

***Nausea Associated with
Dihydroergotamine (DHE) Is a Function
of Maximum Concentration and Not
Route of Administration***

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AHS

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MAP
PHARMACEUTICALS, INC.

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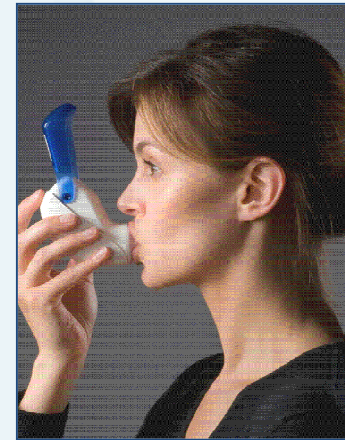
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LEVADEX[®] (MAP0004) Orally Inhaled DHE

- DHE is a standard therapy for resistant migraine
- DHE has inconsistent absorption when administered through routes other than IV
- LEVADEX is a novel orally inhaled form of **DHE** (1.0 mg nominal) (NDA submission)
 - The T_{max} is slightly longer than IV
 - The C_{max} is lower than IV
 - Absorption is consistent
- In a Phase 3 study, LEVADEX met all four primary endpoints and provided both rapid and sustained pain relief in patients with migraine



Rationale

- DHE has been used clinically for over 60 years and nausea is a commonly observed side effect
- Previously reported the results from a LEVADEX Phase 1 study (Cook et al.) , 0 of the 6 LEVADEX subjects had nausea compared to 63% of the 16 IV DHE subjects
- In our Phase 3 trial, double blind period the incidence of nausea in the LEVADEX treated subjects was 4.4%
- As part of the clinical development, IV and orally inhaled administration of DHE were compared in three additional clinical studies in healthy volunteers
- The objective of this analysis is to compare rates of subject-reported nausea between these routes of administration and to also examine if there was a relationship to plasma concentrations of DHE



Table 1: Summary of Clinical Trials

Study	Primary Purpose of Study	Year Performed	Number of Subjects		Population	Sample Period
1. PASP Study	Effects on Pulmonary Artery Systolic Pressure	2010	24	1.0 mg IV over 1 min, 1.0 mg MAP0004 at 0 and 2 hours	Healthy 8M / 16F	4 hr
2. DDI Study	Ketoconazole drug interaction	2010	24	1.0 mg MAP0004, ketoconazole 400 mg plus 1.0 mg, 1.0 mg IV over 1 min	Healthy 8M / 16F	48 hr
3. PK smokers / non-smokers	PK/Tolerability in Smokers and Non-Smokers	2010	47	1.0 mg IV over 1 min, 1.0 mg MAP0004	Healthy (Smokers and non-smokers) 16M / 31F	48 hr
4. Thorough QT Study	Thorough QT, moxifloxacin and placebo control	2010	54	3.0 mg MAP0004 and 400 mg Moxifloxacin	Healthy 20M / 34F	36 hr

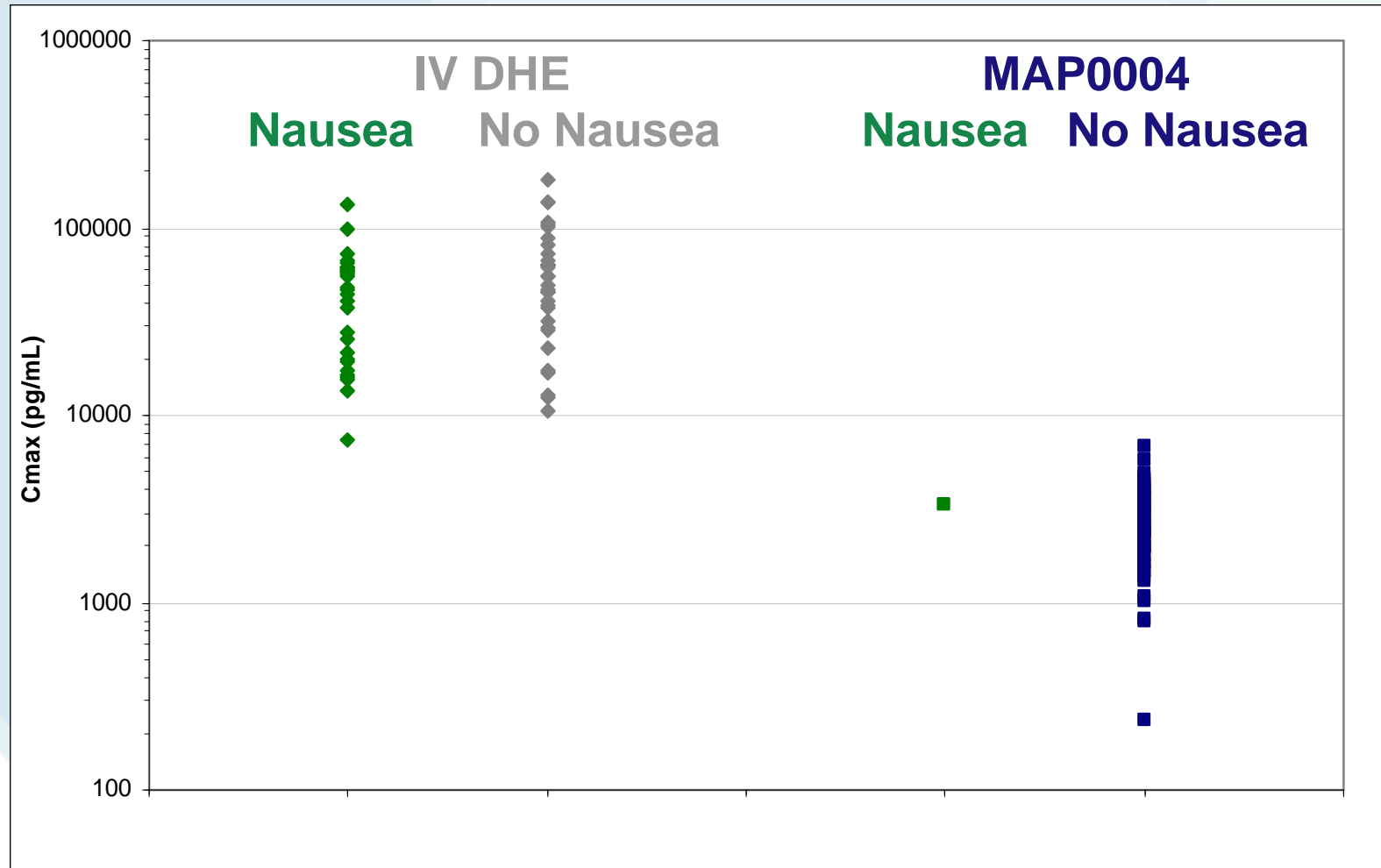


Table 2: Comparative Incidence of Nausea and C_{max} (Geometric Mean) with MAP0004 (1.0 mg) versus IV (1.0 mg) DHE

Study	MAP0004 (1.0 mg nominal)			IV DHE (1.0 mg)		
	n	C_{max} (pg/mL)	Incidence of nausea	n	C_{max} (pg/mL)	Incidence of nausea
PASP Study	24	2,357	4.2%	24	57,558	41.7%
DDI Study	24 pre-ketoconazole	2,583	0.0%	22	27,771	50.0%
	23 post -ketoconazole	2,495	4.2%			
PK Smoker / non- smokers Study	47 (23 smokers: 24 non-smokers)	1,282 (smokers) 2,551 (non-smokers)	2.1%	46 (22 smokers: 24 non-smokers)	60,046 (smokers) 48,428 (non-smokers)	30.4%



Figure 1: Individual Subject C_{max} of Subjects Administered IV DHE (1.0 mg) or MAP0004 (1.0 mg)



Discussion

- Though the difference in C_{\max} and nausea rates is apparent, it is possible that the route of administration of the drug may have contributed to the higher incidence after IV, as only the PASP study was double-blinded.



Thorough QT Study Results

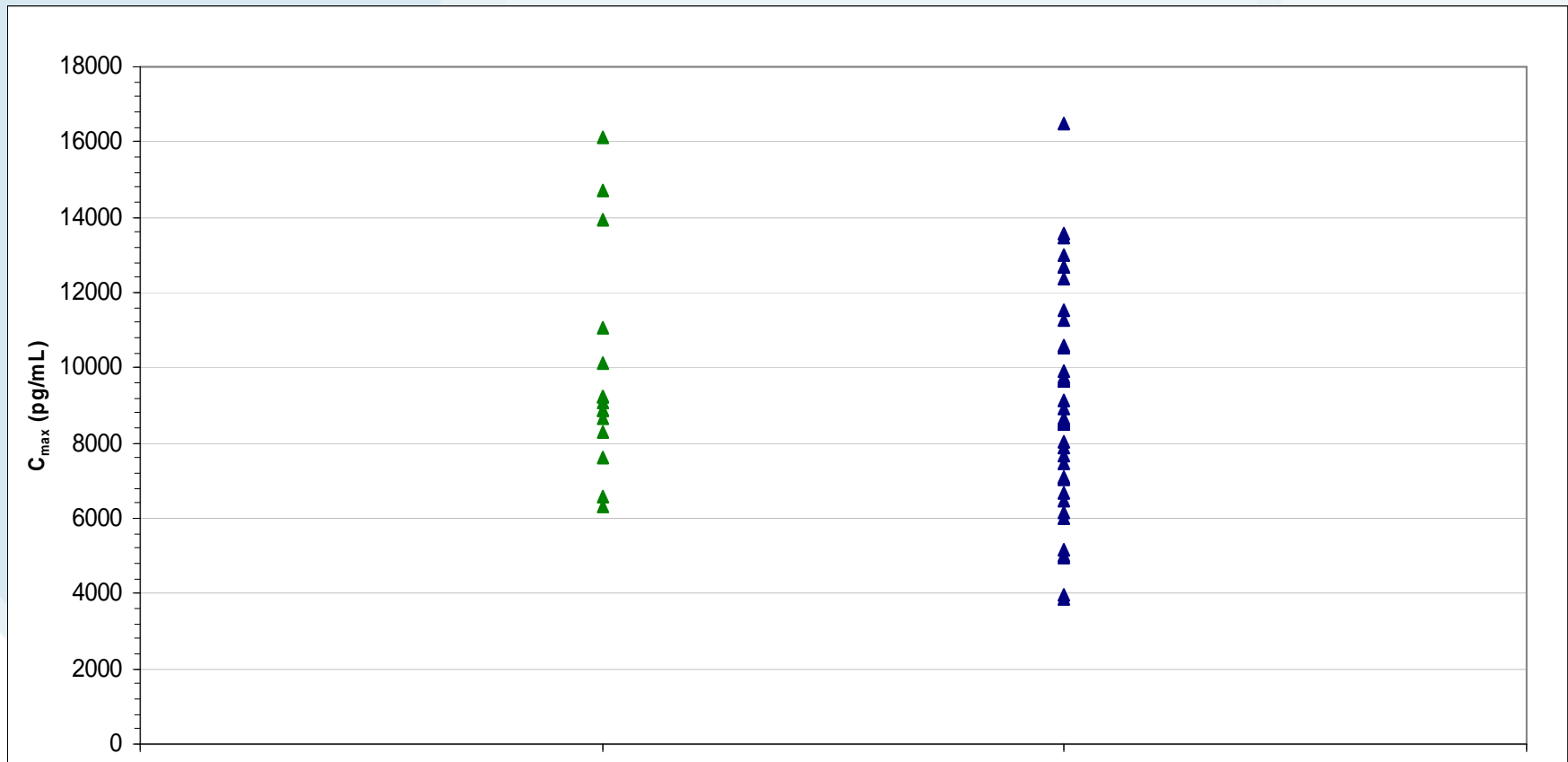
- One additional study was performed in 54 healthy volunteers comparing DHE 3.0 mg via oral inhalation, placebo and moxifloxacin in a blinded crossover design.
 - The C_{max} following orally inhaled DHE was 8,757 pg/mL, slightly more than the three times seen for the 1.0 mg orally inhaled dose and 3 to 6 times lower than that observed following 1.0 mg IV administration.
 - The incidence of nausea for the 3.0 mg orally inhaled DHE was 28% significantly higher than the 0-4% incidence seen with other inhaled studies with 1.0 mg nominal dose of MAP0004



Figure 2: Individual Subject C_{max} of Subjects Administered MAP0004 (3.0 mg nominal)

Nausea

No Nausea



Conclusions

Nausea appears to be related to DHE C_{\max} irrespective of route of administration.

The relatively lower C_{\max} observed after DHE (1.0 mg) via oral inhalation is consistently associated with a low incidence of nausea and much lower than that observed following DHE (1.0 mg) IV administration.



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