

A Thorough QT Study Comparing Supratherapeutic Dose of MAP0004 (Orally Inhaled DHE, 3.0 mg nominal dose), Moxifloxacin (400 mg), and Placebo on the QT Interval in Healthy Volunteers

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RATIONALE

Although dihydroergotamine (DHE) has been used clinically for many years and has not been associated with cardiac arrhythmias, no thorough QT study has been performed on DHE by any route of administration.

The objective of this study was to assess the effect of orally inhaled DHE on the QT interval.

Three treatments were evaluated:

- a supratherapeutic dose of MAP0004 (3.0 mg nominal dose, three times the intended dose)
- 400 mg moxifloxacin (a positive control known to prolong QT interval)
- placebo

The effect on QT interval was assessed using Fridericia and Individualized correction formulas.

METHODS

Fifty-four healthy adult (mean age 28 years) men and women were randomized into a Phase 1, double-blind, placebo-controlled, three-period crossover study.

Each subject received all three treatment combinations over three treatment visits separated by a 48 hour washout period.

Triplicate electrocardiograms were performed at pre-dose baseline and continuously over 24 hours post dose in each treatment period.

Pharmacokinetic (PK) blood samples were collected.

Adverse events were monitored throughout the study.

Table 1: Treatments

Study Arms	Inhaler	Capsule
Moxifloxacin	Placebo Inhaler	One over-encapsulated moxifloxacin 400 mg capsule
MAP0004 3.0 mg nominal dose	Active Inhaler	One placebo capsule
Placebo	Placebo Inhaler	One placebo capsule

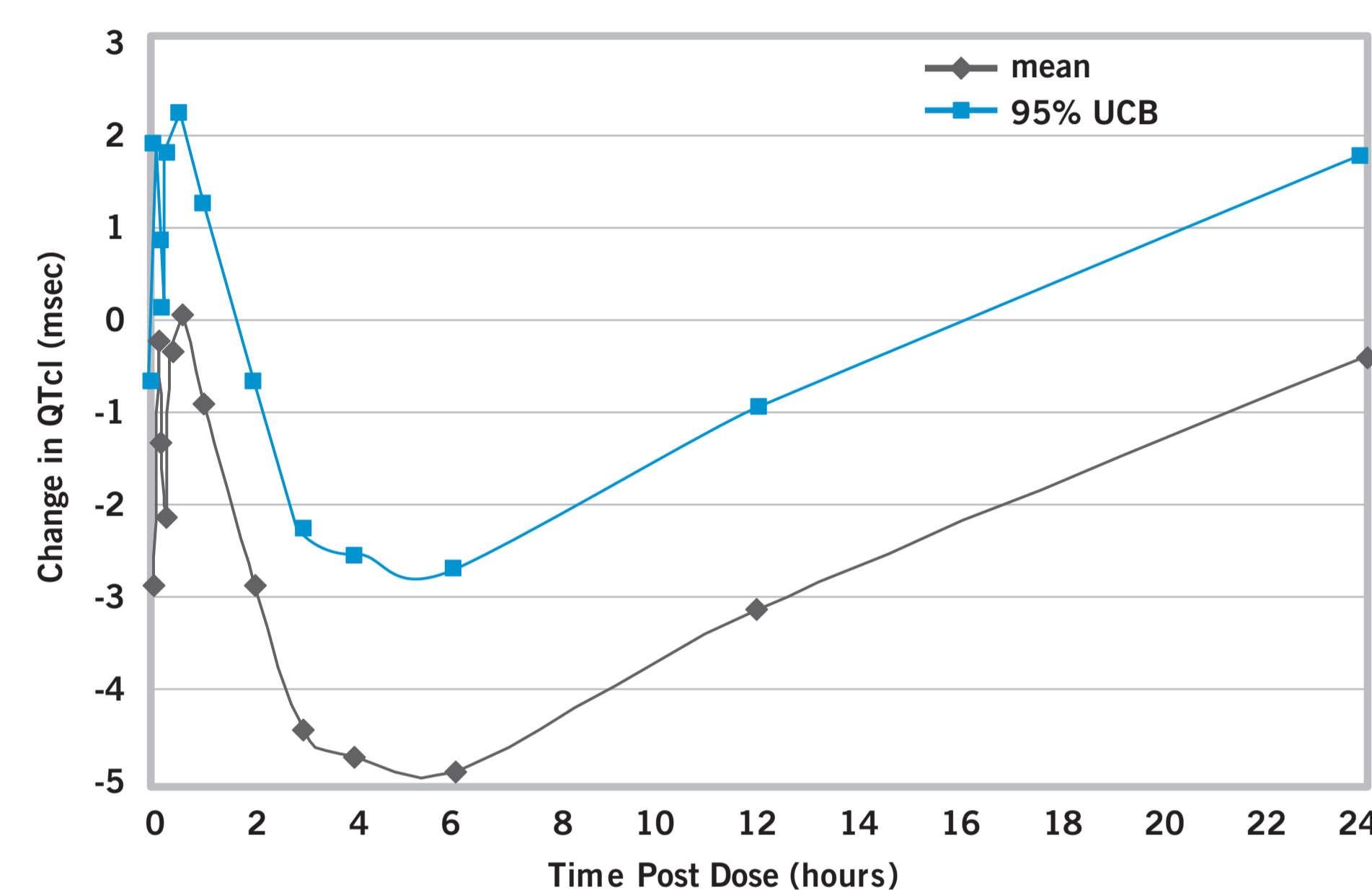
Table 2: Subject Demographic

Demographic (units) N=54 (20 male, 34 Female)	All Subjects Mean ± SD Range
Age (years)	28.0 ± 6.79 19 – 43
BMI (kg/m ²)	25.8 ± 3.19 20 – 32
Height (cm)	168.8 ± 8.72 149 – 189
Weight (kg)	73.7 ± 11.65 51 – 95

RESULTS

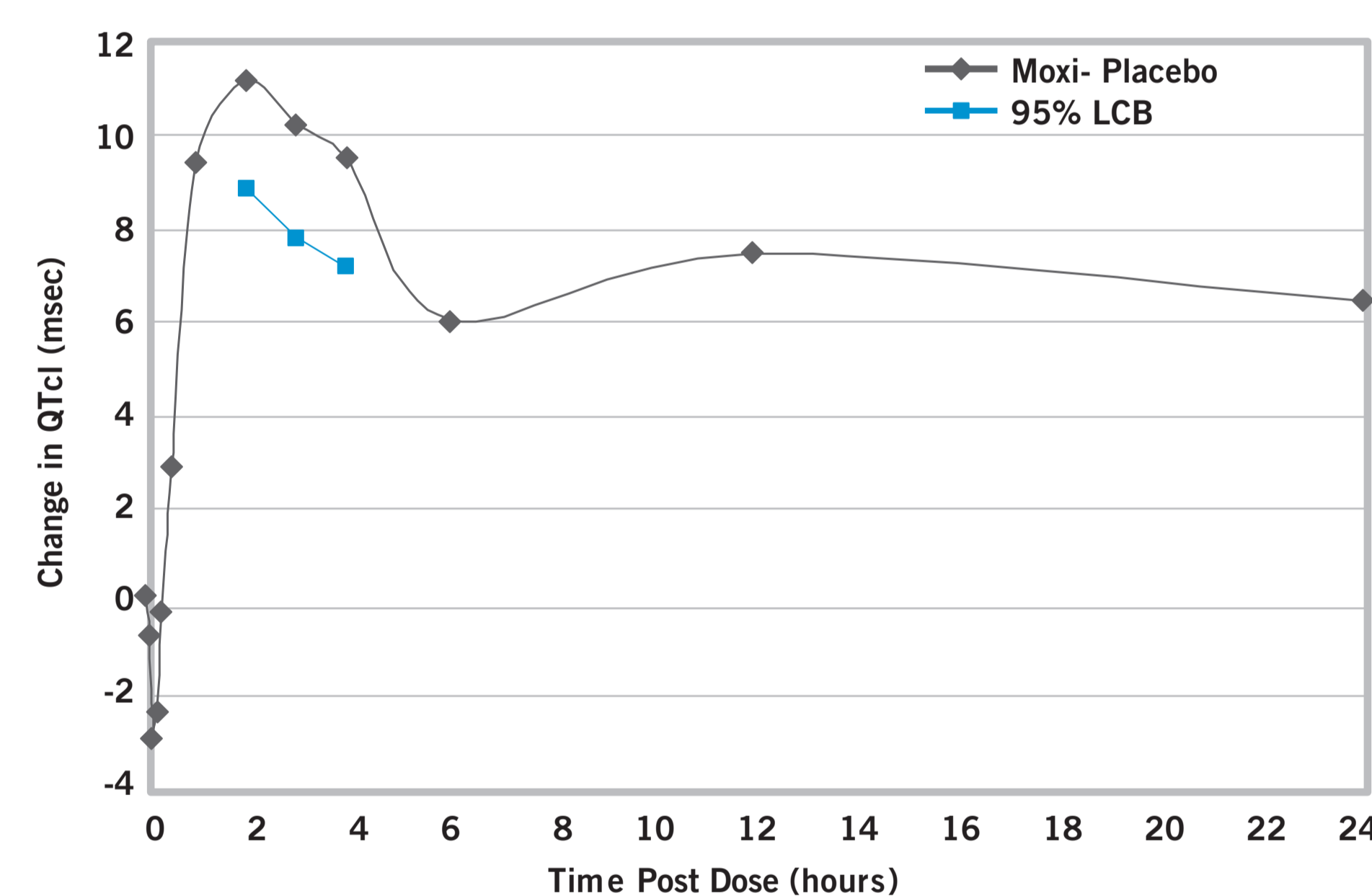
All 54 subjects completed the trial and had measurable plasma levels of DHE after the supratherapeutic MAP0004 dosing.

Figure 1: Mean QTcI Differences from Placebo in Change from Baseline for MAP0004 3.0 mg and Upper 95% Confidence Bounds



- The largest observed mean difference at any time point in the corrected QTcI between the supratherapeutic MAP0004 dose and placebo was 0.08 msec and the largest one-sided 95% upper confidence bound was 2.24 msec, both at 30 minutes after dosing.

Figure 2: Mean Moxifloxacin QTcI Differences from Placebo in Change from Baseline and 95% Lower Confidence Bounds



- Moxifloxacin increased the mean QTcI between 9.57 and 11.28 msec relative to placebo, with a one-sided lower 95% confidence bound between 7.23 and 8.96 msec.
- This confirms that the assay sensitivity was sufficient to detect MAP0004-related effects, had they occurred.

Table 3: Number of Subjects with an Increase in QTc Interval

msec	QTcI Interval		QTcF Interval	
	Placebo (n=54)	MAP0004 3.0mg (n=54)	Placebo (n=54)	MAP0004 3.0mg (n=54)
>450	3	3	1	2
>480	0	0	0	0
>500	0	0	0	0

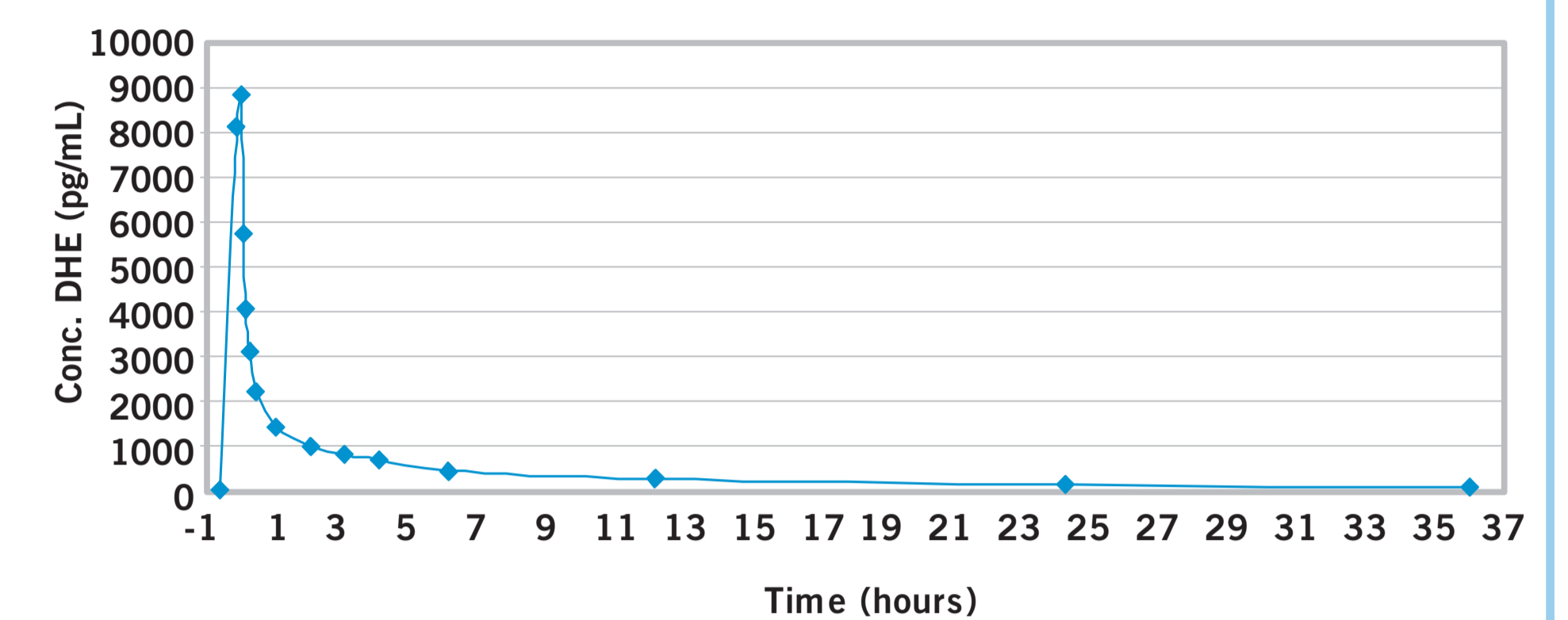
Table 4: Number of Subjects with an Increase From Baseline in QTc Interval

msec	QTcI Interval		QTcF Interval	
	Placebo (n=52)	MAP0004 3.0mg (n=54)	Placebo (n=54)	MAP0004 3.0mg (n=54)
>30	2	1	1	1
>60	0	0	0	0

- None of the subjects had a QRS interval >110 msec that was also a 25% increase over baseline
Or
a PR interval >200 msec that was also a 25% increase over baseline.

RESULTS CONT.

Figure 3: Mean Plasma DHE Concentrations (-0.5 - 36 hours) Following MAP0004 (3.0 mg nominal dose) Linear Scale N=54



- The geometric mean C_{max} was 8757 pg/mL and T_{max} was 5 minutes.
- C_{max} of the MAP0004 3.0 mg nominal dose was approximately 3.8 times that of previously reported 1.0 mg nominal dose. T_{max} and half-life values were similar to those observed in previous studies.

Table 5: Summary of the Five Most Common Treatment Emergent Adverse Events (TEAE)

	Placebo (N = 54)		MAP0004 3.0 mg (N = 54)		Moxifloxacin (N = 54)		All Subjects (N = 54)	
Number (%) of subjects reporting at least one	n	%	n	%	n	%	n	%
TEAE	10	18.5%	26	48.1%	13	24.1%	36	66.7%
Study Drug Related TEAE	4	7.4%	25	46.3%	8	14.8%	27	50%
Most Frequent Adverse Events by Preferred Term Irrespective of Treatment Group								
Nausea	0	0%	15	27.8%	2	3.7%	15	27.8%
Headache	2	3.7%	10	18.5%	2	3.7%	14	25.9%
Dizziness	0	0%	5	9.3%	4	7.4%	8	14.8%
Vomiting	0	0%	4	7.4%	0	0%	4	7.4%
Paraesthesia	0	0%	3	5.6%	0	0%	3	5.6%

- Nausea was the most common adverse event (27.8%).
- All TEAEs were mild to moderate in intensity.
- No TEAE was severe, and there were no serious AEs.
- No subject was discontinued due to a TEAE.

CONCLUSION

A supratherapeutic dose of orally inhaled DHE, three times the intended clinical MAP0004 dose, did not prolong QTc intervals.

The intended commercial dose of 1.0 mg is one-third that of the dose tested in this study.

Nausea was common following 3.0 mg MAP0004 dosing (27.8%), but did not appear to influence the QT interval.