Results of the ADCS Estrogen Treatment Trial for AD

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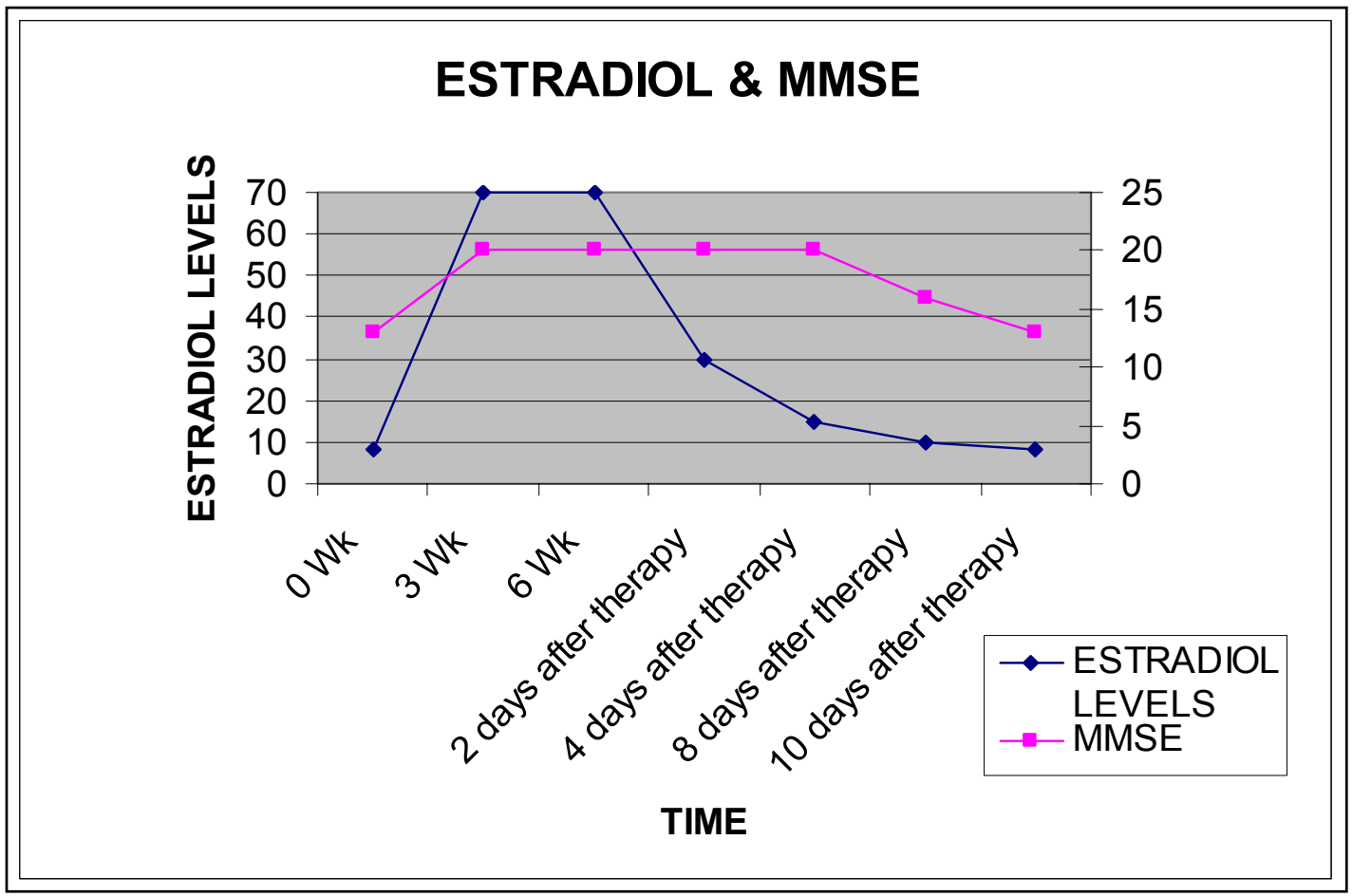
Previous Clinical Studies

- 3 open label trials
- 1 randomized clinical trial
  - Trials were 6-8 weeks duration
  - Small samples of 7-12 women
  - Most did not use standardized diagnostic criteria for subject selection

Small Clinical Study: Fillit, 1986



Published Studies of Estrogen as a Protective Factor for AD

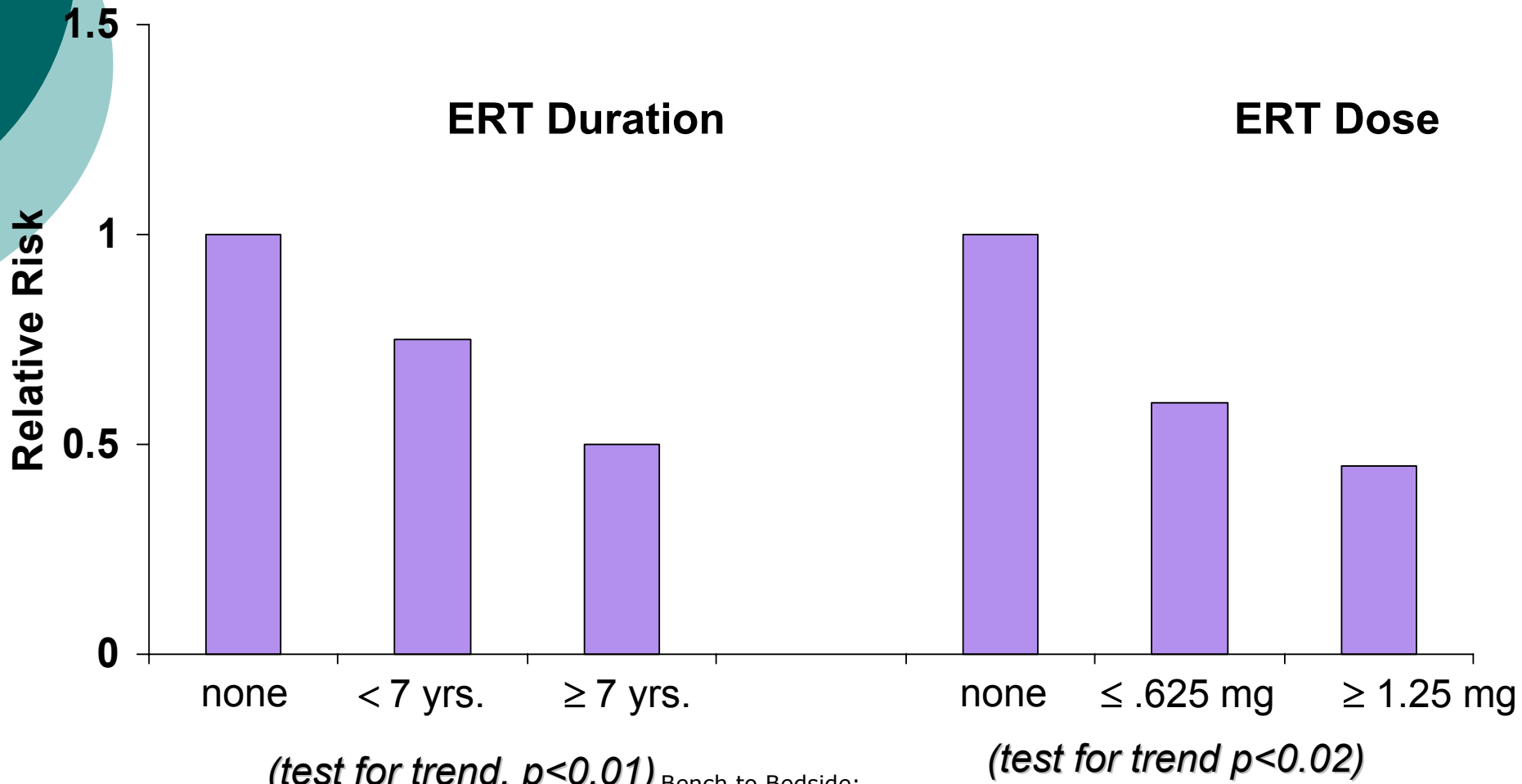
Study	Relative Risk
Paganini-Hill A & Henderson VW (1994 & 1996)	0. 69, 0.65
Henderson VW et al, 1999	0.33
Mortel K & Meyer J, 1995	0.30
Tang M et al, 1996	0.55
Kawas C et al, 1997	0.40
Waring S et al, 1999	0.46

Studies of Estrogen and AD without Protective Effect

Study	Relative Risk
Heyman et al, 1984	2.38
Amaducci et al, 1986	1.67
Broe et al, 1990	0.78
Graves et al, 1990	1.15
Brenner et al, 1994	1.10

Estrogen Replacement Therapy in AD

Effect of Duration and Dose



Bench to Bedside:
Estrogen as a Case Study

adapted from Paganini-Hill 1994

ADCS Treatment Study Design

- Double-blind, placebo-controlled
- Target enrollment: 120 Subjects
- Initial participating sites: 27 sites
- Treatment plan:
  - 12 months of double-blind treatment
  - 3 months of placebo wash-out
  - Assessments at screening, baseline, 2 months, 6 months, 12 months, 15 months, with phone call at 4 months, and safety check at 9 months

Inclusion Criteria

- Diagnosis of mild to moderate AD (MMSE 14-28)
- Female gender
- Previous hysterectomy
- Age > 60
- Absence of major clinical depression (Hamilton < 17)
- Normal gyn, breast, mammography exams

Exclusion Criteria

- Myocardial infarction within 1 yr
- History of thrombo-embolic disease or hypercoagulable state
- Hyperlipidemia
- Use of excluded medications

Enrollment Realities

- **TARGETS**
  - 120 Subjects
    - 40 Placebo
    - 40 Premarin 0.625 mg
    - 40 Premarin 1.25 mg
  - 27 Sites
  - 6 month enrollment
  - Overall completion 21 months (9/95 - 6/97)
- **ACTUAL**
  - 120 Subjects
    - 39 Placebo
    - 42 Premarin 0.625 mg
    - 39 Premarin 1.25 mg
  - 32 sites (5 added)
  - 25 months to enroll
  - Overall completion 41 months (9/95 - 2/99)

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153 Screened

120 Eligible

120 Randomized

Screen Failures (33 total):
(2) History of Pulmonary Embolus
(9) High Triglyceride Level
(1) Death Before Baseline
(3) No Hysterectomy
(5) Changed Mind
(1) No Caregiver
(4) Untestable by Neuropsychological Examination
(1) Abnormal Mammogram Result
(1) Unable to Draw Blood
(3) History of Stroke
(1) Seizure Disorder
(1) Idiopathic Thrombocytopenia
(1) Moving to Distant Location

39 Randomized to Placebo	42 Randomized to Conjugated Equine Estrogens, 0.625 mg/d	39 Randomized to Conjugated Equine Estrogens, 1.25 mg/d
7 Withdrawals 2 Adverse Events 2 Psychiatric Admission/Psychosis 5 Other 1 Medical cond 1 Dizziness 1 Agitation, rash 2 Wanted active drug	7 Withdrawals 7 Adverse Events 4 Vaginal Bleeding 2 Deep Vein Thrombosis 1 Death	9 Withdrawals 4 Adverse Events 2 Deep Vein Thrombosis 1 Death 1 Fall, Hip Fracture 5 Other 2 Wanted Active Drug 2 Nursing Home Placements 1 Rash, Lower Extremity Edema, Elevated Blood Pressure
Completers- 32	**Completers - 35**	**Completers- 30**

Primary Outcome Measure

- **CGIC: Clinical Global Impression of Change**

- **ADCS version of the CGIC is based on an organized but unstructured interview of the patient and informant to assess change from baseline.**
  - **Includes 15 areas under the domains of cognition, behavior, and social and daily functioning.**

Secondary Outcome Measures

- **Other Global Measures**
  - **Mini Mental Status Examination (MMSE)**
  - **Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog)**
  - **Clinical Dementia Rating Scale (CDR)**

Secondary Outcome Measures

- **Mood Measures**
  - Hamilton Depression Scale
  - Multiple Affect Adjective Checklist - Revised
- **Memory Measures**
  - Emotional Face Recognition
  - New Dot Test
- **Attention Measures**
  - Letter Cancellation
  - Trails A
  - Digit Symbol

Secondary Outcome Measures

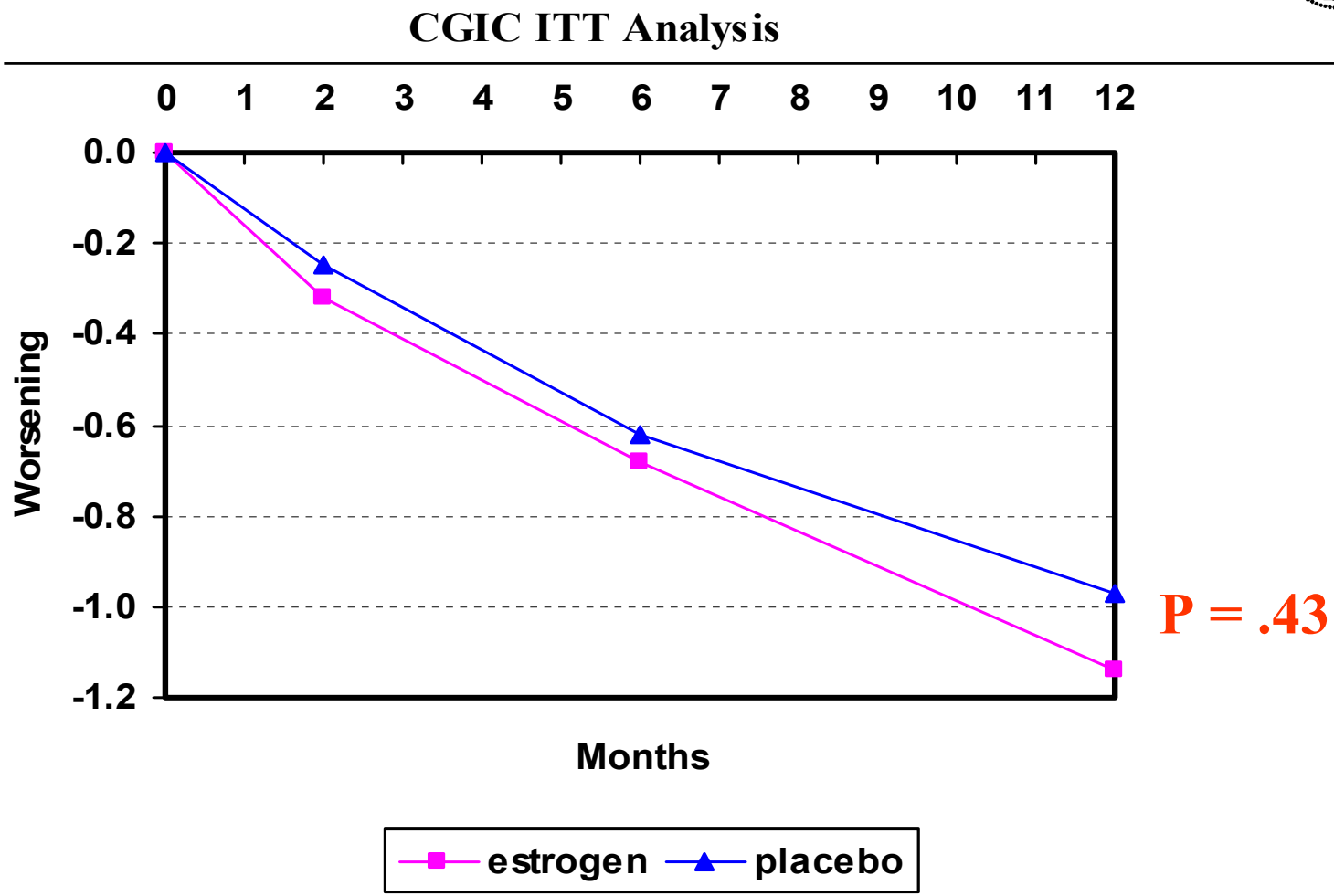
- **Language Measures**
  - Letter Fluency
  - Category Fluency
- **Motor Measures**
  - Grooved Pegboard
  - Finger Tapping
- **Activities of Daily Living Measures**
  - Blessed Dementia Rating Scale
  - Dependency Scale

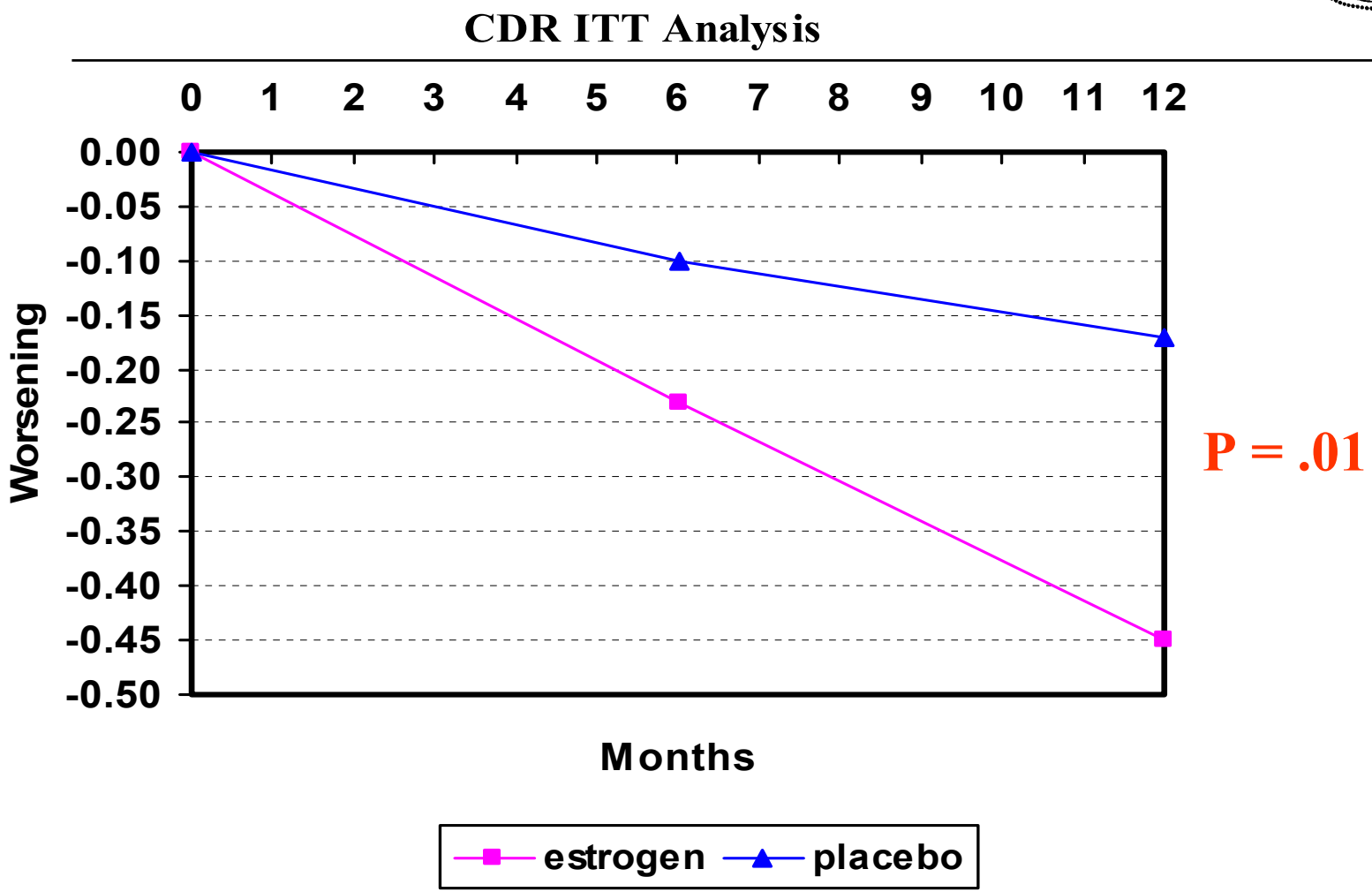
Baseline Demographics

	PLACEBO	ES .625	ES 1.25	TOTAL
AGE (56-91)	74.10	76.76	74.23	75.08
EDUCATION	12.08	12.55	12.00	12.22
HAMILTON	3.82	3.38	3.21	3.47
CDR	1.03	1.15	1.08	1.09
MMSE	21.13	20.17	20.79	20.68
ADAS	22.52	23.68	23.17	23.13

Specific Aim 1, 2

- **To determine whether hysterectomized female patients with AD who take ESTROGEN replacement therapy show improvement or stability after 12 months of therapy**


CGIC ITT Analysis
0 1 2 3 4 5 6 7 8 9 10 11 12
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
Worsening
Months
estrogen
placebo
P = .43



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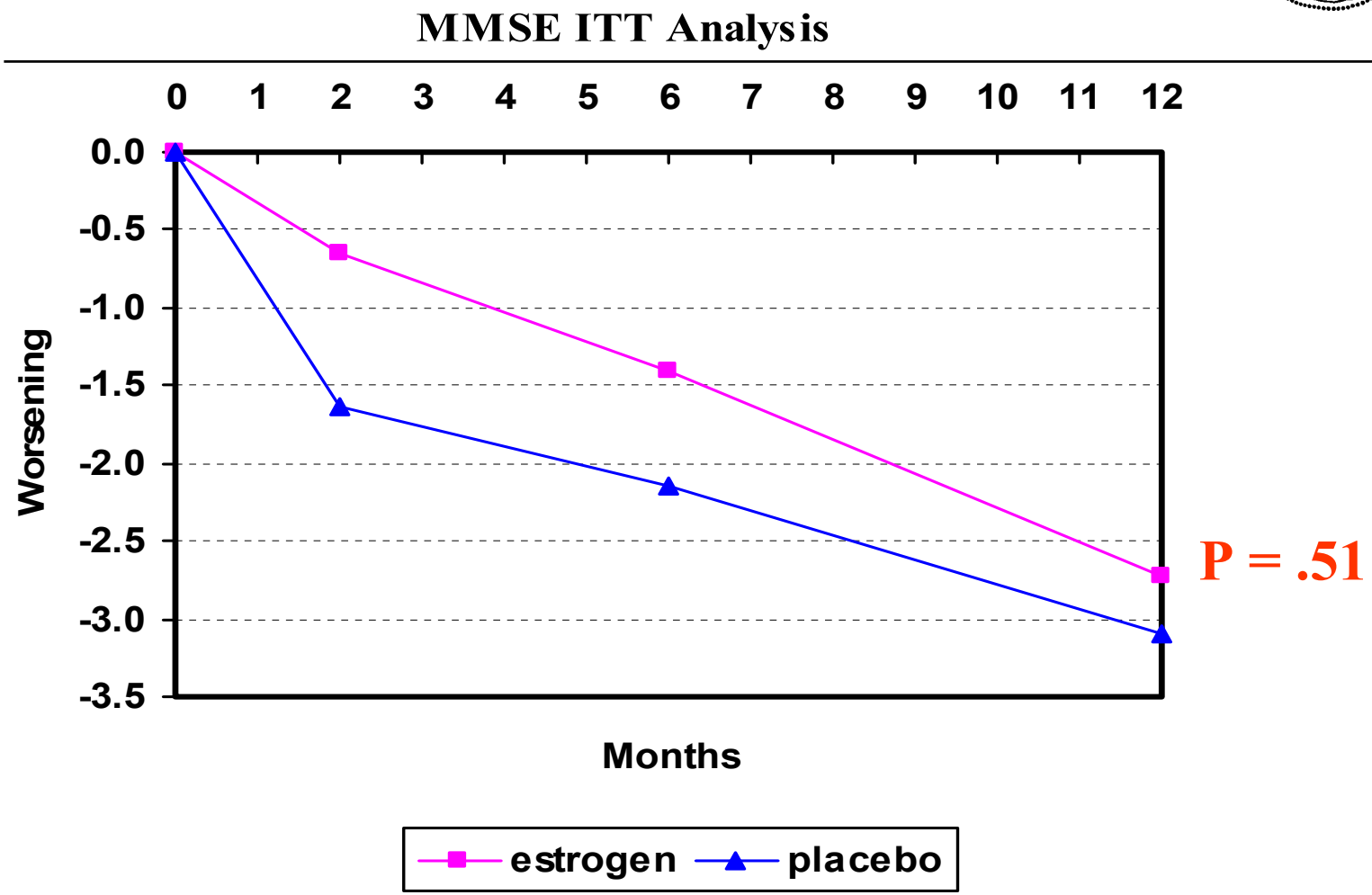
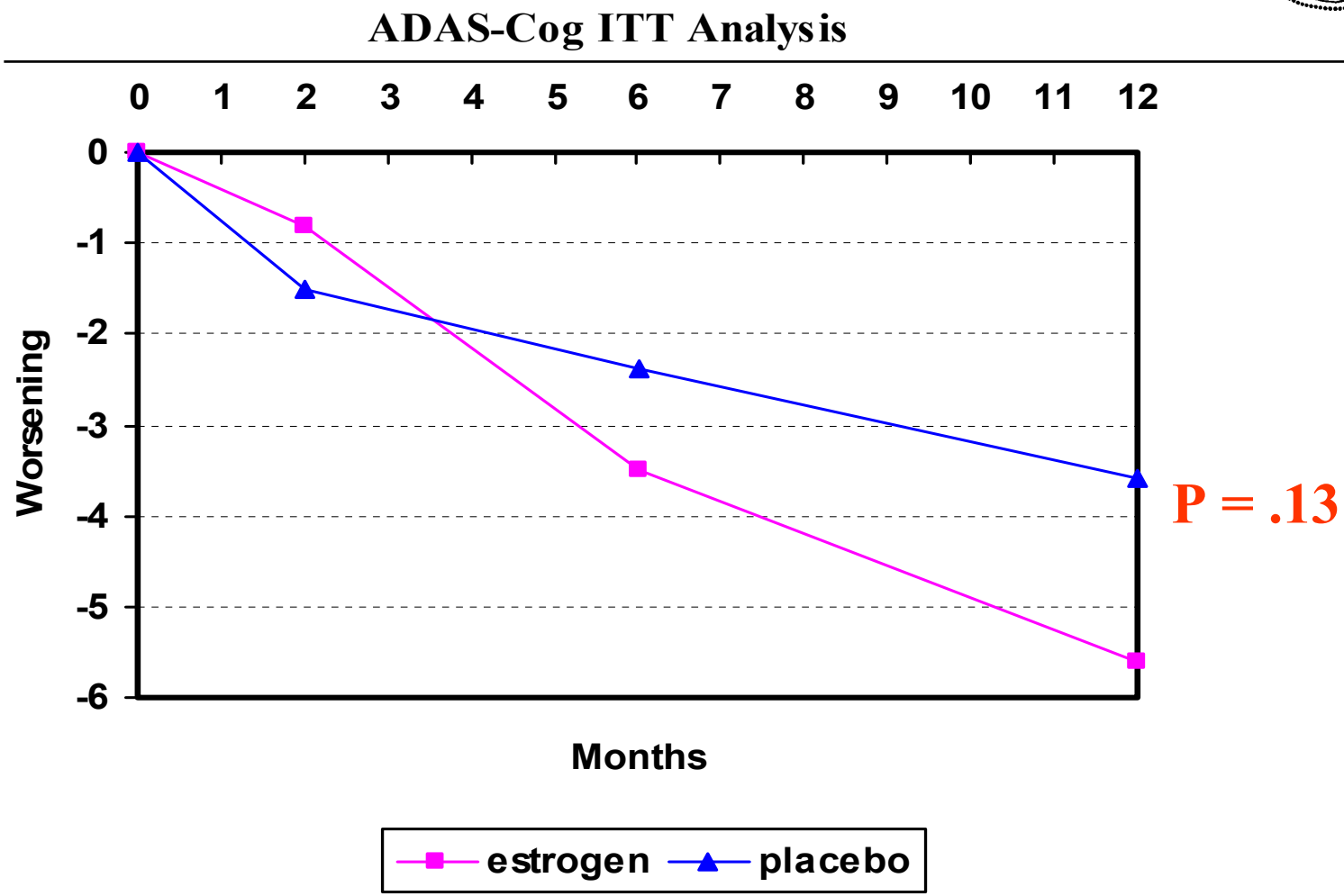

MMSE ITT Analysis
0 1 2 3 4 5 6 7 8 9 10 11 12
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
Worsening
Months
estrogen
placebo
P = .51



MULNARD, ET AL., (2000). JAMA, 283(8), 1007-1015

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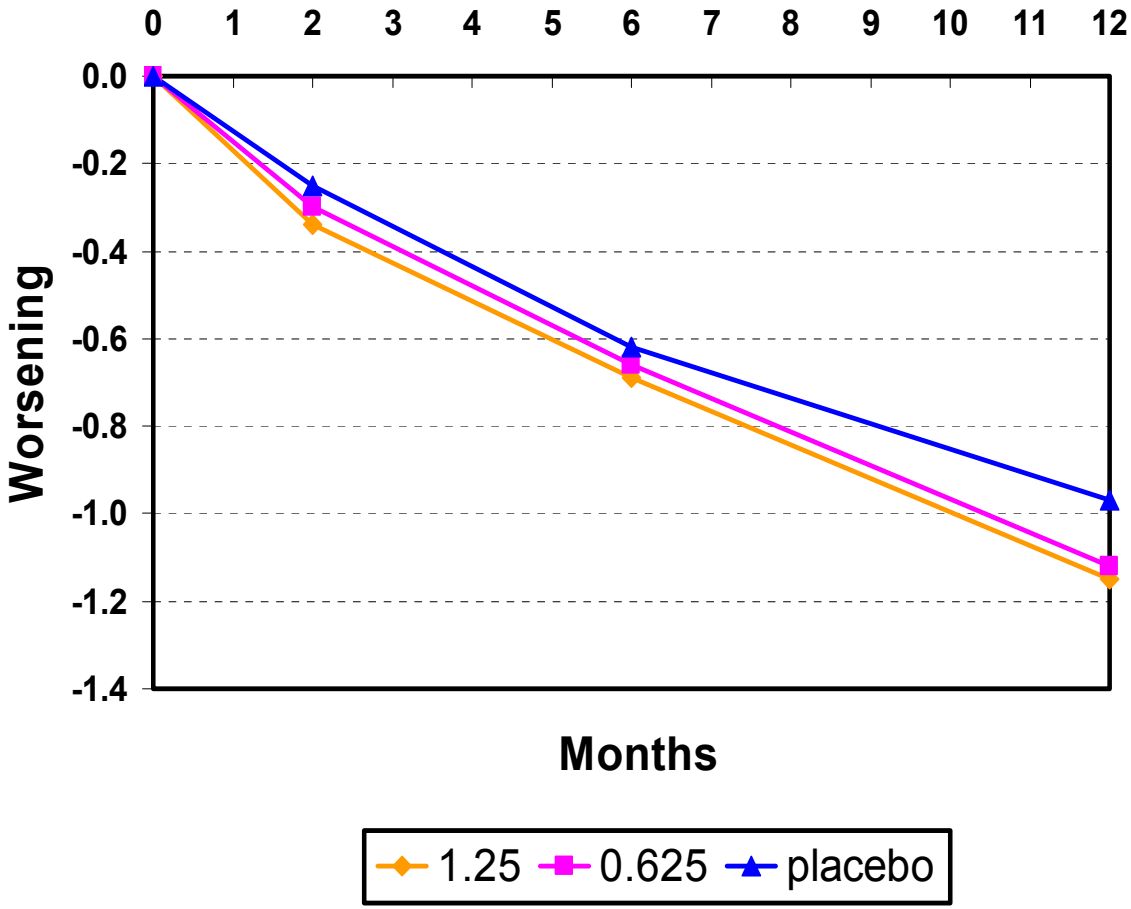
Estrogen as a Case Study

Final figure

Specific Aim 3

- **To determine whether there is a differential response to high and low dose ESTROGEN**

CGIC ITT Analysis



P = .66 (.625mg)
P = .36 (1.25mg)

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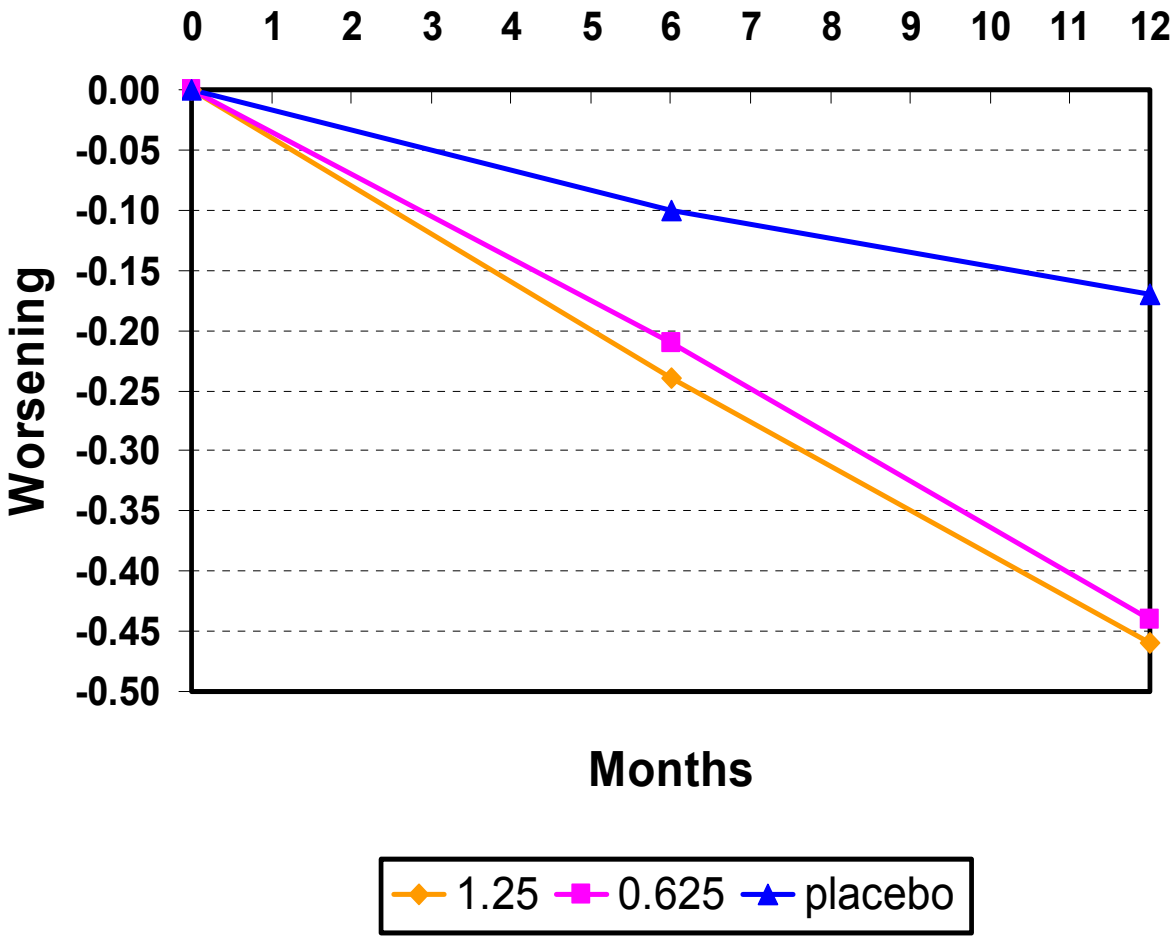
CDR ITT Analysis



P = .03 (.625mg)
P = .01 (1.25mg)

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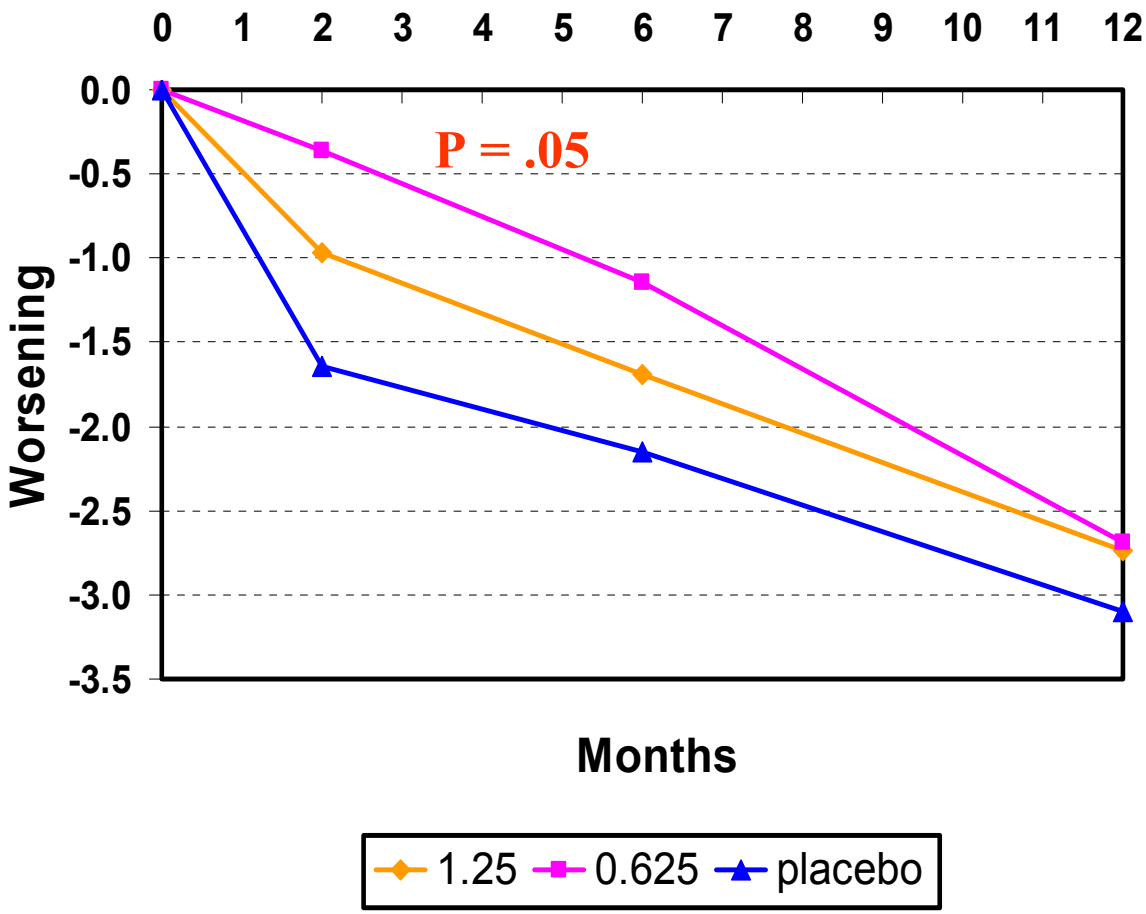
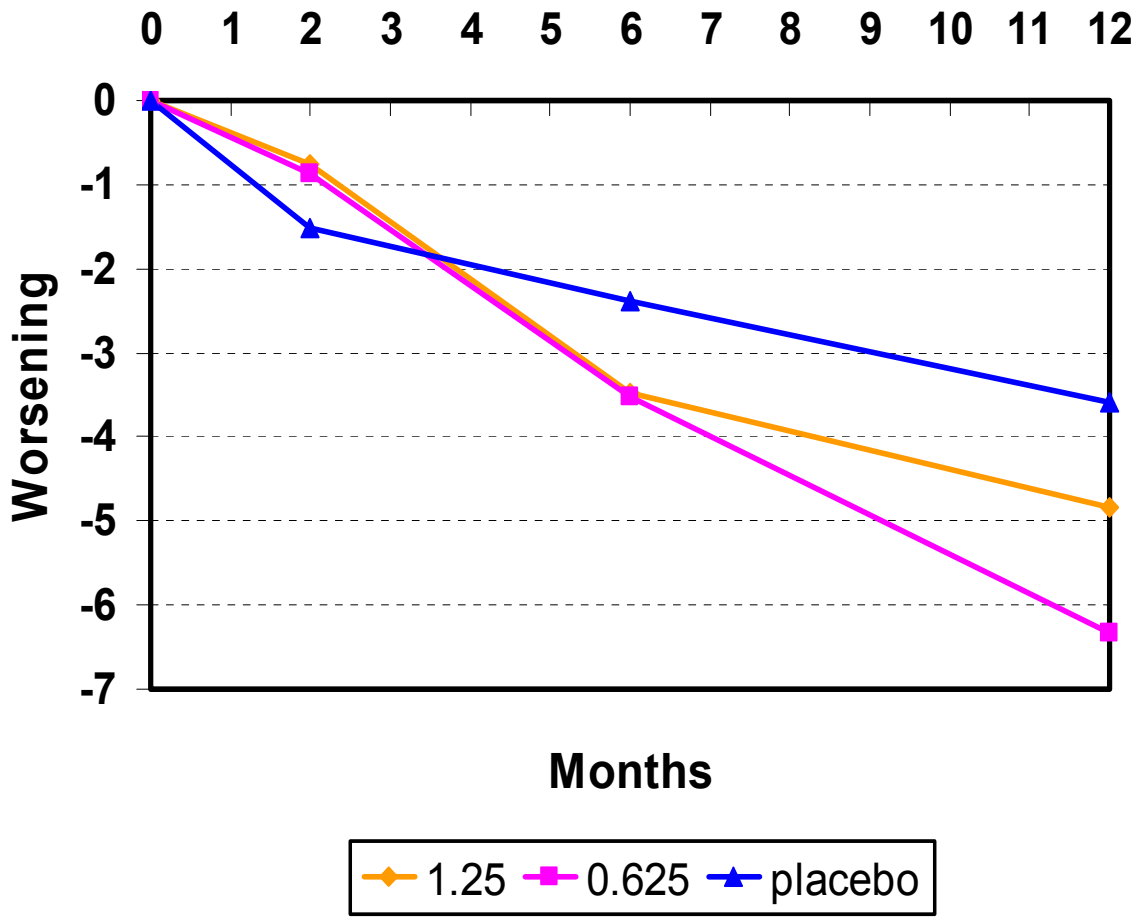
MMSE ITT Analysis



P = .48 (.625mg)
P = .64 (1.25mg)

MULNARD, ET AL., (2000). JAMA, 283(8), 1007-1015

ADAS-Cog ITT Analysis



P = .09 (.625mg)
P = .32 (1.25mg)

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Final figure

Specific Aim 4

- **To establish the safety and tolerability of ESTROGEN in elderly females with AD**

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Adverse Events

EVENT	Placebo (N=39)	Estrogen (N=81)
DEATH	0	2
REPRO	0	4
DVT	0	4
SLEEP	4	0
BEH. DIS.	2	6

MULNARD, ET AL., (2000). JAMA, 283(8), 1007-1015

Conclusion

- Estrogen failed to improve cognition in women with established mild to moderate stage of AD
- Estrogen failed to delay the progression of the disease over a 1 year period of time
- Estrogen therapy is not without risk

Estrogen Replacement Therapy For Treatment of Mild to Moderate Alzheimer Disease: 1-Year Randomized Controlled Trial

JAMA, February 23, 2000
Vol 283, No 8, Pages 1007-1015.

Mulnard RA, Cotman CW, Kawas CH, van Dyck CH, Sano M, Doody R, Koss E, Pfeiffer E, Jin S, Gamst A, Grundman M, Thomas R, Thal LJ for the Alzheimer's Disease Cooperative Study