

TREMHANCE: A Phase 2 study to evaluate the efficacy and safety of TREM2 agonist SAR448851 in early Alzheimer’s disease

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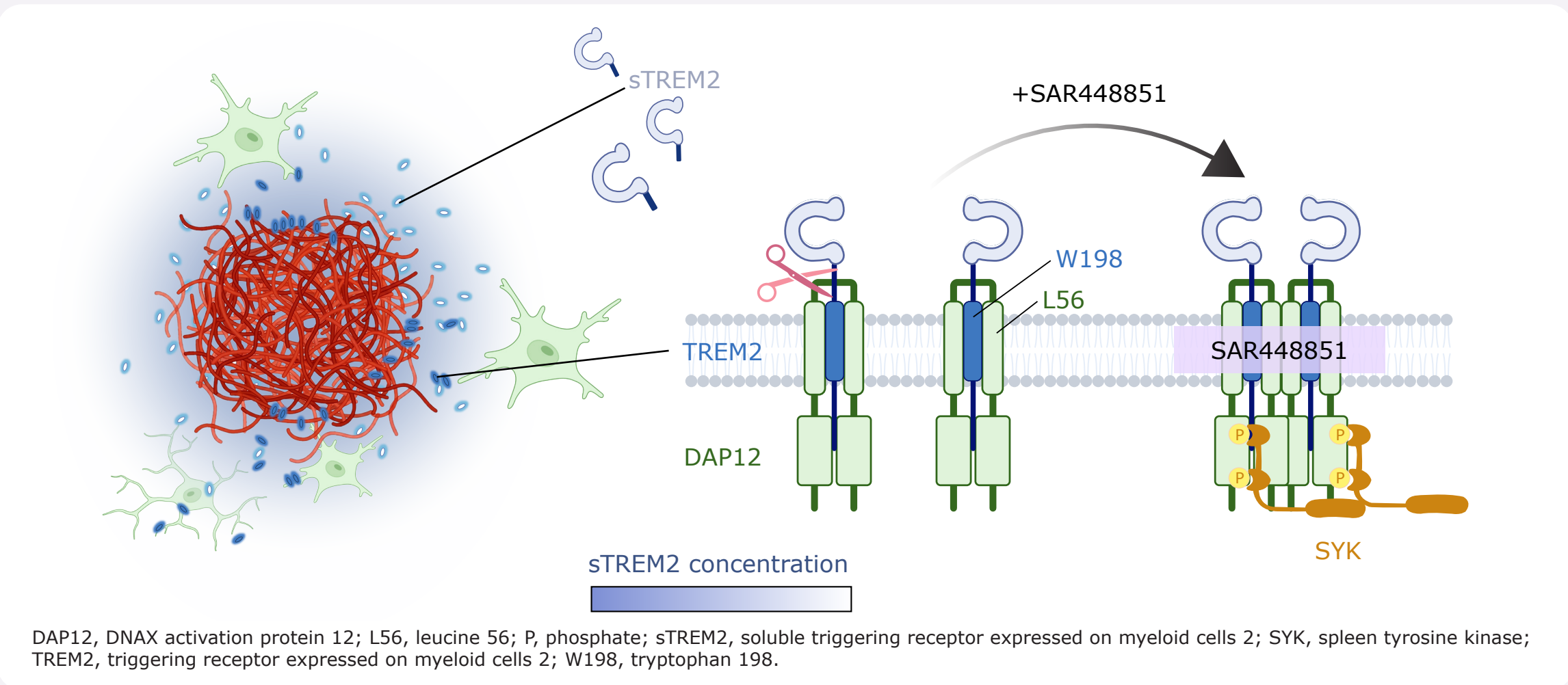
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BACKGROUND

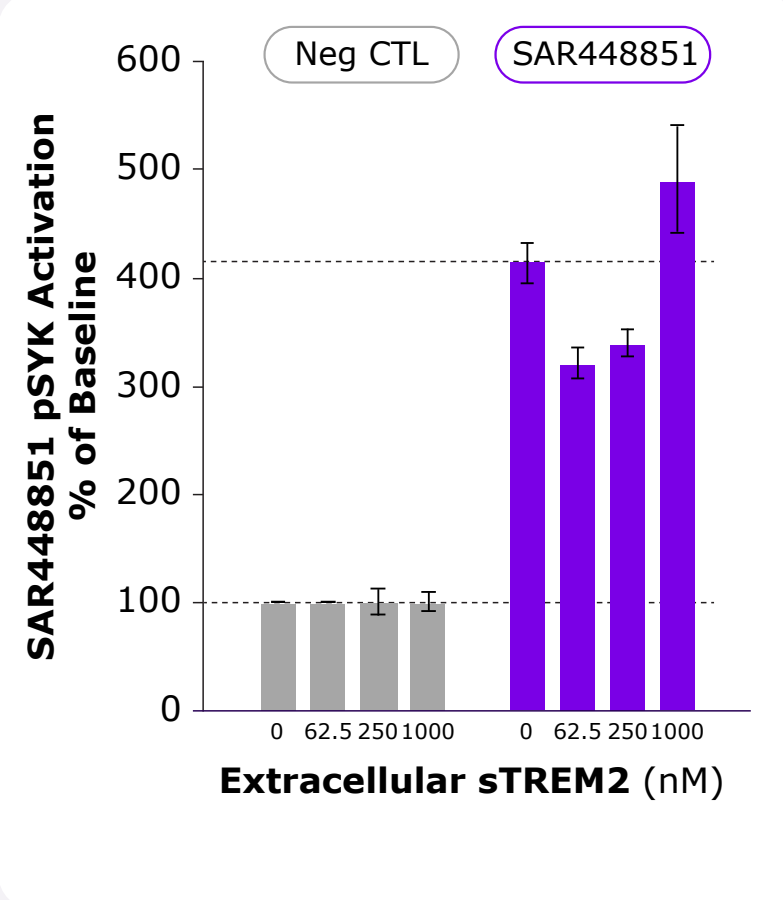
- Microglia play a central role in Alzheimer’s disease (AD) pathophysiology, with dysregulated microglial activation contributing to debris accumulation, synaptic loss, chronic neuroinflammation, and neurodegeneration¹
- Triggering receptor expressed on myeloid cells 2 (TREM2) is a microglial receptor that inhibits amyloid and tau aggregation, and regulates neuroinflammatory responses²⁻³
- Rare genetic variants in the *TREM2* gene result in loss of TREM2 function and increase AD risk²⁻³
- SAR448851 is an oral, brain-penetrant TREM2 agonist small molecule hypothesized to shift microglia towards a neuroprotective state, reducing pathological amyloid beta, tau accumulation, and deleterious neuroinflammation in people with AD⁴⁻⁸

Figure 1. SAR448851 induces the TREM2-DAP12 complex by engaging membrane-bound TREM2, avoiding sequestration by sTREM2



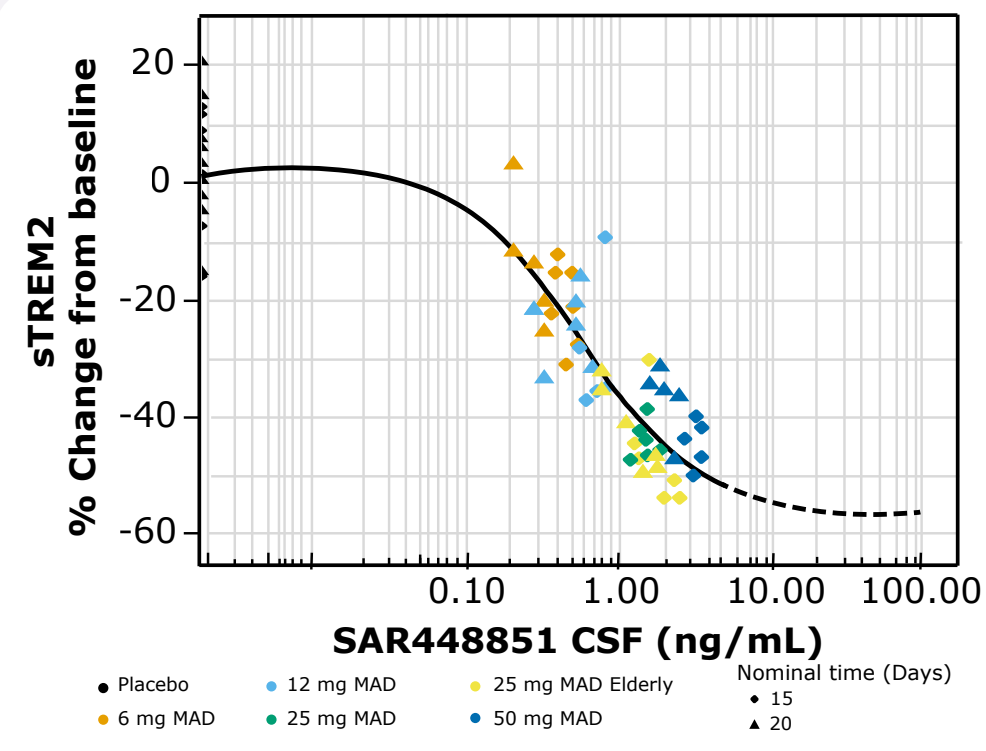
- sTREM2 may act as a sink for TREM2 agonist antibodies that bind the shared ligand domain
- Preclinical data show SAR448851 avoids this sTREM2 sink effect by binding a different site on the transmembrane region of TREM2 and DAP12, bridging them into an active complex and activating microglial protective responses⁹ as shown in **Figure 1**

Figure 2. SAR448851 activity is independent of extracellular sTREM2 levels



¹AL002m is an internally synthesized mAb that, based on Alector’s publicly available information, we developed to be structurally equivalent to AL002. ²p<0.05; ³p<0.01; ⁴p<0.001 compared to Neg CTL. ⁵AD, Alzheimer’s disease; CTL, control; human triggering receptor expressed on myeloid cells 2; mAb, monoclonal antibody; Neg, negative; nM, nanomolar; SM, small molecule; sTREM2, soluble triggering receptor expressed on myeloid cells 2; Tg, transgenic; TREM2, triggering receptor expressed on myeloid cells 2; 5xFAD, five familial Alzheimer’s disease mutations transgenic mouse model.

Figure 4. SAR448851 Phase 1 study demonstrated robust, dose-dependent sTREM2 reduction



AD, Alzheimer’s disease; AE, adverse event; CSF, cerebrospinal fluid; MAD, multiple ascending dose; QD, once daily; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

DISCLOSURES

Disclosures: **C. Mummery**: Speaker Bureau/Honoraria for non-CME from Self, Eisai and Eli Lilly; consultant/advisory board for Self, Biogen, Roche, Eli Lilly, Eisai, Novartis, Neuroimmune, MSD, GSK, Imperial, Immunobrain, and Sanofi; other financial or material support from Self, Biogen, Roche, Eisai, Alector, Alnylam, ARUK. **D. Watson**: Advisor and committee member for numerous pharmaceutical companies as well as Principal Investigator at Alzheimer’s Research and Treatment Center for numerous clinical trials sponsored and funded by various pharmaceutical companies. **J. Cummings**: Has provided consultation to Acadia, Alkermes, ALZpath, AmovisBio, Artelyr, Axsome, Biogen, Bristol-Myers Squibb, Eisai, Fousun, GAP Foundation, IGC, Janssen, Julius Clinical, Kinaxis, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, Novo Nordisk, NRC Therapeutics, Otsuka, ReMYND, Roche, Sanofi, Scottish Brain Sciences, Signant Health, Sincere, and Synaptic Therapeutics. **C. Rowe**: None. **C. Teunissen**: Dr Teunissen reported receiving grants from the European Commission, Marie Curie International Training Network, Innovative Medicines Initiative 3TR (Horizon 2020), EPND (IMI 2 Joint Undertaking), and JPND (dPRIDE, CCAD), European Partnership on Metrology, co-financed by the European Union’s Horizon Europe Research and Innovation Programme and by the Participating States, Horizon Europe, CANTATE project funded by the Alzheimer Drug Discovery Foundation, Alzheimer’s Association, Michael J. Fox Foundation, Health Holland, the Dutch Research Council (ZonMW), Alzheimer Drug Discovery Foundation, Selfridges Group Foundation, and Alzheimer Netherlands; receiving ABCARD, which is a public-private partnership receiving funding from ZonMW and Health Holland, Topsector Life Sciences & Health, receiving JAP-dementia, a ZonMW-funded project in the context of the Dutch National Dementia Strategy, having research contracts with Acumen, ADx, Neurosciences, AC-Immune, Alamar, Arbio, Axon Neurosciences, Beckman-Coulter, BioConnect, Biochrestra, Brainstorm Therapeutics, C2N Diagnostics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly, Fujirebio, Instant Nano Biosensors, Merck, Muna, Nitrase Therapeutics, Novo Nordisk, Olink, PeptideBio, Quantex, Roche, Symex, Toyama, Vaccinex, and Vivoryon; serving as editor in chief of Alzheimer Research and Therapy; and serving on the editorial boards of Molecular Neurodegeneration, Alzheimer’s & Dementia, Neurology: Neuroimmunology & Neuroinflammation, MedRxiv, and as committee member to define guidelines for Cognitive Disturbances, and one for Acute Neurology in the Netherlands; and having consultancy/speaker contracts for Arbio, Biogen, Beckman-Coulter, Cognition Therapeutics, DanaHER, Eisai, Eli Lilly, Janssen, Merck, Neurogen Biomarking, Nordic Biosciences, Novo Nordisk, Novartis, Olink, Quantex, Roche, Sanofi and Veravas. **S. Palmqvist**: has acquired research support (for the institution) from Avid Radiopharmaceuticals and Cerelevents through ADx. In the past 3 years, he has received consultancy/speaker fees from BioArtic, Danaher, Eisai, Eli Lilly, Novo Nordisk, Roche, and Sanofi. **J. Norton**: None. **S. Narasimhan**, **S. Hourcade**, **X. Luo**, **B. Zhu**, and **E. Wallstroem**: Employees of Sanofi (may hold shares and/or stock options in the company). **M. Colonna**: has equity in and is on the scientific advisory board of Halcyon Tx and BioRx; was a member of the scientific advisory board of Vigil Neuroscience, a Sanofi company; receives research support from Ono Pharmaceuticals; is a consultant for CST and Pfizer.

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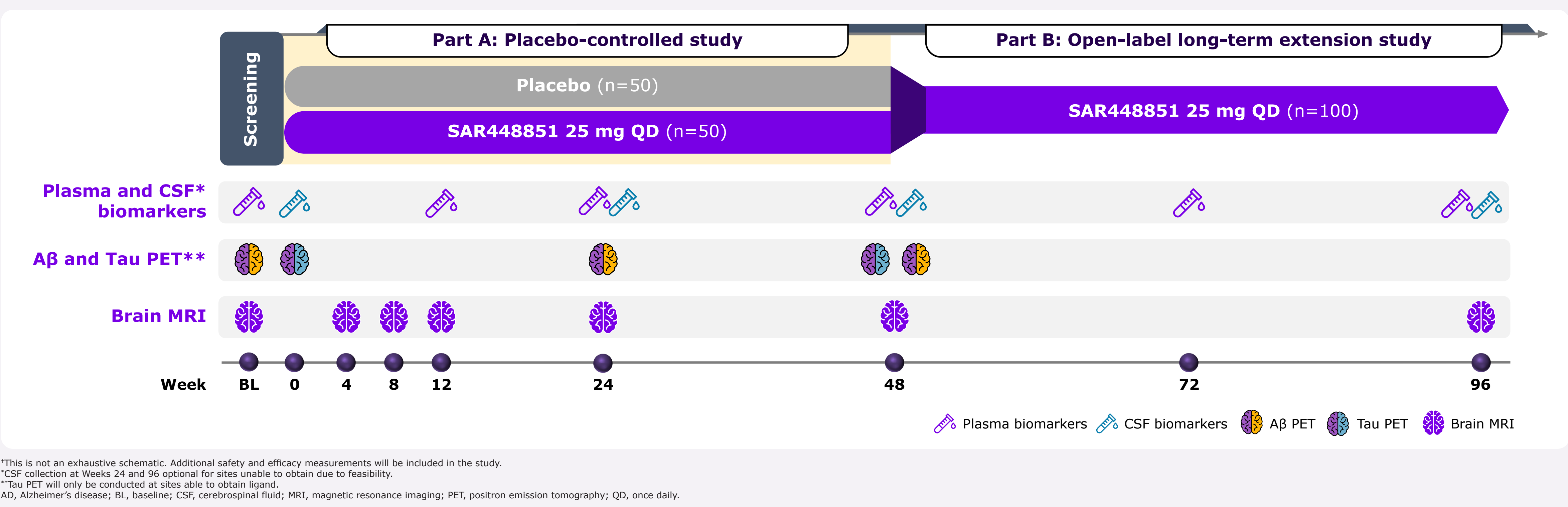
OBJECTIVE

The purpose of the TREMHANCE (NCT07688213) Phase 2 study is to measure efficacy and safety of once daily oral SAR448851 compared to placebo in participants with mild cognitive impairment due to AD or mild AD dementia¹²

METHODS

- Trial design:** Randomized, double-blind, placebo-controlled Phase 2 study to evaluate the efficacy and safety of SAR448851 in early AD participants
- The study consists of 2 parts:**
 - Part A (Weeks 0–48):** Approximately 100 participants will be randomized (1:1) to receive placebo or SAR448851 25 mg QD
 - Part B (Weeks 48–96):** All participants will receive SAR448851 for an additional 48 weeks to assess long-term efficacy and safety

Figure 5. TREMHANCE study design with selected key endpoint measures¹



¹This is not an exhaustive schematic. Additional safety and efficacy measurements will be included in the study. ²CSF collection at Weeks 24 and 96 optional for sites unable to obtain due to feasibility. ³Tau PET will only be conducted at sites able to obtain ligand. AD, Alzheimer’s disease; BL, baseline; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography; QD, once daily.

Table 1. Key inclusion criteria

Criteria	Parameters
Age	55 to 85 years
Diagnosis	MCI (NIA-AA stage 3) or mild AD (NIA-AA stage 4)
CDR	0.5 to 1.0; with CDR-memory box scoring of ≥ 0.5 at screening
Evidence of cerebral amyloid pathology	Confirmed by positive visual read on amyloid positron emission tomography (PET) at screening

Table 2. Key exclusion criteria

Medical history exclusions	Current treatment exclusions
Significant neurological diseases	Receiving or has previously received any anti-amyloid immunotherapy or TREM2 targeting therapy
>4 microhemorrhages (<10 mm in diameter) or superficial siderosis	Receiving anticoagulant therapies
Carries two copies of the apolipoprotein E epsilon 4 (APOE4) allele (APOE4/4)	

AD, Alzheimer’s disease; CDR, clinical dementia rating; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging-Alzheimer’s Association; TREM2, triggering receptor expressed on myeloid cells 2.

CONCLUSIONS

- SAR448851 is an oral, brain-penetrant TREM2 agonist small molecule hypothesized to shift microglia towards a neuroprotective state and promote clearance of AD pathology, offering a mechanistically distinct approach from other AD therapies
- In preclinical models, SAR448851 demonstrated potent and selective agonism for TREM2, resulting in microglial engulfment of amyloid and tau
- In Phase 1, SAR448851 demonstrated favorable safety and tolerability, high CNS penetration, and dose-dependent target engagement
- The TREMHANCE Phase 2 study is in final planning

TREMHANCE is designed to evaluate SAR448851 as a potential oral disease-modifying therapy for early AD through a novel mechanism of TREM2 agonism to enhance microglial function

Table 3. Study endpoints

Endpoints ¹
Primary
Change in plasma p-tau217
Secondary
Change in plasma GFAP and CSF neurogranin
Change in brain amyloid plaque deposition as measured by amyloid PET
Change in CSF sTREM2
Number of participants with TEAEs and SAEs, and discontinuations due to TEAEs and SAEs (including laboratory assessments, vital sign measurements, ECGs and the C-SSRS) ^a
Number of participants with ARIA-E and ARIA-H assessed by brain MRIs ^b
Plasma and CSF concentrations of SAR448851

¹From baseline to Week 48. ²Number of participants experiencing at least one TEAE, SAE or discontinuation due to TEAEs and SAEs; ³Number of participants with at least one ARIA event: adverse event causing brain swelling or bleeding that requires close monitoring; ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemosiderin; CSF, cerebrospinal fluid; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; PET, positron emission tomography; p-tau217, phosphorylated tau 217; SAE, serious adverse event; sTREM2, soluble triggering receptor expressed on myeloid cells 2; TEAE, treatment-emergent adverse event.

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