

An Open-Label, Two-Period, Crossover Study Comparing the Pharmacokinetics and Tolerability of LEVADEX® (MAP0004, orally inhaled DHE, 1.0 mg) and Intravenous DHE (DHE 45®, 1.0 mg) in Smoking and Non-Smoking Adult Volunteers

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RATIONALE

With any inhaled product, there may be some concern that smokers will have higher blood levels than non-smokers and the pharmacokinetic effects will be greater. For example, with a high molecular weight protein such as insulin, higher blood levels have previously been observed in smokers relative to non-smokers for insulin delivered via oral inhalation. The pharmacokinetics of DHE administered via oral inhalation and IV in smokers have not been studied. This study evaluated differences in the absorption and metabolism of MAP0004 and IV DHE between non-smokers and smokers.

METHODS

This was a single dose, 2 period crossover study comparing the pharmacokinetics and tolerability of MAP0004 (0.65 mg emitted, 1.0 mg nominal dose) to 1.0 mg of IV DHE.

47 healthy adult volunteers were randomized: 24 non-smokers (never smoked or total exposure <1 pack year and at least 12 months since last cigarette and negative urinary cotinine result) and 23 smokers (currently smoking at least 10 cigarettes/day for at least 1 year and positive urinary cotinine result).

Following a single dose of study drug, serial blood sample collections, repeat ECGs, spirometry, and vital sign assessments were completed at designated time points for 48 hours.

Adverse events were monitored throughout the study.

Table 1: Subject Demographics

	SMOKERS	NON-SMOKERS
Gender (n)	23	24
Male	8	8
Female	15	16
Mean Age (years)	32.9	30.7
Min	21	19
Max	45	44
Weight (kg)	74.3	73.3
Min	56.8	48.3
Max	106.2	106.3
Height (cm)	169.4	168.6
Min	159	152
Max	197	187

RESULTS

46 subjects completed the study.

MAP0004 was absorbed quickly, with a similar median T_{max} observed for smokers (4.98 mins) and non-smokers (7.02 mins).

The mean half-life for MAP0004 was similar for smokers (16.1 hr) and non-smokers (14.5 hr) and was similar to IV DHE administration (13.3 hr for smokers and 12.4 hr for non-smokers).

The pharmacokinetic parameters for DHE following IV administration were not significantly different between smokers and non-smokers.

After MAP0004 administration, DHE exposure was not higher in smokers compared to non-smokers.

Lower DHE exposure in smokers was evidenced by statistically lower C_{max} , AUC_{0-48} , AUC_{0-inf} , and bioavailable fraction.

Adverse events were less frequent for MAP0004 compared to IV administration.

MAP0004 tolerability was similar in smokers and non-smokers.

Table 2: Summary of the Derived PK Parameters of DHE, MAP0004 1.0 mg nominal dose

TREATMENT	C_{max} (pg/mL)	T_{max} (median mins)	AUC_{0-48} (pg-hr/mL)	$AUC_{0-∞}$ (pg-hr/mL)	$t_{1/2}$	CL (L/h)	Vd (L)	Bioavailable Fraction (F) (nominal)	Bioavailable Fraction (F) (emitted)
MAP0004 Smokers (n = 23)	1,282 ^a	4.98 ^a	3,015	3,393	16.1	-	-	0.291 ^a	0.448 ^a
MAP0004 Non-smokers (n = 24)	2,551	7.02 ^b	4,149	4,516	14.5	-	-	0.372	0.572
IV DHE 1.0 mg Smokers (n = 22)	60,046	1.02	11,049	11,458	13.3	87	1,677	-	-
IV DHE 1.0 mg Non-smokers (n = 24)	48,429	1.02	11,732	12,154	12.4	82	1,473	-	-

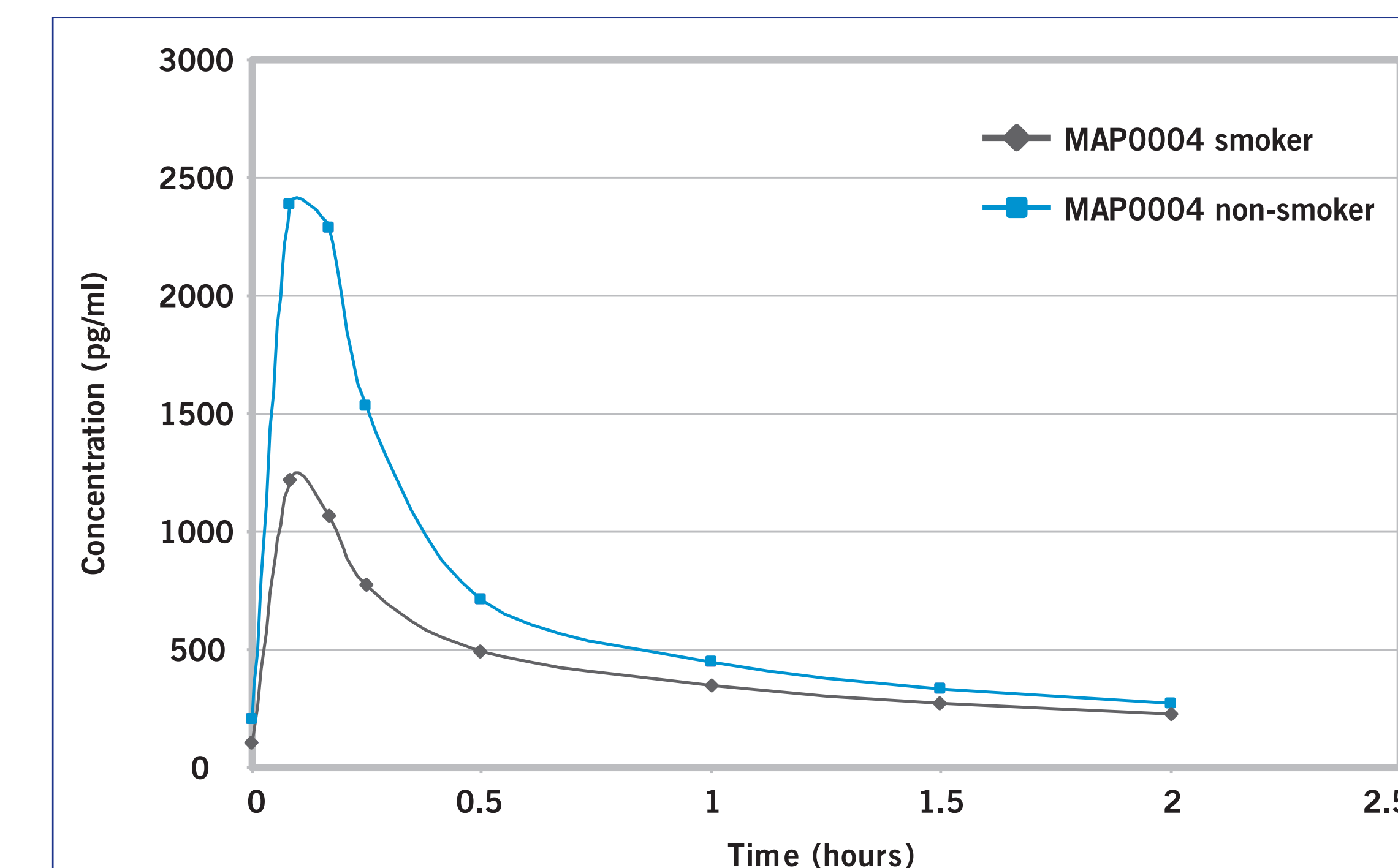
^a n = 22
Source: MAP0004-CL-P203R, Table 14.2.1.1, Summary of Derived PK Parameters of DHE – PK Population

Table 3: Summary of Derived PK Parameters of 8'-OH-DHE, MAP0004 1.0 mg nominal dose

TREATMENT	C_{max} (pg/mL)	T_{max} (median, mins)	AUC_{0-48} (pg-hr/mL)	$AUC_{0-∞}$ (pg-hr/mL)	$t_{1/2}$
MAP0004 Smokers (n = 23)	37	55.5 ^a	75	-	-
MAP0004 Non-smokers (n = 24)	60	15 ^b	148	-	-
IV DHE 1.0 mg Smokers (n = 22)	278	4.98	414	1,027 ^c	13.9 ^c
IV DHE 1.0 mg Non-smokers (n = 24)	320	4.98	483	1,038 ^d	10.7 ^d

^a n = 18, ^b n = 23, ^c n = 11, ^d n = 15
Source: MAP0004-CL-P203R, Table 14.2.1.1, Summary of Derived PK Parameters of Metabolite 8'-OH-DHE – PK Population

Figure 1: MAP0004 Geometric Mean Concentration vs Time (first 2 hours)



- Results demonstrated that plasma concentrations of DHE and 8'-OH-DHE were significantly lower in smoking subjects than in non-smokers, probably related to absorption, as clearance values were not different in smokers or non-smokers

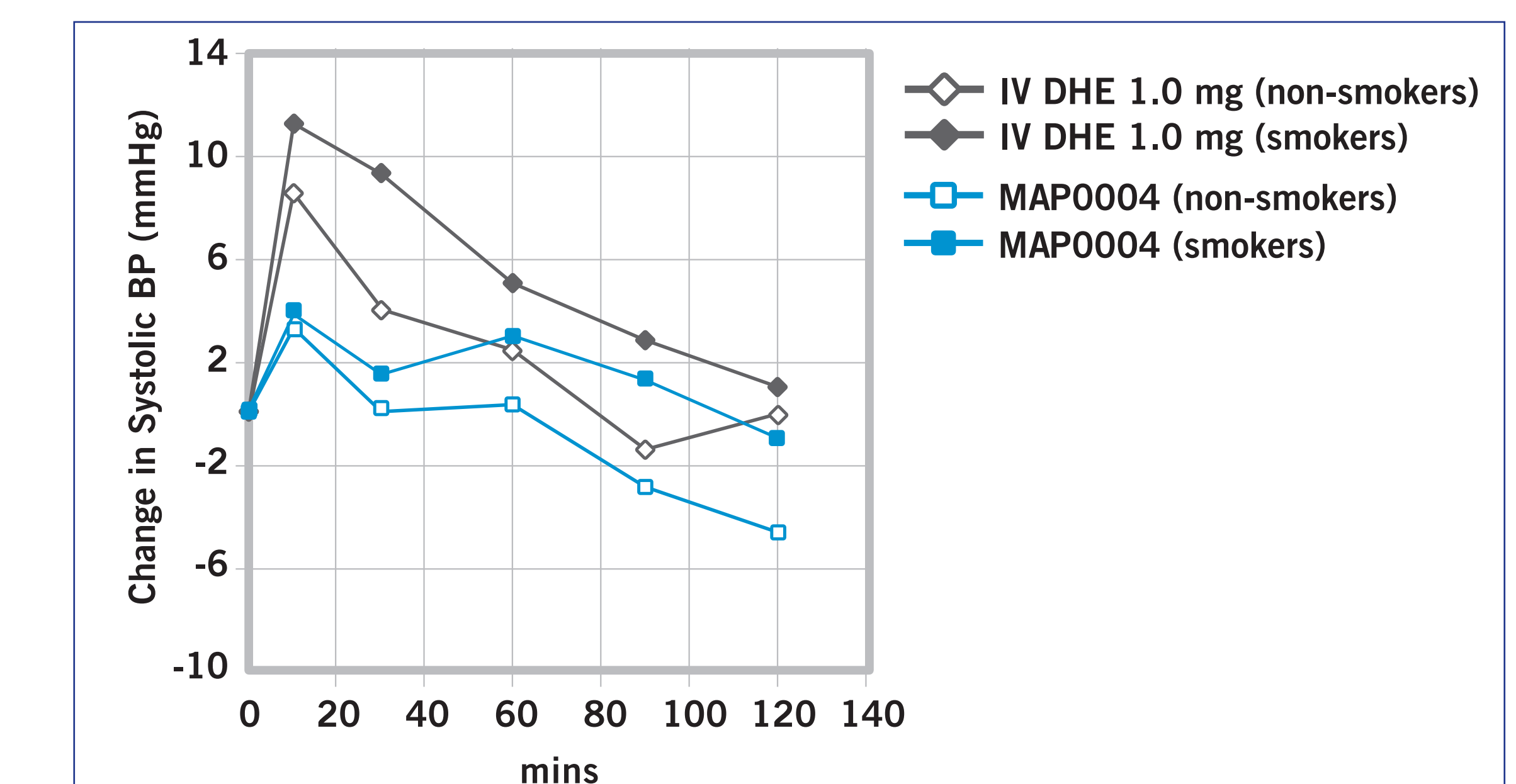
RESULTS

Table 4: MAP0004-CL-P203 Summary of Most Common (>5% in either treatment group) Treatment Emergent Adverse Events

OVERALL SUMMARY OF TREATMENT EMERGENT ADVERSE EVENTS		
	MAP0004 1.0 mg (n = 47)	IV DHE 1.0 mg (n = 46)
Number (%) of subjects reporting at least one	n (%)	n (%)
TEAE	17 (36.2%)	40 (87%)
Serious TEAE	0 (0%)	0 (0%)
Study Drug Related TEAE	6 (12.8%)	38 (82.6%)
TEAE Leading to Early Study Termination	1 (2.1%) ^a	0 (0%)
MOST FREQUENT ADVERSE EVENTS^b		
Nausea	1 (2.1%)	14 (30.4%)
Vomiting	0 (0%)	7 (15.2%)
Headache	4 (8.5%)	16 (34.8%)
Dizziness	2 (4.3%)	8 (17.4%)
Flushing	0 (0%)	7 (15.2%)

^aThe TEAE leading to early study termination after MAP0004 administration was tonsillitis.
^bMost frequent adverse events are presented by preferred term irrespective of treatment group (smokers and non-smokers combined). The five most frequent events experienced are presented. For MAP0004, the most frequent adverse event experienced was headache, all other adverse events were experienced at a frequency of 4.3% or less.

Figure 2: Mean Change from Baseline in Systolic BP (mmHg)



- Tolerability of MAP0004 was better than that observed for intravenous administration in both smokers and non-smokers.
- The effects on systolic and diastolic blood pressure were less following inhaled administration versus IV administration.
- There was no significant effect on lung function in smokers or non-smokers after either route of DHE administration.
- Variations in FEV₁ were larger following IV administration than following inhaled administration.
- There were also no significant effects on blood pressure, heart rate, or ECG parameters in either smokers or non-smokers following 1.0 mg of MAP0004.

CONCLUSION

After MAP0004 administration, DHE and 8'-OH-DHE C_{max} was statistically significantly lower in smokers compared to non-smokers.

However, all C_{max} values are above the known therapeutically effective levels.

Observed differences between smokers and non-smokers was probably due to reduced pulmonary absorption in the smoker population.

These results demonstrate no unique safety issues due to blood levels of DHE in the smoker population relative to non-smokers.