

A Drug Interaction Study Assessing the Effects of CYP3A4 Inhibition on the Pharmacokinetics of LEVADEX® (MAP0004, orally inhaled DHE) in Healthy Volunteers

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RATIONALE

This study was designed to assess the impact of CYP3A4 inhibition on LEVADEX® (MAP0004, orally inhaled DHE) pharmacokinetics. The effect of concomitant administration of ketoconazole on the pharmacokinetics of MAP0004 was evaluated and compared with the pharmacokinetics of both MAP0004 alone and IV DHE.

Currently marketed products containing dihydroergotamine (DHE) have a “black box” label warning about the potential for a serious drug interaction when co-administered with CYP3A4 inhibitors. Such CYP3A4 inhibition is thought to potentially enhance the effect and duration of DHE and/or its metabolites. However, to our knowledge, no formal clinical study had been performed.

METHODS

This was a Phase 1 open-label study. Twenty-four subjects were evaluated in a cross-over design.

Treatments were administered in a defined order:

- MAP0004 (1.0 mg nominal, 0.65 emitted) dosing,
- followed by MAP0004 co-administered with ketoconazole (400 mg administered orally once a day for four days),
- followed by 1.0 mg IV DHE

Pharmacokinetic parameters following the three treatments were determined for both DHE and the primary metabolite of DHE, 8'-hydroxydihydroergotamine (8'-OH DHE).

Adverse events were monitored throughout the study.

TABLE 1. Subject Demographics

n	24 (8 male, 16 female)
Mean Age (years)	29.6
(min, max)	(19, 45)
Weight (kg)	73.8
(min, max)	(52.2, 99.7)
Height (cm)	168.6
(min, max)	(154, 185)

RESULTS

TABLE 2. Summary of the Derived PK Parameters of DHE, LEVADEX 1.0 mg nominal dose and IV DHE 1.0 mg

Treatment	C _{max} (pg/mL)	T _{max} (hr) (median)	AUC ₀₋₄₈ (pg ² ·hr/mL)	AUC _{0-∞} (pg ² ·hr/mL)	t _{1/2} (hr)	CL (L/h)	V _d (L)	F (nominal)	F (emitted)
MAP0004 alone (n = 23)	2,583 (46) ^a	0.17 ^a	3,485 (44)	3,784 (42)	13.5 (17) ^a	-	-	0.38 (59) ^b	0.58 ^b
MAP0004 co-administered with ketoconazole (n = 23)	2,495 (47)	0.17	4,071 (47)	4,323 (45)	11.2 (25) ^a	-	-	0.46 (55) ^c	0.71 ^c
IV DHE 1.0 mg (n = 20)	27,771 (99)	0.08	9,229 (38)	9,592 (38)	11.1 (24)	104 (38)	1,840 (41)	1.0	1.0

^an=21, ^bn=19, ^cn=20

- The DHE C_{max} geometric means were 2,583 pg/mL after MAP0004 alone administration, 2,495 pg/mL after MAP0004 co-administered with ketoconazole, and 27,771 pg/mL after IV DHE administration.
- The pharmacokinetic parameters C_{max}, AUC₀₋₄₈, AUC_{0-∞}, and bioavailable fraction were not statistically significantly different for DHE between MAP0004 administered alone and MAP0004 co-administered with ketoconazole.
- In addition, the half-lives were similar, with a geometric mean half-life of 13.5 hours and 11.2 hours after MAP0004 administered alone and MAP0004 co-administered with ketoconazole, respectively.

RESULTS

TABLE 3. Summary of Statistical Analysis of Derived PK Parameters of DHE

Parameter	p-value
C _{max} : MAP0004 1.0 mg vs. MAP0004 1.0 mg co-administered with ketoconazole	0.8609
C _{max} : MAP0004 1.0 mg vs. IV DHE 1.0 mg	<.0001
AUC ₀₋₄₈ : MAP0004 1.0 mg vs. MAP0004 1.0 mg co-administered with ketoconazole	0.1842
AUC ₀₋₄₈ : MAP0004 1.0 mg vs. IV DHE 1.0 mg	<.0001
AUC _{0-∞} : MAP0004 1.0 mg vs. MAP0004 1.0 mg co-administered with ketoconazole	0.2333
AUC _{0-∞} : MAP0004 1.0 mg vs. IV DHE 1.0 mg	<.0001
F: MAP0004 1.0 mg vs. MAP0004 1.0 mg co-administered with ketoconazole	0.2734

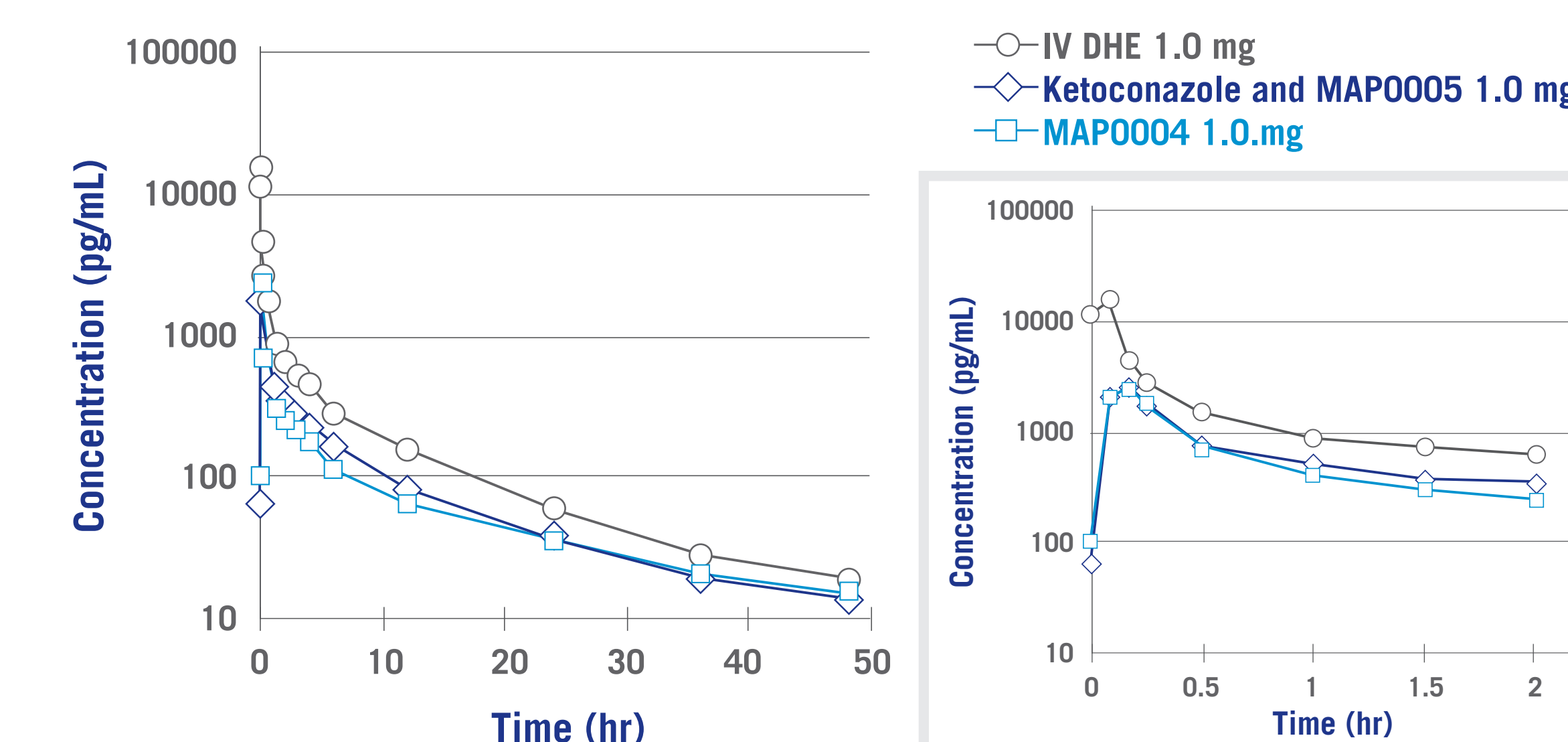
- The 8'-OH DHE C_{max} geometric means were 69 pg/mL after MAP0004 alone administration, 80 pg/mL after MAP0004 co-administered with ketoconazole, and 303 pg/mL after IV DHE administration.
- For 8'-OH DHE, no statistically significant difference in the C_{max} was observed between MAP0004 administered alone and MAP0004 co-administered with ketoconazole.
- A statistically significant difference in 8'-OH DHE AUC₀₋₄₈ and AUC_{0-∞} was observed between MAP0004 administered alone and MAP0004 co-administered with ketoconazole. Nevertheless, the levels of 8'-OH DHE, even at the C_{max} levels, were too low to be pharmacologically relevant.

TABLE 4. Summary of Derived PK Parameters of 8'-OH-DHE, MAP0004 1.0 mg nominal dose and IV DHE

Treatment	C _{max} (pg/mL)	T _{max} (hr) (median)	AUC ₀₋₄₈ (pg ² ·hr/mL)	AUC _{0-∞} (pg ² ·hr/mL)	t _{1/2} (hr)
MAP0004 alone (n = 23)	69 (45)	0.25	99 (135)	260 (93) ^a	12.9 (71) ^b
MAP0004 co-administered with ketoconazole (n = 23)	80 (58)	1.50	420 (114)	905 (58) ^c	9.4 (46) ^d
IV DHE 1.0 mg (n = 22)	303 (39)	0.08	368 (92)	656 (104)	12.4 (35) ^a

^an=22, ^bn=3, ^cn=21, ^dn=15, ^en=12

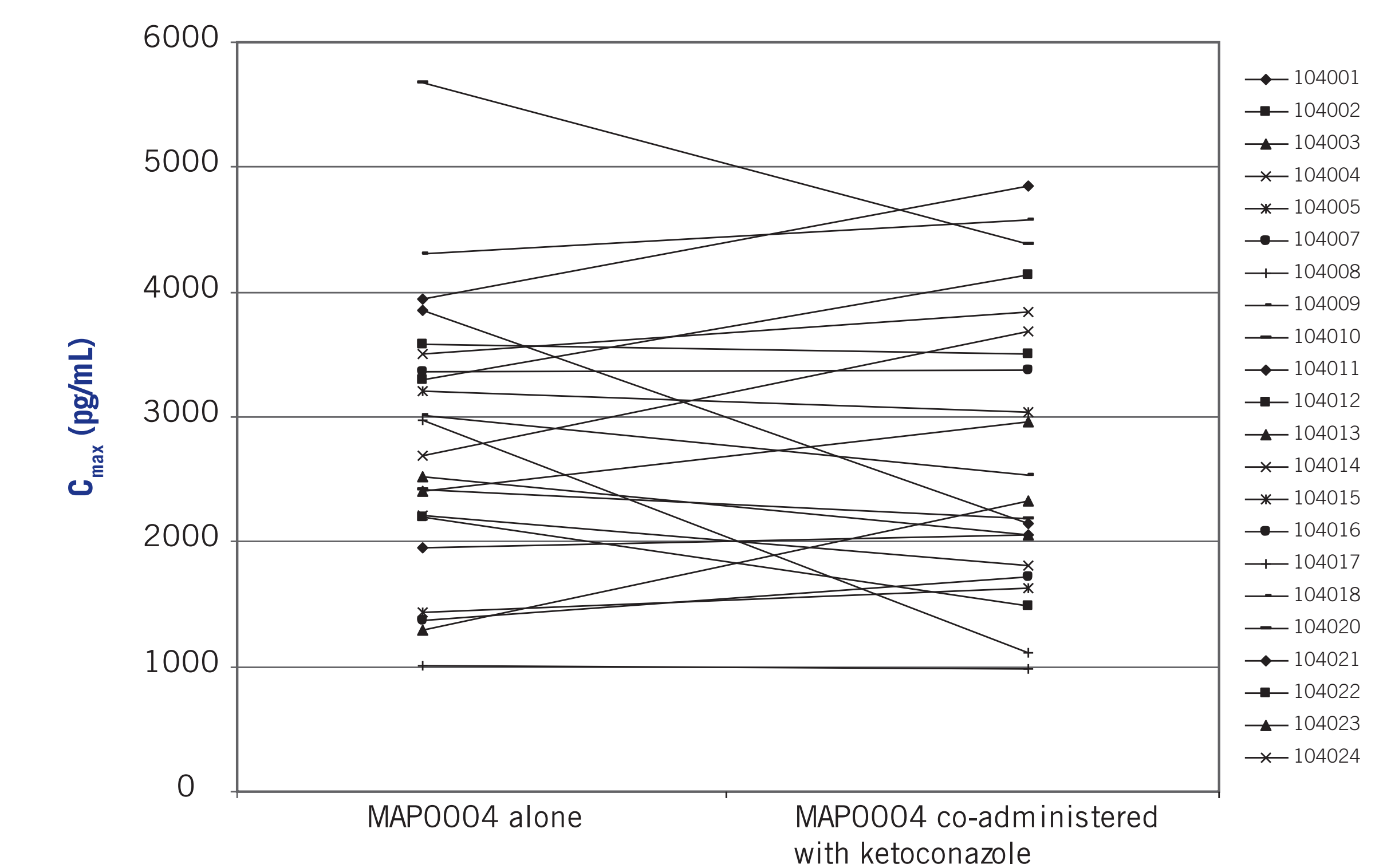
FIGURE 1. Mean Plasma DHE Concentration Time Profiles



- Mean DHE pharmacokinetic values showed there was limited drug interaction with ketoconazole.

RESULTS

FIGURE 2. By Subject Display of C_{max} Following a MAP0004 1.0 mg Nominal Dose Alone and After Co-administration with Ketoconazole



- In addition, a subject by subject display of plasma DHE C_{max} after MAP0004 administration alone and co-administered with ketoconazole shows that there were no subjects with markedly increased plasma DHE concentrations following ketoconazole co-administration.

TABLE 5. Summary of Most Common Treatment Emergent Adverse Events

Most Frequent Adverse Events by Preferred Term	MAP0004 (n = 24)	MAP0004 Co-administered with ketoconazole (n = 24)	IV DHE (n = 22)
Number (% of subjects)	n (%)	n (%)	n (%)
Pain in Extremity	0 (0%)	0 (0%)	4 (18.2%)
Vomiting	0 (0%)	0 (0%)	3 (13.6%)
Nausea	0 (0%)	1 (4.2%)	11 (50%)
Headache	6 (25%)	7 (29.2%)	5 (22.7%)
Dizziness	1 (4.2%)	1 (4.2%)	4 (18.2%)
Flushing	0 (0%)	1 (4.2%)	3 (13.6%)

Most frequent adverse events are presented by preferred term irrespective of treatment group.

- The highest incidence of adverse events was seen in the IV treatment group. Nausea was reported for 50% of subjects after IV DHE dosing, 0% of subjects after dosing with MAP0004 alone, and 4.2% of subjects after MAP0004 was co-administered with ketoconazole.

CONCLUSIONS

The results of this study show no effects of CYP3A4 inhibition on DHE C_{max} or elimination.

The potential for potent CYP3A4 inhibitors to enhance or prolong the pharmacological effects of orally inhaled DHE appears to be minimal.

There is an apparent effect of CYP3A4 inhibition on 8'-OH-DHE elimination, presumably slowing the conversion to 8,10-dihydroxy DHE.

However, the plasma 8'-OH-DHE metabolite concentrations were too low to be pharmacologically relevant.

For other routes of administration of DHE where the 8'-OH-DHE concentrations are higher, the results of this study may not apply.