P.0904

Results of a Phase 1 Trial Investigating the Effect of Cariprazine on the Pharmacokinetics of a Combined Oral Contraceptive

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INTRODUCTION

Cariprazine (CAR) is an orally active potent antipsychotic (AP) approved by the European Medicines Agency (EMA) for the treatment of schizophrenia in adults. (1) Cytochrome P450 CYP3A4 and, to a lesser extent, CYP2D6 are the 2 major enzymes involved in the metabolism of CAR and its metabolites. (1) Oral contraceptives (OC) are believed to be prominent CYP3A4 substrates (2-3); thus, a CYP3A4 inducer could potentially lead to a loss of efficacy, while an inhibitor would have increased side effects but would not jeopardise the contraceptive effect. To support the hypothesis that CAR has no meaningful effect on the pharmacokinetics (PK) of an OC and that OCs can still be considered an adequate method of contraception during CAR treatment, a drug-drug interaction clinical trial was deemed necessary.

STUDY OBJECTIVE

The aim of this study was to assess the effect of CAR on the PK of a combined oral contraceptive (COC) containing ethinylestradiol (EE) and levonorgestrel (LNG).

METHODS

The study consisted of two periods: Treatment Period A (Day 1 – Day 3), when a single dose of COC (30 µg EE and 150 µg LNG) alone was administered on Day 1; Treatment Period B (Day 4 -Day 48) when patients received ascending doses of CAR reaching the target dose of 6.0 mg/day in the morning on Day 7, which continued until Day 34. On Day 31, patients again received a single dose of COC (30 µg EE and 150 µg LNG).

In total, 23 and 24 premenopausal female patients with schizophrenia (aged ≥ 18 and ≤ 50 years, with body mass index 18 kg/m2 ≤ BMI < 30.0 kg/m2 with a bodyweight ≥ 40 kg) were included in the PK and safety analyses, respectively. Plasma samples were analysed for PK parameters of CAR and its metabolites desmethyl-CAR (DCAR) and didesmethyl-CAR (DDCAR), as well as for EE, and LNG, using validated HPLC-MS/MS methods. (**Table 1.)** Furthermore, safety parameters, ie., treatment-emergent adverse events (TEAE), serious adverse events (SAE), pre-treatment adverse event (PTAE), adverse event of special interest (AESI), ending treatment (ET) were also assessed.

Table 1. Summary of the applied methods

Analytical Method		
	CAR, DCAR, DDCAR	**EE, LNG**
Sample preparation	Liquid-liquid extraction after alkalization	1. Liquid-liquid extraction 2. Derivatization 3. Liquid-liquid extraction
Sample volume required	200 µL plasma	500 µL plasma
Calibration range	0.1 – 50 ng/mL for CAR 0.2 – 100 ng/mL for DCAR and DDCAR	2 – 200 pg/mL for EE 40 – 10000 pg/mL for LNG
Internal standards	Deuterated compounds	
Instrument	LC-MS/MS	
Ionization	+ESI with MRM mode	
Pharmacokinetic evaluation		
PK analysis method	Non-compartmental analysis	
Software	Phoenix WinNonlin® version 8.2	

RESULTS

Steady-state has been reached by Day 17 for CAR and DCAR, and the DDCAR concentrations on Day 31-34 were close to the steady-state levels. The measured pre-dose values reached or even exceeded the C_{min} values observed at the maximal recommended daily dose in the pivotal clinical studies, where the PopPK predicted values were 9.4 ng/mL, 2.8 ng/mL and 26.2 ng/mL for CAR, DCAR and DDCAR, respectively. (4) **(Figure 1)** C_{max} for EE showed a 14% decrease in the presence of CAR, with only a small departure from the 90% confidence interval of the geometric mean ratio (90% CI: 77.09 - 96.81) from the bioequivalence range of 80% to 125%. The 90% CIs were within the no-effect boundaries for AUC_{0-t} and AUC_{inf} of EE, as well as for all exposure parameter ratios of LNG**. (Table 2)**

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CONCLUSIONS

The exposure to CAR was adequately high for the drug-drug interaction assessment. CAR coadministration resulted in only a marginal decrease in EE maximum plasma concentration, which is not considered to be clinically relevant. The systemic exposure ratio in terms of AUC was within the no-effect boundaries of 80 to 125% both for EE or LNG, and no pertinent changes of t1/2 or Tmax values of EE and LNG were observed. Therefore, no significant DDI is considered to be present, and COC can be regarded as an adequate method of contraception even if administered in combination with CAR.

Figure 1. Mean Pre-Dose Plasma Concentrations of CAR and its Metabolites after Multiple Oral Administration; PK Analysis population

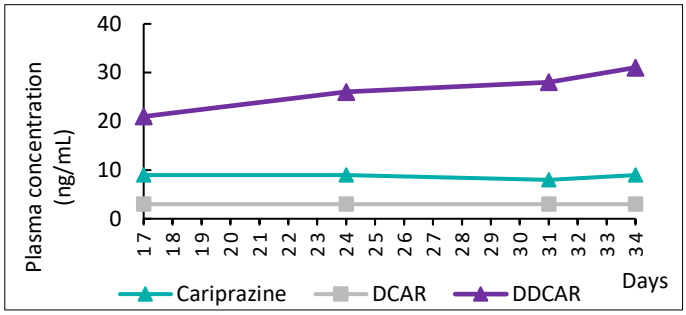
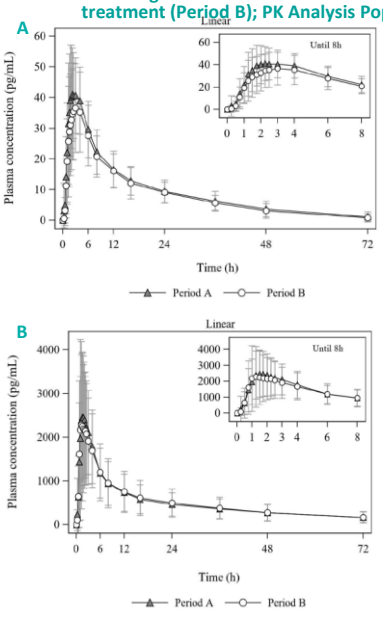


Table 2. The ratio of Geometric Means and its 90% confidence interval for Ethinylestradiol and Levonorgestrel; PK Analysis Population

	Parameter	Period B	Period A	B/A %	CI 90%	Intra CV%	p-value
EE	AUC_{inf} (h*pg/mL)	633	697	90.7	82.35; 99.99	19.3	0.100
	AUC_{0-t} (h*pg/mL)	556	603	92.2	83.26; 102.17	20.4	0.189
	C_{max} (pg/mL)	41.2	47.7	86.4	77.09; 96.81	22.8	0.038
LNG	AUC_{inf} (h*ng/mL)	38.09	40.05	95.1	87.85; 102.97	15.8	0.290
	AUC_{0-t} (h*ng/mL)	30.21	30.85	97.9	91.26; 105.12	14.0	0.619
	C_{max} (ng/mL)	2.51	2.66	94.6	82.72; 108.07	26.9	0.479

Figure 2. Mean (±SD) Levonorgestrel plasma concentration-time profiles following administration of the COC alone on Day 1 (Period A) and following a second administration on Day 31 after multiple-dose CAR treatment (Period B); PK Analysis Population



T_{max} for EE **(Figure 2A)** was at 2.5 h with and without CAR coadministration. For LNG **(Figure 2B),** it was at 1.75 h and 1.5 h in Period A and B, respectively. $t_{1/2}$ values were similar in both periods (EE: 18 h and 17 h; LNG: 33 h and 31 h). However, note that, the determination of $t_{1/2}$ for LNG was based on a sampling period shorter than required for a good estimation because the subjects could not be left without schizophrenia drug for a longer period.

No serious adverse events (SAE) nor adverse event of special interest (AESI) occurred, and no patient was withdrawn from the study due to a treatment-emergent adverse events (TEAE) either.

The study was funded by Gedeon Richter Plc. The authors are employees of the company.