

Abstract #6574

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TREM2 Binding Site Matters: VHB937, an IgSF-Binding TREM2 mAb in Ph2 for AD, Shows a Unique Microglia Activation Profile

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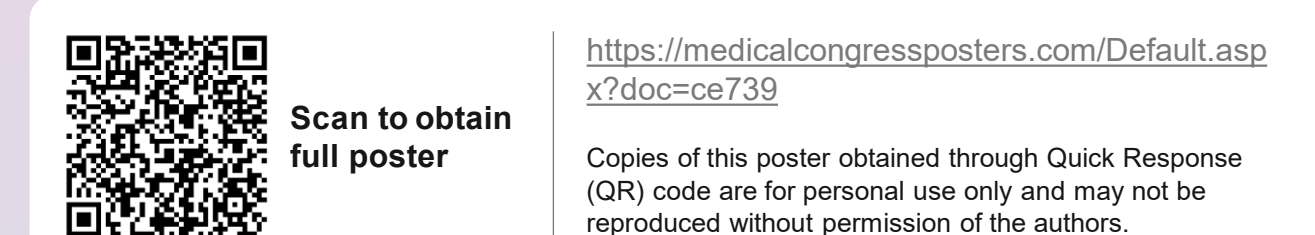
KEY FINDINGS & CONCLUSIONS

VHB937 is a novel, fully human mAb that enters the CNS and targets microglia to potentially promote neuroprotective microglial functions

- The TREM2 binding site is important: by binding to the IgSF domain of TREM2, VHB937 resulted in stabilization of membrane-bound TREM2 and phagocytic activity in contrast to stalk binding⁸
- VHB937 changed the microglial state toward a pro-resolution, neuroprotective phenotype, modulating microglial function both *in vitro* and *in vivo*⁸
- VHB937 demonstrated neuroprotective activity in several different mouse models of neurodegeneration/neuroinflammation⁸

- In healthy participants**
- VHB937 decreased inflammatory biomarkers in the CSF indicating a pharmacodynamic effect (SPP1, sCSF1R, CCL3), as opposed to the increase in pro-inflammatory markers reported with TREM2 stalk binders^{7,8}

- VHB937 clinical development**
- A phase 2 study in AD started in 2025 and is actively recruiting (NCT07094516)¹²
 - A phase 2 study in ALS is ongoing and fully enrolled (ASTRALS, NCT06643481)¹³

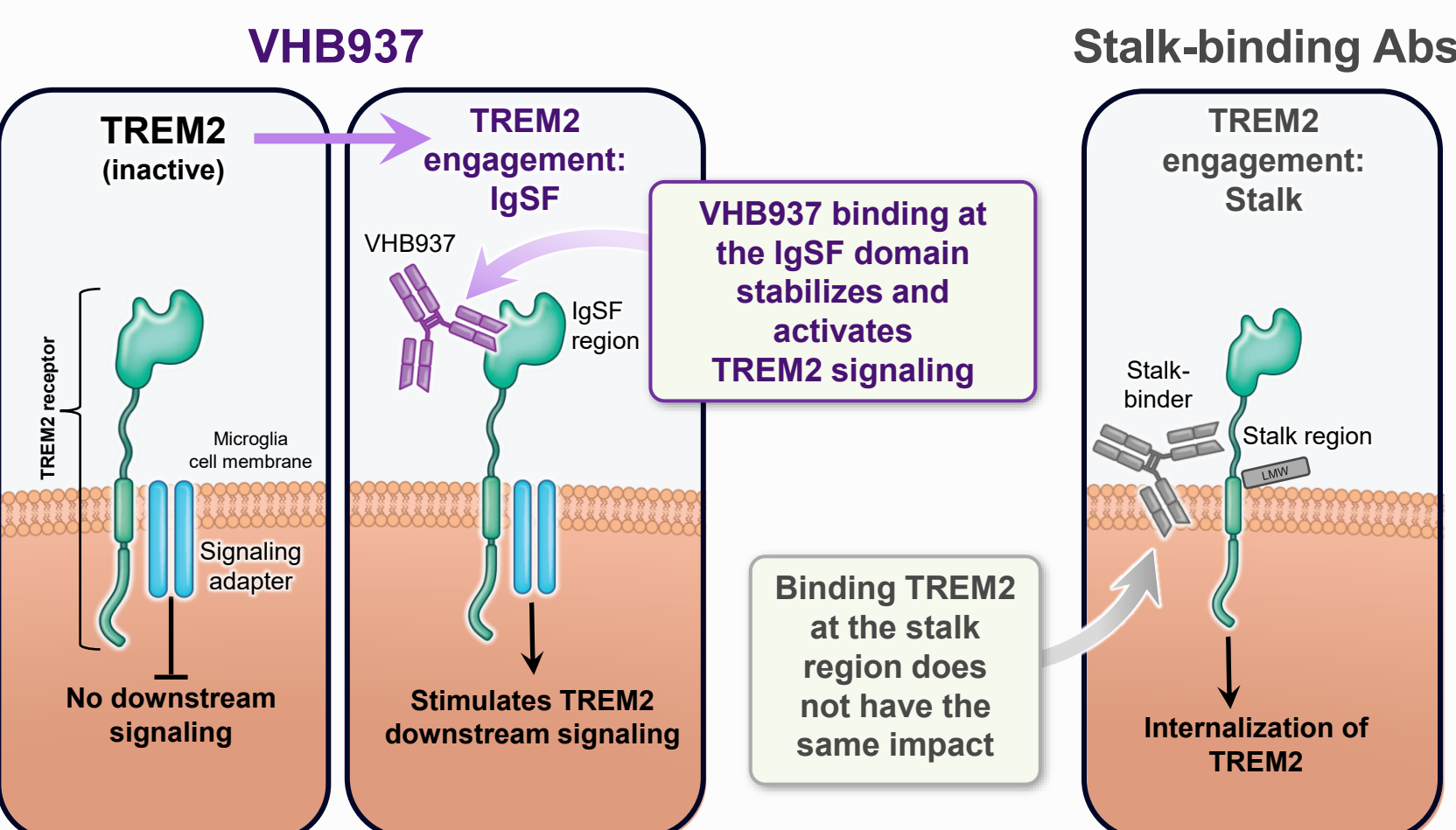


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INTRODUCTION

- Microglia are dynamic immune cells that maintain central nervous system (CNS) health by performing key neuroprotective functions¹
- In the early stages of Alzheimer disease (AD), microglia are protective, promoting the uptake and degradation of apoptotic neurons, amyloid beta (A β) plaques, and tau neurofibrillary tangles^{2–4}
- Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) is a microglial surface receptor and key regulator of microglial activity that is pivotal for microglial responsiveness to insult^{4,5}
- Targeting TREM2 represents a promising therapeutic approach to slow neurodegeneration in disorders such as AD^{4,6}; however, TREM2 agents differ in binding site with different potential consequences for microglial functionalities and inflammation^{7,8}
- Here we share *in vitro*, *in vivo*, and first-in-human (FIH) data examining the impact of VHB937 binding to the immunoglobulin superfamily (IgSF) domain, and compare the results with TREM2-targeting agents that engage the stalk region**

VHB937 Mechanism of Action



- Binding site matters: VHB937 binds to the IgSF domain with different downstream effects vs stalk-binding Abs**
- VHB937 may shift pathogenic microglia from a neurotoxic to a neuroprotective state, with potential to address A β /tau aggregation, neuron damage, and inflammation in AD⁸
 - By selectively binding the TREM2 IgSF domain, VHB937 stabilizes and activates TREM2 expressed on microglia, leading to downstream neuroprotective effects that distinguish it from other investigational TREM2-targeting therapies^{7,8}
 - VHB937 is Fc silenced and thereby exhibits reduced antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity^{9,10}

PRECLINICAL RESULTS

- VHB937 stabilizes TREM2 membrane surface expression, potentially leading to downstream neuroprotective effects that distinguish it from stalk-binding TREM2-targeting therapies (Figure 3)⁸

Figure 3. VHB937 stabilization of membrane-bound TREM2 in hiPSC microglia vs stalk-binding Ab internalization

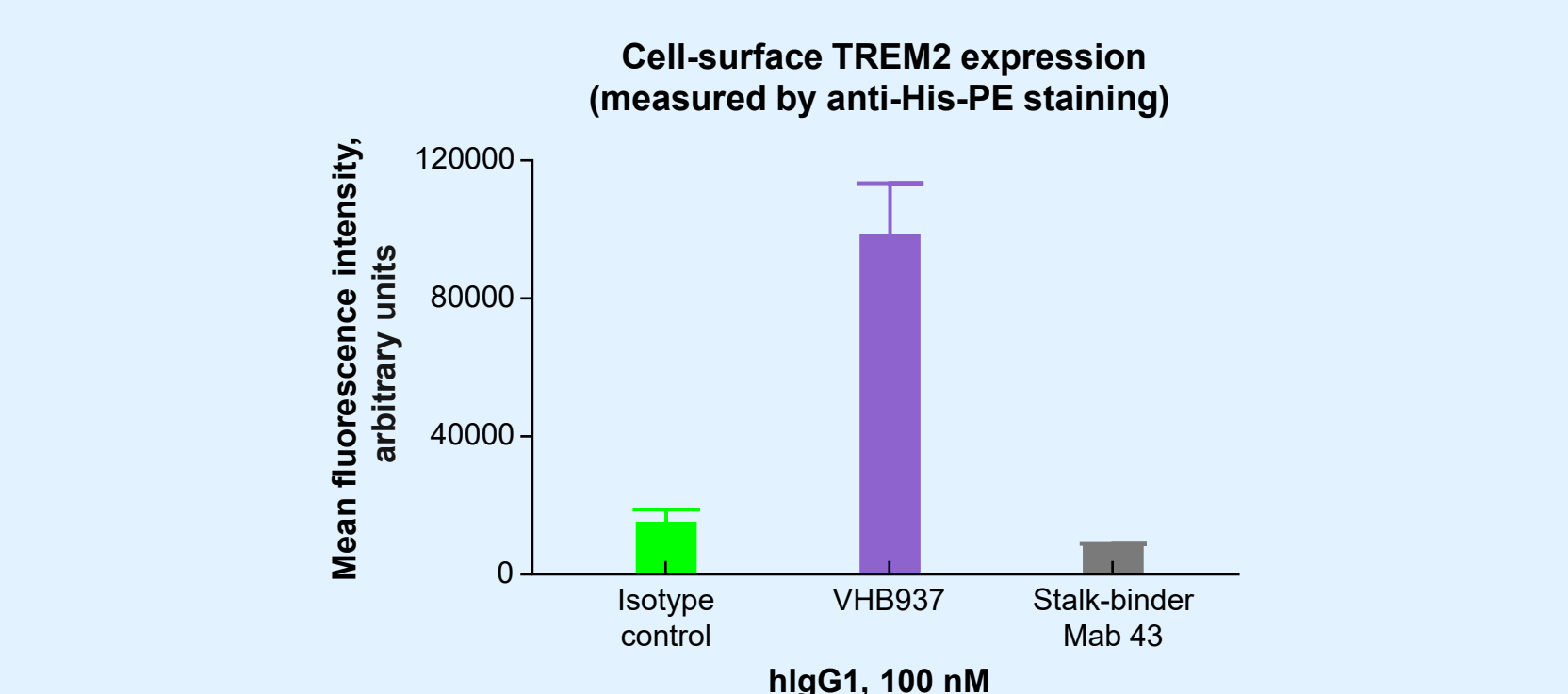
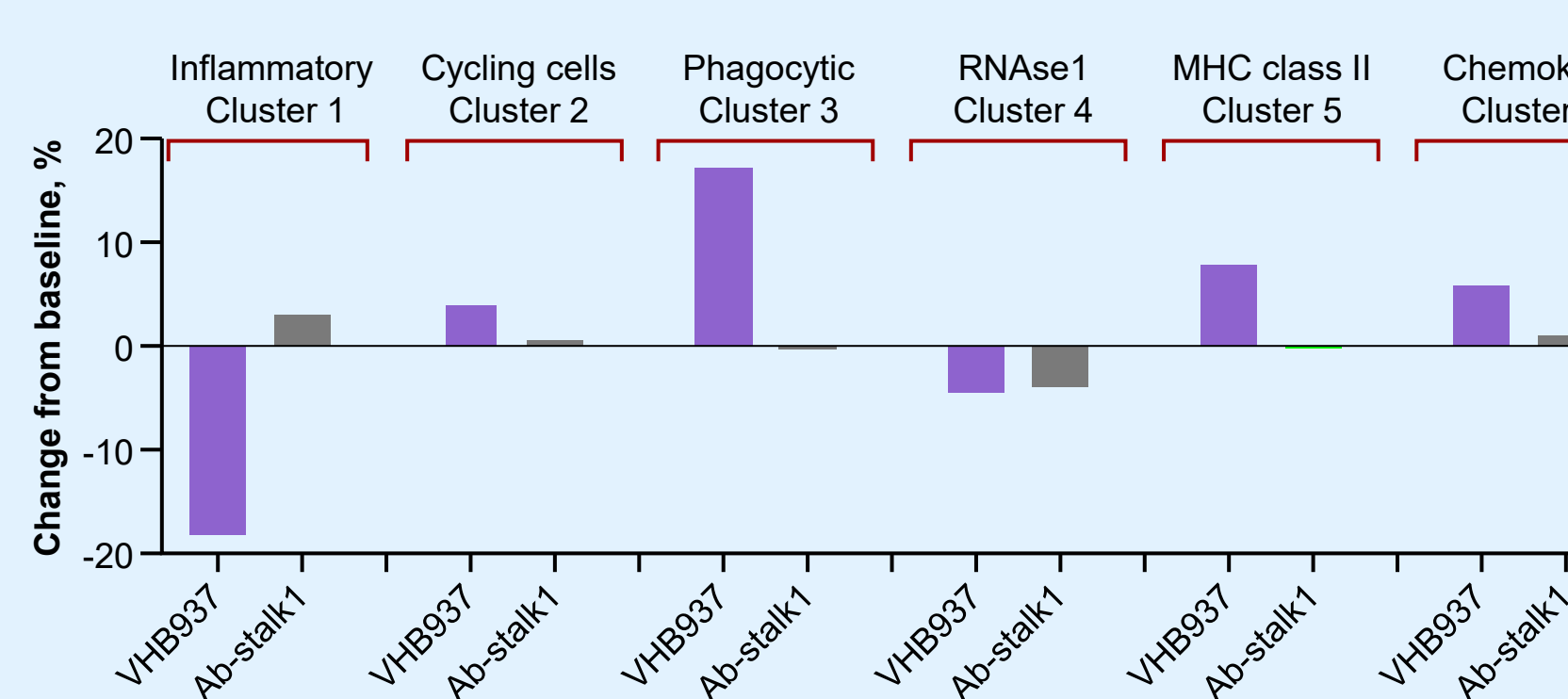


Figure 4. VHB937 treatment results in the expansion of a pro-phagocytic subcluster at the expense of an inflammatory subcluster (single-cell RNAseq) in hiPSC microglia vs stalk-binding Ab



References

- Fumagalli et al. *Nat Neurosci*. 2025 Jul;7(7):1381-1392. 2. Qin Q, et al. *Mech Ageing Dev*. 2021;195:111438. 3. Miao J, et al. *Front Aging Neurosci*. 2023;15:1201982. 4. Shi Q, et al. *Neuroscientist*. 2025;31(2):159-176. 5. Colonna M. *Nat Rev Immunol*. 2023;23:580-594. 6. Yang H, et al. *Int J Mol Sci*. 2025;26(15):7057. 7. Sovago J, et al. Oral presentation AD/PD Congress; April 1-5, 2025; Vienna, Austria. Session 1597. 8. Feuerbach D, et al. Oral presentation at: AD/PD Conference, 16–20 March 2026. Session 4240. 9. Feuerbach D, et al. Poster presentation at: AD/PD Conference, 17–21 March 2026; Copenhagen, Denmark Poster 1751. 10. Data on file (VHB937 Investigator's Brochure; 21 May 2024) 11. Wang S, et al. *J Exp Med*. 2020;217(9):e20200785. 12. ClinicalTrials.gov. (NCT07094516) Accessed 28 May 2026. <https://clinicaltrials.gov/study/NCT07094516> 13. ClinicalTrials.gov. (NCT06643481). Accessed 28 May 2026. <https://clinicaltrials.gov/study/NCT06643481>.

METHODS

Preclinical

- TREM2 antibodies were profiled *in vitro* in recombinant cellular systems and human induced pluripotent stem cell (hiPSC)-derived microglia with endogenous TREM2 expression⁸
- Key pathological features of AD were assessed following treatment with a chimeric version of VHB937 (h/mVHB937, a mouse IgG2a-Fc-silenced antibody with VHB937 variable regions) or isotype control in an AD mouse model (TREM2-APP23-PS45 amyloidosis or TREM2K1xtau58.4 tauopathy)⁹

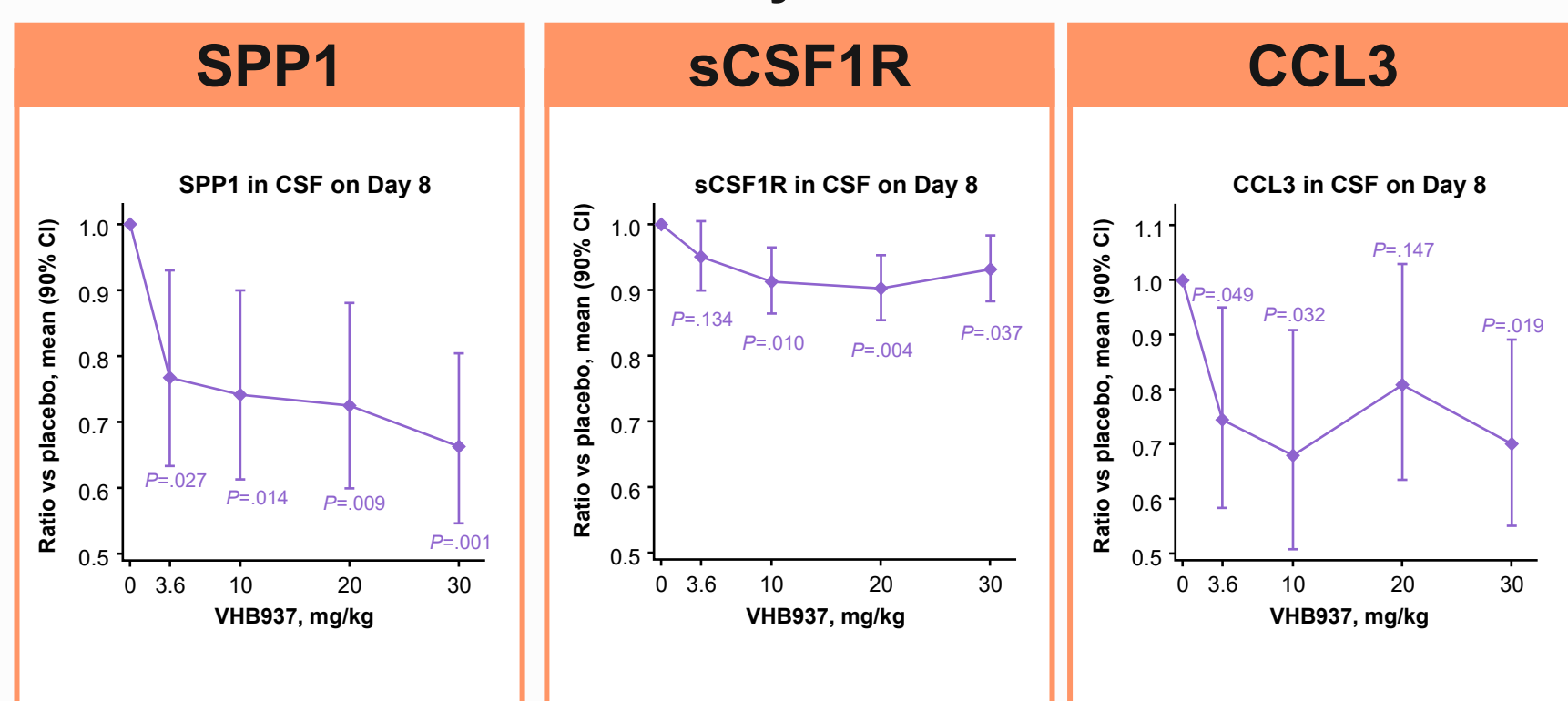
FIH

- The FIH trial was a randomized, double blind, single ascending dose study of VHB937 with 64 healthy adult participants⁷

FIH RESULTS

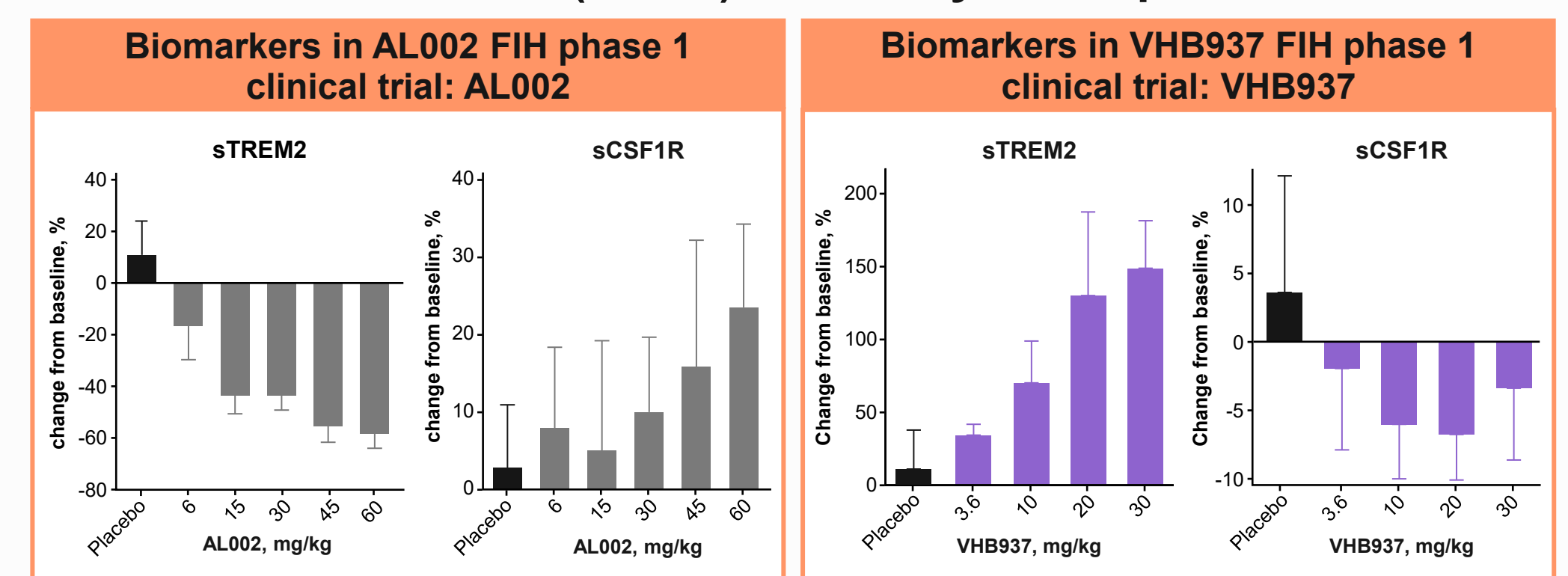
- In an FIH study in healthy participants, VHB937 was detectable in cerebrospinal fluid (CSF), and was associated with clear reductions in proinflammatory biomarkers (SPP1, sCSF1R, CCL3), consistent with effects observed in preclinical models (Figure 1)⁷

Figure 1. VHB937 Lowers Proinflammatory Biomarkers in the FIH Study



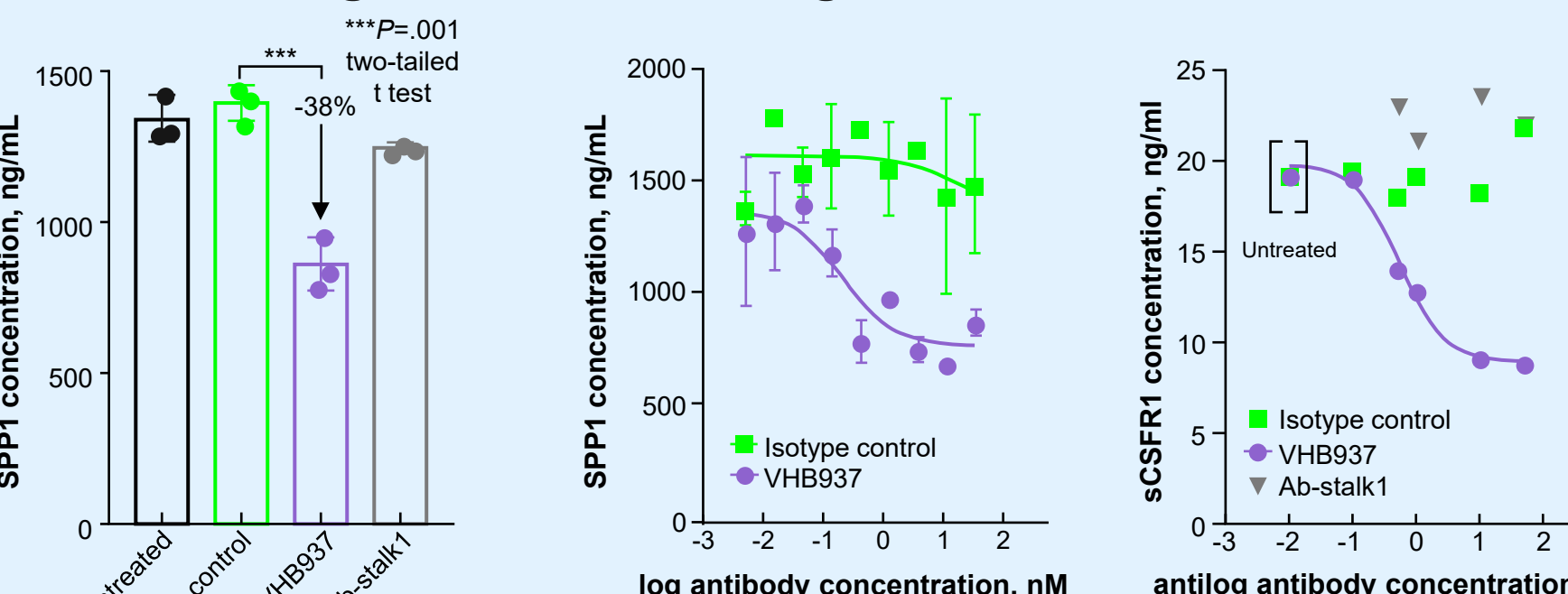
- Safety:** VHB937 was well tolerated and with no new safety signals compared with placebo⁷

Figure 2. Differential Biomarker Responses with TREM2-Targeted Monoclonal Antibodies (mAbs) in Healthy Participants



- Treatment with VHB937 resulted in a consistent reduction in levels of proinflammatory biomarkers, including SPP1 and sCSF1R in hiPSC-derived microglia (Figure 5), whereas stalk-binding Abs had no effect on SPP1 levels and caused a trended increase in sCSFR1 levels⁸

Figure 5. VHB937 reduced the release of SPP1 and sCSF1R in hiPSC microglia vs stalk-binding Ab⁷



- VHB937 reduced dystrophic neurites (mouse amyloidosis model), AT8 p-tau (mouse tauopathy model), and CCL3 levels *in vivo* (Figure 6)⁹
- Reduction in these pathological AD hallmarks may preserve neuronal integrity and cognitive function, demonstrating VHB937 disease-modifying potential⁹

Figure 6. h/mVHB937 treatment reduced dystrophic neurites, pathological p-tau, and CCL3 in different AD mouse models

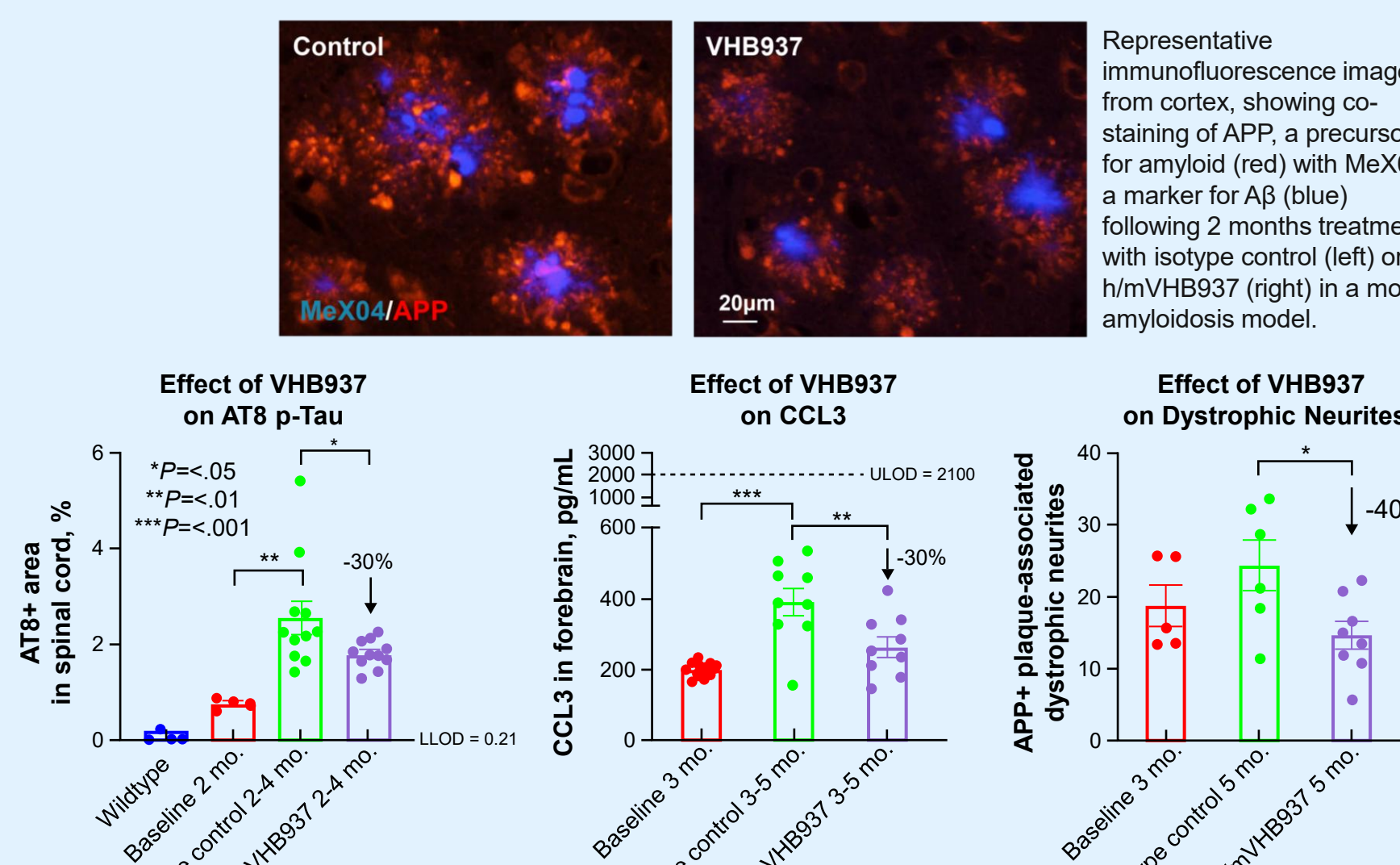


Figure 6. Data are presented as mean $\pm$ SEM. Statistical analysis was performed using one-way ANOVA with Holm–Šidák's multiple comparisons test

Acknowledgments

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Disclosures

All authors are employees of Novartis and hold shares in the company.