

Assessment of QTc Effect of DHE When Delivered Via the Lung by the Tempo® Inhaler

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INTRODUCTION

MAP0004, orally inhaled dihydroergotamine (DHE) delivered by the Tempo® inhaler, is in development for the potential rapid and long lasting treatment of migraine and in Phase 1 and 2 clinical trials was well-tolerated in migraineurs, healthy subjects and subjects with compromised lung function. Additional clinical trials in migraineurs are ongoing.

The orally inhaled pulmonary delivery route offers several potential advantages over current methods of delivering DHE. Other delivery methods (nasal, IV, injectable) have inherent limitations, such as inconvenience, poor tolerability (both drug and administration), slow onset, inconsistency of absorption, and taste.

Since the pulmonary administration route of MAP0004 delivers the drug directly to the left side of the heart, it is important to assess effects on the conduction system of the heart. This study was undertaken to establish the absence of a QTc prolongation effect of MAP0004.

METHODS

This was a three-period, single-dose, dose-escalation, safety, and PK study in healthy adults. Subjects meeting the entry criteria were assigned by block to receive two sequential, escalating doses of MAP0004 followed by the 1.0 mg approved dose of IV DHE (DHE 45, Novartis) dose at 7–12 day intervals. The second inhaled dose was administered after the safety of the preceding dose had been established. **Table 1** summarizes the study treatments for each block.

Table 1: Study Treatments by Block and Visit

Block	N	Study Drug Administration						
		Day 0			Day 9			Day 21
		Nominal	(Systemic Equivalent)	MAP0004	Nominal	(Systemic Equivalent)	MAP0004	
A	6	0.5 mg	(0.22 mg)	MAP0004	2.0 mg	(0.88 mg)	MAP0004	1.0 mg IV DHE
B	6	1.0 mg	(0.44 mg)	MAP0004	3.0 mg	(1.32 mg)	MAP0004	1.0 mg IV DHE
C	6	2.0 mg	(0.88 mg)	MAP0004	3.0 mg	(1.32 mg)	MAP0004	1.0 mg IV DHE

METHODS continued

ECGs were recorded and analyzed before administration and at 10, 30, 60, and 120 minutes and at 24 hours after administration. Data on the maximum drug concentrations around the time of ECG assessment were evaluated. The geometric mean t_{max} for DHE in all MAP0004 treatment groups occurred approximately 9–11 minutes (approximately 0.2 hour) post treatment, while ECGs were recorded 10 minutes post treatment. The geometric mean t_{max} for 8'OH DHE in all MAP0004 treatment groups was more variable among the groups and occurred approximately 13–37 minutes (approximately 0.2–0.6 hour) post treatment, while ECGs were recorded at 30 minutes post treatment.

The dose-response and concentration-response relationship to the QT/QTc prolongation parameters were evaluated. The effect of MAP0004 doses, including results after dosing with 4 and 6 actuations of MAP0004, representing nominal doses of 2 mg and 3 mg respectively of DHE (2 and 3 times, respectively, higher than the anticipated therapeutic dose) was explored. All ECG interval measurements were performed using hand calipers. Only well trained readers at the ECG reading laboratory manually measured the original ECG printed results. Measuring calipers were calibrated each day. To assess heart rate and QT intervals, one RR and the associated QT interval was selected from each of the II, aVF and V5 leads, whenever possible. If one of the leads was not readable, an alternate was used. If arrhythmia was present, the RR/QT intervals were measured over five leads to ensure accuracy.

The QT intervals were measured under illuminated optical magnifier using electronic Vernier calipers from original ECG tracings only. Discrete U waves were excluded from the QT/QTc interval measurement. Bazett's (QTcB) and Fredericia's (QTcF) correction formulae were both used.

Given the average heart rate observed in this study (<60 beats per minute), the ideal correction for this study was considered to be QTcF. In addition to assessing changes in QT/QTc intervals and heart rate, adverse event data for the following conditions were reviewed for potential QT/QTc interval prolongation or proarrhythmic potential: torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures.

RESULTS & DISCUSSION

There were no clinical differences between the mean QTcF and QTcB intervals among treatment groups compared to baseline at any timepoint. No QTcF or QTcB interval was greater than 450 milliseconds. The least square mean QTcF values ranged from 389.4 milliseconds (0.5 mg nominal MAP0004, T=10 minutes) to 405.9 milliseconds (3.0 mg nominal MAP0004, T=10 minutes); QTcB values ranged from 383.9 milliseconds (0.5 mg nominal MAP0004, T = 24 hr) to 405.5 milliseconds (3.0 mg MAP0004, T=10 minutes).

No clinically significant absolute QTc mean values or changes from baseline were observed in any treatment group. No differences were observed between the MAP0004 and IV DHE treatment groups, and no dose-response relationship was suggested within the MAP0004 dose groups.

Table 2: Summary of Least Square Mean QTcF Intervals at 10 Minutes Postdose

	MAP0004 0.5mg (n=6)	MAP0004 1.0mg (n=6)	MAP0004 2.0mg (n=12)	MAP0004 3.0mg (n=11)	IVDHE (n=6)
Absolute Value at 10 Minutes, Number of Subjects (%)					
>450 ms	0	0	0	0	0
>480 ms	0	0	0	0	0
>500 ms	0	0	0	0	0
LS Means in ms (SEM)	389.4 (3.4)	395.3 (3.5)	397.8 (2.3)	405.9 (2.3)	397.1 (1.8)
Change from Baseline at 10 Min., Number of Subjects (%)					
>30 ms	0	0	0	0	0
>60 ms	0	0	0	0	0
LS Means in ms (SEM)	-6.33 (3.4)	-0.63 (3.5)	2.11 (2.3)	10.23 (2.3)	1.43 (1.8)
Diff in LS Means vs. IV DHE (SEM)	-7.8 (3.7)	-2.1 (4.2)	0.7 (2.7)	8.8 (3.0)	---
90% CI	[-14.0, -1.5]	[-9.1, 5.0]	[-3.9, 5.3]	[3.7, 13.9]	---

CI = confidence interval; DHE = dihydroergotamine; Diff = difference; IV = intravenous; LS = least square; ms = milliseconds; SEM = standard error of the mean.

Table 3: Summary of Least Square Mean QTcB Intervals at 10 Minutes Postdose

	MAP0004 0.5 mg (n=6)	MAP0004 1.0 mg (n=6)	MAP0004 2.0 mg (n=12)	MAP0004 3.0 mg (n=11)	IVDHE (n=6)
Absolute Value at 10 Minutes, Number of Subjects (%)					
>450 ms	0	0	0	0	0
>480 ms	0	0	0	0	0
>500 ms	0	0	0	0	0
LS Means in ms (SEM)	392.4 (5.3)	387.1 (5.6)	399.2 (3.6)	405.6 (3.7)	400.7 (2.9)
Change from Baseline at 10 Min., Number of Subjects (%)					
>30 ms	0	0	1 (8.3%)	0	1 (6.3%)
>60 ms	0	0	0	0	0
LS Means in ms (SEM)	-0.67 (5.3)	-5.94 (5.6)	6.17 (3.6)	12.53 (3.7)	7.67 (2.9)
Diff in LS Means vs. IV DHE (SEM)	-8.3 (5.9)	-13.6 (6.6)	-1.5 (4.3)	4.9 (4.8)	---
90% CI	[-18.3, 1.6]	[-24.8, 2.4]	[-8.8, 5.8]	[-3.4, 13.1]	---

CI = confidence interval; DHE = dihydroergotamine; Diff = difference; IV = intravenous; LS = least square; ms = milliseconds; SEM = standard error of the mean.

CONCLUSION

- No subject had a QTc interval at 10 minutes that was greater than 450 milliseconds.
- No subject had a change of QTc interval from baseline to 10 minutes that was greater than 60 milliseconds.
- Two subjects had a change of QTcB interval greater than 30 milliseconds at 10 minutes; however, this observation was not supported by the QTc with Fredericia's correction.
- 6 inhalations (3.0 mg nominal dose) of MAP0004 produced a greater than 10 millisecond increase in QTc at 10 minutes postdose. However, there was no difference in QT between IV DHE and any dose of MAP0004.
- No other (0.5 mg, 1.0 mg, 2.0 mg) MAP0004 group had a mean difference that was greater than 5 milliseconds or the upper bound of CI that was greater than 10 milliseconds. There were no absolute changes from baseline in QT and QTc (preferred measurements) after MAP0004 treatment at 1.0 mg or 2.0 mg nominal dose (two times the therapeutic dose).
- In general, results observed at all other timepoints are similar to those for 10 minutes.
- Based on data collected in this study from healthy adult volunteers, MAP0004 appears to have no greater potential to cause clinically significant prolongation of the QT or QTc interval than the approved 1.0 mg IV DHE dose which has been in clinical use for 60 years.

REFERENCES

- An Active Controlled, Crossover, 3 Period, 6 Single Doses, Phase 1 Study Investigating the Tolerability, Pharmacokinetics and Metabolic Profile of MAP0004. MAP0004 CLN P101 Clinical Study Report for IND 71,265. MAP Pharmaceuticals, Inc. Mountain View CA, USA.
- The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non AntiArrhythmic Drugs – ICH Tripartite Guideline. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Step 4, E14. October 2005.
- Young WB. Appropriate use of ergotamine tartrate and dihydroergotamine in the treatment of migraine: current perspectives. Headache 1997;Supplement 1:S42–S45.
- Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and DHE in the treatment of migraine and status migrainosus. Neurology 1995;45:577–84.