Results of a Phase 2 Randomized Withdrawal Study of Simufilam in Mild-to-moderate Alzheimer's Disease

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Author List and Disclosures

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- **Simufilam is drug candidate under development by Cassava Sciences, Inc. (Austin, TX).**
- **Clinical research with simufilam is funded by Cassava Sciences.**
- **I. Cohen, S. Malhotra and P. Patel are clinical site investigators for simufilam.**
- **B. Murray, L. Jones, A. Hernandez, E. Crow, M. Snyder, L. Burns and J. Kupiec are employees and equity holders of Cassava Sciences, as was the late N. Friedmann.**
- **S. Hendrix and C. Mallinckrodt are employees of Pentara and contributed clinical data analysis for studies of simufilam with funding from Cassava Sciences.**
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Simufilam Mechanism of Action

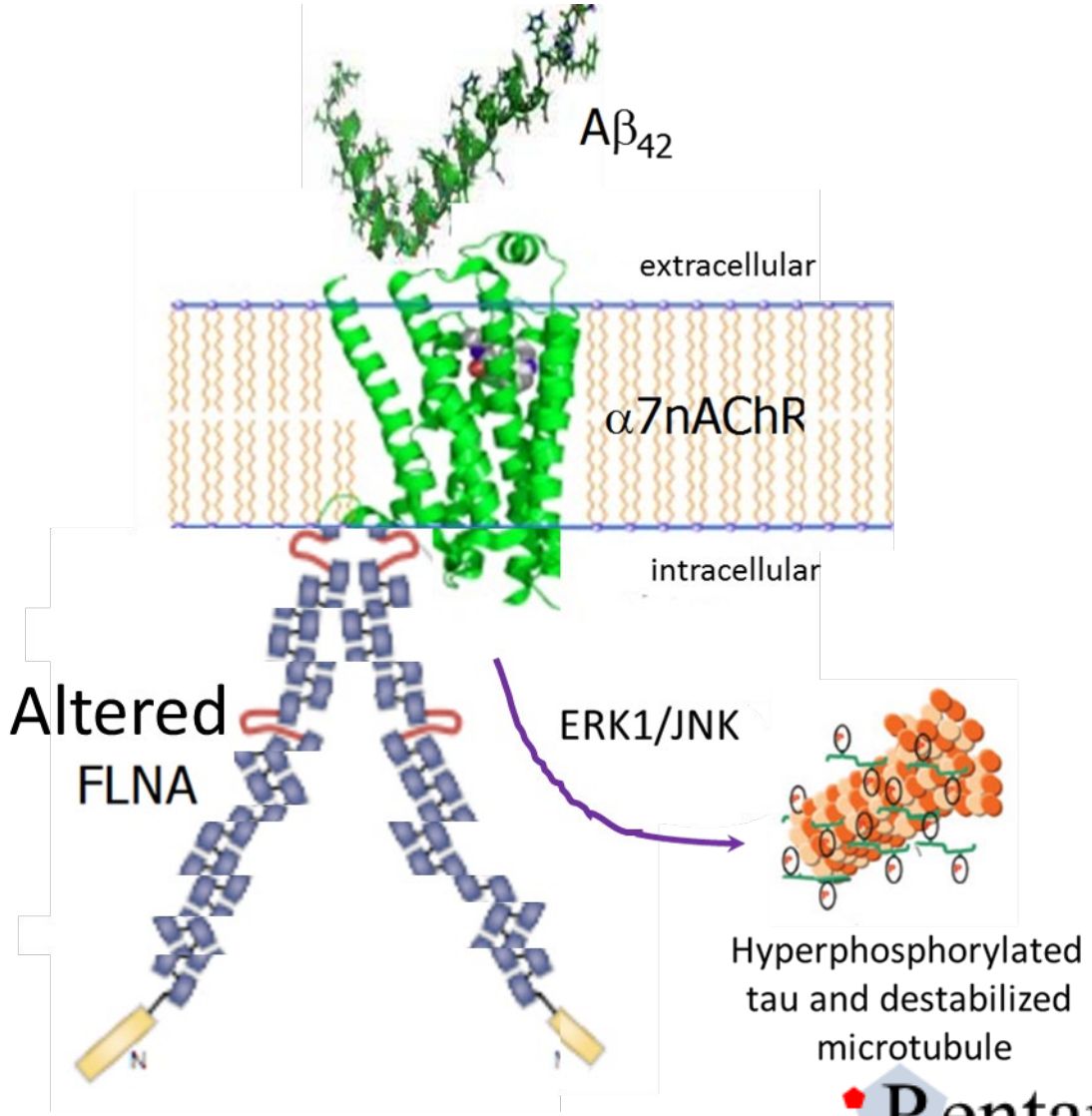
- **Altered FLNA enables Aβ_{42} signaling via two different receptors:**
  1) α7-nicotinic acetylcholine receptor (α7nAChR) → tau hyperphosphorylation
  2) Toll-like receptor 4 (TLR4) → releases inflammatory cytokines

- **Simufilam binds *altered* FLNA, restores its proper shape/function, potently suppressing Aβ_{42} signaling via α7nAChR and TLR4.**

- **Through a single target, simufilam reduces neurodegeneration and neuroinflammation.**

Altered FLNA links to α7-nicotinic acetylcholine receptor

- $A\beta_{42}$ binds α7nAChR and recruits FLNA, altering its shape.
- Altered FLNA linkage to α7nAChR enables a *femtomolar* affinity of $A\beta_{42}$ for α7nAChR and the signaling that hyperphosphorylates tau.



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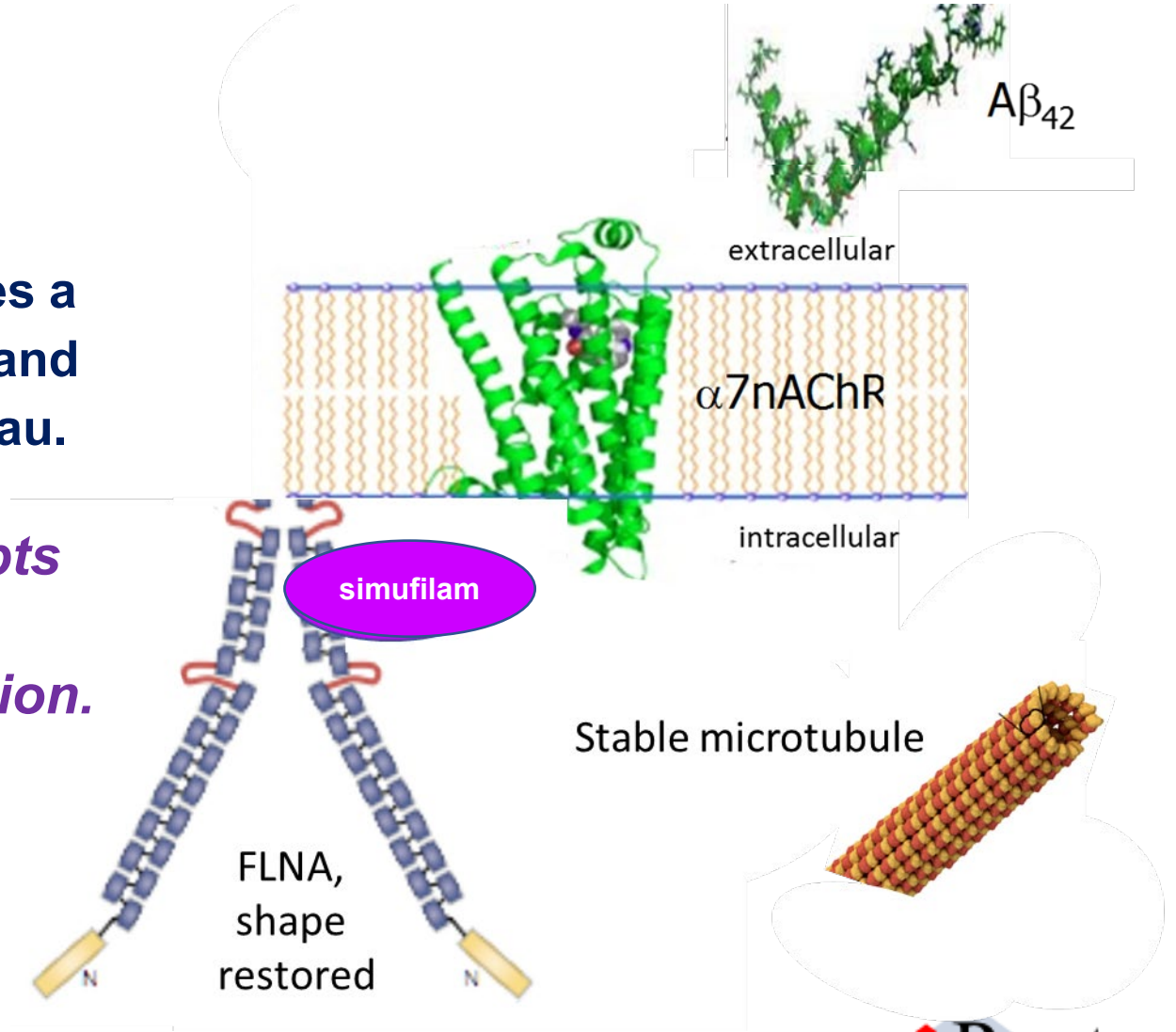
Simufilam binds altered FLNA, disrupts its linkage to α7nAChR, stops $A\beta_{42}$ signaling and tau hyperphosphorylation.



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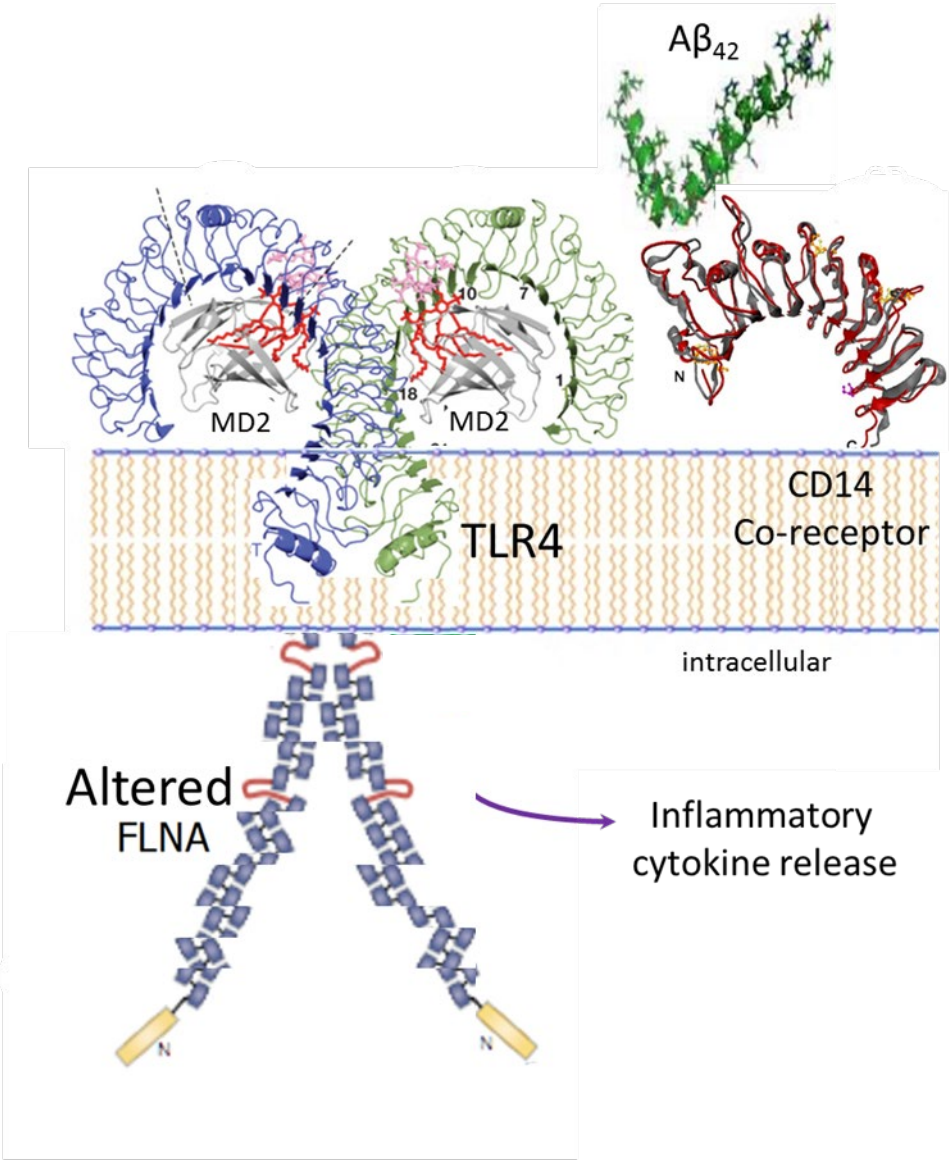
Altered FLNA links to toll-like receptor 4 (TLR4)

- **Altered FLNA linkage to TLR4 enables $A\beta_{42}$ to activate TLR4.**
- **Persistent TLR4 activation results in chronic neuroinflammation.**



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- **Altered FLNA linkage to TLR4 enables $A\beta_{42}$ to activate TLR4.**
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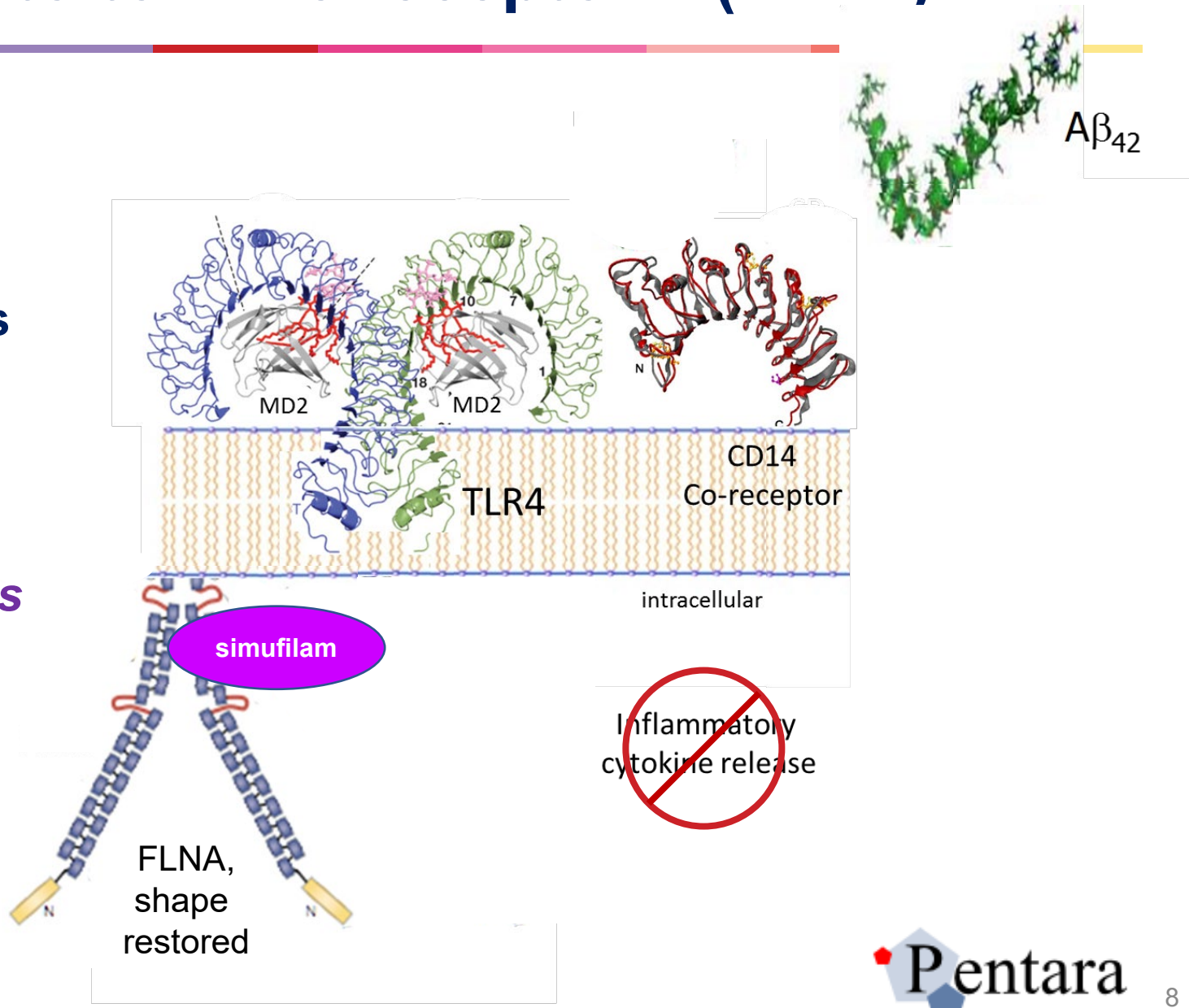
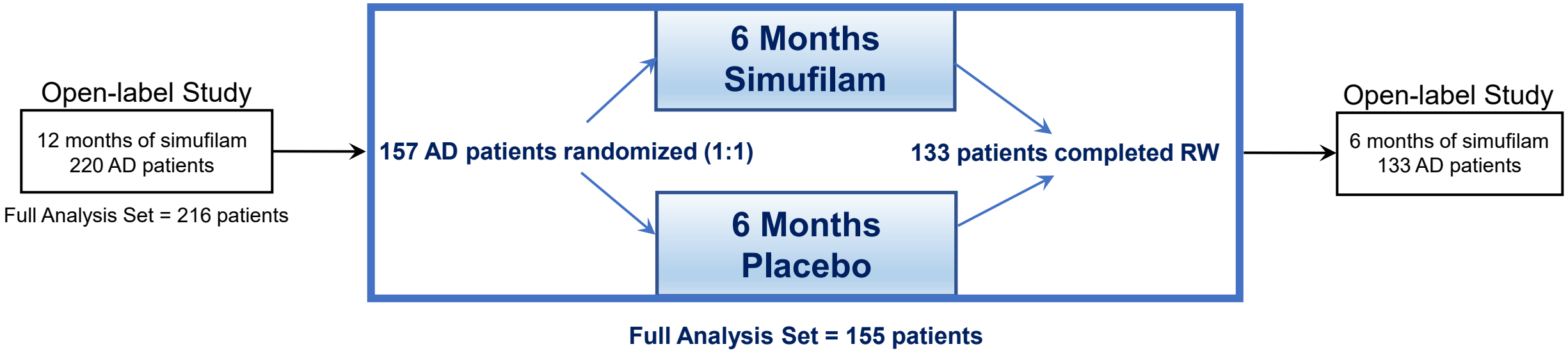
Simufilam binds altered FLNA, disrupts its linkage to TLR4, stops $A\beta_{42}$-induced neuroinflammation.



Randomized Withdrawal (RW) Study Design



- RW followed encouraging results in a 12-month open-label study.
- RW was designed to compare change in cognition over 6 months in AD patients who continue vs. those who discontinue simufilam.
- Any patient who completed 12-month open-label study was eligible to enroll in the RW.

Drug Safety

Adverse Events Observed in 12-month Open-label Study

	Occurrences	Patients N (%)
COVID-19	21	21 (9.5)
Urinary Tract Infection	23	20 (9.1)
Headache	22	17 (7.7)
Diarrhea	15	14 (6.4)
Hypertension	13	13 (5.9)
Insomnia	11	11 (5.0)
Dizziness	10	10 (4.5)
Fall	15	9 (4.1)
Depression	9	9 (4.1)
Nausea	9	8 (3.6)

Drug Safety

Adverse Events Observed in 6-month RW, ≥ 3 Occurrences

	Simufilam 100 mg (n=80)	Placebo (n=77)
Total number of AEs	77	92
COVID-19	5	4
Fall	1	4
Anxiety	2	2
Urinary Tract Infection	1	3
Hematuria	2	1
Headache	2	1

12-Month Open-label Period: Baseline Scores

	Mild (MMSE 21–30)	Moderate (MMSE 10–20)
	N=133	N=83
ADAS-Cog11		
Mean (SD)	15.0 (6.26)	25.7 (9.21)
Min, Max	3.0, 33.3	4.7, 51.7
MMSE		
Mean (SD)	23.8 (2.19)	17.8 (1.86)
Min, Max	21, 30	10, 20

Note: *Patients in prior simufilam studies could enroll in the open-label study regardless of MMSE. New patients were MMSE 16–26, or > 26 with a prior positive amyloid PET scan. This resulted in MMSE range 10–30.*

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12-Month Open-label Period: Top-line Summary

- **47% of patients improved on ADAS-cog.**
  - This group *improved* by a mean of – 4.7 points.
- **An additional 23% of patients declined < 5 points on ADAS-cog.**
  - This group declined by a mean of 2.5 points.
- **Mild patients improved over 12 months.**
  - Mild patients *improved* by a mean of – 0.73 points.
  - Moderate patients declined by a mean of 4.11 points.

Data presented are the Full Analysis Set.

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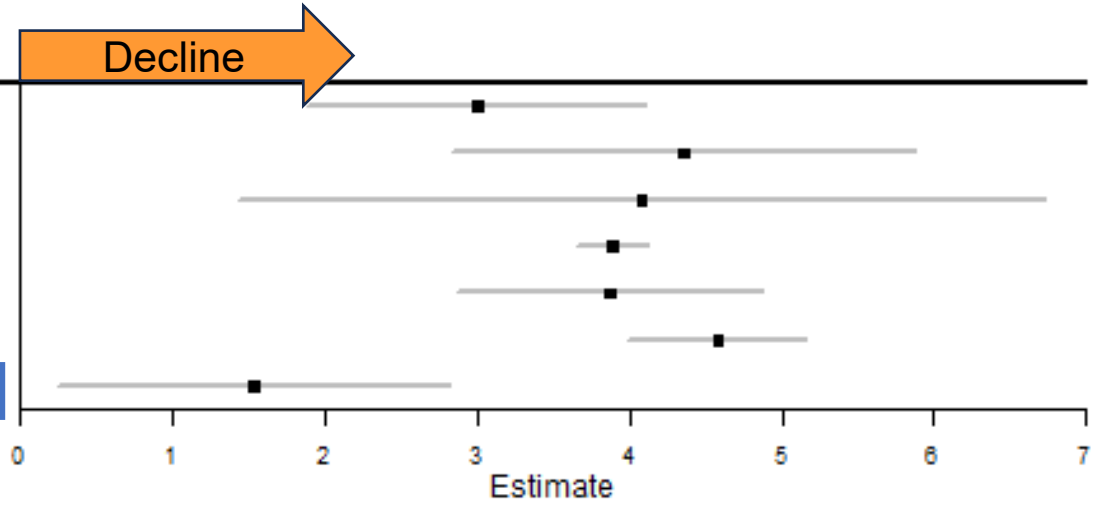
Simufilam vs. Historical Placebo in Mild-to-Moderate AD

Decline on ADAS-Cog, baseline to 12 months

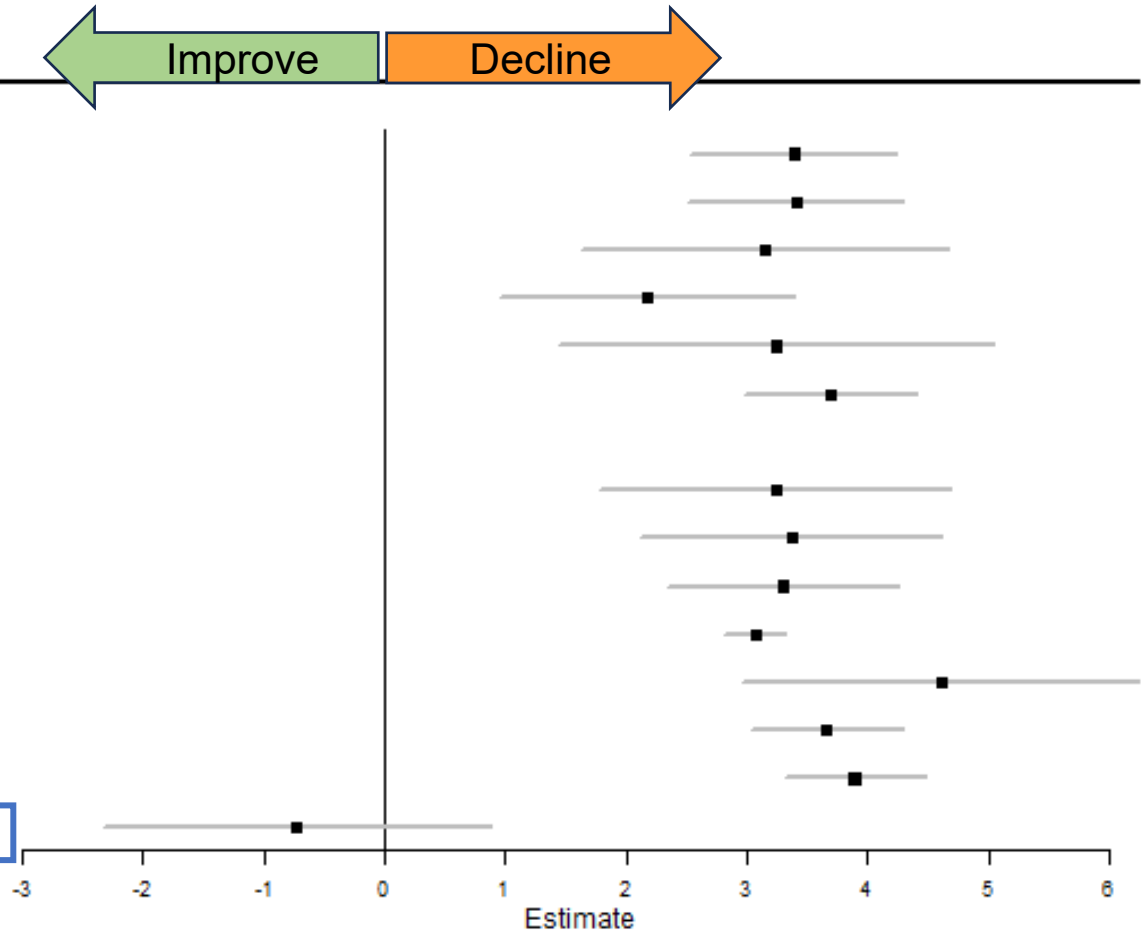
	Study		N	Decline	CI
Placebo	Solanezumab Expedition 1 Mild and Moderate		506	3	(1.89,4.11)
	Solanezumab Expedition 2 Mild and Moderate		519	4.36	(2.83,5.88)
	Solanezumab Expedition 1&2 Mild and Moderate		1025	4.08	(1.44,6.72)
	ADCS Studies Mild and Moderate (Thomas 2016)		3437	3.89	(3.65,4.13)
	Atuzaginstat Mild and Moderate (2022)		217	3.87	(2.87,4.87)
	Meta-analysis Mild and Moderate (Ito 2010)		19972	4.58	(3.99,5.16)
	Simufilam Mild and Moderate	Active	216	1.54	(0.25,2.82)



Simufilam vs. Historical Placebo in Early or Mild AD

Change in ADAS-Cog, baseline to 12 months

	Study	N	Change	CI
	Early AD			
Placebo	Aducanumab ENGAGE	545	3.39	(2.54,4.24)
Placebo	Aducanumab EMERGE	548	3.41	(2.52,4.29)
Placebo	Donanemab TRAILBLAZER-ALZ	90	3.15	(1.63,4.67)
Placebo	Gantenerumab Phase 3	266	2.17	(0.95,3.39)
Placebo	Lecanemab 201	247	3.25	(1.45,5.05)
Placebo	Lecanemab Clarity	859	3.7	(2.98,4.41)
	Mild AD			
Placebo	Solanezumab Expedition 1 Mild	338	3.24	(1.79,4.68)
Placebo	Solanezumab Expedition 2 Mild	325	3.37	(2.12,4.61)
Placebo	Solanezumab Expedition 1&2 Mild	663	3.3	(2.35,4.25)
* Placebo	ADCS Studies Mild (Thomas 2016)	2539	3.07	(2.82,3.32)
* Placebo	ADNI Mild (2022)	214	4.61	(2.97,6.25)
* Placebo	ADNI Mild (Ito 2011)	186	3.66	(3.03,4.3)
Placebo	Meta-analysis Mild (Ito 2010)	12303	3.89	(3.31,4.48)
Active	Simufilam Mild	133	-0.73	(-2.33,0.88)



* Observational studies

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Baseline Demographics in Randomized Withdrawal

	Simufilam	Placebo
N (M,F)	39, 41	34, 43
Mean Age (SD)	70.1 (8.3)	71.1 (7.9)
White, non-Hispanic (N,%)	59, 73.7%	61, 79.2%
Black (N,%)	1, 1.2%	1, 1.3%
Pacific Islander / Hawaiian (N,%)	0, 0%	1, 1.3%
Asian (N,%)	2, 2.5%	2, 2.6%
Hispanic or Latino (N,%)	18, 22.5%	13, 16.9%

157 patients enrolled; 155 in Full Analysis Set

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Randomized Withdrawal Baseline Scores

	Mild (MMSE 21 – 30)		Moderate (MMSE 4 – 20)	
	Placebo N=36	Simufilam N=39	Placebo N=41	Simufilam N=39
ADAS-Cog11				
Mean (SD)	11.0 (5.25)	11.2 (5.73)	31.5 (12.83)	27.9 (11.73)
Min, Max	2.7, 23.7	1.3, 28.3	12.0, 63.7	13.7, 56.0
MMSE				
Mean (SD)	25.1 (2.53)	25.3 (2.34)	14.4 (4.51)	15.2 (4.36)
Min, Max	21, 30	21, 30	5, 20	4, 20

Note: RW baseline follows the 12-month open-label study, which included some patients with baseline MMSE < 16 or > 26. MMSE range for the RW was 4–30.

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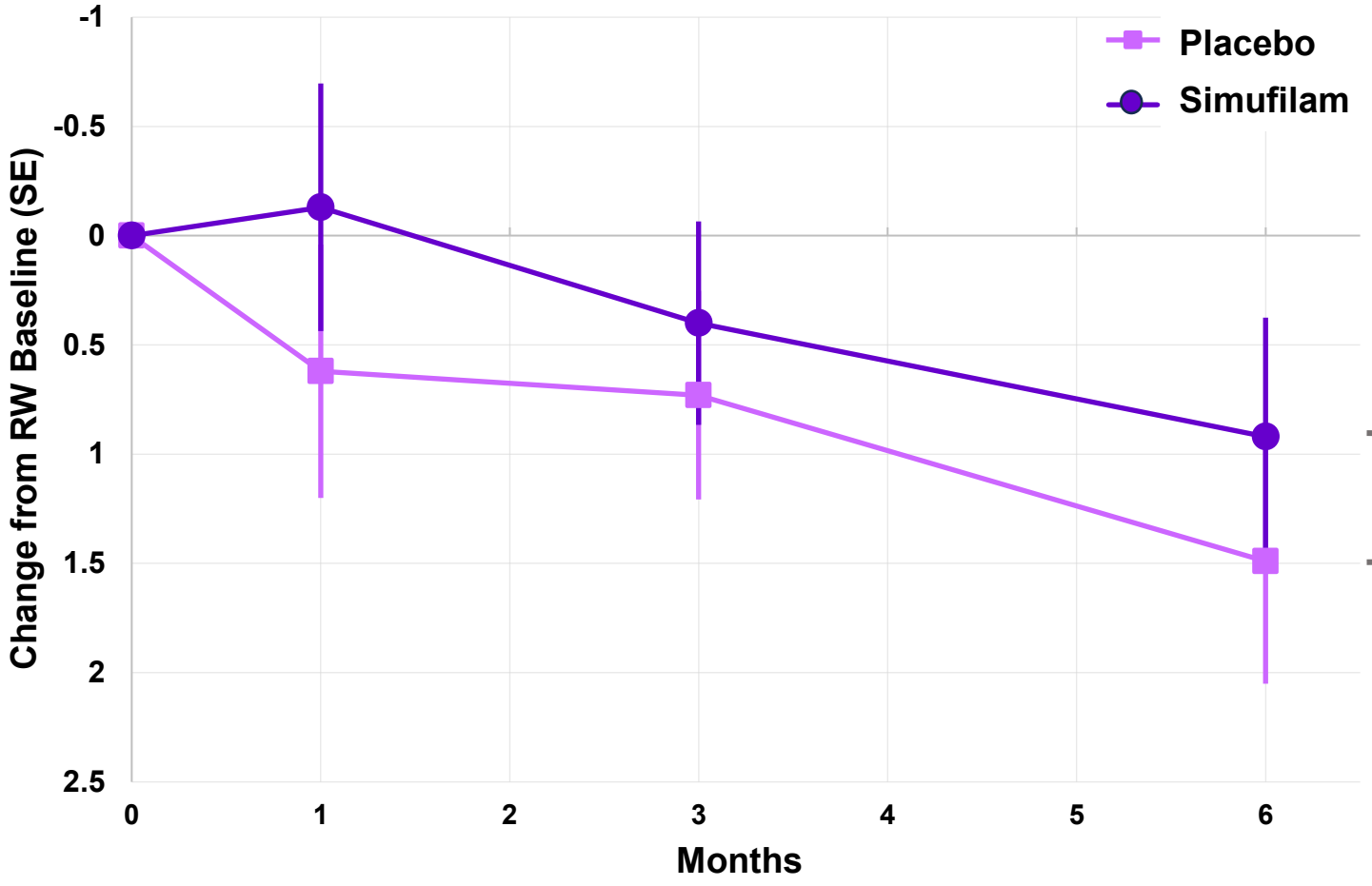
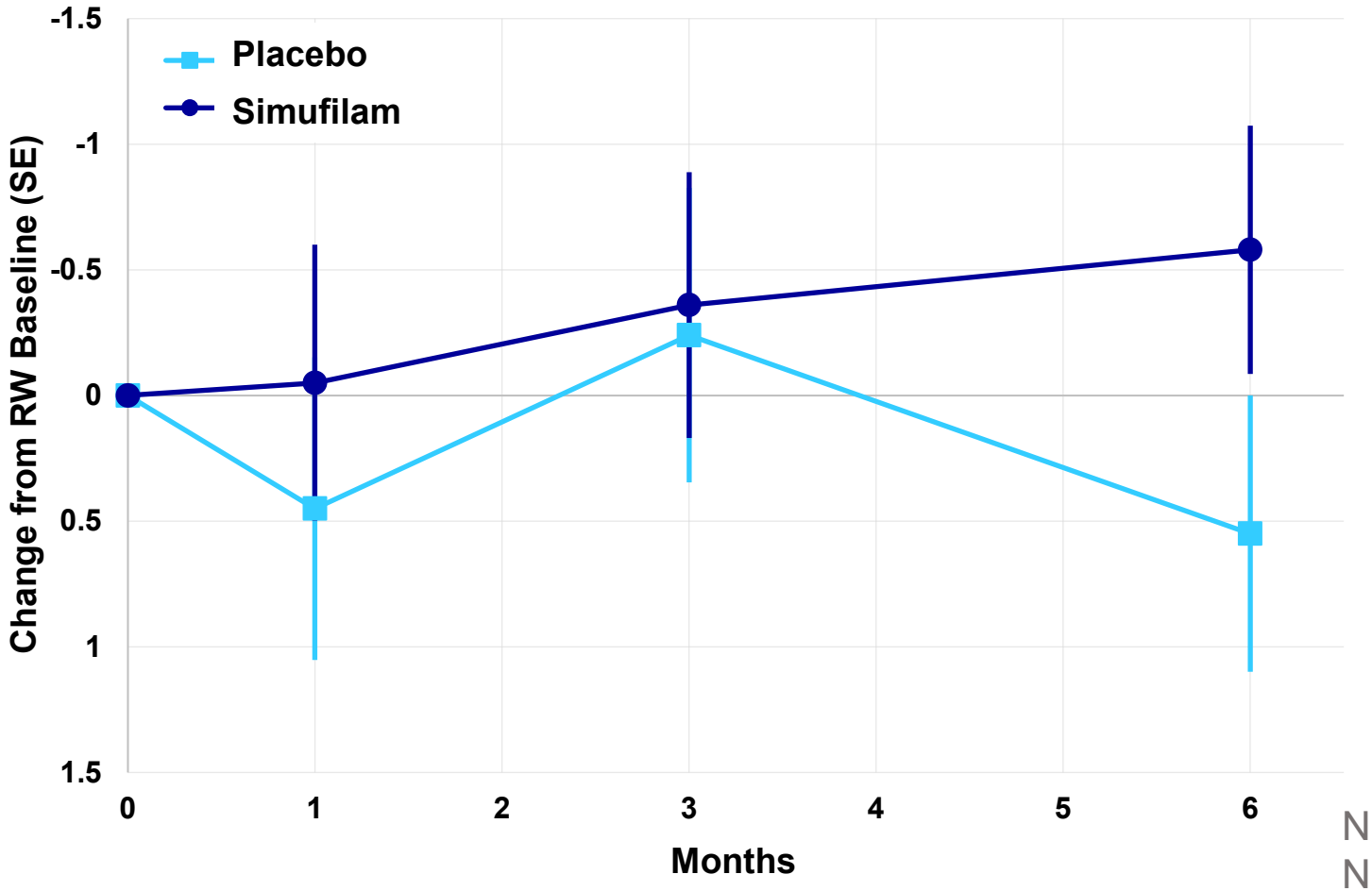
Change in ADAS-Cog11 in RW: Full Analysis Set



38% slowing of decline

N = 77 placebo
N = 78 simufilam

Change in ADAS-Cog11 in RW: Mild AD Patients



205% slowing of decline*

N = 36 placebo
N = 39 simufilam

** 100% slowing of decline + improvement*

Change in ADAS-Cog11 in Randomized Withdrawal

	LS Mean Difference at Month 6 (SE)	Confidence Interval (95%)	Percent Slowing of Decline	P value
Full Analysis Set	–0.56 (0.786)	–2.12, 0.99	38%	0.476
Mild AD Patients (MMSE 21 – 30)	–1.13 (0.745)	–2.63, 0.37	205%	0.136
Moderate AD Patients (MMSE 4 – 20)	0.15 (1.343)	–2.54, 2.84	none	0.912

Note: *The moderate subgroup included severe patients in both treatment arms. Greater difficulty in treating moderate or severe AD is expected.*

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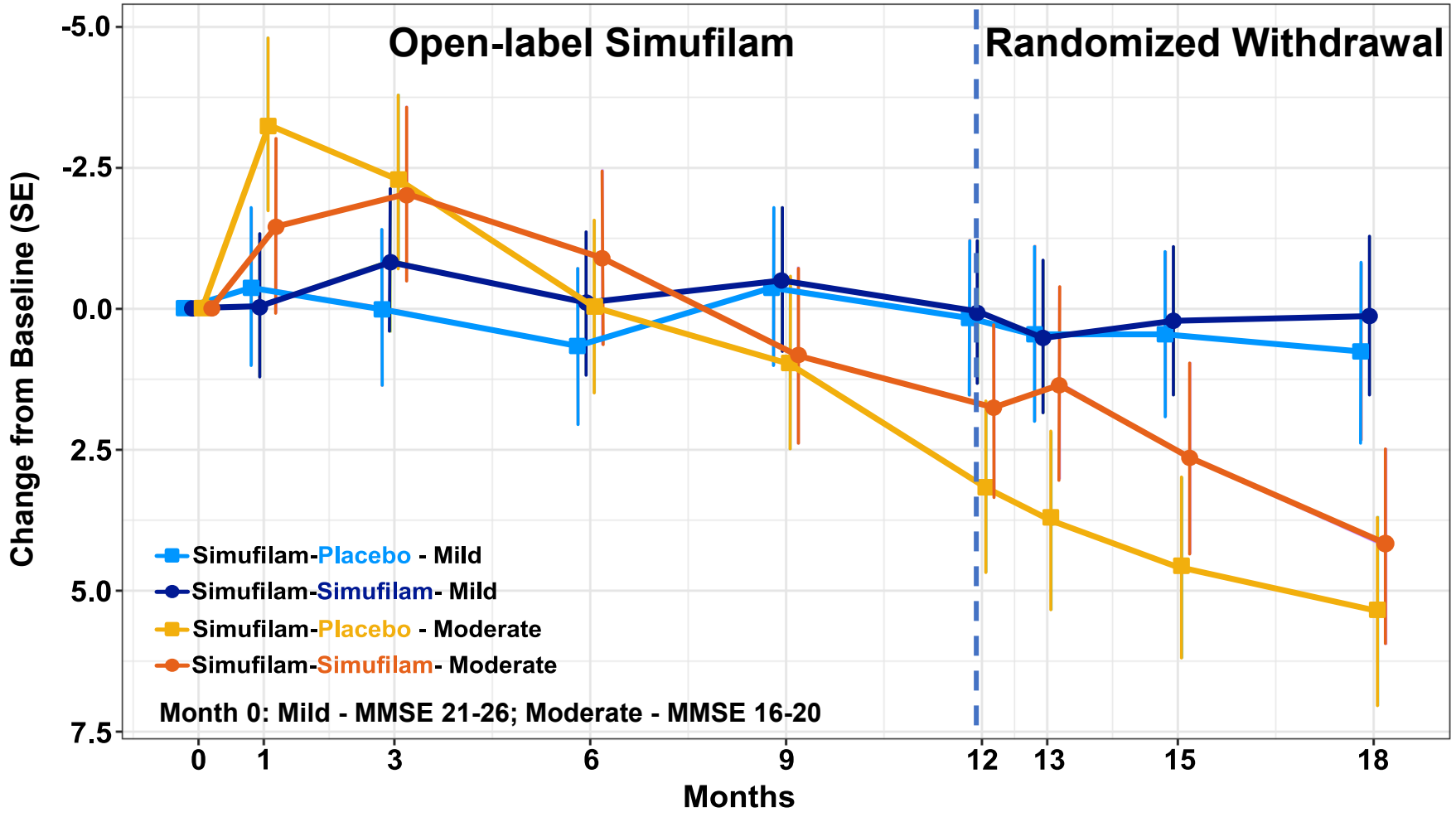
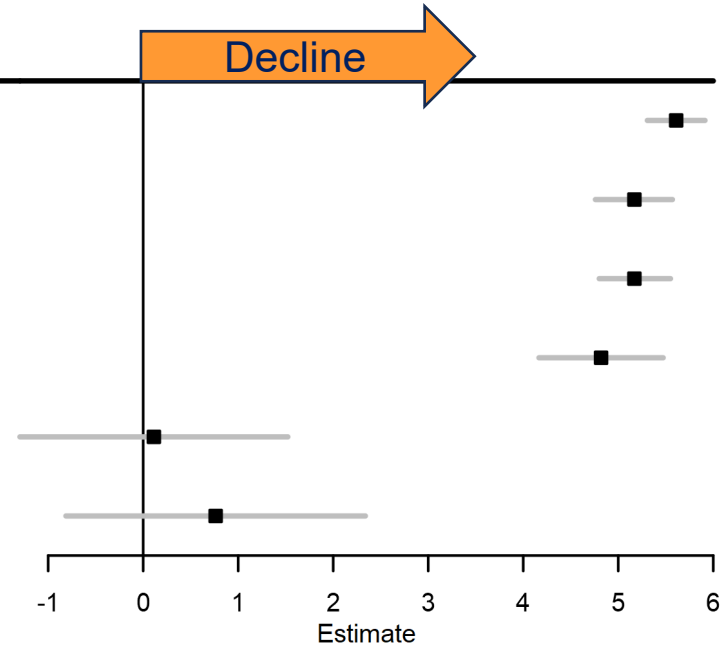
0-18 Months Change in ADAS-Cog11 in Mild vs. Moderate



Simufilam Mild vs. 18-month Early AD Historical Declines

Study	Treatment	MMSE Range	Change from Baseline Estimate	CI
CLARITY	Placebo	22-30	5.61	(5.31, 5.91)
EMERGE	Placebo	24-30	5.17	(4.76, 5.57)
ENGAGE	Placebo	24-30	5.17	(4.80, 5.55)
Trailblazer	Placebo	20-28	4.82	(4.17, 5.47)
PTI-125-04	Simufilam100mg-Simufilam100mg	21-26	0.11	(-1.30, 1.52)
PTI-125-04	Simufilam100mg-Placebo	21-26	0.76	(-0.81, 2.34)



The narrow margin between patients on simufilam for 18 months and those on simufilam and switched to placebo after 12 months is consistent with disease-modifying drug effects.

Summary of Randomized Withdrawal Results

- **Oral simufilam 100 mg appears safe and well-tolerated.**
- **Simufilam slowed cognitive decline by 38% on ADAS-Cog11 at 6 months vs. placebo (not statistically significant) in this study of mild-to-moderate AD.**
- **Simufilam appears to favor patients with mild AD.**
  - In patients with mild AD, simufilam slowed cognitive decline by 205% on ADAS-Cog11 at 6 months vs. placebo (p = 0.14 with N=36 and 39 respectively).
  - In patients with mild AD, simufilam stabilized ADAS-Cog11 scores over 18 months.

Next Steps

- **Oral simufilam is under clinical evaluation in two global, pivotal Phase 3 studies in a total of ~1,900 patients with mild-to-moderate AD dementia.**
    - RETHINK-ALZ is a 12-month study.
    - REFOCUS-ALZ is an 18-month study.
- **~ 60-70% of patients entered Phase 3 with mild AD (MMSE 21-27).**
- **Both Phase 3 studies received a Special Protocol Assessment (SPA) from FDA.**
- **Completion of enrollment in the pivotal Phase 3 program is expected Q4 2023.**

Thank you!