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Bryostatin Phase 2 Trial Cognition & Activities of Daily Living in Moderate to Severe Alzheimer's Disease: Report on Safety and Efficacy

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Developing Topics: Clinical Trials

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Presenter Disclosures

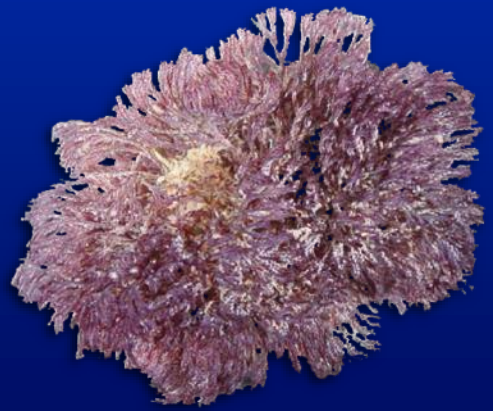
Martin R. Farlow, MD

- Accera, AstraZeneca, Avanir, Axovant, AZTherapies, Biogen, Boehringer Ingelheim, Chase Pharmaceuticals, Eisai, Eli Lilly & Company, FORUM Pharmaceuticals, Genentech, INC Research, KCRN Research, Longeveron, Lundbeck, Medavante, Medtronic, Merck & Co. Inc., Neurotrope Biosciences, Novartis, Proclara (formerly Neurophage Pharmaceuticals), Roche, Suven Life Sciences, Ltd.

Bryostatin:
A Novel Mechanism For Alzheimer's Disease (AD)

- Macrolide lactone, initially isolated from the marine bryozoan *Bugula neritina*
- Potent modulator of protein kinase C (PKC) isozyme ε
- PKCε—plays a key role in synaptogenesis, learning
  - Potential in AD as a disease modifier

Molecular structure of bryostatin-1

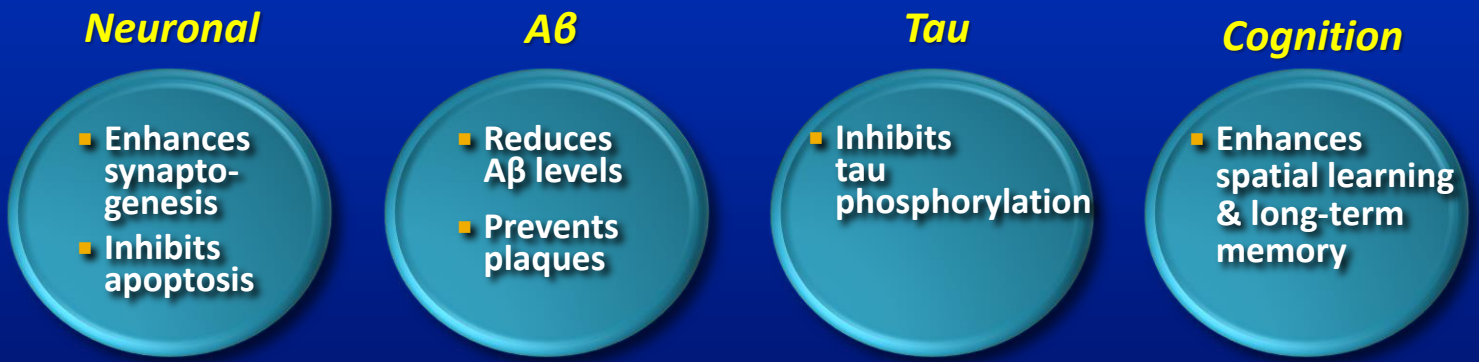


Bugula neritina
California Academy of Sciences

Halford B. *Chemical & Engineering News*. 2011;89(43):10-17; Russo P et al. *Mar Drugs.* 2015;14(1): 5.

Bryostatin:
Rationale for Studies in AD

- ***Autopsy studies:*** synaptic loss correlated tightly with cognitive impairment observed in AD[1]
- ***Preclinical studies:*** Bryostatin was shown to have a multimodal effect[2-6]:



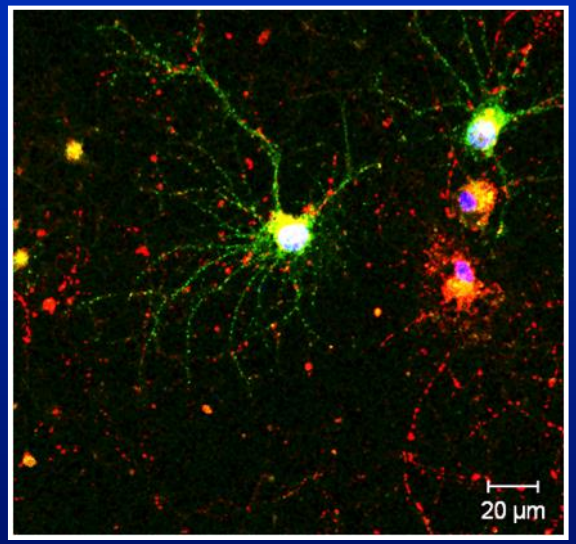
- ***Clinical studies prior to AD trials:***
  - **>1400 patient exposures in NCI cancer studies**
    - **In cancer studies, bryostatin was well tolerated at low doses ≤25µg/m² —myalgia was dose-limiting at higher doses**

[1]Terry RD et al. *Ann Neurol.* 1991;30(4):572-580. [2]Sen A et al. *J Biol Chem.* 2012;287(19):15947-15958. [3]Hongpaisan J et al. *J Neurosci.* 2011;31(2):630-643. [4]Alkon DL et al. *Trends Pharmacol Sci.* 2007;28(2):51-60. [5]Hongpaisan J, Alkon DL. *Proc Natl Acad Sci U S A.* 2007;104(49):19571-19576. [6]Sen A et al. *J Biol Chem*. 2016;291(32):16462-16467.

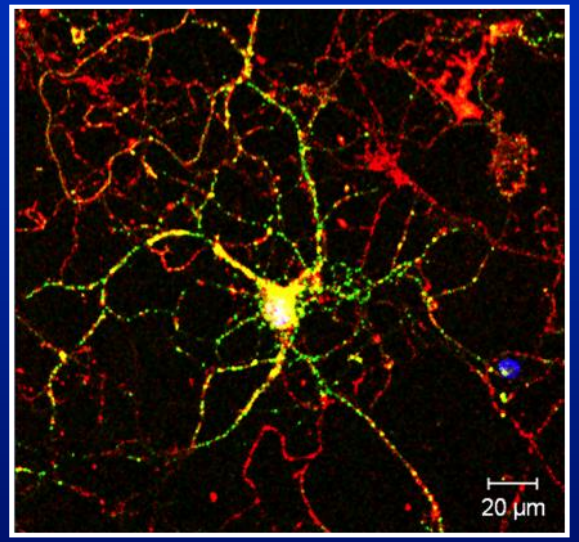
Bryostatin:
Induces Synaptic Networks & Protects Against Aβ Toxicity

- Increased presynaptic & postsynaptic staining indicates increased synaptic formation

Red = Presynaptic staining (Synaptophysin) Green = Postsynaptic staining (PSD-95) Yellow = Merged



Neurons Treated With Aβ Oligomers[a]
Show Decreased Synaptic Integrity



Neurons Treated With Bryostatin
Show Enhanced Growth of Synaptic
Networks & Protection Against Aβ Oligomers

Images courtesy of Daniel L. Alkon, MD

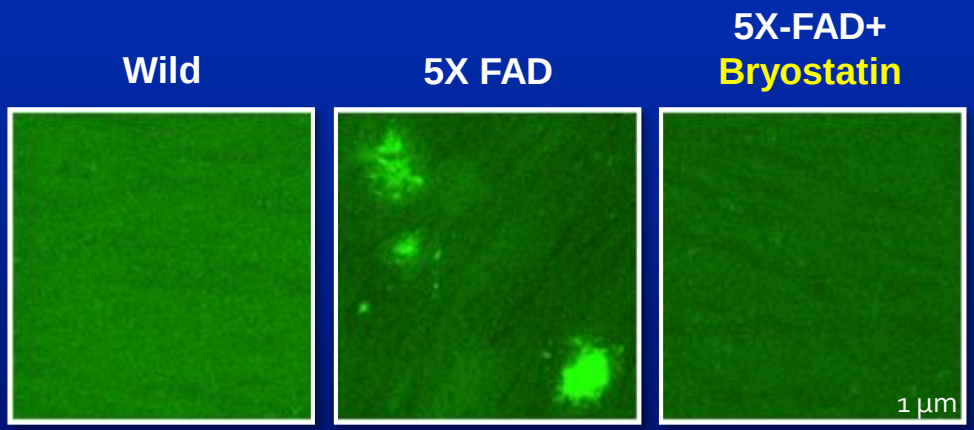
Cultured Rat Hippocampal Neuronal Networks

[a]Amylospheroids (ASPDs)

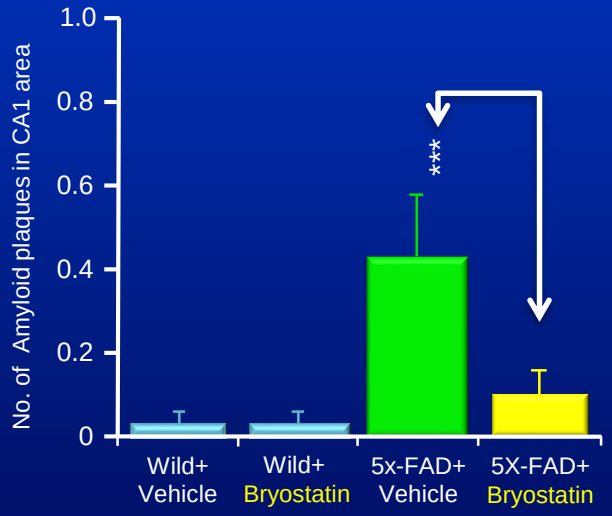
Sen A et al. *J Biol Chem.* 2012;287(19):15947-15958; Sen A et al. *J Biol Chem.* 2016;291(32):16462-16467.

Bryostatin:
Prevents Amyloid Plaque Formation

Bryostatin Reduces Amyloid Plaque Formation
in AD Transgenic Mouse Model (5X-FAD[a])



Amyloid Plaques in Hippocampal CA-1 Area
(Confocal microscopy of amyloid plaques stained by Thioflavin-5)

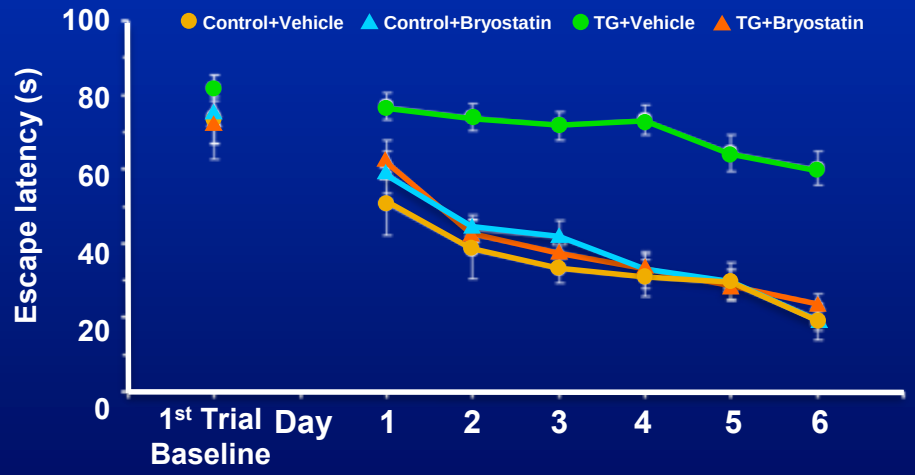


[a]5X-FAD is a mouse strain that has a more aggressive form of AD containing 5 familial Alzheimer's disease (FAD) mutations: Swe, Lon, Flo, M146L, L28V (Hall AM et al. *Brain Res Bull*. 2012;88(1):3-12) Hongpaisan J et al. *J Neurosci.* 2011;31(2):630-643.

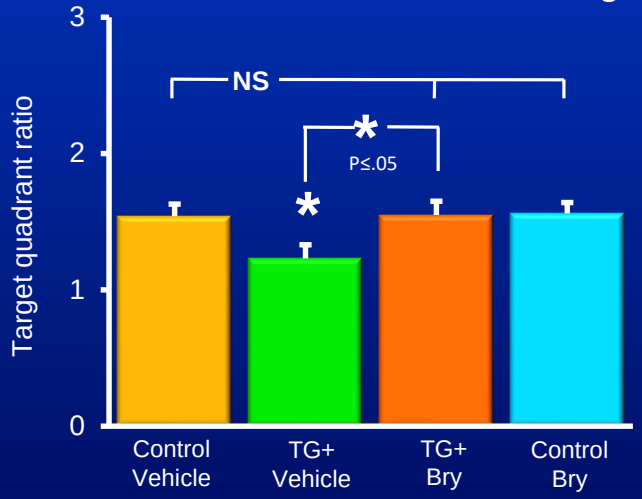
Bryostatin:
Improves Cognitive Function—Prevents Loss of Learning & Memory

Spatial water maze learning & memory retention of 5X-FAD transgenic mice[a]

Learning[b]
Day 1-6 After Dosing



Memory Retention[b]
Observed 2 Weeks After Dosing



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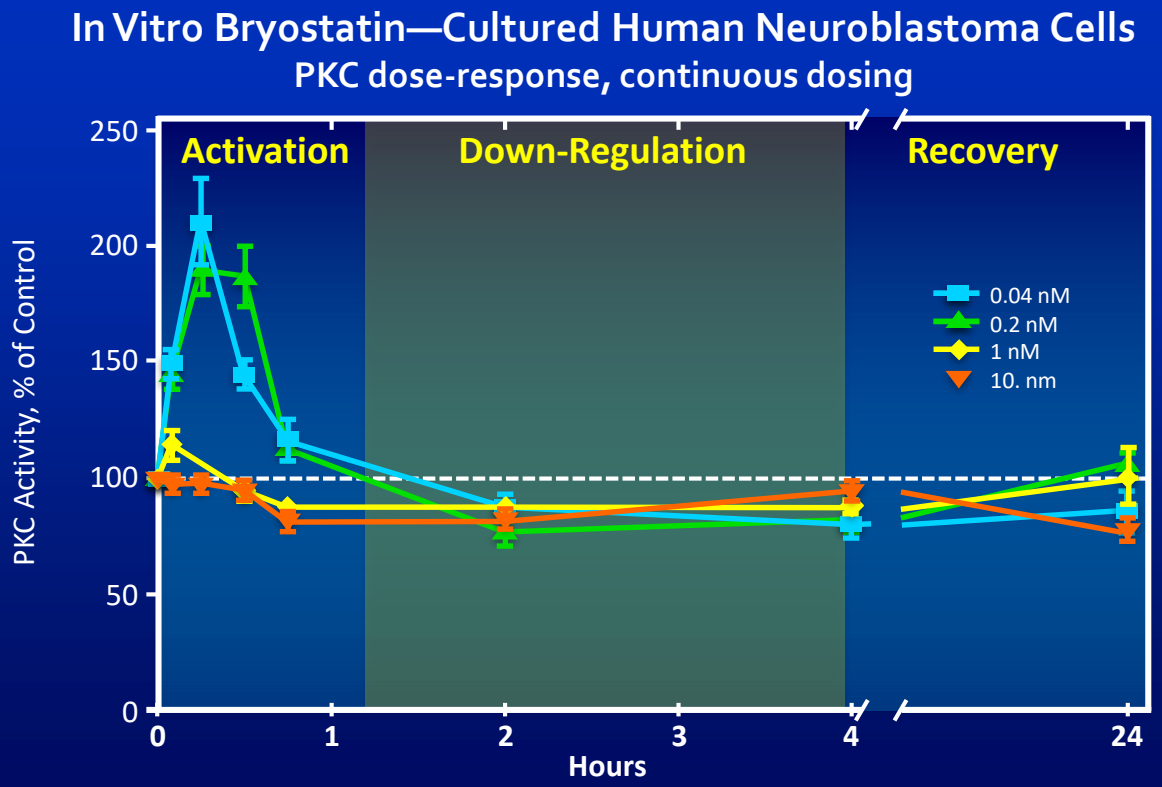
[b]Effects also observed in rabbits, mice & invertebrates
NS=Not significant; TG=Transgenic.
Hongpaisan J et al. *J Neurosci.* 2011;31(2):630-643.

Bryostatin:

PKC Activity Profile in Vitro—Initial Activation, Prolonged Down-Regulation & Recovery



Personal Communication, Daniel L. Alkon, MD

Bryostatin:
Phase 2 Study Report

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Assessing the Safety, Tolerability & Efficacy of Bryostatin in the Treatment of Moderately Severe to Severe Alzheimer's Disease

Bryostatin Phase 2: Objectives

- Primary objective: Assess safety & tolerability, bryostatin vs placebo
- Secondary objectives:
  - Dosing
  - Efficacy at week 13:
    - SIB (primary efficacy end point)
    - ADCS-ADL-SIV

ADCS-ADL-SIV=Alzheimer's Disease Cooperative Study-Activities of Daily Living-Severe Impairment Version; SIB=Severe Impairment Battery.

Bryostatin Phase 2:
Trial Design

- Double-blind, randomized, placebo-controlled trial
- Moderate-to-severe & severe patients (MMSE 4 – 15)
- Stable background therapy with cholinesterase inhibitors &/or memantine allowed
- Three arms (1:1:1)
  - 20µg & 40µg dose levels, placebo
  - 7 doses over 12 weeks: 0*, 1*, 3, 5, 7, 9, 11
  - Efficacy evaluated at weeks 5, 9, 13 (primary end point)

MMSE=Mini-Mental State Examination

*Doses increased 20% for first 2 doses

Bryostatin Phase 2:
Statistical Analysis Plan

- Primary analysis: Mixed Model for Repeated Measures (MMRM) of SIB at week 13
  - Two prespecified primary analysis populations:
    - mITT[a] (at least 1 dose given, at least 1 on-treatment efficacy assessment)
    - Completers: mITT population, completed week 13 assessment
- Screening trial[1]
  - Sample size based on safety
  - 80% power to detect a 6.5 point treatment benefit in SIB
    - $\alpha = 0.1$, one-sided

[a]mITT population: modified intention to treat population

[1]Fleming TR, Richardson BA. *J Infect Dis.* 2004;190(4):666-674.

Bryostatin Phase 2: Analysis Populations

	Placebo	Bryostatin 20µg	Bryostatin 40µg
Randomized Population	50	49	48
Safety Analysis Population (≥ 1 dose)	48	46	47
Completed study	39 (81.3)	38 (82.6)	29 (61.7)
Withdrew early from the study	9 (18.8)	8 (17.4)	18 (38.3)
mITT Population (≥1 dose, ≥1 eff eval)	46	44	45
Completer Analysis Population[a]	42	38	33

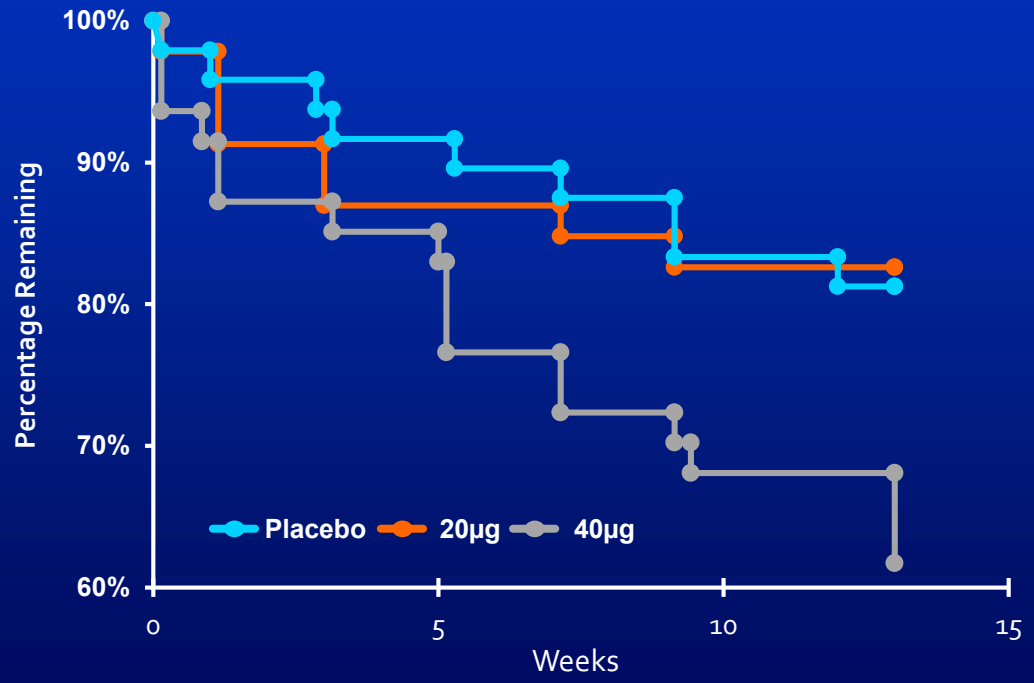
[a.] 7 subjects withdrew early but met prospective criteria for inclusion in the Completer Analysis Population (ie had a week 13 assessment).

Bryostatin Phase 2:
Early Withdrawals

	Placebo	Bryostatin 20µg	Bryostatin 40µg
Withdrew early from the study	9 (18.8)	8 (17.4)	18 (38.3)
Primary reason for early withdrawal			
Noncompliance with the protocol	1 (2.1)	0 (0.0)	1 (2.1)
Adverse event	5 (10.4)	2 (4.3)	4 (8.5)
Investigator termination	1 (2.1)	1 (2.2)	0 (0.0)
Withdrawal of consent	2 (4.2)	4 (8.7)	12 (25.5)
Other	0 (0.0)	1 (2.2)	1 (2.1)

Bryostatin Phase 2:
Dropouts by Time & Dose

Lower dropouts for 20µg & placebo arms vs 40µg arm



Bryostatin Phase 2:

Treatment Emergent Adverse Events (TEAEs)[a]

20µg dose, but not the 40µg dose, had an acceptable safety profile

	Placebo (N=48)	Bryostatin 20 µg (N=46)	Bryostatin 40 µg (N=47)	All Bryostatin (N=93)
Serious AE	3 (6%)	1 (2%)	6 (13%)	7 (8%)
Fatal AE[b]	0	0	1 (2%)[b]	1 (1%)[b]
Any TEAE	28 (58%)	30 (65%)	39 (83%)	69 (74%)
• Myalgia	0	1 (2%)	4 (9%)	5 (5%)
• Diarrhea	1 (2%)	5 (11%)	5 (11%)	10 (11%)
• Fatigue	0	1 (2%)	5 (11%)	6 (7%)
• Infusion site reaction	3 (6%)	8 (17%)	7 (15%)	15 (16%)
• Decreased appetite	2 (4%)	1 (2%)	6 (13%)	7 (8%)
• Weight decreased	0	0	5 (11%)	5 (5%)
• Fall	1 (2%)	1 (2%)	4 (9%)	5 (5%)

[a]TEAEs occurring in >5% in any treatment group and with treatment differences
[b]Fatal AE: Considered unrelated to study drug.

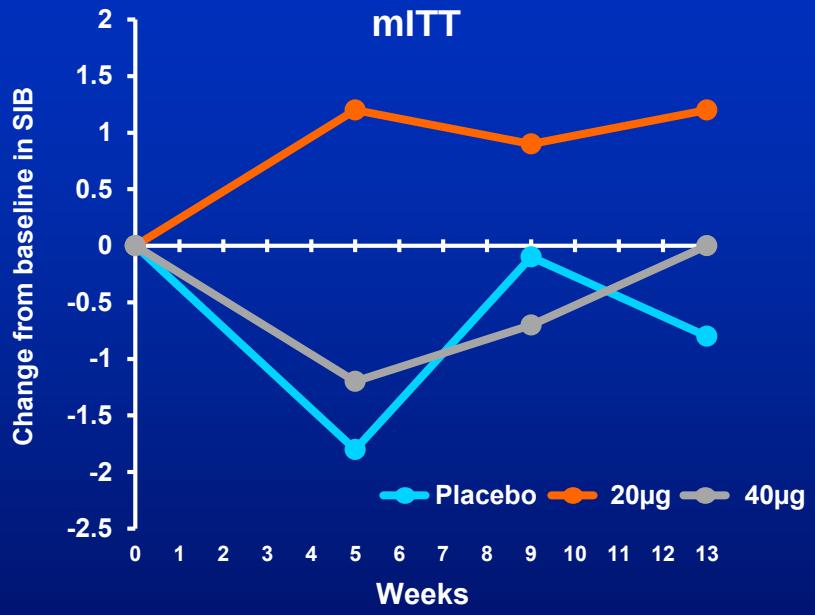
Bryostatin Phase 2:
Subject Demographics & Baseline Data (mITT)

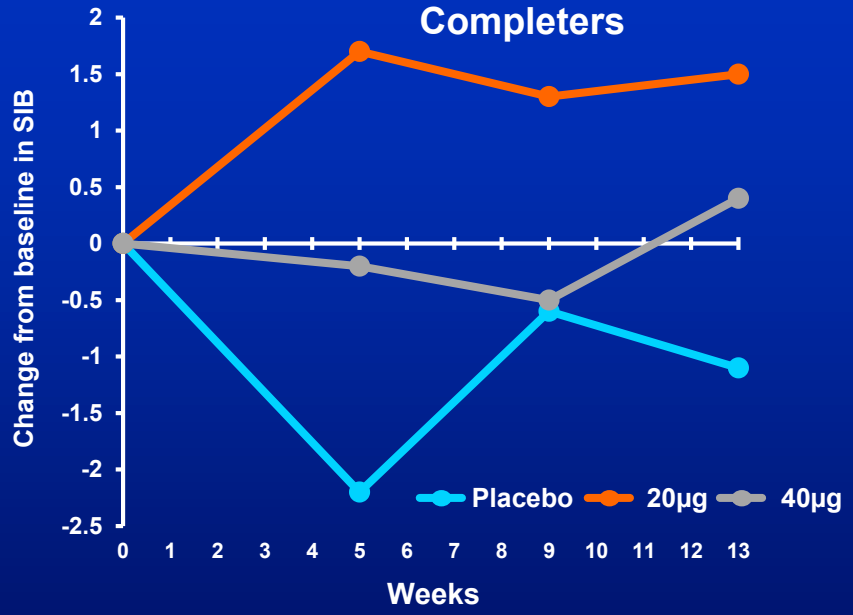
Large % of patients on stable concurrent AD drug treatment

	Placebo (N=46)	Bryostatin, 20 µg (N=44)	Bryostatin, 40 µg (N=45)
Age (mean, sd)	73.4 (7.67)	71.2 (8.20)	70.1 (7.66)
Sex (women, %)	48%	60%	49%
MMSE (mean, sd)	10.0 (3.48)	10.5 (3.25)	10.1 (3.48)
SIB (mean, sd) Range	76.2 (16.70) 27 - 99	79.0 (17.73) 13 - 97	76.2 (19.64) 11 - 96
Years AD diagnosed (mean, sd)	5.5 (2.95)	4.6 (3.05)	5.1 (2.73)
Concurrent AD Drugs n (%)			
Acetylcholinesterase inhibitor	38 (83%)	36 (82%)	38 (84%)
Memantine	30 (65%)	25 (57%)	36 (80%)
Both	28 (61%)	21 (48%)	30 (67%)
None	6 (13%)	4 (9.1%)	1 (2.2%)

SIB Change From Baseline—mITT & Completer Analyses at 13 Weeks

Consistency of effect for 20μg vs placebo across all time points



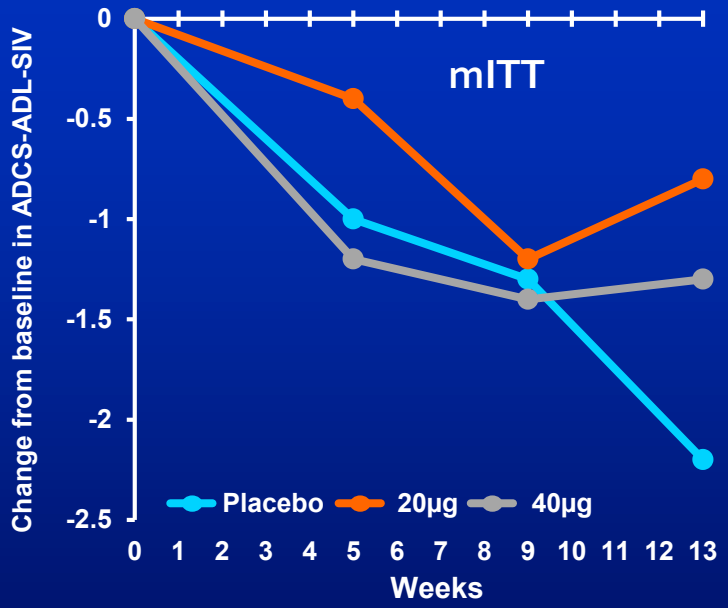


	Week 5	Week 9	Week 13
Difference 20 μg	3.0	1.0	1.9
1-sided p-value	0.056	0.290	0.134
Difference 40 μg	0.6	-0.6	0.8
1-sided p-value	0.368	0.638	0.314

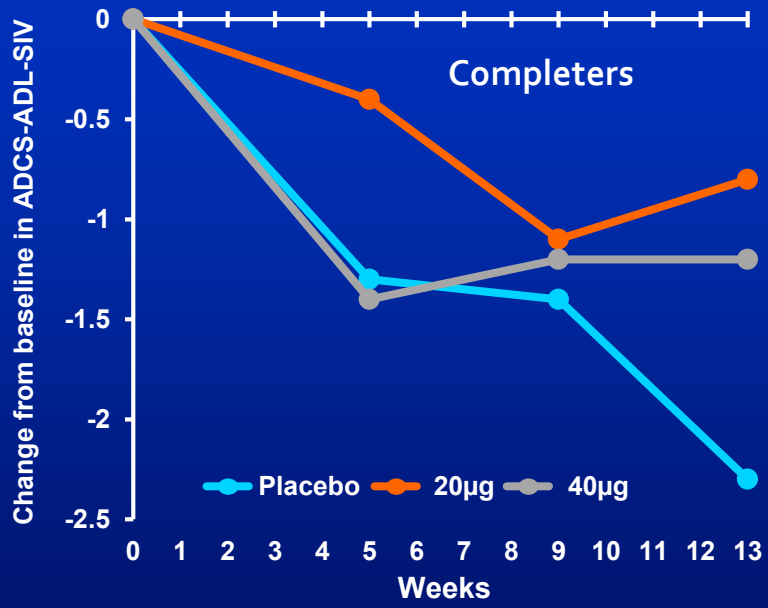
	Week 5	Week 9	Week 13
Difference 20 μg	4.0	1.9	2.6
1-sided p-value	0.016	0.165	0.070
Difference 40 mg	2.1	0.1	1.5
1-sided p-value	0.137	0.476	0.191

ADCS-ADL-SIV Change From Baseline—mITT & Completer Analyses at 13 Weeks

ADCS-ADL–SIV treatment effect strongest at 13 weeks



	Week 5	Week 9	Week 13
Difference 20 µg	0.6	0.1	1.4
1-sided p-value	0.272	0.457	0.104
Difference 40 µg	-0.2	-0.2	0.8
1-sided p-value	0.572	0.560	0.235



	Week 5	Week 9	Week 13
Difference 20 µg	1.0	0.3	1.6
1-sided p-value	0.180	0.383	0.082
Difference 40 µg	-0.1	0.2	1.1
1-sided p-value	0.532	0.406	0.168

SIB & ADCS-ADL-SIV—mITT & Completer Analyses
Cohen's D Comparison[a]

Consistency in Cohen's D effect sizes across both the SIB & the ADCS-ADL-SIV scales

Effect Size: 0.20 = Small Effect, 0.50 = Medium Effect, 0.80 = Large Effect

	Placebo vs 20µg		Placebo vs 40µg	
	Delta	Cohen's D	Delta	Cohen's D
SIB mITT	1.9	**0.25**	0.8	0.10
SIB Completers	2.6	**0.34**	1.5	0.19
ADCS-ADL-SIV mITT	1.4	**0.28**	0.8	0.16
ADCS-ADL-SIV Completers	1.6	**0.32**	1.1	0.22

[a]Cohen's D effect size is the treatment group difference divided by the pooled standard deviation of the change scores, a Cohen's D of 0.30 is 30% of a standard deviation of difference between the groups. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.

Bryostatin Phase 2:
Summary & Conclusions

- Bryostatin is the first PKCε activator tested in AD clinical trials—a new MOA
- Bryostatin has multimodal effects in AD models—potential disease modifier
- Exploratory Phase 2 study designed to assess safety, dosing, & potential efficacy in moderate to severe AD
  - First placebo-controlled, multi-dose trial of bryostatin in AD patients
  - Safety & tolerability: better for 20µg than the 40µg dose
  - Efficacy : consistent treatment effect for SIB & ADCS-ADL-SIV at 13 weeks for the 20µg dose
  - Observed effects added onto standard-of-care regimens
- 20µg dose is appropriate for additional study

Bryostatin Phase 2:
Future Development

- Additional studies warranted:
  - Optimal dose finding & regimen
  - Larger study to assess efficacy
  - Longer treatment duration
  - Earlier stage disease

- Also exploring:
  - Follow-on studies for target engagement/biomarkers
  - Different routes of administration:
    - subcutaneous injection
    - oral