgestrel; OC, oral contraceptive; SD, standard deviation; t_{max}, time to reach C_{max}.

Safety and tolerability

- There were no serious or severe AEs reported and there were no clinically significant abnormalities of haematological, clinical chemistry, urinalysis, ECG or vital sign data
- The most commonly reported AEs belonged to the system organ class of psychiatric and nervous system disorders and included mild to moderate dizziness, hallucinations and headache. These AEs spontaneously resolved, usually within a few hours of onset, and did not require any pharmacological intervention

Discussion

- The key finding of this study was a lower exposure of LNG, when given concomitantly with mavoglurant, whereas EE exposure remained unchanged. Such a selective reduction of LNG exposure is unexpected given that both LNG and EE are primarily metabolized by CYP3A4 making a disproportionate induction unlikely. However, it has also previously been reported upon concomitant administration of other drugs such as lamotrigine, efavirenz or felbamate[5-7]
- It has been hypothesised that the finding could be due to a modulation of protein binding given that LNG is known to exhibit stronger binding than EE to certain proteins such as sex-hormone binding globulin (SHBG).[8] However, we could not identify any relevant impact of mavoglurant on the degree of LNG binding to SHBG (Novartis, data on file)

Conclusions

- In summary, EE PK was unchanged, whereas C_{max} and AUC_{last} of LNG were 19% and 32% lower when administered with mavoglurant
- The impact of the reduced LNG exposure on the efficacy of the combination OC in preventing ovulation cannot be judged on the basis of this PK study alone. Further clinical investigation is warranted regarding the impact of this finding on contraceptive efficacy

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Disclosures

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