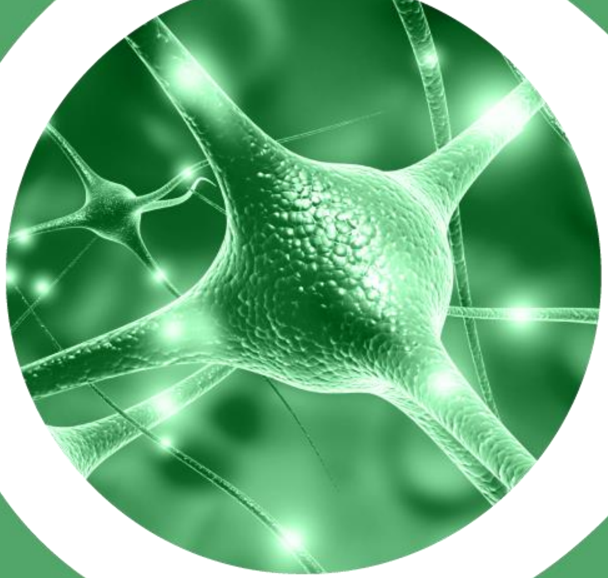
Neuronix Ltd.’s neuroAD™ Therapy System De Novo Request (DEN160053)

Meeting of the Neurological Devices Advisory Panel

March 21, 2019



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Agenda

- Introduction
- Company Background
- Explanation of the De Novo Pathway
- Alzheimer’s Disease, Transcranial Magnetic Stimulation (TMS)
- neuroAD™ Therapy System
- Clinical Evidence
  - US Pivotal Study
  - Supportive Data
- Clinical Significance of Outcomes
- Physicians’ Perspective & Conclusions

Main Speakers

Eyal Baror, MSc
CEO & President

Alvaro Pascual-Leone, PhD, MD
Professor of Neurology and Assoc. Dean for Clinical and Translational Science, Harvard Medical School
Chief, Division of Cognitive Neurology and Berenson Allen Center for Brain Stimulation, Beth Israel Deaconess Medical Center Boston, MA
Site PI for US Pivotal Study

Marwan Sabbagh, MD
Director, Cleveland Clinic Lou Ruvo Center for Brain Health
Camille and Larry Ruvo Endowed Chair for Brain Health
Site PI for US Pivotal Study

Lon S. Schneider, MD
Professor of Psychiatry, Neurology, and Gerontology, Keck School of Medicine of the University of Southern California

Susan Alpert, PhD, MD
Regulatory Consultant
Former Director Office of Device Evaluation (ODE), CDRH, FDA 1993-1999
Former SVP Global Regulatory Affairs, Medtronic

Philip Lavin, PhD
Principal, Lavin Consulting LLC

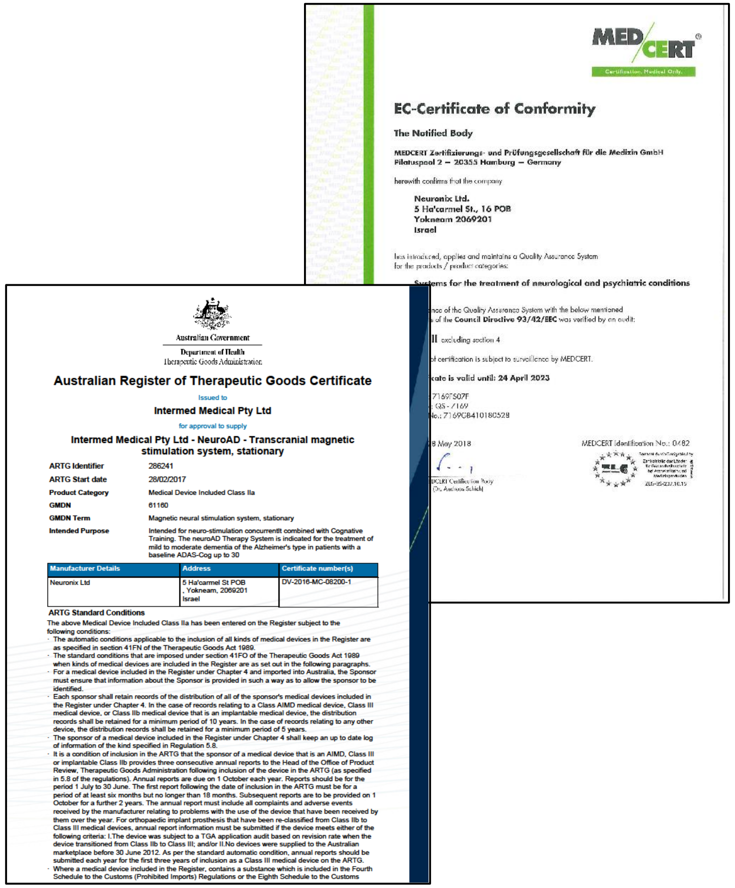
Moran Ploznik, B.Eng. MBA
VP of Clinical and Regulatory Affairs

Additional Speakers

	Marc E. Agronin, MD Affiliate Associate Professor of Psychiatry and Neurology, University of Miami Miller School of Medicine Senior Vice President for Behavioral Health, and Chief Medical Officer, The MIND Institute Miami Jewish Health, Miami, Florida Site PI for US Pivotal Study
	Babak Tousi, MD Head Clinical Trials Program, Cleveland Clinic Lou Ruvo Center for Brain Health – Cleveland, Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine Site PI for US Pivotal Study
	Stella Karantzoulis, PhD, ABPP-CN Founder & President, Modern Brain Center, LLC Former Assistant Professor of Neurology & Associate Director of the Pearl Barlow Center for Memory Evaluation and Treatment, NYU, Langone Medical Center Site PI for US Pivotal Study

About Neuronix Ltd.

- Established 2008
- Focused on dementia of the Alzheimer's disease type
- First-in-man study in 2009
- Multiple studies published to date, with 13 supporting current FDA submission
- Device approved and in clinical use in EU, Australia and Israel:
  - EU, Israel (2012) – mild to moderate AD
  - Australia (2017) – mild to moderate AD with baseline ADAS-Cog ≤30
- Current status:
  - Over 400 subjects enrolled in different clinical settings



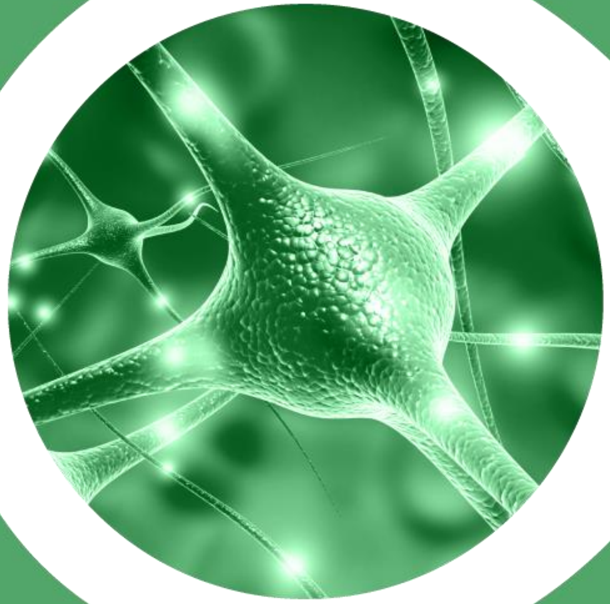
Proposed Indications for Use

- The neuroAD^{TM} Therapy System is intended for neuro-stimulation concurrently combined with cognitive training.
- neuroAD^{TM} Therapy System is indicated for the treatment of mild to moderate dementia of the Alzheimer’s type in patients with a baseline ADAS-Cog score up to 30.
- neuroAD^{TM} Therapy System may be used in conjunction with other pharmacological and non-pharmacological therapies.

Overview of neuroAD^{TM} Clinical Data

- neuroAD^{TM} consistently shown to be a safe treatment
- There is evidence of a clinically defined population that shows meaningful benefits
- Benefit is demonstrated on both cognitive and functional endpoints – ADAS-Cog and ADCS-CGIC
- US Pivotal Study findings were confirmed by additional independent studies as well as experience in clinical practice
- Benefits are in addition to standard of care
- Real world data from selected territories – France, Italy, UK, Australia – support clinical trial findings
- Probable benefits outweigh probable risks – the De Novo standard

Explanation of the De Novo Pathway



S. Alpert, PhD, MD

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The Unmet Need – FDA's Breakthrough Device Program

(formerly Expedited Access Pathway (EAP))

- EAP/Breakthrough status intended to speed approval of devices that treat life-threatening or irreversibly debilitating diseases and address an unmet need
- Due to the unmet need, FDA guidance states that:
  - ***"May accept greater extent of uncertainty if balanced by probable benefit for patients including earlier access to the device"***
- Furthermore, FDA allows for enhanced opportunity for balance between pre / post-market data collection
    - "***FDA intends to use timely postmarket data collection . . . to facilitate expedited and efficient development and review of the devices***".

De Novo Risk – Benefit Standard

- FDA guidance for de novo classification notes that it is intended to **reduce time to market for low-to-moderate risk products** where probable benefit outweighs probable risk
- neuroAD™ study design provides data that support that probable benefit outweighs the probable risk for this device
- When these products go to market there are appropriate requirements put in place continue to assure that each one shows that benefits outweigh the risks

neuroAD^{TM} Meets De Novo Risk – Benefit Standard & EAP Guidelines

- Risks associated with the device are low
- Benefits observed at 12 weeks in clinical testing for the neuroAD^{TM} are clinically meaningful and outweigh the low risks associated with the device:
  - ADAS-Cog
  - ADCS-CGIC
  - Dual end-point
- Proposed therapy is adjunctive to existing medications
- Accompanied by carefully planned post-marketing surveillance study

Additional Considerations

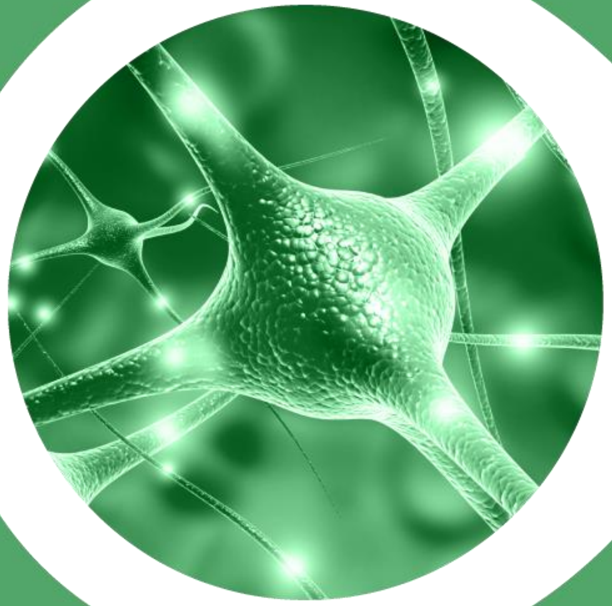
- FDA recognizes importance of "voice of the patient"; we will hear from patients and caregivers in the OPH
- Independent survey of 200 clinicians noted that combined benefit on ADAS-Cog and ADCS-CGIC is clinically meaningful
  - in particular when risks are low and therapy is adjunctive
- *Letter – Researchers Against Alzheimer's* (May 2017)

"If the FDA were to reject, individually, several safe and well-tolerated therapies with complementary mechanisms of action that each demonstrate a modest clinical benefit, it would unwittingly deprive patients of potentially substantial advances in the quality of treatment over the long run with a combination of therapies. Most researchers believe the future of Alzheimer's disease treatment lies in combination therapy…."

Alzheimer’s Disease Background

TMS Background and neuroAD™ Therapy System Overview

A. Pascual-Leone, PhD, MD



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Current Treatment Options for Alzheimer's Disease

- 5.7 million people living with Alzheimer's in the US alone; third leading cause of death (previously sixth)
- No disease-modifying or preventative treatments
- Only approved interventions are pharmacologic, which have side effects and limited efficacy in magnitude and duration

Drug Treatments	
Cholinesterase Inhibitors (ChEI)	Donepezil; Rivastigmine; Galantamine
N-methyl-D-aspartate (NMDA) Inhibitors	Memantine
Combination	Memantine + Donepezil (Namzaric)

- No new drug types have been approved in the last 20 years; 99.6% of all reported AD drug trials, or over 400 compounds, failed to show a measurable benefit over placebo

Cummings, J, Morstorg, T & Zhong, K, Alzheimer’s disease drug-development pipeline: few candidates, frequent failures, Alzheimer’s Research & Therapy, 2014, 6:37 (available at https://alzres.biomedcentral.com/track/pdf/10.1186/alzrt269); Janssen Halts Clinical Studies of Alzheimer’s Candidate (May 18, 2018), Genetic Engineering & Biotechnology News, *available* at https://www.genengnews.com/news/janssen-halts-clinical-studies-of-alzheimers-candidate/.

Evolution of Treatment Options

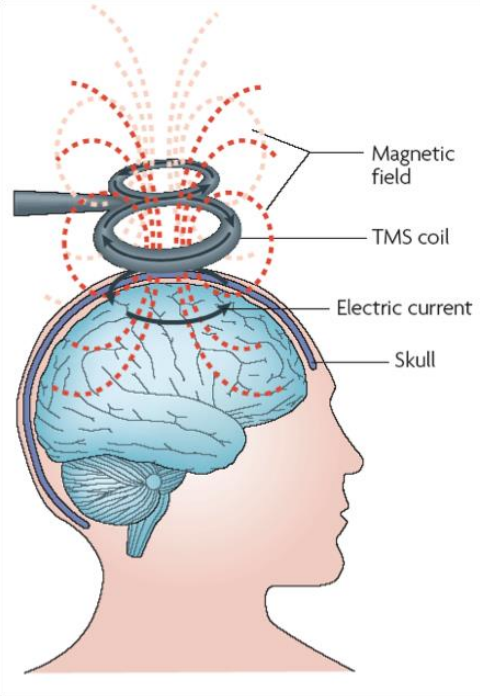
- Multi-modal treatment is of growing interest
- Unmet need for complementary treatment options
  - Different targets
  - New mechanisms of action
  - Measureable effect
  - Favorable safety profile

- neuroAD™ is a fully integrated therapy incorporating TMS with computerized cognitive training
  - TMS primes specific brain networks to enhance plasticity, lasting beyond acute stimulation period
  - Cognitive training engages these primed networks, leading to enhanced learning
  - Specific combination of TMS and Cognitive training results in consolidated benefit over time

Transcranial Magnetic Stimulation (TMS) Experience & Safety

A non-invasive electromagnetic technique which allows for stimulation of cortical regions

- FDA-cleared for major depression, migraine and obsessive compulsive disorder
- Today, TMS is in widespread clinical use worldwide
- For past 20 years, IFCN (International Federation of Clinical Neurophysiology) Consensus Group has reviewed the safety of TMS and made practice recommendations*
  - Adverse Effects – transient headache, neck pain, local pain, tooth ache, paresthesia
  - Demonstrated to be safe for use in an elderly population



*Wassermann EM *"Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation"*, **Electroencephalography and clinical Neurophysiology** 108 (1): 1–16, 1998

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., Safety of TMS Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, 120(12), 2008-2039.

https://www.prnewswire.com/news-releases/neurostar-advanced-therapy-hits-2-million-treatments-during-national-depression-awareness-month-300729351.html

FDA TMS Clearances

2008 NeurosStar TMS System™
(Refractory MDD)

2013 Brainsway Deep TMS™
(Refractory MDD)

2013 Cerena Transcranial Magnetic Stimulator™
(Migraine)

2014 SpringTMS™
(acute treatment of pain associated with migraines)

2015 Rapid^2 Therapy System™
(Refractory MDD)

2015 MagVita TMS Therapy System™
(Refractory MDD)

2016 Neurosoft TMS™
(Refractory MDD)

2017 SpringTMS™
(acute treatment and prophylactic treatment for migraines)

2017 Horizon Therapy System™
(Refractory MDD)

2017 Nexstim Navigated Brain Therapy (NBT) System 2™
(Refractory MDD)

2018 Brainsway Deep TMS (DTMS) System™
(Refractory MDD)

2018 Apollo TMS Therapy System™
(Refractory MDD)

2018 MagVita TMS Therapy System W/Theta Burst Stimulation™
(Refractory MDD)

2018 Brainsway Deep Transcranial Magnetic Stimulation™
N=100
(OCD)

Technological Features and Principles of Operation

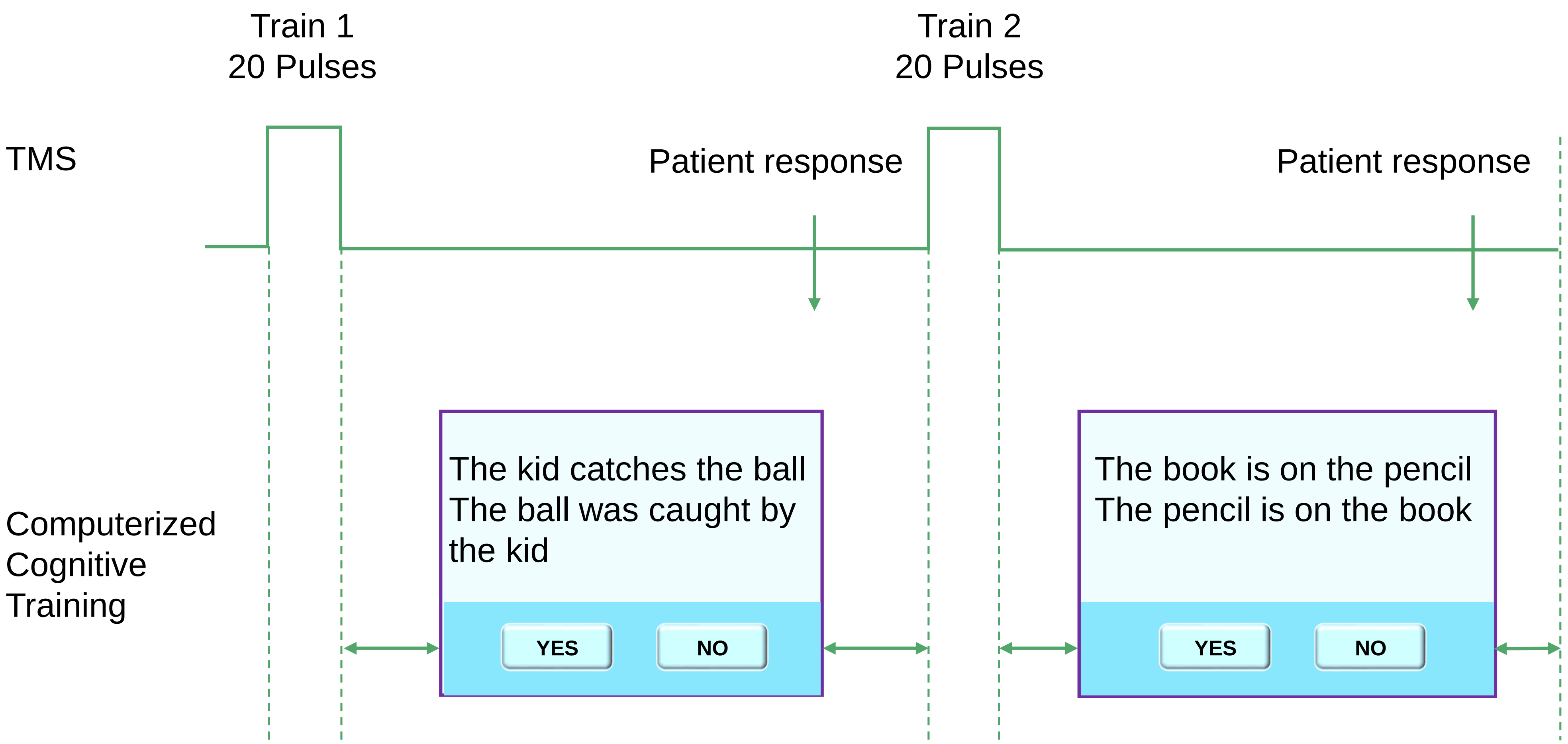
- Prior to intervention:
  - Patient undergoes structural MRI scan
  - 6 anatomic regions of the cerebral cortex are identified by neuroanatomist by macroanatomical landmarks (i.e., Broca, Wernicke, dorsolateral prefrontal cortex (left & right), parietal cortex (left & right))
  - Marked MRI is uploaded to navigation unit
- Treatment course:
  - Protocol: 5 daily 1 hour sessions per week, for 6 weeks
  - During daily session, 3 alternate spatially discrete regions are treated (1300 pulses of 10Hz)
  - TMS intensity is based on the patient's daily motor threshold (MT) as determined by standard procedure*

*Schutter et al. 2006

neuroAD™ Navigation Unit

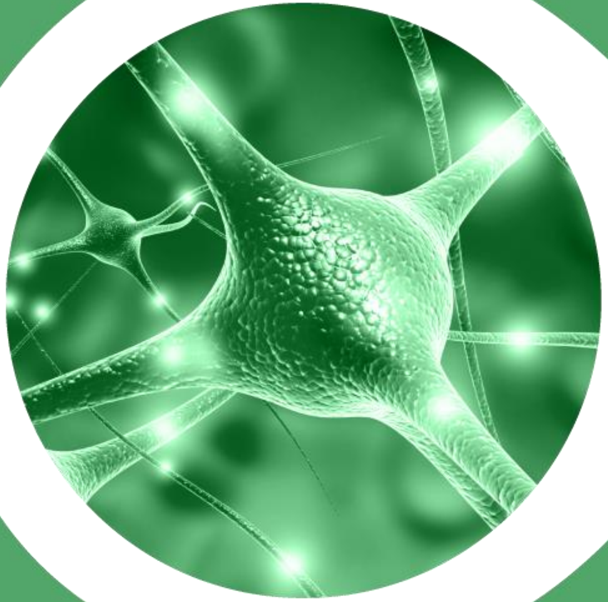
neuroAD™ Base Unit

Treatment Stimulation



Clinical Evidence – Overview

A. Pascual-Leone, PhD, MD



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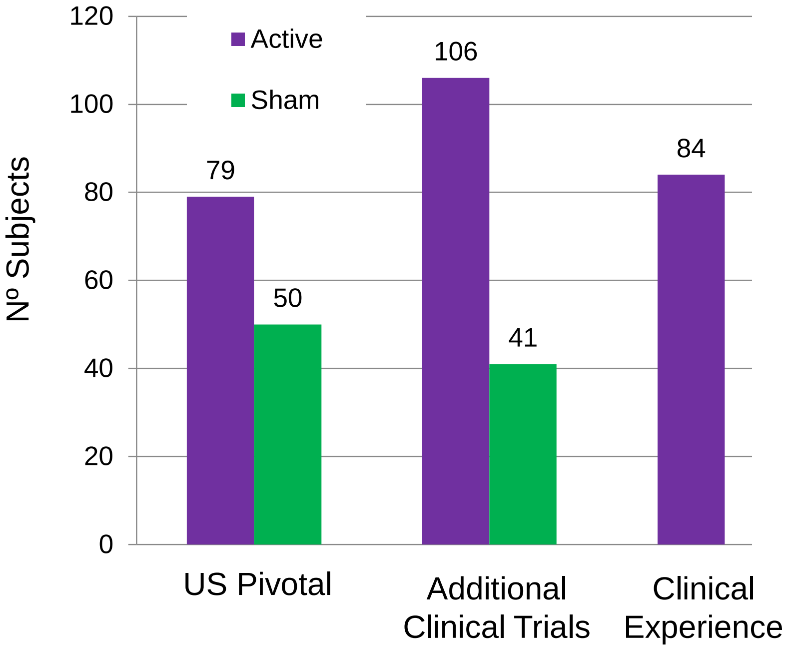
All Data Sources

374 Subjects Overall



US Pivotal Study (n=130)
Active – 59 (+20 Run in)
Sham – 50

Korean Pilot Study (n=26)
Active – 18
Sham – 8

Korean Pivotal Study (n=22)
Active – 11
Sham – 11

Assaf-1 Study (n=8)
Active – 8

Assaf-2 Study (n=15)
Active – 7
Sham – 8

Harvard Study (n=21)
Active – 10
Sham – 6
Cog Only – 5

Assaf-3 Study (n=16)
Active – 10
Sham – 6

NNX Clinic Study (n=30)
Active – 30

Italian Study (n=13)
Active – 6
Sham – 2
Cog only – 5

Thailand Study (n=9)
Active – 6
Cog only – 3

Clinical Experience

NNX Clinic Israel (n=54)
Active – 54

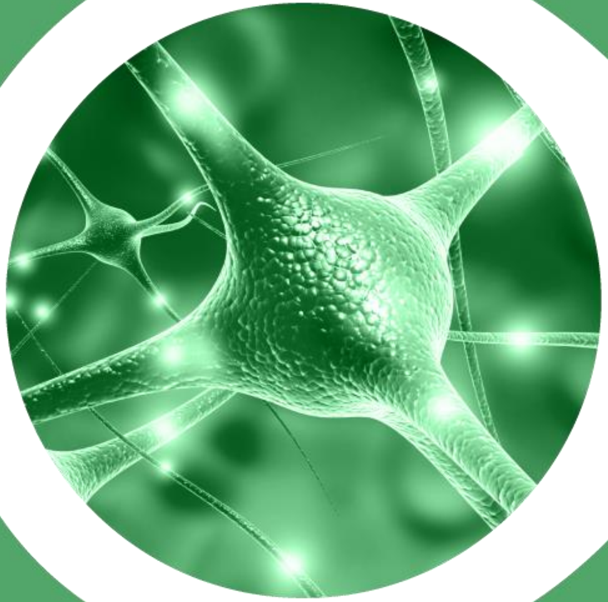
Nantes (n=10)
Active – 10

High Wycombe (n=6)
Active – 6

NNX Clinic UK (n=4)
Active – 4

Orsay (n=10)
Active – 10

US Pivotal Study – Study Design



A. Pascual-Leone, PhD, MD

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US Pivotal Study – Design

- Prospective, double-blind, sham controlled (NCT01825330)
  - Active intervention was provided by neuroAD^{TM} therapy session, combining real TMS and real cognitive training
  - Sham intervention was sham TMS (lights and noise) and sham cognitive training (non-interactive movie)
- Study was designed in consultation with FDA
- Multi-center (9 sites in the US and 1 site in Israel)
- Mild to moderate AD
- 12-week study duration (6 weeks treatment + 6 weeks follow-up)
- Randomization and blinding
  - Raters, investigators, subjects and caregivers were blinded to subjects' group assignment
  - Each site had 2 "run-in" unblinded subjects undergoing active treatment – included in safety analyses only
  - Blinding was confirmed using a questionnaire given to patients/caregivers/raters

US Pivotal Study – Sites

Site #	N	Site Name	Principal Investigator
101	8	Lou-Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV	Charles Bernick, MD, MPH
102	9	Banner Sun Health Research Institute, Sun City, AZ	Marwan Sabbagh, MD
103	6	NYU Langone Medical Center, New York, NY	Steven H. Ferris, PhD Stella Karantzoulis, PhD
104	31	Palm Beach Neurology and Premiere Research Institute, West Palm Beach, FL	Carl Sadowsky, MD
105	19	Cleveland Clinic, Cleveland, Ohio	Babak Tousi, MD
106	8	Beth Israel Deaconess Medical Center, Harvard, Boston, MA	Alvaro Pascual-Leone, MD, PhD
107	18	Miami Jewish Health Systems, Miami, FL	Marc Agronin, MD
108	13	ATP Clinical Research, Costa Mesa, CA	Gustavo Alva, MD
109	6	Roskamp Institute, Sarasota, FL	Andrew P. Keegan, MD
201	12	Asaf-Harofe Hospital, Beer-Yakov, Israel	Carmel Armon, MD

US Pivotal Study – Key Eligibility Criteria

<table>
<tr><th>Key Inclusion Criteria</th><th>Key Exclusion Criteria</th></tr>
<tr><td>
• Male/female age 60–90 years
• Diagnosed with Alzheimer’s disease (DSM-IV), in mild or moderate stages
• MMSE score 18 to 26
• ADAS-Cog above 17
• Hearing & vision adequate for device use
• Minimum of 8th grade education
• If medicated for AD, then use of Cholinesterase Inhibitors, Memantine or Ginkgo-biloba
– Started at least 3 months before
– On stable dose for at least 2 months;
– Will continue use during study
</td><td>
• CDR 0, 0.5 or 3
• Severe agitation, mental retardation, or unstable medical condition
• History of Epileptic Seizures or Epilepsy
• Contraindication for MRI scanning, or for TMS
• Currently taking medication that lowers the seizure threshold
• Subjects on which TMS motor threshold cannot be found
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<tr><td colspan="2">MRIs required to map brain regions and to rule out non-Alzheimer's pathology (e.g., tumor)</td></tr>
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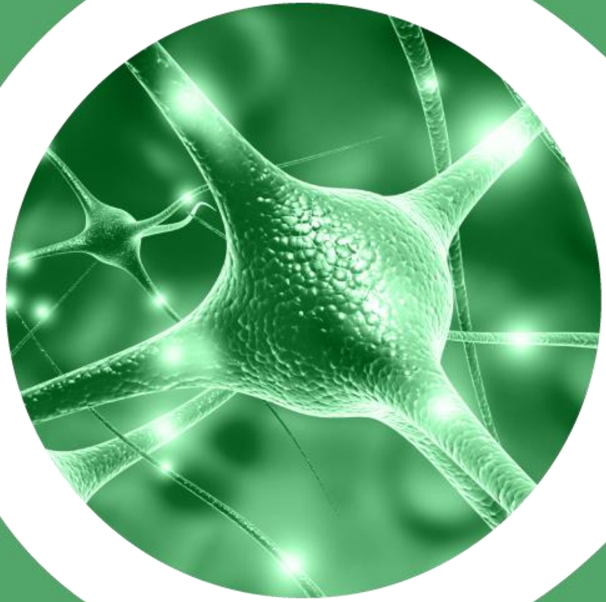
US Pivotal Study – Endpoints

Endpoints	Description
Primary Efficacy	Change from baseline to 7 weeks in ADAS-Cog
Secondary Efficacy	• Change in ADAS-Cog between baseline and 12 weeks; • ADCS-CGIC (CGIC) at 7 weeks; and • ADCS-CGIC (CGIC) at 12 weeks.
Safety	Adverse events (including SAEs) occurring at any time during the trial or follow-up, whether or not deemed related to the study device

*ADAS-Cog and CGIC raters were independent and blinded to performance on the other scale

US Pivotal Study – Subject Disposition and Baseline Characteristics

M. N. Sabbagh, MD



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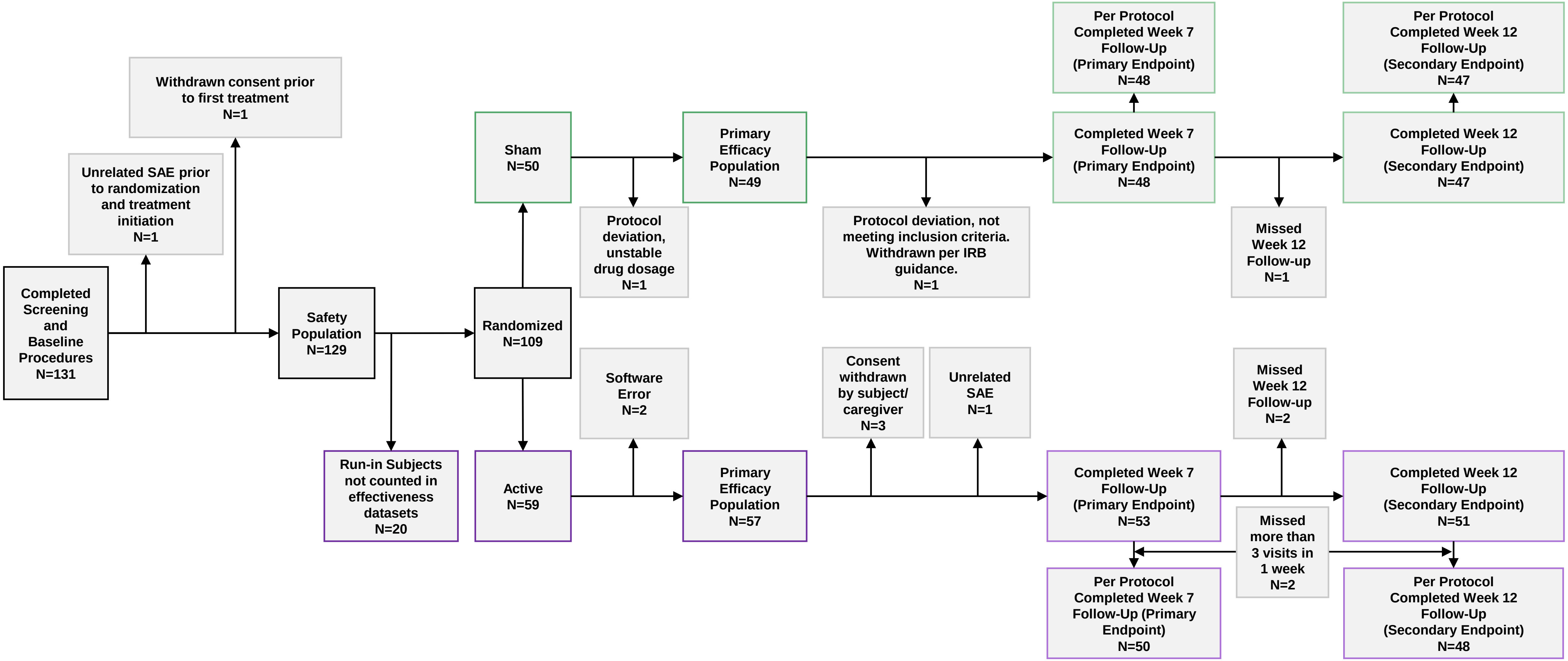
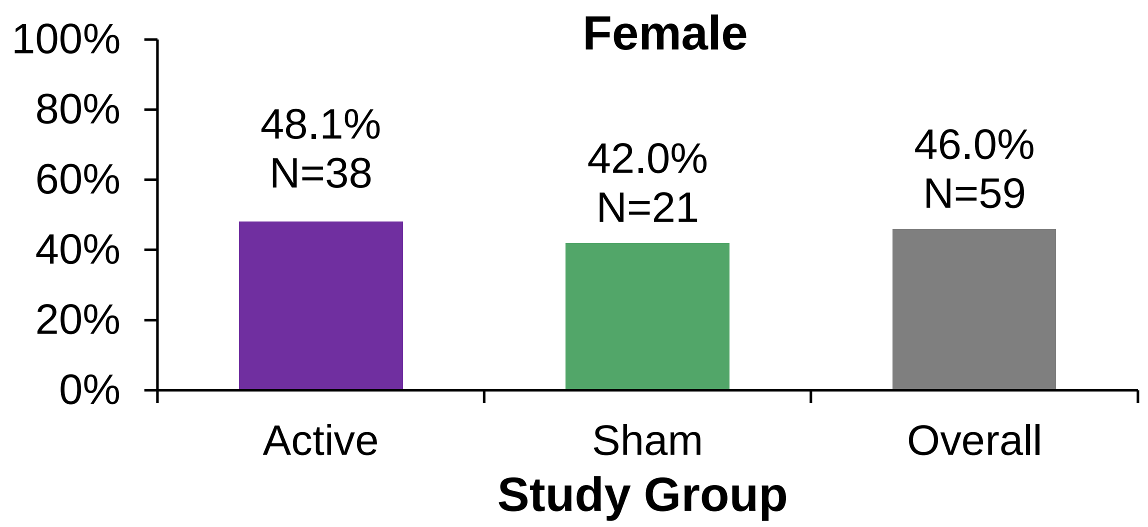
US Pivotal Study – Subject Disposition

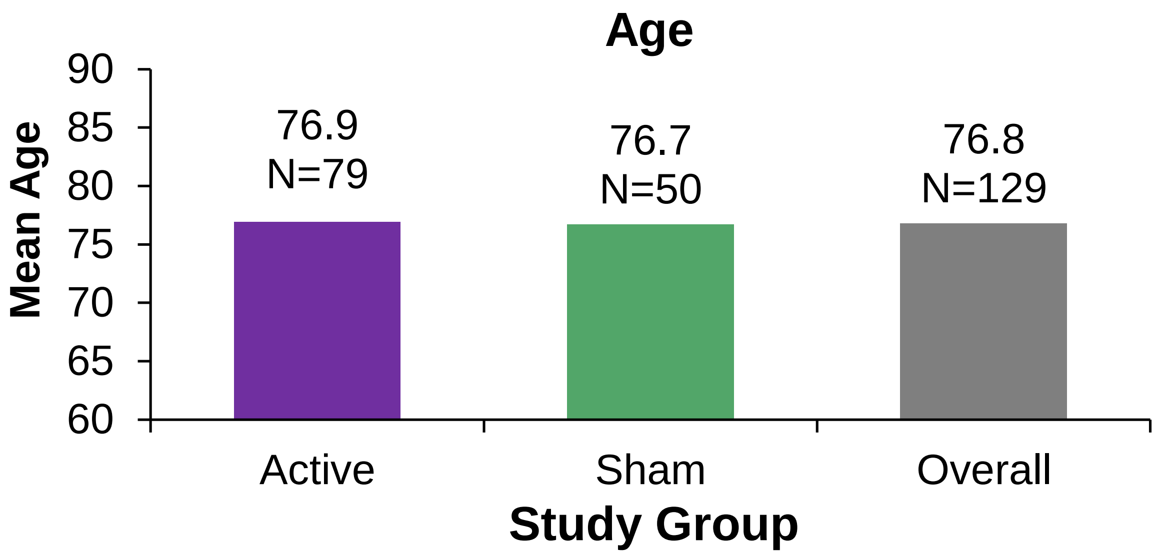


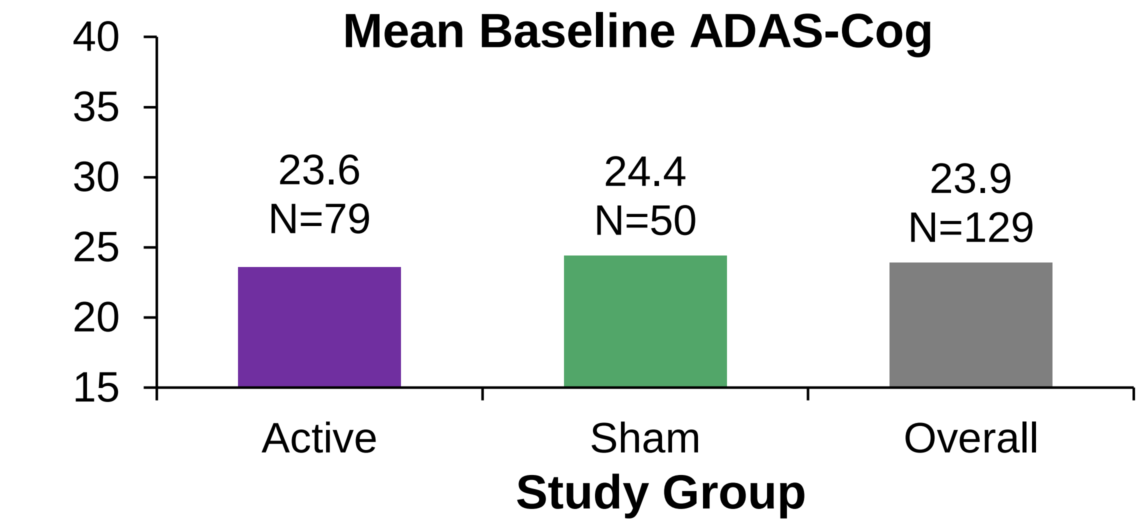
US Pivotal Study – Adherence

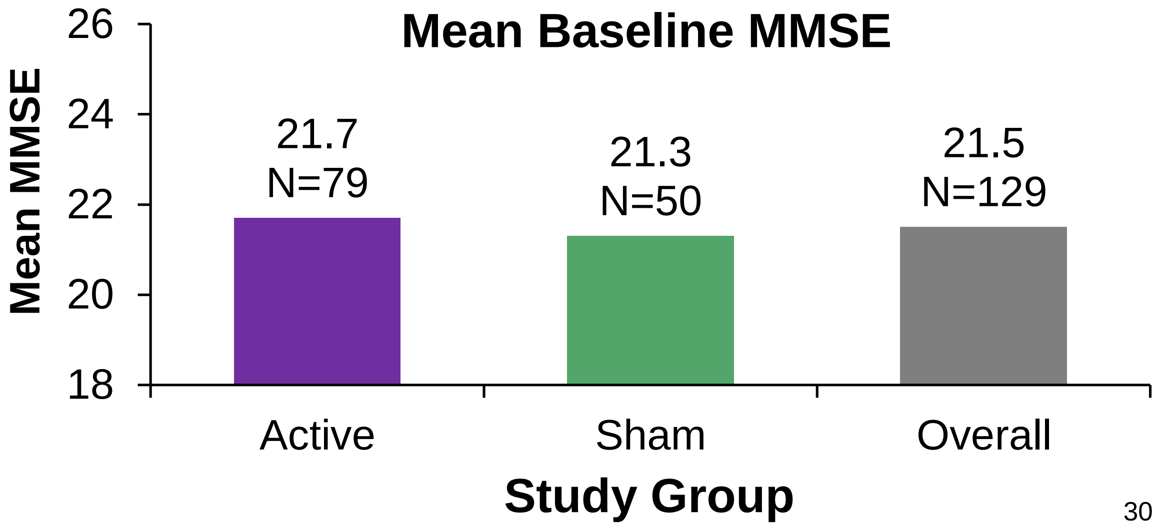
- High adherence over a 6-week period with 30 treatment sessions (over 90% of subjects attended at least 90% of the sessions)
- 90% of randomized subjects attended final study follow-up

US Pivotal Study – Selected Baseline Characteristics

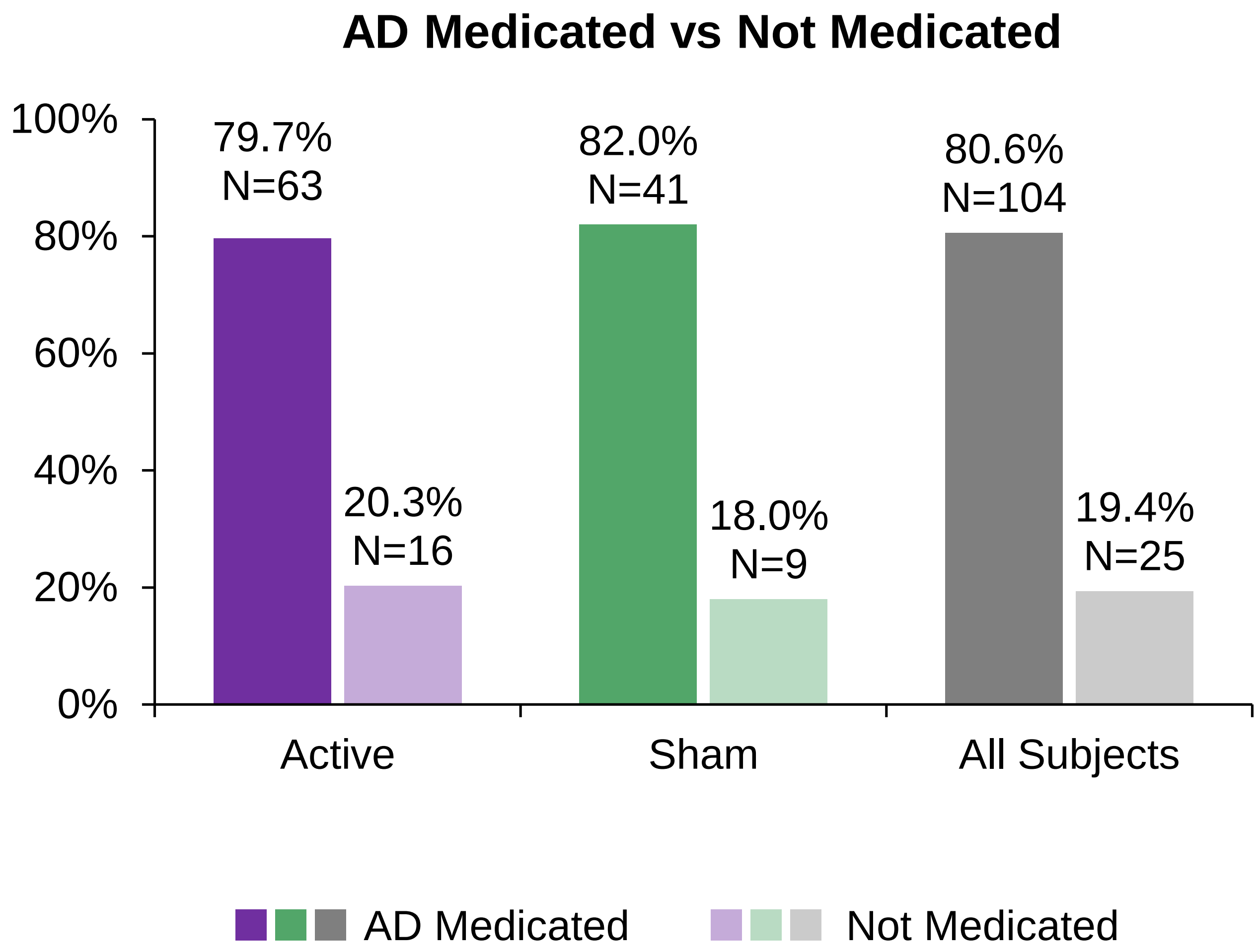






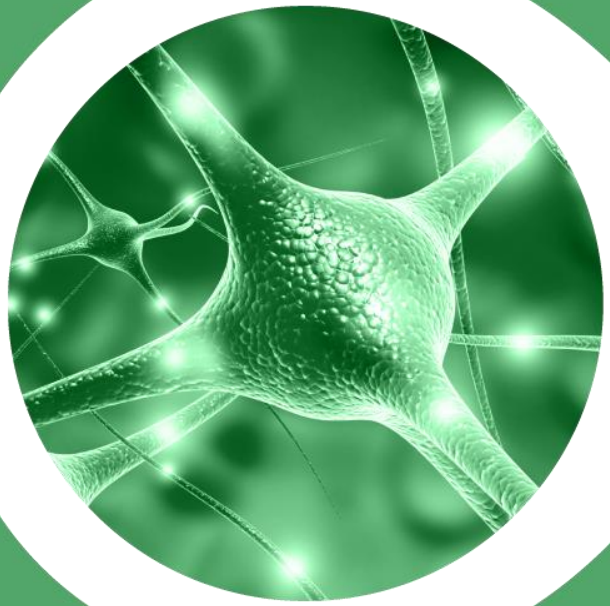


US Pivotal Study – AD Medication Usage



- 80% were on stable AD medications during the study
  - 22 of 101 took no AD drug
  - 39 of 101 took ChEI only (any form)
  - 13 of 101 took memantine only
  - 27 of 101 took both memantine and ChEI

US Pivotal Study Results – Safety



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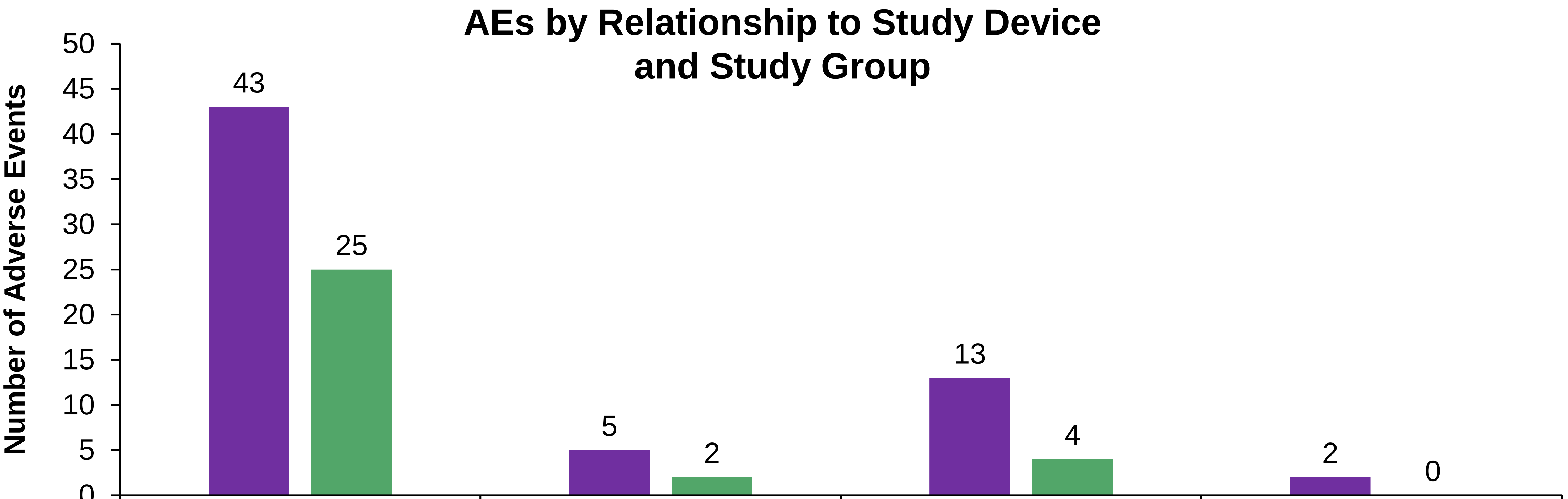
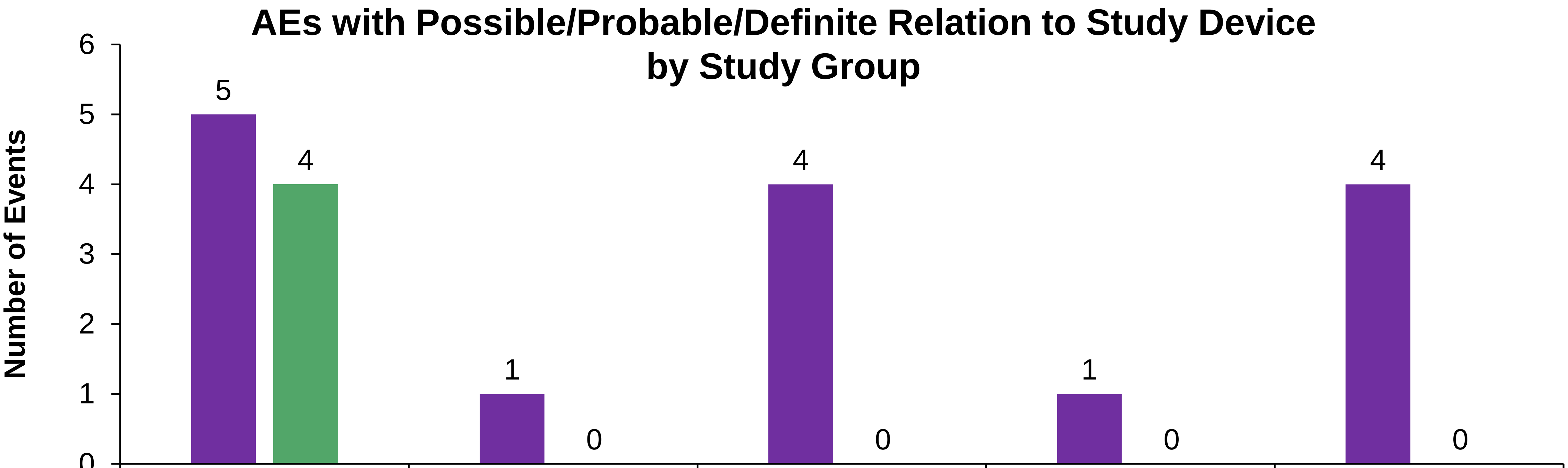
US Pivotal Study – Adverse Events – Total



	Not Related	Unlikely	Possible/Probable	Definite
Active	43	5	13	2
Sham	25	2	4	0

- 14% of Active group subjects experienced a related AE

US Pivotal Study – Related Adverse Events by Type



	Headache	Muscle Twitching	Skin Discomfort/ Sensitization	Fatigue	Neck Pain
Active	5	1	4	1	4
Sham	4	0	0	0	0

- All related AEs were mild and transient; no patient withdrew from study due to AEs

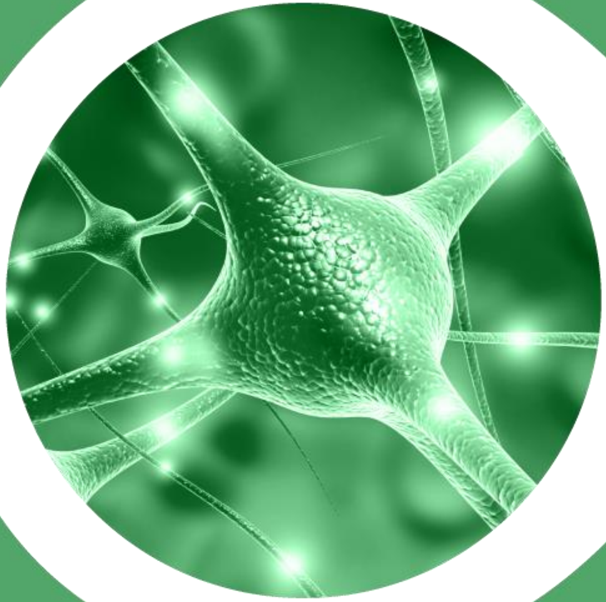
US Pivotal Study – Serious Adverse Events

- No related Serious Adverse Events (SAEs) were reported during the study
- No seizure events reported
- 4 unrelated SAEs reported in randomized or run-in subjects

US Pivotal Study – Unrelated SAEs

Group	Events	Description
Active	2	• 1 case of unrelated death • 1 case of asthenia, which resolved in 6 days
Sham	1	• Serious urinary retention event
Pre-Randomization	1	• Cervical fracture due to a fall at home (discontinued)

US Pivotal Study Results – Efficacy



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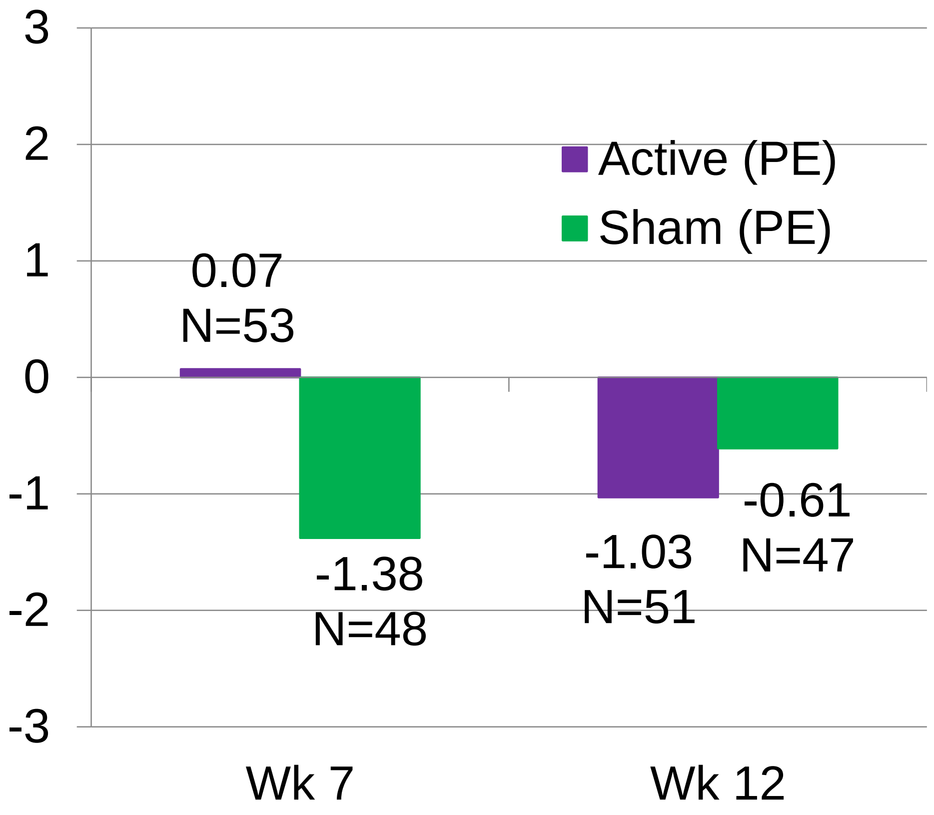
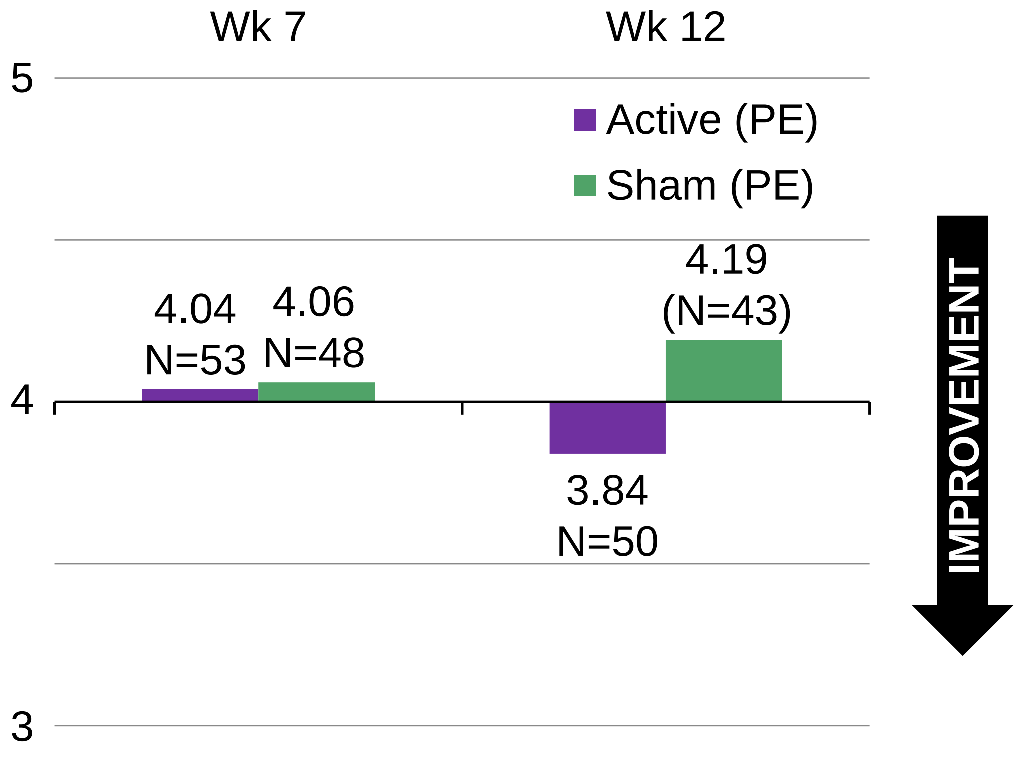
US Pivotal Study - Primary and Secondary Endpoints (PE Population)

Mean Change from Baseline ADAS-Cog



Diff at 7 Weeks = 1.45 favoring Sham (NS)
Diff at 12 Weeks = -0.42 favoring Active (NS)

Mean Change from Baseline ADCS-CGIC



Diff at 7 Weeks = -0.02 favoring Active (NS)
Diff at 12 Weeks = -0.35 favoring Active (*P* = 0.037, Chi-squared)

US Pivotal Study – Identification of Indicated Population – Statistical Considerations

- As part of primary analysis, baseline ADAS-Cog was prospectively included as a covariate to be evaluated*
- Analysis found statistically significant interaction between treatment group outcome and baseline ADAS-Cog at both 7 weeks (P = 0.029) and 12 weeks (P = 0.0072)

*Alzheimer's & Dementia 6 (2010) 39–53; Disease progression meta-analysis model in Alzheimer's disease; Kaori Ito, Sima Ahadieh, Brian Corrigan, Jonathan French, Terence Fullerton, Thomas Tensfeldt, Alzheimer's Disease Working Group

US Pivotal Study – Identification of Indicated Population Based on Disease Progression Literature

- Published literature demonstrates that more severe subjects progress differently through the disease.
- In particular, patients with **baseline ADAS-Cog >30** deteriorate **more rapidly**:
  - ***Ito et al.*** performed a meta-analysis on 52 AD studies (including approximately 20,000 AD patients) and found that:
    - Baseline ADAS-Cog is a significant covariate affecting the rate of disease progression; and
    - Patients with baseline ADAS-Cog >30 deteriorate faster than patients with baseline ADAS-Cog ≤30.
  - ***Stern et al.*** examined 1-year change in ADAS-Cog among various states of disease severity, and concluded that subjects with baseline ADAS-Cog=30 deteriorate about 50% faster than subjects with baseline ADAS-Cog=20

Doraiswamy PM et al., The *Alzheimer's Disease Assessment Scale: Patterns and Predictors of Baseline Cognitive Performance in MultiCenter Alzheimer's Disease Trials.* Neurology 1997;48:1511-151. Stern RG et al, *A longitudinal study of Alzheimer's disease: measurement, rate and predictors of cognitive deterioration.* Am J Psychiatry, 1994; 151: 390-96. Ito, K et al. *Disease progression meta-analysis model in Alzheimer's disease*. Alzheimer & Dementia 2010; 6, 39-53.

US Pivotal Study – Identification of Indicated Population Based on Independent TMS Studies

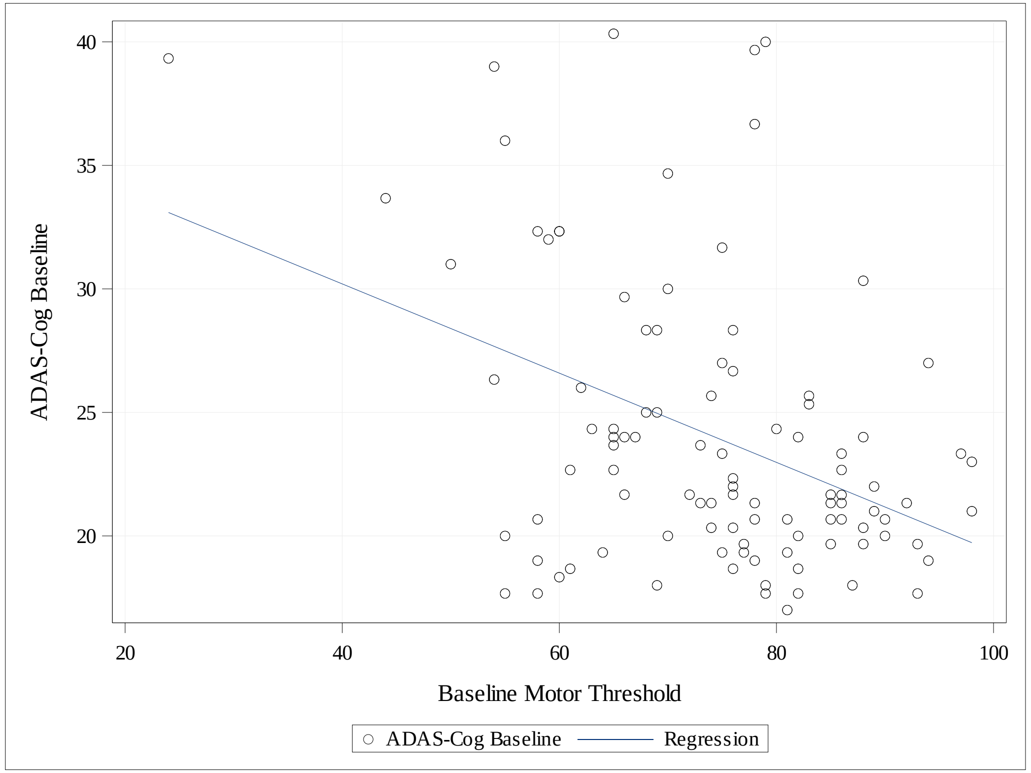
- Furthermore, per literature review, it was estimated that subjects with baseline ADAS-Cog ≤30 will respond better to TMS intervention:
  - ***Rutherford et al. (2015)*** conducted a study of a TMS/cognitive training intervention and concluded that patients with **baseline ADAS-Cog ≤30** responded better than patients with baseline ADAS-Cog >30
  - ***Lee et al. (2016)*** conducted a study using neuroAD™ System and concluded that **mild patients with baseline ADAS-Cog ≤30** responded better to the intervention than patients with baseline ADAS-Cog >30
  - ***Zhao et al. (2017)*** conducted a study of a TMS/cognitive training intervention and concluded that **mild patients** responded better to the intervention

Rutherford et al., *Short and Long-term Effects of rTMS Treatment on Alzheimer's Disease at Different Stages: A Pilot Study*, J. Experimental Neuroscience, 2015; 9 43-51. Lee et al., *Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Neurol. 2016 Jan;12(1):57-64. Zhao et al., Repetitive transcranial magnetic stimulation improves cognitive function of Alzheimer's disease patients. Oncotarget, 8(20), 33864-33871.*

US Pivotal Study – Indicated Population is Confirmed by Motor Threshold Differences

- Setting cut-off on baseline ADAS-Cog of ≤30 is supported by observations in both components of the neuroAD™: Magnetic Stimulation & Cognitive Training

- For the **Magnetic Stimulation** component, there are distinct differences in **Motor Threshold (MT)** between groups –
  - There is a significant correlation (*P* < 0.001) between baseline ADAS-Cog and Motor Threshold, with correlation coefficient -0.4
  - Subjects with ADAS-Cog≤30 had higher baseline Motor Threshold values, thus **higher TMS power settings** (*P* = 0.0028)

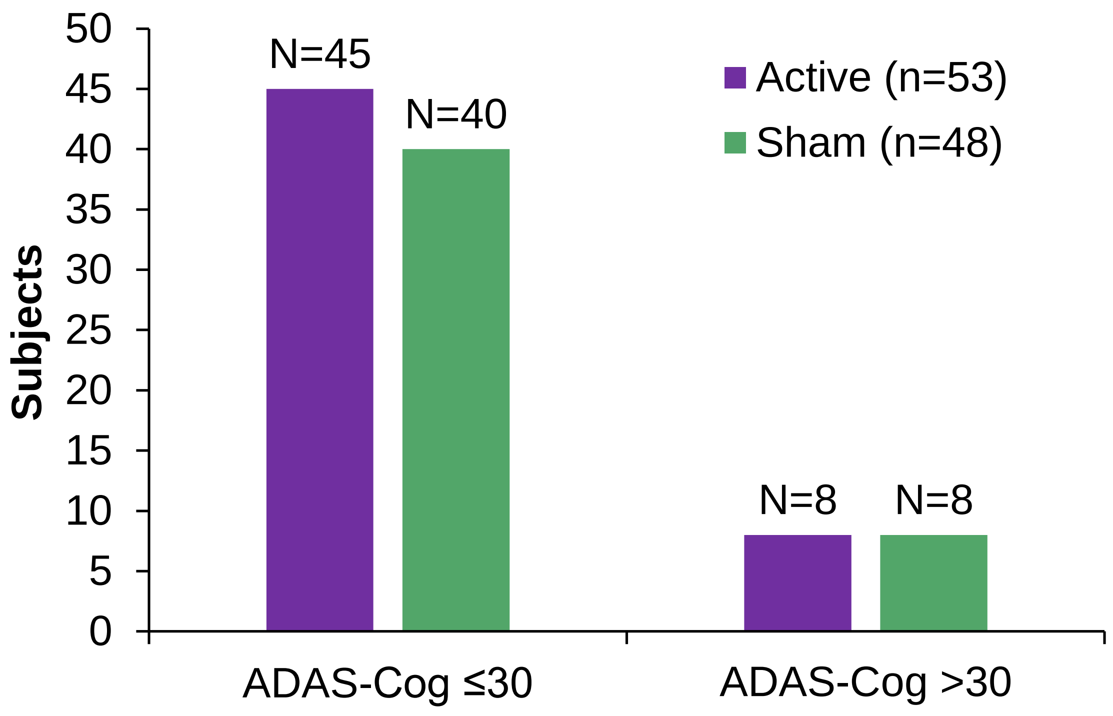


US Pivotal Study – Indicated Population is Confirmed by Cognitive Training Differences

- When considering the **Cognitive training** component:
  - Subjects with baseline ADAS-Cog ≤30 **advanced significantly more on the cognitive training scales** (*P* < 0.001)
  - This implies that these subjects benefit more from the cognitive training

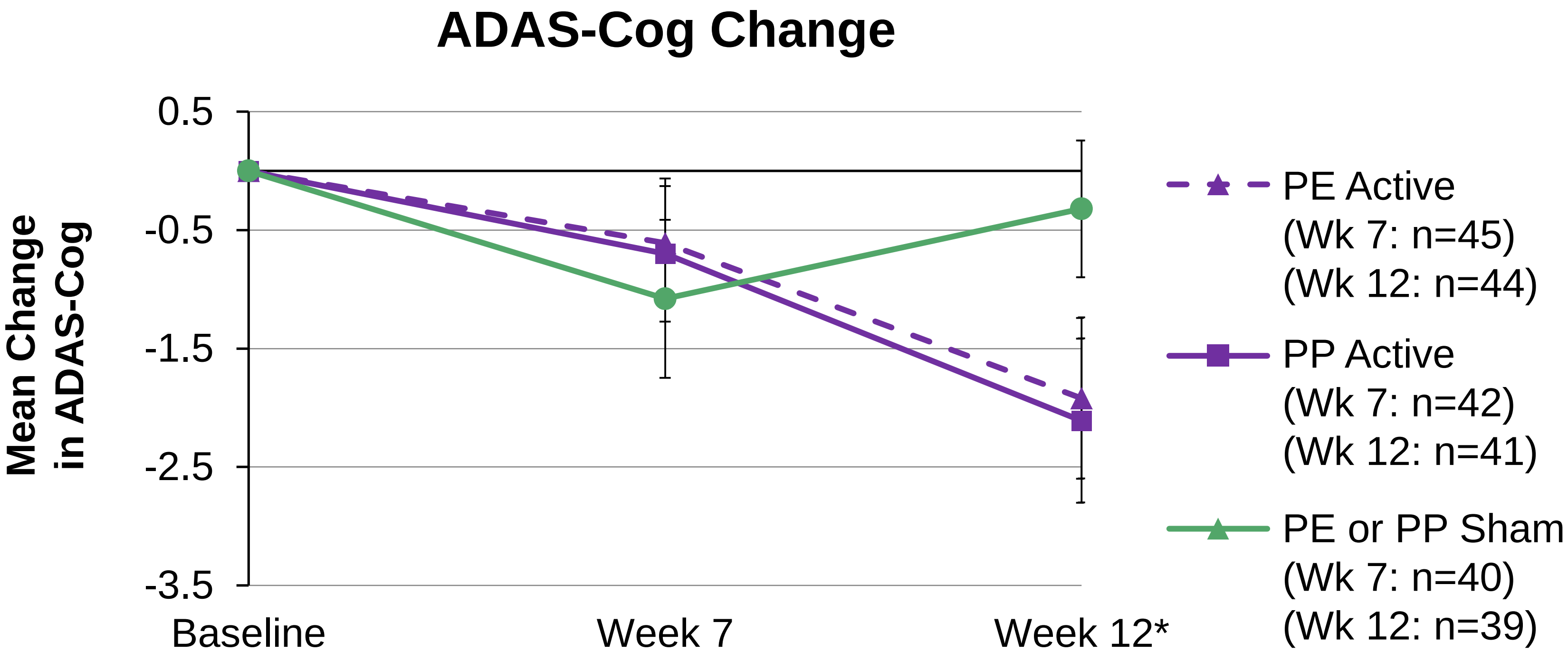
- Thus, the combination of these pre-specified and additional analyses, as well as the literature described, led to the identification of a **clinically meaningful subgroup of subjects with baseline ADAS-Cog ≤30**

ADAS-Cog ≤30 vs ADAS-Cog >30



ADAS-Cog ≤30 represents 85% of the study population

US Pivotal Study – Indicated Population, ADAS-Cog



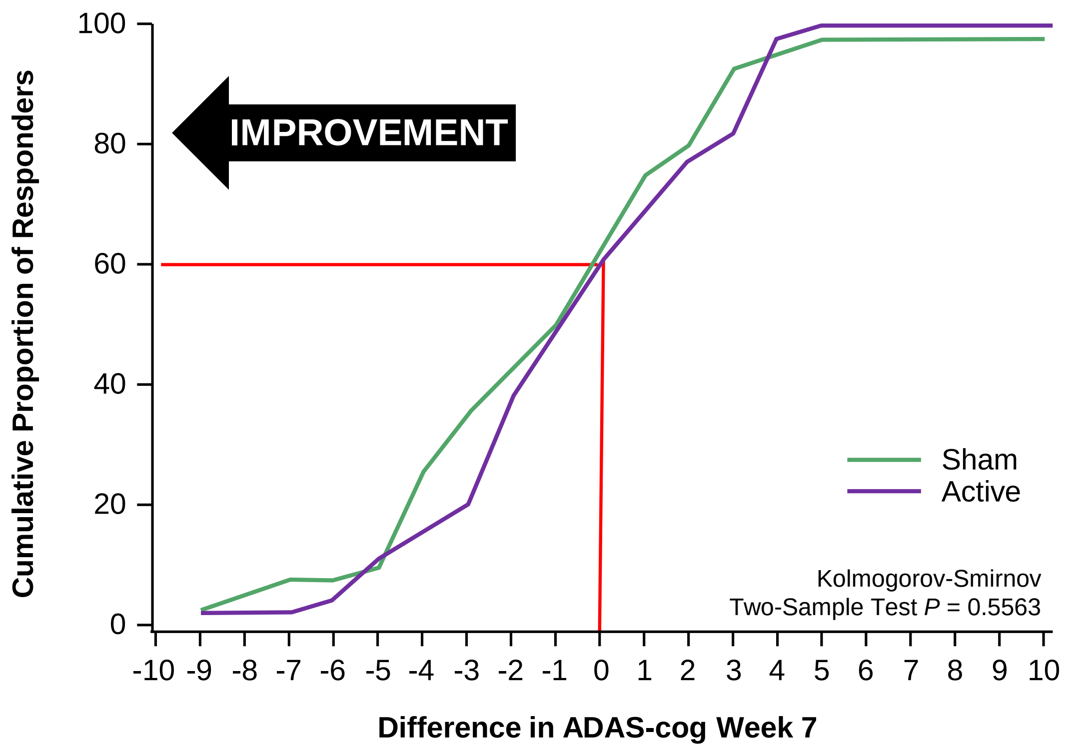
ADAS-Cog Change (Baseline ADAS-Cog ≤30) PE Population		n	Mean	*P* value
ADAS Cog Change FU-1 (Week 7)	Active	45	-0.61	0.536
	Sham	40	-1.08	
ADAS Cog Change FU-2 (Week 12)	Active	44	-1.92	0.077
	Sham	39	-0.32	

ADAS-Cog Change (Baseline ADAS-Cog ≤30) PP Population		n	Mean	*P* value
ADAS Cog Change FU-1 (Week 7)	Active	42	-0.7	0.620
	Sham	40	-1.08	
ADAS Cog Change FU-2 (Week 12)	Active	41	-2.11	0.049
	Sham	39	-0.32	

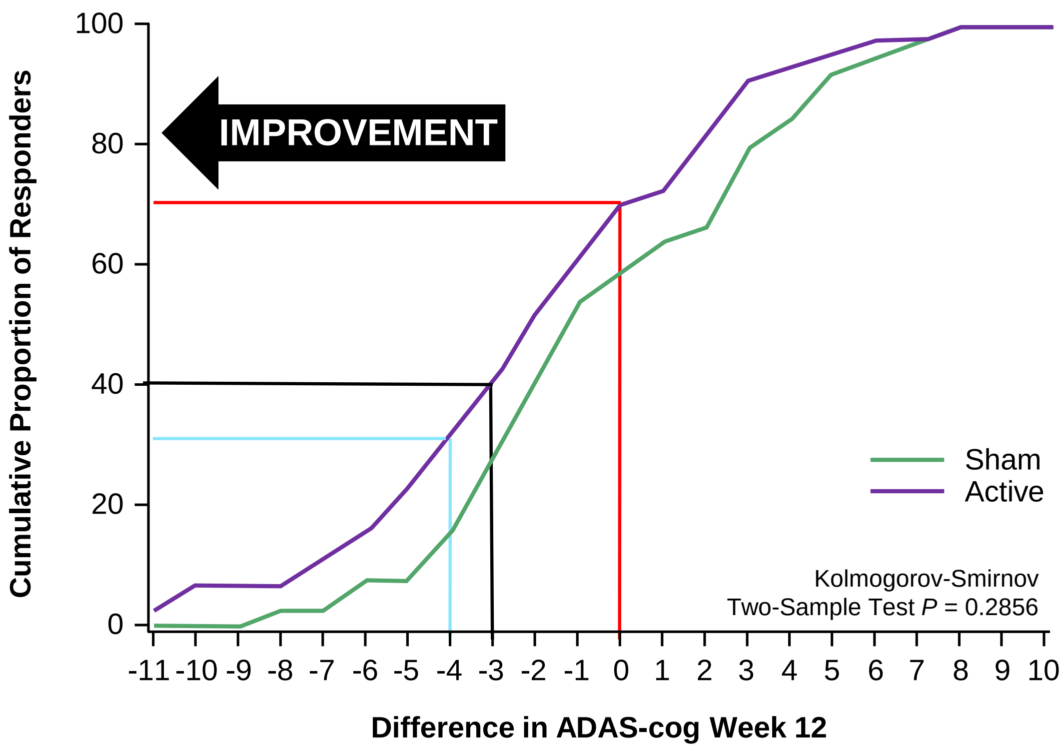
US Pivotal Study – Indicated Population, S-Curve of ADAS-Cog Change from Baseline

Indicated Population
(Baseline ADAS-Cog ≤30; PE)

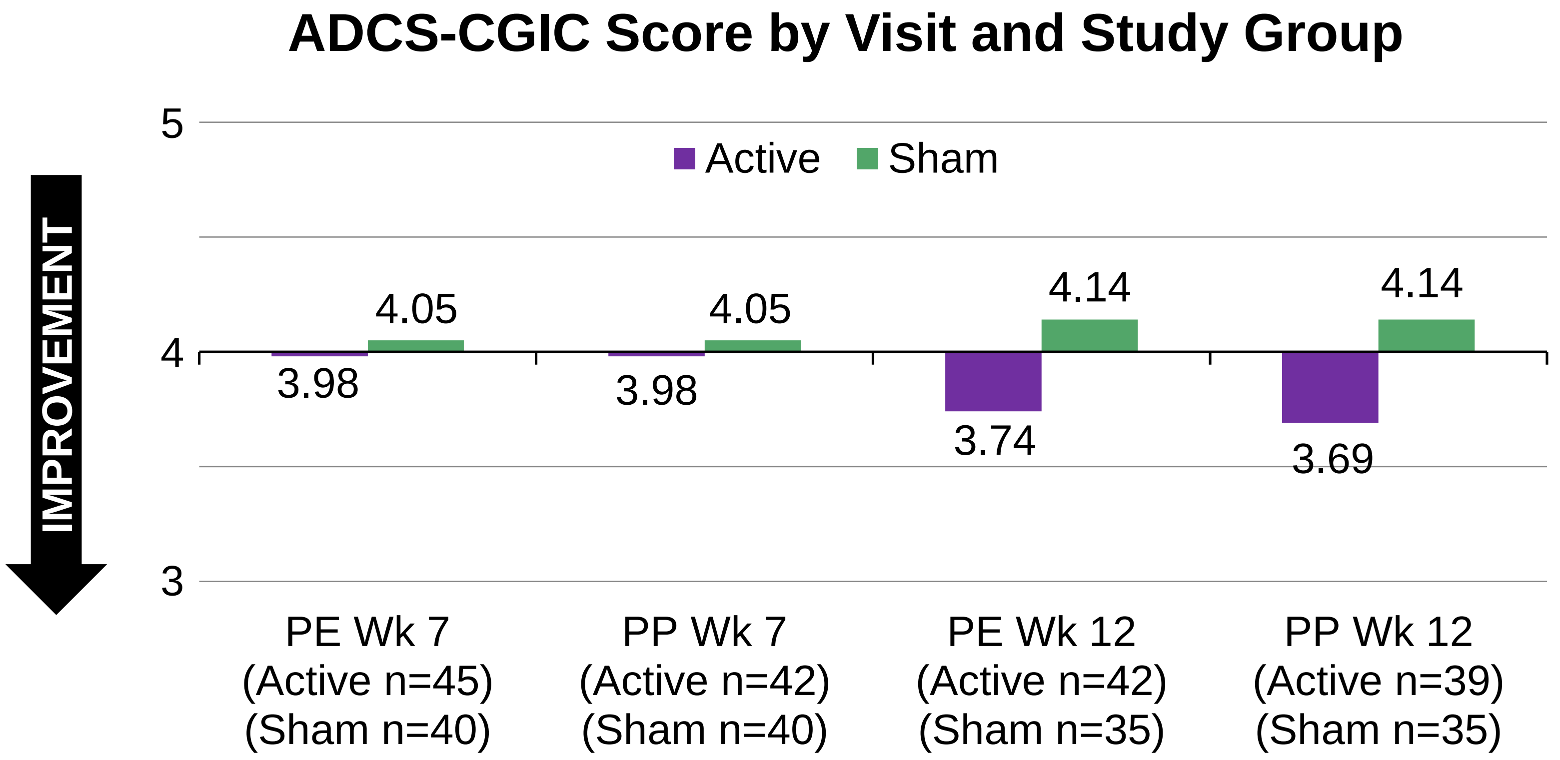
7 Weeks



12 Weeks



US Pivotal Study – Indicated Population, ADCS-CGIC

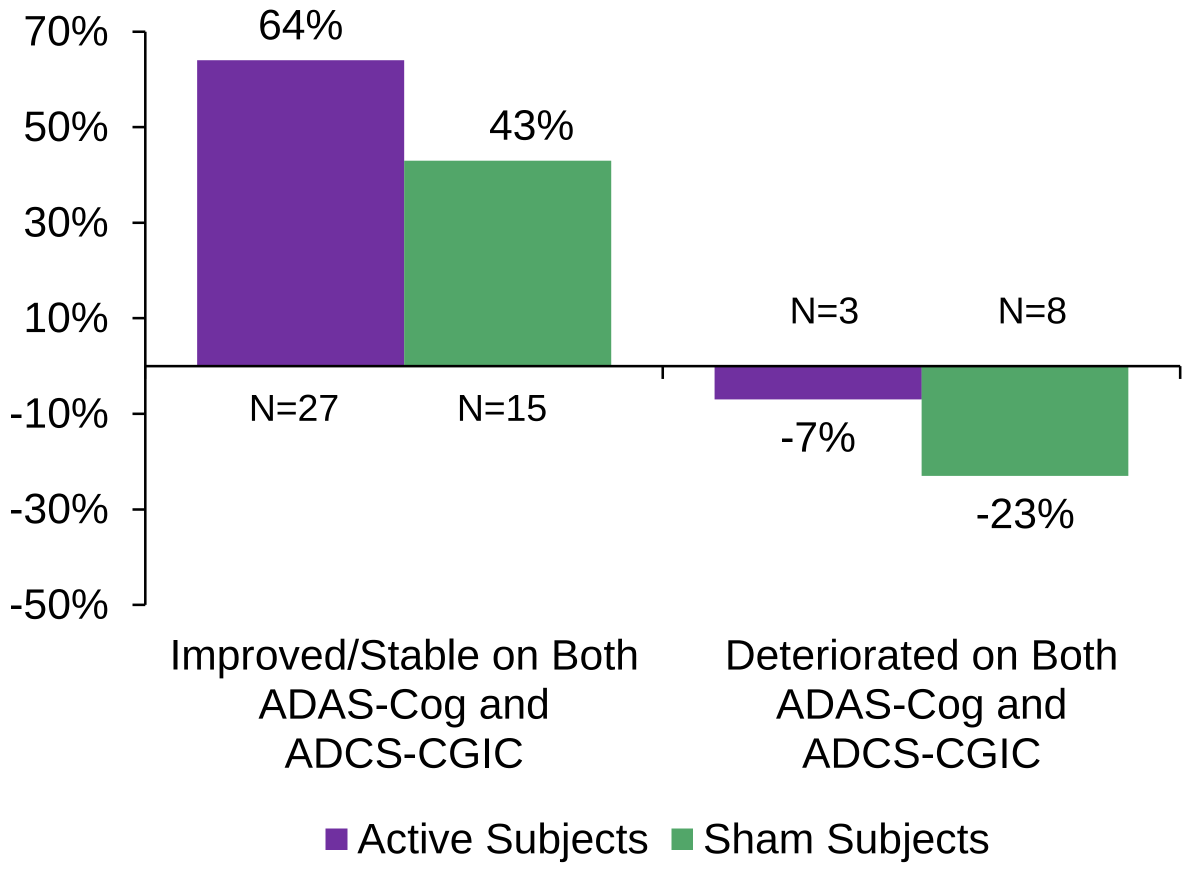


PE Population		Mean	*P*-value Wilcoxon	*P*-value Chi-Square
7 Weeks	Active Group	3.98	0.703	0.729
	Sham Group	4.05		
12 Weeks	Active Group	3.74	0.100	0.041
	Sham Group	4.14		

PP Population		Mean	*P*-value Wilcoxon	*P*-value Chi-Square
7 Weeks	Active Group	3.98	0.711	0.703
	Sham Group	4.05		
12 Weeks	Active Group	3.69	0.074	0.035
	Sham Group	4.14		

US Pivotal Study – Indicated Population
12-Week Post-hoc Dual Endpoint Outcomes

- When assessing a combined endpoint of ADCS-CGIC and ADAS-Cog in the Indicated population at 12 weeks, the Active group performs statistically better than the Sham (Fisher's Exact Test, *P* = 0.046)



US Pivotal Study – Key Findings

Treatment is **SAFE** with high adherence rate

Indicated population selection is based on established **RELATIONSHIP** between baseline ADAS-Cog and outcome

BENEFIT is additive— **80%** of all subjects were on stable AD medications throughout study

<u>12-Weeks Efficacy in Indicated Population</u>

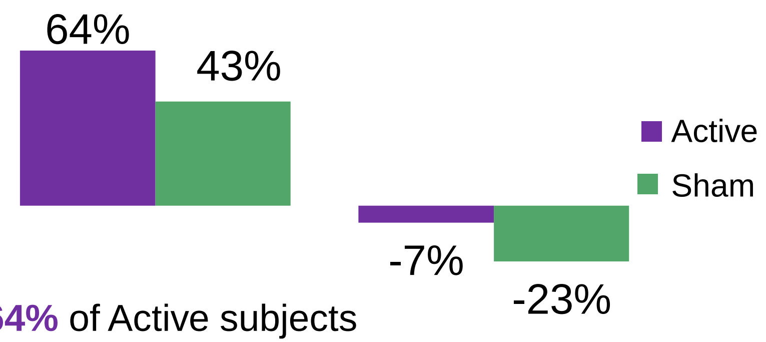
ADAS-Cog Endpoint

- Clinically meaningful benefit between Active and Sham, with **-1.61 points** difference
- Over **40%** of Active subjects show at least 3-point improvement and more than **70%** show some improvement at 12 weeks compared to baseline

ADCS-CGIC Endpoint

- Clinically meaningful benefit > Active outperforms Sham by **-0.40 points**

Dual Endpoint ADAS-Cog & ADCS-CGIC in Indicated Population (12-weeks)



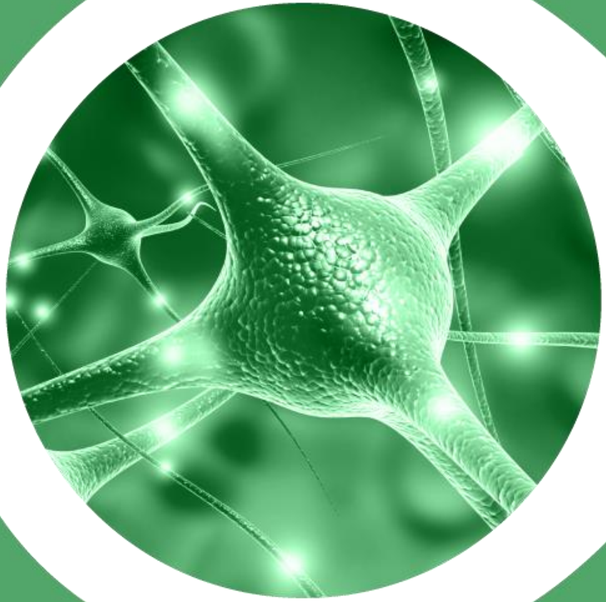
64% of Active subjects improved/no change on both measures compared to **43%** of Sham

Only **7%** of Active subjects deteriorated on both measures compared to **23%** of Sham

Conclusion

Safety and efficacy is established for Indicated Population

Clinical Evidence – Supportive Data



A. Pascual-Leone, PhD, MD

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US Pivotal, Korean Pilot & Pivotal Studies Population and Timelines

2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018

US Pivotal protocol
Mild to moderate AD subjects

US Pivotal protocol
Start date – Sep 2013

US Pivotal
Finish date –
data unlock
Mar 2016

Korean Pilot protocol
Mild to moderate AD subjects (18 Active + 8 Sham)

Korean Pilot to follow
US Pivotal protocol;
Start date – Feb 2013

Korean Pilot
Finish date – Feb 2014

Korean Pivotal protocol
Mild AD subjects with baseline ADAS-Cog≤30 (11 Active + 11 Sham)

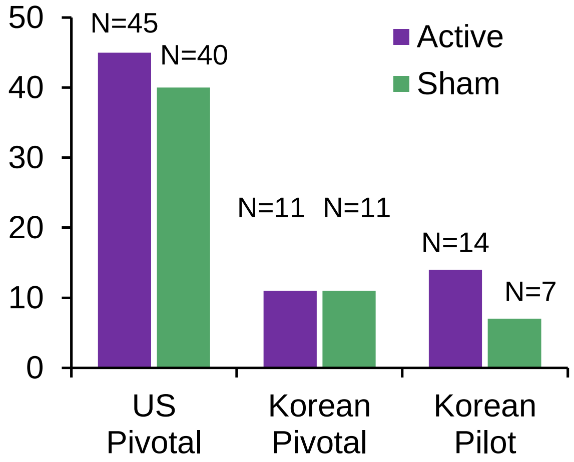
Korean researchers conclude best population
is mild AD with baseline ADAS-Cog ≤30.
Set protocol for Korean Pivotal study
Nov 2014

Korean Pivotal
Start date – Mid 2015

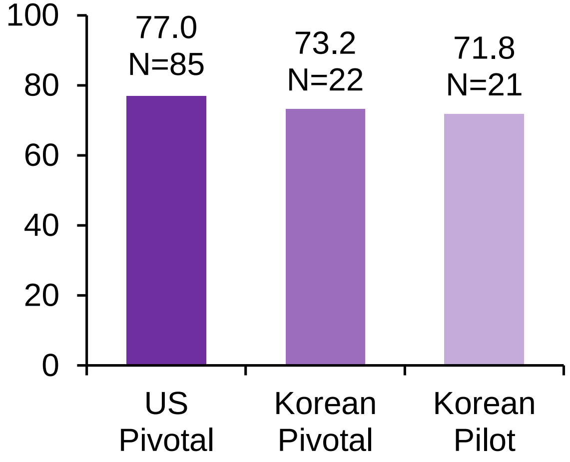
Korean Pivotal
Data transfer
to Neuronix
Jul 2017

Comparison of Key Baseline Characteristics in the US Study and Korean Studies (Indicated Population)

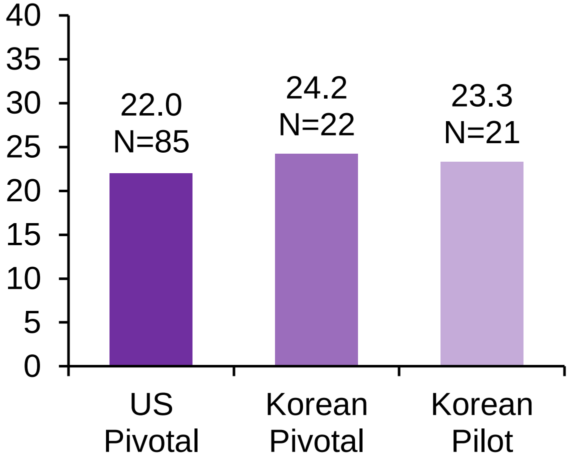
Subjects Disposition for Indicated Population
Baseline ADAS-Cog≤30



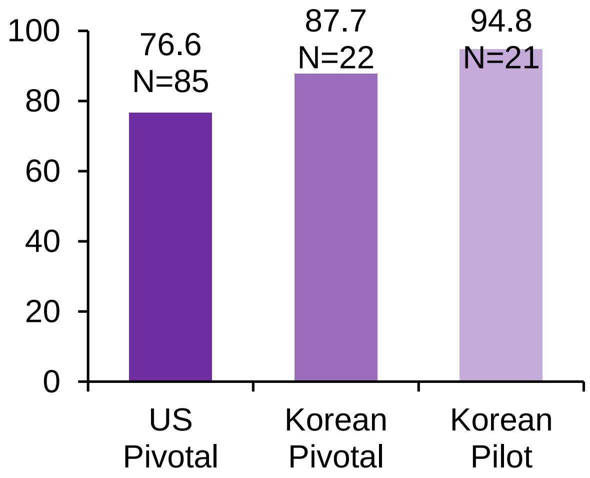
Age

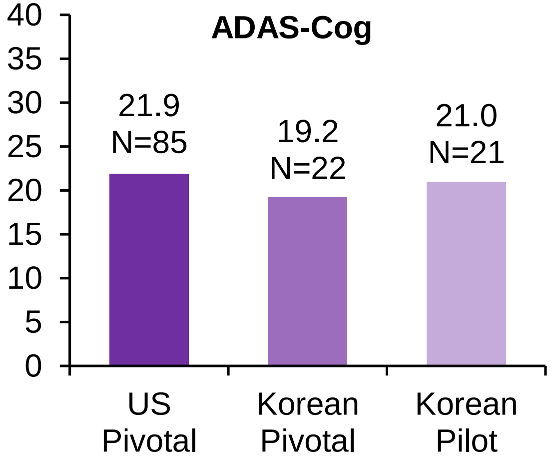


MMSE



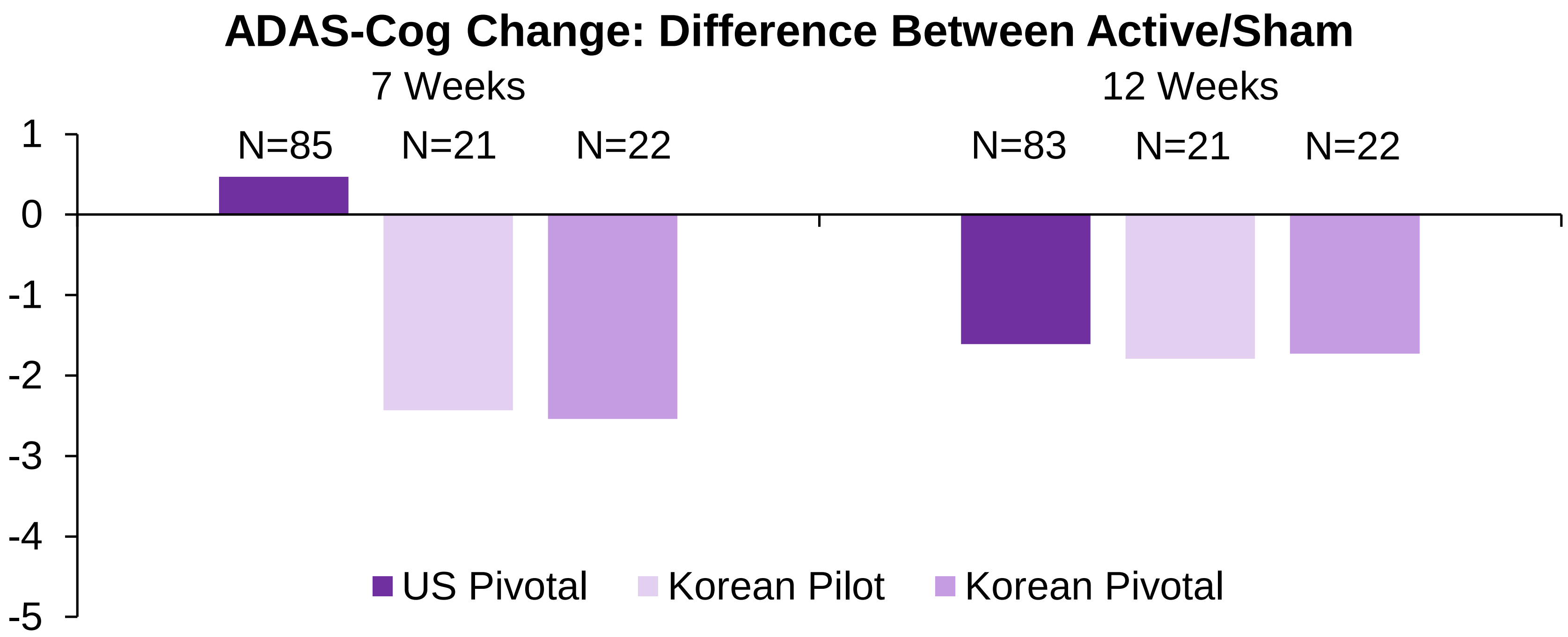
Motor Threshold





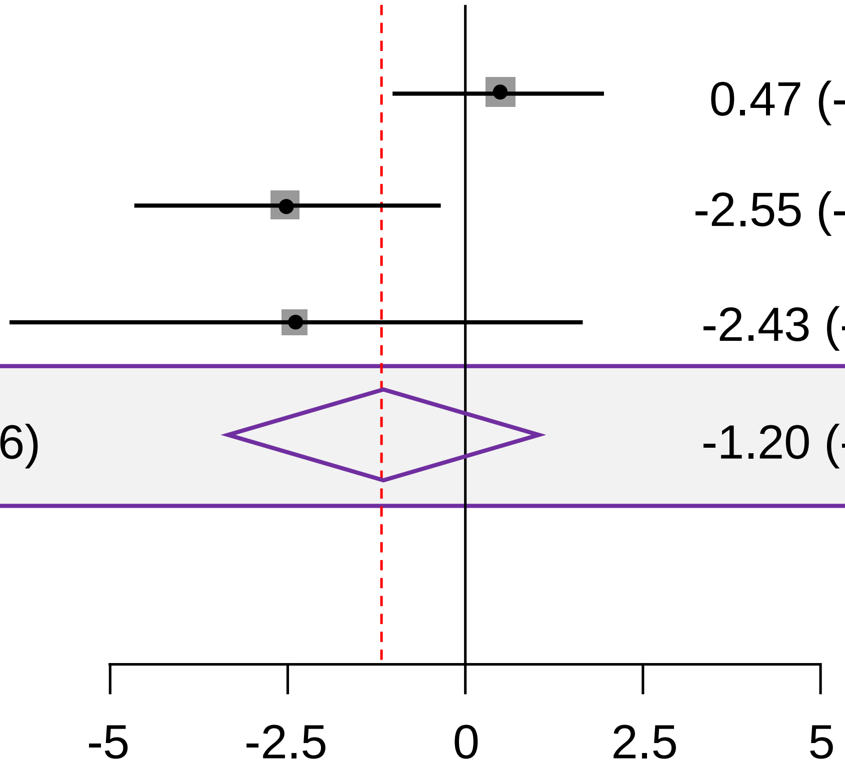
ADAS-Cog Results in Korean Pilot and Pivotal Studies

- Both Korean studies confirm US pivotal study safety profile
- Both Korean studies confirm US pivotal study efficacy at 12 weeks
- Korean studies show efficacy as early as 7 weeks

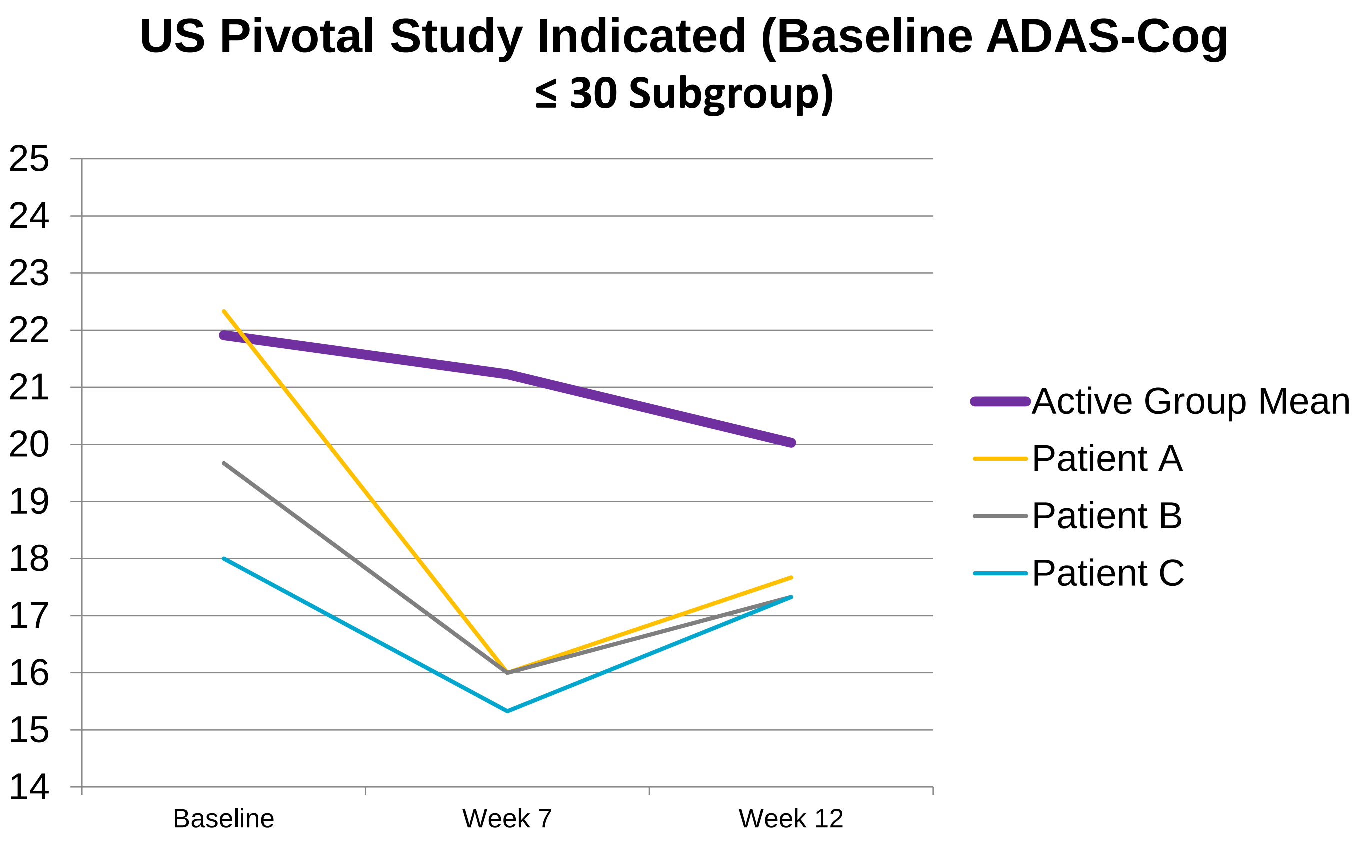


Meta-Analysis at 7 Weeks (WMD)
Indicated Population (ADAS-Cog ≤30)

Study	Country	Sample Size	WMD (95% CI)	% Weight	*P*-Value
US Pivotal	USA	85	0.47 (-1.02, 1.96)	43.68	
Korean Pivotal	Korea	22	-2.55 (-4.74, -0.35)	36.16	
Korean Pilot	Korea	21	-2.43 (-6.51, 1.65)	20.17	
Overall (I squared = 65.3%, *P* = 0.056)			-1.20 (-3.53, 1.12)	100.00	***P* = 0.31**



Effect of neuroAD over Time



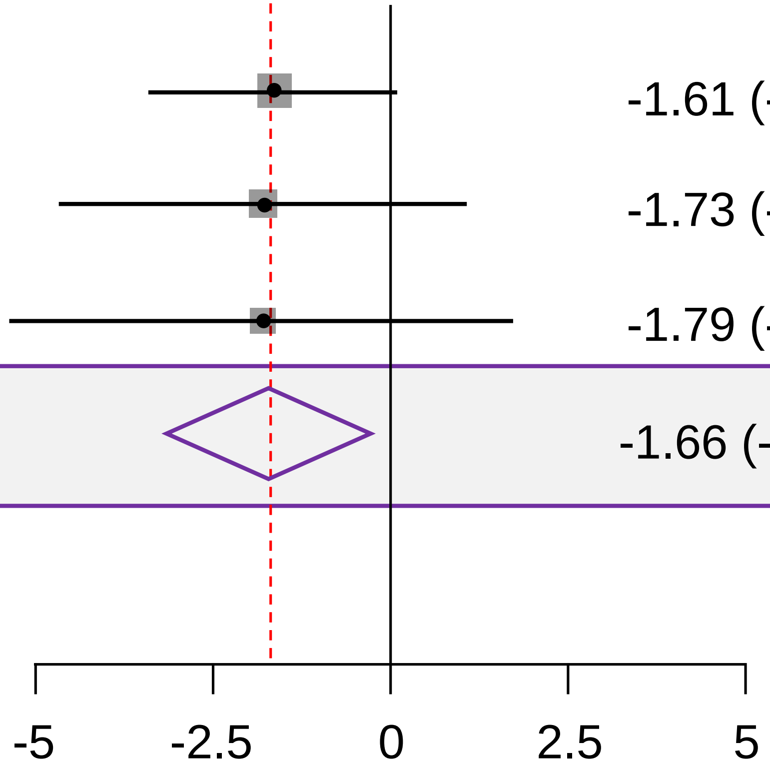
- Time to achieve maximum benefit varies across patients

neuroAD^{TM} Effects Over Time

- FDA raises questions about why the effect of the neuroAD may increase after the end of treatment
- Time to achieve maximum benefit may vary across patients
- Although mechanism is not fully defined, this may reflect time required for consolidation of effect
- Consistent with other TMS effects lasting long beyond the end of treatment for various indications:
  - Naeser et al. (2005): increasing benefit of TMS on nonfluent aphasia over year following 2 week TMS course
  - Obermann et al. (2015): increasing cognitive benefits in autism after 2 week course of TMS
  - Pallanti et al. (2016): 12 month durability of benefits after 3 week TMS course in OCD
  - Dunner et al. (2016): 6 week TMS treatment of MDD demonstrated stable to increasing effect over subsequent 12 months

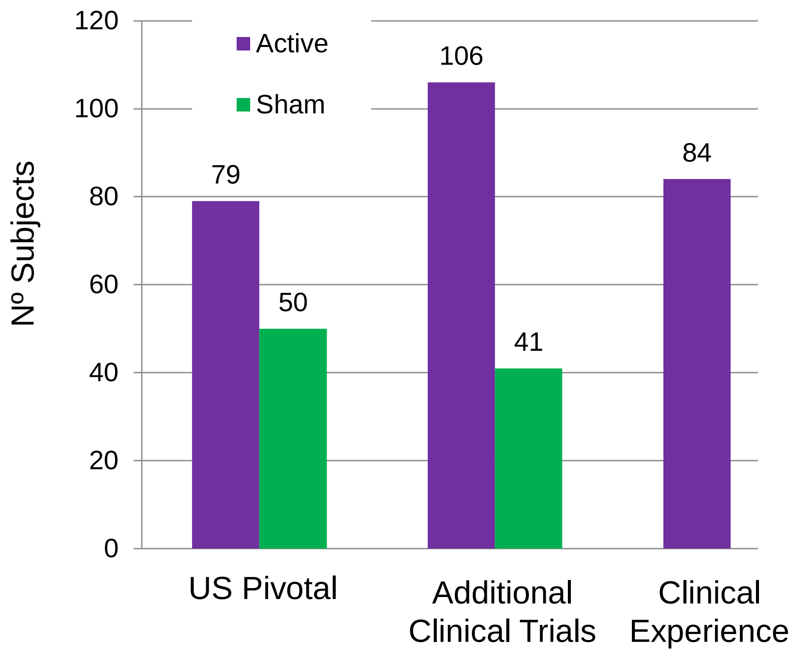
Meta-Analysis at 12 Weeks (WMD)
Indicated Population (ADAS-Cog ≤30)

Study	Country	Sample Size	WMD (95% CI)	% Weight	*P*-Value
US Pivotal	USA	85	-1.61 (-3.36, 0.14)	61.29	
Korean Pivotal	Korea	22	-1.73 (-4.55, 1.09)	23.66	
Korean Pilot	Korea	21	-1.79 (-5.32, 1.75)	15.05	
Overall (I squared = 0.0%, *P* = 0.995)			-1.66 (-3.03, -0.29)	100.00	***P* = 0.017**



All Data Sources

374 Subjects Overall



US Pivotal Study (n=130)
Active – 59 (+20 Run in)
Sham – 50

Korean Pilot Study (n=26)
Active – 18
Sham – 8

Korean Pivotal Study (n=22)
Active – 11
Sham – 11

Assaf-1 Study (n=8)
Active – 8

Assaf-2 Study (n=15)
Active – 7
Sham – 8

Harvard Study (n=21)
Active – 10
Sham – 6
Cog Only – 5

Assaf-3 Study (n=16)
Active – 10
Sham – 6

NNX Clinic Study (n=30)
Active – 30

Italian Study (n=13)
Active – 6
Sham – 2
Cog only – 5

Thailand Study (n=9)
Active – 6
Cog only – 3

Clinical Experience

NNX Clinic Israel (n=54)
Active – 54

Nantes (n=10)
Active – 10

High Wycombe (n=6)
Active – 6

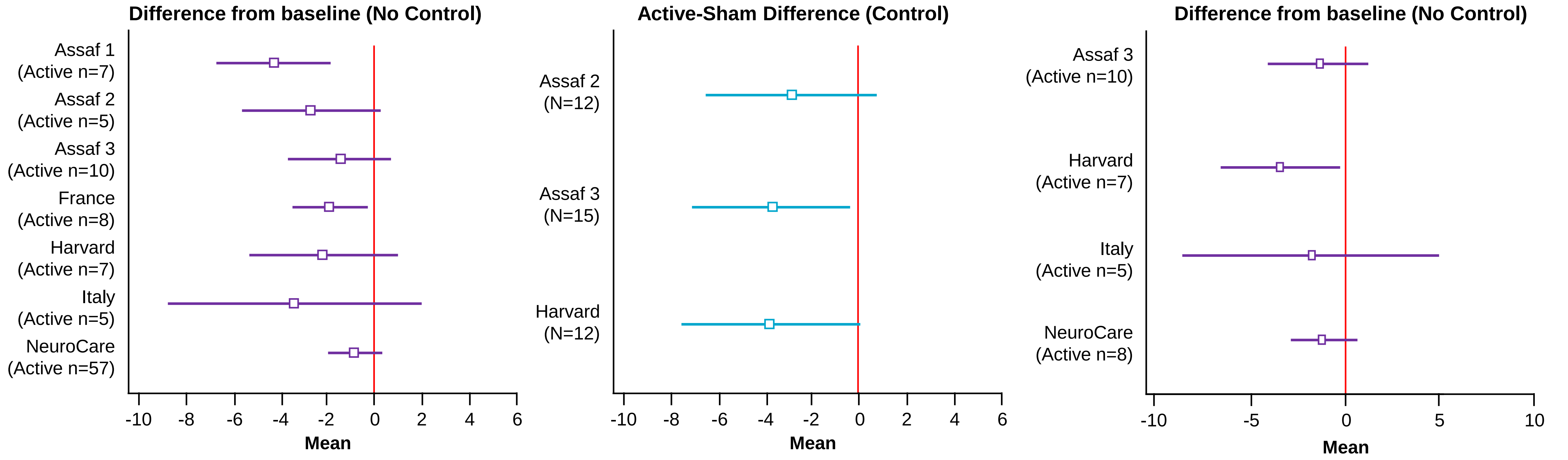
NNX Clinic UK (n=4)
Active – 4

Orsay (n=10)
Active – 10

Results of All Studies and Commercial Use

Mean Change ADAS-Cog FU-1 (6–10 Weeks) Indicated Population (Baseline ADAS-Cog ≤30)

Mean Change ADAS-Cog FU-2 (10–14 Weeks) Indicated Population (Baseline ADAS-Cog ≤30)



FDA Feedback and Questions

- **Is the ADAS-Cog ≤ 30 a clinically valid subset, and does the supplemental data adequately support this subgroup?**
  - Literature
  - Mechanistic argument – TMS, Cognitive training
  - Experimental validation – Korean Studies

FDA Feedback and Questions

- Is the ADAS-Cog ≤ 30 a clinically valid subset, and does the supplemental data adequately support this subgroup?

- **Can the ADAS-Cog be used to select patients?**
  - Experimental evidence – Korean Pivotal
  - Clinical evidence – Australian clinics
  - Company training

FDA Feedback and Questions

- Is the ADAS-Cog ≤ 30 a clinically valid subset, and does the supplemental data adequately support this subgroup?

- Can the ADAS-Cog be used to select patients?

- **How should the 7-week versus 12-week results be viewed?**
  - Objective assessment of results across studies
    - Overlapping confidence intervals at 7 weeks
    - Consistent effects at 12 weeks
  - Mechanistic considerations
  - Individual differences in time course of effects

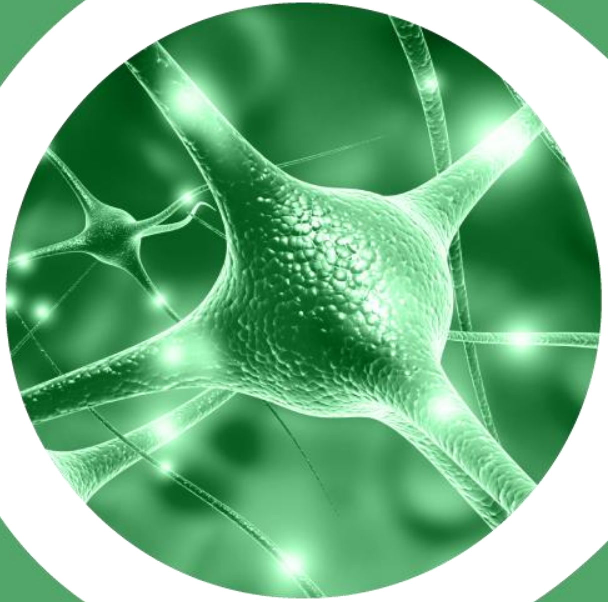
FDA Feedback and Questions

- Is the ADAS-Cog ≤ 30 a clinically valid subset, and does the supplemental data adequately support this subgroup?
- Can the ADAS-Cog be used to select patients?
- How should the 7-week versus 12-week results be viewed?
- **In totality, does benefit outweigh risk?**
  - Nearly 400 subjects across studies
  - neuroAD™ is safe
  - Consistency of beneficial effect across studies
  - Clear benefit for some patients – nearly 50% ≥ -3 pts on ADAS-Cog

FDA Feedback and Questions

- Is the ADAS-Cog ≤ 30 a clinically valid subset, and does the supplemental data adequately support this subgroup?
- Can the ADAS-Cog be used to select patients?
- How should the 7-week versus 12-week results be viewed?
- In totality, does benefit outweigh risk?
- **Is the benefit clinically meaningful?**
- **What is an appropriate MCID for the selected scales, ADAS-Cog and ADCS-CGIC?**

Clinical Significance of Outcomes



L. Schneider, MD, MS

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Considerations

- My background

- FDA panel question #2:

  – *"When the neuroAD is used as an <u>adjunctive therapy</u>, the Panel will be asked to discuss and make recommendations on <u>what minimum amount of improvement in ADAS-Cog alone is clinically meaningful</u>, as well as the minimum amount of <u>clinically meaningful improvement in the CGIC</u>. [page 10]"*

- FDA perspective on minimum improvement for mild to moderate Alzheimer dementia has been consistent since 1989:
  – A cognitive battery ["composite"] supported by a global [clinical/functional] or functional outcome
  – *De facto* has been the [ADAS-cog + CGIC] or [ADAS-cog + ADCS-ADL]

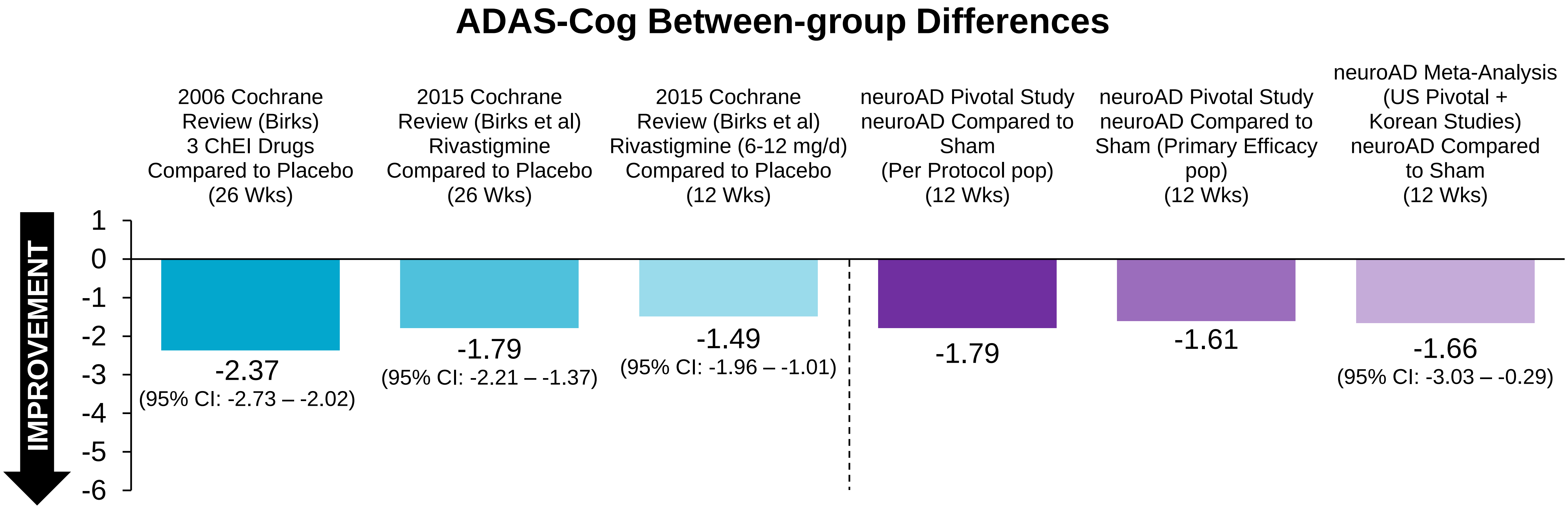
Clinical Significance of Outcomes

- ADAS-Cog as the cognitive outcome for AD regulatory drug trials
  – Drug-placebo differences for marketed ChEIs: -1.49 to -2.37
  – No stand-alone minimal, *mean,* clinically meaningful (or important) drug-placebo *difference* has been established
  – No *absolute* minimal, clinically meaningful *change* established by data analysis, opinion, or consensus
  – Clinical importance generally relies on supportive clinical/functional/behavioral outcomes

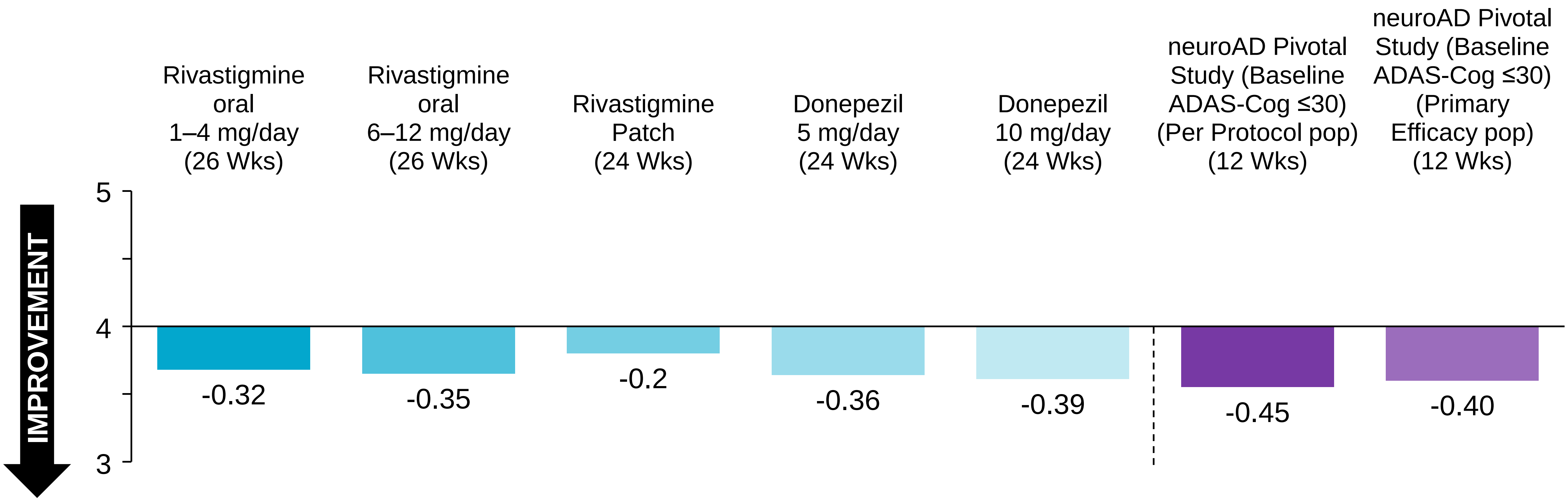
- Global ratings, CIBIC+ (e.g., ADCS-CGIC) support clinical meaning
  – "If a experienced and unbiased clinician can detect a global change in an AD patient solely on an interview…then that change is assumed to be clinically relevant" (FDA 1991, Paul Leber, DNPP, CDER)

ADAS-Cog Outcomes – Cholinesterase Inhibitors and neuroAD^{TM} Studies

- Cholinesterase inhibitors are the only marketed drugs for mild to moderate AD
- neuroAD^{TM} outcomes similar to donepezil/rivastigmine/galantamine
- neuroAD^{TM} trials allow add-on to ChEIs



ADCS-CGIC Outcomes – Cholinesterase Inhibitors and neuroAD™ Studies

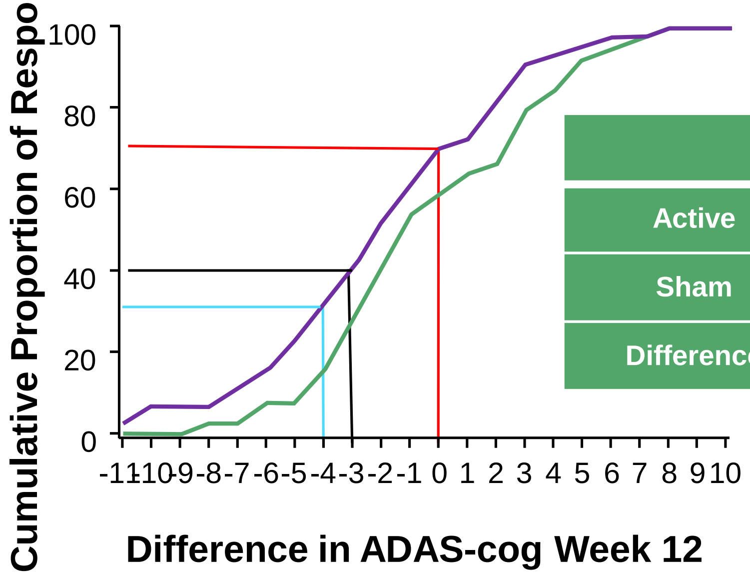


- neuroAD™ treatment differences similar to donepezil/rivastigmine/galantamine
- neuroAD™ studies allow add-on to ChEIs
- Any change on CGIC is meaningful because it is recognized by a clinician (Schneider & Olin, 1996; Leber, 1991)

Minimum Clinically Important Difference ADAS-Cog

- Within regulatory studies, there is no minimum
- Any designated minimum difference is likely to be attained in a statistically significant trial, e.g., 2, 3, or 4

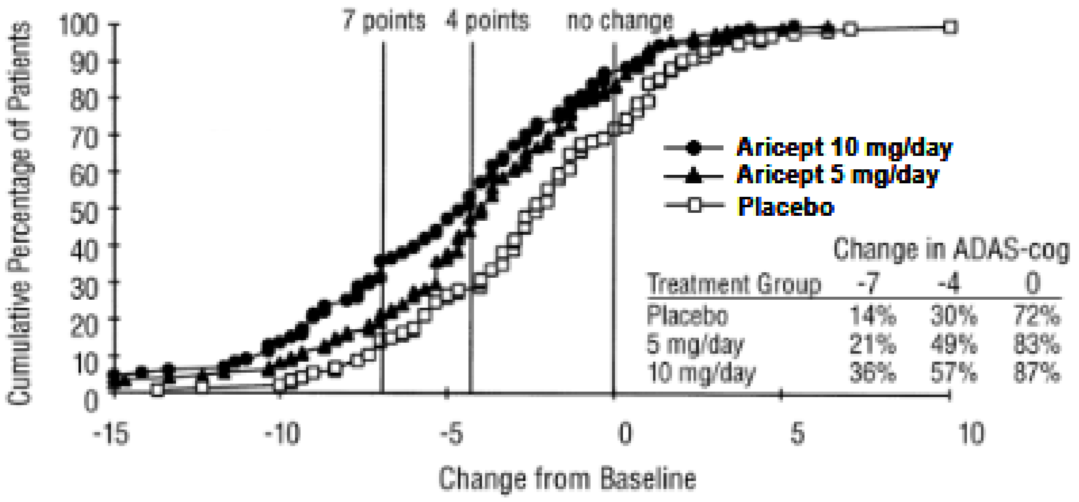
Cumulative Percentage of Patients with Specified Change from Baseline



	≤-4	≤0
Active	32%	70%
Sham	15%	59%
Difference	17%	11%

neuroAD™, ADAS ≤30 pop, 12 weeks

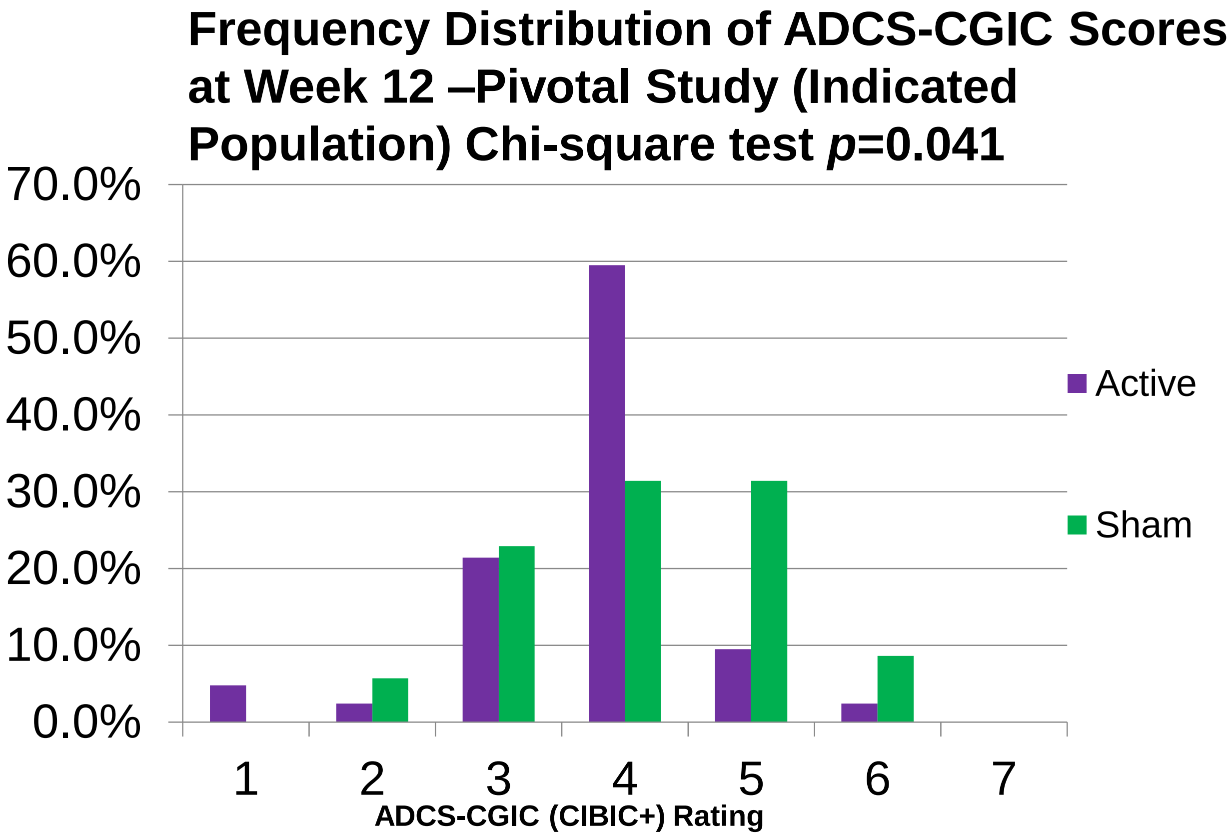
Figure 5. Cumulative Percentage of Patients with Specified Changes from B
Treatment Group Who Completed the Study Were: Placebo 93%, 5 mg/day 90



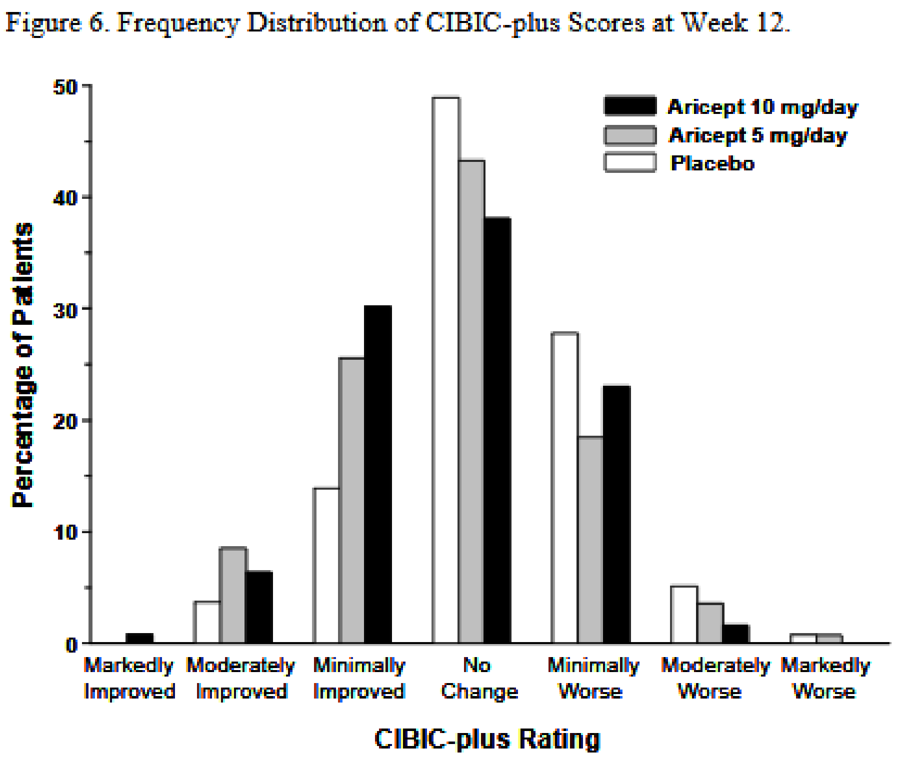
Aricept (donepezil) prescribing information, 12-wk trial

Minimum Clinically Important Difference ADCS-CGIC

- Any statistically significant difference on a CGIC (CIBIC+) is clinically important: means that ≥ 1 more patient improved with treatment than without



neuroAD™, ADAS ≤30 pop, 12 weeks

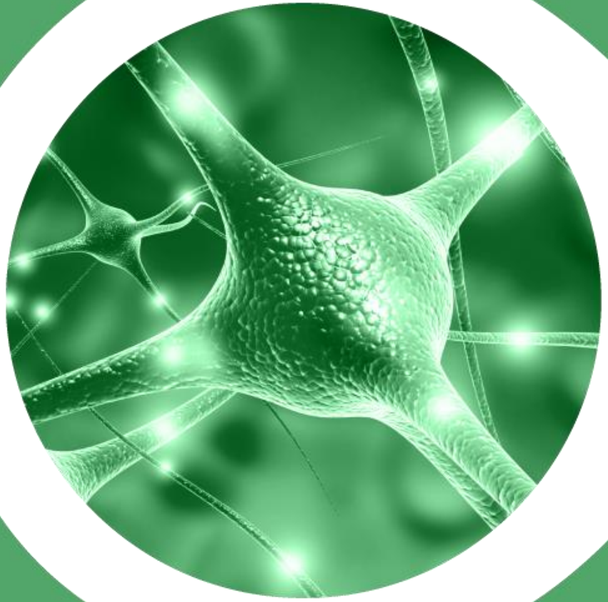


Aricept (donepezil) prescribing information, 12-wk trial

Clinical Importance of ADAS-Cog and ADCS-CGIC

- ADAS-Cog [composite] demonstrates overall cognitive benefits
- ADCS-CGIC indicates clinical meaningfulness
  - (By definition) if an interviewer determines change then it's clinically meaningful
  - When it converges with an ADAS-Cog effect within the context of a given trial it supports a meaningful cognitive effect
- At 12-weeks in the neuroAD^{TM} subgroup, the ADAS-Cog and ADCS-CGIC outcomes together can be taken to support clinical meaningfulness

Physician Perspectives & Conclusions



M. Sabbagh, MD
A. Pascual-Leone, PhD, MD

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Summary – Marwan N. Sabbagh, MD

- Unmet clinical need for additional effective treatment options
- neuroAD™ shows favorable risk/benefit profile
  - Safety profile demonstrated – clear low risk
  - Effectiveness – indicated population shows clear clinically meaningful benefit (ADAS-Cog, ADCS-CGIC, and dual endpoint)
- Indicated population is confirmed over multiple independent studies
- Benefit was demonstrated over and above SOC medication, not compared to placebo alone
- 12 weeks is the more clinically relevant time point;
- **The totality of evidence strongly supports that there is meaningful clinical benefit that outweighs the minimal risk presented**

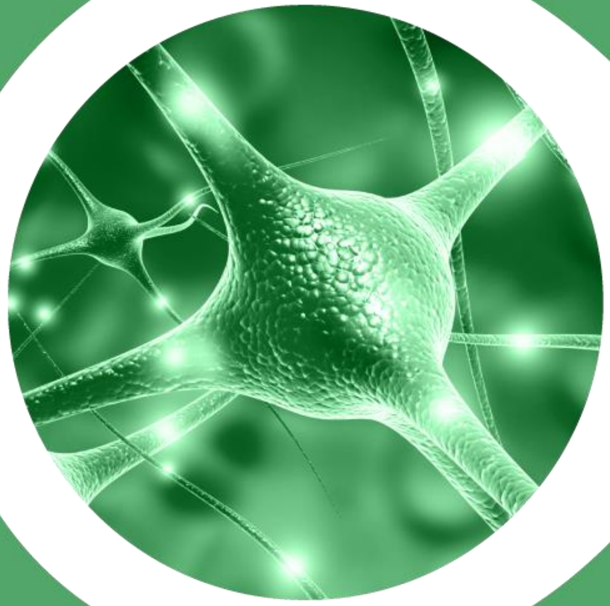
Summary – Alvaro Pascual Leone, PhD, MD

- neuroAD™ addresses the urgent need for multi-modal therapy options
- neuroAD™ fulfills required criteria for new adjunctive therapy
  - Different target √
  - New mechanisms of action √
  - Measurable effect √
  - Favorable safety profile √
- **neuroAD™ delivers dramatic benefit for ~1/3 of patients, and some benefit for an additional 1/3 of the population, on top of standard of care.**

Final Notes – Eyal Baror

- Neuronix has devoted the last 10 years to development of the neuroAD™ system, and is committed to continued ongoing research in the post-market setting
- Neuronix is further committed to providing appropriate training and customer support, as it has done outside the US where the device is already in commercial use
- We thank the FDA and panel members for giving us the opportunity to present our data
- We are grateful for the commitment of our clinicians, patients and caregivers who have participated in our programs to date

Thank You



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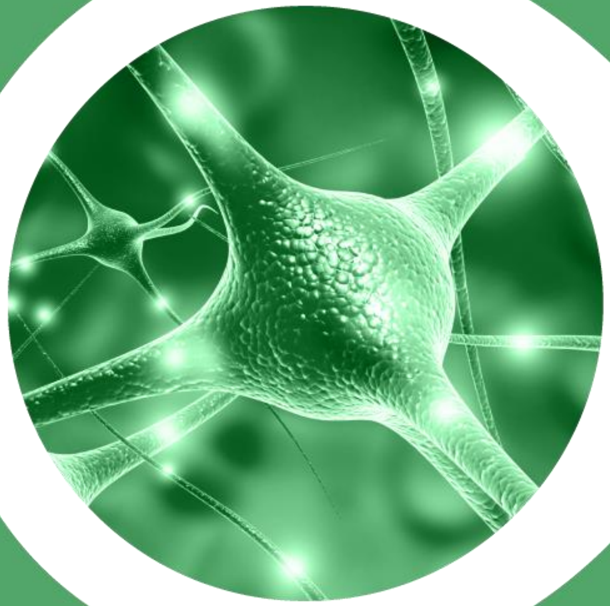
Question and Answer Slides Shown



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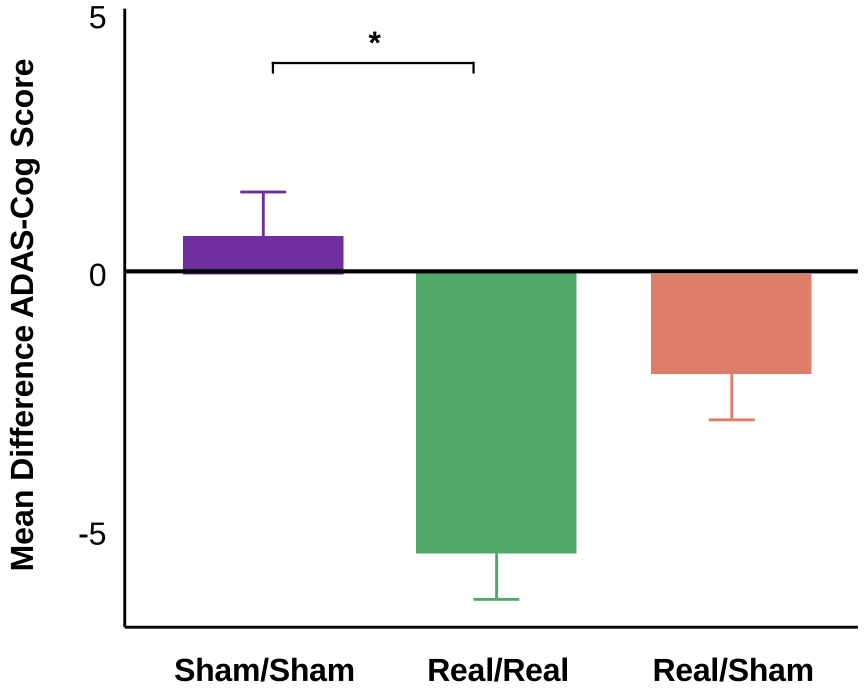
Beth Israel Deaconess Medical Center (Harvard) – ADAS-Cog

- Treatment Protocol:
  - 6 weeks of 5 sessions per week
- 21 patients in the analysis:
  - 10 patients in Treatment arm
  - 6 patients in Placebo arm (Sham CgT / Sham TMS)
  - 5 patients in Cognitive arm (Real CgT / Sham TMS)
- Treatment Arm ADAS-Cog Results:
  - -6.1 points difference to Sham
  - -3.4 points difference to Cognitive alone



1. Gonsalvez I. et al., "Therapeutic Noninvasive Brain Stimulation in Alzheimer's Disease", **Current Alzheimer Research**, 2017, 13, 1-15
2. Brem A.K. et al., "Combined brain stimulation and cognitive training in Alzheimer's disease", **Submitted for publication**

Observed Mean Difference in ADAS-Cog by Baseline ADAS-Cog Score at 12 Weeks (PE Population)

Observed Mean Difference in ADAS-Cog by Baseline ADAS-Cog Score, 12 week timepoint

Baseline ADAS-Cog	≤18	≤20	≤25	≤30	≤35	≤40	≤45
Mean difference (Active-Sham) (95% CI)	-3.78 (-7.26, -0.31)	-1.64 (-4.96, 1.68)	-1.46 (-3.40, 0.47)	-1.61 (-3.39, 0.17)	-0.95 (-2.68, 0.78)	-0.35 (-2.13, 1.43)	-0.42 (-2.19, 1.35)
n (active/sham)	7/2	14/13	37/34	44/39	50/42	51/46	51/47

US Pivotal Study – Summary of Adverse Events (1/2)

Adverse Event	Sham (n=50) # Events	Active (n=79) # Events
Abdominal distension	0	1
Abdominal pain	0	2
Abdominal pain upper	2	0
Agitation	0	1
Anxiety	1	0
Asthenia	0	1
Asthenopia	0	1
Atrial flutter	0	1
Back pain	3	4
Blood pressure fluctuation	1	0
Chronic obstructive pulmonary disease	0	1
Confusional state	1	0
Death	0	1

Adverse Event	Sham (n=50) # Events	Active (n=79) # Events
Diarrhea	0	1
Disturbance in attention	1	0
Dizziness	3	1
Dry eye	0	1
Eyelid ptosis	0	1
Fall	1	2
Fatigue	0	2
Gastrointestinal disorder	0	1
Headache	6	8
Hiatus hernia	1	0
Hordeolum	1	0
Humerus fracture	0	1
Laceration	0	4

US Pivotal Study – Summary of Adverse Events (2/2)

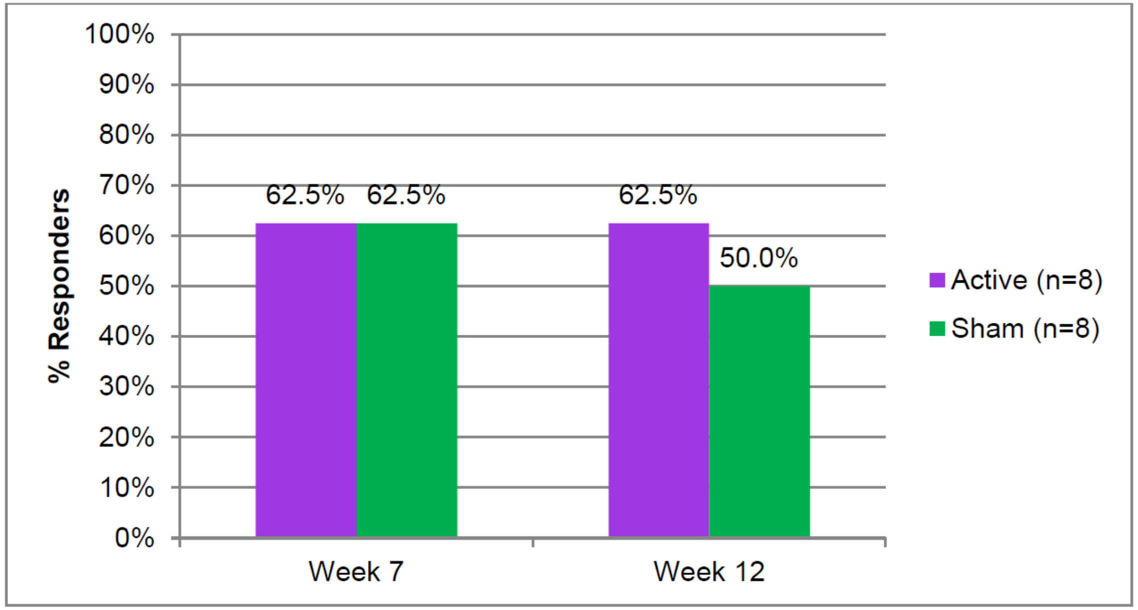
Adverse Event	Sham (n=50) # Events	Active (n=79) # Events
Ligament sprain	0	1
Muscle twitching	0	1
Musculoskeletal pain	0	1
Musculoskeletal stiffness	0	2
Nasopharyngitis	0	2
Nausea	1	2
Neck pain	0	5
Paraesthesia	1	0
Rash	0	1
Rhinitis	1	0
Sciatica	1	0
Skin discomfort	0	3
Skin sensitisation	0	1

Adverse Event	Sham (n=50) # Events	Active (n=79) # Events
Squamous cell carcinoma	0	1
Subcutaneous abscess	0	1
Tooth abscess	1	1
Upper respiratory tract infection	1	2
Urinary retention	2	0
Urinary tract infection	1	1
Vision blurred	0	1
Vitamin D deficiency	0	1
Vomiting	0	1
Wrist fracture	1	0
Total AEs by Group	**31**	**63**

Subjects with Baseline ADAS-Cog >30 Benefit on ADCS-CGIC Scale

- When measured on ADCS-CGIC, Active subjects outperform Sham subjects
  - Results are opposite in trend to ADAS-Cog outcomes

Figure 4: US Pivotal Study Responder Rate on CGI-C, Baseline ADAS-Cog > 30 (CGI-C Scores 1-4 = responder)

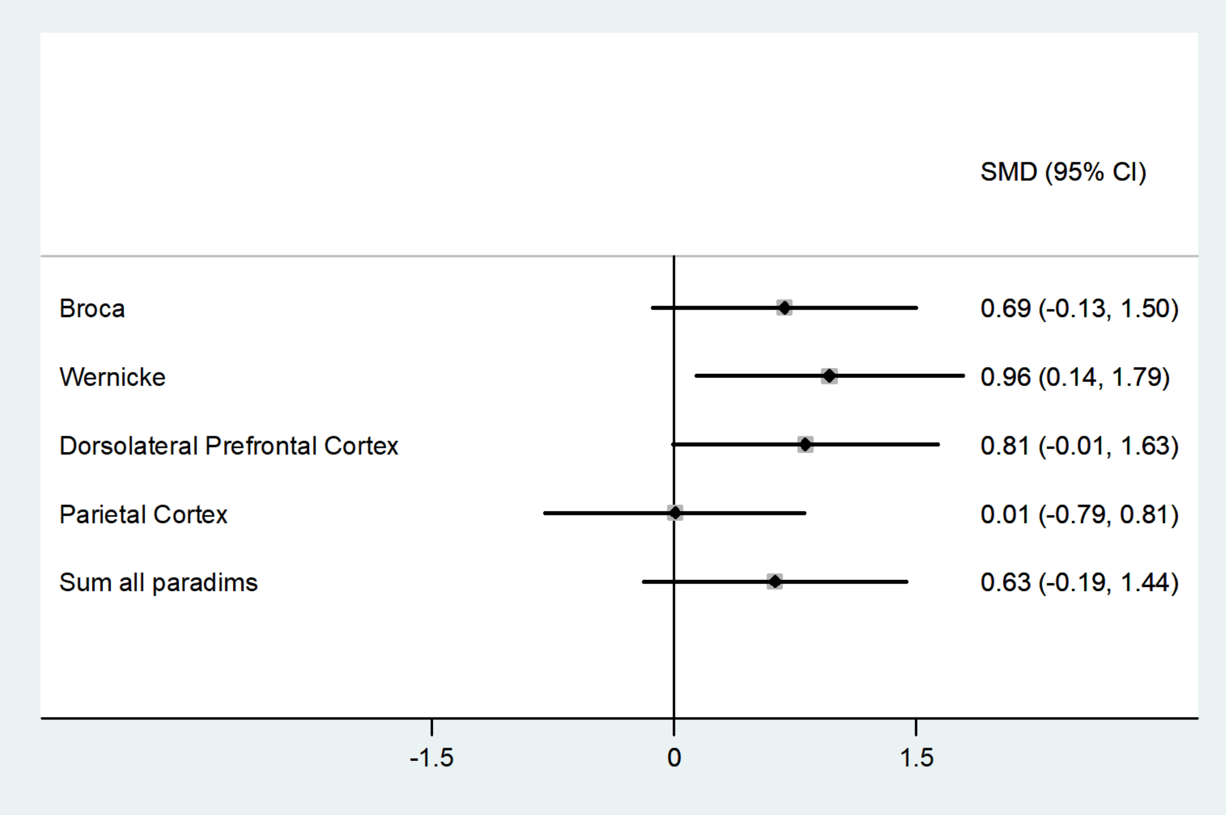


Cognitive Task Progression during Intervention

- Harvard study and Italian study had 3 arms
- US Pivotal Study only had 2 arms (Real/Real vs. Sham/Sham)
- Harvard and Italian studies showed significantly faster progression of the Real(TMS)/Real(CT) vs. the Sham(TMS)/Real(CT)

Correlation Between Baseline ADAS-Cog and Cognitive Training Progression

- Overall level of performance and progress of patients on Cognitive Paradigms was statistically different, with subjects with baseline ADAS-Cog ≤30 significantly outperforming subjects with baseline ADAS-Cog >30 (*P*-value < 0.01)
  - Effect size of difference was 0.63 (moderate to large effect size)
- When classifying the different Cognitive Paradigms according to their respective stimulation regions, all 4 regions showed greater improvement for subjects with baseline ADAS-Cog ≤30 (3 of 4 regions reaching statistical significance)
  - In 3 statistically significant regions, effect size of difference was in the range of 0.69 to 0.96 (moderate to large effect size)



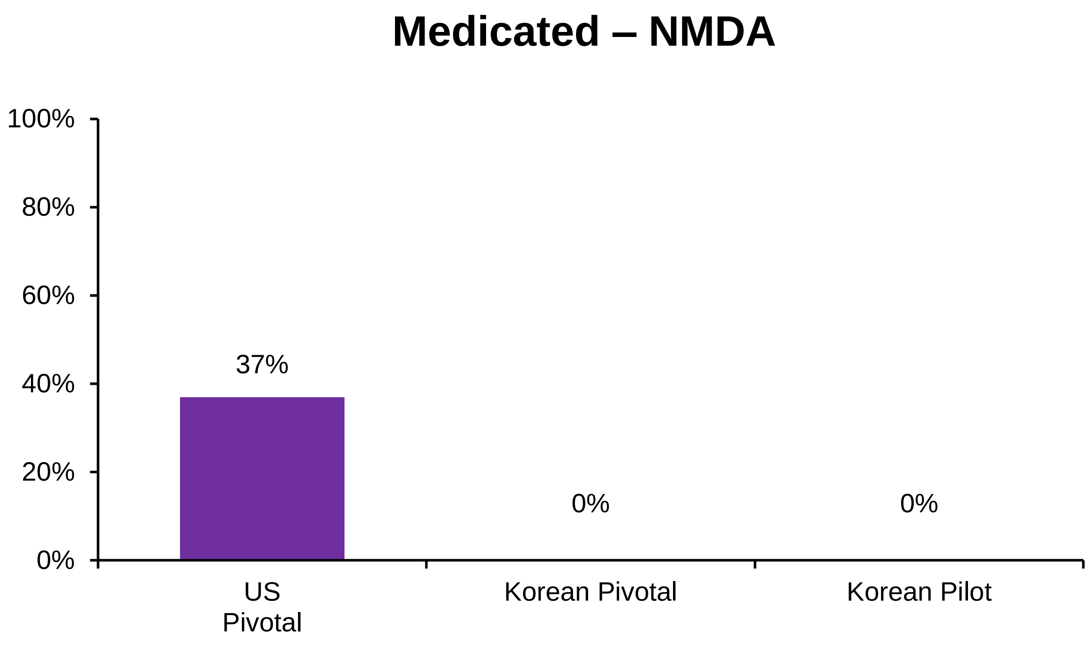
TMS as 'Treatment' – Delayed Effect

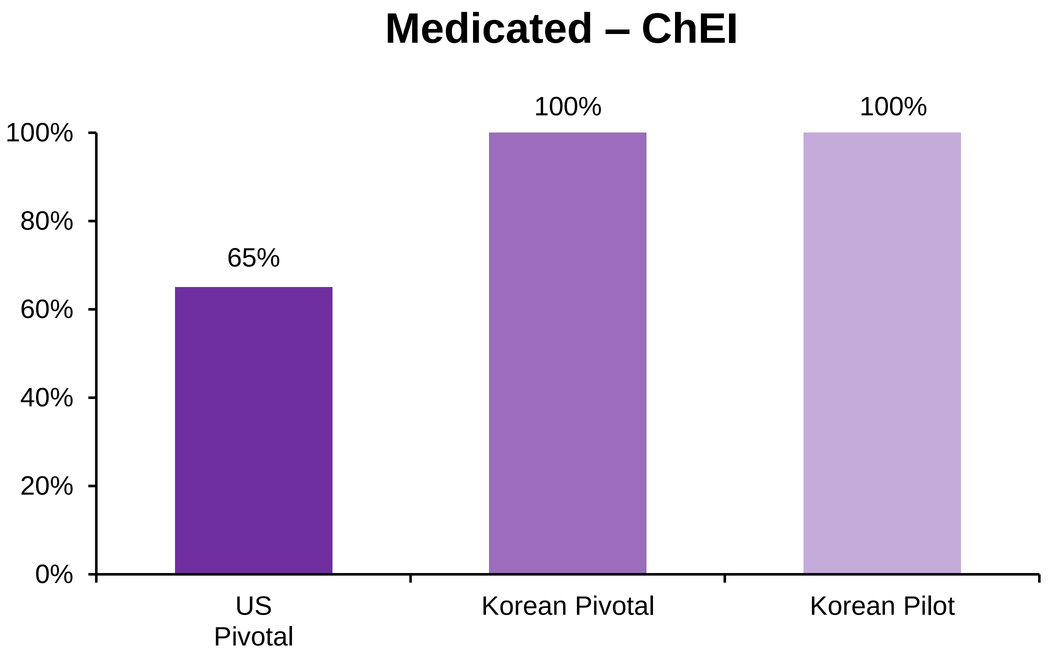
- 7 week time point and 12 week time points are BOTH after completion of the intervention ≠ after the end of the therapeutic effect
- TMS therapeutic applications (MDD, preventative headache treatment, OCD) all reflect such 'off-line effects'
- Off-line effects develop over time, and the time line is variable across patients and across indications

- Such lag effects apply to other TMS interventions:
  - Naeser et al. 2005 – nonfluent aphasia improvement after TMS combined with constraint speech therapy, effects build over time following a 2 week intervention
- Such lag effects are not unique to TMS, also with other neuromodulation interventions, e.g., DBS for dystonia

Medication Effects

- All patients in the Korean studies were on donepezil (8.1 ± SD of 2.5 mg), but none were on memantine





Medication Effects on Time of Response in US Pivotal Study

- Patients on appropriate dose of medication, including memantine, respond faster to neuroAD^{TM}

Change in ADAS-Cog From Baseline to 7 Weeks, Active, Indicated Population

Use of ChEI or NMDA	N	Mean	Std Dev	
No	12	-2.1950	3.7994	
Yes	33	-0.0394	2.6919	
Difference		-2.1556	3.0142	*P* = 0.0397

Change in ADAS-Cog From Baseline to 12 Weeks, Active, Indicated Population

Use of ChEI or NMDA	N	Mean	Std Dev	
No	12	-2.0000	3.7557	
Yes	32	-1.8972	4.5080	
Difference		-0.1028	4.3237	*P* = 0.9443

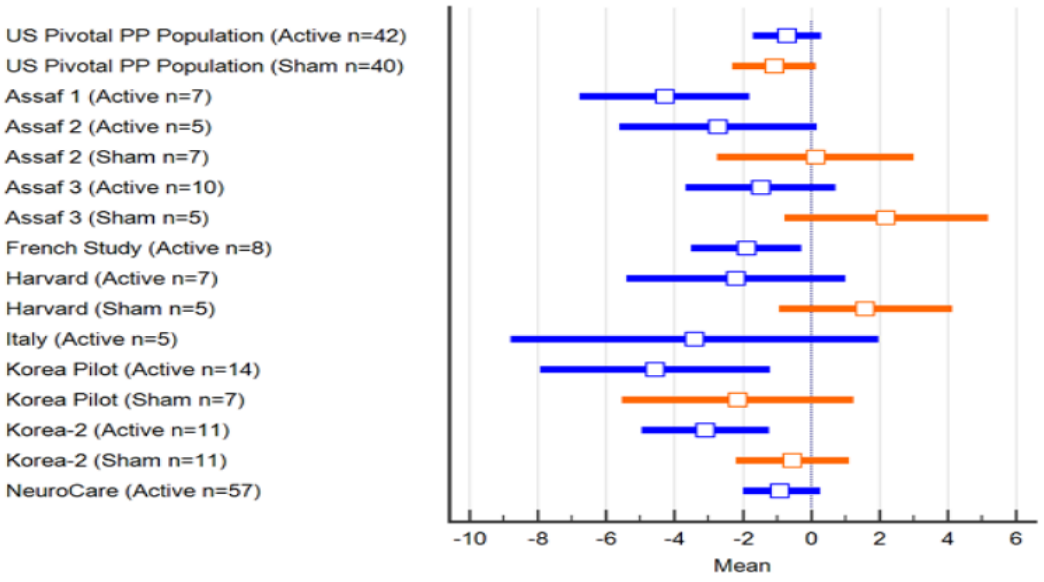
AD Confirmation

- Inclusion criteria required:
  - Patients diagnosed with mild or moderate stage of Alzheimer’s Disease, according to the DSM-IV criteria
  - MMSE score 18–26 [* MMSE 18–20 for moderate Alzheimer’s patients; MMSE 21–26 for mild Alzheimer’s patients]
  - ADAS-Cog above 17
- All subjects had a structural MRI in order to mark targeted brain regions, and was also used to identify excluded disorders including non-Alzheimer brain pathology

Forest Plot of All Available Studies

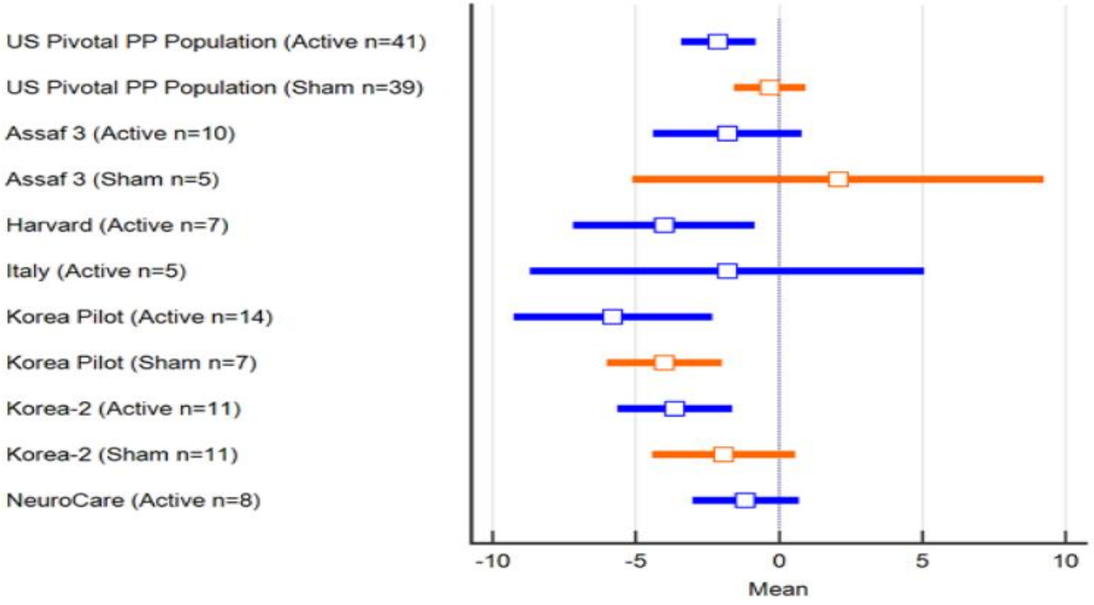
- Investigations into the neuroAD's safety and performance have been underway for more than a decade, in several locations across the globe

Mean ADAS-Cog Change FU-1 (6-10 wks from BL)



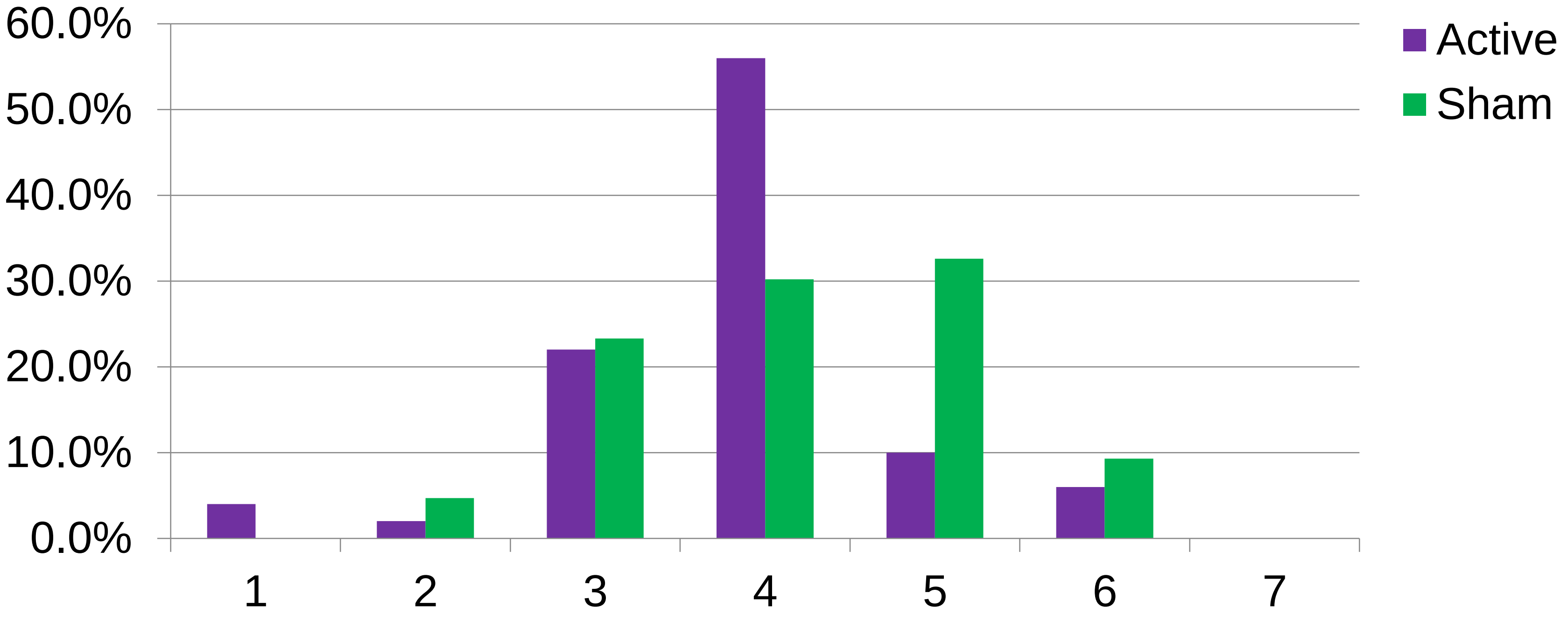
*Active is blue and sham is orange.
**The single sham patient from the Italy study is not included.

Mean ADAS-Cog Change (10-14 weeks)



* Active is blue and sham is orange.
**The single sham patient from the Italy study is not included.

ADCS-CGIC Distribution at Week 12 – US Pivotal Study (PE Population)

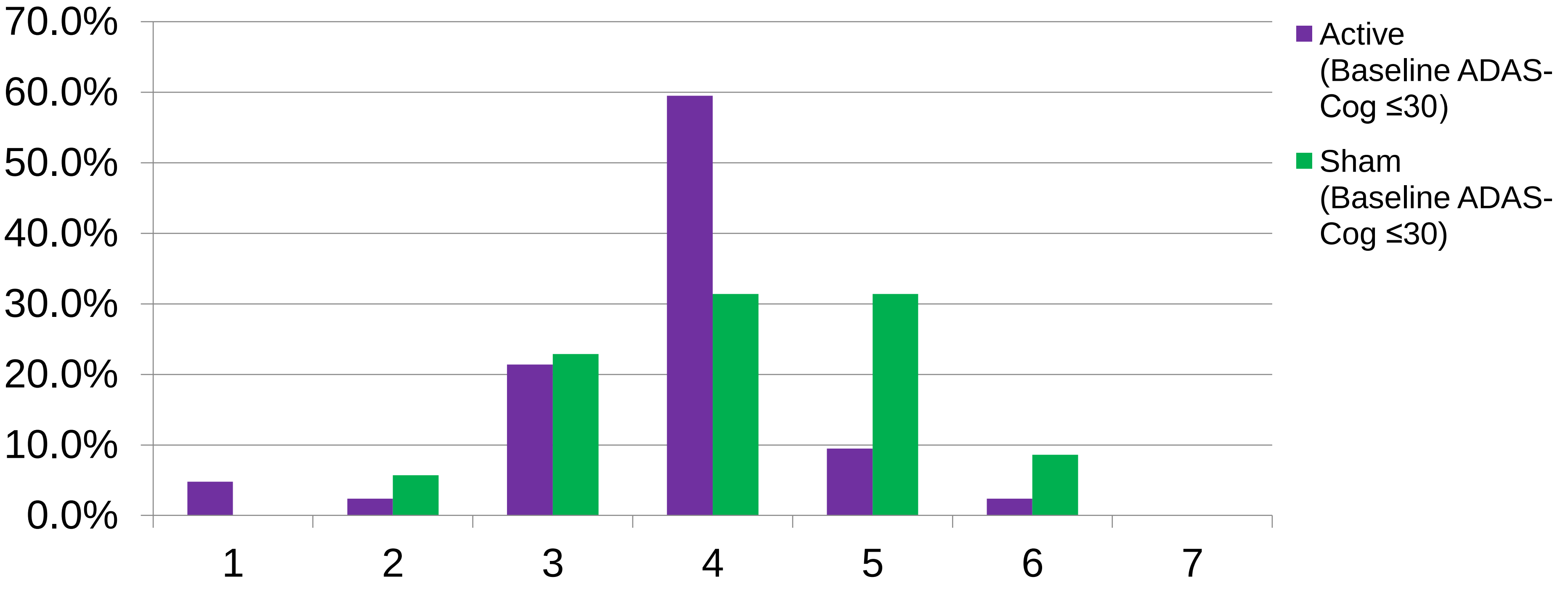


Chi-square test *P* = 0.037

84% of Active vs. 58% of Sham ADCS-CGIC ≤ 4 at 12 weeks (Fisher exact test *P* = 0.01)

ADCS-CGIC Distribution at Week 12 – US Pivotal Study (Indicated Population, Baseline ADAS-Cog ≤30)

- Results are similar to the PE population, but with slightly improved results



Chi-square test $P = 0.041$

88% of Active vs. 60% of Sham ADCS-CGIC ≤4 at 12 weeks (Fisher exact test $P < 0.01$)