

# A pharmacokinetic interaction study on the CYP450 inducing properties of NXP900 in healthy male volunteers

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## BACKGROUND

NXP900 is a potent inhibitor of non-receptor kinases from the SRC family of kinases (SFks), including YES Proto-Oncogene 1 (YES1) and SRC proto-oncogene kinases, in development for the treatment of patients with advanced cancers. Based on *in vitro* data, the potential of NXP900 to induce cytochrome P450 (CYP) enzymes was investigated in this study.

## METHODS

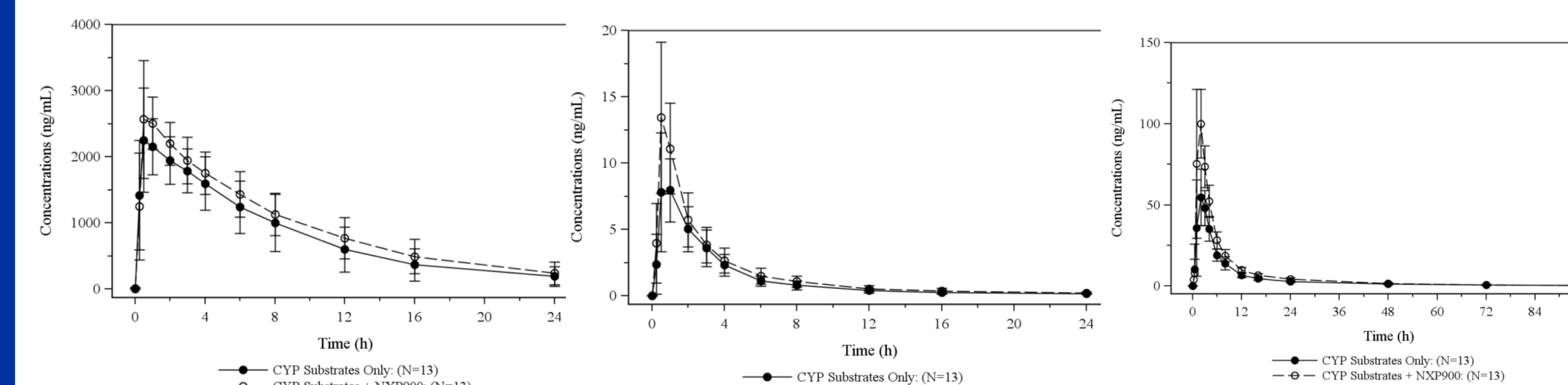
- Phase 1, open-label, single-cohort, single-site, single sequence study in 14 healthy male volunteers.
- Cocktail of the following CYP substrates: 100 mg caffeine (1A2), 2 mg midazolam (3A4), and 75 mg bupropion (2B6).
- On Day 1, a single oral dose of the CYP substrates cocktail and from Day 5 to Day 13 multiple oral doses of 200 mg NXP900 once daily with concomitant dosing of the CYP substrates cocktail on Day 10.
- Blood samples for the bioanalysis of the substrates and their metabolites as well as NXP900 were collected at pre-selected timepoints.

## RESULTS and CONCLUSIONS:

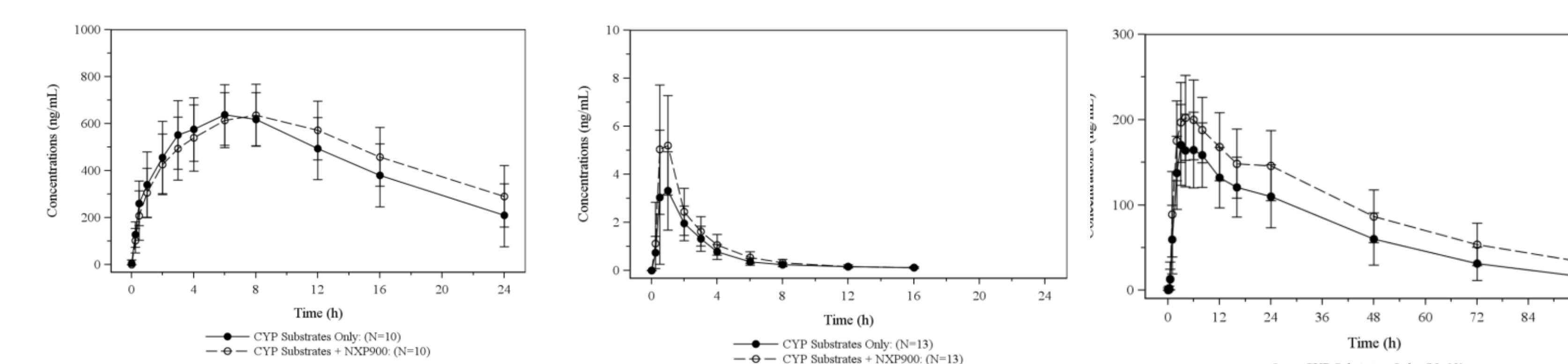
- On Day 10, trough plasma concentrations of NXP900 were approaching maximal levels.
- Observed GMR (90% CI) values of  $AUC_{0-inf}$  were:
  - Caffeine: 124.05% (113.47%, 135.62%)
  - Midazolam: 131.78% (122.04%, 142.31%)
  - Bupropion: 152.03% (137.29%, 168.34%)
- Diarrhea and non-infection related increases in white blood cell counts were the most common adverse events reported, and all were mild in intensity.

There were no CYP450 (1A2, 3A4 and 2B6) inducing properties of NXP900 observed in healthy male volunteers

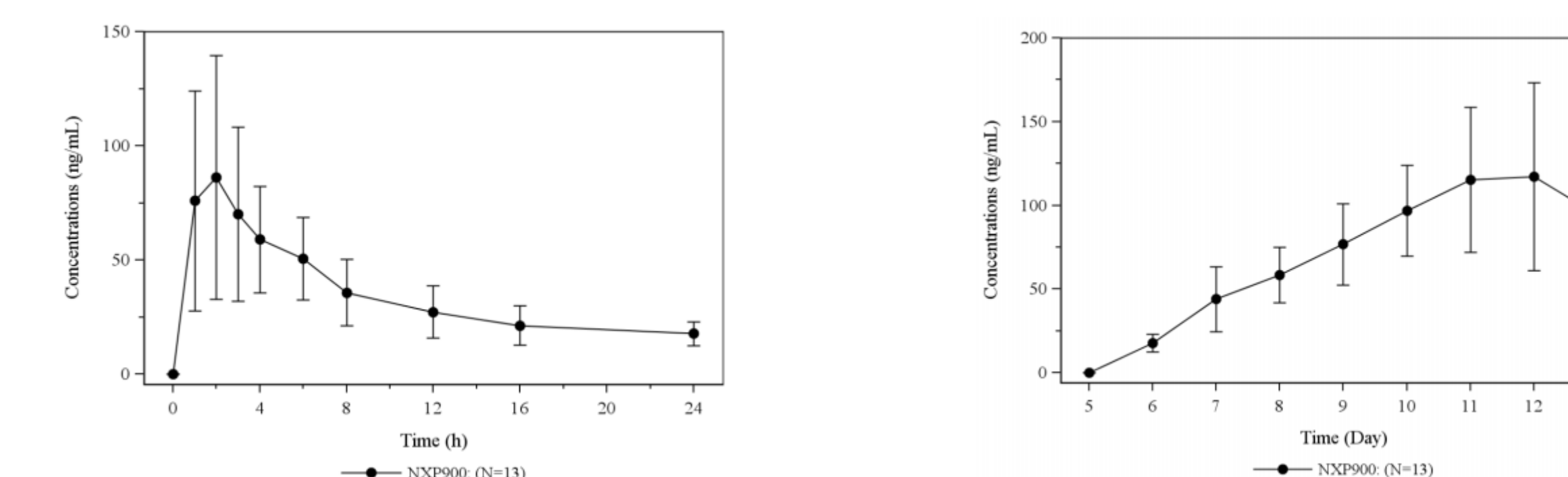
Mean (SD) plasma caffeine (left), midazolam (middle) and bupropion (right) concentrations in the absence and presence of NXP900



Mean (SD) plasma paraxanthine (left), 1-hydroxymidazolam (middle) and hydroxybupropion (right) concentration in the absence and presence of NXP900



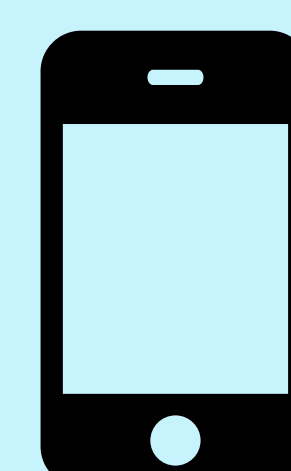
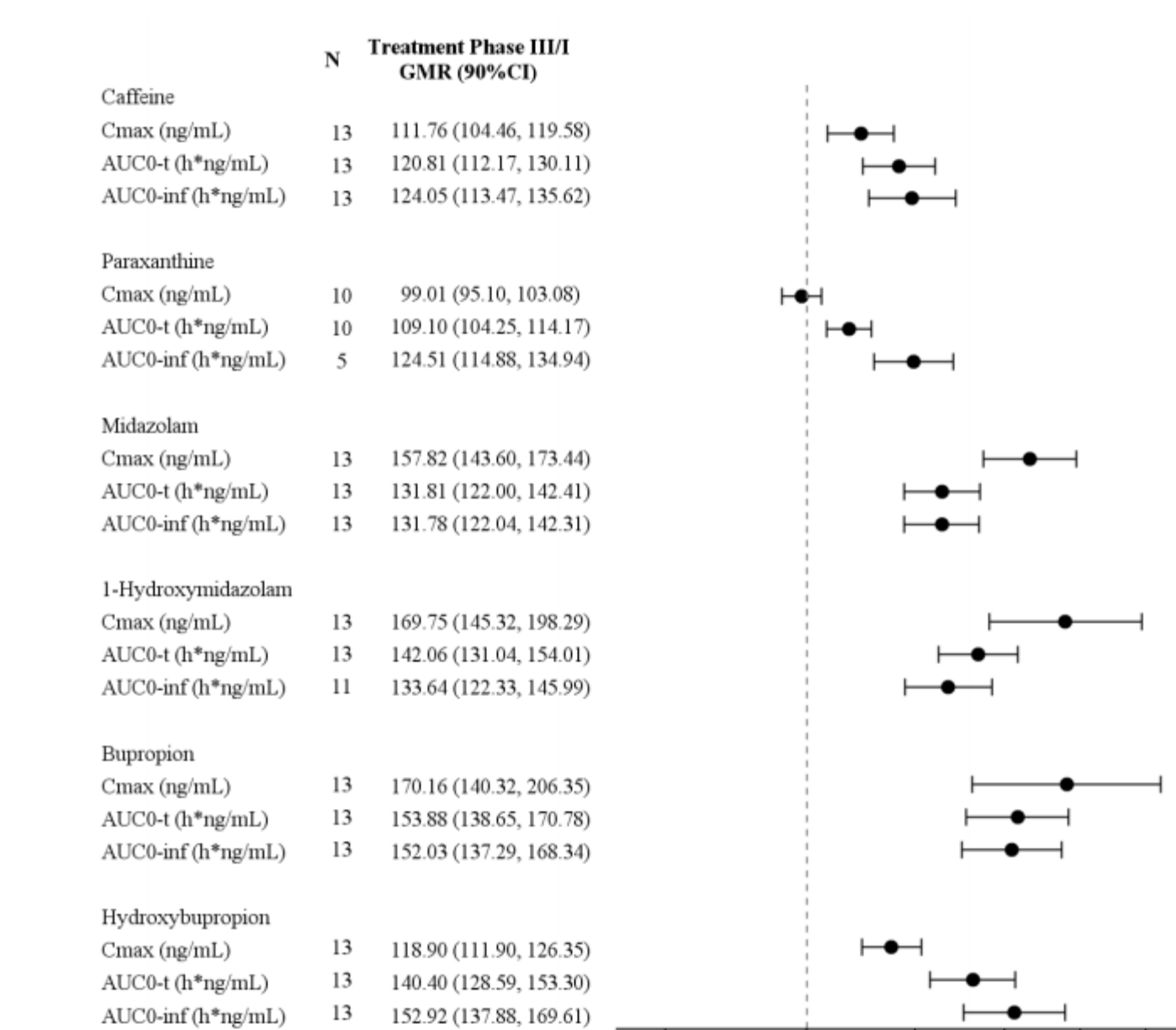
Mean (SD) plasma NXP900 concentrations upon the first day of NXP900 dosing (left) and at pre-dose on Days 5-13 (right)



Summary of primary PK parameters of various P450 substrates (left) and Forest plots of geometric mean ratios and 90% confidence intervals for the various P450 substrates and their metabolites (right)

analyte	parameter	CYP substrates only			CYP substrates + NXP900		
		n	mean <sup>1</sup>	CV%	n	mean <sup>1</sup>	CV%
caffeine	C <sub>max</sub> (ng/mL)	13	2420	26.1	13	2700	23.8
	AUC <sub>0-∞</sub> (h*ng/mL)	13	19500	44.4	13	24200	38.3
midazolam	C <sub>max</sub> (ng/mL)	13	8.41	41.1	13	13.3	40.7
	AUC <sub>0-∞</sub> (h*ng/mL)	13	28.3	37.2	13	37.3	35.8
bupropion	C <sub>max</sub> (ng/mL)	13	58.6	31.1	13	101	27.8
	AUC <sub>0-∞</sub> (h*ng/mL)	13	411	19.1	13	625	18.8

<sup>1</sup> Geometric mean



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