

Assessment of the Consistency of Pharmacokinetic Parameters of LEVADEX® (MAP0004, orally inhaled DHE) in Healthy Volunteers – Results from Three Clinical Studies

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RATIONALE

This analysis assessed the clinical pharmacokinetics of LEVADEX® (MAP0004, orally inhaled dihydroergotamine (DHE)) and its primary metabolite across three recent clinical studies.

Rapid and consistent absorption of a drug is important for achieving efficacy in treating an acute migraine. IV DHE has been used to treat migraine for more than 60 years. MAP0004 has been shown to be effective in the acute treatment of migraine. Here we analyze the data from three separate pharmacokinetic (PK) studies to assess the consistency, adequacy, and speed of absorption of DHE through this new route of administration.

METHODS

Three clinical studies in healthy volunteers at two different sites compared the administration of MAP0004 1.0 mg nominal and 1.0 mg IV DHE.

- a study to assess the difference in PK between smokers and non-smokers
- a drug-drug interaction (DDI) study to assess the effect of co-administration of ketoconazole on MAP0004
- a study to assess the acute effects of MAP0004 on pulmonary artery systolic pressure (PASP)

TABLE 1. Summary of Studies Conducted and PK Parameters Measured

Study	Primary Purpose of Study	Number of Subjects	Population	Primary Purpose of Study	Sample Period	PK Parameters Measured
P203	PK/Tolerability in Smokers and Non-Smokers	47	Healthy (Smokers and non-smokers) 16M/31F	PK/Tolerability in Smokers and Non-Smokers	48 hr	C_{max} , T_{max} , AUC_{0-48} , $AUC_{0-\infty}$, $t_{1/2}$, V_d , CL , F
P102	Effects on Pulmonary Artery Systolic Pressure (PASP)	24	Healthy 8M/16F	Effects on Pulmonary Artery Systolic Pressure (PASP)/PK/PD	4 hr	C_{max} , T_{max} , AUC_{0-2} , AUC_{0-4}
P104	Ketoconazole drug interaction (DDI)	24	Healthy 8M/16F	PK/Ketoconazole drug interaction (DDI)	48 hr	C_{max} , T_{max} , AUC_{0-48} , $AUC_{0-\infty}$, $t_{1/2}$, V_d , CL , F

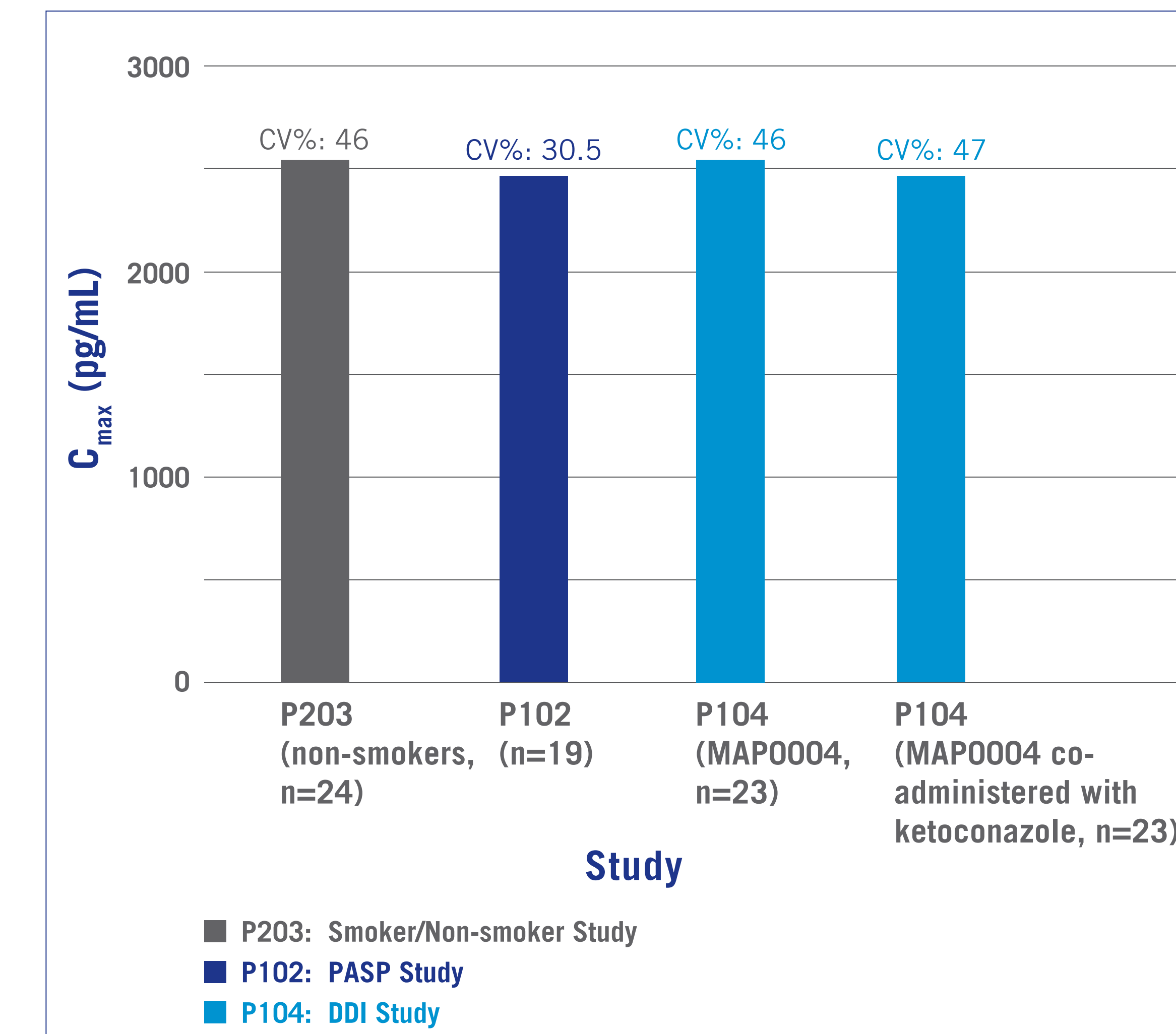
TABLE 2. Summary of Study Demographics

	P104 DDI Demographics	P203 Non-smokers only Demographics	P102 PASP Demographics
n	24	24	24
	(8 male, 16 female)	(8 male, 16 female)	(8 male, 16 female)
Mean Age (years)	29.6	30.7	26.6
(min, max)	(19, 45)	(19, 44)	(19.9, 40.1)
Weight (kg)	73.8	73.3	81.8
(min, max)	(52.2, 99.7)	(48.3, 106.3)	(51.7, 112.4)
Height (cm)	168.6	168.6	169.7
(min, max)	(154, 185)	(152, 187)	(153.7, 191.5)

RESULTS

Administration of MAP0004 resulted in rapid absorption of DHE with a mean T_{max} range of 7-11 minutes.

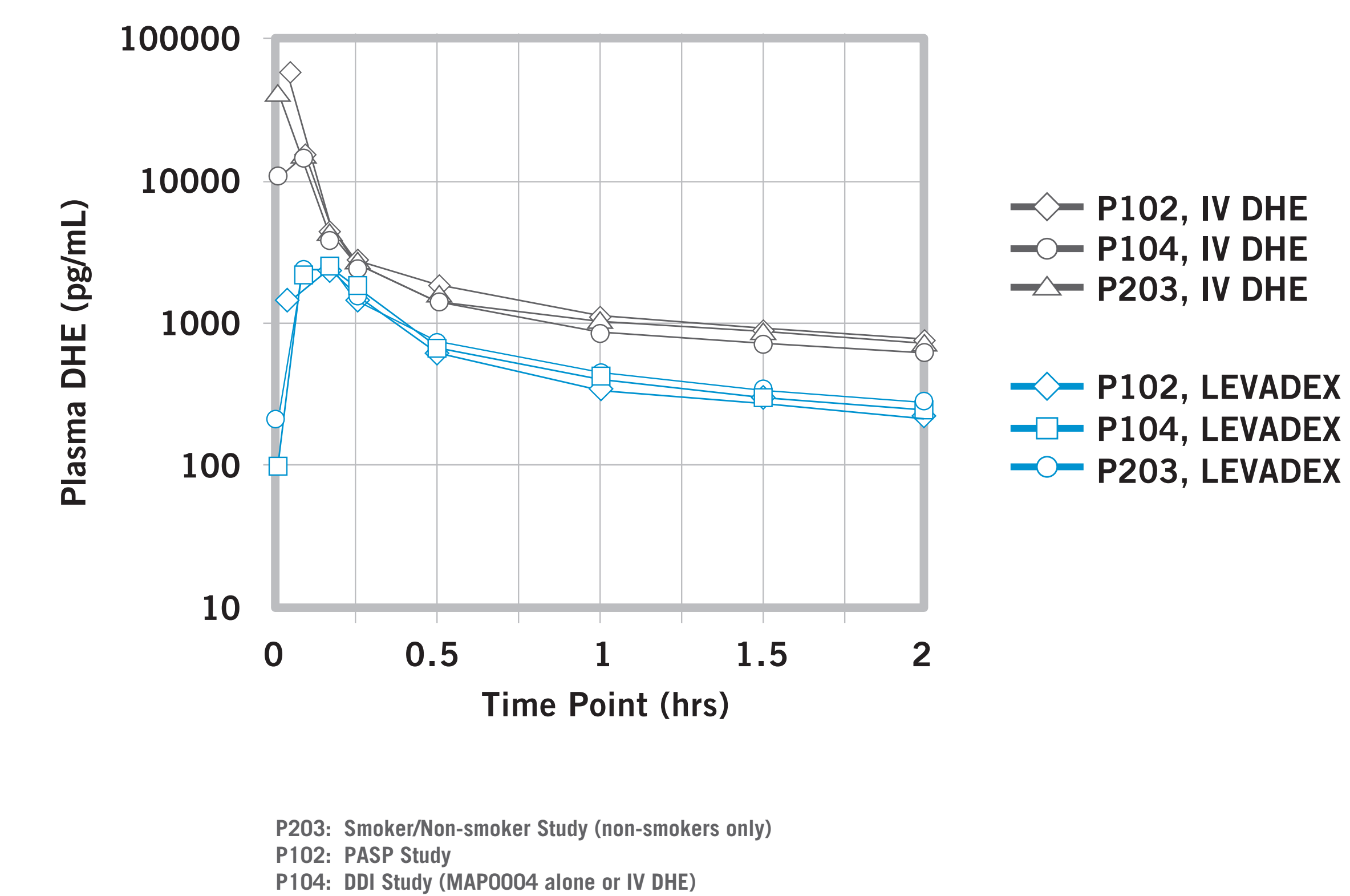
FIGURE 1. Geometric Mean DHE C_{max} across Studies



- Peak plasma concentration of DHE was also consistent across the studies in non-smokers, with a C_{max} geometric mean range of 2475-2551 pg/mL following administration of MAP0004 1.0 mg nominal dose.

In addition, MAP0004 C_{max} values were consistently approximately 20 times lower than those for intravenous administration (average C_{max} of ~45,000 pg/ml).

FIGURE 2. Geometric Mean DHE Plasma Concentrations over 2 hours following LEVADEX 1.0 mg nominal and IV DHE 1.0 mg Administration

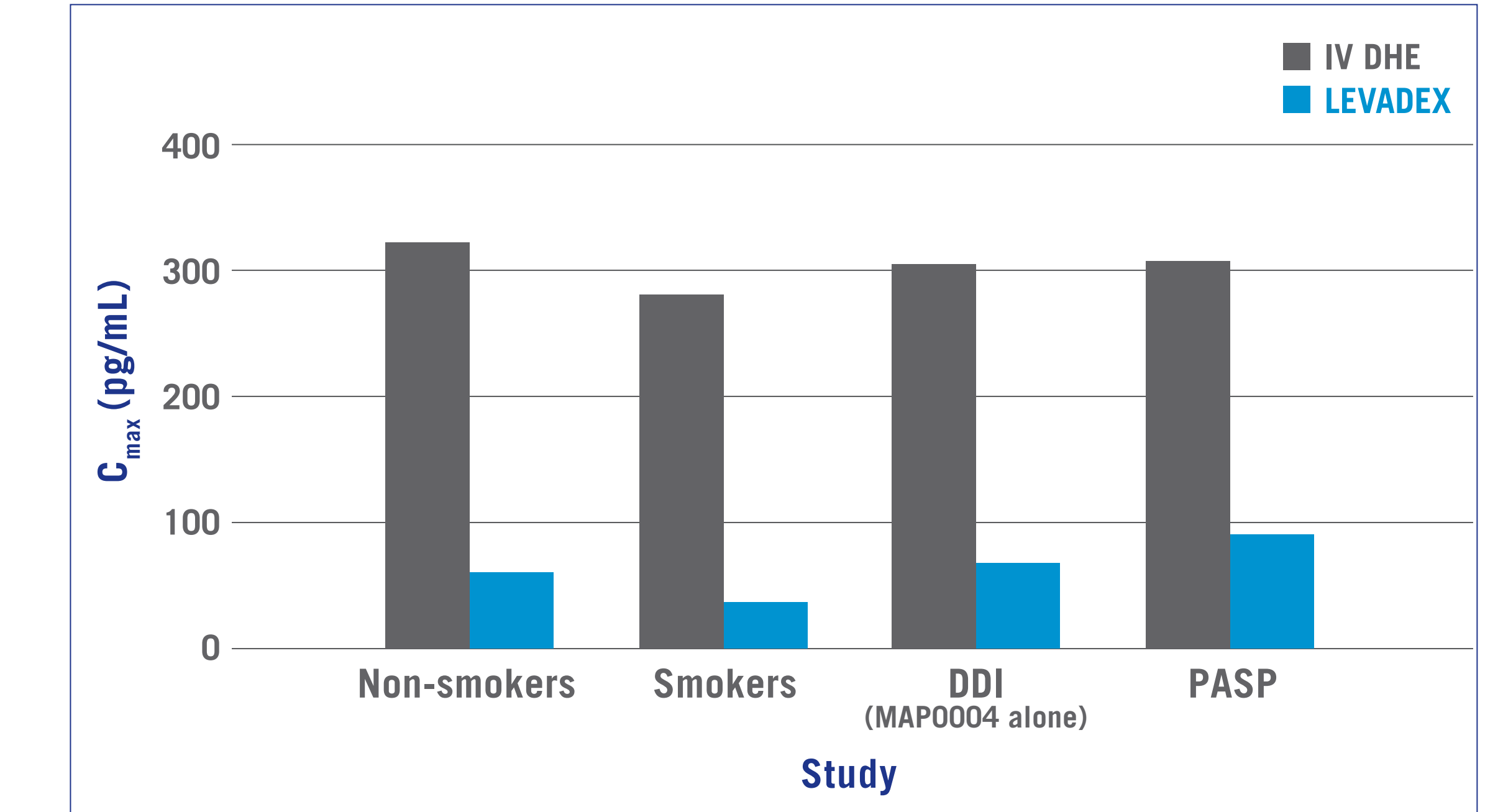


RESULTS

Metabolism

The observed concentrations of the primary metabolite (8'-OH-DHE) after MAP0004 administration were low (average C_{max} of <100 pg/mL vs a C_{max} of approximately 300 pg/mL after IV DHE administration) and too low to be pharmacologically relevant.

FIGURE 3. 8'-OH-DHE C_{max} after LEVADEX 1.0 mg nominal and IV DHE 1.0 mg Administration



- For all three studies, C_{max} of the 8'-OH-DHE was considerably higher following IV administration than inhaled administration.

In our studies, following IV DHE and inhaled DHE administration, only the 8'-OH-DHE and dihydrolysergic acid amide (DHLSA) metabolites were present in plasma at concentrations above the lower limit of quantitation with a specific validated method.

CONCLUSIONS

Across these studies MAP0004 showed consistent pharmacokinetic results and rapid absorption via the pulmonary route of administration.

MAP0004 C_{max} values were consistently lower than those for IV DHE administration.

Plasma 8'-OH-DHE (the major metabolite) concentrations after MAP0004 administration were less than 10% of DHE and much less than those seen after 1.0 mg IV DHE administration and, therefore, unlikely to be pharmacologically relevant.