CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206439Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: November 23, 2014

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 206-439 (Namzaric; memantine HCl ER and donepezil HCl; Forest Laboratories, Inc.)

NDA 206-439 is a 505(b)(2) application, submitted on February 26, 2014, to support marketing approval for Namzaric for treatment of moderate to severe Alzheimer's disease. Namzaric is a combination product, containing memantine HCl (MEM) ER and donepezil HCl (DPZ). Doses recommended by the sponsor are 28 mg MEM and 10 mg DPZ (14 mg MEM and 10 mg DPZ for patients with severe renal impairment). Clinical development of the combination was conducted under IND 109,763.

In support of this application, the sponsor cross-referenced two previously approved NDAs for MEM (NDA 21-487 for Namenda; NDA 22-525 for Namenda XR) and stated a reliance on FDA's previous findings of safety and effectiveness for Aricept (DPZ; NDA 20-690). In addition, the following nonclinical study reports were provided:

- Two pharmacology studies of the combination in rodent (MEM-PH-10; MEM-PH-14)
- acute dose study of the combination in female rat (MEM-TX-29)
- 28-day neurotoxicity study of the combination in rat (MEM-TX-27)
- TK/MTD study of the combination in rat (MEM-TX-30)

These studies were reviewed by Dr. Hawver (*cf. Pharmacology/Toxicology NDA Review and Evaluation, NDA 206-439, David B. Hawver, Ph.D., 10/25/2014*). Dr. Hawver notes that the studies MEM-TX-27 and MEM-TX-29 have previously been submitted and reviewed; therefore, his review focused on the pharmacology and TK/MTD studies. Based on his review, Dr. Hawver has concluded that the NDA is approvable, from a pharmacology/toxicology standpoint.

I concur with Dr. Hawver's recommendation on the approvability of the application and his conclusion that the pharmacology data provided do not support the sponsor's claims regarding any synergistic effects of MEM and DPZ on brain acetylcholine levels or on cognitive function (sponsor's labeling, Section 12.2). Additional comments on labeling will be provided separately.

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/s/

LOIS M FREED
11/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206-439
Supporting document/s:	1
Applicant's letter date:	February 26, 2014
CDER stamp date:	February 26, 2014
Product:	Memantine HCl ER and Donepezil HCl
Indication:	Moderate to severe dementia of the Alzheimer's type
Applicant:	Forest Laboratories, Inc.
Review Division:	Neurology Products
Reviewer:	David B. Hawver, Ph.D.
Supervisor:	Lois M. Freed, Ph.D.
Acting Division Director:	Billy Dunn, M.D.
Project Manager:	Teresa Wheelous

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206-439 are owned by Forest Laboratories or are data for which Forest Laboratories has obtained a written right of reference.
Any information or data necessary for approval of NDA 206-439 that Forest Laboratories does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 206-439.

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1 Executive Summary

1.1 Introduction

This submission is a 505(b)(2) NDA for a once-daily oral capsule fixed dose combination of two drugs already approved for marketing in the U.S. for the treatment of patients with Alzheimer's disease: memantine HCl extended release (ER), and donepezil HCl. For nonclinical studies to support this NDA, the sponsor is largely relying on studies previously submitted to approved NDAs for Namenda (NDA 21-487) and Namenda XR (NDA 22-525), and on the Agency's previous findings of safety and effectiveness for the reference listed drug (RLD), Aricept (NDA 20-690).

1.2 Brief Discussion of Nonclinical Findings

Five nonclinical studies were included in the current submission. Two of these, single- and repeated-dose oral neurotoxicity studies in rat, showed that the combination of memantine (MEM) and donepezil (DPZ) increased the incidence, severity, and distribution of neurodegeneration compared with memantine alone. These results have already been reviewed and are adequately described in the current labeling for memantine and donepezil products. The third combination toxicity study consisted of an acute oral dose-ranging study in female rats, with MEM at 100 and 200 mg/kg ± DPZ at 10 and 20 mg/kg, and DPZ alone at 20 mg/kg. Combination treatment increased mortality and the incidence and severity of clinical signs (e.g., convulsions, acrocyanosis, tremors, prostration, ataxia, labored breathing, and excessive salivation) compared to MEM or DPZ alone. This study is reviewed in Section 5 below.

The final two studies were pharmacology studies that are reviewed in detail in Section 4 below. The first study compared the effects of 3-week treatments with MEM, DPZ, and placebo on performance on the Delayed Non-Matching To Sample object recognition task and on hippocampal levels of acetylcholine (ACh) using microdialysis in rats after a partial lesion of the fimbria-fornix. Treatment of lesioned rats with MEM in the drinking water for 3 weeks significantly improved performance on the memory task compared to placebo, but levels of brain ACh were not significantly affected. This experiment also included an acute treatment with MEM or DPZ after the 3-week treatments. However, all results reported in this study were difficult to interpret and unreliable due to the lack of concurrent acute placebo controls, insufficient numbers of animals per group, and/or the absence of individual animal data to allow independent analyses.

The second pharmacology study explored the effects of 3-month treatments with sucrose (control), MEM, DPZ, or MEM + DPZ on performance in the Morris Water Maze and brain Aβ levels in triple transgenic 3xTg-AD mice age 6 to 9 months (young mice); and the same parameters, as well as brain levels of APP, C99, C83, HT7-reactive tau, PHF-1-reactive phosphor-tau, and AT8-reactive phospho-tau, in 3xTg-AD mice age 15 to 18 months (old mice). Treatment of

young mice with the combination of MEM + DPZ improved performance on the MWM, but did not change brain levels of APP, soluble Aβ40 or Aβ42, or insoluble Aβ40 or Aβ42 compared to controls. Treatment of old mice with the combination MEM + DPZ also improved performance on the MWM, but increased brain levels of AT8-reactive phospho-tau and insoluble Aβ40 and Aβ42 compared to controls. These pathophysiological changes would seem to be in the opposite direction of those expected for an effective treatment for Alzheimer's disease, according to most current theories. No explanation was provided for the apparent mismatch between effects on performance and effects on AD-related pathophysiology. No statistical comparisons were made between the groups treated with the combination of MEM + DPZ and the groups treated with MEM or DPZ alone. Finally, individual animal data were not provided to allow independent analyses, so all conclusions based on these data cannot be verified.

1.3 Recommendations

1.3.1 Approvability

From a Pharmacology/Toxicology perspective, this application is approvable.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The following changes should be made to sections of the sponsor's proposed labeling that contain nonclinical information:

1. References to the maximum recommended human dose (MRHD) should be revised such that they refer to the MRHD of 28 mg/10 mg NAMZARIC rather than to the MRHD of MEM or DPZ.

2. Dose comparisons of NOAEL doses of DPZ in animals to the MRHD should be based on 10 mg/day DPZ in the MRHD of 28 mg/10 mg, rather than on (b) (4).

3. Descriptions of the nonclinical studies in Section 8.4 Pediatric Use in the current label for Namenda XR should be inserted into the same section of the label for Namzaric.

4. (b) (4)

5. In Section 13.2 Animal Toxicology and/or Pharmacology, the heading (b) (4)

Detailed labeling recommendations are located in Section 5 of this review.

2 Drug Information

2.1 Drug

Brand Name: Namzaric

Generic Name: Memantine HCl Extended Release (ER) and Donepezil HCl Fixed Dose Combination Capsules

Code Name: MDX-8704

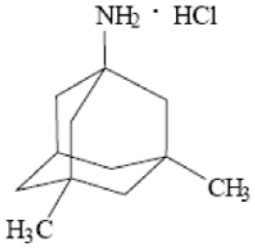
Chemical Name:
Memantine HCl: 1-amino-3,5-dimethyladamantane hydrochloride
Donepezil HCl: (±)-2, 3-dihydro-5, 6-dimethoxy2-[[1-(phenylmethyl)-4 piperidinyl]methyl]-1H-inden-1-one hydrochloride

Molecular Formula:
Memantine HCl: $C_{24}H_{29}NO_3$•HCl
Donepezil HCl: $C_{12}H_{21}N$•HCl

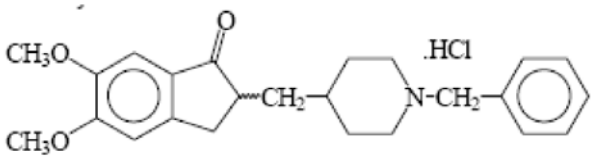
Molecular Weight:
Memantine HCl: 215.77
Donepezil HCl: 415.95

Structure or Biochemical Description:

Memantine HCl:



Donepezil HCl:



Pharmacologic Class:
Memantine HCl: N-methyl-D-aspartate (NMDA) receptor antagonist
Donepezil HCl: Acetylcholinesterase inhibitor

2.2 Relevant INDs and NDAs

IND 109763 Memantine HCl ER and Donepezil HCl Fixed Dose Combination for Moderate to Severe Dementia of the Alzheimer's Type
NDA 21-487 Memantine HCl (Namenda) for Moderate to Severe Dementia of the Alzheimer's Type
NDA 22-525 Memantine HCl ER (Namenda ER) for Moderate to Severe Dementia of the Alzheimer's Type
NDA 20-690 Donepezil HCl (Aricept) for Mild to Severe Dementia of the Alzheimer's Type

2.3 Drug Formulation

Size 1 blue opaque oral capsules containing 28 mg memantine HCl ER/10 mg donepezil HCl.

Size 2 green opaque oral capsules containing 14 mg memantine HCl/10 mg donepezil HCl.

Memantine HCl is formulated as (b) (4), consisting of sugar sphere (b) (4)

Donepezil HCl is formulated as (b) (4)

2.4 Comments on Novel Excipients

No novel excipients were used in the clinical formulation.

2.5 Comments on Impurities/Degradants of Concern

No concerns.

2.6 Proposed Clinical Population and Dosing Regimen

Namzaric 28 mg/10 mg is indicated for the treatment of patients with moderate to severe dementia of the Alzheimer's type who are currently stabilized on memantine HCl (10 mg twice daily or 28 mg extended release once daily) and donepezil (10 mg once daily).

Namzaric 14 mg/10 mg is indicated for the treatment of patients with moderate to severe dementia of the Alzheimer's type who have severe renal impairment and are currently stabilized on memantine HCl (5 mg twice daily or 14 mg extended release once daily) and donepezil (10 mg once daily).

2.7 Regulatory Background

This is a 505(b)(2) NDA submission for a fixed dose combination oral capsule formulation for the treatment of moderate to severe dementia of the Alzheimer's type. As such, it relies on the Agency's previous findings of safety and effectiveness for the RLD, Aricept (NDA 20-690), and references approved NDAs for Namenda (NDA 21-487) and Namenda XR (NDA 22-525) previously submitted by the current sponsor, Forest Laboratories, Inc. IND 109763

Donepezil HCl (oral tablets; 5 mg, 10 mg) was approved on November 25, 1996, for the treatment of mild to moderate dementia of the Alzheimer's type (NDA 20-690 Aricept, Eisai America, Inc.). The indication was expanded to include severe Alzheimer's disease on October 13, 2006. Donepezil HCl 23 mg (oral tablet) was approved on July 23, 2010, for the treatment of moderate to severe dementia of the Alzheimer's type (NDA 22-568 Aricept 23 mg, Eisai, Inc.).

Memantine HCl (oral tablet; 5 mg, 10 mg) was approved on October 16, 2003, for the treatment of moderate to severe dementia of the Alzheimer's type (NDA 21-487 Namenda, Forest Laboratories, Inc.). Memantine HCl XR (oral capsule; 7 mg, 14 mg, 21 mg, 28 mg) was approved on June 21, 2010, for the treatment of moderate to severe dementia of the Alzheimer's type (NDA 22-525 Namenda XR, Forest Laboratories, Inc.).

IND 109763 was submitted by Adamas Pharma, Inc., on September 15, 2010, to support the development of ADS-7803 (memantine HCl and donepezil HCl) capsules for the treatment of moderate to severe dementia of the Alzheimer's type. The initial proposed clinical protocol was allowed to proceed.

At an End of Phase 2 meeting with Adamas Pharma, Inc., on October 13, 2011, the only nonclinical issue discussed was the need for a single-dose oral neurotoxicity study in rats with memantine alone, donepezil alone, and both drugs in combination: "We continue to recommend that the study be conducted concurrent with Phase 3 clinical trials; however, if the study is not available at the time of NDA submission, it will be a post-marketing requirement, unless we have determined that you no longer need to conduct the study." This study was submitted as a post-marketing requirement to NDA 22-525, and has also been submitted to the current NDA.

At a Type C meeting with Adamas Pharmaceuticals, Inc. on June 20, 2013, no nonclinical issues were discussed.

IND 109763 was transferred from Adamas Pharma, Inc. to Forest Research Institute, Inc., a subsidiary of Forest Laboratories, Inc., on July 12, 2013.

At a Pre-NDA meeting with Forest Research Institute, Inc. on November 19, 2013, the Division agreed that the completed pharmacology and toxicology

program that led to FDA's previous finding of safety and effectiveness for the RLD, Aricept, reference to the completed pharmacology and toxicology program submitted for the approval of Namenda, as well as the additional studies described in the Pre-NDA briefing package, supported the review and potential approvability of MDX-8704 (ADS-7803) for the indication of moderate to severe dementia of the Alzheimer's type.

NDA 206-439 Namzaric (memantine HCl ER and donepezil HCl) for the treatment of moderate to severe dementia of the Alzheimer's type was submitted on February 26, 2014, by Forest Laboratories, Inc.

3 Studies Submitted

3.1 Studies Reviewed

Combined Effect of Donepezil and Memantine on Hippocampal Acetylcholine Release and Recognition Memory in Freely Moving Rats
(Study MEM-PH-10)

Therapeutic Administration of Donepezil and Memantine in the Triple Transgenic Mice: Evaluation for Treatment of Established Neuropathology and Cognitive Impairments
(Study MEM-PH-14)

Memantine/Donepezil: Toxicokinetic/Maximum Tolerated Dose Study in Rats
(Non-GLP Study MEM-TX-30)
(Not previously submitted or reviewed; results were used to select doses for GLP Study MEM-TX-29)

3.2 Studies Not Reviewed

Memantine/Donepezil: A 28-Day Oral Toxicity Study in Rats
(GLP Study MEM-TX-27)
(Previously reviewed under IND (b) (4))

Memantine/Donepezil: A Single Oral Dose Toxicity Study in Female Rats
(GLP Study MEM-TX-29)
(Previously reviewed under IND (b) (4))

3.3 Previous Reviews Referenced

IND (b) (4) Memantine for AD Pharmacology/Toxicology Review dated October 12, 2012, David B. Hawver, Ph.D.; Single Dose Oral Combination Neurotoxicity Study in Rat

IND (b) (4) Memantine for AD Pharmacology/Toxicology Review dated June 03, 2010, David B. Hawver, Ph.D.; 28-Day Oral Combination Neurotoxicity Study in Rat

NDA 22525 Namenda ER for AD Pharmacology/Toxicology Review dated June 15, 2010, David B. Hawver, Ph.D.

NDA 21487 Namenda for AD Pharmacology/Toxicology Review dated October 09, 2003, Kathy Haberny, Ph.D.

NDA 20690 Aricept for AD Pharmacology/Toxicology Review dated July 24, 1996, Barry N. Rosloff, Ph.D.

4 Pharmacology

4.1 Primary Pharmacology

Two primary pharmacology studies were submitted in support of the sponsor's proposed changes to the mechanism of action section of the labeling for Namzaric from the language used in the current labels for each component drug; neither study was needed to support approval of NDA 206-493. These studies are reviewed below.

Combined effect of donepezil and memantine on hippocampal acetylcholine release and recognition memory in freely moving rats

(Study MEM-PH-10; conducted by [redacted](b) (4) Final report May 22, 2008)

Methods

A total of 49 male Wistar rats (National laboratory animal center, [redacted](b) (4)) weighing 400–550 g (age 32 weeks) at the beginning of the experiment were used for the study. The animals were first trained to delayed non-match to sample object recognition task performance (DNMS task). The training phase was continued until the animal reached a criterion of 80% or more correct choices on three consecutive testing days (pre-lesion performance). Thereafter the rats were divided into the following 5 treatment groups:

Group A (sham lesion + placebo + acute MEM 5.0 mg/kg), 13 rats
Group B (FF-lesion + subchronic MEM 30 mg/kg/day + acute DPZ 2.5 mg/kg), 8 rats
Group C (FF-lesion lesion + subchronic DPZ 2.5 mg/kg/day + acute MEM 5.0 mg/kg), 14 rats
Group D (FF-lesion + placebo + acute MEM 5.0 mg/kg), 6 rats
Group E (FF-lesion + placebo + acute DPZ), 8 rats

Each animal was randomly assigned to sustain either sham lesion or a partial fimbria-fornix lesion. The lesion group received bilateral electrolytic lesions, produced by passing 500 µA anodal current for 40 sec through a tungsten electrode (0.1 mm in diameter, un-insulated about 0.75 mm at the tip of the electrode). The lesion coordinates were 1.5 mm posterior to bregma; 0.7 mm and 1.6 mm lateral to midline; 4.4 mm and 4.5 mm below dura for fornix and fimbria, respectively. The sham-lesioned group was treated identically, but the electrode tip was only lowered 2.0 mm below dura and no current was applied. Finally, the microdialysis guide cannula ([redacted](b) (4)) was implanted just above the right dorsal hippocampus (mm from bregma: AP -4.4 mm; L – 2.5 mm; V – 1.6 mm).

One day prior to initiation of microdialysis experiments, the microdialysis probe was inserted through the guide cannula and the hippocampus was continuously perfused with the Ringer solution (145 mmol/L NaCl, 2.7 mmol/L KCl, 1.2 mmol/L $CaCl_2$, and 1.0 mmol/L $MgCl_2$) at a rate of 0.5 µL/min for 18 h ([redacted](b) (4),

(b) (4)). The next day, the perfusion speed was increased to 2 µL/min and 750 nM neostigmine was added to the perfusion fluid to prevent hydrolysis of ACh during sample collection. The perfusion was continued for the next 2.5 h before sampling the dialysate. The total sampling time was 2 h 30 min and included 12 samples (each 10 min, 20 µL).

Delayed non-match to sample object recognition task
The rectangular apparatus was made of perspex glass (41 x 27 x 35 cm; length, width height) and was divided into two compartments. On the opposite side of the apparatus (goal area) was a separate hole-board (23 x 13 x 1 cm) that had six drilled food wells (2.0 cm in diameter and 1.0 cm in depth) in two evenly spaced parallel rows. The objects were glued onto a square, thin metal plate (4 x 4 cm). The rats were able to easily remove the objects from the top of the food well.

Pre-training: During the first days of pre-training, each animal was handled and allowed to explore test apparatus for 20 min. The animals learned to displace the object above the food consistently within 3-5 days.

Training: On the second week of training, the delayed non-match to sample (DNMS) protocol was introduced. Each animal received 20 trials per day. The training phase continued until the animal reached a criterion of 80% or more correct choices on three consecutive sessions (pre-lesion performance). The rats reached the criterion approximately after 5.5 weeks of training.

Test 1: Test 1 took place 17 days after fimbria-fornix lesion. The animals were pre-trained on the task three days before Test 1 was performed. The result of Test 1 was calculated as the mean score on two testing days.

Test 2: Test 2 took place one day after Test 1. The animals were treated acutely either with memantine (5.0 mg/kg) or donepezil (2.5 mg/kg) 1 h before task performance.

ACh levels in microdialysis samples were determined using LC-MS methods validated according to the FDA guideline on bioanalytical method validation. The limit of quantification was 0.15 nM (1.5 fmol injected) and linearity was maintained over the concentration range of 0.15 – 73 nM. Minimum sample size was 15 µL. The accurate placement of microdialysis cannulae, the size of the fimbria-fornix lesion, and AChE staining density were verified in all animals by histological analysis after histochemical staining of sections for AChE.

Results

Part A. Object recognition task

Model validation
Prior to lesioning of the fimbria-fornix, 5.5 weeks of training on the DNMTS task was sufficient for all groups to reach the pre-specified criterion of 80% or greater correct choices on three consecutive testing days.

Bilateral electrolytic lesion of the fimbria-fornix resulted in impaired performance on the DNMTS object recognition task compared to sham-lesioned animals and compared to pre-lesion performance, as well as a decrease in the number of AChE-positive neurons in the dorsal hippocampus of more than 50% compared to sham-lesioned rats.

Subchronic drug effects
Oral administration of MEM for 3 weeks significantly improved performance of lesioned rats on the DNMTS task compared to treatment with placebo, whereas treatment with DPZ resulted in a modest improvement that was not statistically different from treatment with placebo.

Acute drug effects
No significant differences were observed in DNMTS performance among the following groups: sham lesioned + 3 wks placebo + acute MEM; lesioned + 3 wks MEM + acute DPZ; lesioned + 3 wks DPZ + acute MEM; lesioned + 3 wks placebo + acute MEM; and lesioned + 3 wks placebo + acute DPZ. No statistical comparisons were provided for values in Figure 6 vs those in Figure 7. In view of the lack of concurrent control groups receiving acute placebo treatment, no conclusions can be drawn from these data.

Part B. Hippocampal acetylcholine release during object recognition task
Model validation
As shown in the sponsor's Figure 8 below, hippocampal extracellular ACh levels measured using in vivo microdialysis increased from a baseline of ~20 nM to peak of ~47 nM during exploration of the empty holeboard, then to successive peaks of ~65 nM during the two trials of the DNMTS object recognition task. Though not explicitly stated, it seems likely that the values in Figure 8 were obtained from a single representative animal, since no error bars were included and the peak values are different from the mean baseline, holeboard, and task values presented in Figure 9 below. The sponsor notes that "The task-induced fluctuation in ACh release was similar in all treatment groups," which is reflected in Figure 9.

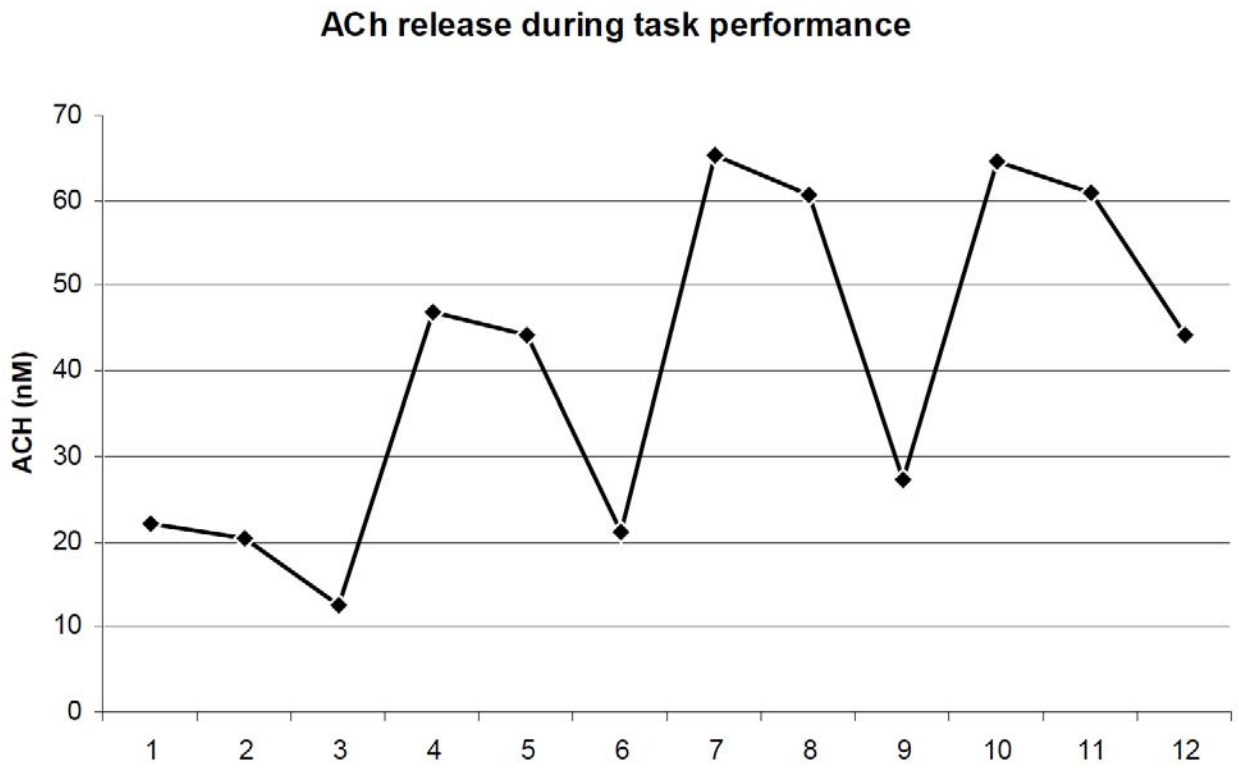


Figure 8. Hippocampal acetylcholine release during the DNMS task performance. Baseline (samples 1-3), empty holeboard (sample 4), task phases (samples 7 and 10). Each sample was collected during a 10-minute interval.

Subchronic drug effects

As shown in the sponsor's Figure 9 below, no significant differences were observed between groups in the hippocampal extracellular ACh levels measured at baseline, during holeboard exploration, or during task performance. The sponsor notes that the lack of reduction in ACh release due to the fimbria-fornix lesion (i.e. lesion + placebo vs. sham + placebo), most likely reflects a compensatory increase in ACh release from the remaining cholinergic terminals, since the fimbria-fornix lesion was intentionally only partial. The sponsor cites two earlier studies showing no change in hippocampal ACh release after similar fimbria-fornix lesions (Erb et al., 1997, Neurosci Lett 231(1):5-8; and Lapchak et al., 1991, J Neurosci 11(9):2821-2828). The group treated with MEM for 3 weeks showed an apparent modest increase in ACh levels at all three timepoints, but the increases were not statistically significant compared to the lesion + placebo group.

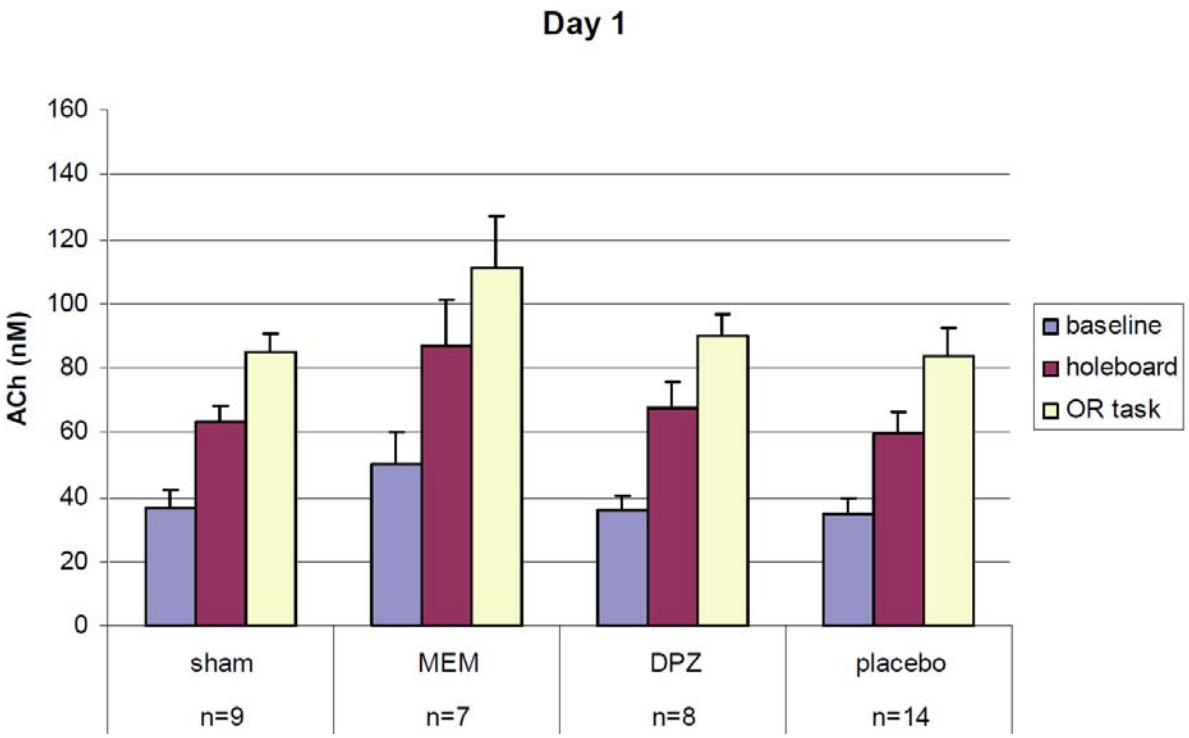


Figure 9. Effects of subchronic drug administration and task phase on hippocampal acetylcholine release in male Wistar rats. Data are given as means ± SEM. ANOVArm: F(3,34)=0.8, P=0.49 (between groups); F(2,31)=57.8, P<0.001 (task phase).
sham = sham lesion + placebo
MEM = fornix lesion + MEM (30 mg/kg/day p.o.) for 3 weeks
DPZ = fornix lesion + DPZ (2.5 mg/kg/day p.o.) for 3 weeks
placebo = fornix lesion + placebo

Acute drug effects

As shown in the sponsor's Figure 10 below, acute administration of MEM or DZP resulted in some statistically significant differences in the level of extracellular ACh in the hippocampus among the groups tested. However, once again, the lack of appropriate concurrent control groups makes these differences difficult to interpret. For example, ACh levels were significantly increased in rats receiving MEM for 3 weeks followed by acute DPZ compared to those receiving DPZ for 3 weeks followed by acute MEM (P=0.001). It is unclear whether this difference is due to the differences in subchronic treatment, acute treatment, or both. The groups receiving acute MEM after subchronic DPZ or subchronic placebo showed higher ACh levels than those receiving acute DPZ after subchronic MEM or subchronic placebo (P=0.003); while this may be due to the acute MEM, the difference in subchronic treatments complicates the issue. Even a direct comparison of the two subchronic placebo groups (placebo + acute MEM vs. placebo + acute DPZ) would not be as informative as comparing each of those to a group receiving subchronic placebo + acute placebo. Finally, the difference in ACh levels between the DPZ + acute MEM group and the placebo + acute MEM group was not statistically significant (P=0.11). Whether this means that the subchronic DPZ treatment did not meaningfully change the hippocampal response to acute MEM, or that

the number of animals in each group was too small (N=7-8) to confirm that such a change may have occurred is unclear. The sponsor also notes, correctly, that acute DPZ would not be expected to increase ACh levels under the conditions tested, because AChE is already maximally inhibited by the 750 nM neostigmine present in the microdialysis perfusion medium to prevent breakdown of ACh before it can be measured.

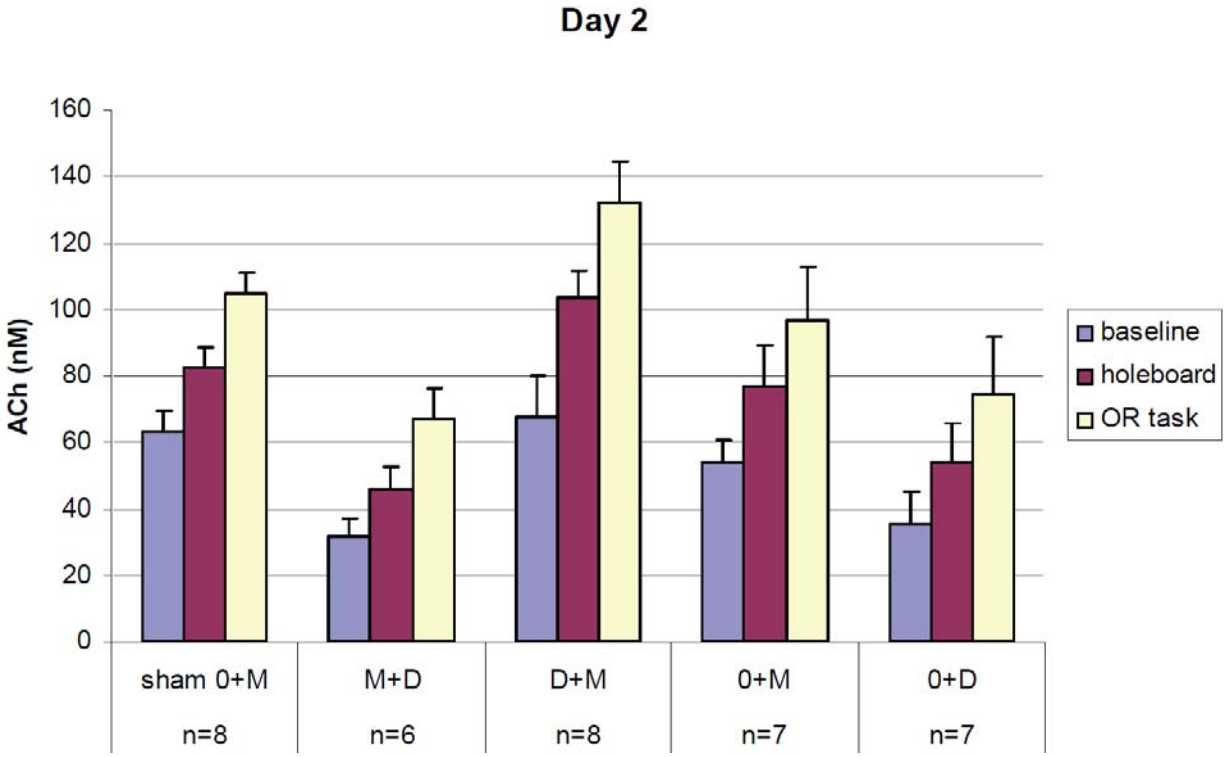


Figure 10. Effect of acute drug injection and task phase on hippocampal acetylcholine release. Data are given as means ± SEM.

Overall statistics:
– ANOVArm: F(4,31)=5.0, P=0.003 (between groups); F(2,30)=58.9, P<0.001 (task phase).
– One-way ANOVA: baseline P=0.021; holeboard P=0.001; OR task P=0.008 (between groups)

Selected group comparisons:
– acute MEM groups (D+M and 0+M) vs. acute DPZ groups (M+D and 0+D): ANOVArm: F(1,25)=10.5, P=0.003 (between groups); t-test: baseline P=0.012, holeboard P=0.001, OR task P=0.009.
– comparison between acute MEM groups (D+M vs. 0+M): ANOVArm: F(1,13)=2.9, P=0.11 (between groups).
– order of administration D+M vs M+D: ANOVArm F(1,12)=18.09, P=0,001 (between groups).

sham 0+M = sham lesion + placebo + acute MEM (5 mg/kg i.p.)
M+D = fornix lesion + MEM (30 mg/kg/day p.o.) for 3 weeks + acute DPZ (2.5 mg/kg i.p.);
D+M = fornix lesion + DPZ (2.5 mg/kg/day p.o.) for 3 weeks + acute MEM (5 mg/kg i.p.);
0+M = fornix lesion + placebo + acute MEM (5 mg/kg i.p.)
0+D = fornix lesion + placebo + acute DPZ (2.5 mg/kg i.p.)

In Figure 11 below, the sponsor has directly compared baseline extracellular hippocampal ACh levels on Day 1 (with no acute treatment) to those on Day 2 (following acute treatment with MEM or DPZ). All groups treated with acute MEM showed statistically significant increases in baseline ACh levels compared to baseline levels on the previous day without any acute treatment (however, no N's were provided). No statistical comparisons were provided for Day 2 vs. Day 1 ACh measurements made during the holeboard exploration and object recognition task phases of the experiment, though they appear to be moving in the same direction as the baseline measurements, based on comparison of Figure 10 with Figure 9. As noted previously, concurrent controls would provide more reliable data than comparisons between experiments on successive days.

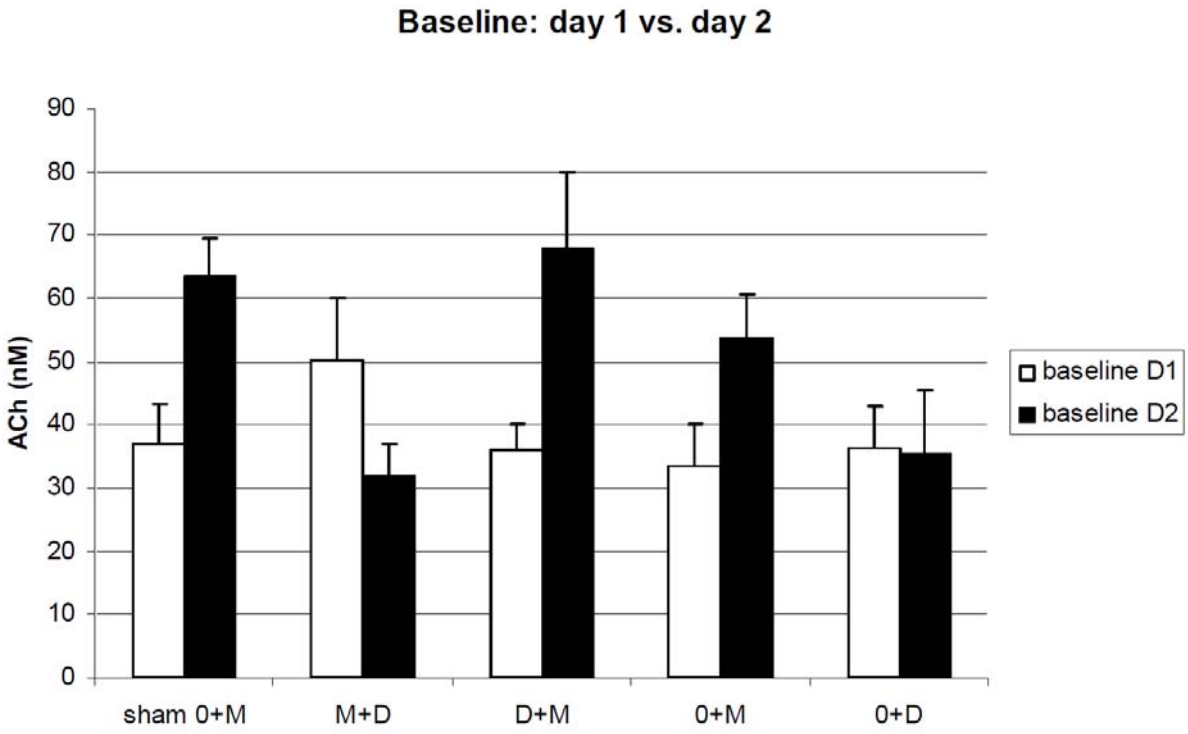


Figure 11. Comparison of baseline acetylcholine levels between microdialysis days 1 and 2. Data are given as means ± SEM.
Baseline day1 vs. day 2 (within groups, paired-samples t-test):
- sham 0+M: P=0.006
- M+D: P=0.08
- D+M: P=0.006
- 0+M: P=0.013
- 0+D: P=0.89

sham 0+M = sham lesion + placebo + acute MEM (5 mg/kg i.p.)
M+D = fornix lesion + MEM (30 mg/kg/day p.o.) for 3 weeks + acute DPZ (2.5 mg/kg i.p.);
D+M = fornix lesion + DPZ (2.5 mg/kg/day p.o.) for 3 weeks + acute MEM (5 mg/kg i.p.);
0+M = fornix lesion + placebo + acute MEM (5 mg/kg i.p.)
0+D = fornix lesion + placebo + acute DPZ (2.5 mg/kg i.p.)

Sponsor's Conclusions

- The partial fimbria-fornix lesion resulted in significant reduction of performance on the DNMTS object recognition task in male Wistar rats (60% correct choices in lesioned + 3-week placebo vs. 78% in sham-lesioned + 3-week placebo).

- Treatment of lesioned rats with 30 mg/kg/day MEM in the drinking water for 3 weeks improved performance on the DNMTS object recognition task compared to treatment with placebo. In contrast, treatment of lesioned rats with 30 mg/kg/day DPZ for 3 weeks, acute 5 mg/kg i.p. MEM, or acute 2.5 mg/kg i.p. DPZ failed to show significant changes in performance on this task.

- Hippocampal extracellular ACh levels consistently increased during performance of the DNMTS object recognition task compared to baseline.

- Baseline hippocampal extracellular ACh levels were increased ~60 to 90% in response to acute 5.0 mg/kg i.p. MEM in lesioned rats pretreated for 3 weeks with DPZ (2.5 mg/kg/day) or placebo. ACh levels were slightly (but not statistically significantly) increased after treatment for 3 weeks with 30 mg/kg/day MEM in the drinking water.

- The sponsor mistakenly concludes that "Both the memory improvement and increase in ACh release after memantine was higher in the group first receiving subchronic memantine compared to the group receiving memantine after placebo." The data showed that subchronic MEM treatment significantly improved performance on the DNMTS task (but acute MEM treatment did not), and that acute treatment with MEM after subchronic placebo significantly increased hippocampal ACh levels (but subchronic MEM treatment did not).

Reviewer's Conclusions

The data submitted are inadequate to support the conclusion that administration of MEM in combination with DPZ enhances memory performance and/or ACh release in the hippocampus of rats. First, no individual animal data were provided to allow independent analysis. Second, the numbers of animals used was too small (N=5-9 in each drug group) to allow meaningful conclusions to be drawn from these results. Finally, as noted previously, lack of appropriate concurrent controls in some experiments compromised the validity of the sponsor's conclusions.

Therapeutic administration of donepezil and memantine in the triple transgenic mice: Evaluation for treatment of established neuropathology and cognitive impairments

(Study MEM-PH-14; conducted by [redacted] (b) (4) Final report October 1, 2010)

Methods

Homozygous 3xTg-AD mice ($PS1_{M146V}$/ $PS1_{M146V}$; APP_{Swe} +/+; Tau_{P301L} +/+) aged 6 or 15 months were treated for 3 months with sucrose, donepezil (DPZ; 1 mg/kg/day), memantine (MEM; 30 mg/kg/day), or DPZ (1 mg/kg/day) + MEM (30 mg/kg/day) via drinking water. Age- and sex-matched non-transgenic (NonTg) mice were used as additional controls (see sponsor's table, below.)

Table 1: Proposed groups

	Age of 3xTg-AD mice	
	6 -9 months	15-18 months
Control group	10	15
Donepezil and memantine	10	15
Donepezil	10	15
Memantine	10	15
	Age of NonTg mice	
	6 -9 months	15-18 months
Control group	10	15
Donepezil and memantine	10	15
Donepezil	10	15
Memantine	10	15
Total number of animals in study = 200	**80**	**120**

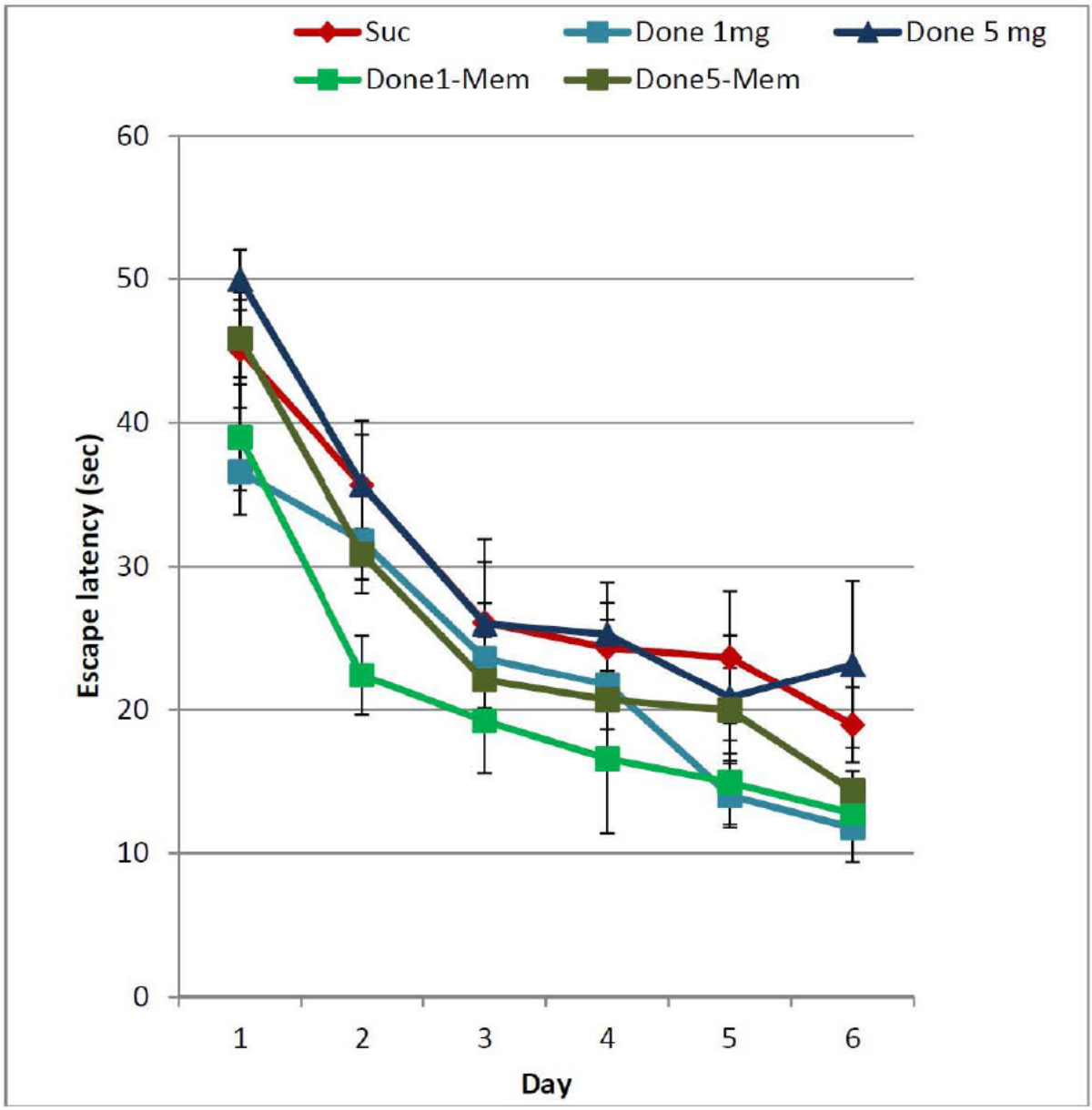
(Sponsor's Table 1; page 2 of Study Report)

Brain levels of soluble and insoluble Aβ40 and Aβ42 were measured using sandwich ELISA *(see Oddo et al., 2003, Neuron 39(3):409-421 for details)*, while steady state levels of holo-APP, C99, secreted APP, tau, and hyperphosphorylated tau were measured using western blots. Spatial memory was evaluated using the Morris Water maze (MWM) task *(see Billings et al., 2005, Neuron 45(5):675-688).*

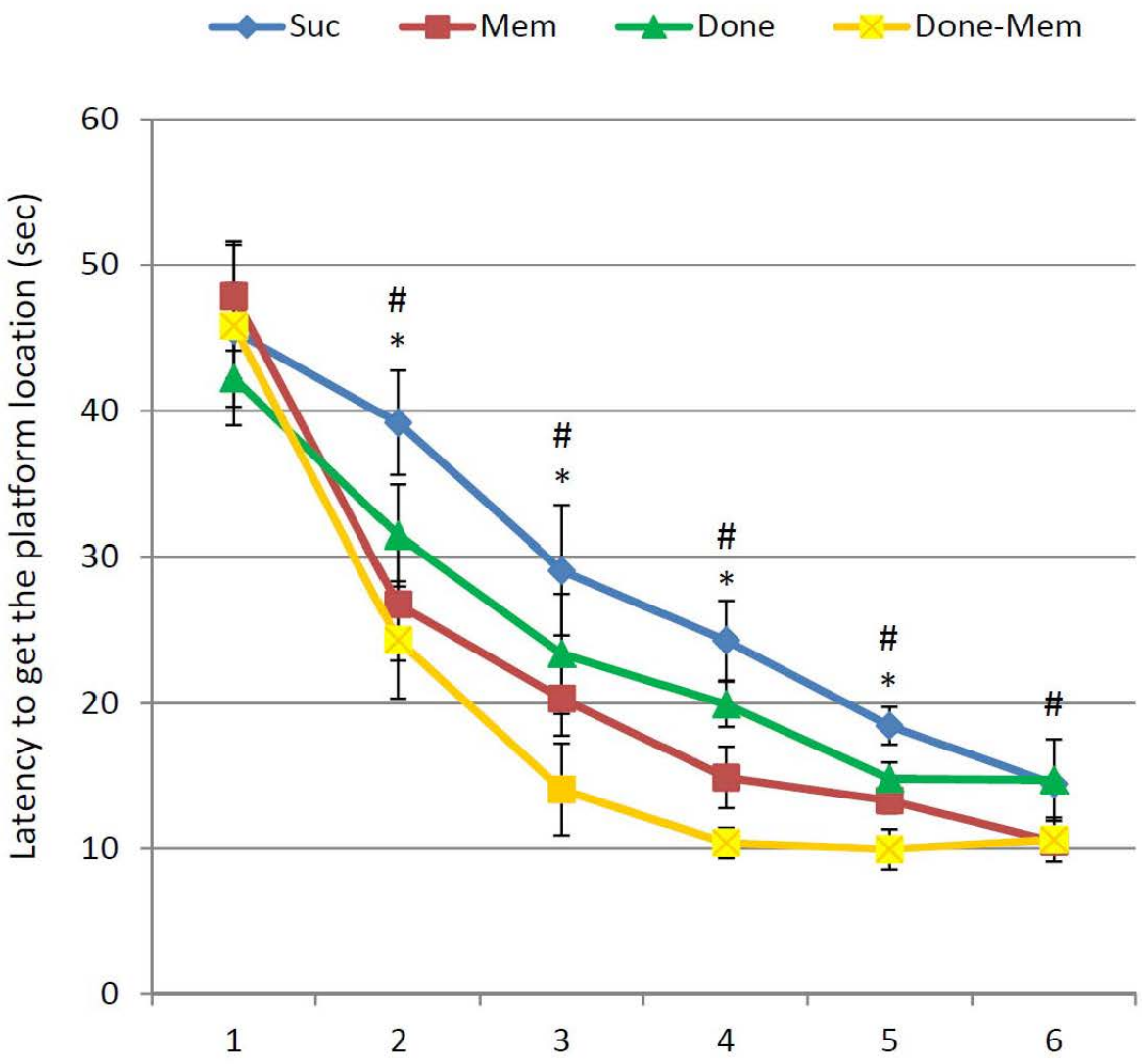
Results

As shown in the sponsor's figure below, treatment of 9-month old 3xTg-AD mice for 3 weeks with 1 mg/kg/day DPZ ± 30 mg/kg/day MEM (but not 5 mg/kg/day ± 30 mg/kg/day MEM) showed significantly improved acquisition of spatial memory on the MWM (reduced number of days to criterion [finding the platform within 20 seconds]; $P<0.05$) compared to sucrose controls. Those treated with either dose of DPZ in combination with 30 mg/kg/day MEM showed improved acquisition compared to DPZ

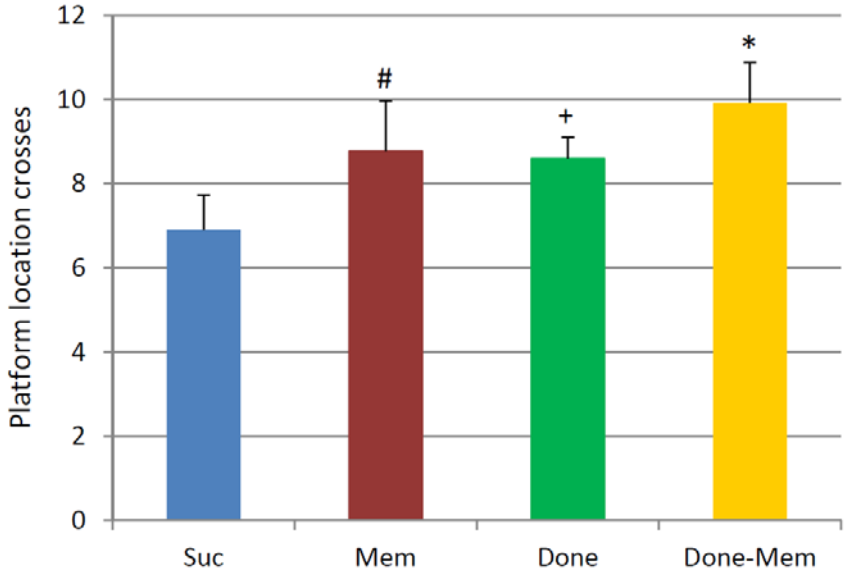
alone. None of the treatments resulted in significant improvements in retention of spatial memory compared to controls (number of crosses of platform location or latency to cross platform location; data not shown). Based on this preliminary experiment, the dose of 1 mg/kg/day DPZ was chosen for the subsequent 3-month studies.



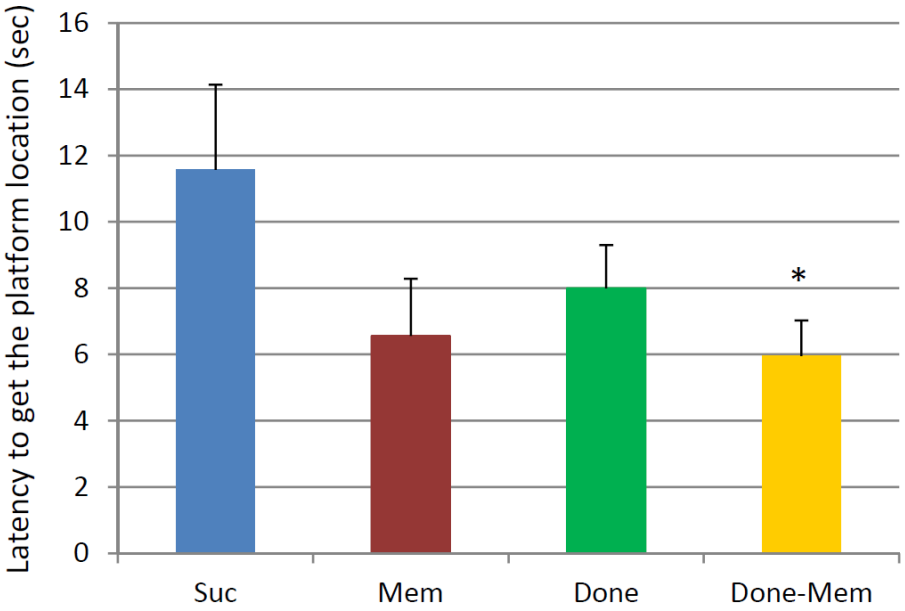
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 6 months to age 9 months with 1 mg/kg/day DPZ + 30 mg/kg/day MEM or 30 mg/kg/day MEM alone (but not 1 mg/kg/day DPZ alone) resulted in significantly improved acquisition of spatial memory in the MWM compared to sucrose controls (P<0.05).



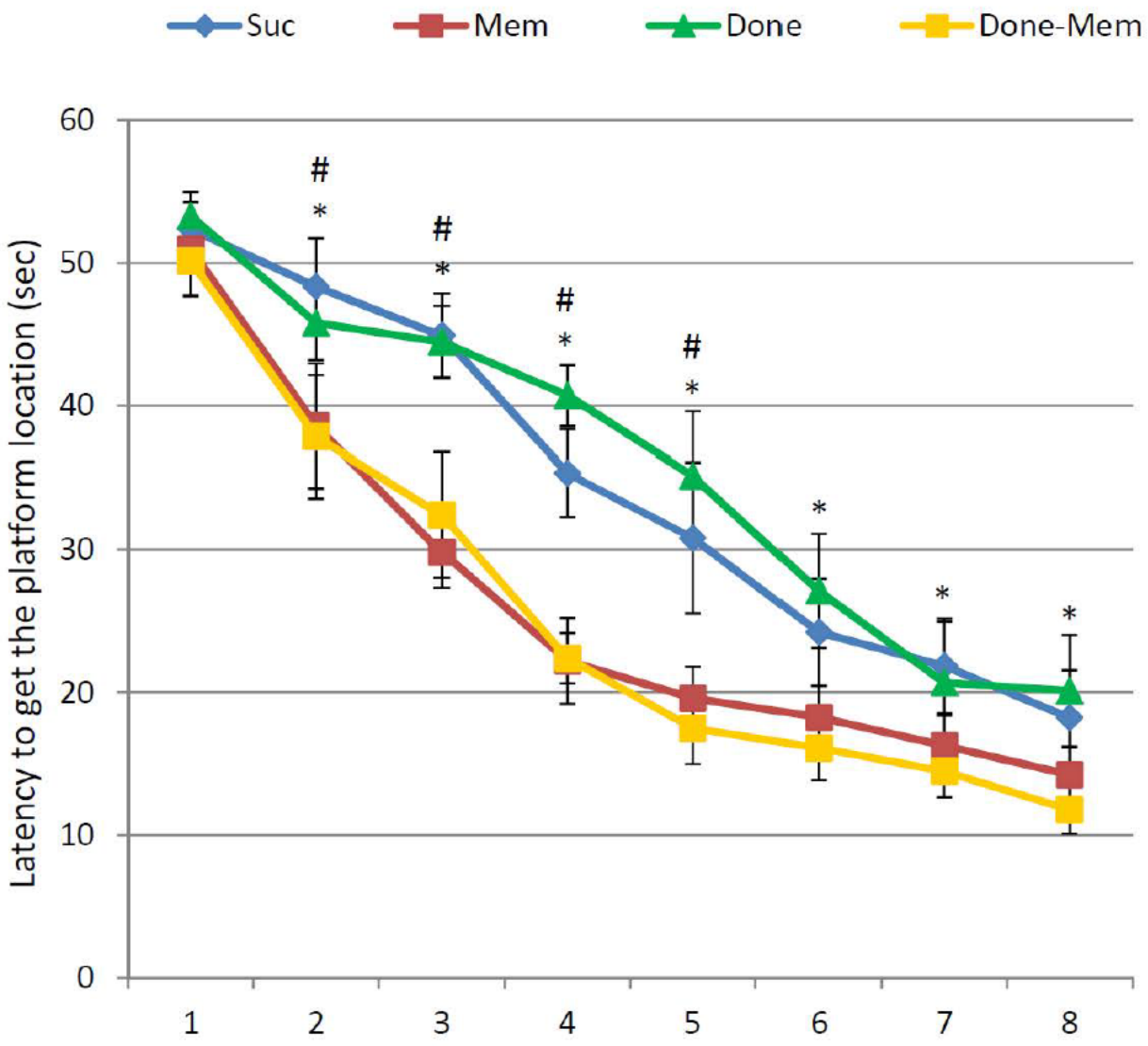
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 6 months to age 9 months with 1 mg/kg/day DPZ alone, 30 mg/kg/day MEM alone, or 1 mg/kg/day DPZ + 30 mg/kg/day MEM resulted in significantly improved retention of spatial memory in the MWM compared to sucrose controls (P<0.05; number of crosses over the platform location; 24 hrs after training).



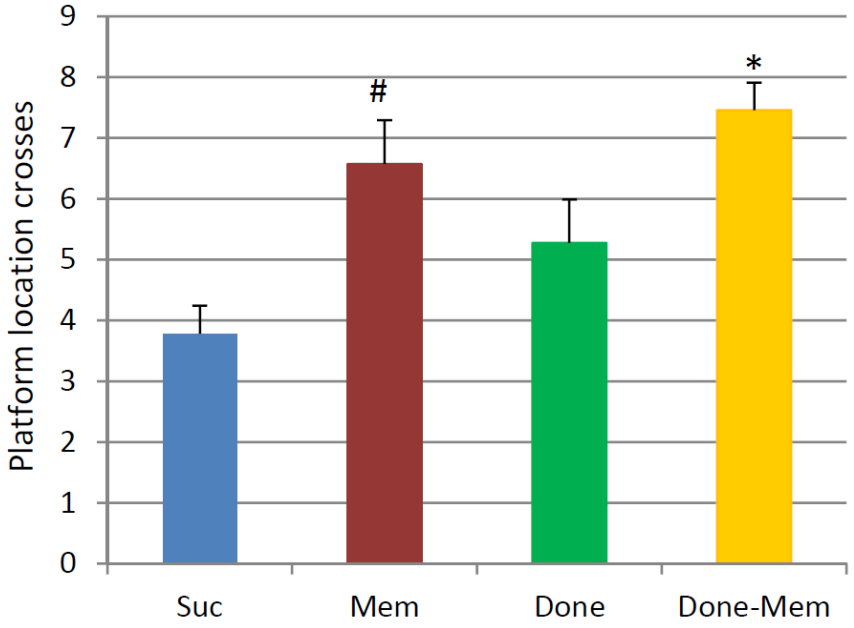
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 6 months to age 9 months with 1 mg/kg/day DPZ + 30 mg/kg/day MEM resulted in significantly improved retention of spatial memory in the MWM compared to sucrose controls (P<0.05; latency to cross the platform location; 24 hrs after training).



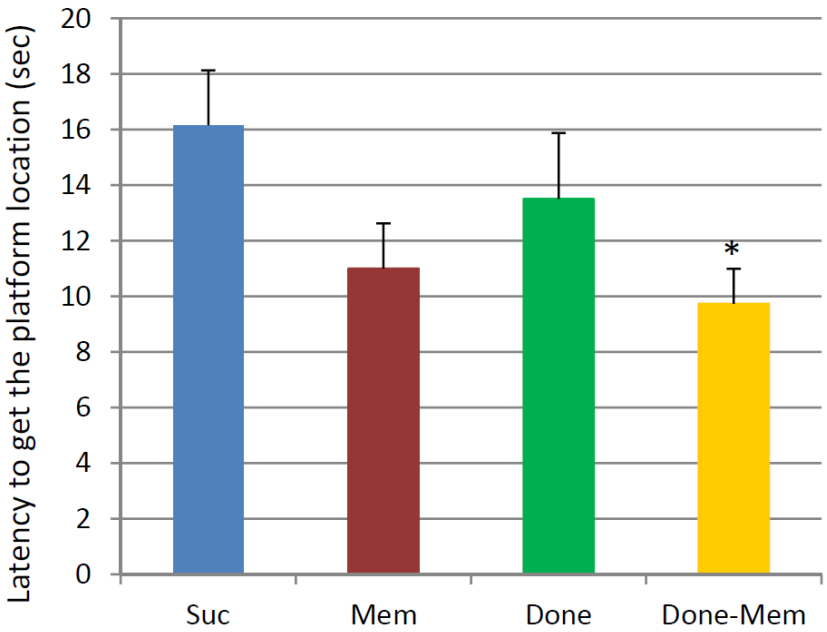
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 15 months to age 18 months with 1 mg/kg/day DPZ + 30 mg/kg/day MEM or 30 mg/kg/day MEM alone (but not 1 mg/kg/day DPZ alone) resulted in significantly improved acquisition of spatial memory in the MWM compared to sucrose controls (P<0.05).



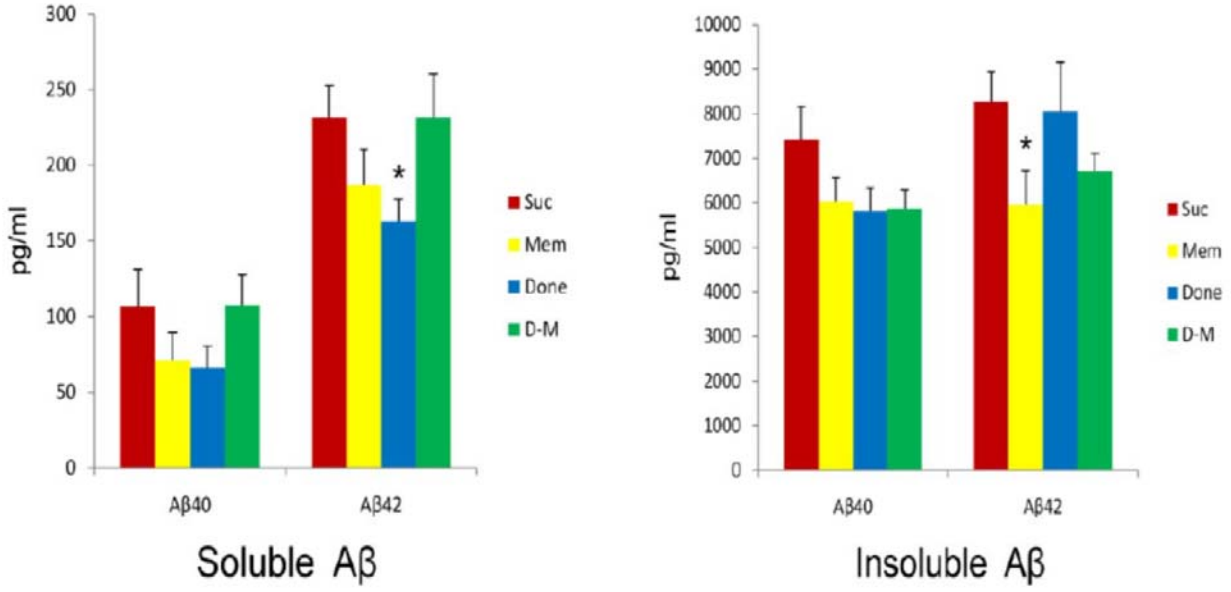
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 15 months to age 18 months with 30 mg/kg/day MEM alone or 1 mg/kg/day DPZ + 30 mg/kg/day MEM resulted in significantly improved retention of spatial memory in the MWM compared to sucrose controls (P<0.05; number of crosses over the platform location; 24 hrs after training).



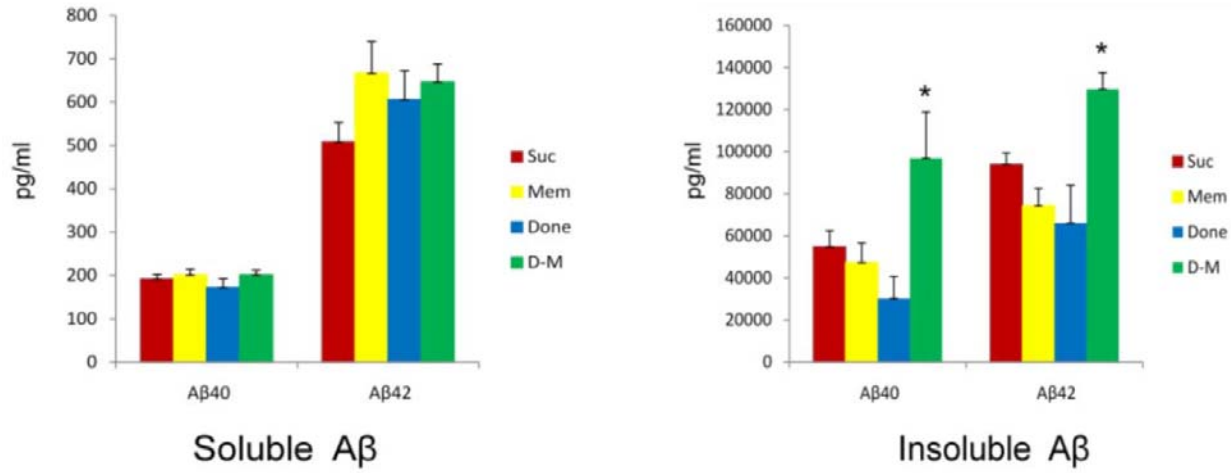
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 15 months to age 18 months with 1 mg/kg/day DPZ + 30 mg/kg/day MEM resulted in significantly improved retention of spatial memory in the MWM compared to sucrose controls (P<0.05; latency to cross the platform location; 24 hrs after training).



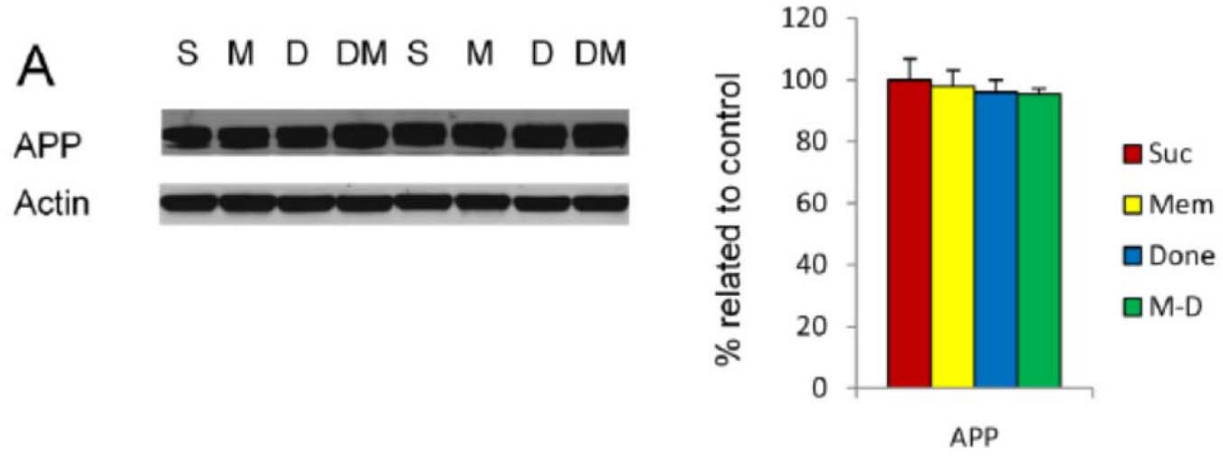
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 6 months to age 9 months with 1 mg/kg/day DPZ + 30 mg/kg/day MEM did not result in significant changes in brain levels of soluble or insoluble Aβ40 or Aβ42 compared to sucrose controls. However, treatment with 1 mg/kg/day DPZ alone resulted in a significant reduction in soluble Aβ42 ($P<0.05$), while treatment with 30 mg/kg/day MEM resulted in a significant reduction in insoluble Aβ42 ($P<0.05$) compared to sucrose controls.



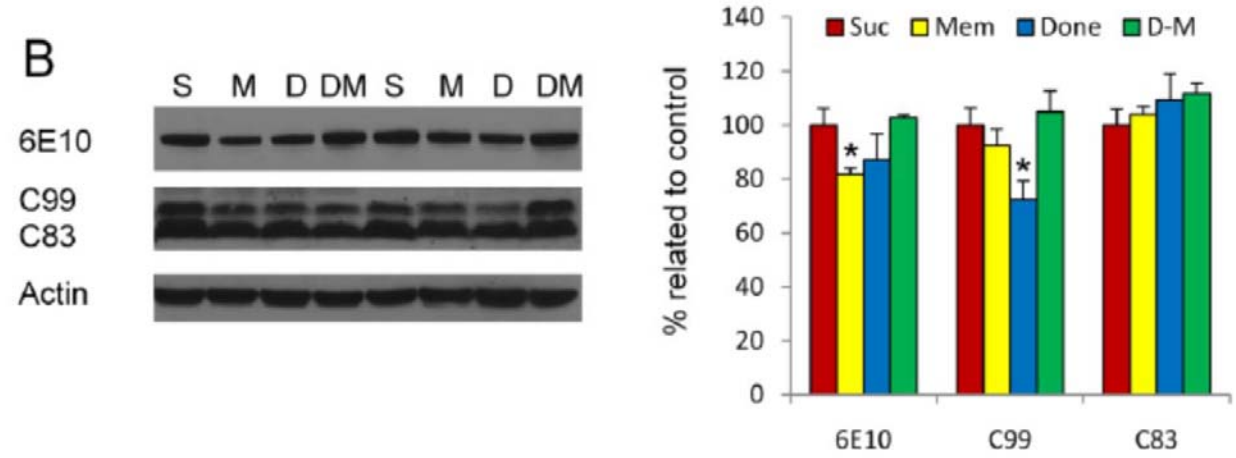
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 15 months to age 18 months with 1 mg/kg/day DPZ + 30 mg/kg/day MEM resulted in significant increases in brain levels of insoluble (but not soluble) Aβ40 and Aβ42 compared to sucrose controls ($P<0.05$), whereas no significant changes were observed with MEM or DPZ alone.



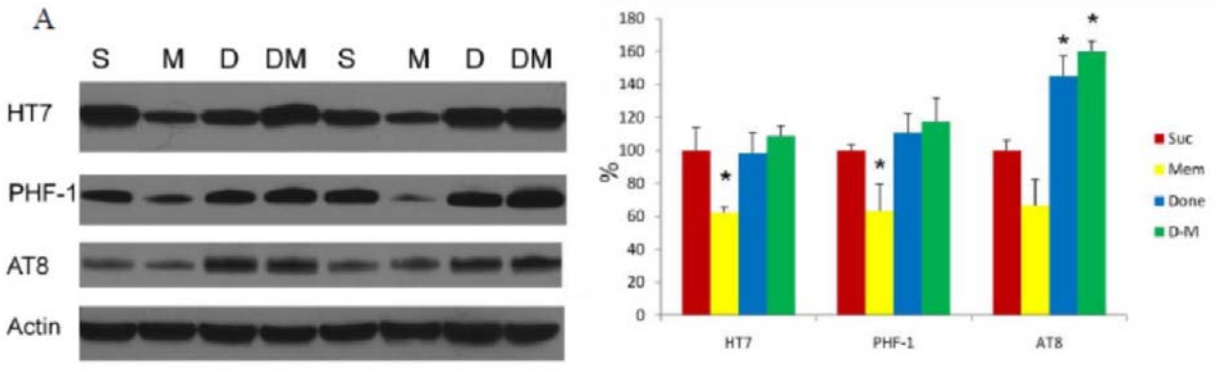
As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 6 months to age 9 months with 1 mg/kg/day DPZ + 30 mg/kg/day MEM, or MEM or DPZ alone, did not result in significant changes in brain levels of APP (as measured by semi-quantitative western blotting) compared to sucrose controls; no changes were observed in brain levels of C99 fragment either (data not shown).



As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 15 months to age 18 months with 1 mg/kg/day DPZ + 30 mg/kg/day MEM did not result in significant changes in brain levels of APP, C99, or C83 (as measured by semi-quantitative western blotting) compared to sucrose controls. However, treatment with MEM alone slightly reduced the brain level of APP compared to sucrose controls, while DPZ alone slightly reduced the brain level of the C99 fragment of APP.



As shown in the sponsor's figure below, treatment of 3xTg-AD mice from age 15 months to age 18 months with 30 mg/kg/day MEM alone resulted in decreased brain levels of tau and hyperphosphorylated tau as measured by semi-quantitative western blotting using antibodies HT7 and PHF-1, respectively, while treatment with 1 mg/kg/day DPZ alone or MEM + DPZ resulted in increased brain levels of AT8-immunoreactive hyperphosphorylated tau compared to sucrose controls. Neither tau nor hyper-phosphorylated tau levels were measured in the younger cohorts because previous studies had shown that severe tau pathology is present only in aged 3xTg-AD mice.



Sponsor's Conclusions

The sponsor's conclusions were not included in this study report.

Reviewer's Conclusions

- Treatment of 3xTg-AD mice from age 6 months to age 9 months with the combination of MEM and DPZ resulted in the following, compared to sucrose controls:
  - improved acquisition and retention of spatial memory in the MWM
  - no changes in brain levels of APP, or soluble or insoluble Aβ40 or Aβ42

- Treatment of 3xTg-AD mice from age 15 months to age 18 months with the combination of MEM and DPZ resulted in the following, compared to sucrose controls:
  - improved acquisition and retention of spatial memory in the MWM
  - increased brain levels of AT8-immunoreactive hyperphosphorylated tau and insoluble Aβ40 and Aβ42
  - no changes in brain levels of APP, C99, C83, or HT7- or PHF-1-immunoreactive hyperphosphorylated tau

- Post-hoc statistical analyses were limited to comparisons of each treated group to the concurrent sucrose-treated control group. Therefore, although some of the graphs above appeared to show improved performance with the combination compared to MEM or DPZ alone, it was not clear if these differences were statistically significant.

- The lack of individual animal data precluded an independent analysis; therefore, the results cannot be verified.

5 Toxicology

Memantine/Donepezil: Toxicokinetic/Maximum Tolerated Dose Study in Rats

(Non-GLP Study MEM-TX-30 conducted by (b) (4) Final Report dated January 18, 2012)

Methods

Retired female breeder Sprague-Dawley rats (Groups 2-8, 5/group) were gavaged once with 100 or 200 mg/kg MEM or 20 mg/kg DPZ, or 100/10, 100/20, 200/10 or 200/20 mg/kg MEM/DPZ in combination. The dose volume was 10 mL/kg for all dose groups. At the end of the treatment period, all surviving animals were euthanized and necropsied. Satellite animals (Groups 2-9, 9/group) were similarly dosed, and an additional group (Group 1) was dosed with 10 mg/kg Memantine and bled on Day 1 for toxicokinetic analysis. (Animals were 7-8 months of age at initiation.) Other parameters evaluated during the study were: viability, clinical observations, body weights, food consumption, clinical pathology (termination) and macroscopic observations. No histopathological examinations were conducted. (See sponsor's table, below.)

	Daily Dose				Number of Animals			
					Total	TK	Main	Necropsy Day 3
Groups	Memantine (mg/kg)	Donepezil (mg/kg)	Volume (mL/kg)	Conc. (mg/mL)	F	F	F	F
1	10	0	10	1	9	9	0	0
2	100	0	10	10	14	9	5	5
3	200	0	10	20	14	9	5	5
4	0	20	10	0/2	14	9	5	5
5[c]	100	10	10	10/1	14	9	5	5
6	100	20	10	10/2	14	9	5	5
7	200	10	10	20/1	14	9	5	5
8	200	20	10	20/2	14	9	5	5

[a]Doses represent active ingredient (no correction factor was used for any of the formulations)
[b]Toxicokinetic (TK) samples were collected on Day 1. Group 1 animals were used for TK purposes only.
[c]The 100/10 mg/kg dosage was the first administered of the combination treatment groups.
The first day of dosing was defined as Day 1 of the Study.

Results

All dose formulations were within ±10% of nominal concentrations. Mortality (found dead or moribund sacrifice) was observed in all combination groups (3 at 100/10, 9 at 100/20, 11 at 200/10, and 13 at 200/20 [mg MEM/mg DPZ]), but not in groups given

either drug alone (100 or 200 mg MEM, or 20 mg DPZ). Almost all deaths occurred on Day 1.

As shown in the sponsor's table below, clinical signs were increased in incidence and severity with the combination compared to MEM or DPZ alone, and convulsions and acrocyanosis were only observed with the combination. The following signs were sometimes observed in groups given 100 or 200 mg MEM (± 20 mg DPZ) on the days following administration of the single dose: chromodacryorrhea, ataxia, decreased activity, excessive salivation, hunched appearance, and anogenital stains. The only clinical sign observed in rats treated with DPZ alone was tremors (2/5 main study animals).

Text-Table 3.4-1: Relative incidence (%) of rats showing the more frequent clinical signs during the first 4 hours post dose

Memantine (mg/kg)	100	200	0	100	100	200	200
Donepezil (mg/kg)	0	0	20	10	20	10	20
Excessive salivation	0	40	0	60	80	100	60
Labored/shallow breathing	0	20	0	40	80	100	60
Acrocyanosis	0	0	0	20	60	20	60
Ataxia	60	20	0	40	20	80	40
Prostration	20	40	0	40	60	100	60
Tremors	0	20	40	0	40	100	20
Convulsions	0	0	0	0	40	20	0

Effects on body weight and body weight gain could not be determined due to the lack of concurrent controls. Food consumption was reduced in rats receiving 200 mg MEM alone compared to other evaluable groups (combination groups including 20 mg DPZ or 200 mg MEM were not evaluable due to unscheduled deaths). Hematology, coagulation, clinical chemistry, and gross pathology were not clearly affected by treatment in the evaluable groups, but concurrent controls were omitted, and Historical Control Data for retired female breeders aged 7-8 months was not available for comparison.

As shown in the tables below, combination treatment did not consistently result in increases or decreases in the Cmax of MEM or DPZ compared to treatment with either drug alone; AUC exposures could not be compared, due to missing concentration data at later time points.

Text Table 3.2-1. MEMANTINE TOXICOKINETIC PARAMETERS

Group	*Memantine (mg/kg)*	*Donepezil (mg/kg)*	*C_{max} (ng/mL)*	*T_{max} (h)*	*AUC_{0-t} (ng*h/mL)*	*$T_{1/2}$ (h)*
1	10	0	349	0.5	2624 [a]	3.6
2	100	0	4611	2	52820 [a]	9.6
3	200	0	5419	4	101194 [a]	15.6
4	0	20	N/A	N/A	N/A	N/A
5	100	10	5415	2	50872 [a]	13.9
6	100	20	4756	12	44471 [b]	NC
7	200	10	11827	12	77728 [b]	NC
8	200	20	5986	0.5	6844 [c]	1.9

a AUC_{0-24}
b AUC_{0-12}
c AUC_{0-2}
N/A Not applicable
NC Not calculated

(Sponsor's table, page 31 of Study Report)

Text Table 3.2-2. DONEPEZIL TOXICOKINETIC PARAMETERS

Group	*Memantine (mg/kg)*	*Donepezil (mg/kg)*	*C_{max} (ng/mL)*	*T_{max} (h)*	*AUC_{0-t} (ng*h/mL)*	*$T_{1/2}$ (h)*
1	10	0	N/A	N/A	N/A	N/A
2	100	0	N/A	N/A	N/A	N/A
3	200	0	N/A	N/A	N/A	N/A
4	0	20	618	1	5520 [a]	6.7
5	100	10	385	2	3107 [a]	13.5
6	100	20	743	12	6607 [b]	NC
7	200	10	485	12	2619 [b]	NC
8	200	20	459	0.5	478 [c]	1.2

a AUC_{0-24}
b AUC_{0-12}
c AUC_{0-2}
N/A Not applicable
NC Not calculated

(Sponsor's table, page 32 of Study Report)

Conclusions

Treatment with the combination of MEM and DPZ increased mortality and incidence and severity of clinical signs compared to MEM or DPZ alone. The maximum tolerated dose (MTD) was 100 mg MEM; 100 mg MEM + 10 mg DPZ exceeded the MTD. Combination treatment did not consistently result in increases or decreases in the Cmax of MEM or DPZ compared to treatment with either drug alone.

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/s/

DAVID B HAWVER
10/24/2014

LOIS M FREED
10/25/2014