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Consensus Guidelines

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# Anti-Amyloid Monoclonal Antibodies for the Treatment of Alzheimer Disease: Intersocietal Recommendations for Their Appropriate Use in Switzerland

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**Abstract**
The association of Swiss Memory Clinics (SMC) provides intersocietal recommendations for the use of anti-amyloid monoclonal antibodies (mAbs) in Switzerland. The

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recommendations are the result of extensive interdisciplinary discussions in a group of Swiss dementia experts from August 2023 until December 2024. They reflect the opinion of all societies involved in the diagnosis and treatment of dementia patients in Switzerland. Special emphasis is given to aspects that are specific to the Swiss landscape, including recommendations for infrastructural and personnel standards for institutions aiming to administer anti-amyloid mAbs in Switzerland.



## Introduction

The Swiss Memory Clinics association (SMC) comprises 52 outpatient services and encompasses the vast majority of Memory Clinics in Switzerland. SMC specialists represent all societies involved in the diagnosis and treatment of dementia in Switzerland, namely, the societies of Neurology, Old Age Psychiatry and Psychotherapy, Neuropsychology, and Geriatrics. Currently, 50 Memory Clinics are members of the organization, representing the vast majority of Memory Clinics in Switzerland. They are located all over the country (Fig. 1). SMC has previously published national recommendations for the diagnosis and treatment of dementia in Switzerland [1, 2] and has been engaged in the definition and implementation of structure and process quality indicators for Memory Clinics. Therefore, SMC decided to take the lead to create intersocietal appropriate use recommendations for the use of anti-amyloid monoclonal antibodies (mAbs) in Switzerland.

Lecanemab and donanemab are immunoglobulin gamma 1 (IgG1) mAbs that target different epitopes of β-amyloid. By binding either to oligomers, protofibrils and insoluble fibrils (lecanemab) or to the N-terminal truncated and pyroglutamate modified form of β-amyloid in the brain (donanemab), they both promote plaque removal through microglial-mediated phagocytosis. Lecanemab was approved by the Food and Drug Administration (FDA) for the treatment of Alzheimer disease (AD) in the USA in July 2023, followed by a growing number of countries including Japan, China, and the UK. Final approval in the European Union has been granted in April 2025. The Australian Therapeutic Goods Administration (TGA) decided in October 2024 not to approve lecanemab. Donanemab got full approval by the Food and Drug Administration (FDA) for the treatment of AD in the USA in July 2024, followed by Japan and the UK. In many other countries, including Switzerland, regulatory authorities' approval is pending for both drugs.

The indication of anti-amyloid mAbs includes patients with early-stage AD (mild cognitive impairment (MCI) or mild dementia) whose pathophysiology has been confirmed using cerebrospinal fluid (CSF) biomarkers or PET-CT. The prescribing information for both drugs made available by the FDA, based on data from populations of selected AD patients in the phase III studies [3, 4], describes its indications and its methods of use and administration. Initial recommendations for appropriate use of lecanemab in a general population of AD patients were published by Cummings et al. [5] in March 2023, those for donanemab are currently in preparation [6].

While many aspects of the published appropriate use criteria can be transferred to other countries, some aspects have to be modified on a country-specific level. Moreover, since the publication of the lecanemab criteria, data from additional analyses, case reports, feedback, and comments have been published, providing an additional basis for discussion of the development of these criteria for use [7–9]. This is why we are issuing country-specific recommendations in view of the potential approval of lecanemab and/or donanemab in Switzerland, addressing indications and contraindications. In the absence of available data on long-term benefits, our recommendations are based primarily on the risk/benefit ratio, with particular emphasis on limiting the risk of adverse events, in particular amyloid-related imaging abnormalities (ARIA).

These recommendations do not replace the clinician's judgment or the indications for prescribing which will be issued by Swissmedic after potential approval but aim to prepare physicians and institutions for the upcoming new treatment options in the field of AD. They can serve as recommendations for good clinical practice to specialists who will prescribe, deliver, and provide follow-up for anti-amyloid mAbs. The recommendations may change depending on the follow-up data collected and the information derived from them. The practical use of these recommendations requires additional resources in some fields of medicine. The SMC has recently published an extensive analysis of the available resources in Switzerland and potential bottlenecks in the case of approval of new anti-amyloid drugs [10].

## Method

A task force of experts was appointed in August 2023 by SMC, made up of neurologists, geriatricians, old-age psychiatrists, neuropsychologists, neuroradiologists, and

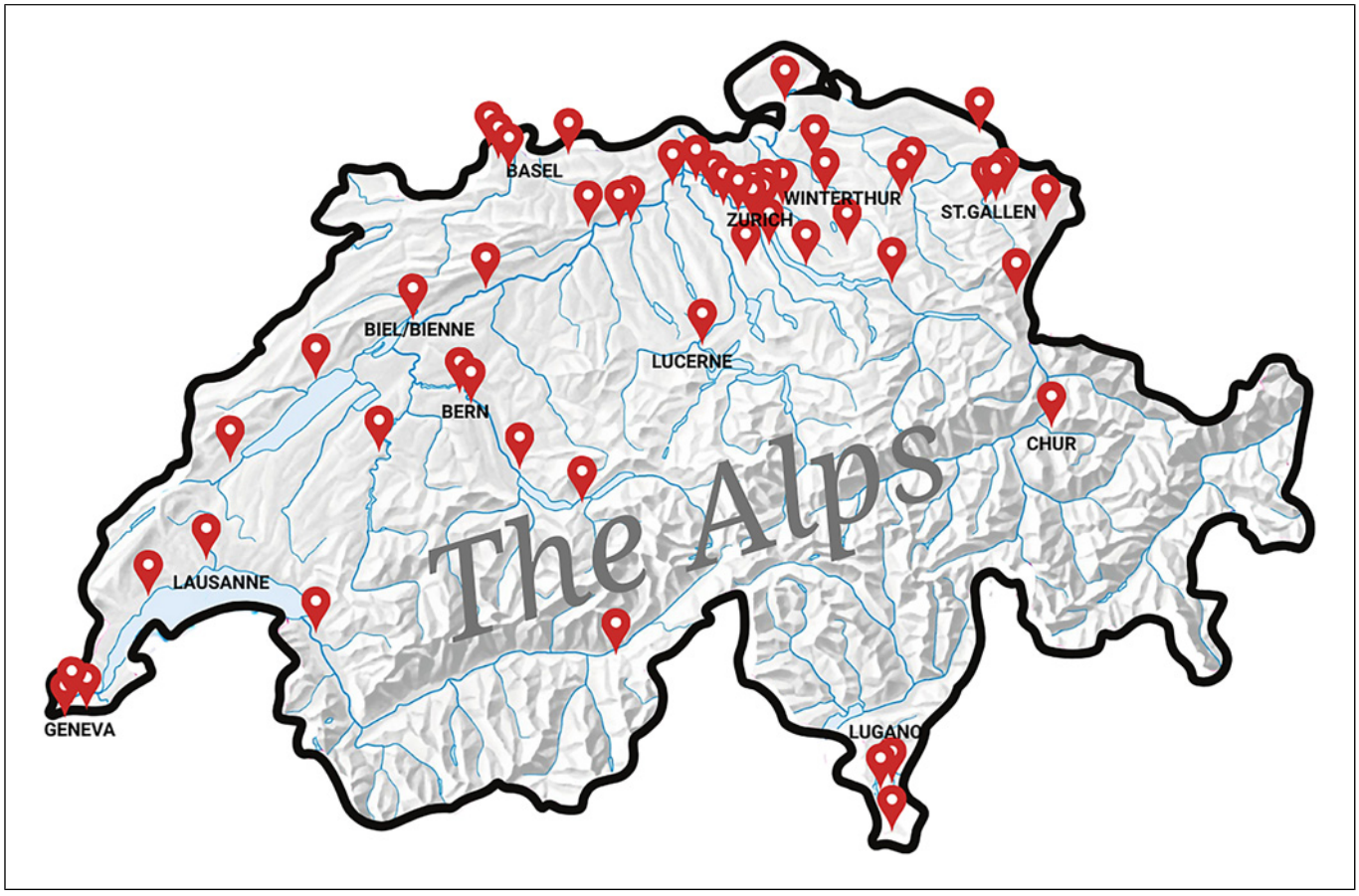


**Fig. 1.** Location of Memory Clinics that are affiliated to the Swiss Memory Clinics association (SMC).

patient organizations, including representatives of academic and non-academic memory clinics. The task force met regularly by videoconference to reach a consensus on use recommendations in Switzerland, based on a critical analysis of the FDA's indications for prescription, published data from clinical trials (phase II and phase III), published results obtained with other anti-amyloid treatments, an analysis of recent literature on AD and the respective drugs, US recommendations [5], and the advisory opinions of other international experts from Belgium, France, Israel, and Japan.

*Eligible Patients for Treatment with Anti-Amyloid mAbs*

After potential approval, we recommend the use of lecanemab and donanemab for patients with AD in its early clinical stage, i.e., minor neurocognitive disorder (MCI) or mild stage of major neurocognitive disorder (mild dementia) according to DSM 5 classification [11], with evidence of β-amyloid and hyperphosphorylated tau pathology (Table 1).

How Do We Recommend Determining an Early Clinical Stage of AD?

A Montreal Cognitive Assessment (MoCA) score greater than or equal to 15/30, or a Mini-Mental Status Examination (MMSE) score greater than or equal to 20/30 [3, 4, 12], is required and must be associated with a global functional score on the Clinical Dementia Rating (CDR) scale of 0.5 or 1. If low education levels or linguistic limitations influence cognitive testing, the CDR scale of 0.5 or 1 can outweigh lower scores of MoCA or MMSE. To determine this global CDR score in clinical practice, each item may be scored using a simplified score based on the clinician's observation and judgment, the neuropsychological assessment, the information from the patient and her or his caregiver and/or an instrumental

**Table 1.** Diagnostic criteria for mild cognitive impairment (MCI) due to AD and probable mild AD dementia with evidence of the AD pathophysiological process

| Syndrom | Definition |
|---|---|
| MCI | A) Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition)<br>Cognitive concerns by the patient, knowledgeable informant, or the physician<br>Substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment<br>B) The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required)<br>C) The cognitive deficits do not occur exclusively in the context of delirium<br>D) The cognitive deficits are not better explained by another mental disorder |
| Mild dementia | A) Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment<br>B) the cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)<br>Mild stage of dementia requires difficulties with instrumental activities of daily living (e.g., housework, managing money) but not with basic activities of daily living (e.g., dressing, feeding, personal hygiene)<br>C) The cognitive deficits do not occur exclusively in the context of delirium<br>D) The cognitive deficits are not better explained by another mental disorder |
| Probable AD with evidence of the AD pathophysiological process | • History of worsening of cognition by report or observation<br>• The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:<br>• Amnestic presentation (medial temporal type)<br>• Non-amnestic presentations (logopenic variant of PPA or cortical posterior atrophy)<br>• Positive amyloid and Tau biomarker |
| Cognitive impairment severity | MoCA 15–30 or MMSE score of 20–30 and CDR 0.5–1 to define MCI and mild dementia |

Severity measures such as the MMSE or MoCA and CDR scale are used to define MCI and mild AD dementia. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; PPA, primary progressive aphasia.

activities of daily living (IADL) scale. The global score shall be determined by the CDR's own algorithm based on the data entered for each item.

Which Clinical Phenotypes of AD Can Be Treated?

After potential approval, we recommend the use of anti-amyloid mAbs for patients presenting a common phenotype of AD according to criteria of the International Working Group (IWG) [13], i.e., a progressive amnestic syndrome or a logopenic variant of primary progressive aphasia or a posterior cortical syndrome. The phase III studies included patients with an amnestic phenotype of AD [3, 4]. The literature is consistent in considering that the other common phenotypes of AD have an identical pathophysiology but affect different brain regions [14].

### How Do We Recommend Proving the Pathophysiological Evidence of AD?

The biological definition of AD is the combination of amyloidopathy and tauopathy, which determine an A+/T+ biological status [13]. We recommend a lumbar puncture as a first option and the gold standard test for identifying AD pathophysiology with observation of an abnormally significant decrease of AB42 level and an abnormally significant increase in phosphorylated tau protein (pTau-181) in the CSF. Regarding β-amyloid, ratios like the AB42/AB40 ratio, the Tau/AB42 ratio or the pTau/AB42 ratio are recommended rather than AB42 alone to reduce false negatives and false positives [15]. In the case of normal or gray zone amyloid ratio status (+10% below threshold) and T+ status with a common AD phenotype, we recommend completing the analysis with an amyloid PET in order to eliminate false negative results [16, 17].

Currently, there is little evidence to provide a clear recommendation for treating subjects with an A+T- status. However, relatively low levels of tau pathology have been found to be associated with better clinical outcomes [4]. Therefore, borderline/gray zone results for CSF pTau [18] in patients that are A+ and have a common phenotype may be considered (see special cases below). If lumbar puncture is not possible due to contraindications, an amyloid PET-CT confirming the presence of diffuse cortical amyloid plaques will be sufficient if the clinical phenotype is common. In this specific case, if positive, we accept this second option test without knowing the T status (A+/T?) and recommend treatment given the high probability of having AD [19].

### Special Cases

We recommend that indication to treatment is discussed in multidisciplinary settings such as memory boards or exchanges with other dementia experts to validate that AD pathophysiology explains the clinical phenotype in eligible patients in the following situations.

(1) Patients with an uncommon AD phenotype [13] (i.e., behavioral, dysexecutive, non-fluent primary progressive aphasia, semantic dementia, corticobasal syndrome), with an A+/T+ status. These phenotypes are more frequently characterized by non-AD pathology.
(2) Clinical symptoms or imaging findings suggestive of a mixed degenerative pathology (e.g., Lewy body disease plus AD) with an A+/T+ status.
(3) CSF pTau biomarkers in the gray zone (-10% below threshold) with a positive amyloid status and a common phenotype of AD.

### For Which Conditions Do We Not Recommend Treatment with Anti-Amyloid mAbs?

*Relevant Clinical Features*. We recommend adopting most of the exclusion criteria of the phase III trials while allowing medical judgment for individual circumstances (Table 2). On the other hand, we recommend excluding patients with a history of epileptic seizures until further data are available. This is because epilepsy is a possible clinical manifestation of treatment complications (ARIA) and represents a potential source of diagnostic confusion for the follow-up of treated patients [20]. Patients with uncontrolled cancer, organ failure (cardiac, respiratory, digestive, renal), and/or other uncontrolled neurological or chronic diseases are excluded due to the risks associated with lack of compliance with treatment or the consequences of treatment for these diseases. Patients currently suffering from major depression or at risk of suicide are also excluded from treatment, as are patients suffering from another mental illness (psychosis or other cause) which does not allow them to consent and/or to discern about the treatment and its modalities and/or to comply with the necessary follow-up. Patients who do not have a family carer can only be treated with anti-amyloid mAbs if they receive very close medical care from nursing staff or other medical referents. Carefully obtained informed consent must be available.

In the absence of exclusion criteria, we recommend that the clinician's judgment takes into account the patient's functional status, quality of life, and life expectancy in order to assess the medium- and long-term benefit of the treatment. In older patients a standardized comprehensive geriatric assessment is recommended, and the advance directive or an advanced care plan should be discussed with the patient.

*Concomitant Medications Relevant to Anti-Amyloid mAbs*. Cholinesterase inhibitors or memantine can and, whenever possible, should be taken together with mAbs. Lecanemab and donanemab may increase the risk of cerebral hemorrhage. Patients treated with warfarin, vitamin K antagonists, direct oral anticoagulants (dabigatran, rivaroxaban, edoxaban, apixaban, betrixaban), or high-dose heparin, should be excluded until more evidence has been accumulated regarding the safety of administering anti-amyloid drugs to patients on anticoagulants. On the other hand, anti-amyloid mAbs can be used in patients taking standard doses of aspirin (up to 325 mg/day) or other antiplatelet agents (clopidogrel, prasugrel, ticagrelor; at standard therapeutic doses) in monotherapy. Patients on dual antiplatelet therapy that meet all other criteria for treatment should be treated with caution, as well as those receiving selective serotonin reuptake inhibitors (SSRI) antidepressant treatment. Several studies have demonstrated a slightly increased intracerebral bleeding risk under SSRI exposure [5, 21].

**Table 2.** Inclusion and exclusion criteria used in the CLARITY-AD study and corresponding Swiss proposals of the Appropriate Use Recommendations (AUR)

| Inclusion and exclusion criteria applied in the Clarity-AD Trial of lecanemab | AUR for patients considered for treatment with lecanemab or donanemab |
|---|---|
| Inclusion | |
| Diagnosis of MCI or mild AD dementia | Clinical diagnosis of MCI or mild AD dementia as defined in Table 1 |
| Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII) | Progressive amnestic syndrome of the "hippocampal type."<br>Objective impairment in episodic memory<br>Progressive impairment in single-word retrieval and in repetition of sentences<br>Progressive disturbance of visual±other posterior cognitive functions |
| Positive biomarker for brain amyloid pathology<br>50–90 years of age | Positive amyloid and tau biomarker for brain AD pathology<br>Physician judgment used for patients outside the 50–90 year age range |
| Mini-Mental State Examination (MMSE) score >22 at screening and baseline and <30 at screening and baseline<br>Body mass index (BMI) greater than 17 and less than 35 | MMSE 20–30 or MoCA 15–30 score compatible with early AD. CDR of 0.5–1.0<br>Physician judgment used for patients at the extremes of BMI |
| If receiving an acetylcholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine or both must be on a stable dose for at least 12 weeks prior to Baseline | Patients on cognitive enhancing agents (donepezil, rivastigmine, galantamine, or memantine) for AD are eligible for treatment |
| Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to Baseline | Patients on standard of care for other medical illnesses (see below for specifics regarding anticoagulation or other specifics medications) |
| Have an identified study partner | Have a care partner or a medical referent who can ensure very close medical care and support needed to be treated with mAbs |
| Provide written informed consent | Patients, care partners, and appropriate family members should understand the requirements for anti-amyloid mAbs therapy and the potential benefit and potential harm of treatment |
| Exclusion | |
| Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD | Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment or any non-AD MCI or dementia |
| More than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; multiple lacunar infarcts or stroke involving a major vascular territory; severe small vessel disease; or other major intracranial pathology | Probable CAA, according to Boston 2.0 criteria or CAA-ri, evidence of vasogenic edema; multiple lacunar infarcts or stroke involving a major vascular territory; severe small vessel (Fazekas 3); or other major intracranial pathology |
| Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD | MRI evidence of non-AD dementia |
| History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of screening | Recent history (within 12 months) of stroke or transient ischemic attacks or any history of seizures |
| Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant | Mental illness (e.g., psychosis) that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements |

**Table 2** (continued)

| Inclusion and exclusion criteria applied in the Clarity-AD Trial of lecanemab | AUR for patients considered for treatment with lecanemab or donanemab |
|---|---|
| Geriatric Depression Scale (GDS) score >8 at screening | Major depression that will interfere with comprehension of the requirements, potential benefit, and potential harms of treatment; patients for whom disclosure of a positive biomarker may trigger suicidal ideation. Patients with less severe depression or whose depression resolves may be treatment candidates |
| Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic mAbs (or derivatives of mAbs), systemic immunosuppressants, or plasmapheresis during the study | Any history of immunologic disease (e.g., lupus erythematosus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants, immunoglobulins, or mAbs or their derivatives |
| Participants with a bleeding disorder that is not under adequate control (including a platelet count 1.5 for participants who are not on anticoagulant treatment, for example, warfarin) | Patients with a bleeding disorder that is not under adequate control (including a platelet count 1.5 for participants who are not on anticoagulant) |
| Participants who are on anticoagulant therapy should have their anticoagulant status optimized and be on a stable dose for 4 weeks before Screening | Patients on anticoagulants (coumadin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban, or heparin) should not receive anti-amyloid mAbs |
| Any other medical conditions (example, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which could affect the participant's safety or interfere with the study assessments | Unstable medical conditions that may affect or be affected by anti-amyloid mAbs therapy |

Swiss AUR encounter information from lecanemab and donanemab trials. CAA, cerebral amyloid angiopathy; CAA-ri, cerebral amyloid angiopathy-related inflammation.

In the absence of available data, patients treated with immunosuppressive drugs, immunomodulators or other immunotherapies should be excluded. The same applies to patients who have received anti-amyloid treatment (passive or active immunotherapy, action on secretases) as part of previous therapeutic trials due to the increased risk of ARIA [22].

*Imaging Exclusion Criteria*. Brain MRI performed not more than 3 months prior to treatment initiation is mandatory. Individuals who are unable to undergo MRI due to claustrophobia, non-MRI-compatible pacemakers, defibrillators or metallic implants are not eligible for treatment with anti-amyloid mAbs as ARIA cannot be monitored. Specific protocols for screening and monitoring patients eligible for treatment will be published by the Swiss Society of Neuroradiology.

Patients with signs of vasogenic edema; with more than two lacunar infarcts or strokes involving a major vascular territory; with white matter abnormalities corresponding to microangiopathy with a Fazekas score of 3; with signs of beta-amyloid angiitis; inflammation associated with cerebral amyloid angiopathy (CAA); with criteria for probable CAA according to Boston 2.0 criteria [9, 23, 24] or other major intracranial pathology likely to cause cognitive impairment are excluded (Table 3). Importantly, we recommend excluding patients that show cortical superficial siderosis, even though they were included in the donanemab phase III trial. In order to detect all relevant imaging exclusion criteria, a combination of widely available T2*, diffusion-weighted and FLAIR images will be proposed for imaging these patients.

Appropriate Use of Apolipoprotein E Genotyping

The apolipoprotein E-4 (APOE4) genotype increases the risk of CAA and common AD co-pathologies such as cerebrovascular disease. APOE4 carriers (particularly homozygotes) have an increased risk of ARIA (x3 to x6), symptomatic ARIA (x6) and recurrent ARIA [25]. They have an increased risk of CAA-related inflammation and amyloid-beta related angiitis, additional risk factors for ARIA. APOE genotyping should be mandatory for all treatment candidates prior to initiation of anti-amyloid mAbs. This information will be important for safety considerations and risk/benefit discussions with patients and caregivers. Our expert group mentions that the APOE4 homozygous subgroup of the phase III trials had less benefit of treatment, while having significantly more side effects.

**Table 3.** MRI criteria for probable cerebral amyloid angiopathy-related inflammation

| |
|---|
| Probably CAA-ri |
| Age ≥40 years of age |
| Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH |
| MRI shows unifocal or multifocal WMH lesions (cortico-subcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH |
| Presence of ≥1 of the following cortico-subcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis |
| Absence of neoplastic, infectious, or other cause |
| MRI shows unifocal or multifocal WMH lesions (cortico-subcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH |
| Presence of ≥1 of the following cortico-subcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis |
| Absence of neoplastic, infectious, or other cause |
| MRI Criteria for probable CAA according to Boston 2.0 |
| Demonstrates either at least two of the following strictly lobar hemorrhagic lesions on T2[a]-weighted MRI, in any combination: intracerebral hemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis (multiple distinct foci are counted as independent hemorrhagic lesions) or convexity subarachnoid hemorrhage (multiple distinct foci are counted as independent hemorrhagic lesions) OR one lobar hemorrhagic lesion plus one white matter feature (severe perivascular spaces in the centrum semi ovale or white matter hyperintensities in a multispot pattern) in the absence of any deep hemorrhagic lesions on T2[a]-weighted MRI AND other cause of hemorrhagic lesions[a] |

CAA, cerebral amyloid angiopathy; CAA-ri, cerebral amyloid angiopathy-related inflammation. [a]Hemorrhagic lesion in cerebellum not counted as either lobar or deep hemorrhagic lesion.

### Risk-Reduction of Treatment-Related Side Effects

The most frequent treatment-related side effects are infusion reactions which can be handled in the setting of infusion centers. However, access to an Emergency Department should be given in close vicinity to the infusion center. ARIA are the most relevant treatment-related side effects of lecanemab and donanemab, presenting as edema (ARIA-E) or hemorrhage (ARIA-H). As most ARIA are asymptomatic, frequent MRI imaging is mandatory during the first 6 months of treatment. The FDA label demands MRI imaging after the second, third, and sixth month of treatment with lecanemab and after the first, second, third, and sixth month of treatment with donanemab, as well as in any case of symptoms compatible with ARIA (e.g., new-onset headache, confusional state, seizure, stroke-like symptoms). In case of ARIA, treatment with anti-amyloid mAbs might be suspended or the dose reduced, depending on the severity of MRI findings and symptoms.

### Management of Stroke and Stroke-Like Symptoms under Treatment with Anti-Amyloid mAbs

Symptomatic ARIA can present clinically with symptoms of stroke, e.g., aphasia, hemianopsia, confusional state or hemiparesis. After a potential approval of anti-amyloid mAbs, it will be important to educate physicians in Stroke Units on how to handle patients on anti-amyloid drugs with stroke symptoms. Patients should carry documents that disclose their treatment and hospital records should be marked accordingly.

Anti-amyloid mAbs significantly increase the risk of intracerebral bleeding with thrombolysis. During the phase III trials and in the following post-marketing use of lecanemab and donanemab there have been several reports of massive bleeding and even fatal outcomes following intravenous thrombolysis. Emergency MRI should be performed to rule out ARIA as the cause of the symptoms. If there are no signs of ARIA, but stroke with large vessel occlusion, thrombectomy is the first choice for stroke treatment. Patients on anti-amyloid mAbs should only receive intravenous thrombolysis after exclusion of ARIA with MRI and thorough individual benefit/risk discussions. Recommendations for stroke treatment of patients on anti-amyloid mAbs have recently been published by the American Heart Association [26].

Follow-Up and Evaluation of Treatment Efficacy

At the time of writing, there are limited data available regarding length of treatment and stop criteria. In the phase III trial of donanemab, the drug was stopped after amyloid-load in PET fell under a defined centiloid level ("amyloid-negativity") [4]. No stop criterion was defined in the lecanemab phase III trial [3]. The expert group proposes – in view of missing data – the use of clinical and amyloid PET criteria. If a patient progresses to a disease state of moderate or severe dementia (corresponding to a CDR of 2 or 3), the treatment with anti-amyloid mAbs should be stopped. Additionally, as soon as amyloid-negativity is proven, physicians might discuss to stop treatment with donanemab and to extend treatment intervals in the case of lecanemab. The rationale for the differential recommendation lies in different study data and modes of action. This topic clearly needs to be addressed in future clinical trials.

*Minimal Structural and Functional Quality Standards for the Delivery of Anti-Amyloid mAbs*

We endorse the statements from the US Appropriate Use Recommendations for lecanemab [5], and specifically the following.

Resources for Safe and Effective Use of Anti-Amyloid mAbs

(1) Clinicians skilled in the assessment of cognition to identify individuals with MCI or mild dementia due to AD
(2) MRI available for baseline assessment of cerebrovascular pathology and for monitoring of ARIA
(3) Radiologists, neurologists, or other clinicians expert in the identification and interpretation of cerebrovascular lesions and ARIA
(4) Amyloid positron emission tomography or lumbar puncture capability to determine the amyloid status of treatment candidates
(5) Radiologists, nuclear medicine specialists, neurologists, or other specialists skilled in the interpretation of amyloid imaging or neurologists, radiologists, or other clinicians skilled in the conduct of lumbar puncture
(6) APOE genotyping resources
(7) Genetic expertise to counsel patients on the implications of APOE genotyping
(8) Expertise in communicating with patients and care partners regarding anticipated benefits, potential harm, and requirements for administration and monitoring while on anti-amyloid mAbs
(9) Infusion settings that can be made available every 2 weeks to patients receiving therapy
(10) Knowledgeable staff at infusion sites capable of recognizing and managing infusion reactions
(11) Communication channels established between experts interpreting MRIs and clinicians treating patients with anti-amyloid mAbs
(12) Communication channels established between clinicians treating patients with anti-amyloid mAbs and the patient and care partner
(13) Availability of hospital resources including intensive care unit
(14) Expertise in the management of seizures and status epilepticus for patients with severe or serious ARIA
(15) Protocol with standard operating procedures for management of serious and severe ARIA

Resources for Management of ARIA

(16) Emergency department with resources to assess suspected or known ARIA including an intensive care unit
(17) 3T MRI scanners readily available for unscheduled scanning of symptomatic patients
(18) Knowledgeable MRI readers proficient in detection and interpretation of ARIA
(19) Clinicians with experience in the management of cerebral edema or ARIA
(20) Hospital ward for monitoring and management of ARIA
(21) Electroencephalography available to inpatients
(22) Neurologist with experience in management of seizures and status epilepticus

The above-mentioned statements are operationalized and translated to the Swiss environment.

*Features Specific to the Swiss Environment*

Infrastructure and Personnel Standards

(1) The delivery of anti-amyloid mAbs will require both (i) analytical expertise for the interpretation of cognitive assessment (by board-certified neuropsychologists) and individual biomarker positivity/negativity (by board-certified neuroradiologists, nuclear medical specialists, and clinical chemistry physicians) and (ii) clinical expertise to integrate cognitive and biomarker results in the larger clinical context (by the dementia specialist). The dementia specialist can be a clinical neurologist, old-age psychiatrist, or geriatrician (US Recommendations #1, #3, #5). When mAb treatment is performed in a team without board-certified specialists from all three clinical disciplines, neurological, old age psychiatric and geriatric expertise must be given within the team or in close collaboration.
(2) The group of Swiss dementia experts acknowledges that volumes of activity and biomarker use can be used as proxies of expertise. The panel strongly

recommends that the dementia specialist who will prescribe and deliver MABs will have (i) skills for a medical exam including neurological status, assessment of behavioral and psychological symptoms of dementia (BPSD), interpretation of brain MRI, interpretation of amyloid/tau PET, and interpretation of AD fluid biomarkers, and (ii) 3 years of cumulative experience with clinical decision-making responsibilities in a memory clinic of at least medium size (200 new diagnostic workups/year or more) and extensive use of diagnostic biomarkers (US Recommendations #1, #3, #5).

(3) According to the Swiss regulations, genetic counseling for specific diseases and conditions can be delivered by disease specialists (US Recommendation #7).

(4) Memory clinics where anti-amyloid mAbs are delivered by the dementia specialist should comply with the quality criteria of the SMC network and have the capacity of 200 new diagnostic workups/year or more, to ensure a sufficient frequency of anti-amyloid mAb candidates. Memory clinics which do not qualify for the above criteria may wish to e.g., carry out assessment and make diagnosis and refer patients to qualified Memory Clinics for mAb treatment. The referring Memory Clinics may wish to retain the clinical follow-up of treated patients to collect over time sufficient experience to qualify as a mAb treatment provider (US Recommendations #1 to #15);

(5) In the CLARITY-AD trial with lecanemab, 25/898 participants had symptoms related to ARIA-E, with 41 clinical presentations. Of these, 12% had focal symptoms (diplopia, aphasia, ataxia, paresthesias, speech disorder, and partial seizures with secondary generalization), 51% had non-focal symptoms (blurred vision, reduction of visual acuity, visual impairment, amnesia, cognitive disorder, generalized tonic-clonic seizures, headache, reduced responsivity to stimuli, behavior disorder, and hallucinations), and 37% had aspecific symptoms (tinnitus, retinal hemorrhage, nausea, vomiting, fatigue, fall, dizziness, confusion). The symptoms of ARIA-H were 11% focal, 33% non-focal, and 56% aspecific, respectively. The single most frequent presentation of ARIA-H and ARIA-E was headache (29% and 31%), and the second most frequent was confusion for ARIA-H (10%) and dizziness for ARIA-E (23%) [27]. Access to neurological expertise in addition to the dementia specialist (if not a neurologist) is strongly recommended to support the dementia expert for the first diagnosis of ARIA and follow-up and treatment-related decision making.

Standard Operating Procedures

(6) Standard operating procedures (SOPs) should be available for mild and moderate infusion-related severe adverse reactions as well as for emergencies related to severe infusion-related adverse reactions. Ideally, an Emergency department should be available on the same premises or nearby (US Recommendations #10, #12, #13);

(7) SOPs should be available for the management of severe adverse events (e.g., stroke, seizures, ARIA, etc.). In case of serious new neurological symptoms, SOPs should make the referral to a nearby Hospital with a Neurological Department mandatory. SOPs should include criteria for hospitalization and admission to a nearby Emergency department and Stroke unit, preferably in an institution with a neurology department. SOPs will include management of severe symptomatic ARIA (US Recommendations #10, #11, #12, #13, #14, #15). The Emergency Department and Stroke Unit must not necessarily be on the same premises or in the same institution as the Memory Clinic. Nevertheless, they should be in the same geographic area as the Memory Clinic, and patients should be informed of where to apply in case of need and should be given a mAb information card (US Recommendations #13);

(8) SOPs should be available for ARIA not requiring access to an Emergency Department. The SOPs should stipulate that these ARIA should be managed in the Memory clinic (US Recommendations #10, #11, #12);

(9) SOPs should be known to and signed by all parties involved (US Recommendations #11, #12);

(10) All SOPs will need to be validated by the local medical director, chief physician, or chief medical officer (US Recommendations #15).

Registry

(11) SMC endorses the development of a registry of treated and, if possible, untreated memory clinic patients.

(12) The registry should preferably be country-wide and its ontology should be harmonized to the homologous European and US registries. If a Swiss-wide registry will not be available, regional or local

registries are strongly encouraged but in any case with a harmonized ontology to facilitate data sharing.

## Quality Assurance and Compliance

SMC provides professional recommendations and quality standards for the correct diagnosis of MCI and mild dementia due to AD [2], that are crucial in identifying subjects suitable for anti-amyloid mAbs. SMC supports a country-wide gradual approach to MAB delivery, where clinical and organizational criteria will be stricter in the early days. Criteria will be adapted as the medical community acquires familiarity with the drugs.

SMC will – together with its collaboration partners – promote the development of forums for dementia specialists to share challenges and opportunities for the use of anti-amyloid mAbs in the clinic and individual case discussions. These will help maximize patient safety and cost-effectiveness and harmonize practices throughout Switzerland. For instance, clinical case discussion forums, discussion on organizational barriers and issues, monitoring of anti-amyloid mAb uptake and use across centers, and educational courses.

If both a memory clinic and a specialty service (geriatrics, psychiatry, neurology) are present in the same organization, they are encouraged to offer patients a single point of contact and delivery. SMC supports the development of a strong synergy with primary care and pertinent professional scientific societies, with the aim of a concerted management of access and expectations. This publication is regarded as a dynamic document. Regular revisions of this document are envisioned.

## Conflict of Interest Statement

A.F. received speaker and consultancy fees from Biogen Pharma AG, Eisai Pharma AG, Eli Lilly SA, Fujirebio GmbH, GE Healthcare GmbH, OM Pharma SA, Roche Pharma AG, Sandoz Pharmaceuticals AG, Schwabe Pharma AG, and Zur Rose Swiss AG. O.R. received speaker and consultancy fees from OM Pharma AG, Eli Lilly SA, Schwabe Pharma AG, and Roche Pharma AG and is an investigator in clinical trials (Novo Nordisk and Nestlé). A.L. received speaker and consultancy fees from MaxiVAX SA, Novo Nordisk Pharma AG, and Silamed. G.A. received speaker and consultancy fees from Eli Lilly SA, Roche Pharma AG, and Schwabe Pharma AG. T.M.-H. received speaker fees from OM Pharma SA. A.M. received speaker and consultancy fees as well as travel expenses from pharma companies (not detailed). K.-O.L. received speaker and consultancy fees from Biogen Pharma AG and Eli Lilly SA. S.B. received speaker and consultancy fees from Eisai Pharma AG and OM Pharma SA. J.P. received speaker and consultancy fees from Eisai Pharma AG and OM Pharma SA, Eli Lilly SA, Fujirebio GmbH, Roche Pharma AG, Schwabe Pharma AG, and Zur Rose Swiss AG. J.P. received research funding from OM Pharma, Synapsis Alzheimer's Research Switzerland, and Swiss National Science Foundation. M.B. received speaker and consultancy fees from Eli Lilly SA, Roche Pharma AG, and F. Hoffmann-La Roche Ltd (Roche Diagnostics). K.L. received travel expenses from OM Pharma SA. A.G. received speaker and consultancy fees from Biogen Pharma AG, Eli Lilly SA, Eisai Pharma AG, NeuroImmune AG, and Schwabe Pharma AG; was an investigator in clinical trials (Biogen Pharma AG); participated in research and project collaborations (NeuroImmune AG) and a project collaboration Schwabe Pharma AG; and has received funding by the Swiss National Science Foundation, the Synapsis Foundation, the EMPIRIS Foundation, and the Stiftung für Naturwissenschaftliche und Technische Forschung, Liechtenstein. H.H.J. received consultancy fees from Eli Lilly SA. D.G. received speaker and consultancy fees from Biogen Pharma AG, Eisai Pharma AG, H. Lundbeck A/S, OM Pharma Suisse SA, and Schwabe Pharma AG. R.M. received speaker and consultancy fees from Eisai Pharma AG. G.B.F. has received funding through the Private Foundation of Geneva University Hospitals from A.P.R.A. – Association Suisse pour la Recherche sur la Maladie d'Alzheimer, Genève; Fondation Segré, Genève; Ivan Pictet, Genève; Race Against Dementia Foundation, London, UK; Fondation Child Care, Genève; Fondation Edmond J. Safra, Genève; Fondation Minkoff, Genève; Fondazione Agusta, Lugano; McCall Macbain Foundation, Canada; Nicole et René Keller, Genève; Fondation AETAS, Genève. G.B.F. has also received funding through the University of Geneva or Geneva University Hospitals for IISSs from ROCHE Pharma AG, OM Pharma SA, EISAI Pharma AG, Biogen Pharma AG, and Novo Nordisk Pharma AG; and for competitive research projects from H2020, Innovative Medicines Initiative (IMI), IMI2, Swiss National Science Foundation, and VELUX Foundation. G.B.F. also received speaker and consultancy fees via institution from Biogen Pharma AG Eli Lilly SA, GE Healthcare GmbH, Novo Nordisk Pharma AG, and Roche Pharma AG. M.S. and N.B.-B. have no conflicts of interest to declare. Prof. Gilles Allali was a member of the journal's Editorial Board at the time of submission.


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## Author Contributions

All authors contributed to the conception of the work, interpretation of data, and working group discussions; approved the final version of the manuscript; and are accountable for all aspects of the work. A.F. and G.B.F. drafted the manuscript. O.R., A.L., G.A., M.S., T.M.-H., A.U.M., K.-O.L., S.B., N.B.-B., J.P., M.B., K.L., A.G., H.H.J., D.G., and R.M. reviewed the work critically and delivered important intellectual content.

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