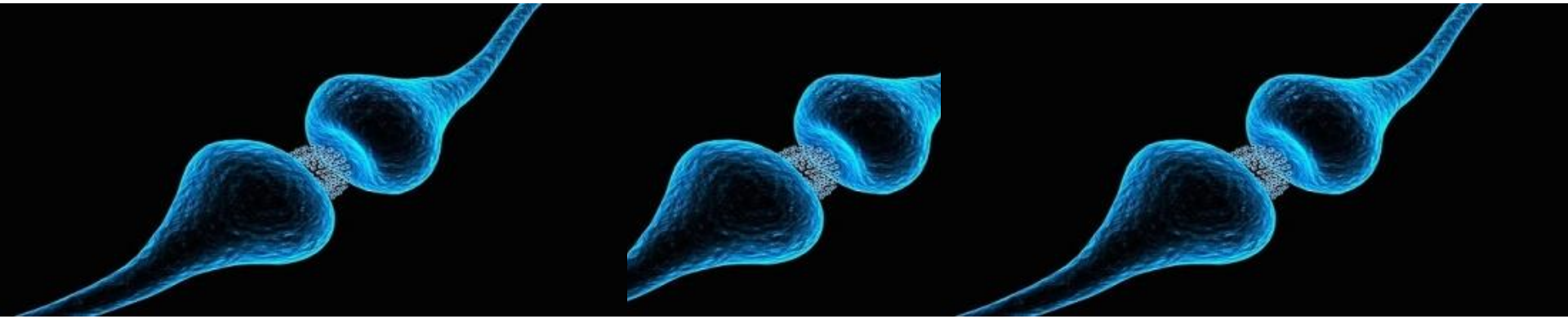


Neurotrope Phase 2 Trial

Evidence that Bryostatin Improves Cognitive Function in Advanced Alzheimer's Patients

January 7, 2018

Bryostatin Phase 2 Trial Design

- Double-blind, randomized, controlled, exploratory trial
- Moderate to severe patients (MMSE 4-15)
- Stable background therapy with cholinesterase inhibitors and/or memantine
- Three arms (1:1:1) 20µg, 40µg and control
- 7 doses over 12 weeks: 0, 1, 3, 5, 7, 9, 11
- Efficacy evaluated at weeks 5, 9, 13 (primary and secondary endpoints)
- Week 15: 30-day safety & efficacy exploratory endpoint
- Post-Hoc endpoints: memantine vs. non-memantine (background therapy)
- All p-values one-tailed as pre-specified in the statistical analysis plan, unless specified otherwise

Scientific Review Summary

Top Line Results of 150 Patients Exploratory Phase 2 Trial:

- Safe, sustained improvement in SIB (Severe Impairment Battery) in 20µg dosing arm (but not the 40µg*) compared to control group through week 13
- The primary efficacy endpoints with SIB were pre-specified to be tested on the mITT and the Completers (CAS) population*

Exploratory Analyses:

- Improvements in SIB sustained at week 15 (30 days after last dose at week 11)

Post-Hoc Analyses:

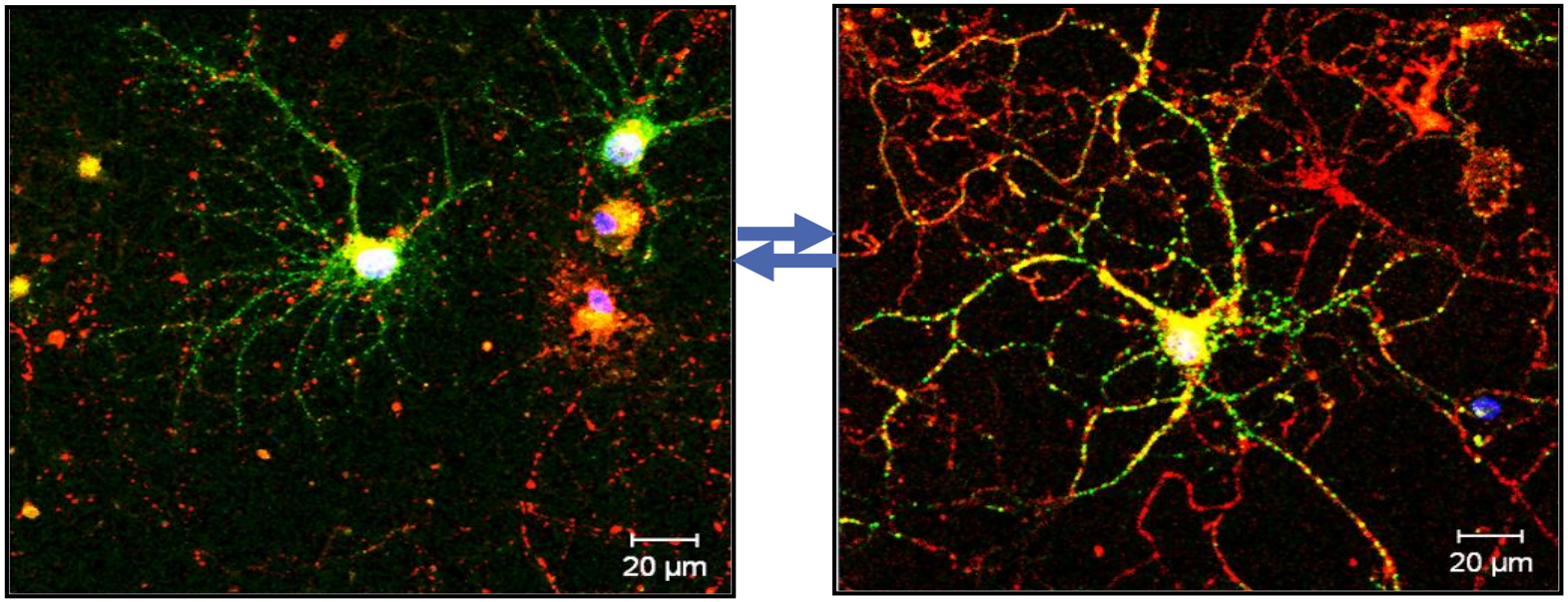
- Increased cognition (SIB) observed in the absence of memantine (an NMDA receptor antagonist) as background therapy
- Efficacy at week 5 (reported at AAIC 2017) was significantly correlated with week 9, 13 efficacy - evidence of sustained improvement
- 20µg dose validated as effective by body surface area (BSA)
- Multiple sensitivity analyses reinforce prospective statistical model

* 40 µg – ineffective, explained by PKC downregulation

Pre-Clinical Studies: PKCε Signaling Pathways Integral to Memory and Learning

- Bryostatin/PKCe activity generates new synaptic networks (synaptogenesis), enhances cognition, prevents neuronal death, and reduces Aβ and hyper-phosphorylated tau

Cultured Rat Hippocampal Neuronal Networks



Treated With Aβ Oligomers[a]

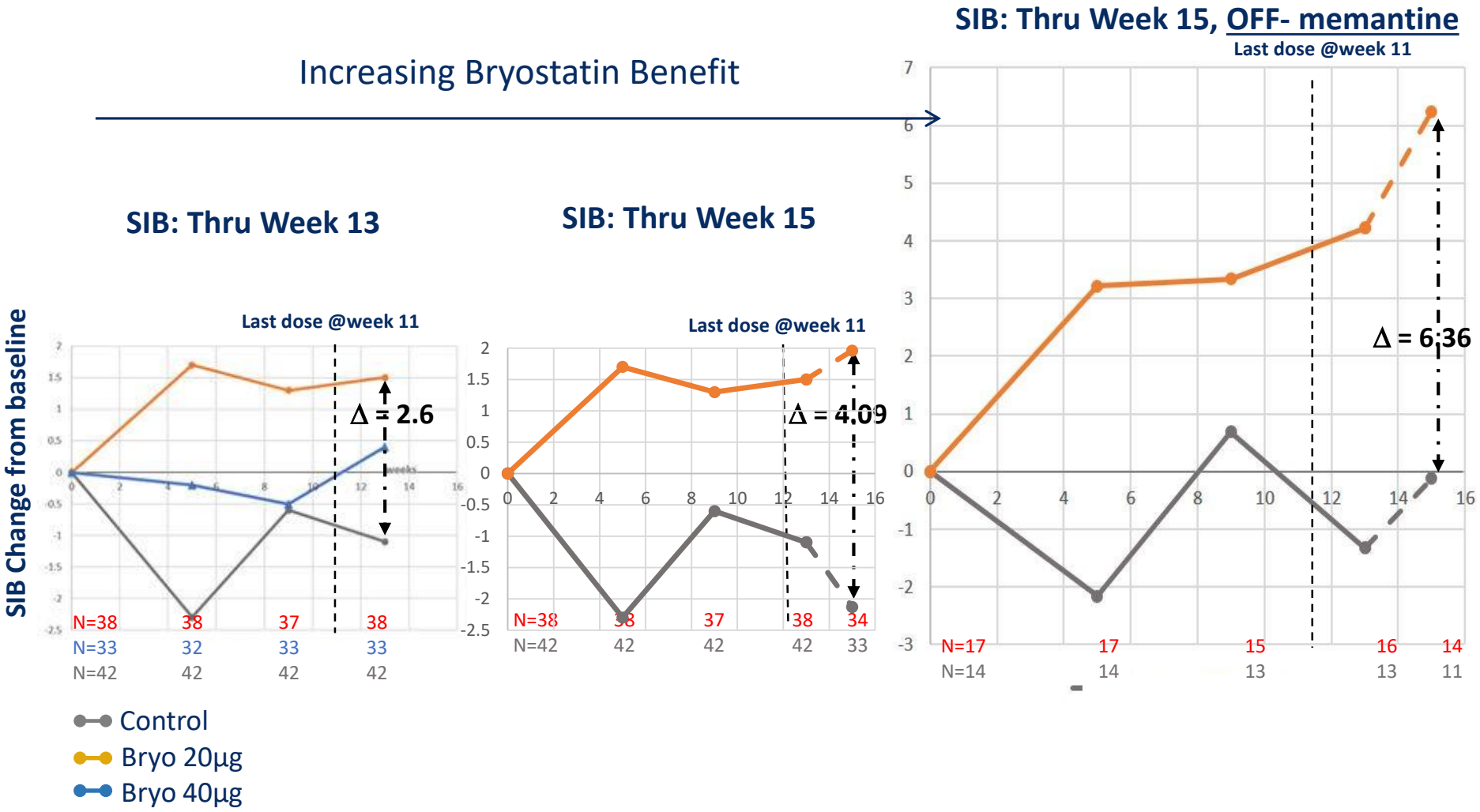
Treated With Bryostatin & Aβ Oligomers

Red = Presynaptic staining (Synaptophysin) **Green** = Postsynaptic staining (PSD-95) **Yellow** = Merged, Synaptic Formation

*Increased red, green (yellow) overlapping of presynaptic & postsynaptic staining indicates increased synaptic formation
Sen A et al. *J Biol Chem.* 2012;287(19):15947-15958. Sen A et al. *J Biol Chem*. 2016;291(32):16462-16467. Image courtesy of Daniel L. Alkon, MD.

Bryostatin SIB Improvement by Visit (Completers)

Increasing Bryostatin Benefit



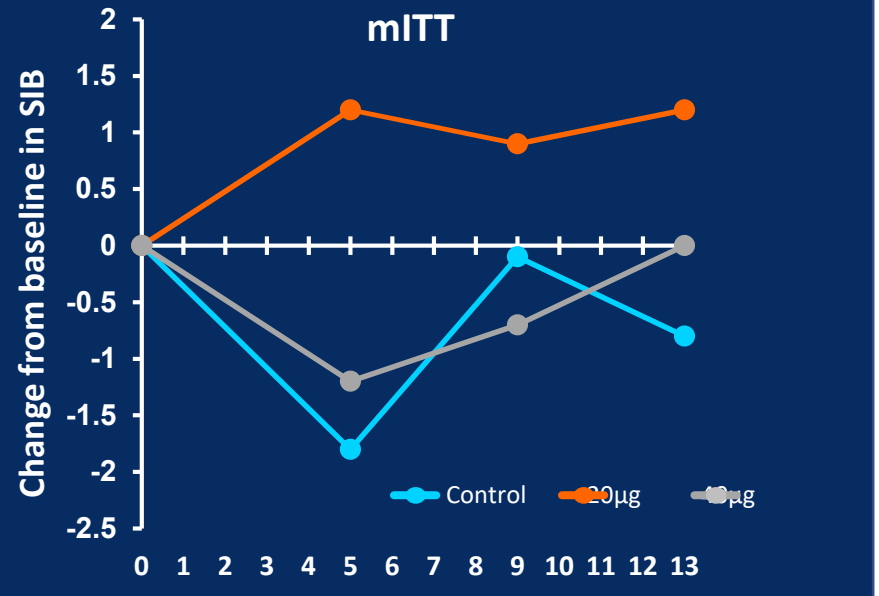
Sustained Benefit

Persistent Benefit
30 Days Post-Dosing

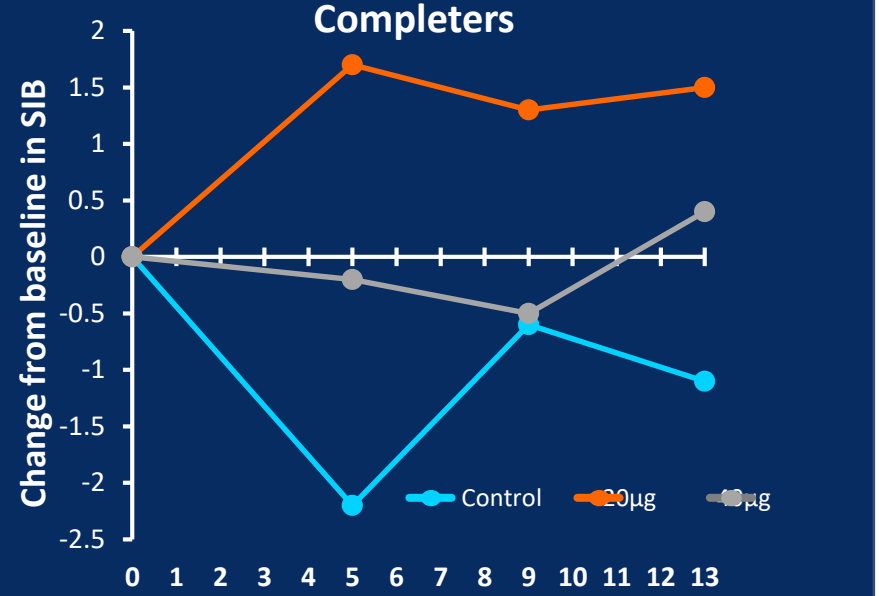
Enhanced Benefit
Off memantine

Topline Phase 2: SIB Change From Baseline mITT & Completer (CAS) Analyses at Week 13

- Consistent effect for 20µg vs control across all time points
- Lack of effect for 40µg vs control across all time points



	Week 5	Week 9	Week 13
Difference 20µg	3.0	1.0	1.9
1-sided p-value	0.056	0.290	0.134
Difference 40µg	0.6	-0.6	0.8
1-sided p-value	0.368	0.638	0.314



	Week 5	Week 9	Week 13
Difference 20µg	4.0	1.9	2.6
1-sided p-value	0.016	0.165	0.070
Difference 40µg	2.1	0.1	1.5
1-sided p-value	0.137	0.476	0.191

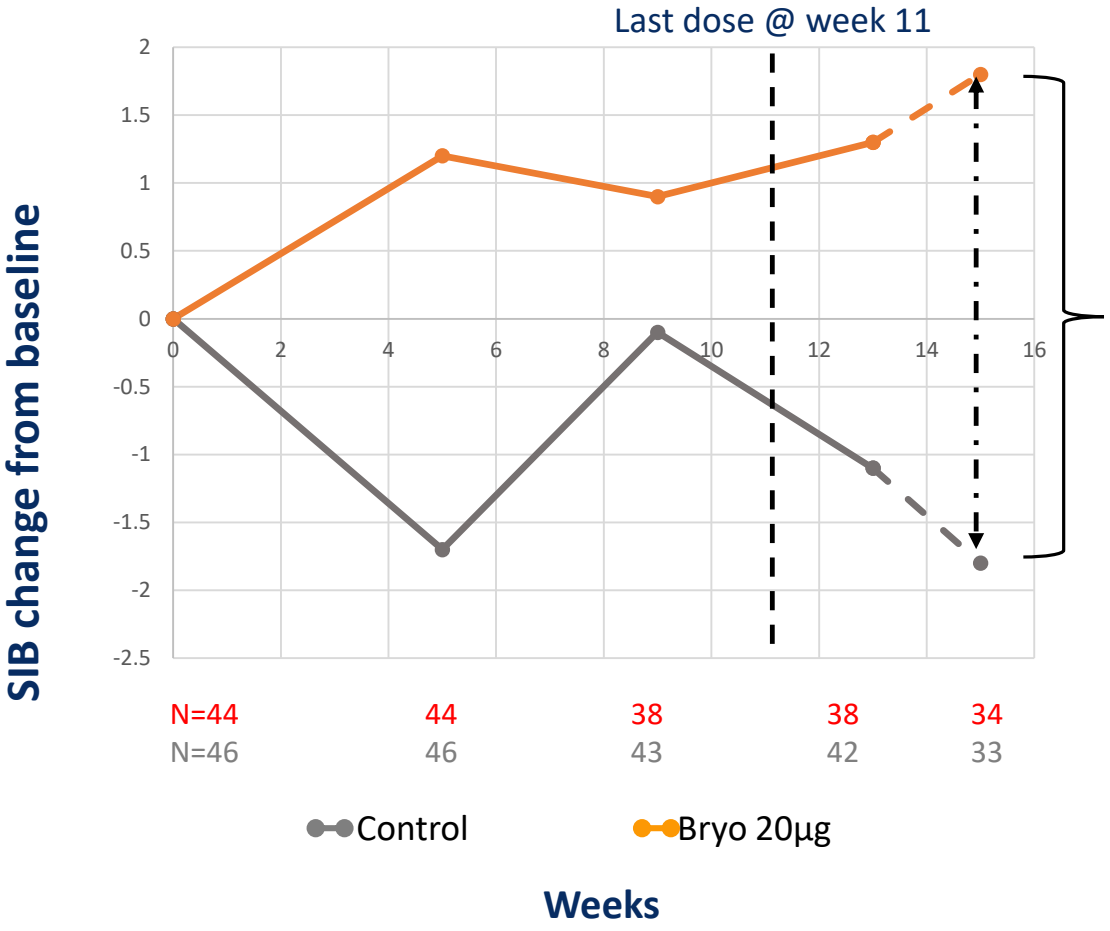
Cf. NTRP AAIC 2017
One-tailed; powered p <0.1

30 Day Post-Dosing Data – Exploratory End Pt.

Evidence for Persistent, Enhanced Benefit

SIB by Visit: 30 Day Post Dosing in mITT Group

- Consistent SIB effect across time points, increased D at week 15



D = 20 µg treatment effect minus control

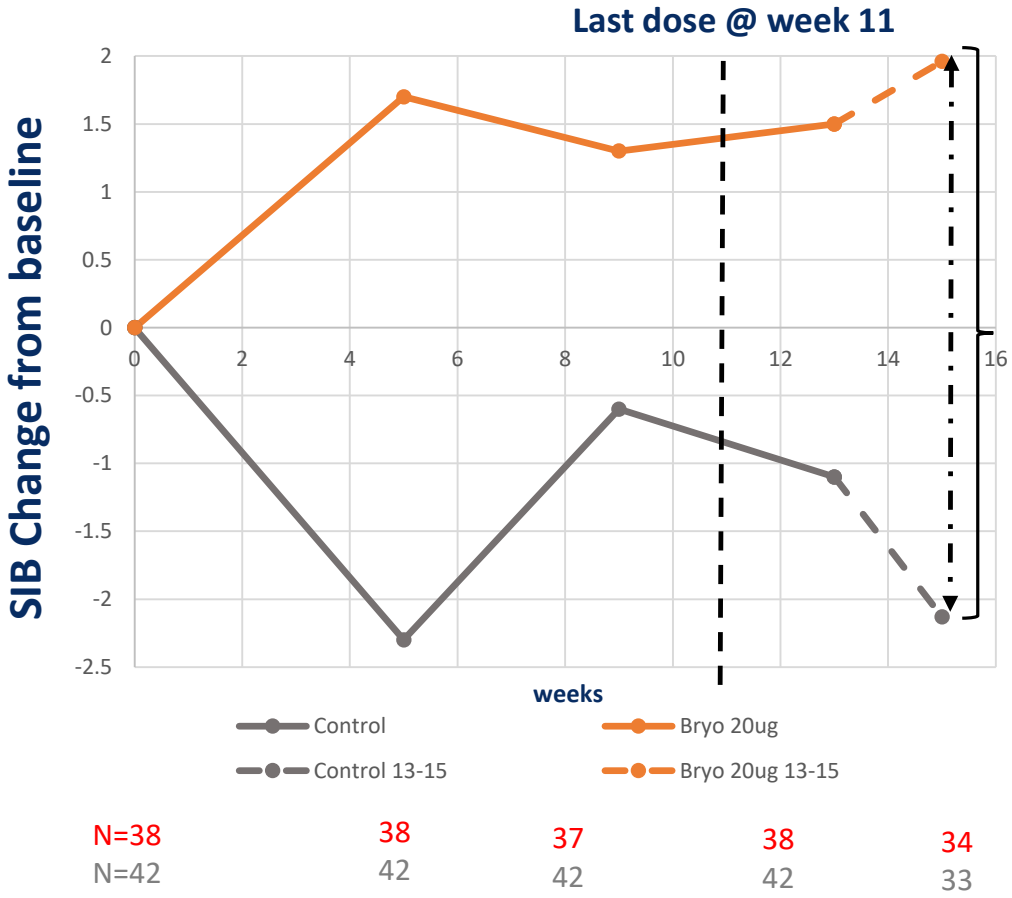
Δ = 3.59
p < 0.0503

- Cognitive improvement sustained 30 days post dosing
- Week 15 data show increased treatment effect due to:
  a) improving efficacy signal
  b) sustained decline of control groups

* for all subjects who were not re-randomized

SIB by Visit: 30 Days Post Dosing in Completers (CAS)

- Consistent SIB Effect across time points, increasing D at week 15*



D = 20 µg treatment effect minus control

$\Delta = 4.09$

$p < 0.0293$

Week 15 data show increased treatment effect due to:

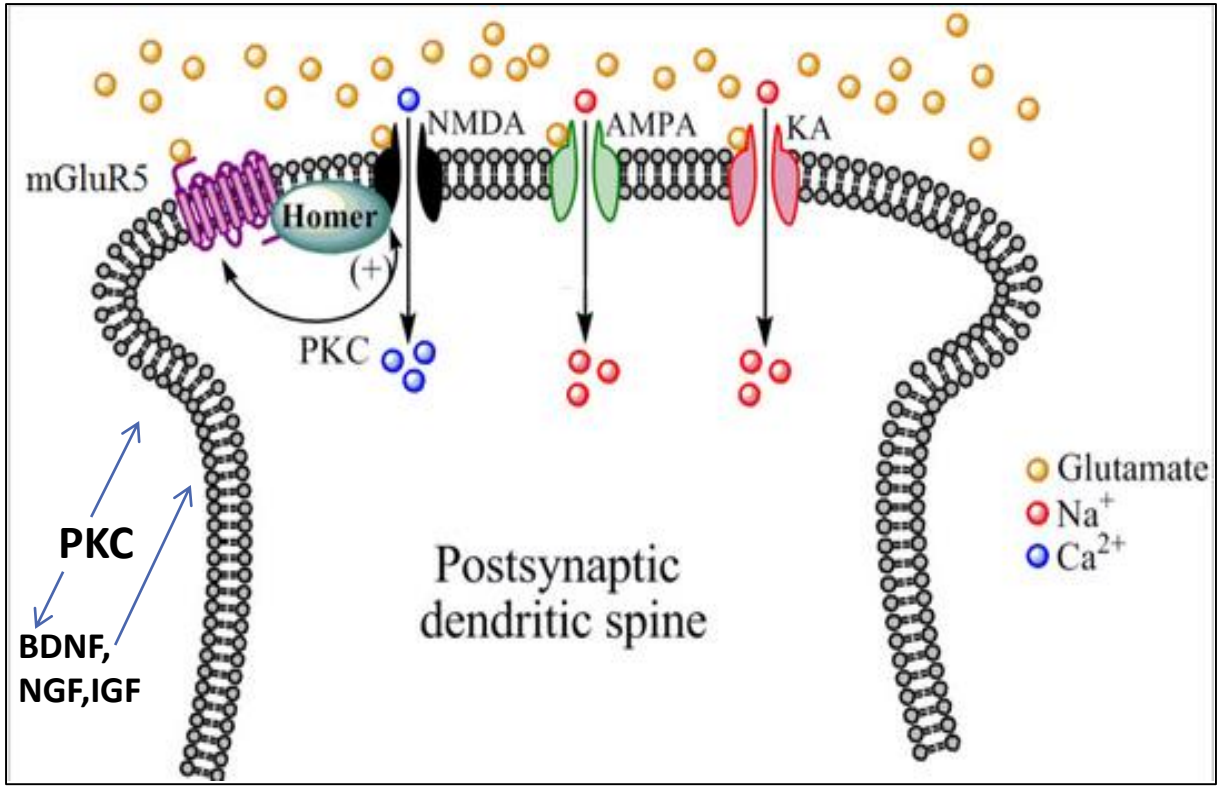
a) improving efficacy signal

b) sustained decline of control groups

* for all subjects who were not re-randomized

Post-Hoc Analyses:
Evidence of Memantine's Negative Impact on Bryostatin's Therapeutic Benefits

PKC, Activated by Bryostatin, Regulates NMDA Receptor Function in Multiple Pathways



Protein kinase C (PKC), which is activated by mGluR5 receptor stimulation, phosphorylates NMDA receptors to increase the cationic conductance of this receptor. PKC can also phosphorylate mGluR5 receptors to modulate their function.

Pathways Include:

- **Synaptogenesis**
- NMDA Receptor Traffic
- NMDA Conductance
- mGluR5-NMDA modulation

References

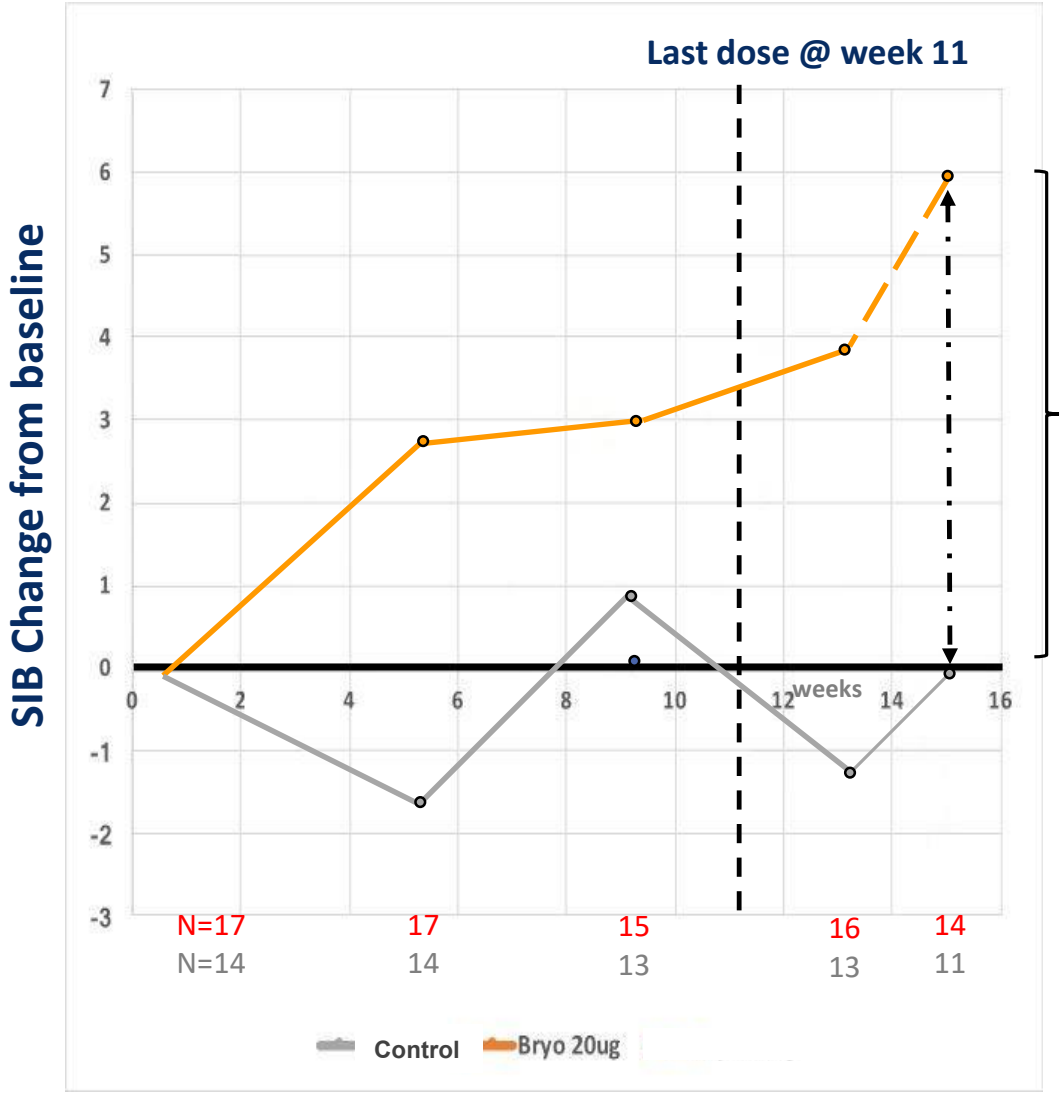
Pharmaceuticals (Basel). 2013 Feb; 6(2): 251–268. Published online 2013 Feb 6.,

The Journal of Biological Chemistry, 2011 July; 286,25187-25200,

Nature Neuroscience, 2001, April, Vol. 4, no 4

Sen A et al. *J Biol Chem*. 2016;291(32):16462-16467

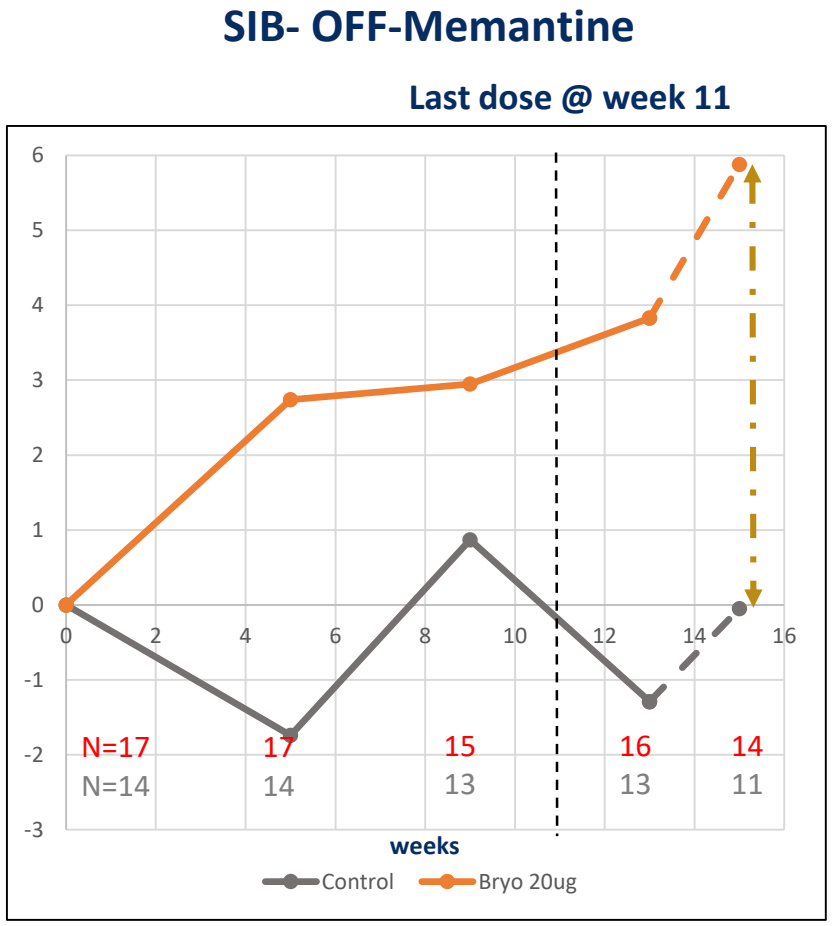
SIB By Visit: OFF-Memantine patients in mITT Group at weeks 13 and 15



D = 20 µg treatment effect minus control

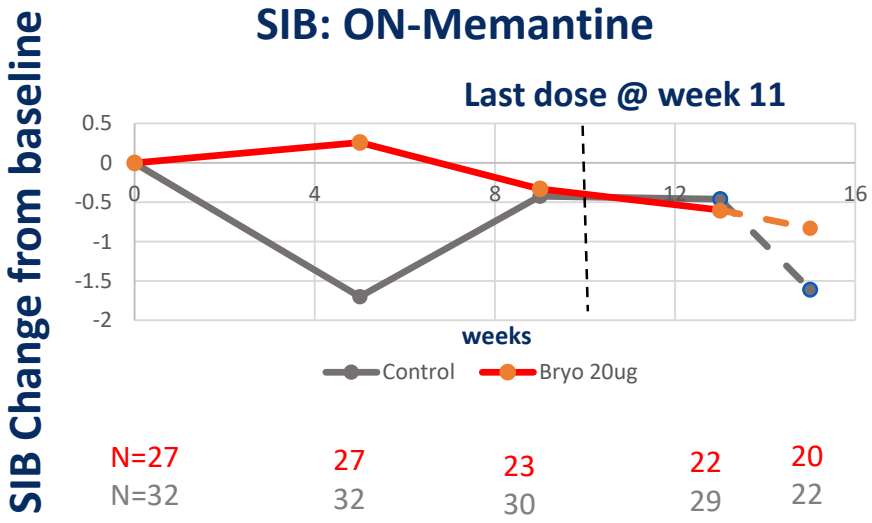
Δ= 5.93
p < .0576

SIB By Visit: Comparison of OFF vs. ON-Memantine in mITT Group at Weeks 13 and 15

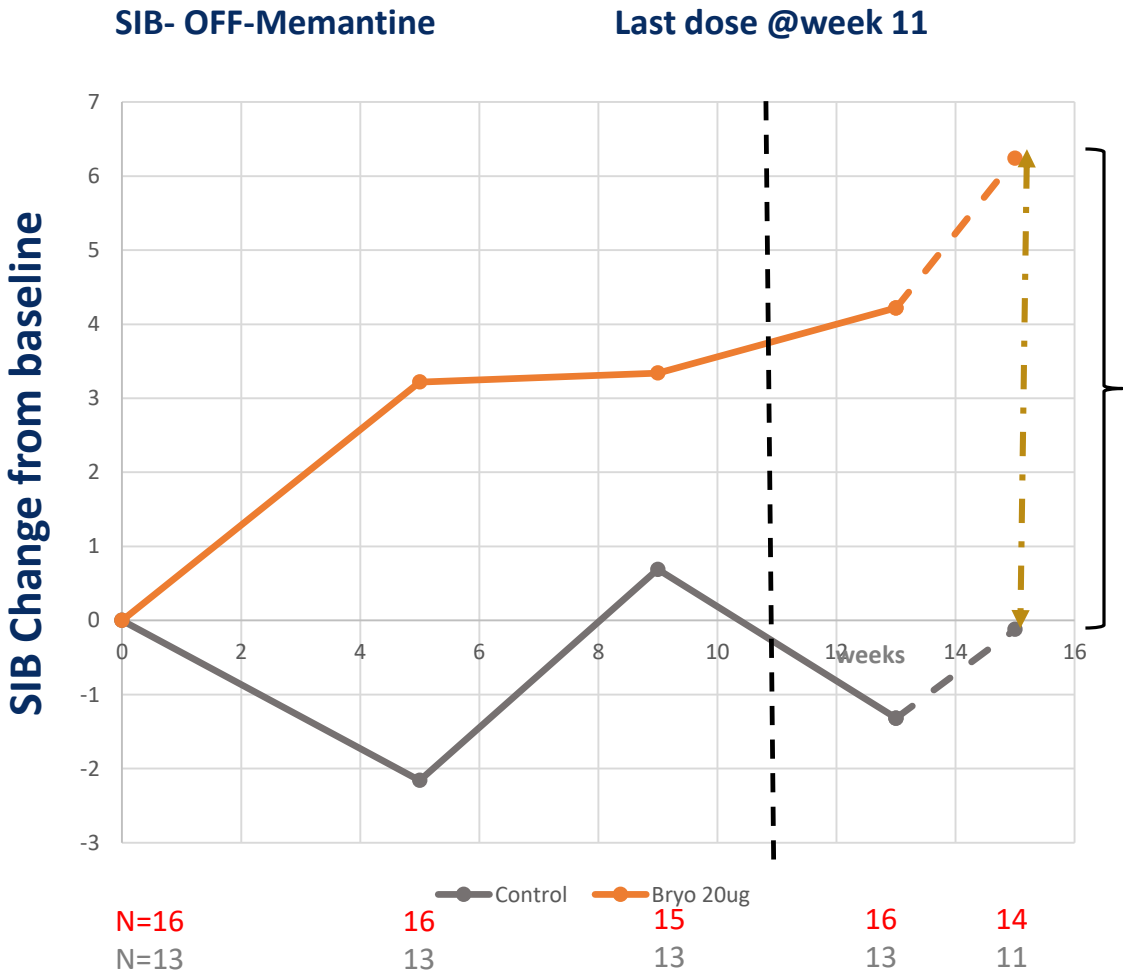


D = 20 µg treatment effect minus control

Δ= 5.93



SIB By Visit: OFF-Memantine Completers (CAS) at Weeks 13 and 15

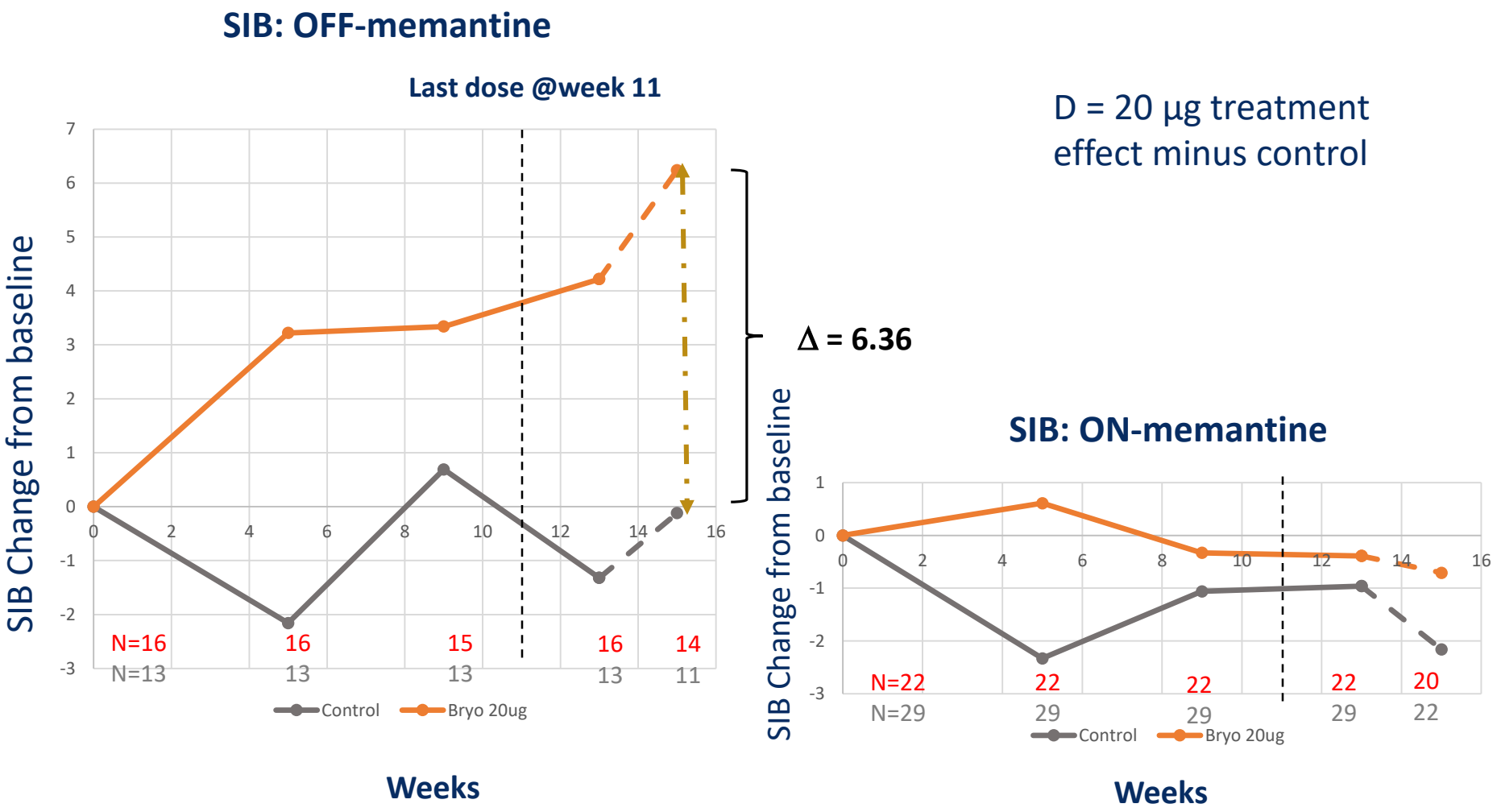


D = 20 µg treatment effect minus control

$\Delta = 6.36$

$p < 0.0488$

SIB By Visit: Comparison of OFF vs. ON-Memantine in Completers at Weeks 13 and 15



*Results from Week 15 are from a model that included all visits, all other results are consistent with the CSR results (Tables 14.2.1.3 for FAS and 14.2.1.4 for Completers) that did not include Week 15

Memantine Blocks Bryostatin SIB Improvement

- Larger treatment effects were seen in patients treated with 20µg bryostatin OFF-memantine vs. ON-memantine in MITT and Completer groups

SIB	20 µg bryostatin vs. control	mITT		Completer (CAS)	
		Off memantine	On memantine	Off memantine	On memantine
Week 5	Δ	4.48	1.96	5.38	2.94
	p-value*	0.0857	0.1973	0.0487	0.1016
Week 9	Δ	2.08	0.09	2.66	0.90
	p-value*	0.2597	0.4847	0.2071	0.3522
Week 13	Δ	5.11	-0.14	5.53	0.56
	p-value*	0.0437	0.4752	0.0338	0.3988
Week 15	Δ	5.93	0.79	6.36	1.45
	p-value*	0.0576	0.3927	0.0488	0.3120

*All p- value are one-tailed as pre-specified unless otherwise denoted

Top Line: SIB Improvement at Weeks 5, 9 & 13 Was Significantly Correlated for the 20μg Dose

- Significant correlations (p <.001) between SIB values for 20μg (vs. control) at successive weeks – 5, 9,13

- Shows that the same patients who improved at week 5 improved throughout the trial.
  - Improvement, and not only reduction in the rate of decline, suggests treatment of disease vs. symptomatic relief

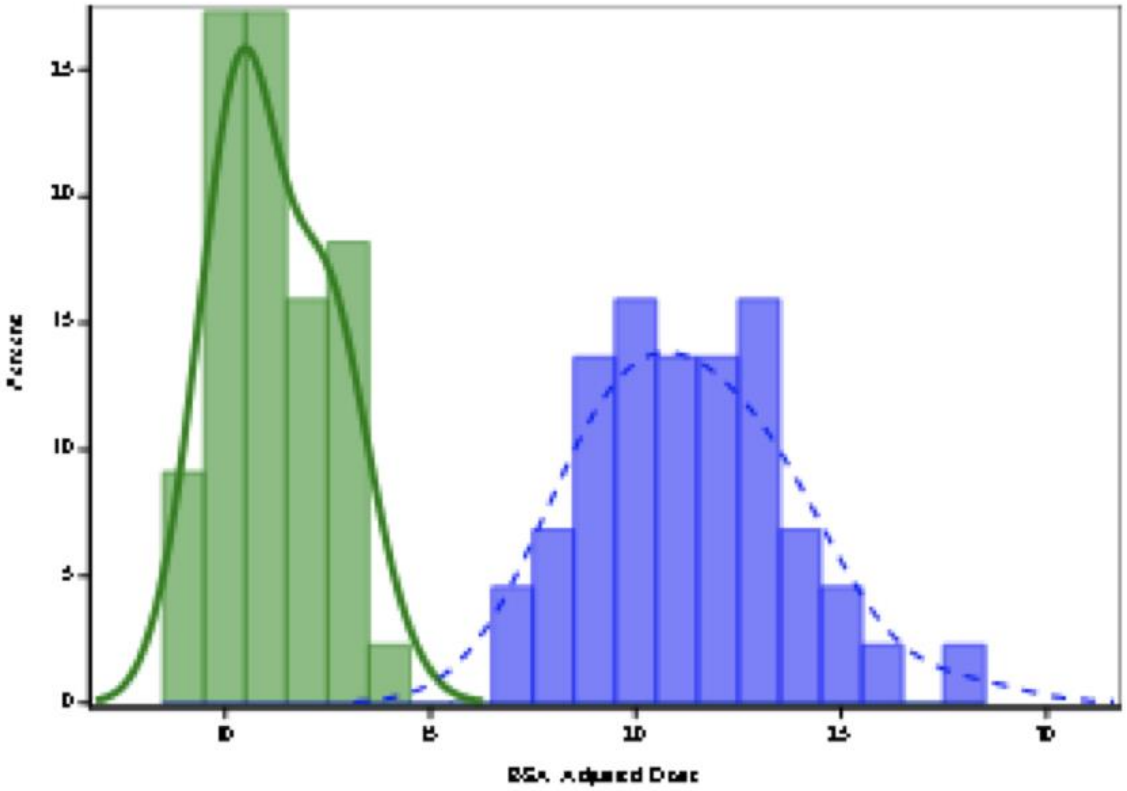
- Supports the sustained nature of the 20μg dose efficacy

*mITT: modified intent-to-treat population, +P-values for correlations are two-tailed

Bryostatin - 20µg Dose Further Validated as Effective by Body Surface Area (BSA) Analysis

- Normalization of the 20µg dose to each patient's BSA revealed that the 20µg doses (on a per-patient-basis) were tightly distributed around the 12.5µg/m^2. The week 13 mean dose adjusted for BSA was 11.33 µg/m^2 in the 20µg dose arm.

Narrow Dose Response Distribution around 11.33µg/m^2 for 20µg/dose



F-ratio for 20µg vs. 40µg variance of 3.97 and a corresponding 2-sided p-value of <0.0001, supported a conclusion of unequal variances between the two dosage groups.

Concluding Observations:

1. 20µg bryostatin showed evidence of safely produced, sustained cognitive improvements (SIB scores) in advanced AD patients

2. These improvements, not just reduction in the rate of decline, persisted at week 15 (30 days after the last dose at week 11) – suggesting treatment of disease in addition to symptomatic relief.

3. Greater cognitive improvement in the 20µg arm was observed in the absence of memantine – a known partial NMDA receptor antagonist

4. 20µg dose validated as an effective, safe dose by Body Surface Area

5. Sensitivity analyses generally agreed with the results of the analysis by Mixed Model for Repeated Measures (MMRM) and included:
   - ANCOVA – similar to MMRM used here
   - Imputation of drop outs also similar to MMRM
   - Adjusting for additional baseline covariates
   - Pooling sites
   - Linear vs. quadratic model over time

Next Steps in Clinical Development Program

A confirmatory trial in advanced AD, non-memantine patients

1. Leverage Phase II data by incorporating memantine-free patients into the study

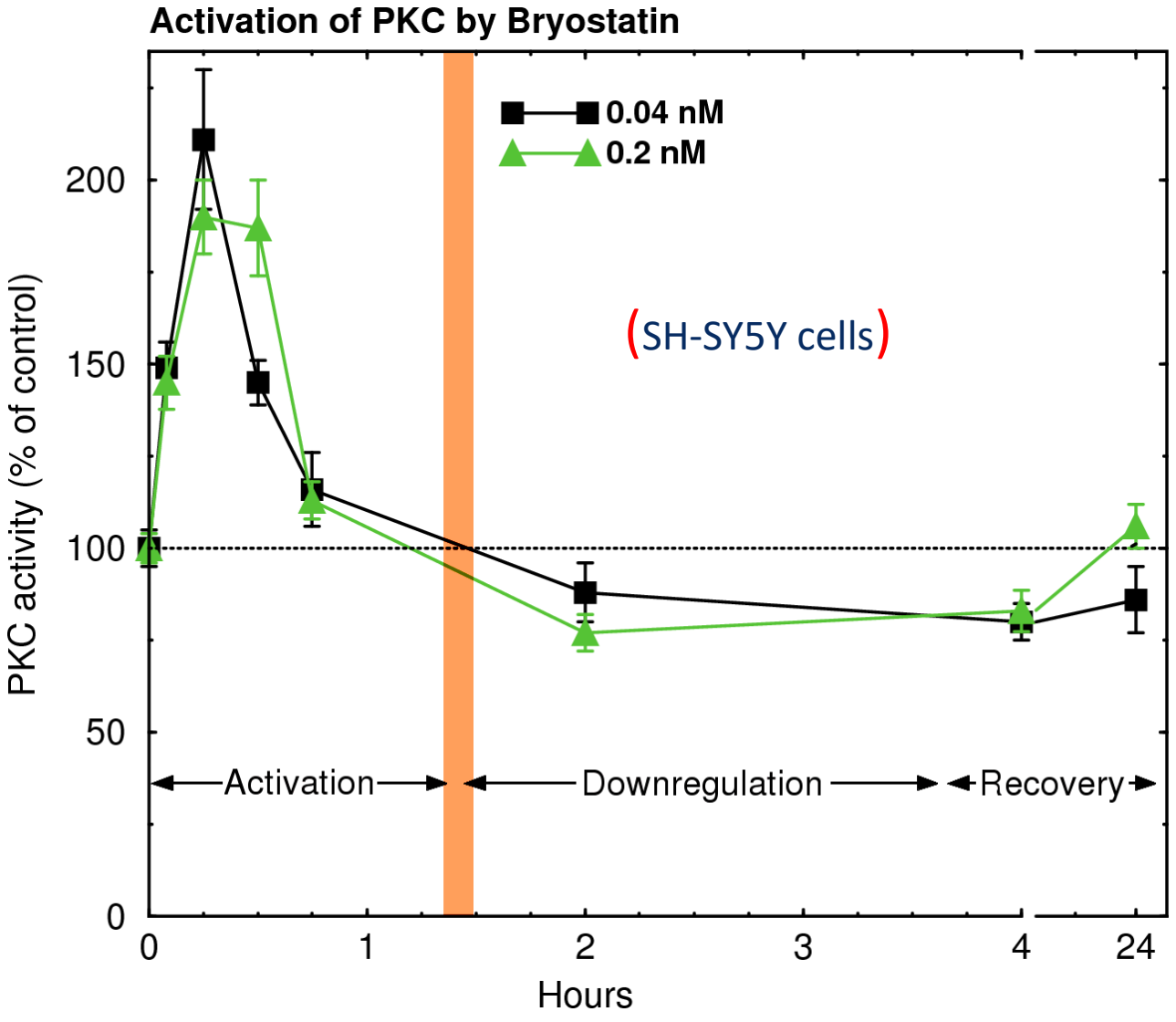
2. Confirm marked improvement in SIB scores among memantine-free patients

3. Draw conclusions on possible long-term effects of bryostatin on SIB improvement from baseline

   - Trial expected to begin in early 2018

Supplemental Slides

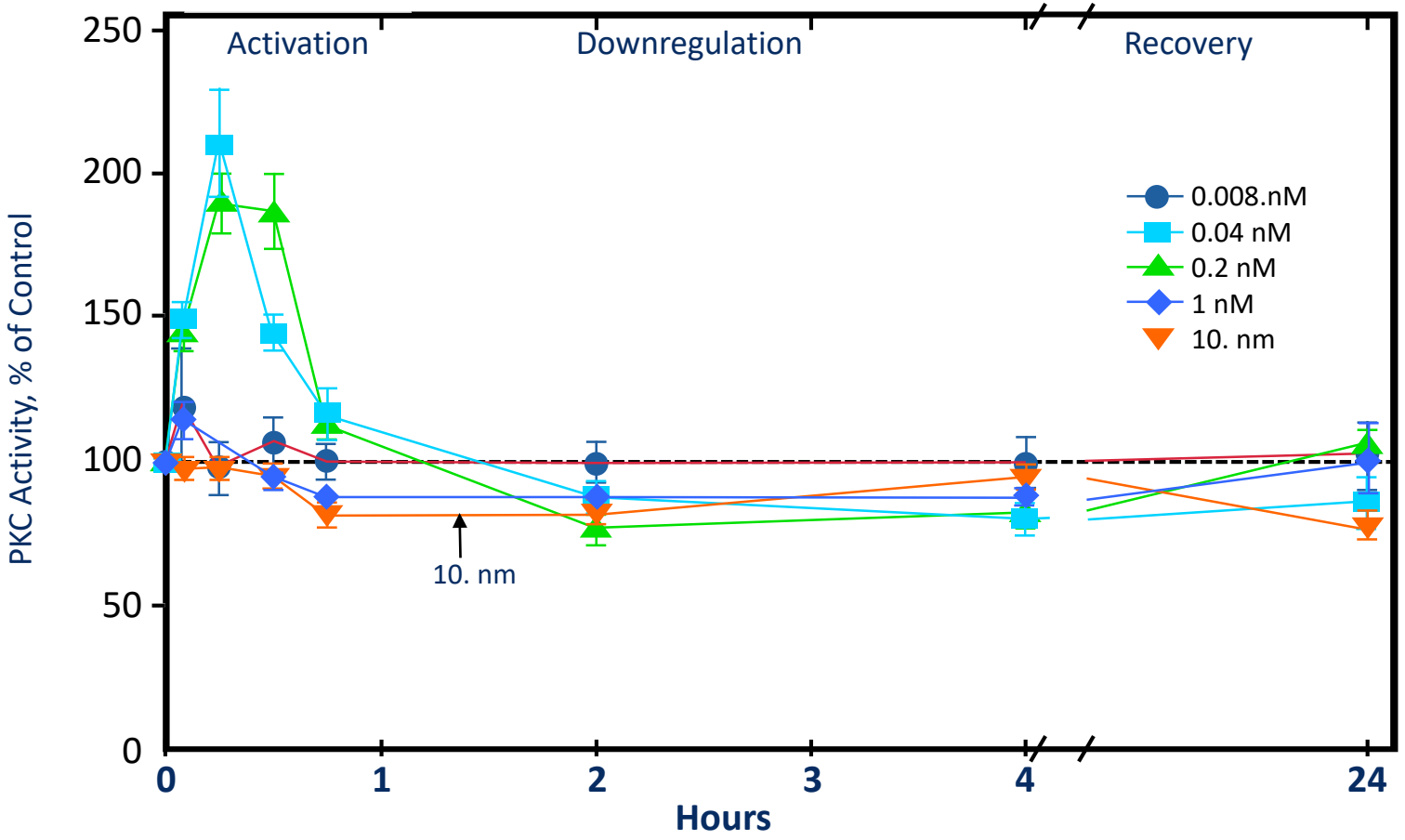
Appendix: PKC Dosing in AD: Increase Activation, *Avoid* Downregulation



- High dose downregulates PKCε (oncology), **lower dose leads to increased activation of PKCε** (Cognitive Disorders) and *de novo* synthesis of PKC**ε**.
- **The primary objective** of treatment of cognitive disorders with bryostatin is the sustained activation of PKCε, not down-regulation as was attempted in oncology.
- **The Next Clinical Trial** will optimize dosing by maximizing PKC activation and minimizing down regulation.

D. Alkon: In Vitro Bryostatin unpublished Results; courtesy of Daniel L. Alkon, MD

Stepwise Increases of Bryostatin Doses PKC Activation, Prolonged Down Regulation & Recovery



20µg Group Showed Persistent SIB Improvement 30 Days Post-Dosing

- At week 15 (30 days after last dose at week 11), 20µg arm showed a persistent SIB improvement over baseline as compared to the control group in both mITT and Completers (CAS). The week 15 endpoint was an exploratory endpoint.

SIB		20µg Bryostatin	
		mITT	Completer @ week 13
N* (N=15 wk)	20µg	44	38 (34*)
	Control	46	42 (33*)
Week 15	D	3.59	4.09
	p-value **	**0.0503**	**0.0293**

- mITT: At week 15, 20µg treated patients showed an lsmean SIB improvement of 1.77 while the control group showed a decline in lsmean SIB scores of -1.82 for an overall treatment D of 3.59 from baseline; p = 0.0503).
- Completers (CAS): At week 15, 20µg treated patients showed an lsmean SIB improvement of 1.96, while the control group showed a decline in lsmean SIB scores of -2.13 for an overall treatment D of 4.09 from baseline; p = 0.0293).

* For all subjects in model at any visit, only subjects who were not re-randomized at week 15.
**All p- value are one-tailed as pre-specified unless otherwise denoted.