Interim MRI safety analysis from a 76-week Phase 3 clinical trial of simufilam in Alzheimer's Disease

Luc Bracoud[1], Joyce Suhy[2], Laura Rodriguez[3], Lindsay H. Burns[3] and James W. Kupiec[3]

[1] Clario, Lyon, France; [2] Clario, San Mateo, CA; [3] Cassava Sciences, Inc., Austin, TX, USA

BACKGROUND

Simufilam is a novel drug candidate being evaluated in a Phase 3 clinical program in patients with mild-to-moderate Alzheimer's disease (AD) dementia. This oral small molecule targets an altered form of filamin A (FLNA) found in AD. The drug disrupts FLNA's aberrant linkage to the α7 nicotinic acetylcholine receptor (α7nAChR), thereby blocking soluble amyloid beta$_{1-42}$ (Aβ_{42})'s signaling via the α7nAChR that hyperphosphorylates tau. Simufilam also disrupts aberrant linkages of FLNA with toll-like receptor 4 (TLR4) and other inflammatory receptors to prevent their activation by Aβ_{42}, suppressing neuroinflammation.

Patients enrolled in one of the Phase 3 studies at selected research sites could also participate in an optional, volumetric MRI sub-study to investigate anatomical correlates of disease progression.

OBJECTIVE

To evaluate interim, blinded MRI data for the presence of treatment-emergent amyloid-related imaging abnormalities (ARIA) in Alzheimer's patients enrolled in an on-going Phase 3 clinical trial of simufilam.

STUDY DESIGN

A global 76-week Phase 3 clinical study (REFOCUS-ALZ) is evaluating the safety and efficacy of twice-daily simufilam, 50 and 100 mg vs. placebo (1:1:1 randomization), to slow cognitive and functional decline in >1,000 patients with mild-to-moderate AD (NCT05026177). Enrolled AD patients, ages 50-87, presented clinically with Stage 4 or 5 on the Alzheimer's disease continuum (NIA–AA 2018[1]), an MMSE ≥ 16 and ≤ 27, a CDR Global Score of 0.5, 1 or 2, and either confirmed PET or fluid biomarker evidence of AD pathophysiology prior to randomization.

Significant vascular pathology on screening MRI was exclusionary. A protocol amendment provided additional examples of vascular pathology, including ≥ 10 micro-hemorrhages (MCHs), cortical superficial siderosis (CSS), or extensive white matter lesions (i.e., Fazekas grade 3).

The volumetric MRI sub-study is investigating anatomical correlates of disease progression (brain volume, including whole brain, ventricles and hippocampus). Patients are scanned at screening, Week 40 and Week 76.

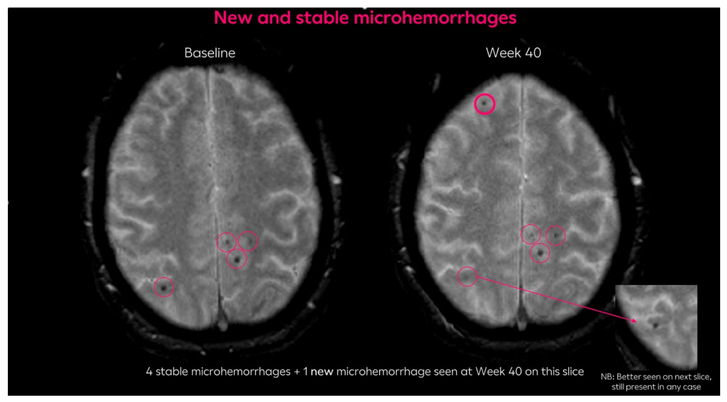
METHODS

The MRI protocol was conducted on 1.5T and 3T scanners and consisted of 3DT1, FLAIR, T2*, T2 and DWI sequences. Neuroradiologists continuously assess follow-up MRI scans at Weeks 40 and 76 to monitor for new imaging abnormalities, including ARIA-E and ARIA-H. Quantitative changes in brain volume (whole brain, ventricles and hippocampus) will be determined at the conclusion of the study based on segmented 3D T1-weighted images using FreeSurfer 6.0 software. All image handling, QC, processing, qualitative and quantitative assessments are conducted within a fully 21 CFR part 11 compliant environment. Study participants, clinical research staff, and scientists at Cassava Sciences, Clario, and Premier Research all remain blinded to treatment assignments.

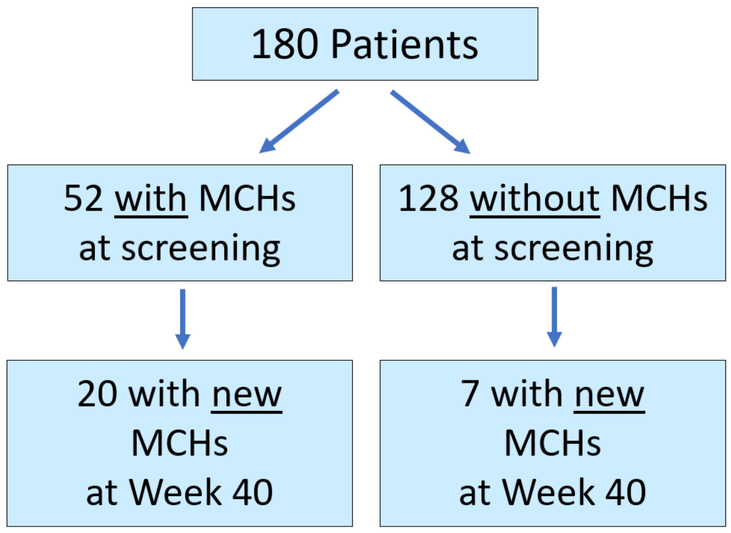
RESULTS

Of the 222 patients in the volumetric MRI sub-study, 181 reached Week 40 by September 1, 2023, and evaluable safety reports were issued for 180 patients.

Representative MRI findings of new MCHs and CSS



- ARIA-E was not observed in any patients.
- No clinically significant findings were identified in 160 patients (89%) at screening or Week 40.
- 13 patients (7%) had clinically significant findings at screening that persisted at Week 40, including infarcts (n=7), unifocal CSS (n=4), multifocal CSS (n=1), or other abnormalities (n=1).
- 7 patients (4%) had new clinically significant findings at Week 40, including: cortical or lacunar infarcts (n=3); CSS in patients with either pre-existing CSS in other areas and/or ≥4 MCHs at screening (n=3); and one case of unifocal CSS in a patient with an e4/e4 ApoE genotype.
- At screening, 71% of patients did not exhibit MCHs; 19% had 1-4 MCHs, 6% had 5-9 MCHs and 4% had ≥10 MCHs. Of those without MCHs at screening, 95% did not develop new MCHs, while 5% had 1 or 2 (no predominant ApoE genotype). Overall, 85% of patients did not develop new MCHs. Twenty patients with MCHs at screening exhibited new MCHs at Week 40 (14 had 1-4, and 6 had ≥ 5).



Patients without MCHs at Screening who developed MCHs by Week 40

AGE	SEX	ApoE	Anti-platelet or Anti-coagulants	Miscellaneous
71	M	e3/e3		
63	F	e4/e4	ASA 81 mg QD	
82	F	e3/e4	ASA 81 mg QD	
72	M	e3/e4	ASA 81 mg QD	
81	F	e3/e3	ASA 325 mg QD Plavix 75 mg QD	Right MCA stroke (Wk 25)
77	M	e2/e4		
79	F	e3/e3		Unifocal CSS at screening

DISCUSSION

Recognized risk factors for ARIA include exposure to therapeutic anti-Aβ monoclonal antibodies, the presence of pre-existing MCHs and ApoE4 carrier status. In patients with AD who have not been administered anti-Aβ antibodies, ARIA-E prevalence is < 0.1% to 0.8%, and ARIA-H prevalence (including both MCHs and CSS) ranges between 9.2% and 33%.[2] In the APOLLOE4 Phase 3 trial of the oral drug ALZ-801 in ApoE4/4 homozygotes, baseline MRIs showed 32% of patients had MCHs and 9% had superficial siderosis.[3]

Treatment-emergent ARIA-H in clinical AD studies is also commonly observed. In the CLARITY (lecanemab) Phase 3 study in early AD, the treatment-emergent incidences of MCHs and CSS in patients on placebo were 7.6% and 2.3%, respectively, over 18 months[4].

In this interim, blinded MRI cohort, ARIA-E was not observed in any patient, while ARIA-H was observed in 29% of patients at screening. The absence of treatment-emergent ARIA-E is consistent with simufilam's mechanism of action, which does not disrupt cerebrovascular integrity like anti-Aβ antibodies.

Likewise, the incidence of treatment-emergent ARIA-H in patients without MCHs at screening (5%) is within the range for placebo in long-duration studies such as CLARITY.

Considering the overlap in the pathophysiology of ARIA-E and ARIA-H, the incidence of ARIA-H in this on-going Phase 3 study may be similar between the simufilam and placebo treatment arms.

CONCLUSIONS

This interim neuroradiologic evaluation of blinded Week-40 MRIs from 180 patients in the REFOCUS-ALZ Phase 3 clinical study suggests simufilam is not associated with ARIA-E emergence. The incidence of new ARIA-H in this blinded dataset is consistent with other placebo reports. New MCHs occurred predominantly in patients with pre-existing MCHs: 38% of patients with pre-existing MCHs vs. 5% of patients without pre-existing MCHs.

REFERENCES

1. Jack C, Bennett D, Blennow K, et al (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease; Alzheimer's and Dementia 14(4):535-562
2. Hampel H, Elhage A, Cho M, et al (2023) Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics; BRAIN (Epub ahead of print, JUN 2023)
3. Abushakra S, McLaine R, Barakos J, et al (2023) Prevalence of cerebral MCHs and CSS in APOE4/4 homozygotes with early AD; AAIC2023 poster 82916
4. Van Dyck CH, Swanson C, Aisen P, et al (2022) Lecanemab in early AD; NEJM 29 NOV 2022