Lecanemab – the world's first disease-modifying drug against Alzheimer's disease

In 2023, lecanemab was approved in the US and Japan as a treatment for early Alzheimer's disease, and in early 2024 the drug was also approved in China. In the approved markets the drug is sold under the brand name Leqembi. Applications for market approval have been submitted in many other markets. Lecanemab is the first fully approved drug for early Alzheimer's disease that slows or stops the progress of the disease and reduces cognitive degeneration. BioArctic's researchers are now working on several preclinical projects with differentiated antibodies against Alzheimer's disease with the goal of continuing to improve the lives of patients and their relatives.

Alzheimer's disease is caused by proteins folding improperly, aggregating and forming what are known as protofibrils, which damage nerve cells. Lecanemab is a monoclonal antibody that slows or stops the progress of the disease by binding specifically to these soluble forms of protofibrils/oligomers. The body's immune system can thus detect and break them down. The high selectivity for protofibrils specifically is unique for lecanemab. For example, the antibody binds 1,000 times more strongly to these harmful protofibrils than to the harmless monomers. Lecanemab binds approximately 10 times more strongly to protofibrils than to fibrils that form plaque. The antibody also reduces plaque in the brain.

The first drug to slow or stop the progress of the disease

Today, some 30 million people around the world are living with various stages of Alzheimer's disease. Lecanemab, which originates from the antibody mab158, was developed 2005 by Professor Lars Lannfelt and his research group at Uppsala University. The drug is the first in the world to not only alleviate the symptoms but has also been shown to slow the progress of the disease and reduce the cognitive and functional deterioration in adult individuals with early Alzheimer's disease. In July 2023, lecanemab obtained full approval in the US, and the next approval came in September 2023, this time in Japan. Approval in China followed in the first quarter of

2024. In all markets where the drug has been approved lecanemab is marketed under the brand name Leqembi. Approval in the US was preceded by a meeting of the Food and Drug Administration's Advisory Committee, which scrutinized and discussed Leqembi in detail. In addition to a review of all efficacy and safety data from the large global confirmatory Phase 3 study, Clarity AD, the patient perspective was also highlighted. It was verified that patients, their families, and the physicians administering the therapy appreciate that treatment can begin at an early stage and that the progression can be slowed in the early phases of the disease.

In conjunction with approval in the US, the Centers for Medicare & Medicaid Services (CMS) announced that Medicare, which includes almost all US citizens over the age of 65, would expand coverage of Leqembi in accordance with the FDA-approved prescription information.

Applications for approval have been submitted in several countries and regions. These regulatory procedures are being managed by the global Japanese pharma company Eisai, which has held the global licensing rights to lecanemab since 2007. Eisai are, together with their partner Biogen, responsible for the sale of Leqembi worldwide, with the exception of the Nordic region where BioArctic and Eisai are jointly responsible.

Approval based on convincing Phase 3 data for lecanemab

In September 2022, Eisai reported the results from Clarity AD, the global pivotal Phase 3 study with lecanemab. The detailed findings of the study were published in the New England Journal of Medicine[1]. Clarity AD was a placebo-controlled, double blind, randomized study of 1,795 individuals with early Alzheimer's disease. The treatment group was administered 10 mg/kg of lecanemab every other week. The results showed a statistically highly significant reduction (p=0.00005) in clinical impairment measured using the Clinical Dementia Rating – Sum of Boxes (CDR-SB) cognitive measurement. Compared with the placebo, clinical impairment decreased by 27 percent for the patients treated with lecanemab for up to 18 months and there was an explicit, statistically significant difference compared with a placebo synthesis after only six months of treatment. Even all secondary endpoints – such as the reduction of amyloid levels in the brain after 18 months of treatment compared with the placebo – displayed a high degree of statistical significance. The incidence of the ARIA-E side effect, a type of edema – often symptom-free – that occurs in treatment with anti-amyloid antibodies, was 12.6 percent in the lecanemab group and 1.7 percent in the placebo group. Symptomatic ARIA-E, however, occurred in only 2.8 percent of the lecanemab group and the symptoms were serious in only 0.8 percent of the cases. This was lower than has been shown for other anti-amyloid antibodies. Lecanemab is the first drug to target the cause of the disease that, in a major clinical Phase 3 program, demonstrated significant effect on clinical degeneration in Alzheimer's disease.

A clear value for both patient and society

In March and May 2023, two different modeling studies were published in Neurology and Therapy[2,3] that investigated the potential clinical benefit of lecanemab for Alzheimer's patients in early stages. The simulation model was based on the results from Clarity AD, the clinical Phase 3 study. The first study

Alzheimer's disease in brief

Alzheimer's disease is characterized by the death of brain cells, which causes a gradual impairment of memory and cognitive skills such as intellectual capacity, language, orientation, recognition, and learning ability. The disease is caused by the misfolding and clumping together of the protein amyloid beta into increasingly larger aggregates. When amyloid beta circulates in tissues, the blood, and other bodily fluids as an individual molecule – called a monomer – the protein is harmless. But in Alzheimer's disease, the monomers begin binding to each other and forming larger aggregates. These aggregates accumulate more and more molecules, and when these accumulations – called oligomers or protofibrils – are formed, nerve cells are damaged and the disease develops. Finally, insoluble fibrils are formed that cause plaque in the brain tissue.

1) New England Journal of Medicine, November 29, 2022, doi: 10.1056/NEJMoa2212948
2) Neurology and Therapy, April 2, 2023, doi: 10.1007/s40120-023-00473-w
3) Neurology and Therapy, May 15, 2023, doi: 10.1007/s40120-023-00492-7

concluded that treatment with lecanemab resulted in a delay of two to three years in the average time until the development of more severe stages of Alzheimer's disease compared with the group of patients who received only the standard treatment. The second article studied the social value of lecanemab, with the conclusion that treatment with lecanemab would improve health and quality of life as well as reduce medical costs, the costs of public care, and the burden of care for individuals with early Alzheimer's disease and their caregivers.

Subcutaneous lecanemab under development

Lecanemab is currently administered intravenously (IV) once every two weeks, and monthly maintenance treatment is being developed. To increase user-friendliness and accessibility to the treatment, Eisai is also developing a subcutaneous formulation of lecanemab that can be easily injected under the skin. This facilitates self-treatment at home or in outpatient care. At the CTAD scientific congress in 2023, Eisai reported the six-month findings, which showed that subcutaneous doses of lecanemab resulted in higher levels of exposure, a greater reduction of amyloid plaque than IV at the dosage levels tested, a better side-effect profile as regards infusion reactions, and ARIA at similar levels as previously. Eisai also submitted a registration application in the US for intravenous maintenance treatment and a subcutaneous maintenance treatment is expected to be filed in 2024.

Lecanemab is also being evaluated in asymptomatic disease

In 2020, Eisai initiated a new global clinical Phase 3 study program (AHEAD 3-45) to evaluate the efficacy of lecanemab on individuals with preclinical asymptomatic Alzheimer's disease (i.e. who have not yet developed symptoms but have intermediate or elevated levels of amyloid in the brain). The program is conducted in partnership with the Alzheimer's Clinical Trials Consortium (ACTC), a network for clinical testing in the US that seeks to identify and treat Alzheimer's disease at an early stage. In total, AHEAD 3-45 will include approximately 1,400 people who, after joint screening, will be included in one of the program's two trials, A3 or A45, depending on amyloid levels in the brain as measured with PET. The study aims to prevent development of clear clinical indications of the disease, and thereby also dementia, in the very early stages.

In November 2021, the DIAN-TU research network decided to include lecanemab in a clinical study, Tau NextGen, as the backbone treatment for hereditary Alzheimer's disease in combination with treatment for tau. Tau is a protein that, like amyloid, appears in increased amounts in the brain in conjunction with Alzheimer's disease, but not as early on in the course of the disease.

Additional antibodies under development

BioArctic has four additional antibody projects against Alzheimer's disease in its project portfolio, all of which are in the research or the preclinical phase. These antibodies have unique mechanisms of action and the potential to be developed into new disease-modifying treatments. BAN1503 and BAN2803 are antibody projects against PyroGlu Aβ, which are truncated forms of amyloid beta that have a pronounced tendency to aggregate and create toxic forms that could cause Alzheimer's disease. The mechanism of action for BAN2802 and AD2603 has not yet been communicated. BAN2802 and BAN2803 (PyroGlu Aβ with BT) are two antibody projects against Alzheimer's disease that are being combined with BioArctic's blood-brain barrier technology – BrainTransporter, or BT – to facilitate uptake of antibodies in the brain. In 2023, the candidate antibodies for these projects were selected and are in the preclinical phase. The decision has been made to commence clinical preparatory activities. BioArctic owns rights to all four projects.

4) Alzheimers Association 2015: Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars

350 billion USD

in estimated annual costs for Alzheimer's disease in the US alone. One half of these costs comprises the cost of direct care, and the other half indirect costs.[4]

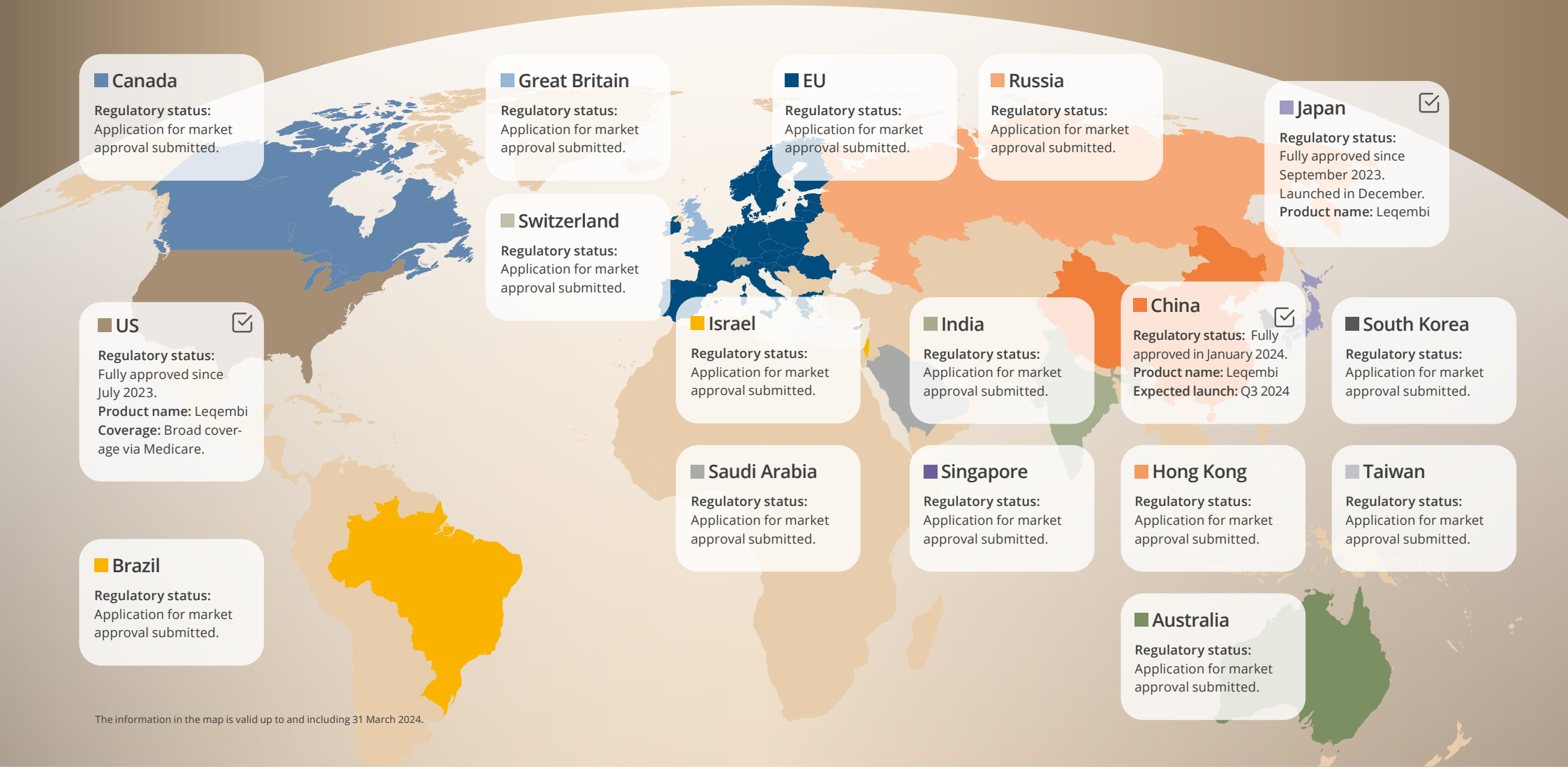
83 billion USD

in potential savings for health care in the US five years after introduction of a treatment that slows the onset of Alzheimer's disease.[4]

Licensing agreement with Eisai provides revenue to BioArctic

Eisai acquired the global rights to lecanemab for treatment of Alzheimer's disease in 2007 and the rights to lecanemab back-up in 2015. The agreements mean that BioArctic has not incurred any costs for the clinical development of lecanemab, and grant the right to a maximum of M 222 EUR (approximately 2.4 billion SEK) in milestone payments. As of December 31, 2023, up to M 84 EUR (~M 900 SEK) in milestone payments remained to be received from Eisai. BioArctic and Eisai have agreed on a joint structure for commercialization and marketing (co-promotion) of lecanemab in the Nordic countries, on the basis of a 50/50 split of costs and income. In addition to milestone payments and co-promotion income, BioArctic will receive royalties. These royalty payments, which have the potential to provide BioArctic with significant revenue, total 9 percent of the global sales of lecanemab excluding sales in the Nordic region.

Eisai has commenced the **global launch of lecanemab**



Canada
Regulatory status: Application for market approval submitted.

Great Britain
Regulatory status: Application for market approval submitted.

EU
Regulatory status: Application for market approval submitted.

Russia
Regulatory status: Application for market approval submitted.

Japan
Regulatory status: Fully approved since September 2023. Launched in December.
Product name: Leqembi

Switzerland
Regulatory status: Application for market approval submitted.

US
Regulatory status: Fully approved since July 2023.
Product name: Leqembi
Coverage: Broad coverage via Medicare.

Israel
Regulatory status: Application for market approval submitted.

India
Regulatory status: Application for market approval submitted.

China
Regulatory status: Fully approved in January 2024.
Product name: Leqembi
Expected launch: Q3 2024

South Korea
Regulatory status: Application for market approval submitted.

Saudi Arabia
Regulatory status: Application for market approval submitted.

Singapore
Regulatory status: Application for market approval submitted.

Hong Kong
Regulatory status: Application for market approval submitted.

Taiwan
Regulatory status: Application for market approval submitted.

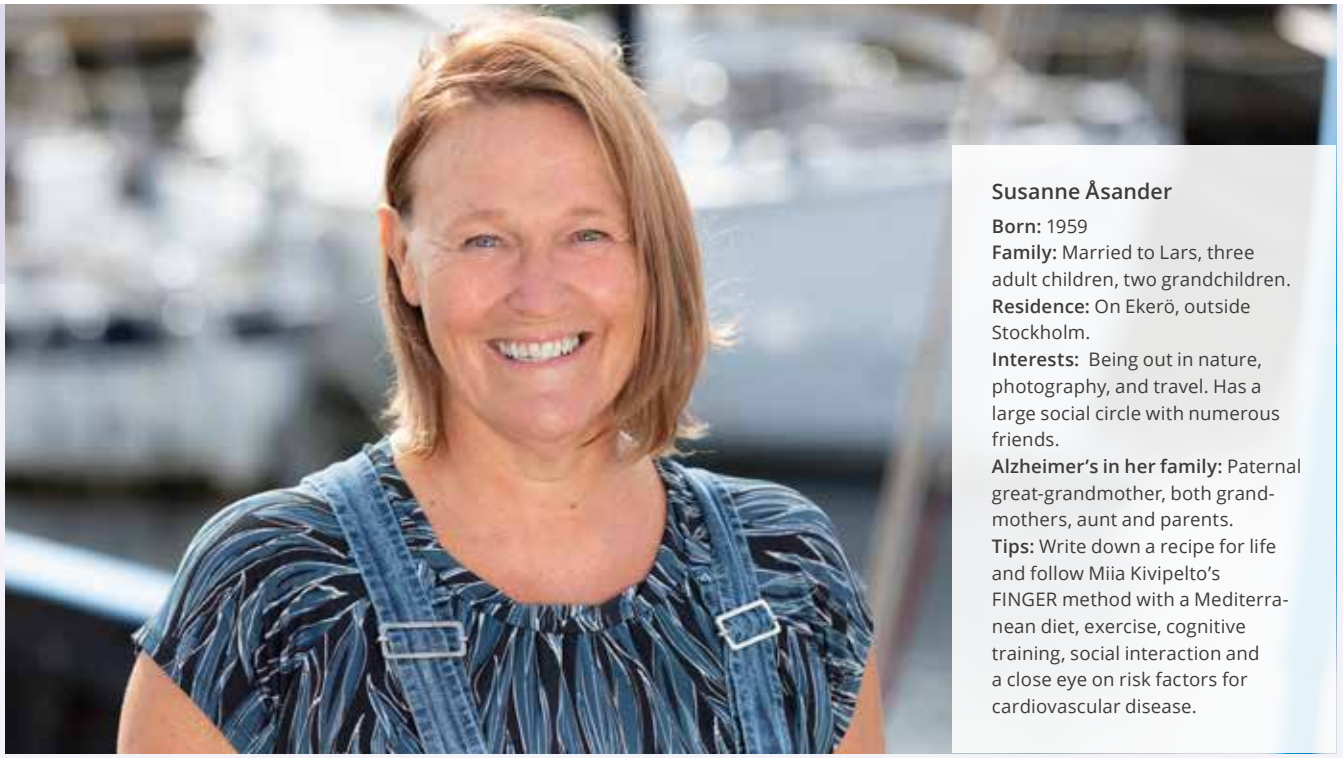
Brazil
Regulatory status: Application for market approval submitted.

Australia
Regulatory status: Application for market approval submitted.

The information in the map is valid up to and including 31 March 2024.

We make **every day count**

Susanne Åsander was convinced that her stress, depression, and poor memory were due to exhaustion and an unsustainable work situation. When she was instead diagnosed with Alzheimer's disease in 2018, it came as a shock. But five years later, she and her husband Lars have made the best of the situation, living life on their terms.



Susanne Åsander

Born: 1959
Family: Married to Lars, three adult children, two grandchildren.
Residence: On Ekerö, outside Stockholm.
Interests: Being out in nature, photography, and travel. Has a large social circle with numerous friends.
Alzheimer's in her family: Paternal great-grandmother, both grandmothers, aunt and parents.
Tips: Write down a recipe for life and follow Miia Kivipelto's FINGER method with a Mediterranean diet, exercise, cognitive training, social interaction and a close eye on risk factors for cardiovascular disease.

Susanne has had a long, high-paced career as an IT consultant, traveling the world for international companies. In the autumn of 2016 she got a new job that seemed exciting at first but, owing to nonexistent resources in the operations, did not turn out at all as she had hoped.

"I had a job that looked fun on paper, but it couldn't be done in practice."

In conjunction with the company reducing its staff in Stockholm in 2018, Susanne opted to resign. She did not at all enjoy the job, feeling stressed and absent-minded in a way she didn't recognize. Lars, who had previously gone on sick leave for exhaustion, thought that he recognized the symptoms.

"I was not surprised, considering Susanne's work situation over the past few years, with a lot of stress and a poor atmosphere at work."

Her stress and depression didn't seem to pass, despite rest and dialogue with a counselor. Given her family history, with both parents having suffered from Alzheimer's disease, Susanne decided to go to her physician to rule out her symptoms being due to the disease.

"Most of all, I wanted to be rid of the worry I had so I could let these thoughts go."

In the spring of 2018, Susanne went to her health care center for an examination. The simple tests did not show any cognitive disorder, but when she mentioned that many of her family members had been afflicted, she got a referral to the memory clinic at Karolinska University Hospital in Huddinge.

Susanne got an appointment there early in the summer of 2018 and underwent new, more extensive testing. This time, things did not go so well. A lumbar puncture was also performed to investigate whether she had elevated levels of biomarkers for Alzheimer's disease in her spinal fluid.

Susanne received a notice in November for her next appointment, and she went alone in the belief that it would confirm the symptoms were due to exhaustion. Instead, she was diagnosed with Alzheimer's.

"Afterward, Lars and I realized it was absolutely ridiculous to have gone there alone, but it didn't say anywhere in the notice that I should bring a family member."

Seven years to live

Susanne does not remember much about the visit apart from the brochure, which informed her that she likely had about seven years left to live, and being asked if she had driven there and if she had any weapons at home. Since she was there alone,

she also had a meeting with a counselor.

"I was given a death sentence, a conversation with the counselor about how I could put everything in order with sick leave and a follow-up appointment six months later. But no plan for care, nobody to call if I had questions, or any additional information on what I could expect."

After the appointment, Susanne got in her car and drove home, but does not remember anything about the trip. When Lars came home later, he found Susanne having a breakdown. After reading the brochure as well, he began Googling for more information.

"I didn't understand that Alzheimer's was that kind of a fatal disease, and the things I found on the Internet didn't put us any more at ease – it was just one horror story after another." The lack of a care plan and information from health care did not improve the matter.

Clinical study was the turning point

During her visit to the memory clinic, Susanne registered her interest in participating in clinical trials, but it was only after she brought it up again that she was invited to apply. The first study Susanne applied to deemed her too healthy, but in July 2020 she finally received an invitation to join Eisai's study with BAN2401 (lecanemab).

"The difference in how I was treated was incredible. Since I joined the study, I've met with my physician every other week in conjunction with receiving treatment. They arrange everything, from tests and follow-ups to referrals and assistance. I feel very well looked after."

For the first 18 months, Susanne was given a placebo, and she switched to the active compound only after the primary study was concluded. Despite this, Susanne is very glad to have been part of the study.

"I have gotten fantastic medical treatment that I couldn't otherwise have gotten, so now I encourage everyone in my situation to apply to clinical studies. It's incredibly important that people are willing to participate, even if there are risks. Otherwise, developing new medicines would be difficult."

Different forms of cognition are affected differently in different people. In Susanne's case, social cognition is largely unaffected except for the difficulty in remembering names and keeping track of time, which is bound up with short-term memory being markedly affected. When Susanne and Lars meet others who took part in the study, it is also clear that there are major individual differences in how quickly the disease progresses.

"We're thankful that the progress of the disease for Susanne is this slow. In 2018, we didn't think we'd be sitting here like we are today."

Lars says that he laid out his worst-case scenarios immediately, and that helped him cope with the information. That, and mathematics. He calculated that seven years is 2,555 days.

"Whether there are more or fewer of them later on, we decided that we would make the best we could of those days. 2019 was probably our best year ever. We traveled and did other things we had on our bucket list, and we were a bit lucky because then the pandemic came."

Susanne says that it may sound like empty talk, but her quality of life is in fact better today than it was before the diagnosis, largely because she has learned to be present in the moment.

"If you've been given a death sentence, you know how important it is to live, so now I try to make the most of every day."

Fighting to amplify the patient's voice

Alzheimer's disease is often mentioned as a family disease, which became apparent when Susanne received her diagnosis. There is very little information and support aimed directly at patients.

"I was really angry at the beginning – I'm the one who's sick, nobody else." Throughout most of the progression of the disease, the patient is still a fully functional human being who can take in information and make decisions.

Susanne is involved in several different projects, including being an ambassador for the Swedish Alzheimer's Fund, and

she and Lars follow the research closely.

"One important reason that I chose to take part in the study, and why we follow the research, is our three children and my family history as a homozygous carrier for the Alzheimer's marker ApoE4. Our children all have at least one set of those genes, and I want to do everything I can to avoid them suffering from this disease."

The recent advances in research give Lars hope that an even more efficacious drug will soon be available, if Susanne's disease only continues to progress as slowly as it has done so far. In the future, they hope a medicine will come that not only slows or stops the progress of Alzheimer's disease but could also heal the damage that has arisen in the nerve cells.

"Our dream, of course, is that researchers will find a way to prevent Alzheimer's disease in future generations," Susanne says.

New treatments could change views of Alzheimer's disease

Disease-modifying treatments inspire hope that more will begin to regard Alzheimer's disease as a serious but treatable disease. A welcome change in attitude, says Moa Wibom, chief physician and head of operations at the Cognitive Medicine clinic at Ängelholm Hospital who has long fought for everyone suffering from Alzheimer's disease to be treated with respect and an action-oriented approach.

What are the most important adjustments health care needs to make in order to leverage the new possibilities with disease-modifying treatments?

"Major investments in both competence development and personnel recruitment are needed. When this category of drug reaches everyday clinical practice, it will be crucial for us to ensure that the right individuals are receiving treatment. This is key for confidence over the long term. Even though there will be forms to fill out to make these assessments, ultimately it is specific individuals who will be assessed, and this requires highly competent personnel who also understand when to deviate from the form.

"We also need to expand the capacity for MR examinations in order to perform the safety follow-ups that are required. Overall, there needs to be many more of us working with this. Primarily the number of nurses needs to increase, but also physicians and other occupational categories like counselors. This will require a reallocation of resources, and it's about time for that. This is an area of therapy that has long lagged behind."

How will the new treatment possibilities affect the view of Alzheimer's disease?

"If you are suffering from Alzheimer's disease today, you are put in a patient population that is still somewhat vaguely regarded as having dementia and is scarcely offered any care – just solicitude. The inequity is enormous compared with other serious diseases such as cancer, where you are treated completely differently and the resources put into care are something else entirely. I think that with the new treatments, more people will finally begin to regard Alzheimer's disease as the well-defined and serious illness it actually is and that patients can be taken seriously. Right now is a fantastic time to be working in this field. We are facing a paradigm shift, and the efforts now being made could enable major improvements for many individuals, both today and in the future."

There is a discussion about how much the progression of the disease needs to be slowed for it to be relevant to the people suffering from it. What is your view?

"Everything that can slow down the forest fire raging in the brain of a person with Alzheimer's disease is of value. We must welcome the advances being made. Both for those who are affected and their families, every moment in the healthier stages is invaluable. I don't understand how anyone could conclude otherwise. We should remember that this is a disease that develops over 20 years, and most people are gravely ill only during the last few years.

> Everything that can slow down the forest fire raging in the brain of a person with Alzheimer's disease is of value.

"Again, the comparison with cancer: for decades we have invested in drugs that, on average, have not always extended survival dramatically but where the value for the individual is still apparent. For quality of life, the significance of having hope should not be underestimated. Moreover, by always welcoming the advances that have been made, overall survival in cancer has drastically improved over time. That is how health care should regard this field as well. We need to invest now in order to accomplish the achievements that are possible over the longer term.

With new treatments, **diagnostics are more important than ever**

Once there are disease-modifying treatments, more people with memory problems will likely look for care earlier on. This increases the pressure on health care for correct diagnoses. Kaj Blennow, chief physician and professor of neurochemistry at Sahlgrenska Academy, has been part of developing new blood tests for early identification of Alzheimer's disease. Together with BioArctic and Eisai, he is also planning a new research project that will evaluate whether blood analyses can also be used for early identification of the patients affected by the ARIA side effect.

What role does diagnostics play in the shift that is now coming in care for Alzheimer's disease?

"Diagnostics are more important than ever. Once there are disease-modifying treatments, more people will want to be examined, which in turn will lead to a larger population of patients who have other conditions with similar symptoms – memory problems due to stress, for example. It is then a matter of identifying as quickly as possible which patients are to be referred onward to specialist clinics, and which patients can have Alzheimer's disease ruled out. Today, there are two ways of showing that cerebral amyloidosis and Alzheimer's disease are actually involved – either through amyloid PET or lumbar puncture. In Sweden, lumbar puncture is the general practice and the development of blood tests will be a crucial component of this."

What remains to be done before diagnostic blood tests can begin to be used in broad clinical practice?

"We have come far enough that a blood test, together with cognitive tests in research studies can make the correct diagnosis with 90 percent certainty. What remains is to standardize which tests should be used. If everyone gets similar results, it makes things easier. But I think that blood tests will begin to be used in broader clinical practice in specialist health care already in 2024. The goal is for primary care to also use blood tests in the initial assessment, but it will be a bit longer before we see broader use there."

Will biomarkers be used to monitor side effects?

"We think so. There is significant academic interest, and plans to conduct a study in the Nordic region. Once lecanemab is available, we want to monitor patients who are put into treatment from the start in order to measure the concentration of neurofilament light (NFL) in blood samples. Elevated levels of NFL are a signal for some type of nerve damage. It is a sensitive method, but it is not specific for any particular disease. Since ARIA – which is a side effect to be avoided – leads to effects on nerve cells, our hypothesis is that early signs of ARIA could be identified through NFL. But we can only find this out by measuring NFL at every infusion and subsequently compare it with the results from the PET examinations that everyone receiving treatment will undergo. If our hypothesis is valid, it is conceivable that, in the future, patients can be monitored via blood tests instead of PET examinations. To achieve this, we have to investigate whether there is a connection and if it is predictable. The study we are planning is a first step."

> "I think that blood tests to identify Alzheimer's disease will begin to be used in broader clinical practice in specialist health care already in 2024.

What do you think the new diagnostics could bring over the longer term?

"Apart from a broad implementation of the new diagnostics, I am hoping for more studies that begin administering disease-modifying treatments earlier in the progression of the disease. We have seen even clearer effects with treatments longer than 18 months, so I believe in using the diagnostic tests that already exist to try to identify patients very early on.