

A Randomized, Double-Blind, Placebo Controlled, Three-Period Crossover Study Comparing the Acute Effects of LEVADEX® (MAP0004, Orally Inhaled DHE) and Intravenous DHE on Pulmonary Arterial Systolic Pressure

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BACKGROUND

Parenteral dihydroergotamine (IV DHE) is used for acute treatment of migraine headache. A new orally inhaled formulation (MAP0004) (shown below) is under development. Acute pharmacokinetic (PK) and pharmacodynamic (PD) effects of MAP0004 1.0 mg nominal (0.65 mg emitted) dose versus IV DHE 1.0 mg versus Placebo on cardiac function and pulmonary systolic pressure (PASP) changes were evaluated.



OBJECTIVES

Primary:

- Compare the acute effect of DHE 1.0 mg delivered Intravenously (IV) and by oral inhalation (MAP0004 1.0 mg) on Pulmonary Arterial Pressure during the first 2 hours post dose as determined by echocardiography

Secondary:

- Assess pharmacokinetics of DHE and its metabolites in relation to the parent compound
- Assess effects of DHE delivered by oral inhalation (MAP0004 1.0 mg) versus delivered Intravenously (IV DHE 1.0 mg) on cardiac function
- Compare the pharmacodynamics and pharmacokinetics of DHE delivered by oral inhalation (MAP0004, two 1.0 mg doses administered 2 hours apart) as compared to a single dose of DHE (DHE 1.0 mg) delivered intravenously (IV)

METHODS

- Twenty-four healthy adult males (8) and females (16) were randomized into a double-blind, placebo-controlled, 3-period crossover study and received active and/or placebo drug in the following combinations:
 - Treatment A: IV DHE (Active) + MAP0004 (Placebo) followed 2h later by MAP0004 (Placebo)
 - Treatment B: IV DHE (Placebo) + MAP0004 (Active) followed 2h later by MAP0004 (Active)
 - Treatment C: IV DHE (Placebo) + MAP0004 (Placebo) followed 2h later by MAP0004 (Placebo)
- Each subject received all three treatment combinations over 3 treatment visits one week apart
- Serial vital signs (VS), PKs, ECGs, PASPs by echocardiogram and adverse events (AEs) were collected at the following time points:
 - PASP echocardiogram: at 3, 5, 7, 10, 12, 15, 20, 25, 30, 60, 90 and 120 min post each dose
 - Full echocardiogram at 30 min before dose and at 30 and 90 min post each dose
 - PKs: at 2 hours before dose and at 2, 10, 15, 30, 60 and 90 min post each dose
 - ECGs: at 30 min before dose and then recorded continuously for 2 hours post each dose
- Absolute PASP changes were assessed comparing AUC₀₋₁₂₀ using ANOVA model for a 3-period crossover trial

TABLE 1. Treatments

TREATMENTS			
	Treatment A	Treatment B	Treatment C
First Dose (at 0 min)	Inhaler Placebo IV DHE	MAP0004 IV Placebo	Inhaler Placebo IV Placebo
	2 hours of study assessments: PK sampling, Echocardiogram, 12-lead ECG, vital signs		
Second Dose (at 120 min)	Inhaler Placebo	MAP0004	Inhaler Placebo
	2 hours of study assessments: PK sampling, Echocardiogram, 12-lead ECG, vital signs		

RESULTS

TABLE 2. Baseline Demographics

PARAMETER	VALUE
Age (years)	18-45
Mean	26.6
Min, Max	19.9, 40.1
Gender (n, %)	24
Male	8 (33.3%)
Female	16 (66.7%)
Ethnicity and Race	
Hispanic or Latino	1
American Indian	1
Black or African American	10
White or Caucasian	12

RESULTS

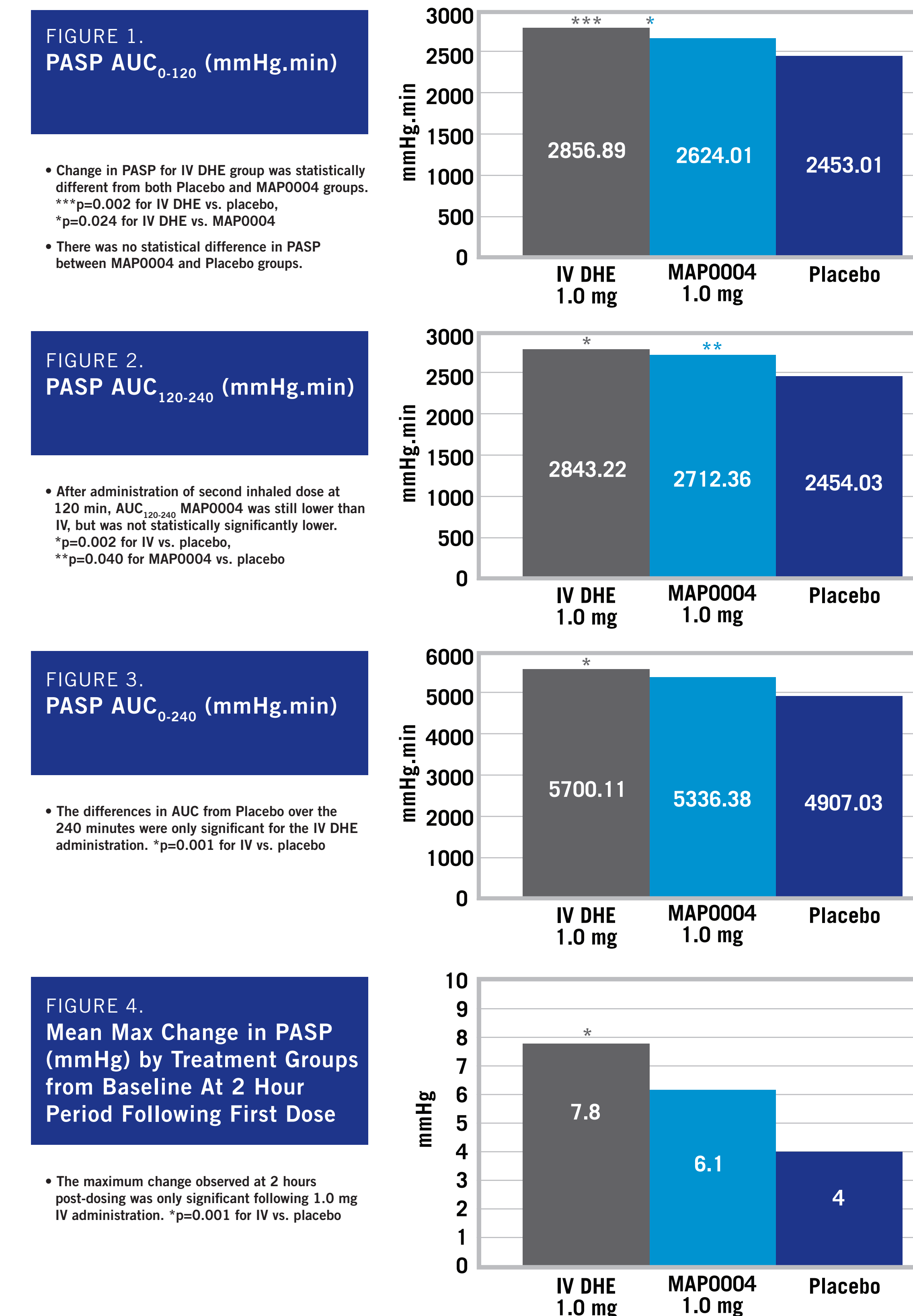
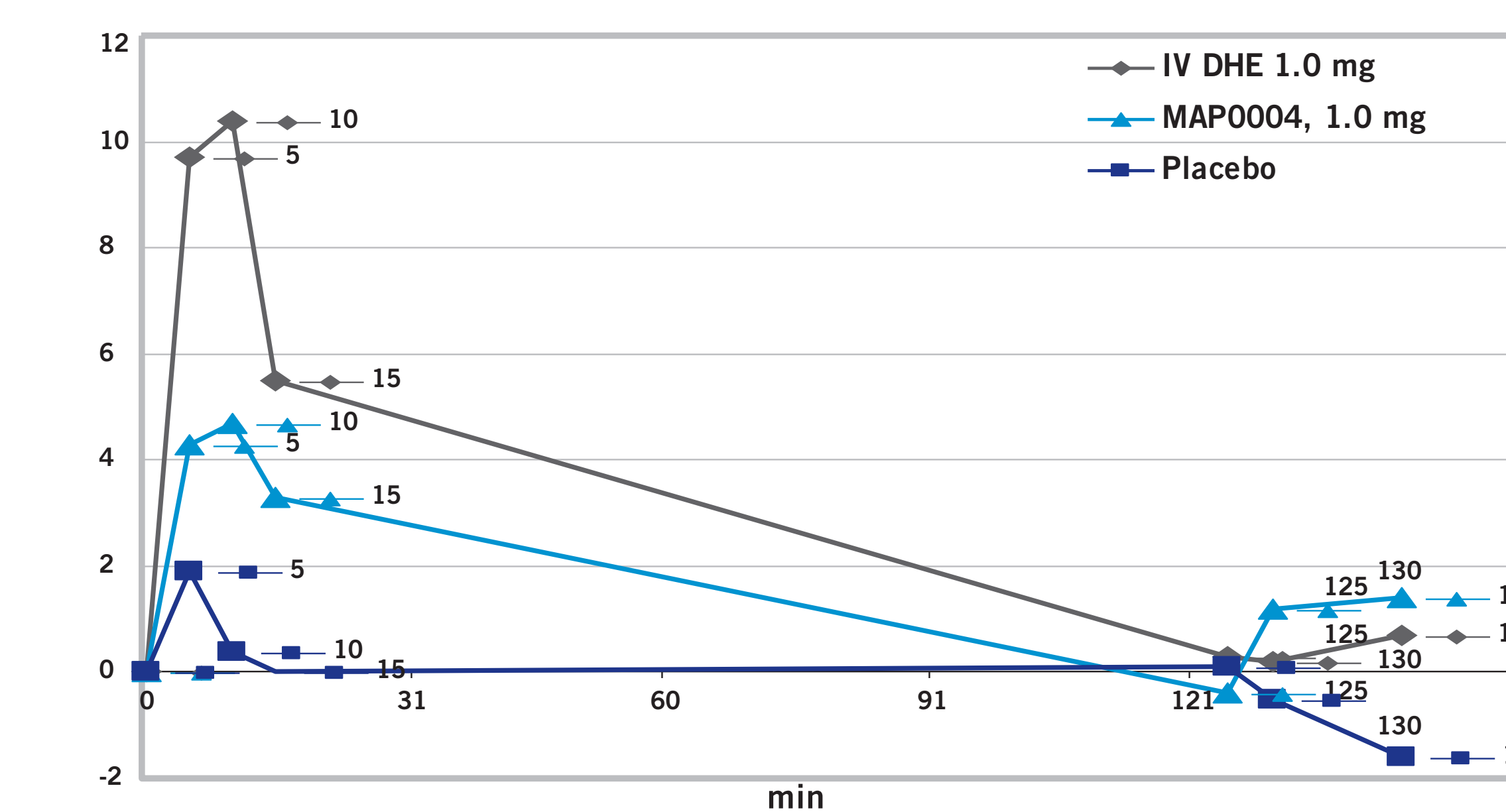
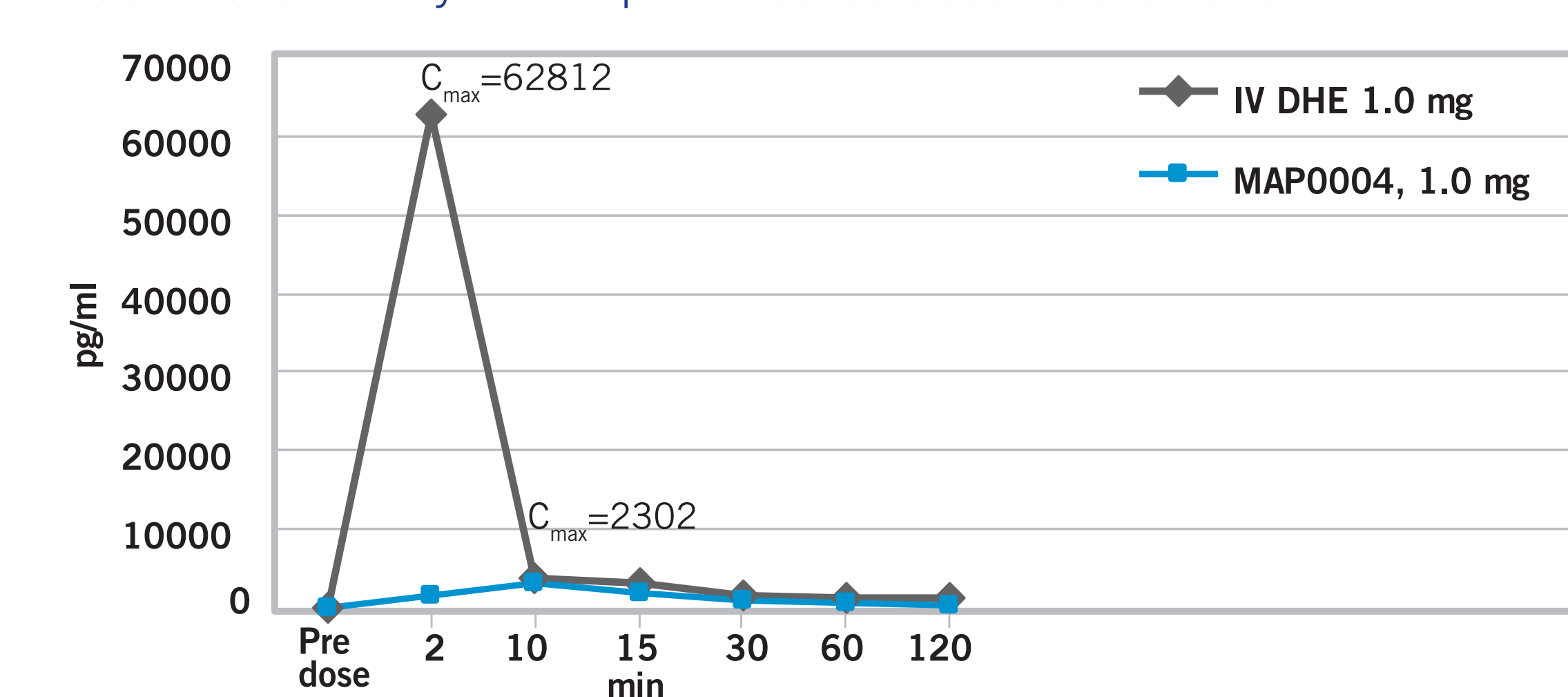


FIGURE 5. Change in Systolic BP from Baseline to 15 Minutes After Dose 1 and Dose 2



The greatest change in systolic blood pressure was observed after IV DHE administration. None of the treatment groups produces statistically significant change in blood pressure.

FIGURE 6. Summary of DHE plasma concentration over time for IV DHE



RESULTS

FIGURE 7. Summary of DHE plasma concentration over time for MAP0004

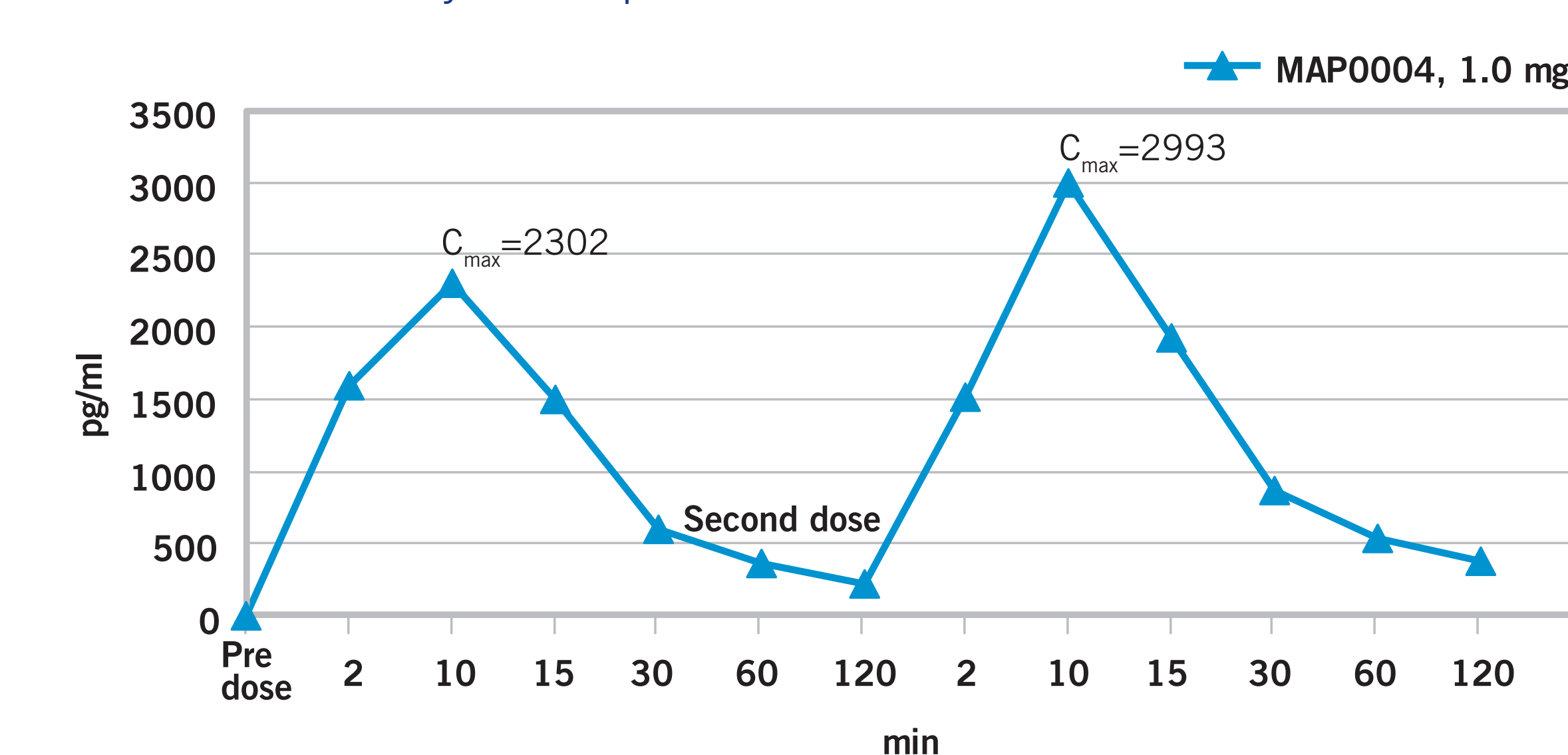


TABLE 3. Summary of Adverse Events reported by 3 or more subjects: NO SAE's

System Organ Class	IV DHE n=20	MAP0004 n=20	Placebo n=20
Nausea	10 (41.6%)	1 (4.2%)	0
Feeling hot	8 (33.4%)	0	0
Headache	6 (25%)	5 (20.8%)	1 (4.2%)
Burning sensation	4 (16.7%)	0	0
Dizziness	3 (12.5%)	2 (8.3%)	1 (4.2%)
Paraesthesia	3 (12.5%)	0	0

DISCUSSION & CONCLUSION

The study showed no statistically significant difference between MAP0004 and placebo groups among all subjects with valid AUC values (n = 20). Pulmonary arterial pressure in the IV DHE group was significantly higher than both MAP0004 and placebo groups. Further, for PASP over time post second dose (evaluated by AUC₀₋₂₄₀), there was no statistically significant difference between MAP0004 vs. IV DHE and placebo groups; however, PASP in the IV DHE group was significantly higher than the placebo group.

In regard to secondary endpoints assessed, there were no significant changes in the cardiovascular parameters (QTc, PR, QRS), and there was no increase in mean QTc in the MAP0004 group at 14 minutes post-dose. The plasma concentrations of DHE were much higher after IV dosing than after inhaled dosing. The levels of the 8-OH metabolite were very low compared with the parent compound.

MAP0004 also had a good safety and tolerability profile, with primarily mild study drug-related AEs and no SAEs. Most of the AEs occurred in the IV DHE treatment group with 1 AE that led to study discontinuation (headache and nausea). Changes in laboratory values, vital signs, and physical findings were all insignificant.

Based on the results of this Phase 1 study, the effects of inhaled DHE (MAP0004) on the cardiac circulation appear to be less than that of IV administration and may be therapeutically preferable.