



# LACK OF HEMODYNAMIC EFFECT OF MEM 1003, A DIHYDROPYRIDINE CALCIUM-CHANNEL BLOCKER: AN EXPOSURE-SAFETY RELATIONSHIP ASSESSMENT

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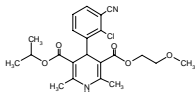
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## BACKGROUND

Dihydropyridines (DHPs), such as nimodipine, are widely viewed as selective L-type calcium blockers and are frequently prescribed for hypertension. DHPs also possess some neuroactive properties that may offset the cognitive symptoms and/or disease progression of Alzheimer's disease. MEM 1003 is a DHP developed to preserve this central bioactivity while lacking significant effects on blood pressure.

Nonclinical studies of MEM 1003 in the dog suggested that its hemodynamic effects were exerted in a dose-, and thereby, exposure-dependent manner. To confirm this exposure-driven relationship, we examined the hemodynamic effects, particularly blood pressure lowering, of MEM 1003 in a clinical study consisting of elderly volunteers with probable Alzheimer's disease.

## METHODS



### Nonclinical:

A cardiovascular telemetry study was carried out in dogs. Eight conscious female beagle dogs were given MEM 1003 at escalating dose levels of 0, 1.25, 5, 10, 15, 20, 25 and 30 mg/kg and monitored for changes in blood pressure (systolic, diastolic and mean arterial), heart rate, ECG parameters, and core body temperature. The pharmacokinetics of MEM 1003 was determined in 4 dogs at each dose level (1.25, 5, 10, 15, 20, 25, and 30 mg/kg) in the dog telemetry study. Whole blood samples were collected through 4 hours of dosing and the resulting plasma analyzed for MEM 1003 concentrations.

### Clinical:

Vital signs were collected in a single, double-blind, randomized, placebo-controlled, study that enrolled 81 elderly volunteers with probable Alzheimer's disease aged 50–74 years. MEM 1003 dosages escalated from 60 mg BID to 120 mg BID. Supine and postural vital signs were monitored at baseline, prior to morning dosing, and at various times for 24 hours. Whole blood samples were obtained concurrently and the resulting plasma analyzed for MEM 1003 concentrations.

### Plasma/Pharmacokinetic Analysis:

MEM 1003 plasma concentrations were measured using a validated LC-MS/MS bioanalytical method. Non-compartmental pharmacokinetic parameters were calculated WinNonlin Pro v4.1.

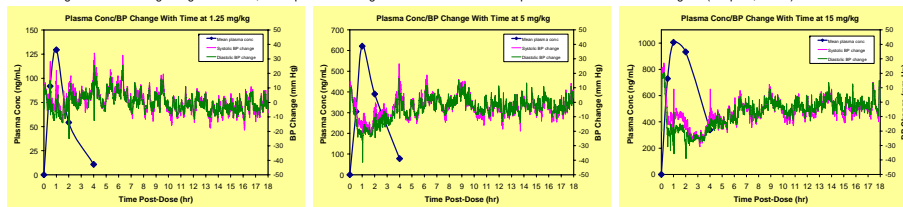
### Electrophysiology:

Acute cell suspensions were prepared in the following solution (mM): 150 choline-Cl, 10 HEPES, 2 CaCl<sub>2</sub>, 1 MgCl<sub>2</sub>, pH 7.4. Cells were transferred to DynaFlow plates coated with PolyHema (Sigma) to inhibit cell adhesion. Whole cell patch clamp recordings were performed using pipettes (4–6 M $\Omega$ ) filled with (mM): 140 CsCl, 10 HEPES, 4 Mg-ATP, 1 EGTA, pH 7.2. Calcium currents were evoked from GFP+ cells at a holding potential of either -80 or -50 mV with a test potential that evoked the maximum current (typically between -20 and 0 mV). Cells were exposed to either MEM 1003 or nimodipine, or both, and IC<sub>50</sub> values were determined by scanning the cell across a range of drug concentrations (1–1000 nM).

## RESULTS & DISCUSSION

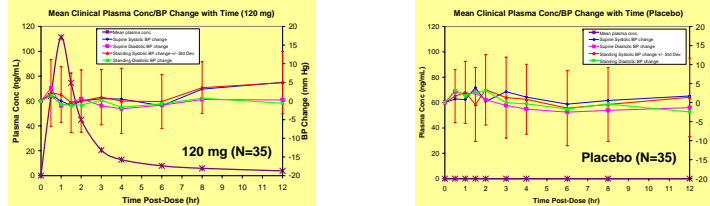
### Nonclinical:

No effect on any parameter was observed in the low (1.25 mg/kg) dose group. This dose was selected to provide plasma exposures in the anticipated clinical range (~100 ng/mL, Graph 1, below). At doses between 5 and 20 mg/kg the magnitude of the temperature and hemodynamic effects resulted in values that were generally within the normal range for female beagle dogs. However, blood pressure changes became more evident at plasma concentrations >400 ng/mL (Graph 2, below)

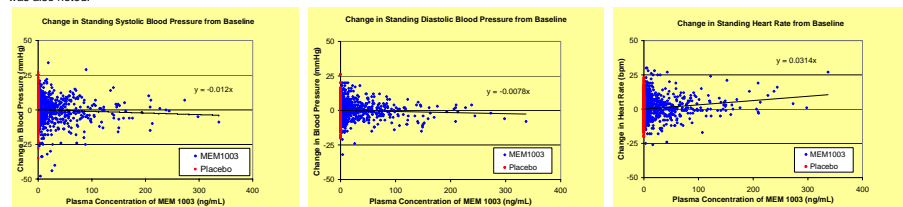


### Clinical:

At anticipated therapeutic exposures, MEM 1003 produced minor and generally asymptomatic changes in supine and standing vital signs. Compare 120 mg and placebo graphs below.



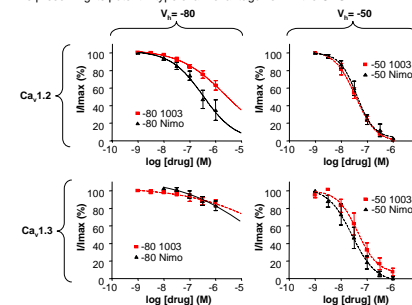
During the clinical study, plasma concentrations ranged from 0 to 337 ng/mL. Scatter plots of concentrations versus change in blood pressure (BP) and heart rate were evaluated for possible relationships. Minimal evidence of correlation with plasma exposures was found for blood pressure and heart rate. High variability in placebo response was also noted.



The respective slope of the regression lines above give the change in BP or HR per ng/mL of MEM 1003 concentration in plasma (Systolic  $\Delta$ BP = -0.012 mm Hg per ng/mL; Diastolic  $\Delta$ BP = -0.0078 mm Hg per ng/mL;  $\Delta$ HR = 0.0314 bpm per ng/mL). The BP changes can be contrasted to those obtained for nifedipine (systolic  $\Delta$ BP = -0.48 mm Hg per ng/mL) given in Reference 1. The comparison suggests that MEM 1003 produces much lower hypotensive effects (~40x lower systolic  $\Delta$ BP).

### Possible Explanation for Absence of Hemodynamic Effects:

In excitable cells (e.g., neurons) that depolarize frequently, MEM 1003 is a potent a1C blocker. In cells that remain at resting potentials (e.g. smooth muscle cells), MEM 1003 lacks potency. This voltage- and state-dependence may explain the lack of vascular effects while preserving its potent L-type channel antagonism in the CNS.



Holding Potential	MEM 1003 EC <sub>50</sub>	Nimodipine EC <sub>50</sub>
-80 mV	>2000 nM	327 nM
-50 mV	36 nM	33 nM
Ratio (-80/-50)	>55x	10x

## CONCLUSIONS

From the clinical study, there were no consistent clinically relevant trends in vital signs. Specifically, there appeared to be no detectable effect of MEM 1003 compared to placebo in the frequency or incidence of orthostatic hypotension. Additional PK/PD analyses presented here further indicated that the hypotensive effects of MEM 1003 were much lower compared to at least one other dihydropyridine calcium-channel blocker, nifedipine. Based on the results of the clinical study, we concluded that MEM 1003 can be safely administered to elderly AD patients at anticipated therapeutic doses for further clinical efficacy studies. We believe that the voltage-dependent binding of MEM 1003 may account for its superior CNS activity without peripheral side effects (especially blood pressure lowering).

## REFERENCE

- Donnelly et al. "Factors Determining the Response to Calcium Antagonists in Hypertension." *J Cardiovasc Pharmacol* 1988; 12(Suppl. 6): S109-S113.