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Applied Translational Medicine

# Lessons from an Intranasal, Neuroprotective Peptide, NAPVSIPQ. Why did it Fail?

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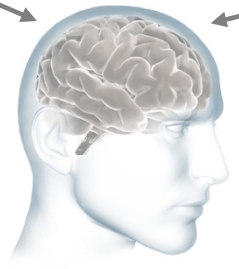
# Davunetide Discovery

Disease

Injury



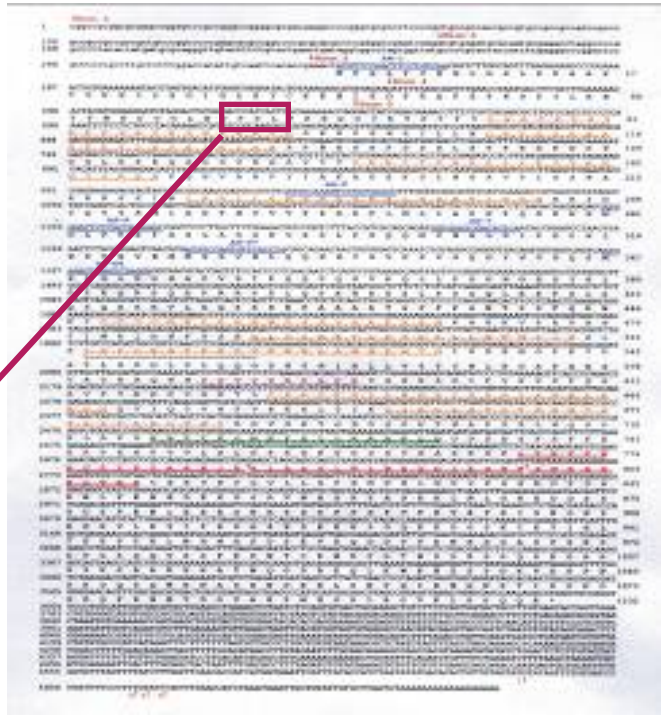
**Glial-derived neuroprotectants**

Activity Dependent
Neuroprotective Protein (ADNP)

Davunetide

NAPVSIPQ peptide

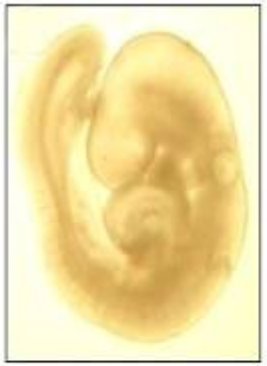
AL-108, AL-208



J. Neurochem. 1999; 72, 1283-1293
J. Mol. Neurosci. 2004; 24, 181-187
CNS Drug Rev. 2005;11(4):353-68
Current Alzheimer's Res. 2005; 2(2): 149-153
Pharmacol Ther. 2007; 114(2): 146-154
J. Biol. Chem. 2007; 282: 34448-34456

# ADNP is a Natural Neuroprotectant

- Essential for brain development
- Synthesized in response to injury
- Important in learning and memory
- Neuronal expression (cerebellum, mesencephalon, pons, medullar oblongata)
- Cytoplasmic & axonal localization
- Heterozygous animals (ADNP +/-): memory impaired
- Davunetide ameliorates impairment

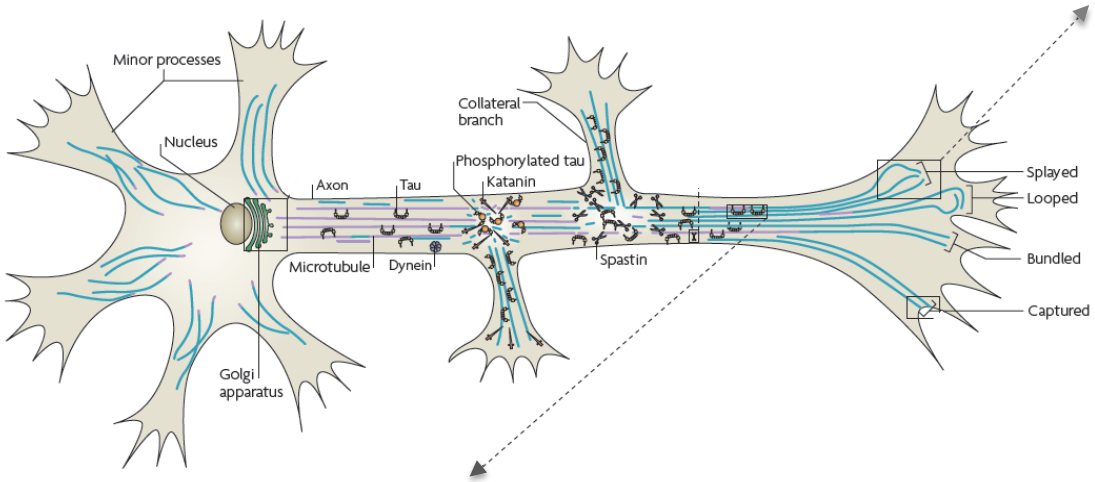


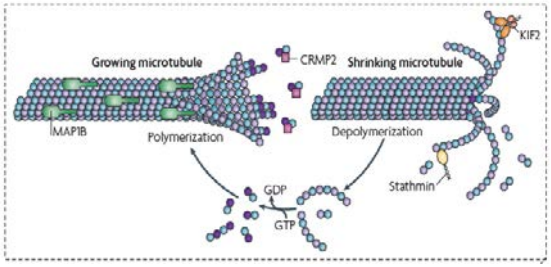
Normal Embryo

ADNP Knockout has disrupted brain formation: Dies in utero

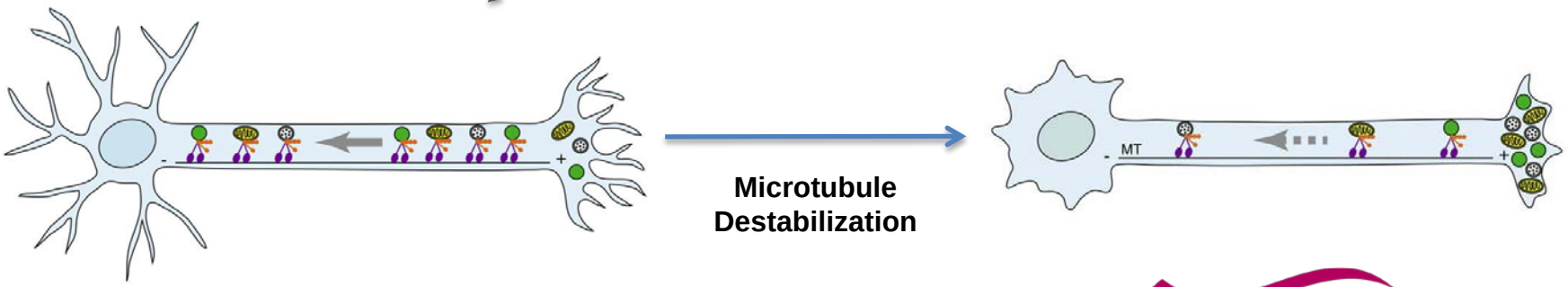
# Role of Microtubules

- Microtubules essential for neuronal structure & function
- Destabilization occurs in many neurodegenerative diseases




Conde & Caceres, *Nat Rev Neurosci* 2009: 10; 319-332




Perlson, et al. *TINS* 2010: 33; 335-344



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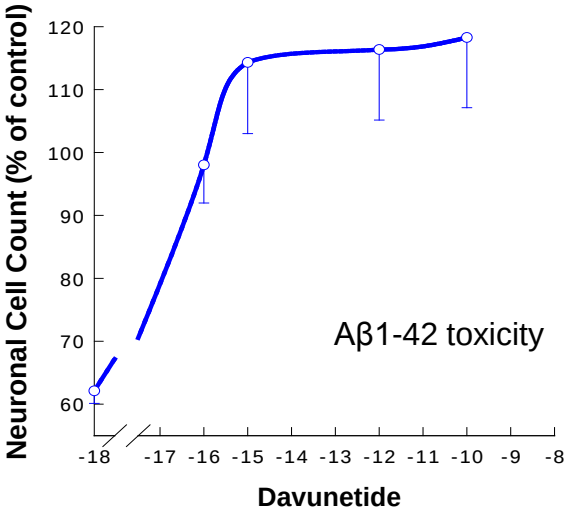
# Summary of Davunetide Pharmacology

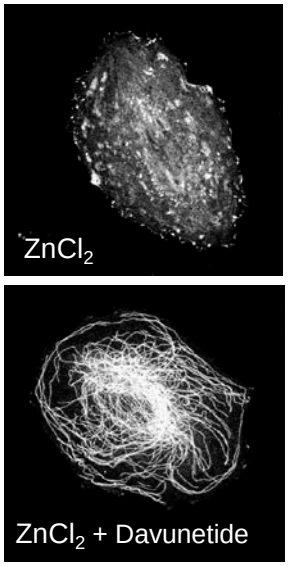
## Neuroprotection




Davunetide promotes neuronal survival against a variety of insults including :

- Excitotoxicity
- Glucose deprivation
- Oxidative stress
- MPP+
- Microtubule poisons

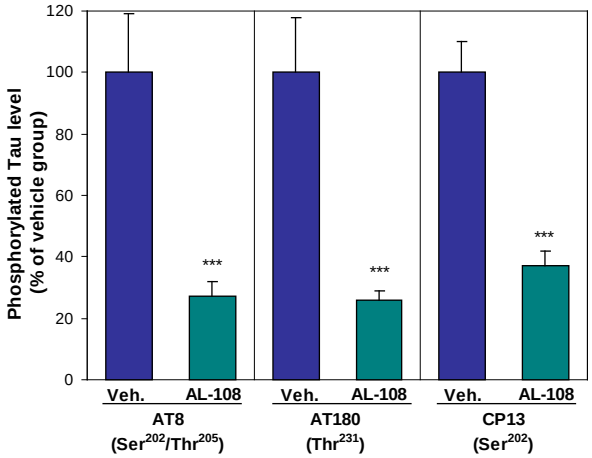
## Microtubule stabilization




Davunetide stabilizes microtubules and protects the organization of the cytoskeleton

*J Biol Chem. 2004; 279:28531-8*

## Reduction of tau Phosphorylation




Davunetide reduces tau phosphorylation in the triple transgenic AD model ($PS1_{M146V}$, $APP_{SWE}$, and $tau_{P301L}$)

*J. Mol. Neurosci. 2007; 31: 165-170*
*JPET, 2008; 325:146-53*

# Clinical Development

**P/C & Phase I** →
- Safety/PK Studies
- Safety to 60 mg/day
- CSF penetration
- Brain via systemic distribution
- Healthy/aged, AD, FTD
- 35 P/C studies in 17 models

**PIIa – Mild Cognitive Impairment**
- 144 participants
- 2 doses (5 mg QD, 15 mg BID)
- 12 weeks
- Randomized, placebo controlled, double blind
- 17 US sites

**PIIa – Schizophrenia**
- 63 participants
- 2 doses (5 mg QD, 15 mg BID)
- 12 weeks
- Randomized, placebo controlled double blind
- 7 US sites

**PIIa – Schizophrenia Imaging Biomarker**
- 18 participants
- 2 doses (5 mg QD, 15 mg BID)
- 12 weeks
- Randomized, placebo controlled double blind
- 3 US sites

→ **PII/III Pivotal Study**
- Progressive Supranuclear Palsy
- Tau pathology
- Rapid decline
- No effective treatment
- Validated rating scale
- Powered as a pivotal study



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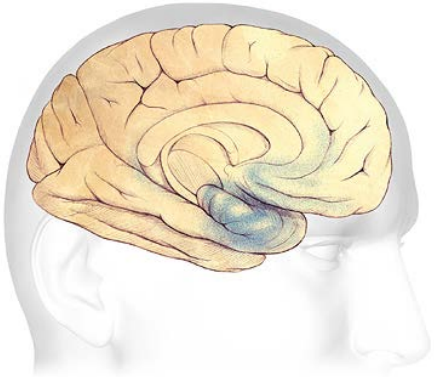
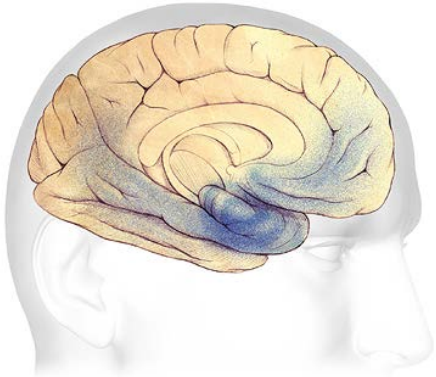
# Amnestic MCI : Tau-related cognitive loss

## Amnestic MCI



- Cognitive impairment of short-term memory
- Tangles appear to be responsible for memory impairment
- High rate of conversion to AD

## Mild to moderate AD



Alzheimer's Association

- Davunetide impacts tau/tangle pathology (preclinical)
- Impact on tangle pathology in aMCI patients should improve memory function

Markesbery et al., 2006
Petersen et al., 2006
Jicha et al., 2006

# Davunetide: Phase II amnestic MCI

- 144 participants amnestic MCI
- 17 clinical sites in the U.S.
- Randomized, placebo controlled, double blind
- Two doses (5 mg QD; 15 mg BID) for 12 weeks
- Placebo matched to both low and high dose davunetide
- Cognitive assessments at weeks -4, 0, 4, 8, 12, 16

# Summary of Adverse Events

- Treatment-emergent Adverse Events Occurring in ≥5% of Subjects: Safety Population

| | Placebo N=48 | Davunetide 5 mg QD N=48 | Davunetide 15 mg BID N=47 | All N=95 |
|---|---|---|---|---|
| | | n (%) | | |
| ≥1 Adverse Event | 25 (52) | 27 (56) | 25 (53) | 52 (55) |
| Headache | 3 (6) | 6 (13) | 6 (13) | 12 (13) |
| Nasopharyngitis | 1 (2) | 4 (8) | 4 (9) | 8 (8) |
| Nasal Discomfort | 1 (2) | 3 (6) | 1 (2) | 4 (4) |
| Constipation | 0 | 3 (6) | 0 | 3 (3) |
| UTI | 0 | 3 (6) | 0 | 3 (3) |
| Musculoskeletal Pain | 0 | 0 | 3 (6) | 3 (3) |
| Rhinorrhea | 2 (4) | 3 (6) | 0 | 3 (3) |

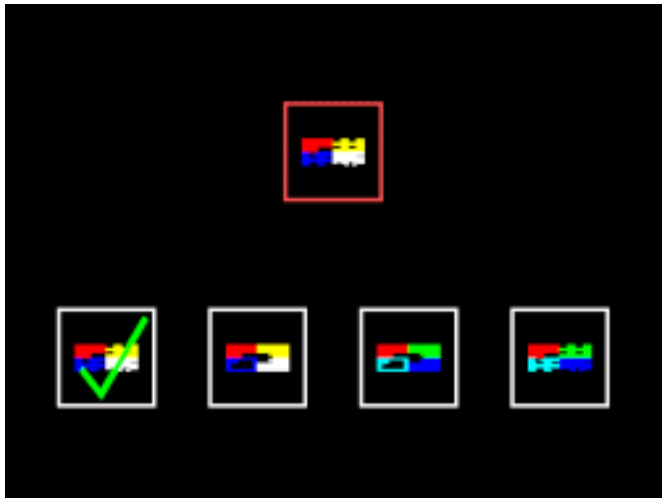
- Davunetide is safe and well tolerated in aMCI patients

# Efficacy Endpoints: Change from Baseline

- Delayed Match-to-Sample
  (recognition, short term and working memory)
- Digit Span Forward/Backward
  (short term memory)
- Spatial Working Memory
  (working memory and strategy use & executive function)
- Paired Associates Learning
  (episodic memory and associative learning)
- One Touch Stockings of Cambridge
  (executive function and motor control)
- Spielberger State & Trait Anxiety

# Delayed Match-to-Sample (DMTS)

- Measures working memory, recognition memory and short term memory
- After a complex pattern is presented to the patient, four similar patterns are shown and the patient must identify the correct match
- Simultaneous, 0, 4 second delays only measure focus and attention not memory
- Conversely, the 12 second delay is a well validated test of memory function



*Swainson et al, Dementia & Geriatric Cognitive Disorders, 2001*



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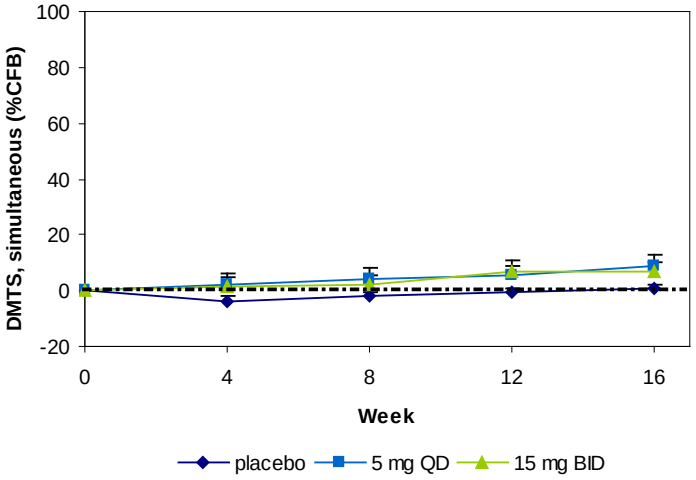
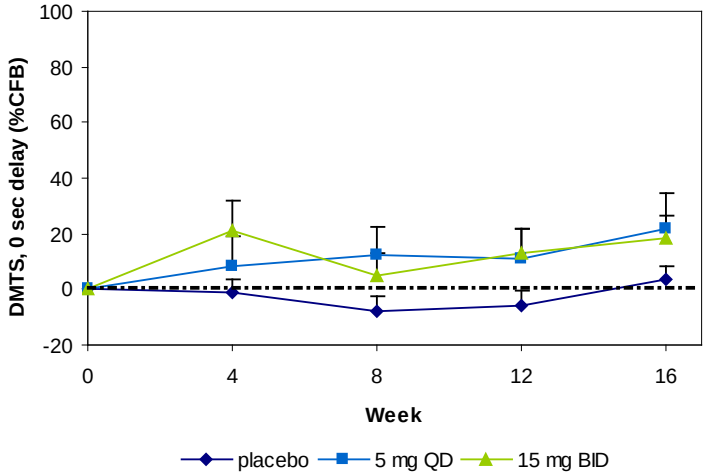
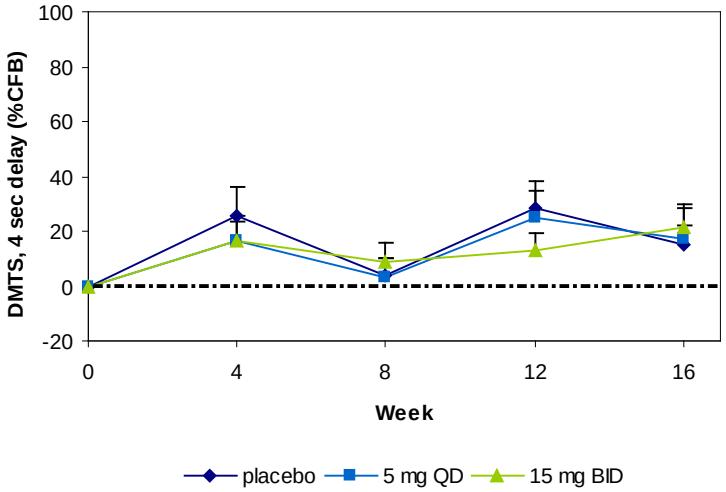
# DMTS – short delays




No impact seen at simultaneous, 0, and 4 second delay when only attention and focus are measured



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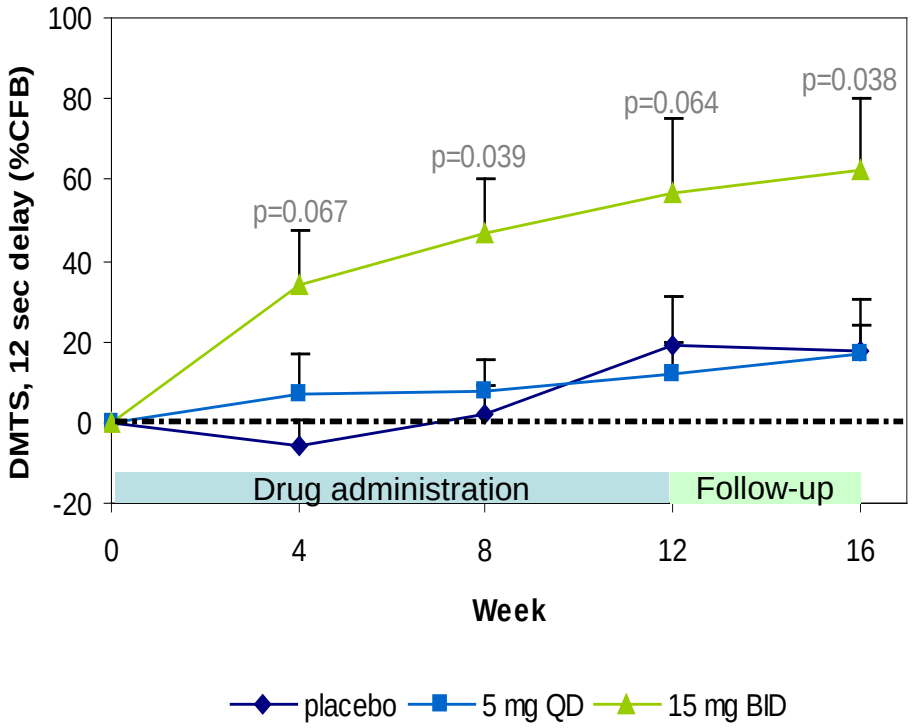
# Delayed Match to Sample, 12 second delay

## Improvement on Memory Activity on Visual Working Memory




- Statistically significant, dose dependent and durable impact seen at 12 second delay when memory is measured



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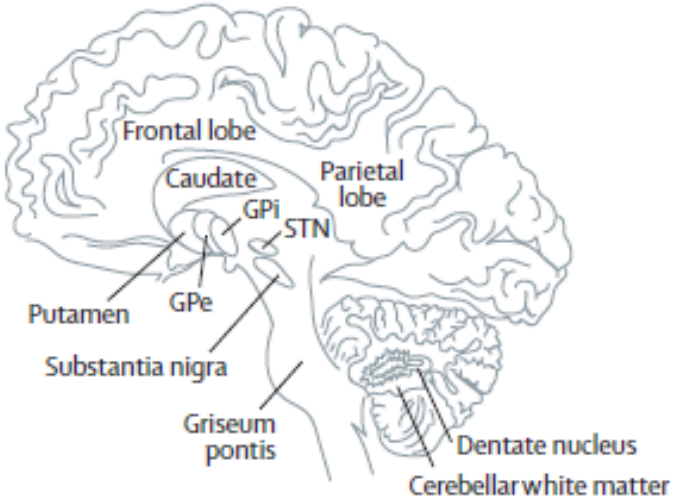
# aMCI Summary

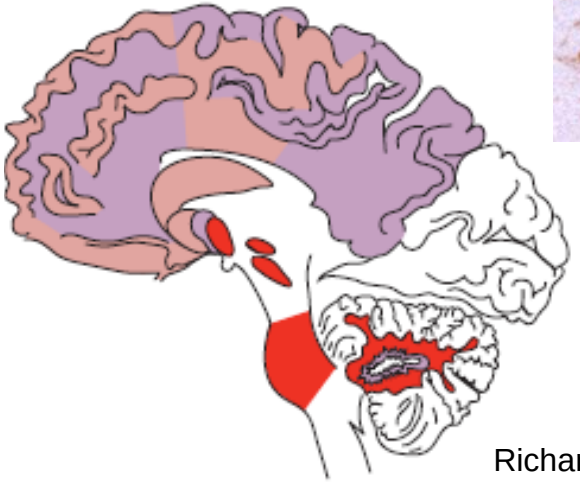
- Statistically significant improvement (2 of 5)
  - DMTS (visual-spatial memory)
  - Digit Span Forward (attention-working memory)
- Significance not observed on the primary endpoint which was a composite score of the memory and executive function measures
- Trending observed on other endpoints
- Drug was safe and well tolerated with modest adverse events

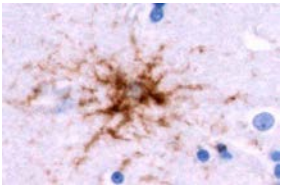
# Progressive Supranuclear Palsy (PSP)

- A degenerative disease involving the brain stem, basal ganglia, cerebellum
- Clinical symptoms (movement problems, cognitive impairment) apparent result of the underlying tau pathology in the brain region controlling those functions

Steele JC, Richardson JC, Olszewski J. 1964 *Arch Neurol*;10: 333–59.





Richardson's Syndrome

Williams and Lees; *Lancet Neurol* 2009; 8: 270–79

# Why PSP?

- Early-onset dementia characterized by tau pathology
- No available treatment
- Significant future potential in other sub-types of frontotemporal dementia and Alzheimer disease

- US Orphan granted (20,000 patients)
  EU Orphan granted (50,000 patients)
- Fast Track granted by FDA
- Appears to meet criteria for single study approval
- Phase II/III study powered as a pivotal study

# PSP Study Design

- Phase II/III study in PSP
  - Recruited 313 patients
  - 1:1 active-to-placebo
  - Treated for 1 year
  - 47 clinical sites in US, Canada, Australia, Germany, UK and France
- Clinical Endpoints
  - Safety (adverse events, con meds)
  - Efficacy (disease severity, daily living, cognitive, mood)
    - Co-Primary endpoints (PSPRS, SEADL)
  - Volumetric MRI
  - CSF biomarkers
  - DNA (tau genotype)
  - Study unblinded in Dec 2012



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# Demographics

# Demographics (Safety Pop)

| | Davunetide (N=156) | Placebo (N=156) |
|---|---|---|
| Age (years) | | |
| Mean (SD) | 68 (6.3) | 67 (6.9) |
| Median (Min, Max) | 68 (49, 84) | 68 (45, 84) |
| Sex (Female) - n (%) | 75 (48.1) | 72 (46.2) |
| Race: White - n (%) | 137 (87.8) | 137 (87.8) |
| Region: North America | 101 (64.7) | 102 (65.4) |

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# Baseline Characteristics (Safety Pop)

| | | Davunetide (N=156) | Placebo (N=156) |
|---|---|---|---|
| Baseline PSPRS | Mean (SD) | 40 (11.4) | 39 (10.3) |
| | (Min, Max) | (12, 73) | (15, 68) |
| Baseline SEADL | Mean (SD) | 0.5 (0.22) | 0.5 (0.22) |
| | (Min, Max) | (0.1, 0.9) | (0.1, 1.0) |
| Modified Hachinski Score | 0 | 59 (37.8) | 56 (35.9) |
| | 1 | 77 (49.4) | 78 (50.0) |
| | ≥2 | 18 (11.5) | 22 (14.1) |
| MMSE | Mean (SD) | 26 (3.5) | 26 (3.5) |
| | (Min, Max) | (15, 30) | (15, 30) |
| CoQ10 | Use | 31 (19.9) | 31 (19.9) |
| Tau Haplotype - n (%) | H1/H1 | 120 (76.9) | 110 (70.5) |
| | H1/H2 | 6 (3.8) | 8 (5.1) |
| | Unknown | 30 (19.2) | 38 (24.4) |

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# Clinical Endpoints

Figure 14.2.1a: Mean (SE) Progressive Supranuclear Palsy Rating Scale by Visit
(observed data – Mean +/– SE)
Full Analysis Population

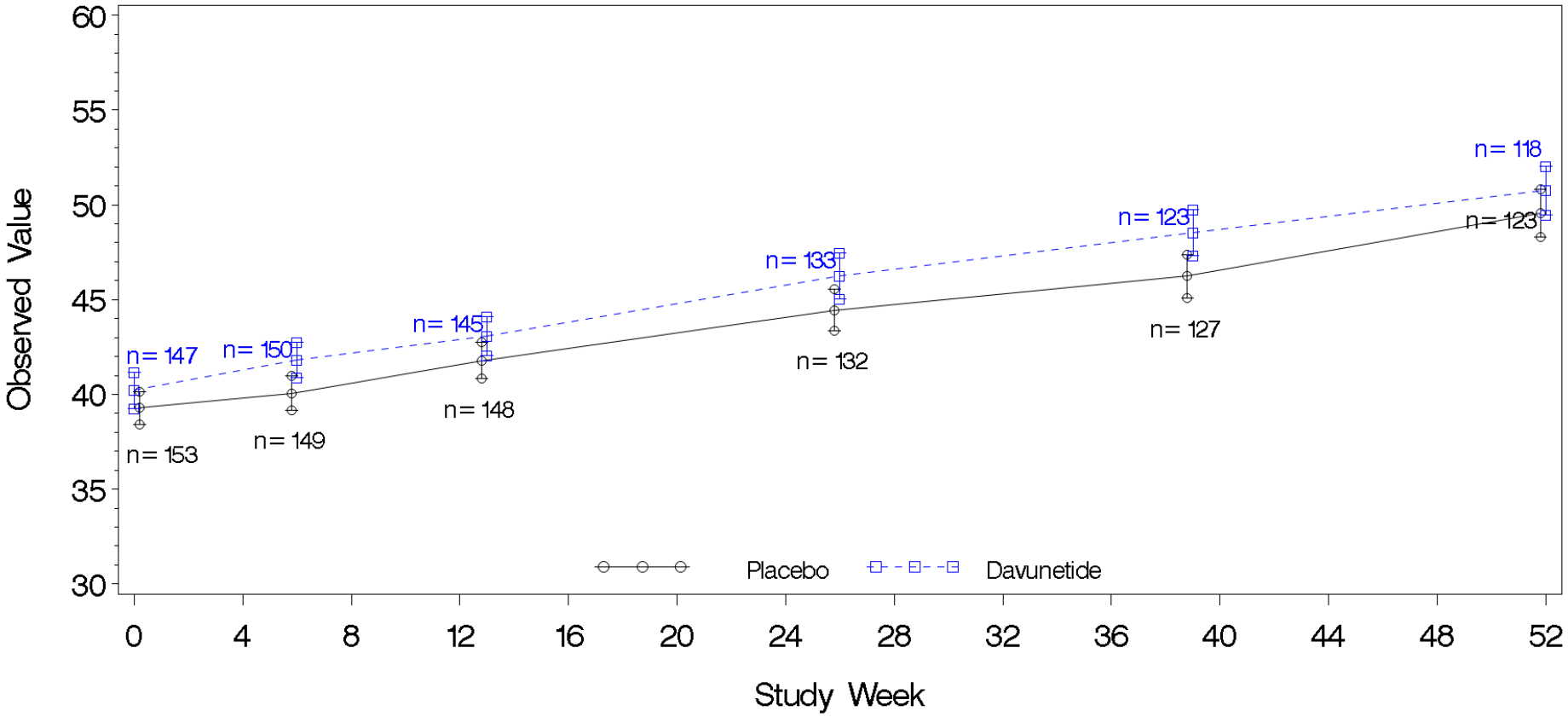
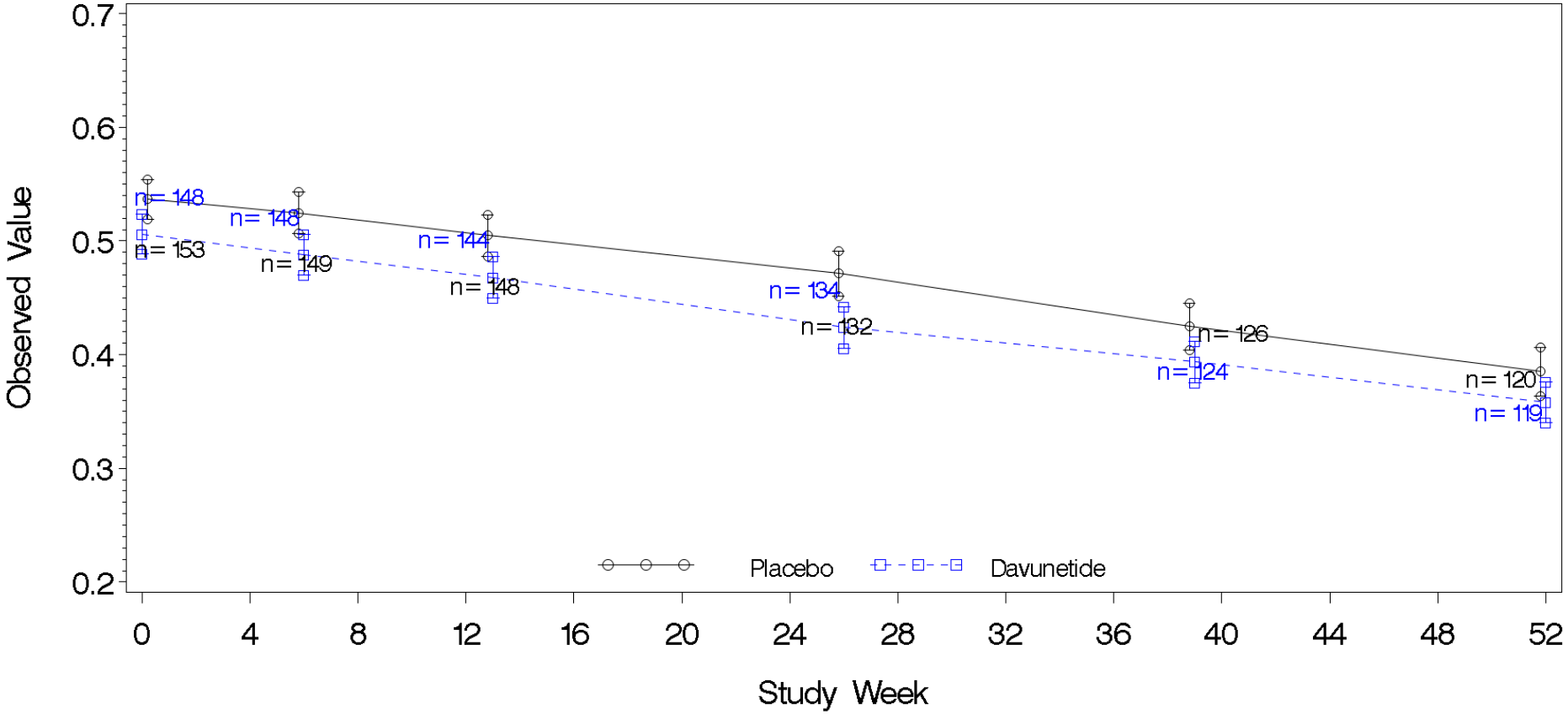


Figure 14.2.1b: Mean (SE) Schwab and England Activities of Daily Living Scale by Visit
(observed data — Mean +/— SE)
Full Analysis Population



# Sensitivity Analyses

- Age
- Gender
- Baseline PSPRS
- CoQ10 use
- Geographical region

Not different from primary analysis

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# Why Negative Results?

## PSP, right patient population?

- Patients have established pathology, not possible to intervene?
- Clinical instruments not sensitive to detect drug effect?
- Poor translation from aMCI to PSP?

## Retrospective Risk-Mitigation

- Run pilot PSP study (Phase II)
  - Multiple doses (dose-response)
  - Biomarker intensive

Note: post-hoc analysis of the Phase II/III data suggests correlation between MRI, CSF and sub-scales of PSP-RS

# Additional retrospective thoughts…

Right dose? Sufficient drug exposure?

- More intensive understanding of PK-PD
- Intranasal administration?

- Marker for target engagement
- Ability to verify mechanism of action

# Acknowledgements


## Former colleagues at Allon Therapeutics

- Lesley Parker
- Michael Gold
- Sue Ann Crocker
- Daniela Nenciu
- Catherine Campbell
- Alistair Stewart
- Mina Virtusio
- Jacqueline Tiong


A double-blind, placebo-controlled, ascending-dose, randomized study to evaluate the safety, tolerability and effects on cognition of AL-108 after 12 weeks of intranasal administration in subjects with mild-cognitive impairment (2013) *Dement Geriatr Cogn Disord*. **35(5-6)**:325-36

Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial (2014) *Lancet Neurol* **13(7)**:676-85




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**Questions?**

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