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Oral Simufilam in Mild-to-moderate Alzheimer's Disease: Baseline Characteristics in RETHINK and REFOCUS Phase 3 Trials

Lindsay Burns, PhD
SVP Neuroscience - Cassava Sciences, Inc.

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Forward-Looking Statements & Other Notices

Simufilam is our investigational drug product candidate. It is not approved by any regulatory authority in any jurisdiction and its safety, efficacy or other desirable attributes, if any, have not been established in patients. Data from our clinical studies to date are all inherently exploratory in nature, should be interpreted with caution and should not be interpreted as clinical evidence of therapeutic safety or benefit for simufilam.

Drug development involves a high degree of risk, and only a small number of research and development programs result in regulatory approval and subsequent commercialization of a product. In addition, our clinical results from earlier-stage clinical trials may not be indicative of full results or results from later-stage or large-scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on our earlier-stage clinical trial results we present or publish.

This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: the design, scope, conduct or intended purpose of our two-year, open-label safety study or Phase 3 program of simufilam in patients with Alzheimer's disease; the ability of simufilam to provide patients with drug effects; the apparent ability of simufilam to favor patients with mild Alzheimer's disease; the apparent safety or tolerance of simufilam in our open-label clinical trials; our current expectations regarding timing of clinical data for our Phase 3 studies; any expected clinical results of Phase 3 studies; the treatment of people with Alzheimer's disease dementia; the safety or efficacy of simufilam in people with Alzheimer's disease dementia; any findings or recommendations by the DSMB relating to the interim safety of simufilam in our on-going Phase 3 clinical trials; interim MRI safety data for the Phase 3 program, including ARIA; the risk of current or future findings of treatment-emergent ARIA in our clinical program of simufilam; the suitability of clinical data from our Phase 3 program to support the filing of an NDA; our ability to obtain FDA approval for simufilam, even with an NDA filing and positive clinical Phase 3 results and data; comments made by our employees regarding simufilam, drug effect, and the treatment of Alzheimer's disease; and potential benefits, if any, of our product candidates. These statements may be identified by words such as "may," "anticipate," "believe," "could," "expect," "would", "forecast," "intend," "plan," "possible," "potential," and other words and terms of similar meaning.

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Author List, Disclosures, Acknowledgements

Lindsay Burns, David Watson, C. Ian Cohen, R. Scott Turner, Po-Heng Tsai, Jonathan Liss, Anton Porsteinsson, Paul Solomon, Roger Clarnette, SangYun Kim, Antonio Hernandez, Tracy Owen, Carrie Crowley, Leslie Jones, Emmalee Crow, Melissa Snyder and James Kupiec

- Simufilam is a novel, small-molecule drug candidate wholly owned by Cassava Sciences, Inc. (Austin, Texas). This investigational drug candidate is not approved for the treatment of any health condition.
- Cassava Sciences is the sponsor of two on-going Phase 3 clinical trials of simufilam in Alzheimer's disease, named RETHINK-ALZ (NCT04994483) and REFOCUS-ALZ (NCT05026177).
- D. Watson, C.I. Cohen, R.S. Turner, P-H. Tsai, J. Liss, A. Porsteinsson, P. Solomon, R. Clarnette and SY Kim are independent trial site investigators for RETHINK or REFOCUS Phase 3 trials.
- L. Burns, A. Hernandez, T. Owen, C. Crowley, L. Jones, E. Crow, M. Snyder, and J. Kupiec are employees and equity holders of Cassava Sciences.
- Simufilam benefits from scientific and financial support from the NIA (AG050301, AG056166, AG060878, AG065152, AG067972).
- We would like to thank the patients, their families and caregivers who have participated in clinical studies of simufilam, along with trial site investigators and their staff, and vendor partners.

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Simufilam Phase 3 Program

- **Oral simufilam is a small molecule drug candidate under clinical evaluation in two global, pivotal Phase 3 studies in 1,929 patients with mild-to-moderate AD.**
  - rethinkALZ is a 12-month study
  - reFOCUSALZ is an 18-month study

- **Both Phase 3 studies are sponsored by Cassava Sciences and being conducted by Premier Research, an independent clinical research organization (CRO).**

- **Both Phase 3 studies are fully enrolled.**
  - ~ 70% of patients in each Phase 3 trial entered with mild AD (MMSE 20-27).

Two Parallel Phase 3 Trials

rethinkALZ

REducing Tau Hyperphosphorylation and INflammation Kinetically

A 52-week trial of simufilam 100 mg b.i.d or placebo (1:1) in 804 mild-to-moderate AD patients

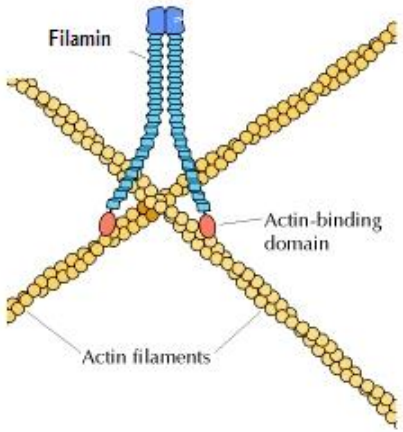
refocusALZ

REstoring Filamin A's nOrmal [CU] Shape

A 76-week trial of simufilam 50 mg or 100 mg b.i.d or placebo (1:1:1) in 1,125 mild-to-moderate AD patients

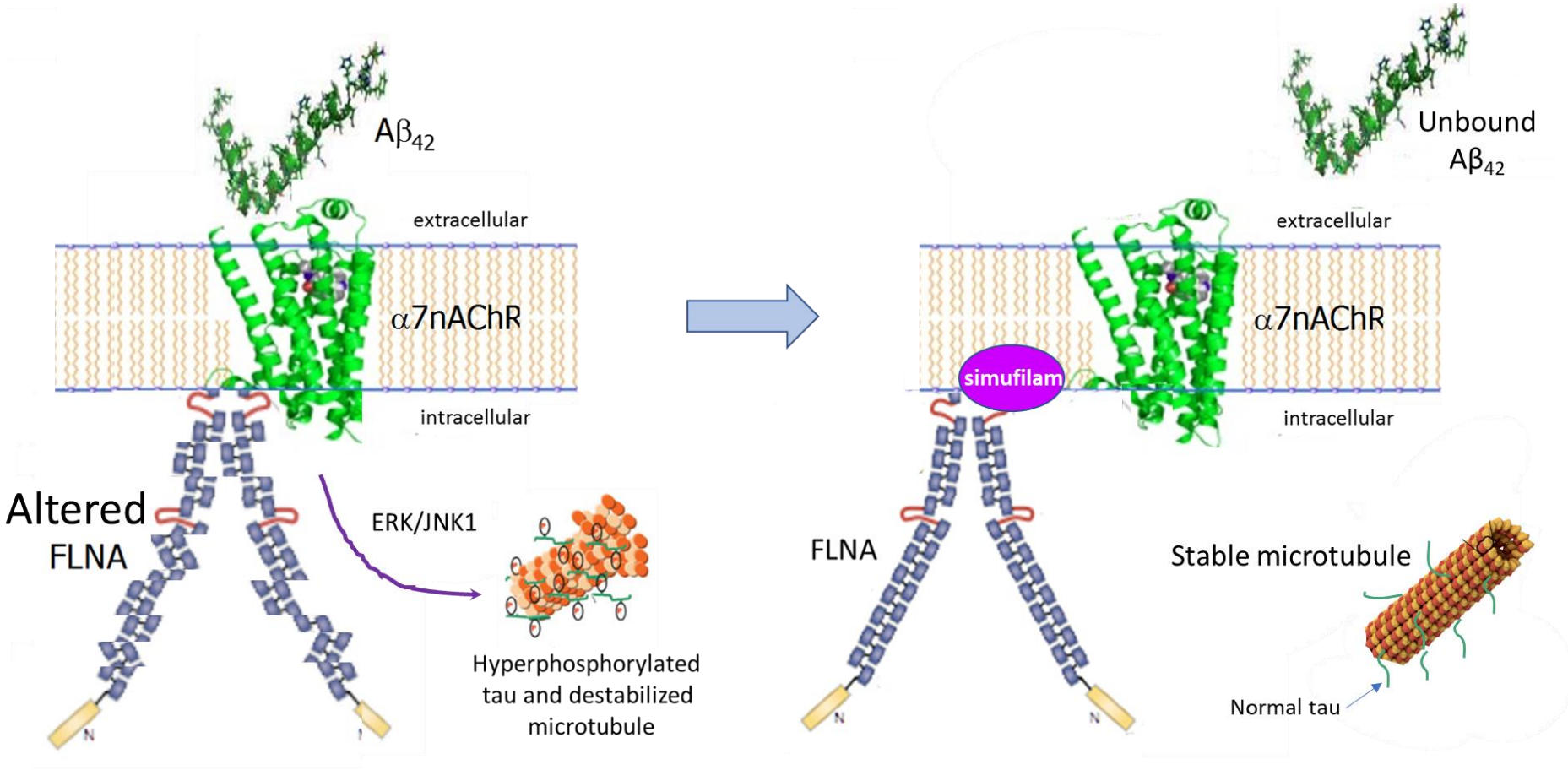
Simufilam Targets *Altered* Filamin A (FLNA)

- **FLNA is an intracellular scaffolding protein anchored in the cell membrane.**
- **FLNA interacts with > 90 different proteins, influencing many signaling pathways.**



- **The AD brain carries an *altered* conformation of FLNA, critical to $A\beta_{42}$ toxicity.**

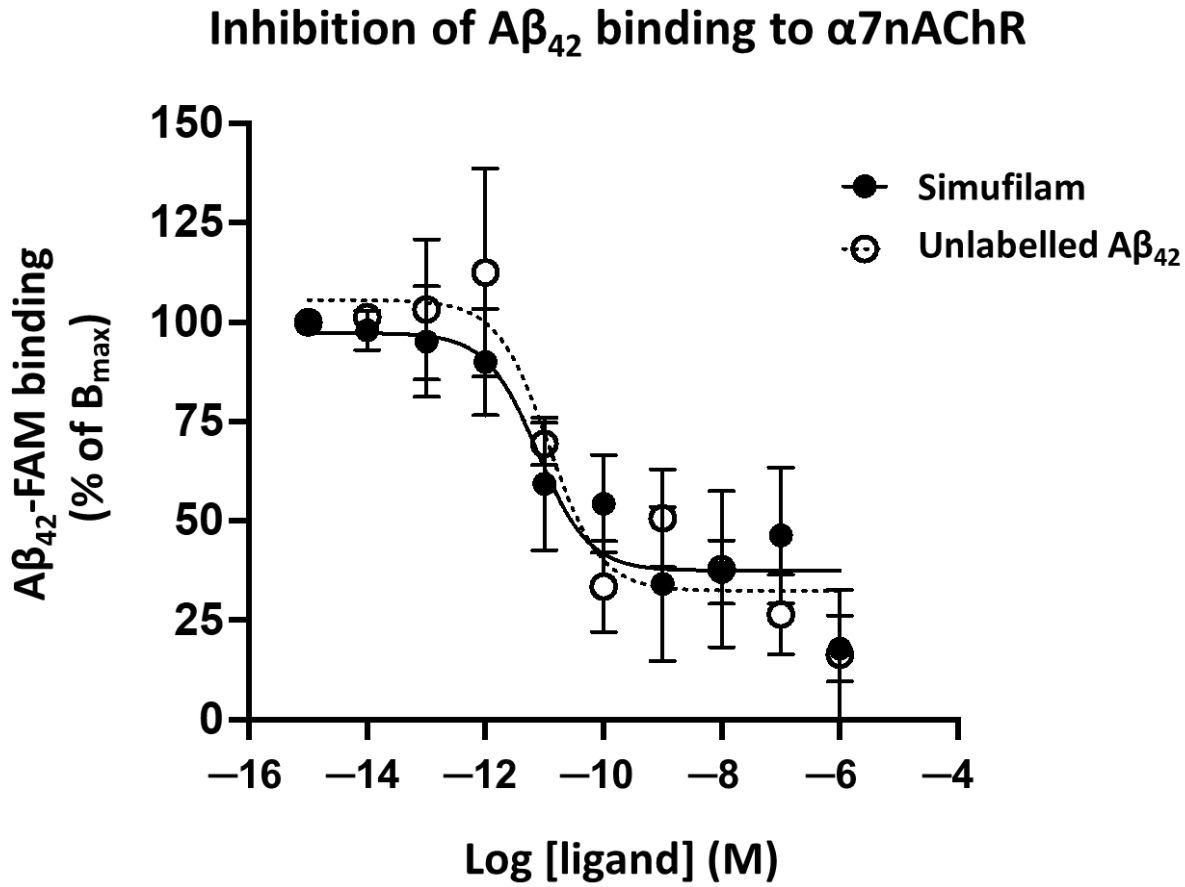
Altered FLNA links to α7nAChR to enable tau phosphorylation



Simufilam binds altered FLNA and restores its normal shape to disrupt both the FLNA linkage to α7nAChR and the $A\beta_{42}$ signaling that hyperphosphorylates tau.

Image from Burns et al 2023; ***Drug Dev Res*, 84:**1085-95.

Reduced $A\beta_{42}$ binding to α7nAChR shown by TR-FRET



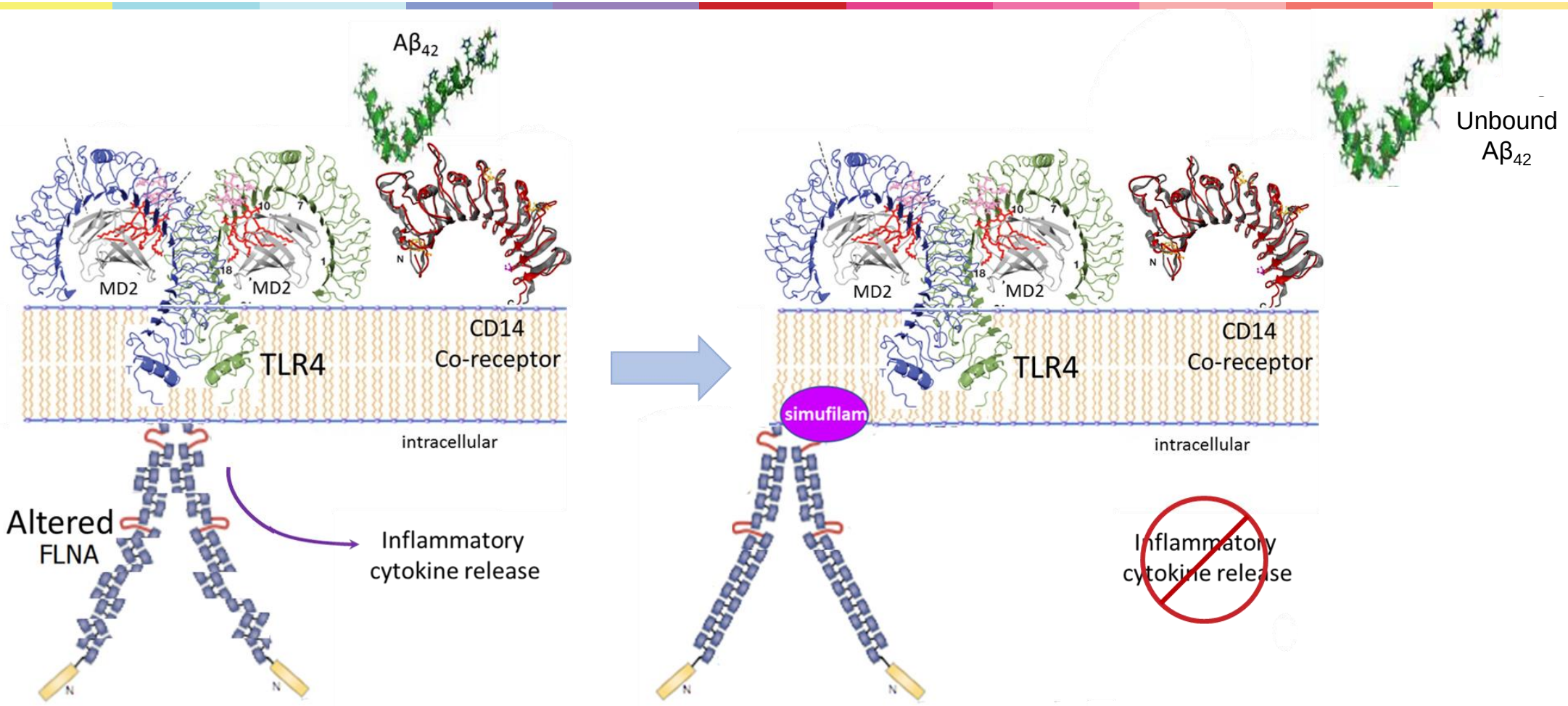
Experiment conducted by Erika Cecon of Université Paris Cité, Institut Cochin in an assay she developed:

Cecon et al 2019; *Br J Pharmacol;* **176**:3475-3488.

In a cell-based assay designed to test drug candidates' ability to disrupt $A\beta_{42}$ binding to α7nAChR, simufilam shows a 12 picomolar IC_{50} and is 92% as effective as unlabeled $A\beta_{42}$.

Figure 1 from Wang et al 2023; ***Int J Mol Sci, 24*:13927.**

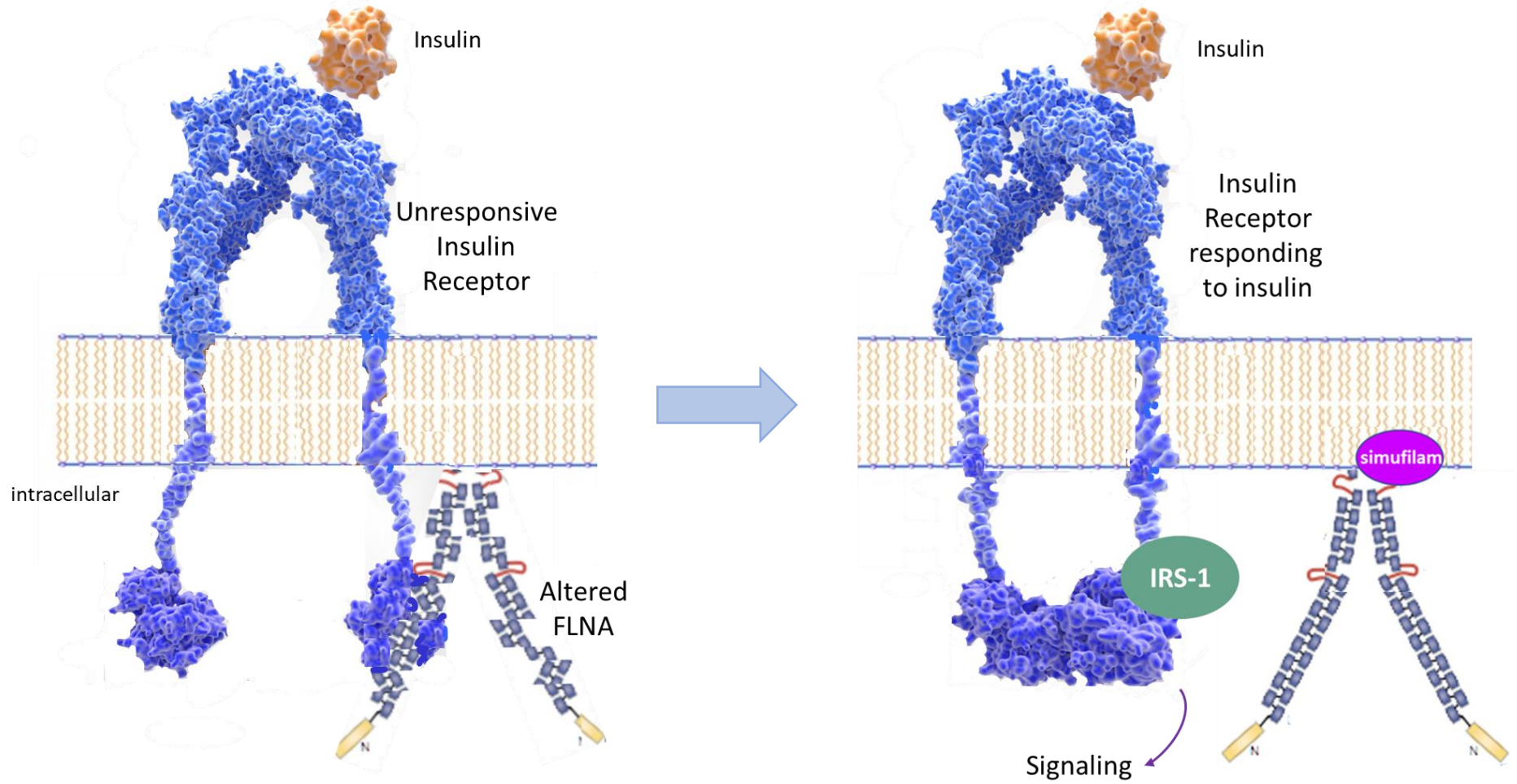
Altered FLNA links to TLR4 to enable neuroinflammation



Simufilam binds altered FLNA and restores its normal shape to disrupt both the FLNA linkage to TLR4 and its activation by $A\beta_{42}$ that causes neuroinflammation.

Additional inflammatory receptors described in Wang et al 2023; ***Int J Mol Sci, 24*:13927.**

Altered FLNA does not unlink from IR when insulin binds



Simufilam binds altered FLNA and restores its normal shape to allow its dissociation from IR upon insulin stimulation. This allows IRS-1 recruitment to IR and IR signaling.

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Described in Wang et al 2023; ***Front. Aging,*** **4:**1175601.

Simufilam Mechanism of Action Summary

- **Altered FLNA enables $A\beta_{42}$ signaling via two different receptors:**
  - 1) α7-nicotinic acetylcholine receptor (α7nAChR) → tau hyperphosphorylation
  - 2) toll-like receptor 4 (TLR4) → releases inflammatory cytokines
- **Altered FLNA also promotes insulin resistance in Alzheimer's brain.**
- **Simufilam binds *altered* FLNA, restores its proper shape/function, suppressing $A\beta_{42}$ signaling via α7nAChR and TLR4 and improving insulin receptor signaling.**
- **Through a single target, simufilam reduces neurodegeneration, neuroinflammation and brain insulin resistance.**

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Simufilam Phase 2 Trials in Mild-to-moderate AD

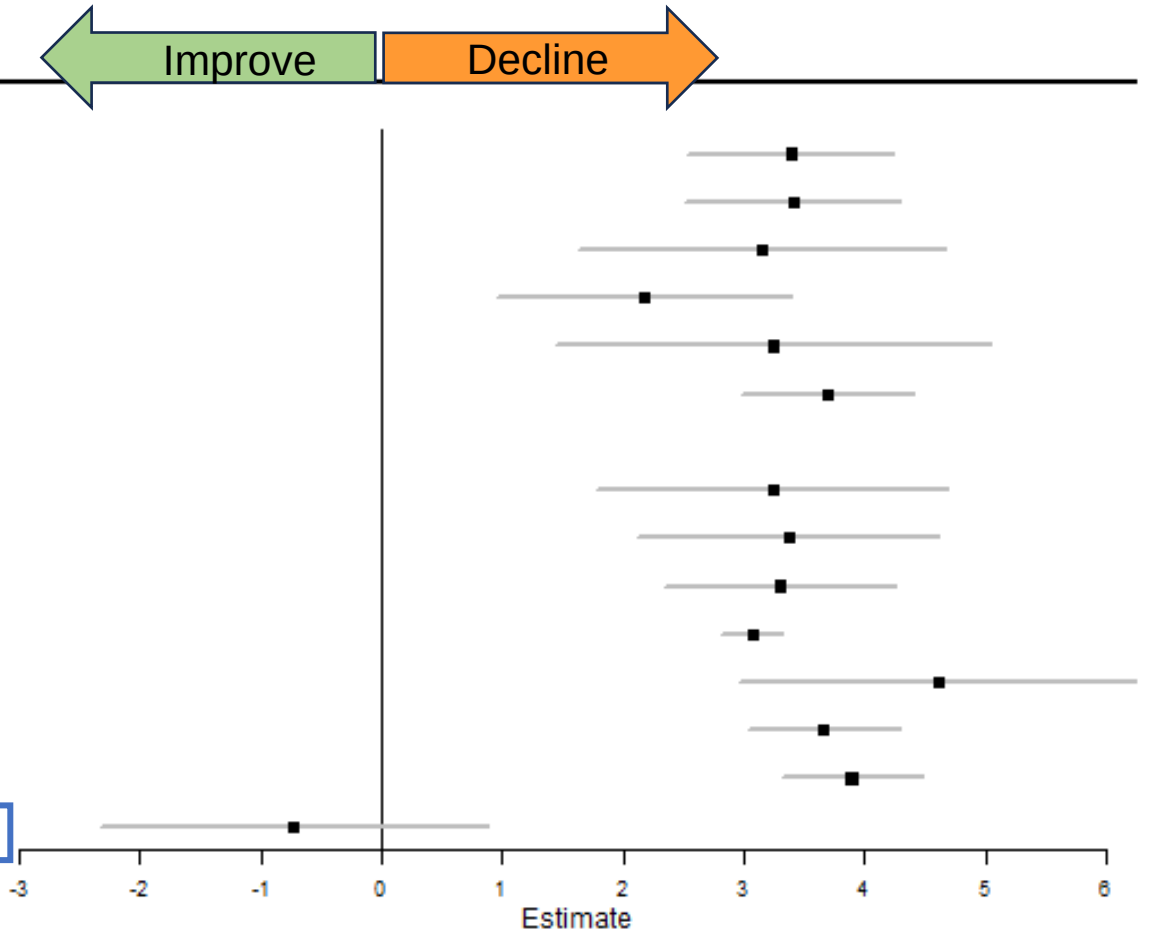
- **1-month, placebo-controlled safety trial of simufilam 50 & 100 mg in 64 patients**
  - Improvements observed in research-use-only CSF biomarkers
  - Encouraging effects on cognition (two tests of CANTAB battery)

- **12-month, open-label safety trial of simufilam 100 mg in 216 patients**
  - 47% of patients improved on ADAS-cog11.
  - Mild AD patients (MMSE 21-26) improved on ADAS-Cog11 by –0.73 points [95% CI –2.33 to 0.88].
  - Full Analysis Set (MMSE 16-26) declined on ADAS-Cog11 by 1.54 points [95% CI 0.25 to 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)
*	ADCS Studies Mild (Thomas 2016)	2539	3.07	(2.82,3.32)
*	ADNI Mild (2022)	214	4.61	(2.97,6.25)
*	ADNI Mild (Ito 2011)	186	3.66	(3.03,4.3)
	Meta-analysis Mild (Ito 2010)	12303	3.89	(3.31,4.48)
Active	Simufilam Mild	133	-0.73	(-2.33,0.88)



* Observational studies

Forest plot by Pentara Corporation. Data sourced from placebo groups in randomized, controlled trials of monoclonal antibodies in early or mild AD. Placebo data shown include trials of lecanemab (Eisai); EMERGE and ENGAGE P3 trials of aducanumab (Biogen); and TRAILBLAZER P3 trial of donanemab (Lilly).

Simufilam Phase 2 Trials in Mild-to-moderate AD

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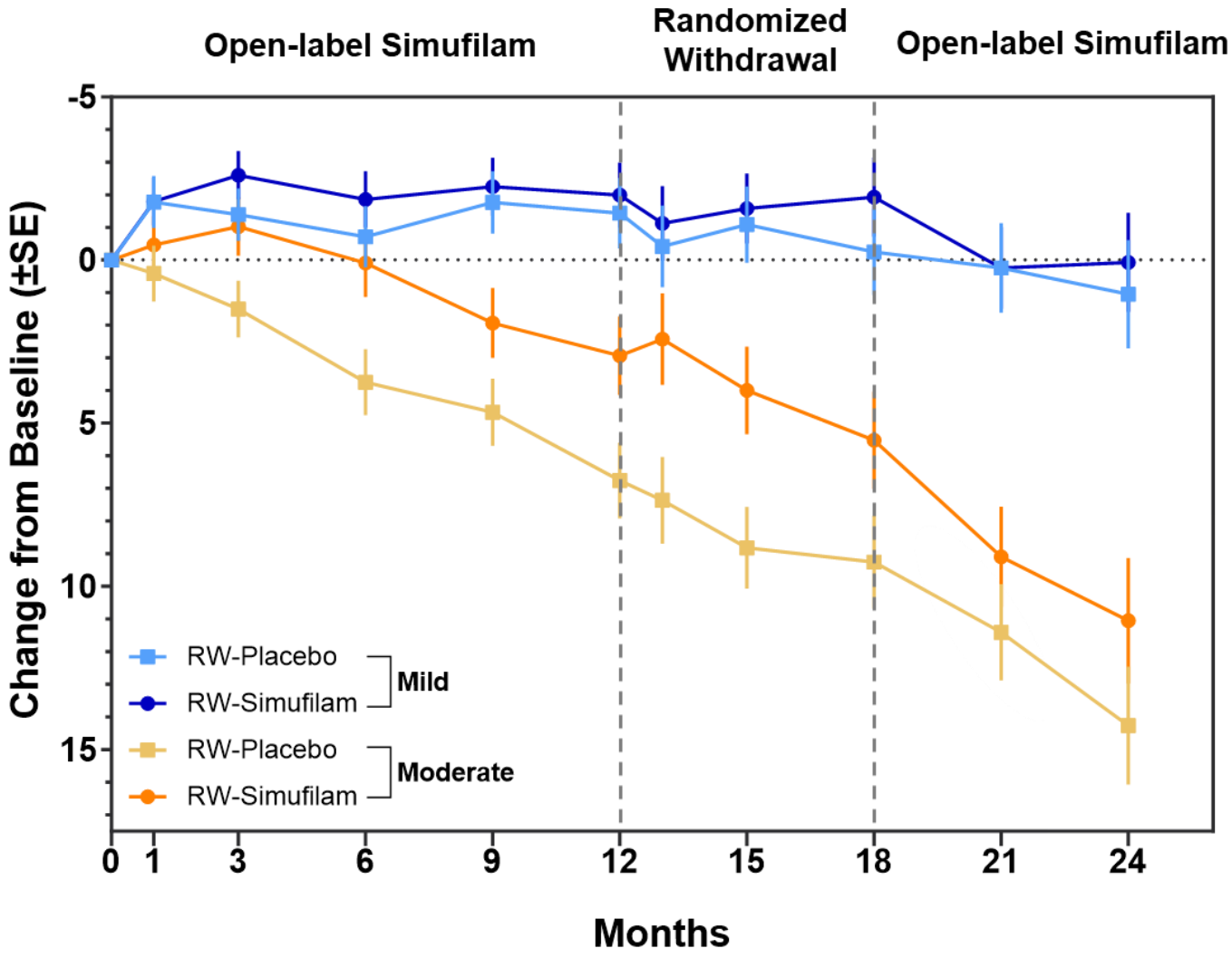
- **6-month, randomized withdrawal study in 154 patients**
  - In the Full Analysis Set, 38% slowing of decline versus placebo
  - In mild AD patients, an improvement on simufilam compared to a decline on placebo (p=0.14)

Change in ADAS-Cog11 in Mild vs. Moderate



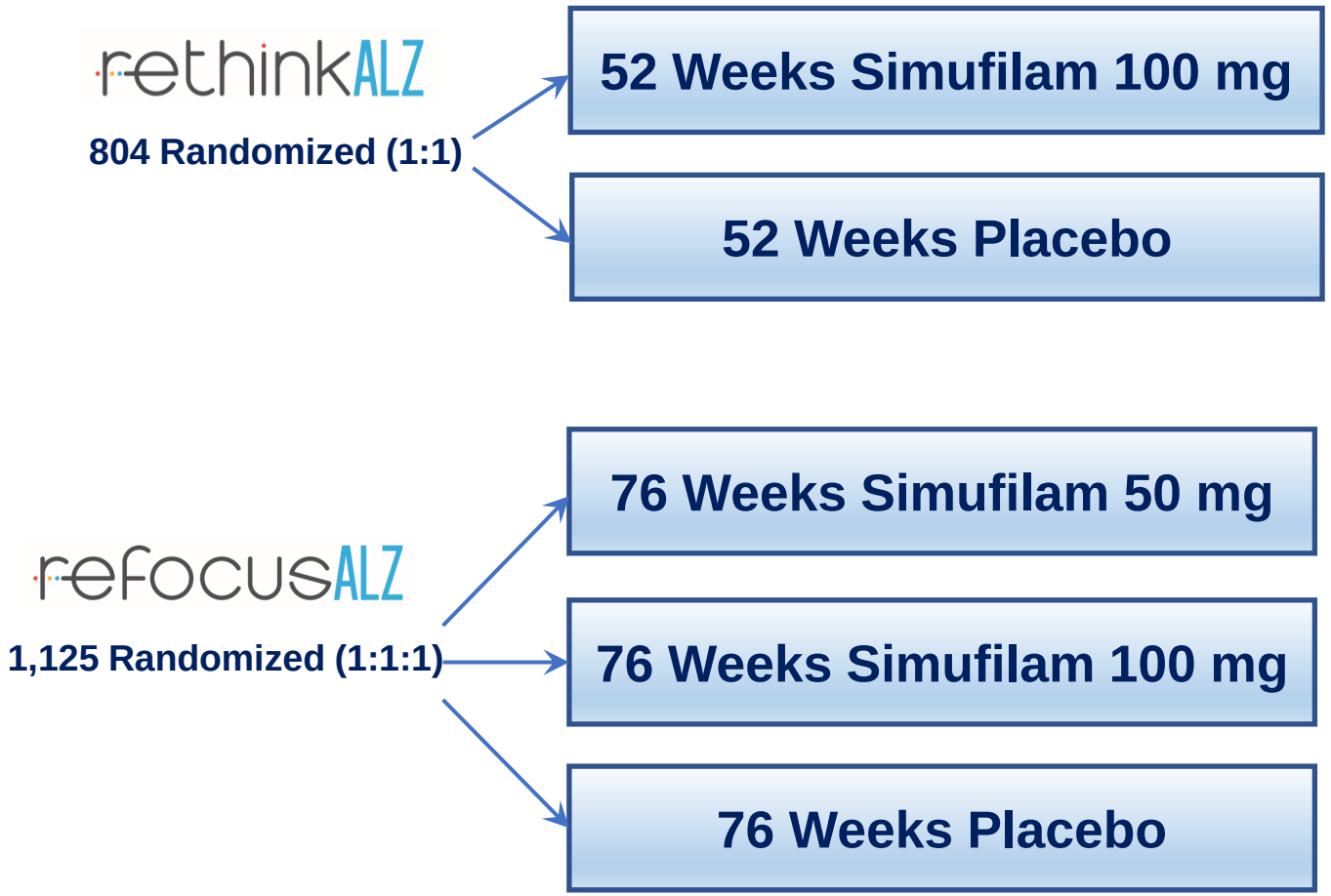
Mild: MMSE 21-26; > 26 allowed for Phase 2b participants (n=2) or previously confirmed AD pathology (n=8).

Moderate: MMSE 16-20; < 16 allowed for Phase 2b participants (n=1).

Drug Safety

- **Simufilam 100 mg tablets appear safe, well tolerated in Phase 2 trials.**
- **Adverse events have been typical for an elderly age group.**
  - Covid-19 and UTIs are the most frequent.
- **No theory for causing cerebral microbleeds (ARIA), unlike anti-amyloid antibody therapies**
- **In September 2023, a DSMB monitored interim safety data from Phase 3 program.**
  - DSMB recommended Phase 3 trials continue without modification.

Phase 3 Study Design



Efficacy endpoints:

ADAS-Cog12 (Cognition)

ADCS-ADL (Function)

iADRS (Cognition/Function)

NPI (Neuropsychiatric symptoms)

CDR-SB (Cognition/Function)

ZBI (Caregiver burden)

Sub-studies:

Plasma biomarkers

CSF biomarkers

Amyloid PET

Tau PET

Volumetric MRI

} REFOCUS only

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Key Eligibility Criteria

- Age 50-87
- Clinical Stage 4 or 5 of the Alzheimer's continuum (NIA/AA criteria 2018)
- MMSE ≥ 16 and ≤ 27
- CDR-Global Score of 0.5, 1 or 2
- Elevated plasma p-tau181 or prior evidence of AD pathology by PET or CSF
- Background AD medications stable for 12 weeks prior to randomization
- Not more than 2 doses of anti-amyloid antibodies
- Other inclusion/exclusion criteria

Plasma P-tau181 Assay

- **Plasma phosphorylated-tau181 (p-tau181) was the sole qualifier of AD pathophysiology in both Phase 3 studies of simufilam.***
  - **This immunoassay uses the Quanterix® platform.**
  - **Antibodies from ADx Neurosciences, an independent research company.**
  - **Performed by Neurocode Labs Inc., an independent, Cap-accredited, CLIA-certified laboratory.**

*Unless patients had pre-existing PET or CSF biomarkers confirming AD pathology

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Preliminary Demographics

	RETHINK (n=797)	REFOCUS (n=1123)
Mean Age (SD)	74.0 (7.7)	73.9 (7.9)
Female (%)	442, 55.5%	628, 55.9%
White (N,%)	736, 92.3%	969, 86.3%
Black (N,%)	38, 4.8%	60, 5.3%
Asian (N,%)	11, 1.4%	82, 7.3%
Native Hawaiian / Pacific Islander (N,%)	3, 0.4%	0, 0.0%
American Indian / Alaska Native (N,%)	1, 0.1%	4, 0.4%
Mixed or Other (N,%)	4, 0.6%	1, 0.1%
Hispanic or Latino (N,%)	112, 14.1%	82, 7.3%

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Note: Preliminary demographics are for the safety analysis set and may differ in the final dataset.

Preliminary Baseline Characteristics

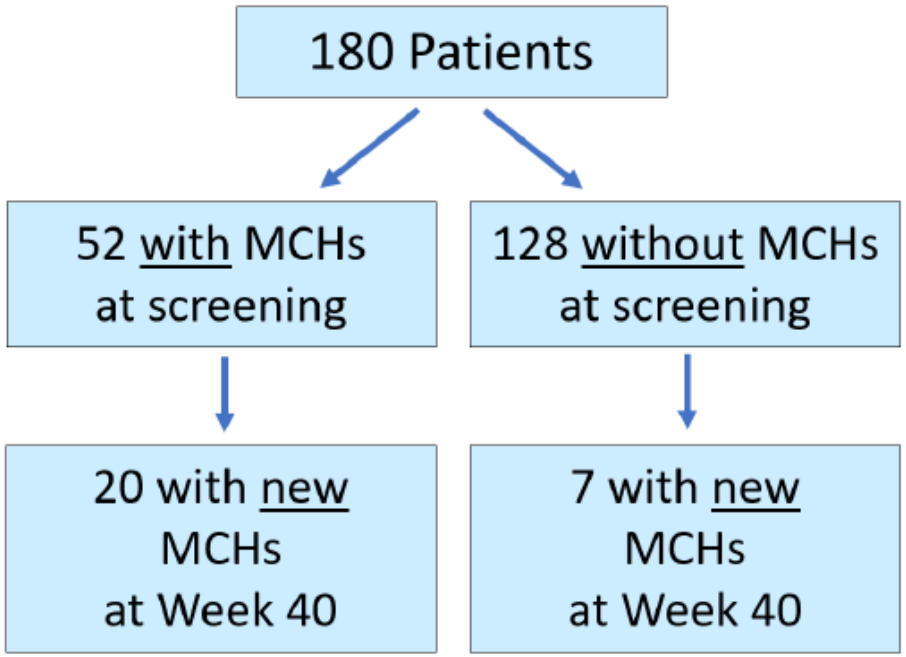
	RETHINK (n=797)	REFOCUS (n=1123)
Mild AD (N,%)	569, 71.4%	797, 71.0%
APOE ε4 carrier (N,%)	472, 59.2%	645, 57.4%
One APOE ε4 allele (N,%)	383, 48.1%	529, 47.1%
ε4 homozygotes (N,%)	89, 11.2%	116, 10.3%
AChEI and/or memantine use for AD symptoms (N,%)	508, 63.7%	627, 55.8%
MMSE (mean, SD)	21.7 (3.2)	22.0 (3.5)
ADAS-Cog12 (mean, SD)	25.1 (8.7)	24.7 (9.5)
ADCS-ADL (mean, SD)	65.0 (9.2)	65.4 (9.2)
CDR – Global (mean, SD)	0.79 (0.36)	0.75 (0.3)
CDR – SB (mean, SD)	4.7 (2.2)	4.31 (2.1)

Note: Preliminary baseline characteristics are for the safety analysis set and may differ in the final dataset.

Interim Phase 3 Safety Data on ARIA

Blinded Interim MRI Safety Analysis Suggests Simufilam is Not Associated with Treatment-emergent ARIA

- Week-40 MRIs were examined for 180 of 222 AD patients in a volumetric MRI sub-study.
- ARIA-E was not observed in any patient.
- ARIA-H (microhemorrhages or MCHs) was a common finding at screening (29%).
- Incidence of new ARIA-H was similar to other placebo reports.
- 85% of patients did not develop new MCHs.



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Phase 3 Efficacy Considerations

- **All efficacy data remains blinded; no interim analyses.**
- **Details of the statistical analysis plans (SAPs) for the P3 trials are being negotiated with FDA and will be prospectively defined, documented and finalized prior to unblinding of data.**
- **The pre-specified SAPs will be carried out on efficacy endpoints by Pentara Corporation, an independent consulting firm that specializes in complex statistical analysis of clinical trial results (Suzanne Hendrix, PhD).**

Efficacy endpoints:

ADAS-Cog12 (Cognition)

ADCS-ADL (Function)

iADRS (Cognition/Function)

NPI (Neuropsychiatric symptoms)

CDR-SB (Cognition/Function)

ZBI (Caregiver burden)

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Top-line Phase 3 Results Expected Year-end 2024

rethinkALZ

- **Patient enrollment completed October 2023.**
- **Last patient last visit expected October 2024.**
- **Top-line results expected approximately year-end 2024.**

refocusALZ

- **Enrollment completed November 2023.**
- **Last patient last visit expected May 2025.**
- **Top-line results expected approximately mid-year 2025.**

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Thank you!