Alzinova

Sector: Biotech

Unique vaccine angle on Alzheimer's

Alzinova offers investors a rare exposure to disease-modifying therapies in the vast potential of Alzheimer's. Peak sales of its potential blockbuster, the unique ALZ-101 vaccine, could exceed USD 4 billion. News flow should be positive as its funded phase Ib study moves ahead after a credible pre-clinical phase.

Vast potential in Alzheimer's

We argue that Alzheimer's disease might be the indication with largest unmet medical need at present. Unless drugs that can change the course of the disease pattern get approved, the societal cost burden will reach alarming levels.

Uniquely positioned

The vaccine approach is highly cost-effective and long-lasting that suit the life-long disease of Alzheimer's well. We judge the case for ALZ-101 targeting of the neurotoxic amyloid beta (Aβ) oligomers as scientifically and empirically strong. We therefore claim ALZ-101 to be one of the very most promising drug candidates for disease-modification in Alzheimer's. Our peak sales estimate is appropriately conservative at this stage of development, but nonetheless reflects ALZ-101's vast potential.

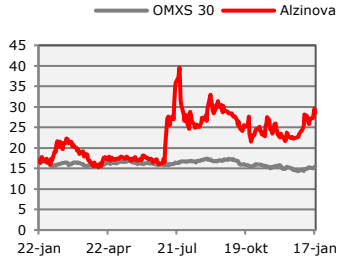
Valuation offers upside

Our discounted cash flow analysis puts Alzinova's fair value at SEK 36 per share. Against this Base Case, our Bull and Bear Cases are SEK 65 and SEK 15 per share, respectively. With an encouraging news flow and the attractive position of ALZ-101, we see significant short- and long-term potential for the stock.

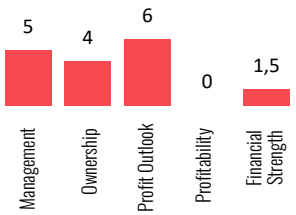
FAIR VALUE RANGE

BEAR	BASE	BULL
15	36	65

ALZ.SS VERSUS OMXS30



REDEYE RATING



KEY STATS

Ticker	ALZ.SS
Market	Spotlight
Share Price (SEK)	29.7
Market Cap (MSEK)	224
Net Debt 19E (MSEK)	-47
Free Float	72 %
Avg. daily volume (MSEK)	1.0

KEY FINANCIALS (SEKm)	2016	2017	2018E	2019E	2020E	2021E
Net sales	0	0	0	0	0	0
EBITDA	0	0	-15	-24	-46	-37
EBIT	0	0	-15	-24	-46	-37
EPS (adj.)	0,0	0,0	-2,0	-3,2	-6,1	-5,0
EV/Sales	N/A	N/A	N/A	N/A	N/A	N/A
EV/EBITDA	N/A	N/A	N/A	N/A	N/A	N/A
EV/EBIT	N/A	N/A	N/A	N/A	N/A	N/A
P/E	N/A	N/A	N/A	N/A	N/A	N/A

ANALYSTS

Anders Hedlund

anders.hedlund@redeye.se

Klas Palin

klas.palin@redeye.se

Table of Content

Investment Case

Solid delivery, inflection points still ahead

Strong stock performance since IPO

Alzinova offers a rare investment opportunity on the Scandinavian equity markets as one of the very few disease-modifying approaches to Alzheimer's disease (AD). Since its listing on Spotlight (previously Aktietorget) in 2015, the company has met the pre-clinical timeline for ALZ-101, its lead candidate. While this has supported the stock's strong performance, we see the real inflection points for the company as still ahead.

Uniquely positioned, huge unmet needs

A devastating disease with poor treatment alternatives

AD may be the indication with the highest current medical need. Without the breakthrough of disease-modifying therapies - drugs that can change the course of the progressive state and ultimately prolong survival - its cost burden will reach alarming levels.

The market for AD drugs has been a major disappointment. None has been approved since 2002, and no disease-modifying therapy is available on the market. However, the scientific understanding of the disease has increased in the last decade. It has fed the current pipeline with some promising drug agents…

A vaccine aimed at neurotoxic Aβ oligomers

… ALZ-101's approach of targeting a specific type of **Aβ aggregates (Aβ oligomers) is the best supported in the field**, in our view, since the evidence suggests that these are the neurotoxic agents in AD. Furthermore, the only two therapies (non-vaccine candidates) that have shown clinical benefits on patients have a similar binding profile as ALZ-101.

The vaccine approach suits well for a life-long indication such as AD and is potentially superior in cost-effectiveness. Moreover, the vaccine pipeline is competitively far less crowded than the pipeline for treatment with monoclonal antibodies (passive immunotherapies).

We view ALZ-101's oligomer-specific vaccine approach as unique in the AD pipeline. Due to the promising profile, we forecast ALZ-101's potential annual peak sales at more than USD 4 billion. While this is conservative due to the early stage of the vaccine's development, it highlights the vast potential in this indication.

Valuation Summary

Base Case: SEK 36 per share

We initiate coverage of Alzinova with a **Base Case valuation of SEK 36 per share**.

ALZ-101 on the verge of clinical trials on mild AD patients

Alzinova recently completed two successful rights issues, with only a limited portion ending up with the guarantors. The company has now funded its operations until mid-2020, including the phase Ib trial. Alzinova is now in the process of a listing on OMX Nasdaq First North; we expect this to take place in the first half of 2019. For the ALZ-101 project, we expect a phase Ib initiation **on mild AD patients** to start in the first half of 2019.

With a funded phase Ib trial and interesting news flow for ALZ-101, we argue for a continued momentum of the stock price. A significant external catalyst will be the presentation of phase III results (expected beginning 2020) of the project run by Biogen; Aducanumab. Positive top-line results will serve as a major catalyst to the whole Aβ field and more than any other drug candidate, strengthen the rationale of ALZ-101.

Our Bull Case reflects the optimistic scenario that Alzinova could be granted fast-track designation, with a subsequent launch one year earlier than in the Base Case. We also hypothesize that ALZ-101 gets in-licensed to a partner before a phase II program. Lastly, we

adjust peak sales potential to exceed USD 5 billion. Our Bull Case gives a valuation of SEK 65 per share.

Our Bear Case factors in a possible delay in ALZ-101. New funding might then be needed before the phase Ib trial completes. Reflecting the dilution this would involve, our Bear Case values the company at SEK 15 per share.

Key risks

We acknowledge a number of key risks in the Alzinova case.

Financial and organizational risks

The company has not made its last series of funding. The next series of funding will be of larger scope; to support larger clinical studies and strengthen its negotiation position against potential partners. Alzinova has clear incentives from this perspective to strengthen the ownership structure in the next two years and also strengthen the in-house organization.

Highly partner-dependent

For a small biotech company within one of the world's largest indication, the company is highly dependent on partners to advance ALZ-101.

Significant development risk

Alzinova's development risk is high from several perspectives:

- Because of the early-stage nature of ALZ-101
- The risk is abundant already in the phase Ib trial as it will be conducted on mild AD patients in their first-in-human trial
- Alzinova is, at this stage, a single project company whose success depends on the progress of ALZ-101
- AD is a heterogeneous and complex indication. Even though much scientific effort has increased knowledge of the disease, AD remains very challenging.

Patent pressure

Patent expiry is a general risk that biotech firms are facing. As drug development is subject to long life-cycles, it is sensitive to delays that could jeopardize sales exclusivity. We hope that Alzinova will pursue an active patent strategy in the years ahead to further protect the key patent - AβCC technology and ALZ-101, with the ultimate aim of postponing the date of expiry.

Company Description

Founded in 2011, listed since 2015

Alzinova is a Swedish biotech company focusing on research and development of disease-modifying therapies against Alzheimer's disease (AD). Alzinova was founded in 2011 by the inventors of the company´s proprietary technology platform, AβCC, in close collaboration with MIVAC Development AB and GU Ventures, the holding company at the University of Gothenburg.

The AβCC technology gives Alzinova long-term capabilities in developing therapeutics and tools to improve AD research. Alzinova's lead candidate, ALZ-101, is an oligomer-specific vaccine candidate that is expected to enter a phase Ib trial on mild AD patients in H1'19.

Alzinova, which emphasises agility and makes use of expert consultants, listed its shares on the Swedish Spotlight market (previously Aktietorget) in 2015. It intends to list on OMX First North in the first half of 2019. In this context, we expect the company to take the next step organizationally and sort of moving from academia rooted, virtual organization to a clinical stage biotech firm.

Alzinova: Selected historical highlights	
2011	- Alzinova is founded - Patent families are transferred from MIVAC Development AB into Alzinova AB.
2014	- Proof-of-principle shown in an animal model
2015	- Per Wester is appointed CEO - Approved patent for the AβCC technology in Japan - Alzinova lists its shares on Spotlight Stock Exchange (previously Aktietorget) - Approved patent for the AβCC technology by European Patent Office (EPO)
2016	- Alzinova receives patent approval for ALZ-201 by EPO - The company completes a pharmacologic study of ALZ-101 in an animal model. The study shows that the vaccine causes an immune response. The study also shows a good safety profile - Alzinova signs an agreement with a global pharmaceutical company to collaborate on a 1-year project related to the AβCC technology - Alzinova enters into a research agreement with a CRO to prepare ALZ-101 for a first-in-human trial
2017	- New patent granted for the AβCC technology in Japan - Alzinova receives EUR 50,000 in funding from the European Commission (Horizon 2020 step 1) - The company receives a notice of allowance related to its patent submission for the AβCC technology in the US - The company completes a pharmacological study of ALZ-101 in an animal model. Doses of adjuvant and antigen are established. - Alzinova performs a study on non-human primates (pre-GLP-toxicological study. The study reports a clear immune response, with no major side effects
2018	- ALZ-201 shows positive results in animal models of AD - Approved patent for ALZ-101 and the AβCC technology in the US - Alzinova performs a GLP-toxicology study of ALZ-101. The study results conclude that the drug is safe, with no side effects related to the test item and a strong immune response of the desired type

Source: Alzinova prospectus (2018), Redeye Research

Alzheimer's – a devastating disease

Background and epidemiology

At a molecular level, Alzheimer's disease (AD) is due to protein misfolding. Misfolded proteins tend to get sticky and form aggregates. In AD, the aggregates are made by two proteins that form deposits in the brain - amyloid-β (Aβ) peptide and Tau protein. We will come back to these in more detail below.

The most common form of neurodegenerative disorder and of dementia

AD is the most common form of neurodegenerative disorder and the most common form of dementia. Approximately 70 percent of the dementia cases are due to AD. It is manifested clinically as deterioration of cognitive and functional abilities. As the deterioration is progressive, eventually fatal (average survival after diagnosis is four to eight years, Datamonitor), and lacks a cure – it is a devastating disease, both for the patient and the caregivers. It is currently the only disease among the top ten causes of death that lacks a cure.

According to Datamonitor, there were over 22 million cases of AD and Mild Cognitive Impairment due to AD (MCI-AD) in the five biggest EU markets (France, Germany, Italy, Spain, and the UK), the US, and Japan. Driven primarily by an aging population, Datamonitor expects the prevalent cases to exceed 33 million (AD and MCI-AD) by 2035.

Pathological hallmarks

AD pathological hallmarks: Aβ senile plaques and Tau

Although the causation of AD is subject to ongoing debate, the pathological hallmarks of the disease are well understood. Through post-mortem examinations of patient brains, two pathological hallmarks have been identified: extracellular senile plaques of Aβ and intracellular fibrillary tangles of Tau.

The amyloid-β peptide – where the action is

Aβ is a peptide that is generated through cleavage of the amyloid precursor protein (APP) by β- and γ-secretases into different sizes. The most common Aβ peptides comprise 40 – 42 amino acids.

Since the discovery of Aβ as the major constituent in the pathology of AD brains, the research has come to a more sophisticated stage. Several research findings suggest that the different sizes of the Aβ matter. For instance, the longer Aβ42 peptide is more prone to form neurotoxic aggregates than its shorter Aβ counterparts. Researchers have also come to focus on understanding Aβ fibrillogenesis, the transformational change from single chain Aβ peptides to the senile plaques in the brain:

- Misfolded, single-chain Aβ peptides (monomers) readily form aggregates.
- Soluble aggregates of Aβ (oligomers/protofibrils) are considered to be an intermediate step in the fibrillogenesis, but may also constitute distinct species.
- Aβ aggregates eventually transform into insoluble, mature **fibrils** and senile **plaques** in the brain.

Increased research attention on Aβ oligomers

Interestingly, findings have shown that the end-product (Aβ plaque) is not related to the severity of the disease but rather viewed as a biomarker of a brain incapable of balancing the production and clearance of Aβ. During the last two decades, increasing attention has instead been placed on soluble the aggregates (oligomers/protofibrils). It is a general research consensus today that they are the most neurotoxic aggregates.

The strongest supporters of the Aβ field has attributed it not only as the major pathological hallmark but as the causative agent of the neurodegenerative process. The approach is named "The amyloid cascade hypothesis" which can be summarized as follows:

1. Due to genetic factors and increasing age, there is an imbalance in the production and clearance of brain Aβ. The Aβ42 peptide tends to have a sticky character in the brain and readily form aggregates as it accumulates.
2. However, not all Aβ aggregates are neurotoxic; the revised amyloid cascade hypothesis focuses on the soluble oligomer aggregates.
3. Soluble oligomers are the initiating agent in the downstream cascade of the neurodegenerative process.

The Amyloid cascade hypothesis

Imbalance between production and clearance of Aβ	--->	**Soluble, neurotoxic aggregates in the brain**	--->	**Downstream cascades:** - Neuroinflammation - Oxidative stress - Synaptic dysfunction - Tau phosphorylation	--->	**Neuronal death / volumetric brain shrinkage**	--->	**Cognitive and functional impairment**

Source: Redeye Research

Thus, according to the amyloid cascade hypothesis, developing drug agents that aim to reduce Aβ levels in the brain is the most effective way to disease-modification in AD.

There are many different approaches to either reduce the production or clear the aggregates of Aβ. Accordingly, the therapeutic approaches vary based on their mechanism of action and type of molecule. From a disease-modifying perspective, the immunotherapies, to which ALZ-101 belong, are currently gaining highest attention and most promise. The common denominator of immunotherapies is that those aim to stimulate the body's immune system to clear brain Aβ.

Disappointing results in clinical trials…

The Aβ cascade hypothesis is scientifically well-supported. Several mutations in the APP have been discovered in recent decades. Those mutations either increased Aβ production or stabilized the oligomeric forms, causing autosomal dominant forms of early-onset AD. At the same time, the hypothesis is subject to ongoing debate. Criticisms against the amyloid cascade hypothesis focus on two issues:

- There have been many clinical setbacks with molecules targeting the Aβ peptide
- Amyloid deposits in the brain are commonly observed in cognitively normal, elderly people.

There is no argument that there have been major clinical setbacks in the 21st century for drugs targeting the Aβ peptide. Severe disappointments include the immunotherapies Solanezumab (Eli Lilly) and Bapineuzumab (Pfizer/J&J). These and other related drug agents carried significant investments and high hopes. We believe the failures of Solanezumab, Bapineuzumab, and other Aβ drug candidates stem from:

…creating a 'lessons learned' approach for more recent Aβ drugs in development

1. *A wrong target approach*. Solanezumab is a monoclonal antibody directed towards the Aβ single-chain peptides, i.e., it is specific to the monomers. Bapineuzumab has an unspecific binding, recognizing all forms of Aβ aggregates. Thus, the first generation of Aβ immunotherapies most likely had a too unspecific binding profile.

2. *Poor patient enrollment* in the clinical trials. Post-analysis of trials in the field has shown that as many as 30 percent of the patients enrolled did not have AD. Hence, they were incapable from the very beginning of showing signs of efficacy. Moreover, as AD involves several processes that contribute to the death of nerve cells, it is crucial to intervene as early as possible. Failed trials have likely enrolled patients that have progressed too far to have a good downstream therapeutic effect on these processes.

3. *Too low dosage – side effect risks*. One of the most common side effects in immunotherapies with high affinity for plaques has been ARIA. It stands for Amyloid-Related Imaging Abnormalities and is seen as edema (ARIA-E) or hemorrhages (ARIA-H) when imaging the brain. It is both dose and APOE4 (see below) dependent. Although it is not clear what causes ARIA, it seems to be associated with the clearance of vascular amyloid, present in already weakened vasculature. The passive immunotherapies that have shown a high degree of ARIA have been forced to lower the dose, possibly at the expense of clinical efficacy. It should be noted that ARIA is less likely to occur in ALZ-101: s drug class, the active immunotherapies.

In recent years, we have witnessed two Aβ immunotherapies that have demonstrated clinical benefits in trials:

- Aducanumab (Biogen/Eisai)
- BAN2401 (Eisai/Biogen)

These molecules are more precisely targeted towards the neurotoxic oligomers/protofibrils, which is the same target as ALZ-101. In trials with Aducanumab and BAN2401, the enrolled patients were PET scanned for amyloid at the start of the treatment. This was to ensure meeting the criteria for MCI-AD and Mild AD.

It might be that the early clinical setbacks in the Aβ field have created a "lessons learned" approach. The next generations of Aβ immunotherapies are so far more successful, due to a more precise Aβ target profile, and better designed clinical trials. Furthermore, the first generations of Aβ did show signs of improvement after conducted sub-analysis. It provides further support that it is an improvement aspect from the first generation of Aβ drug candidates, rather than outright rejecting the hypothesis based on the initial results.

The other main criticism of the amyloid cascade hypothesis is that Aβ aggregates are commonly observed in apparently healthy elderly people. To address this criticism, we must look at how AD evolves. The symptomatic progress in AD is now generally categorized into three different stages:

- Preclinical AD
- MCI-AD
- Dementia due to AD

Pathological changes precede symptomatic onset by 10 – 20 years

We focus here on the first stage, the preclinical AD and will elaborate more on the latter two in the Diagnosis section below. Preclinical AD is the stage where the patient is cognitively normal but where PET imaging would reveal pathological changes in the brain. These pathological changes occur 10 – 20 years before clinical onset. As a result, Aβ aggregates in cognitively normal humans might not necessarily reject the amyloid hypothesis, as these humans could be preclinical AD patients. Furthermore, we emphasize that there are various forms of Aβ aggregates; a cognitively normal person could have Aβ load where the non-neurotoxic aggregates dominate.

What about the Tau protein?

A protein found in neurons

The Tau protein is predominantly found in neurons, where they carry out different functions related to microtubule (the cell's "skeleton") assembly and stabilization. In an AD brain, the Tau protein is found as intracellularly, neurofibrillary tangles (NFTs).

The process of tauopathy is hyperphosphorylation, a chemical change which increases unbound Tau due to its disengagement from the microtubule. Normally, the binding of Tau to microtubules is a controlled process. Under tauopathy, hyperphosphorylation activates kinases which eventually releases it from axons and initiates the formation to neurotoxic aggregates.

The strongest supporters of Tau as the major disease driver claim no interaction between Aβ and Tau hyperphosphorylation. The Tau view emphasizes that the Tau hyperphosphorylation is more devastating to neurons and is closer correlated with the degree of cognitive decline than Aβ aggregation. Tau is therefore, according to the 'Tauists,' a more relevant target.

The Tau view

Hyperphosphorylation Tau	--->	**Abnormal Tau aggregates leads to neurofibrillary tangles (NFTs)**	--->	**Toxic Tau aggregates spreads autonomously from neuron to neuron** - induce synaptic and mitochondrial dysfunction	--->	**Neuronal death**	--->	**Cognitive and functional impairment**

Source: Redeye Research

A source of scientific discourse between 'Aβ cascade hypothesis' and the 'Tauists' is which protein that first exhibit pathological change in AD. The Tau view relies on findings that tauopathy has been seen in certain parts of the brain, in the absence of Aβ deposition, in some young individuals (Braak et al., 2011; Elobeid et al., 2012). As noted, the amyloid cascade hypothesis instead puts Aβ as the initiator of the pathogenesis; it is supported by several autosomal dominant mutations in the APP or the genes coding for the cleavage of APP.

Agnostics to either approach tend to rather see Tau and Aβ as 'partners-in-crime,' some studies do point to an interdependency between them. It could suggest that a combination therapy involving Tau and Aβ would demonstrate a strong, clinical efficacy for patients.

Several approaches to target anti-Tau

There are several approaches to targeting Tau. Some drug candidates aim to stabilize the microtubule, as it is the main function of Tau. Moreover, hyperphosphorylation is believed to be a crucial aspect in the neurodegeneration cascade. The phosphorylation of Tau is a dynamic process that requires a balance between the activities of protein kinases and phosphatases. Thus, inhibition of kinases to decrease the phosphorylation activity, alternatively activate phosphatases could be attractive targets.

Of the enzymes involved in the phosphorylation, Glycogen synthase kinase 3 (GSK-3 is the only target that has entered clinical trials. As GSK-3 has also been implied to interfere with Aβ formation, it is not a specific target for Tau. GSK-3 is thought to regulate Aβ production by interfering with APP cleavage at the γ-secretase.

Another anti-Tau approach is to halt the fibrillization by inhibiting Tau-Tau binding. Several small molecules have shown such capabilities in vitro. It includes methylene blue, the Tau compound that has advanced the furthest in the clinic. However, significant challenges do exist in developing therapeutics against Tau fibrillization. Protein-protein inhibitors often act via an unknown mechanism of action; it is hence a risk that it could lead to undesired off-

target effects. Furthermore, pharmacological attempts of inhibiting protein-protein interaction have historically proven difficult regarding required specificity and potency.

Anti-Tau immunotherapies have been a popular strategy during the last decade (Khanna et al., 2016). As far as we are aware, there are currently seven Tau immunotherapies in clinical development.

It is notable that Tau immunotherapy has become the primary therapeutic target. It was for long debated if it would be a viable strategy, as the antibodies have to cross the blood-brain barrier (BBB) and reach their target intracellularly. Studies have demonstrated that anti-Tau antibodies can diffuse across the BBB and be taken up by neurons via the endosomal/lysosomal system. It has also been suggested that the spread of neurodegenerative Tau pathology may occur via cell-to-cell transmission, suggesting that anti-Tau antibodies may not need to be incorporated into the neurons to provide efficacy. We note that these studies have been preclinical, primarily using a transgenic mouse model.

Increased interest in the last decade, even though Tau is not as well studied target as Aβ

In summary, the Tau protein is not a well-studied target as Aβ, even though it has gained more attention in the last decade. Tau has also yet to demonstrate clinical benefits in a larger patient population – Aβ is beyond that step. However, we presume that Tau will continue gaining increased interest and we find it interesting that it is in close correlation with cognitive decline.

AD classification and diagnosis

Different forms of AD

Alzheimer's is either early-onset AD (<65 yrs) or late-onset AD (>65 yrs)

Regardless of the therapeutic approach to treating AD, two forms of the disease are widely acknowledged; early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD).

EOAD manifests before 65 years of age. It is a familial condition, with aggressive progression. Less than five percent of all cases are EOAD. Approximately 10 percent of the EOAD cases are due to autosomal dominant mutations in APP or the genes encoding for the enzymes necessary for APP cleavage; presenilin1 (PSEN1) and presenilin2 (PSEN2).

LOAD has its symptomatic emergence after 65 years of age. It is considered as the sporadic type of AD. More than 95 percent of all cases are LOAD; the form carries both genetic- and environmental factors. Even though the etiology of LOAD is less understood than EOAD, two predictors are widely acknowledged. The first is increasing age. The older we get, the more likely to develop AD. As increasing age is a global megatrend, the need for disease modification therapies rises accordingly.

Increasing age and a cholesterol protein allele (APOE4) are the most acknowledged predictors

The other predictor for LOAD is a cholesterol carrier, apolipoprotein E (APOE). It is the main, genetic determinant. APOE carries either of the three gene types; APOE ε2 (APOE2), APOE ε3 (APOE3), and APOE ε4 (APOE4). It is known that the gene types differently regulate the production and clearance of the Aβ peptide. APOE4 carriers are at an increased risk of developing AD compared to APOE3 carriers whereas APOE2 carriers have a decreased risk of developing AD. A further explanation for the increased risk of APOE4 carriers might be that APOE4 is less efficient as a transporter of lipids to synaptic maintenance. The worldwide frequency of APOE2, APOE3, and APOE4 is 8, 78, and 14 percent, respectively (Liu et al., 2013).

Diagnosis of AD

As the understanding of the disease has increased, it has become apparent that AD is best viewed as a continuum that spans several decades and does not only involve the dementia stage. The National Institute on Aging and the Alzheimer's Association (NIA-AA) established a working group in 2011 to revise the criteria for AD diagnosis. The ultimate goal for the revision was to encourage the industry and society towards earlier intervention in the disease. Three different stages of the disease are now recognized:

- Preclinical Alzheimer's disease *(preclinical-AD)* is the diagnosis described previously. It is the pre-symptomatic stage but where pathological changes have emerged. It is difficult to diagnose patients that are cognitively normal. The diagnostic criteria must, therefore, rely on a novel, easily accessible (preferably blood-based), cost-effective biomarkers that can accurately predict the underlying pathology.
- Mild cognitive impairment due to Alzheimer's disease *(MCI-AD).* At this stage, cognitive impairment becomes apparent, but the individual has not developed full dementia. The stage is mainly determined by the expression of cognitive deficits in different domains. It should also be a clinical change from the previous stage. Challenges of diagnosis in this step are that MCI can have many reasons and commonly misinterprets as 'normal aging forgetfulness.
- Dementia due to Alzheimer's disease *(dementia AD)* is the stage where the patient progress into dementia. Symptoms become more pronounced, and the disease starts to impact the day-to-day living and quality of life. While a definitive diagnosis of AD can only be made on autopsy, the dementia AD stage is the easiest stage for diagnosis of probable and/or possible AD, as the clinical manifestations are apparent. However, diagnosis made at this progressed stage has poor treatment alternatives. Dementia AD is subcategorized as:
    - Mild (an MMSE score between 21-26)
    - Moderate (an MMSE score between 10-20)
    - Severe (an MMSE score below 10)

AD is underdiagnosed

AD is, as of today, an underdiagnosed disease. Datamonitor refers to a diagnosis rate of 45 percent, and even lower for the early stages of the disease. The main reasons are:

- A scarcity of specialists in geriatric and neurology makes diagnosis heavily relied on primary care physicians.
- Stigmatization of the disease makes a diagnosis in the primary care undisclosed or neglected.
- A feeling by physicians that there is nothing that can be done
- Difficulties in obtaining an accurate diagnosis in the early stage make the disease easily confused with normal aging and forgetfulness.

From an immunotherapy perspective, the last reason is crucial. More objective measures are necessary for the early stages to halt the progression. This is where AD biomarkers come in.

Biomarkers – badly needed in early AD

It is crucial that the development of disease-relevant biomarkers goes hand-in-hand with the development of new drugs. In AD, biomarkers could allow for:

Crucial for disease-modifying therapies

- Earlier diagnosis → earlier treatment intervention.
- Patient stratification in clinical trials → more homogenous patient groups, better-defined endpoints, and objective validation of treatment effect

There are currently five established biomarkers in AD, which Jack C.R et al. (2010), divides into two major categories:

1. Measures of brain Aβ deposition
    a. Quantification of *Aβ42 in the cerebrospinal fluid (CSF).* Low Aβ42 in CSF indicates that the peptide has formed fibrillar deposits in the brain.
    b. *PET amyloid imaging*. Provides an image of Aβ brain deposits.

2. Measures of neurodegeneration
    a. Quantification of *total Tau (t-Tau) and phosphorylated Tau (p-Tau) in CSF*. These molecules are released by nerve cells as a result of neurodegeneration. Elevated levels are thus consistent with AD pathology.
    b. *FDG PET* is a biomarker to measure synaptic activity. AD patients show a pattern of decreased glucose uptake in specific parts of the brain that can be measured by FDG PET. The greater the decrease of glucose uptake, the more severe is the cognitive impairment.
    c. *Brain atrophy by MRI* is a volumetric measure of the brain. The biomarker indicates possible brain shrinkage. However, brain shrinkage is not specific for AD.

AD biomarker's aid earlier diagnosis

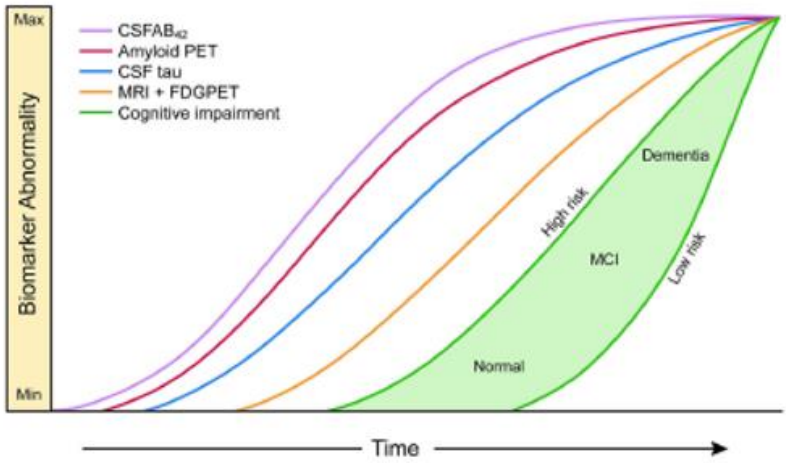
The most relevant of the established biomarkers for early diagnosis is subject to ongoing debate. Here again, we see an 'Aβ hypothesis' versus 'Tauists' discourse. It is suggested that biomarkers of Aβ deposition are measures of a dysfunctional brain. Aβ deposits have been found in cognitively normal people but are always present in AD patients which suggest that Aβ deposition is better viewed as a risk factor. Such a biomarker is not by itself a good predictor for the presence of AD but can prove useful to identify probable preclinical-AD patients in need of preventive treatment intervention.

T-Tau and P-Tau are proposed as better linked to neurodegeneration. However, findings suggest that those are not as prominent in the very early stages of AD but become progressively abnormal as time to dementia decreases. Note that this view disregards the findings made by Braak et al., (2011), arguably because aberrant Tau in young individuals is too early to represent the beginning of AD.

Below is a revised (original model presented in 2010), the hypothetical model proposed by Jack et al., (2013). The figure illustrates biomarker abnormality in relation to AD pathology. Time is depicted on the horizontal axis and biomarker abnormality on the vertical axis. The three different stages of AD are illustrated in the green zone. According to the model, CSF Aβ42 is showing abnormality first, followed by CSF Tau, and MRI + FDG PET. However, CSF Aβ42 is always most abnormal, at any given time.

Note that all biomarkers are sigmoid-shaped in the figure; they are accelerating in the initial stages to decelerate as a function of time eventually. The figure is also sensitive to individuals' unique response to pathophysiology. Individuals that are at high risk of developing cognitive impairment due to AD pathophysiology are shifted to the left in time.

Hypothetical model of AD Biomarker abnormality over time



In summary, the hypothetical model follows the order where Aβ biomarker becomes abnormal first, followed by biomarkers for neurodegeneration, and then manifestation of clinical symptoms.

Source: Jack et al., 2013

AD biomarker's aid better clinical trials

AD biomarkers increasingly established in clinical trials to control for patient stratification and 'harder' data endpoints

The ADAS-Cog score test is the golden standard endpoint in AD clinical trials. ADAS-Cog has been used to support registration of all marketed drugs as of today. It is a battery of 11 cognitive items, such as the patient's ability to recall words and comprehend to instructions. ADAS-Cog provides an overall summary score from 0 (no impairment) to 70 (severe impairment).

Other common trial endpoints include the Mini-Mental State Examination (MMSE) and The Clinical Dementia Rating – Sum of Boxes (CDR-SB). The MMSE is an 11-item test where total score ranges from 0 (severe cognitive impairment) to 30 (no cognitive impairment). An MMSE score between 21 and 26 is regarded as mild AD. MMSE is deemed to be less sensitive to retrieve drug-placebo differences than ADAS-Cog. However, it is the most common test to set diagnosis and has been increasingly incorporated in clinical designs as well. The test includes assessments of memory, language, praxis, and orientation. CDR aims to measure the increase in dementia over time, by looking at six categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR-SB then retrieves a sum-of-the-boxes, numerical score.

Clinical measures of cognitive test scores might become less feasible as the pipeline moves into the early AD continuum. Biomarkers could instead step in and offer "harder data points." For some therapeutic approaches, for instance, AD vaccines, it will likely be necessary to measure specific biomarkers. The alternative is to measure time to diagnosis in comparison to placebo; such an approach will require very long follow-up periods.

Even though biomarkers are becoming more established in clinical trials, it is yet to be as the primary endpoint. Moreover, the use of biomarkers as primary endpoints in clinical trials is not without controversy. Criticisms include the poor correlation between some of the biomarkers and the clinical progression. A smaller and perhaps more logical step could be the combination of biomarkers and cognitive test scores as primary endpoints in early AD trials. However, a combination of endpoints to constitute one would need to address the challenge of how they should weigh against each other.

Lastly, biomarkers could be a significant factor to control for a more homogenous patient group in clinical trials. As post-analysis has shown that many patients enrolled in trials did not have AD, it is of high relevance.

Medical needs in AD biomarkers

The overlap in pathology between AD and other neurodegenerative disorders, and the presence of AD-like lesions in some healthy individuals prevents CSF and PET biomarkers from achieving a definite diagnosis. There is also a lack of biomarkers that are more closely related to the deterioration of cognitive ability, as well as those able to accurately detect preclinical AD. Also, a biomarker specific for Aβ oligomers may turn out to be the most accurate biomarker for the disease, developments are made in this area. The medical need is thus still very high, especially when considering that approximately 15 percent of the diagnosed patients in the western world get their AD diagnosis when they are in the severe dementia stage of the disease. We find it to be a remarkably high figure – poor treatment alternatives can be offered at this stage.

New biomarkers in development

AD blood-tests may be on the horizon

A 'holy grail' in the development of AD biomarkers is the establishment of assays measuring plasma biomarkers. Cost-effective blood tests would probably be a necessity for mass screening populations for neurodegenerative disorders. Blood sampling has the advantage of being more accessible and less invasive than CSF sampling. However, it has proved difficult to develop reliable blood biomarkers since:

- The bloodstream is not directly connected to the brain, as CSF is. Only a fraction of brain proteins enter the blood. The blood-brain barrier (BBB) controls the passage between the bloodstream and the brain. The BBB is made up of endothelial cells and plays an important role to make sure waste products don't reach the brain. On the contrary, the BBB makes it difficult to deliver large molecules (e.g., immunotherapies) into the brain. Studies have revealed that the concentration of antibodies in the brain represents a mere 0.1 percent of the levels in serum.
- Proteases and enzymes will degrade brain proteins and rapidly remove them. There might hence be a poor correlation between brain proteins found in the plasma and brain pathology.

Promising plasma biomarkers are Aβ, Tau, and NfL

Nonetheless, proposed plasma biomarkers are Aβ (lower Aβ plasma levels indicate brain pathology change), Tau (increased Tau plasma levels indicate brain pathology change), and neurofilament light (NfL). NfL is a protein that, upon injury, is released from the axons and diffuses into the CSF and ultimately also into the blood. Rising levels of NfL in the CSF and the blood have been shown to correlate. As rising NfL plasma levels are not a feature specific for AD, but other neurodegenerative disorders as well, it holds as a promising biomarker for a first-in-line screening test for patients starting to show cognitive impairment. Such a test would demonstrate that the symptoms are likely the cause of underlying neurodegenerative brain pathology.

Tau PET tracers in late-stage

Another medical need among biomarkers is the development of PET imaging that can detect Tau deposition. Eli Lilly announced in 2018 that its Tau agent, Flortaucipir had met its primary endpoint in phase III, defined as predicting brain tau pathology and predicting AD diagnosis. With the advance of Tau imaging, we believe that it can be used in combination with Aβ imaging for a more accurate *in vivo* diagnosis of AD.

Ultimately, as the end-station of the AD pathology is synaptic dysfunction and neuronal death, Blennow & Zetterberg (2018) stress the need for biomarkers that can predict synaptic

degeneration. Promising biomarker candidates include the dendritic protein, neurogranin, and the presynaptic proteins SNAP-25 and SYN1. Increased levels of these proteins in CSF could indicate a synaptic loss and, hence, AD pathology in the brain. Blennow & Zetterberg (2018)

Concluding remarks

The extensive research carried out in AD makes clear that it is a complex and heterogeneous disease. It may even be outdated to attribute the disease to one specific hypothesis. Several reviews emphasize the interdependency between the two pathological hallmarks and that combination therapy is what AD patients could benefit most from.

As this section has been written from a disease-modifying therapy perspective, it should be emphasized that it is also crucial to develop better symptomatic treatments, and also treat down-stream effects of the neurodegenerative cascade (e.g., oxidative stress, neuroinflammation), especially in the more progressed stages.

A future treatment paradigm of AD may consist of a toolbox for the physician which would enable combination therapies and a more case-by-case treatment approach. The toolbox at its core would consist of:

- Therapies targeting oligomeric Aβ and aggregated Tau for disease-modifying effects
- Improved symptomatic treatments and treatments for pathology occurring later in the neurodegenerative cascade
- Biomarkers that accurately detect AD earlier and characterize the progressed state more efficiently

We argue that Aβ will continue to be a key target and an absolute necessity to achieve disease modification. ALZ-101, Alzinova's vaccine candidate, is in a promising position to become a vital part of the future toolbox for treating AD.

Alzinova's Aβ oligomer-specific approach

ALZ-101 – a vaccine

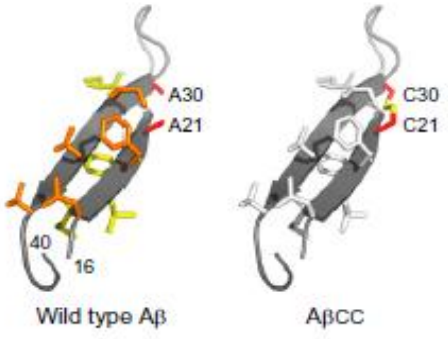
ALZ-101 is Alzinova's lead candidate. ALZ-101 is an active Aβ immunotherapy - a vaccine with the potential to have a disease-modifying effect in AD. The vaccine is currently in the late preclinical stage; we expect ALZ-101 to go into the clinic in the first half of 2019.

The AβCC technology stabilizes Aβ42 oligomers

Alzinova's drug candidates are based on the proprietary AβCC peptide technology. It stems from research carried out at the University of Gothenburg by the founders of the company. The objective behind the AβCC peptide technology was to stabilize Aβ42 in its oligomeric form so it would not form amyloid fibrils. Such fibrils are the major constituent in the conspicuous plaques found in all AD patients, but not the major driver of the disease. Stable oligomers are difficult to produce or isolate since the aggregation process cannot be controlled. The researchers instead attempted to stabilize them using protein engineering. In particular, the AβCC invention aimed at specifically stabilizing a β-hairpin conformation by replacing two amino acids, Ala21 and Ala30, with cysteines. The cysteines have the capability of making covalent sulfur bonds with each other which creates an intramolecular disulfide bond. This covalent bond effectively prevents the conformational change required for the formation of Aβ42 into fibrils.

Sandberg et al. (2010) tested if soluble oligomers indeed consist of β-hairpin and if fibrillogenesis can be halted. They found that it is the case, as long as the bond remains intact. Sandberg et al. (2010) also showed that there is a clear difference between the aggregation pathways of Aβ42CC and Aβ40CC, where the different pathways could explain why the longer peptide is more prone to form neurotoxic aggregates.

Alzinova: The AβCC technology



The figure illustrates the β-hairpin structure of Aβ and Alzinova's method of stabilizing it. As the unstructured amyloid-β peptide aggregates, its C-terminal hydrophobic part forms two β-strand secondary structure elements (dark grey arrows), whereas the rest of the peptide, the N-terminal amino acids 1 to 16, remain unstructured. The β-strands are connected by a loop, thus forming a β-hairpin structure (β-loop-β). Although the secondary structure elements in oligomers and fibrils are similar, the orientation of these elements with respect to each other are different. In the β-hairpin, the faces of the two β-strands of the peptide are oriented side by side, whereas they are facing each other in the cross-β fibril structure. The two different tertiary structures have different properties, where one is soluble and toxic whereas the other is insoluble and fairly inert.
The right figure illustrates the AβCC mutation and how the β-hairpin is stabilized by a cysteine-cysteine bond (colored C30 and C21). This modification generates only the toxic form of the Aβ peptide.

Source: Alzinova, Sandberg et al, 2010

The stabilized oligomers position ALZ-101 attractively for development as a vaccine. This is also the approach Alzinova has prioritized. By intramuscular injections of ALZ-101 together with an aluminum hydroxide adjuvant, the hypothesis is that the body's own immune system will recognize it as a potentially harmful substance and thus start to produce antibodies against it.

Alzinova: ALZ-101 forms stable Aβ oligomers

Left picture illustrates, again, the engineered AβCC-peptide. To the right is a model of how AβCC form stable oligomers.

Source: Lendel et al., 2014

Preclinical data

The preclinical package has so far included pharmacological and toxicological studies, a pivotal GLP-toxicology study, an *in vivo* efficacy study of a transgenic animal model, and a non-transgenic animal efficacy model using physiologically relevant patient-derived material. Alzinova has used non-human primates (macaque monkeys), rabbits and mice in the pharmacological studies and evaluated different doses and dose intervals.

Studies have reported a good safety profile…

The preclinical studies have shown that ALZ-101 has a good safety profile. Furthermore, a strong immune response is stimulated against the antigen after administration, meaning that the immune system indeed recognizes the oligomers as potentially harmful substances and reacts against them. The antibodies produced are specific to the neurotoxic oligomers only, meaning that they do not become neutralized by the Aβ that is always present in the blood. The antibodies can instead cross the blood-brain barrier, a major challenge for immunotherapies, and act in the brain. It should be noted that Alzinova, as of today, has not conducted any measures of the ratio between antibodies in blood and the amount active in the brain. However, as the results from the efficacy study in the mouse model clearly show that the antibodies can reach the brain, we believe it is encouraging data at this stage.

… as well as a good immunogenicity profile

The GLP-toxicology study on macaque monkeys was according to regulatory requirements. It was designed to be supportive of the planned clinical Phase Ib trial. The monkeys were equally randomized to active treatment or placebo. There were no signs of severe adverse events, and a good immunogenicity profile was reported.

AD is a uniquely human disease, and it consequently poses a challenge to induce the disease into an animal model by transgenic methods. Historically, several candidates have shown strong efficacy in transgenic mice models, only to be followed by clinical disappointments.

Encouraging preclinical results involving actual AD patient material

To minimize the risk of evaluating their drug candidates in poor animal models, Alzinova sought to evaluate the efficacy on actual patient material. The company entered into a research collaboration with Petronella Kettunen at the University of Gothenburg, who has developed such a model using zebrafish. The project was partially funded externally by SWElife. In this study, brain extracts from deceased AD patients as well as from non-AD

deceased humans were collected and injected into the brain of zebrafish embryos. Only the extracts from AD patients affected the zebrafish cognitive abilities (measured as the ability of the fish to learn the startle response). By pre-treating the AD brain extracts with Alzinova's antibodies (ALZ-201 or the oligomer-specific antibodies from ALZ-101 vaccination), this cognitive deficit could be completely prevented. The zebrafish study also gave good indications that it is the right type of Aβ oligomers that are neutralized by Alzinova's drug candidates.

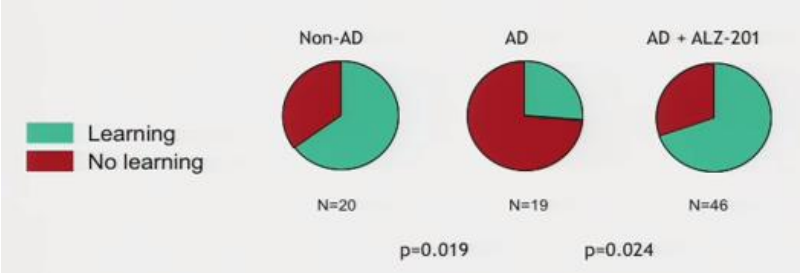
We are encouraged by the results on the zebrafish, yet we believe it should be interpreted with some caution at this stage. The results are illustrated in the pie chart figure below.

Alzinova: Preclinical data

	Pharmacology studies	GLP-toxicology	Non-transgenic efficacy studies	Transgenic efficacy studies
Animal model	Macaque monkeys, mice, rabbits.	Macaque monkeys.	Zebrafish.	Mice carrying human APP with pathological mutations (Swe/Lon)
Scope	Different doses of ALZ-101 and adjuvant in different animal models, including non-human primates.	A GLP-toxicology study conducted on 20 macaque monkeys. One dose of ALZ-101 administered five times. The dose was equivalent to twice the dose intended for humans in the phase Ib trial. The animals were divided equally to an active arm or to placebo.	In a research collaboration with Gothenburg University, Alzinova measured *in vivo* efficacy using brain extracts from deceased AD patients and controls in a zebrafish cognition model.	Effect of multiple administrations of ALZ-101 on behavior, biochemistry, and histology of transgenic mice.
Aim with study	Dose-finding studies with immunogenicity (immune response) and safety assessments.	Toxicologic evaluation and immunogenicity according to regulatory requirements.	Measure efficacy using physiologically-relevant (patient) material in an intact vertebrate CNS.	Assess safety and the effect on brain pathology.
Results	Strong antibody response. A good safety profile.	Strong dose dependent antibody titers. No signs of adverse events related to the test item.	Removing ALZ-101/-201 positive oligomers completely neutralizes toxic effect. See the figure below.	No detrimental effects observed. No significant effect on plaque load, but synapses were protected from damage.

Source: Alzinova, Redeye Research

Alzinova: results in a non-transgenic AD animal model



In the zebrafish group that received AD brain extract pretreated with ALZ-201 (n=46), they showed practically the same learning abilities as the zebrafish group with brain extract from control group (n=20). This should be compared to the zebrafish group of n=19 that got injected with AD brain extract without any pre-treatment of Alzinova's compound; their learning abilities were affected.

Source: Alzinova

Current status

According to the proposed plan, ALZ-101 to enter phase Ib trial on mild AD patients this year

Alzinova is currently preparing ALZ-101 for a phase Ib trial. We expect the trial to commence in the first half of 2019. It is following the company's communication. We haven't taken part in the study design yet. From what has been communicated, ALZ-101 plans to be evaluated in 24 patients with mild AD. The study is single-center and will take place in Finland. Primary endpoints will focus on safety, tolerability, and immunogenicity (immune response). We expect read-out from the primary endpoints in the second half of 2020. In conjunction with the phase Ib study, Alzinova also plans to initiate complementary efficacy studies in animal models as well as ex vivo studies to further increase the attractiveness of the project.

We will focus on the primary endpoints when the results are presented: safety, tolerability, and immunogenicity. We hope to learn that ALZ-101 is safe and tolerable when different doses are evaluated in humans for the first time. In our view, good safety in AD means that the degree of ARIA is mild or non-existent. Further, we hope that no signs of CNS inflammation occur in the trial. CNS inflammation is a possible risk in vaccine trials and was

seen in a subset of patients in the first generation of active Aβ immunotherapies. Side effects related to the site of administration (locally) are also common for injectables, we want to see that those side effects are mild and temporary

Secondly, we hope to learn that ALZ-101 with adjuvant gives strong, dose-dependent antibody titers. The very idea of a vaccine is to create an immunological response. Given the limited patient population and short treatment time, any signs of improvement on biomarkers or cognition will, in our view, be a bonus.

From a production perspective, ALZ-101 is risk-minimized to the extent that Alzinova has started to develop production methods for ALZ-101 according to Good Manufacturing Process (GMP). A first GMP-batch plans to be produced later in the current quarter, Q1'19. ALZ-101 is a synthetic product and is produced according to standard procedures. Alzinova is today able to produce batches that are sufficiently large to support the whole phase Ib clinical package, which includes bioburden, quality release, clinical material, and stability studies.

ALZ-201 – monoclonal antibody

Monoclonal antibody also in the product pipeline

Also developed using Alzinova's AβCC technology, ALZ-201 is the company's murine monoclonal antibody. ALZ-201 binds to oligomers only, not to monomers or insoluble fibrils and thus has a similar binding profile as ALZ-101. The monoclonal antibody is currently in evaluation as both a diagnostic tool and as a potential therapeutic in AD. Considering its attractive mechanism of action, we would believe there are opportunities in going forward with the ALZ-201 project as well.

As Alzinova has stated that their current focus is the development of ALZ-101, ALZ-201 is currently not included in our valuation model. It is likely to stay that way until we see a clear and funded development path for ALZ-201.

Patent situation

Alzinova has two patent families, each consisting of both composition-of-matter- and method patents.

- The first patent family covers the protection for the AβCC technology and ALZ-101.
- The second patent family covers the monoclonal antibody, ALZ-201.

Patent on key markets expires in 2029

Given Alzinova's strategy to prioritize the development of ALZ-101, the most important patents belong to the first patent family. The AβCC technology (ALZ-101) is protected on the most important markets – that is, most of Europe, US, and Japan - until 2029. Patents for the AβCC technology are also approved in China, India, Australia, and Canada. In addition, registered medicinal products can receive prolonged protection with up to five years in all of these markets.

Alzinova has an active patent strategy and plans to conduct pharmacology studies within the next two years that aim to strengthen the patent situation further and prolong the expiration date for ALZ-101.

ALZ-101 - market opportunity and estimates

Current AD drugs market

In comparison to the societal cost burden, the current prescription drug market for AD is tiny. The global costs for AD are likely to exceed USD 1 trillion soon. At the same time, the drug market for AD is currently estimated at a mere USD 3.3 billion. Unless new effective therapies get approved, the market will likely experience a steady decline due to generic erosion.

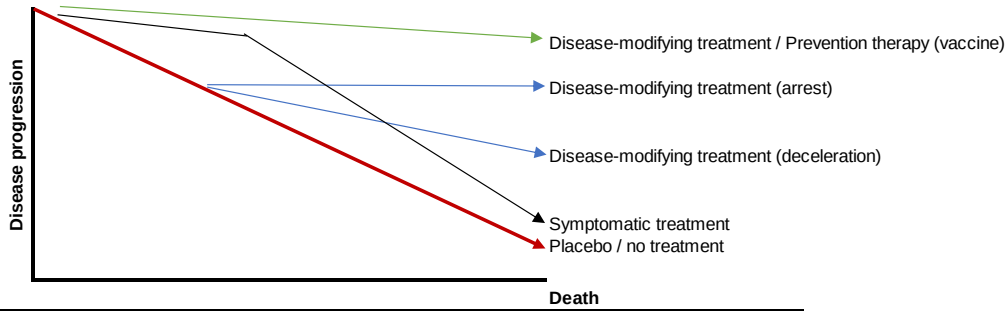
The current prescription drug market for AD constitutes symptom relief treatments only. These are small molecules, with a mechanism of action as either cholinesterase inhibitors or NMDA receptor antagonists. The latest drug approved for AD treatment was in 2002. From this perspective, we argue that the AD market is one of the areas with the highest unmet medical need.

Medical need #1 – disease-modifying therapies

Alzheimer may currently be the indication with greatest medical need

The greatest medical need is for a therapy that has a true disease-modifying effect. The definition of a disease-modifying therapy is its ability to change the course of the progressive state and prolong survival.

Impact of symptomatic versus disease-modifying therapies over the course of the disease



Source: Datamonitor, Redeye Research

Despite the major disappointments, the highest hope and the only drug category that has shown clinical benefits are Aβ immunotherapies. Aβ immunotherapies have also advanced the furthest in clinical development.

Aβ Immunotherapies – active and passive approaches

Either infused externally by monoclonal antibodies (passive) or elicited by the body's own immune system (active)

Aβ immunotherapies either distinguish as active or passive. The common denominator is that the mechanism of action entails antibody-mediated clearance of the target molecules. Antibodies can either be produced externally and injected into the patient on a frequent basis. Those antibodies are typically of human monoclonal type. That is the passive immunotherapy approach. Alternatively, active immunotherapies, to which ALZ-101 belongs, are vaccines where the antigen is injected with an adjuvant to elicit antibody production by the body's own immune system. The approaches both have advantages and disadvantages:

Active Aβ immunotherapies		Passive Aβ immunotherapies	
Pros	**Cons**	**Pros**	**Cons**
- Long-lasting antibody response, maintained through booster doses	- Adjuvant could induce an undesired immune response	- Monoclonal antibodies can be made conformation-specific for a binding site of the targeted protein.	- Frequent infusion of costly anti-Aβ-antibodies
- Potentially more cost-effective and with fewer visits to the doctor	- Vaccine is not suited for all patients, e.g. in truly elderly patients.	- Allows for precise dosing	- Potential that patients develop neutralizing antibodies against the therapy
- Administration-friendly, as delivery injections are not required with the same frequency	- Difficult to stop quickly once the immune system has started a reaction	- Easy to stop quickly if undesired effects occur	

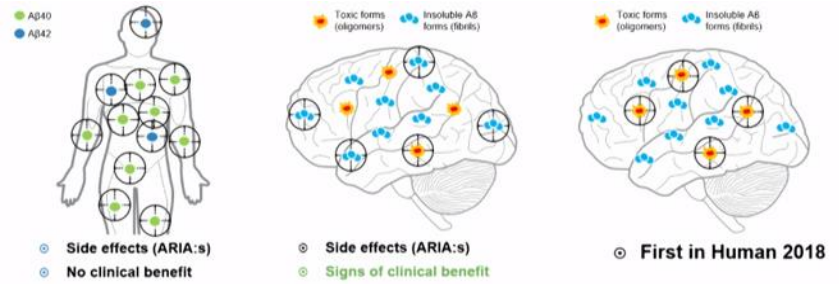
Source: Redeye Research

The first Aβ immunotherapy in clinical trials was a vaccine, AN1792. It was a synthetic form of the whole Aβ42 peptide together with the adjuvant QS-21. AN1792 generated antibodies against an exposed part of the aggregates (the N-terminal) which is accessible in all Aβ types.

AN1792 entered clinical development in 1999. 80 patients with mild to moderate AD were enrolled in four treatment arms. The treatment duration was six months. The trial did not report any adverse events; the drug agent was subsequently advanced to a longer phase IIa trial with treatment duration of 15 months. This trial enrolled a total of 372 patients. It was terminated due to severe adverse events; approximately six percent of the patients developed aseptic meningoencephalitis. It is believed that AN1792 generated an inflammatory response due to the activation of T_H1 lymphocytes. It is known as a cellular mediated immune response; the antibody response was reported as low in these patients. The cell-mediated response was possibly related to the adjuvant, QS-21.

Lessons learned from the AN1792 vaccine thus favored induction of a T_H2-mediated response, i.e., an antibody activation, rather than a cell-mediated T_H1 response (Lemere et al., 2010). Furthermore, antibodies need to be conformation-specific to be able to recognize different Aβ aggregates. The second and especially the third generation of Aβ immunotherapies have increasingly acknowledged the role of oligomers as the neurotoxic agent. Recent studies have even highlighted the great confusion what exactly an Aβ oligomer is and which of them that are toxic. Most oligomers might, in fact, be inactive, meaning that drug agents that can target the small pool of diffusible, bioactive oligomers are likely to be therapeutically most useful (Hong et al., 2018). These findings correspond well with ALZ-101 binding profile and what has been observed in the zebrafish efficacy studies, namely that although a very little amount of Aβ in brain tissue extracts is targeted, it nonetheless leads to a high therapeutic effect.

ALZ-101: the third generation of Aβ immunotherapies



The first generation of immunotherapies were unspecific to Aβ forms. Consequently, these drug agents had little signs of efficacy and a clear side effect profile. As the understanding of the disease has increased, drug candidates that are more oligomer-specific have started to show more adequate signs of clinical benefit.
ALZ-101 is highly specific to a certain type of neurotoxic Aβ oligomers, and has shown no affinity to monomers or fibrils in the preclinical stage.
Source: Alzinova

Current pipeline of active Aβ immunotherapies

In the active Aβ immunotherapy field, we are aware of eight vaccines currently in development. In addition, two vaccines in development are targeting Tau. Of the eight active Aβ immunotherapies, five are in clinical development. If Alzinova delivers according to its proposed timeline, ALZ-101 will start its phase Ib trial in the first half of 2019 and hence be the sixth, clinical-stage Aβ vaccine.

Far fewer Aβ vaccine candidates than Aβ monoclonal antibodies in the clinical pipeline

In comparison to passive Aβ immunotherapies, the active immunotherapy is, from a competitive perspective, far less crowded. We further believe that the active and the passive approach could be complementary in a future treatment paradigm of AD. Some patients might benefit more from a vaccine, and vice versa. In this perspective, we regard the drug candidates within the active Aβ immunotherapy field as the closest competitors to ALZ-101. Below we highlight the candidates we deem the closest competitors to ALZ-101:

- CAD106
- UB-311
- ACI-24
- Lu AF20513
- ABvac40

CAD106

CAD106 has advanced the furthest

CAD106 (Novartis) is the drug candidate that has advanced the furthest in clinical trials. It is currently in an ongoing phase II/III-trial. CAD106 combines multiple copies of Aβ1-6 derived from the N-terminal, which is where the primary B-cell epitope is found. It is coupled to a carrier protein, a virus-like particle QB, and is formulated with the adjuvant aluminum hydroxide. By using the N-terminal of the Aβ1-6 peptide, the hypothesis is to avoid an Aβ-activation of T_H1-cells and consequently CNS inflammation.

From what we have learned, the N-terminus will elicit antibodies to all Aβ; i.e., monomers, oligomers, and fibrils. Based on preclinical findings, CAD106 has been shown to recognize monomers and denatured oligomers, as well as reducing plaque load in transgenic mice. Accordingly, we believe CAD106 has a rather unspecific binding profile.

CAD106 has been evaluated in one phase I-study (n=58) with mild- to moderate AD and in several phase II studies. The phase II-studies have comprised a total of approximately 300

AD patients. The findings in the phase I study favored a good safety profile; no reported incidence of meningoencephalitis or CNS related inflammation. Moreover, the majority of the CAD106-treated patients developed an Aβ antibody response.

In the largest of the phase II studies (n=121), CAD106 was generally well tolerated; no signs of CNS inflammation, six cases of asymptomatic ARIA were reported. In the highest dose regimen (450 µg), over 80 percent of the patients developed an antibody response.

In 2014, Novartis partnered with The Banner Institute as part of their Alzheimer Prevention Initiative (API). API was initiated in 2011 to accelerate disease-modifying treatment in presymptomatic AD patients. The ongoing phase II/III study will determine whether CAD106 and another compound, CNP520 (BACE1 inhibitor; Novartis) can prevent or significantly delay the onset of AD in healthy people that are genetically at risk of developing AD. Hence, the trial pioneers in recruiting healthy people in a late-stage trial. The trial will enroll 1.340 APOE4 homozygotes. We assume it is a pivotal trial for CAD106. As the primary endpoint is time-to-diagnosis (placebo-controlled) it will be a very long study; read-out is not expected until 2023, note that it got initiated in 2014.

We believe that the clinical data package so far has reported that CAD106 is safe and tolerable and creates an immunological response. However, we have not taken part of any data on biomarkers so far.

UB-311

Recently reported positive phase IIa results

UB-311 (United Neurosciences) is a synthetic peptide consisting of a helper T-cell epitope coupled to the Aβ1-14 sequence. The antigen is formulated with aluminum hydroxide and CpG as adjuvants. The approach aims at stimulating a T-helper type 2 (T_H2) immune response instead of a cellular type 1 (T_H1) response. UB-311 recently reported positive early results from a completed phase IIa study.

In vitro and *in vivo* studies in small animals, baboons, and macaques showed that UB-311 generated anti-Aβ-antibodies with N-terminal site-specificity. In a phase I study (n=19 mild- to moderate AD patients), analysis of the generated anti-Aβ-antibodies showed preferential binding to Aβ fibrils, followed by oligomers, and the least to monomers. The phase I study reported on a 100 percent responder rate as well as being safe and tolerated.

United Neurosciences recently (January 2019) reported positive results from a phase IIa study. The study was on 43 mild AD patients. It was a double-blinded and placebo-controlled study with randomization to two dose regimens with UB-311 or placebo. Primary measures were to evaluate safety, tolerability, and immunogenicity.

The company reported on a good safety and a 96 percent immunogenicity responder rate. Secondary measures – for example, amyloid PET burden, CDR-SB, and MMSE – pointed, according to the company, in favor of UB-311. Additional results are to be presented at relevant conferences later in 2019.

In conclusion, UB-311 is so far regarded as safe, tolerable, and with a good immunogenicity profile. Efficacy measures are yet to be evaluated in larger clinical studies.

ACI-24

In ongoing phase II studies

ACI-24 (AC Immune) is a liposome vaccine, aimed at eliciting an antibody response towards aggregated Aβ without T_H1 activation. ACI-24 contains N-terminal fragments, but their anchoring of truncated Aβ1-15 to the surface of liposomes forces the peptide to adopt an aggregated β-sheet structure. Their preclinical findings show that ACI-24 generated N-

terminal specific antibodies effective in decreasing insoluble amyloid deposits as well as soluble Aβ42 in the brain. Hickman et al. (2010) showed that ACI-24 have a factor of two or so stronger binding to oligomers than monomers. We haven't seen any available data on ACI-24s affinity to insoluble fibrils.

In 2009, AC immune initiated a phase I/II study with ACI-24. The study enrolled 198 patients with mild to moderate AD patients who had a positive amyloid PET imaging. The primary endpoint was safety, tolerability, and antibody titers. We haven't taken part in any published data so far from the trial, AC Immune has reported the completion of the study, with positive safety and tolerability. AC Immune has subsequently initiated a phase II trial (n=45) in patients with mild AD. The phase II trial is a double-blind, randomized, and placebo-controlled, with an adaptive design to assess the safety, tolerability, immunogenicity and target engagement with ACI-24. The study is taking place in Sweden and Finland; we believe top-line data are to be presented in 2021.

ACI-24 is also in clinical development as a vaccine for AD in Down's Syndrome. Downs Syndrome has a pathology that is amyloid-related and often causes dementia in mid-life.

Lu AF20513

Developed for improved immunogenicity in elderly patients

Lu AF20513 (Lundbeck) combines three repeats of Aβ1-12 with sequences of tetanus toxin. The construct may improve the ability of the elderly population to mount an immune response to the peptide by stimulation of pre-existing memory T_H-cells. It is formulated with aluminum hydroxide. Preclinical findings concluded that the anti-Aβ-antibodies generated bind to oligomers of Aβ42 with the highest affinity but also monomers and fibrils of Aβ42.

Lu AF20513 is currently conducting an open-label, phase I study on patients with AD. The study is multi-center, taking place in Austria, Finland, and Sweden. A total of 50 mild AD patients are to be enrolled to measure safety, tolerability, and immunogenicity. The phase I study is expected to be completed at the end of 2019.

ABvac40

Differentiated as it targets Aβ40

ABvac40 (Araclon Biotech) is the first vaccine targeting the C-terminus of Aβ40 cross-linked to a carrier protein, KLH (Keyhole Limpet Hemocyanin). Aluminum hydroxide is used as an adjuvant. The approach to target Aβ40 is differentiated against the other vaccines in development and also subject to some controversy in our opinion; Aβ40 is less prone to form toxic aggregates than Aβ42. Some studies have even pointed to neuroprotective properties of Aβ40.

In 2016, Araclon Biotech reported phase I results from a study on 24 mild AD patients. The vaccine appeared safe with no incidents of vasogenic edema or microhemorrhage. In 2017, a phase II trial with ABvac40 was initiated. The study is enrolling 120 patients with MCI-AD or mild AD, and we expect data to be presented in the first half of 2020, at earliest. The study is placebo-controlled and will assess the safety and immune response as primary endpoints. The study will also, as secondary endpoints, compare the change in biomarkers, cognitive scores, and quality-of-life measures.

Competitive summary

The completed trials in the vaccine area have so far reported good safety, tolerability, and eliciting of antibody titers. However, none of them have so far reported any data on disease-modification efficacy on a larger patient group. Given the overall pipeline in AD, we find it interesting that active immunotherapies are rather spared from massive competition. Moreover, the vaccine approach, as highly cost-effective, long-lasting, and administration-

friendly suits an indication such as AD well; it is a life-long, progressive disease where treatment needs to intervene early and throughout the rest of the patient's lives.

ALZ-101 clearly distinguish in the competitive field

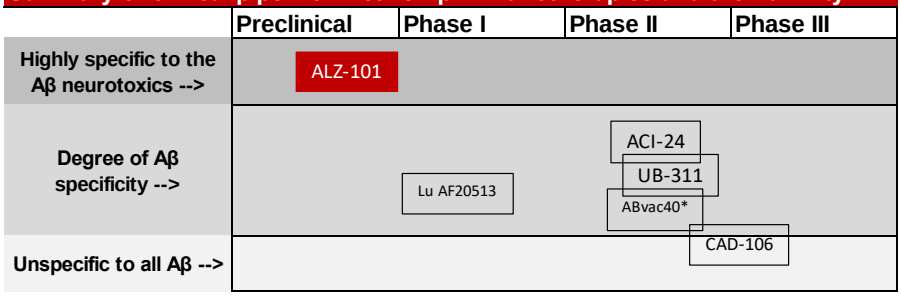
We argue that ALZ-101is differentiated as a vaccine candidate, it has shown no affinity to monomers or insoluble fibrils, only to the neurotoxic Aβ oligomers in the brain. The therapeutic strategy to target oligomers is scientifically the most promising approach today, which, in our view, makes ALZ-101 one of the most promising AD drug candidates.

Summary of clinical pipeline - Active Aβ immunotherapies

Drug Candidate	Company	Current phase	Expected Data	Delivery	Comment
CAD106	Novartis AG	II/III	2023	Subcutaneous injections (SQ)	Phase II/III initiated in 2015, endpoint is time-to-diagnosis.
UB-311	United Neurosciences	II	2019	Intramuscular (IM)	Data from phase IIa study expected in 2019
ABvac40	Araclon Biotech S.L.	II	2020	Intravenous (IV)	Targets Aβ40.
ACI-24	AC Immune, Ltd.	II	2021	IM, SQ	Also evaluated for AD in Down's syndrome patients.
Lu AF20513	H. Lundbeck A/S	I	2019	N/A	
ALZ-101	***Alzinova AB***	***Preclinical***	***H1'20 (Ph Ib)***	***IM***	
AD05	AFFiRiS GmbH	Preclinical	-	N/A	Unknown status of earlier compounds, AD02 and AD04.
AOE1	Research academia (China)	Research	-	N/A	No data available about a possible commercialization effort.

Source: Biomedtracker, Company websites, Redeye Research

Summary of clinical pipeline - Active Aβ immunotherapies and their affinity



* Recognizes monomers, dimers, trimers , and oligomers of Aβ40.
Source: Redeye Research

Recent trials with passive immunotherapies validate the ALZ-101 approach

We argue that the recent, encouraging trials with Aducanumab (Biogen/Eisai) and BAN2401 (Eisai/Biogen) are strengthening the approach of ALZ-101. These monoclonal antibodies have a strong affinity to oligomers/protofibrils. Aducanumab and BAN2401 are the only two AD compounds that have shown disease-modifying benefits in a larger patient group.

Aducanumab

Affinity to Aβ oligomers and fibrils

Aducanumab is a human IgG1 monoclonal antibody against a conformational epitope found on the Aβ peptide. Aducanumab binds to oligomers and fibrils of Aβ, not to monomers. The Swiss biotech company Neurimmune originally developed it after isolating it from a patient with a very stable disease process. In 2007, Neurimmune entered into a collaboration with Biogen to develop novel antibodies (Aducanumab included) for the treatment of AD.

Aducanumab was the first immunotherapy to show clinical improvements on biomarkers, and cognitive test scores (MMSE and CDR-SB). Aducanumab demonstrated these improvements in a clinical phase Ib study on 166 subjects, referred to as PRIME. The patients had to score more than 19 on the MMSE and confirmed as amyloid positive using PET imaging to meet the enrollment criteria. MRI scans were also included during enrollment.

Interim data from PRIME has been presented on several occasions. In 2016, published data demonstrated that Aducanumab, after one year of monthly infusions, reduced Aβ content in the brain in a dose- and time-dependent manner. It was accompanied by clinical improvements based on MMSE and CDR-SB.

Following PRIME interim analysis, Aducanumab was granted fast track designation by FDA in 2016 and subsequently entered into two phase III studies. The phase III studies, named ENGAGE and EMERGE, will enroll approximately 3.200 early AD patients to evaluate the efficacy and safety of Aducanumab. Enrollment criteria include an MMSE between 24 and 30

Aducanumab: study design of phase III trials

Trial	Sample size	Target patients	Study design	Treatment arms	Primary endpoints
ENGAGE	1.605	Early AD patients (MMSE 24 - 30)	Randomized, parallel-assignment, double-blind, placebo-controlled	Arm 1: ApoE4 carrier; titration to 3 or 6mg/kg Arm 2: ApoE4 non- carrier; titration to 6 or 10mg/kg Arm 3: placebo Frequency: monthly IV infusion Duration: 18 months plus 24-month long-term extension	Change from baseline in CDR-SB score at week 78
EMERGE	1.605	Early AD patients (MMSE 24 - 30)	Randomized, parallel-assignment, double-blind, placebo-controlled	Arm 1: ApoE4 carrier; titration to 3 or 6mg/kg Arm 2: ApoE4 non- carrier; titration to 6 or 10mg/kg Arm 3: placebo Frequency: monthly IV infusion Duration: 18 months plus 24-month long-term extension	Change from baseline in CDR-SB score at week 78

Source: Datamonitor, Redeye Research

(note less severe AD patients compared to PRIME) and positive amyloid PET imaging. We believe that read-out from those trials is to be presented in H1'20.

We see Aducanumab as a promising, passive immunotherapy. However, two things should be taken into consideration. Firstly, there is not that much efficacy data. The PRIME study enrolled merely 166 patients, and Aducanumab went directly from PRIME phase Ib to ENGAGE and EMERGE pivotal trials (no phase II trials) due to the fast track designation. Secondly, there might be some concern about the safety data of Aducanumab. The PRIME results revealed a high frequency of ARIA-E (E stands for edema) that has been both dose- and APOE4 dependent. Instances of ARIA-E in the highest dose regimen of 10 mg/kg were up to 55 percent among ApoE4 carriers based on one-year data. The ARIA will need to be taken into close consideration in the ongoing trials.

BAN2401

High affinity to oligomers/protofibrils

BAN2401 (Eisai/Biogen) is the humanized monoclonal antibody based on the mouse monoclonal antibody, mAb158. BAN2401 was originally developed by BioArctic after the discovery of 'The Arctic mutation.' It is a pathogenic mutation of the amyloid precursor protein (APP). The Arctic mutation caused AD in a Swedish family that formed Aβ protofibrils (oligomers) at a faster rate compared to wild-type Aβ. BAN2401 is designed to target these protofibrils with high affinity.

BioArctic signed a license agreement in 2007 with Eisai on BAN2401. In 2014, Eisai entered into a collaboration with Biogen for joint development and commercialization of BAN2401.

In 2015, Eisai reported positive results from a phase I trial with BAN2401 in 80 patients with early AD. BAN2401 was well tolerated at all doses tested. Moreover, the incidence of ARIA-E/H was comparable to that of placebo. The dose regimens used in the phase I gave good data on how to design the later initiated phase IIb trial.

In July 2018, Eisai reported positive, top-line phase IIb results in 856 patients with early AD. The study used a composite score, ADCOMS, that combined domains from ADAS-Cog, MMSE, and CDR-SB, as the primary endpoint to enable a high sensitivity of change in clinical scores. Positive amyloid pathology was confirmed with PET imaging at the start of the trial.

The phase IIb results revealed statistically significant benefits at 18 months in slowing of disease progression (ADCOMS) and reducing the amyloid load in the brain (observed in PET scan). The results were dose-dependent, both regarding reduction in cognitive decline and amyloid PET. The highest dose group of 10 mg/kg bi-weekly demonstrated a slowing of clinical decline by 30 percent compared to placebo at 18 months. The study did not meet its primary endpoint, which was change in ADCOMS from baseline at 12 months to enable a more rapid progression into the phase III program. The twelve months endpoint had high bars set, with criteria of 80 percent probability that BAN2401 demonstrated a meaningful clinical significance. Overall, BAN2401 was well tolerated, with less than 10 percent ARIA in the highest dose regimen.

BAN2401: Study design of phase IIb

Trial	Sample size	Target patients	Study design	Treatment arms	Primary endpoints
Phase IIb	n = 856	MCI-AD or mild AD	Placebo-controlled, double-blind, and parallel grouped. Newly enrolled patients were randomized to treatment arms based on early interim-results to optimize the probability of efficacy.	Patients were randomized to five dose regimens: 2.5 mg/kg twice a month, 5 mg/kg monthly 5 mg/kg twice a month 10 mg/kg monthly 10 mg/kg twice a month Placebo.	Change from baseline in ADCOMS at 12 months.

Source: Datamonitor, Redeye Research

ALZ-101 – valuing the opportunity

Sales models

Below are our peak sales models for ALZ-101:

ALZ-101 sales model of priming shots*

	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037
	Launch					Peak						
MCI-AD prevalence (m)												
US	5.255	5.415	5.574	5.734	5.898	6.078	6.250	6.414	6.574	6.733	6.899	7.051
5EU	6.687	6.821	6.951	7.083	7.222	7.399	7.567	7.726	7.875	8.018	8.171	8.303
Japan	3.466	3.515	3.564	3.615	3.675	3.740	3.801	3.859	3.913	3.964	4.008	4.042
MCI-AD treatment rate (m)												
US	2.102	2.166	2.229	2.294	2.359	2.431	2.500	2.566	2.630	2.693	2.759	2.820
5EU	2.675	2.728	2.780	2.833	2.889	2.960	3.027	3.090	3.150	3.207	3.268	3.321
Japan	1.733	1.758	1.782	1.808	1.838	1.870	1.901	1.930	1.956	1.982	2.004	2.021
Annual market penetration, ALZ-101												
US	0.5%	1.0%	3.0%	5.0%	7.5%	10.0%	7.0%	5.0%	3.0%	1.5%	0.5%	0.0%
5EU	0.5%	1.0%	3.0%	5.0%	7.5%	10.0%	7.0%	5.0%	3.0%	1.5%	0.5%	0.0%
Japan	0.5%	1.0%	3.0%	5.0%	7.5%	10.0%	7.0%	5.0%	3.0%	1.5%	0.5%	0.0%
Newly treated patients, ALZ-101 (m)												
US	0.011	0.022	0.067	0.115	0.177	0.243	0.175	0.128	0.079	0.040	0.014	0.000
5EU	0.013	0.027	0.083	0.142	0.217	0.296	0.212	0.155	0.094	0.048	0.016	0.000
Japan	0.009	0.018	0.053	0.090	0.138	0.187	0.133	0.096	0.059	0.030	0.010	0.000
Price - Priming shots, ALZ-101 ($)												
US	5,500	5,500	5,500	5,500	5,500	5,500	5,500	5,500	5,500	5,500	5,500	5,500
5EU	2,750	2,750	2,750	2,750	2,750	2,750	2,750	2,750	2,750	2,750	2,750	2,750
Japan	4,125	4,125	4,125	4,125	4,125	4,125	4,125	4,125	4,125	4,125	4,125	4,125
Sales - Priming shots, ALZ-101 ($m)												
US	60	120	370	630	970	1,340	960	710	430	220	80	0
5EU	40	80	230	390	600	810	580	420	260	130	40	0
Japan	40	70	220	370	570	770	550	400	240	120	40	0
Total	**140**	**270**	**820**	**1,390**	**2,140**	**2,920**	**2,090**	**1,530**	**930**	**470**	**160**	**0**

* Datamonitor data over MCI-AD prevalence lasts to 2037. From 2038, we estimate a conservative prevalence increase of 1-2 percent annually between the different regions.

Source: Datamonitor, Redeye Research

ALZ-101 sales model of booster doses

	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037
Patients in the need for booster doses (m)	Launch					Peak						
US	0.000	0.011	0.032	0.099	0.214	0.391	0.634	0.809	0.937	1.016	1.056	1.070
5EU	0.000	0.013	0.041	0.124	0.266	0.482	0.778	0.990	1.145	1.239	1.287	1.304
Japan	0.000	0.009	0.026	0.080	0.170	0.308	0.495	0.628	0.724	0.783	0.813	0.823
Compliance rate (m)												
US	0.000	0.007	0.023	0.069	0.150	0.273	0.317	0.283	0.187	0.102	0.053	0.021
5EU	0.000	0.009	0.028	0.087	0.186	0.338	0.389	0.347	0.229	0.124	0.064	0.026
Japan	0.000	0.006	0.018	0.056	0.119	0.216	0.247	0.220	0.145	0.078	0.041	0.016
Price - annual booster dose, ALZ-101 ($)												
US	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000
5EU	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Japan	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500
Sales - booster doses, ALZ-101 ($m)												
US	0	10	50	140	300	550	630	570	370	200	110	40
5EU	0	10	30	90	190	340	390	350	230	120	60	30
Japan	0	10	30	80	180	320	370	330	220	120	60	20
Total	**0**	**30**	**110**	**310**	**670**	**1,210**	**1,390**	**1,250**	**820**	**440**	**230**	**90**

Source: Redeye Research

ALZ-101 total sales estimates

	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037
Total sales, ALZ-101 ($m)	Launch					Peak						
US	60	130	420	770	1,270	1,890	1,590	1,280	800	420	190	40
5EU	40	90	260	480	790	1,150	970	770	490	250	100	30
Japan	40	80	250	450	750	1,090	920	730	460	240	100	20
Total	**140**	**300**	**930**	**1,700**	**2,810**	**4,130**	**3,480**	**2,780**	**1,750**	**910**	**390**	**90**

Source: Redeye Research

Peak sales potential of > USD 4bn in 2031

We have used MCI-AD prevalence data from Datamonitor on the key markets: the US, 5EU (France, Germany, Italy, Spain, and the UK), and Japan. Their market characteristics vary. While 5EU has the largest MCI-AD population, the US is the most important AD market and subject to price premiums. Japan is an important AD market due to its large elderly population and higher treatment rates.

We view MCI-AD as an eligible target group for ALZ-101 at present, even though the stage gets easily misinterpreted for other conditions and available diagnostic tools are limited. However, a vaccination approach must intervene as early as possible, MCI-AD is the patient group in the early stages where we have the most reliable data, even though it is nonetheless quite limited. As ALZ-101progress in development, we see good prospects for a label expansion in AD. However, we reject the notion that ALZ-101 could label on healthy people that are genetically predisposed to develop AD. Pursuing this opportunity, it will target a far larger patient population. However, it would also require very long trials which could jeopardize the sales potential due to patent expiry.

The treatment rate, closely linked to the diagnosis rate, is set to 40 percent overall years for the US and 5EU, and 50 percent treatment rate for Japan. Those are relevant treatment rates as of today, Datamonitor refers to a diagnosis rate of 34 percent for prodromal AD (MCI-AD).

Market launch expected in 2026

We assume market launch at the end of 2026. We consider partner negotiations in our timeline and assume a pivotal trial initiates at the beginning of 2023. Note that, given the medical need in AD, ALZ-101 could be granted fast track designation. That is a possibility we have taken into consideration in our Bull Case (our optimistic scenario).

We assume peak sales in 2031, which translates to a ramp-up period over six years. Over 700 thousand MCI-AD patients will receive priming treatment with ALZ-101, according to our estimates. Sales are based on a ten percent market penetration of newly treated patients that year.

It is arguable whether our market penetration is a high or a low estimate, given that there is no AD vaccine on the market today and that ALZ-101 is at an early development stage. We believe our forecast is a fairly standard approach.

The price for the priming shots is a critical dimension in the forecasted model. Datamonitor forecasts that the most promising passive AD immunotherapies will have an annual treatment cost of roughly USD 25,000 in the US, USD 10,000 in Japan and a price span of USD 7,800 – 14,400 in 5EU (most of the 5EU countries being in the lower end of the price span). We believe AD vaccines should target a lower price, given its cost-effective approach. Given the societal cost pressure, we anticipate that price will not be the big issue. In the initial treatment, we assume three to four priming shots. We keep the prices at steady state during the period. It is more for illustrative purposes and the uncertainty of a relevant price range at the moment.

Our sales erosion from peak sales year relates to patent expiry. If first sales occur in 2026, we believe there are good prospects to prolong patent expiry into the 2030s. Hence, we assume sales erosion from 2032. We assume a more rapid decline of priming shots (newly treated patients) than for maintenance dosing (existing ALZ-101 patients).

We calculate that the patient base for maintenance (booster doses) treatment cumulates as new patients get treated with ALZ-101. We assume annual booster doses for infinite. For the period 2026-2031, we assume a compliance/persistence rate of 70 percent. We believe this is a fair adjustment since AD patients are an elderly population group and a fair share of them will stop treatment of natural causes. After 2031, we adjust for gradually lower compliance rates due to patent expiry.

The estimated price for booster doses is based on annual one-time shots. It should be comparable, or slightly higher than a one-time shot of a priming dose.

License deal assumptions

Our assumptions for a licensing deal with a larger company are:

- A total potential value of USD 600 million
- An upfront payment of USD 60 million (in 2022)
- Milestone payments based on clinical development, regulatory achievements and achieved sales levels
- An applied royalty rate on future sales of 16 percent

Alzinova's business model is to seek a licensee, at earliest after completed phase Ib trial. It will be a strategic consideration by the management team when the company should enter a licensing deal to optimize shareholder value. We model in our main Base Case scenario that Alzinova enters into a partner collaboration after a phase II program. As the planned phase Ib is a rather small study, we anticipate Alzinova to strengthen the attractiveness of the project by further clinical studies. However, in our optimistic Bull Case scenario, we assume a partnership after the phase Ib trial.

Promising AD drug candidates are attractive in-licensing targets

Below is a set of reference deals in the AD immunotherapy field that has served as the basis for our assumptions. The general deal climate in AD is highly dependent on industry success examples. In this context, it is encouraging that a few Aβ drug agents have shown clinical benefits in the last couple of years. It might answer to some of the very significant, total potential deal values in recent years. Given the early clinical setbacks, we anticipate though that licensees have become increasingly selective, only eyeing drug candidates that can present convincing data. The reference deals table also suggests that the original research and development of some of the most promising drug candidates, BAN2401 and Aducanumab included, have originally taken place at relatively small biotech firms. Those have been attractive in-licensing targets, and they continue to be in the AD field.

Reference deals

Licensor	Licensee	Molecule (Target)	Year	Indication	Phase*	Upfront value ($m)	Total deal value ($m)	Comments
AC Immune	Eli Lilly and Company	ACI-3024 (Tau)	2018	AD - Small molecules	Preclinical	80	1709	Original deal was in CHF: Upfront: CHF 80m; Total potential deal value: CHF 1.7bn. Lilly to purchase a USD 50 converitble note. Double digit royalties also included in the deal.
AC Immune	Janssen Pharmaceuticals	ACI-35 (Tau)	2015	AD - Vaccines	Phase Ib	Undisclosed	509	Tiered royalties
AC Immune	Genentech/Roche	Anti-Tau antibody (Tau)	2012	AD - Monoclonal antibodies	Preclinical	Undisclosed	418	Undisclosed royalties included in the deal.
AFFiRiS GmbH	GlaxoSmithKline Biologics	Acquired exlusive rights to two vaccine candidates (Aβ)	2008	AD - Vaccines	Phase I	35	675	Original deal was in EUR: Upfront: EUR 22.5m; Total potential deal value: EUR 430m. Undisclosed royalties
Neurimmune	Biogen	Aducanumab (Aβ)	2007	AD - Monoclonal antibodies	Preclinical	Undisclosed	380	Royalties included in the deal.
BioArctic	Eisai	BAN2401 (Aβ)	2007	AD - Monoclonal antibodies	Preclinical	Undisclosed	218	High single digit royalties included in the deal.
AC Immune	Genentech/Roche	Crenezumab (Aβ)	2006	AD - Monoclonal antibodies	Preclinical	Undisclosed	300	Undisclosed royalties included in the deal.
						Mean	**601**	
						Median	**418**	

* When entered into agreement
Source: Redeye Research

Development costs for ALZ-101

We estimate a total of SEK 30 million for the phase Ib trial. It is following Alzinova's own communication. The phase Ib costs are risk-adjusted in the income statement based on phase success in the preclinical stage. We believe preclinical success is highly likely. We estimate that most of the phase Ib costs will fall under the income statement for 2019.

For the phase II program, we adjust for a larger patient population and a longer study time than phase Ib. We do not speculate any further in the study design of a phase II program at this stage. In total, we have estimated an early AD patient population of at least 150, at a total cost of SEK 200 million. Phase II costs are risk-adjusted based on phase success for the preclinical stage and phase I in the therapy area of neurology (based on aggregated data). We estimate that the phase II costs will start to hit Alzinova's income statement in 2020. The scope of an in-house phase II program will largely depend on the company's future fund-raising abilities.

Likelihood of Approval for reaching the market

LoA of seven percent

We use a risk-adjusted Likelihood of Approval (LoA) of seven percent. This is based on aggregated data of phase success and LoA in the neurology field. Given the many setbacks in the field of AD, the LoA could be adjusted downwards. However, we regard it as far given Alzinova moving ALZ-101 directly into a patient group.

Financials 2018 - 2020

Successful rights issues completed at the end of 2018

Alzinova completed two rights issues – a directed rights issue and a rights issue with preferential rights for existing shareholders, at the end of 2018. We estimate a cash balance of approximately SEK 46.7 million 2018 year-end. That makes the phase Ib trial with ALZ-101 fully funded. Timewise, we believe the recent capital raise is sufficient to fund the company to mid-2020.

Increasing costs as Alzinova moves into clinical stage

We anticipate no revenues in the next several years. Hence, we focus on the operating costs and cash burn. Alzinova has had a low cash burn as a listed company so far, thanks to the management team's execution. As ALZ-101 approaches the clinical stage, there will be a significant increase in costs in the next three years. The costs for clinical development, reviewed in the previous section, fall under the item 'Other external costs.' If a phase II program is conducted by an external party (a licensee) or initiation gets postponed beyond 2020, we estimate EBIT of SEK – 16.4 million for 2020.

As can be seen in the Income statement, we expect a ramp-up in personnel costs from 2020. As ALZ-101 advances, we believe it is relevant to strengthen in-house management with business development, clinical development, and investor relations/finance competencies.

Alzinova: Income statement

(SEKm)	2016	2017	2018E	2019E	2020E
Income	0.0	0.0	0.0	0.0	0.0
Other income	0.4	0.6	0.0	0.0	0.0
Total income	**0.4**	**0.6**	**0.0**	**0.0**	**0.0**
Operating expenses					
Other external costs*	-5.5	-5.7	-12.4	-20.7	-41.0
Personnel costs	-2.7	-2.6	-2.6	-3.1	-5.1
Other operating expenses			-0.1	-0.1	0.0
Total operating costs	**-8.2**	**-8.3**	**-15.0**	**-24.0**	**-46.1**
Operating profit (EBIT)	**-7.8**	**-7.6**	**-15.0**	**-23.9**	**-46.1**
Net financials	0.0	0.0	0.0	0.0	0.0
Profit before taxes	**-7.9**	**-7.7**	**-15.0**	**-23.9**	**-46.1**
Tax	0.0	0.0	0.0	0.0	0.0
Net profit	**-7.9**	**-7.7**	**-15.0**	**-23.9**	**-46.1**

Source: Redeye Research
** 2019 and 2020 development costs are risk-adjusted*

Valuation

Valuation summary

We use a risk-adjusted discounted cash flow (DCF) model to value the ALZ-101 project. Our main Base Case scenario reflects the assumptions in the previous two sections:

- Valuing the opportunity – ALZ-101."
- Financials 2018-2020."

To provide a dynamic view of our valuation of Alzinova, we also model a pessimistic scenario (Bear Case) and an optimistic scenario (Bull Case). These are based on possible outcomes of the ALZ-101 project over the next two years (see below).

The following assumptions apply to all three scenarios:

- Risk-adjustment (LoA) of seven percent
- A tax rate of 20.6 percent (Swedish corporate income tax from 2021)
- Per share valuation is calculated on 7.5 million outstanding shares
- A WACC of 16 percent. This is based on both quantitative and qualitative aspects of the company.

Bear Case 15,0 SEK

- Factors in possible delays in the ALZ-101 project in the coming two years
- Acknowledges the risk of a rights issue before the phase Ib trial is completed (dilution included)

Base Case 36,0 SEK

- Peak sales potential of > USD 4 billion
- Market launch in 2026
- Sales ramp-up over six years, peak sales in 2031
- **Deal structure (after completed phase II):**
  - Total, potential value of USD 600 million
  - Upfront payment of USD 60 million in 2022
  - Payments for achieved milestones in development and sales
  - Royalty on future sales of 16 percent

Bull Case 65,0 SEK

In our Bull Case we fine-tune a few assumptions from our Base Case:

- Peak sales potential of > USD 5 billion in 2030
- ALZ-101 receive fast track designation from regulatory authorities, with a subsequent market launch in 2025
- **Deal structure (after completed phase Ib trial):**
  - Total, potential value of USD 675 million
  - Upfront payment of USD 100 million in 2021
  - Payments for achieved milestones in development and sales
  - Royalty on future sales of 15 percent

Alzinova: Summary of scenarioanalysis

	Bear	Base	Bull
SEK per share	15	36	65
Potential / Risk*	*-49%*	*21%*	*119%*

Source: Redeye Research

* Based on closing price 22 January, 2019

Stock sentiment

Alzinova listed its shares on the Spotlight market in 2015. So far, the stock has gone up more than 100 percent since the IPO, reflecting a solid timeline in the preclinical stage. The stock has had a particularly strong return during the last six months, spurred by a positive sentiment for stocks in the segment of disease-modifying therapies targeting Aβ.

The years on the Spotlight market has primarily attracted retail investors. Alzinova is, in our view, unknown among greater institutions, the international capital, and life science specialist investors. As ALZ-101 moves towards clinical stage during 2019 and will list their shares on OMX Nasdaq First North, we anticipate more substantial interest across a broader investor base.

Despite its successful three years as a public company, Alzinova's real inflection points still lie ahead. We see good prospects for a positive stock price sentiment in the short, medium and long term:

Short-term

- There will be notable news flow from ALZ-101 in 2019. The first-in-human trial is a phase Ib study on mild AD patients. We expect it to commence in the first half of 2019
- In the rights issue with preferential rights to existing shareholders at the end of 2018, the guarantors took up a limited portion. The risk of overhang in the stock in the near-term is highly limited.

Given our outlined bullet points in the short-term, we will not be surprised if the stock price receives momentum and starts to close the gap and beyond to our Base Case.

Mid- to long-term

- What attracts us in the Alzinova case is ALZ-101; a vaccine candidate with no affinity to monomers or insoluble fibrils, only to the neurotoxic Aβ oligomers. We argue that it has the highest scientific and empirical rationale in disease-modifying therapies in AD and the vaccine approach is potentially superior in cost-effectiveness and frequency of administration.

We are eager to learn about the clinical progress of ALZ-101 and how it continues to stand out competitively.

Peer valuation

Alzinova is somewhat of a rarity in the Scandinavian equity markets as one of the very few disease-modifying approaches to AD. We have chosen not to present an explicit peer group analysis since there are too few relevant biotech companies on OMX Nasdaq. This poses the risk that peer group analysis becomes counter-productive.

The most relevant ratio for a biotech peer group analysis is, in our view, Enterprise Value (EV: Market Cap deducted by current cash position). Alzinova has currently an EV of approximately SEK 175 million.

Besides Alzinova, there are, as far as we are aware, two other biotech companies (on OMX Nasdaq Stockholm) with a disease-modifying approach in AD; AlzeCure Pharma and BioArctic. We do not view BioArctic as a relevant peer as its clinical pipeline is broader and more developed. AlzeCure Pharma stands out as a more relevant peer as it is in a comparable development stage. However, its research in AD is towards both disease-modifying treatment and symptomatic treatment.

If we were to compare Alzinova to non-AD biotech companies, we would look at the following characteristics:

- Single project
- In late pre-clinical/planning stage of becoming a clinical-stage
- Not entered into a licensing deal yet with Big pharma/Big biotech
- Addressing a large indication with high unmet medical need

Our sense is that biotechs with these features seldom have EVs above SEK 100 million. However, we emphasize that Alzinova is addressing the market we regard as having the highest current medical need at the moment, and ALZ-101 is attractively positioned competitively. Accordingly, an EV premium is justified in Alzinova's case.

Sensitivity Analysis

Our valuation of Alzinova is highly affected by what WACC we attribute to the company. We have illustrated the WACC's impact on the valuation in a sensitivity analysis below.

Alzinova: Sensitivity analysis WACC*					
	14%	15%	**16%**	17%	18%
SEK per share	44	40	**36**	32	29

Source: Redeye Research

Catalysts

ALZ-101 - Initiation of phase Ib in mild AD patients (0-6 months)

The initiation of a phase Ib in mild AD patients (n=24) with ALZ-101 is an important milestone for the project. We expect the trial to commence in Q2'19.

Strength: Moderate

Listing on OMX Nasdaq First North (0-6 months)

The company is likely to list on the OMX Nasdaq First North in the first half of 2019. We hope that it will raise awareness and traction among a broader investor base.

Strength: Moderate

Efficacy results on complementary, preclinical studies (0-12 months)

Alzinova plans to initiate additional preclinical efficacy- and *ex vivo* studies. We expect results to be presented throughout 2019.

Strength: Moderate

Further capital injections (+ 6 months)

A successful capital raise will be a major catalyst for the stock itself.

Strength: Major

Aducanumbab top-line results (non-Alzinova project, + 12 months)

We saw it happen in the summer of 2018. The encouraging results by BAN2401 were a major boost to the Alzinova stock. Aducanumab has a comparable binding profile as ALZ-101, even though we argue that ALZ-101 has an even more attractive Aβ specificity. The phase III top-line results by Aducanumab are to be presented in the first half of 2020.

Strength: Major

ALZ-101 top-line results of phase Ib in mild AD patients (+12 months)

We expect top-line results from the phase Ib study in mid-2020. We hope to learn that ALZ-101 is safe, well tolerated, and elicit antibody titers of the desired form.

Strength: Major

Partnership deal (running 'Catalyst')

Out-licensing ALZ-101 is an integral part of the company's business model and will serve as a major catalyst. We treat this a running catalyst.

Strength: Major

Appendix 1 – Management and Board of Directors

Name	Position	Holdings	Experience
Management			
Per Wester (1960)	CEO	29.125 shares	Per Wester is the CEO of Alzinova since September 2015. Before joining Alzinova, he was CEO of Mundipharma, a marketing company within the pharmaceutical industry, for 17 years. Per Wester has a finance degree.
Anders Sandberg (1972)	CSO	145.875 shares	Anders Sandberg is CSO, and co-founder of Alzinova. He is also co-inventor to the company's proprietary AβCC technology platform. Anders Sandberg has more than 16 years of experience in protein research, with special emphasis on neurotoxic peptide aggregates during the last nine years. Anders Sandberg holds a PhD in biochemistry.

Source: Alzinova (2018), Redeye Research

Name	Position	Holdings	Experience
Board of Directors			
Björn Larsson (1965)	Chairman of the Board	4.690 shares	Björn Larsson is the Chairman of the Board of Alzinova since 2011. He has more than 20 years of experience from sales and business development roles within medical devices, biotech and pharmaceuticals. Björn Larsson has a degree in civil engineering from Chalmers University, Gothenburg.
Björn Löwenadler (1952)	Board Member	2.345 shares	Björn Löwenadler has extensive experience from biotech and big pharma, working in different positions with preclinical, early clinical and external partnering activities. Oher assignments include, among others, Business Development Director of Toleranzia, where he until previously also operated as CEO. He has also been Director of External Collaborations at AstraZeneca. Björn Löwenadler holds a PhD in immunology from the Karolinska Institute.
Jan Holmgren (1944)	Board Member	3.000 shares	Jan Holmgren has published more than 500 papers in immunology, microbiology and vaccinology. He is also a member of the Swedish Royal Academy of Science and the Swedish Royal Academy of Engineering. Jan Holmgren is Professor of Medical Microbiology and Immunology at the University of Gothenburg as well as Director of Gothenburg University Research Institute.
Clas Malmeström (1965)	Board Member	1.000 shares	Clas Malmeström is Chief Physician at the Department of Clinical Neuroscience at Sahlgrenska University Hospital in Gothenburg. He has experience from big pharma companies, such as Novartis, Roche and Biogen-Idec, where he has been involved in several clinical trials within Multiple Sclerosis. Claes Malmeström has medical doctoral degree.
Anders Waas (1957)	Board Member	-	An educated dentist, Anders Waas has held senior positions at Astra, AstraZeneca, CV Therapeutics, Actogenics, and Tikomed AB. Anders Waas has extensive experience from business development, management, and pharma development.
Carol Routledge	Board Member	-	Carol Routledge is a senior advisor in R&D and pharmaceutical development. Her experience from the pharma- and biotech industry span over thirty years. She is currently the research director at Alzheimer's Research UK. Carol Routledge holds a PhD in neuropharmacology.

Source: Alzinova (2018), Redeye Research

Summary Redeye Rating

The rating consists of five valuation keys, each constituting an overall assessment of several factors that are rated on a scale of 0 to 2 points. The maximum score for a valuation key is 10 points.

Rating changes in the report: -

Management: 5,0

Alzinova's management constitutes of CEO and the CSO. CEO Per Wester has strong leadership capabilities and experience. CSO Anders Sandberg is the co-inventor of the AβCC technology, as well being the co-founder of the company. As Alzinova soon advances into clinical advancement and will be listed on OMX Nasdaq First North, we argue that there is a clear rationale to add in-house competencies to the management team. Specifically, we expect the management team to be strengthened by demonstrated experience in business- and clinical development from the pharmaceutical industry, as well as strong investor relations capabilities. As always, we favor strong incentives from the management team.

Ownership: 4,0

In the directed rights issue, Alzinova welcomed its first institutional investors. However, we believe the ownership situation could be strengthened further. We want to see primarily three things to happen before we feel entitled to raise our rating in this domain:

- Increased ownership among the Board of Directors (CEO included)
- An active (represented on the Board), major shareholder of the company
- A broadened base of investors. Specifically, it means increased institutional ownership. In mid- to long-term, we hope to see a broadened investor base that includes international capital and life science specialist investors.

Profit Outlook: 6,0

The sales potential for disease-modifying therapies in Alzheimer's disease cannot be emphasized enough. If ALZ-101 would demonstrate clear clinical efficacy and make it to the market, it has by far blockbuster potential. In our sales model, we estimate a peak sales opportunity exceeding USD 4 billion at this early stage.

Profitability: 0,0

Alzinova is a biotech company without any history of profitability.

Financial Strength: 1,5

Alzinova recently raised SEK 45 million in a directed rights issue and a rights issue with preferential rights to existing shareholders. It is sufficient to support the company's operations, including the phase Ib trial with ALZ-101 to mid-2020s.

INCOME STATEMENT	2016	2017	2018E	2019E	2020E
Net sales	0	0	0	0	0
Total operating costs	0	0	-15	-24	-46
EBITDA	0	0	-15	-24	-46
Depreciation	0	0	0	0	0
Amortization	0	0	0	0	0
Impairment charges	0	0	0	0	0
EBIT	0	0	-15	-24	-46
Share in profits	0	0	0	0	0
Net financial items	0	0	0	0	0
Exchange rate dif.	0	0	0	0	0
Pre-tax profit	0	0	-15	-24	-46
Tax	0	0	0	0	0
Net earnings	0	0	-15	-24	-46

BALANCE SHEET	2016	2017	2018E	2019E	2020E
Assets					
Current assets					
Cash in banks	25	18	47	23	0
Receivables	0	0	0	0	0
Inventories	0	0	0	0	0
Other current assets	0	1	1	1	1
Current assets	25	19	48	24	1
Fixed assets					
Tangible assets	0	0	0	0	0
Associated comp.	0	0	0	0	0
Investments	0	0	0	0	0
Goodwill	0	0	0	0	0
Cap. exp. for dev.	0	0	0	0	0
O intangible rights	8	13	13	13	13
O non-current assets	0	0	0	0	0
Total fixed assets	8	13	13	13	13
Deferred tax assets	0	0	0	0	0
Total (assets)	33	32	61	37	14
Liabilities					
Current liabilities					
Short-term debt	0	0	0	0	0
Accounts payable	1	2	2	2	2
O current liabilities	0	0	0	0	0
Current liabilities	1	2	2	2	2
Long-term debt	1	1	1	1	24
O long-term liabilities	0	0	0	0	0
Convertibles	0	0	0	0	0
Total Liabilities	1	2	2	2	25
Deferred tax liab	0	0	0	0	0
Provisions	0	0	0	0	0
Shareholders' equity	32	29	58	34	-12
Minority interest (BS)	0	0	0	0	0
Minority & equity	32	29	58	34	-12
Total liab & SE	33	32	61	37	14

FREE CASH FLOW	2016	2017	2018E	2019E	2020E
Net sales	0	0	0	0	0
Total operating costs	0	0	-15	-24	-46
Depreciations total	0	0	0	0	0
EBIT	0	0	-15	-24	-46
Taxes on EBIT	0	0	0	0	0
NOPLAT	0	0	-15	-24	-46
Depreciation	0	0	0	0	0
Gross cash flow	0	0	-15	-24	-46
Change in WC	0	0	0	0	0
Gross CAPEX	-8	-5	0	0	0
Free cash flow	-8	-5	-15	-24	-46

CAPITAL STRUCTURE	2016	2017	2018E	2019E	2020E
Equity ratio	96%	93%	96%	94%	-72%
Debt/equity ratio	3%	3%	1%	2%	-224%
Net debt	-24	-17	-47	-23	23
Capital employed	8	12	12	12	12
Capital turnover rate	0,0	0,0	0,0	0,0	0,0

GROWTH	2016	2017	2018E	2019E	2020E
Sales growth	0%	0%	0%	0%	0%
EPS growth (adj)	0%	0%	0%	60%	92%

DCF VALUATION	
WACC (%)	16,0 %

CASH FLOW, MSEK

Fair value e. per share, SEK	36
Share price, SEK	29.7

PROFITABILITY	2016	2017	2018E	2019E	2020E
ROE	0%	0%	-34%	-51%	0%
ROCE	0%	0%	-33%	-50%	-187%
ROIC	0%	0%	-122%	-195%	-374%
EBITDA margin	0%	0%	-374953%	-598665%	-
EBIT margin	0%	0%	-374953%	-598665%	-
Net margin	0%	0%	-374953%	-598665%	-

DATA PER SHARE	2016	2017	2018E	2019E	2020E
EPS	0,00	0,00	-1,99	-3,18	-6,12
EPS adj	0,00	0,00	-1,99	-3,18	-6,12
Dividend	0,00	0,00	0,00	0,00	0,00
Net debt	0,00	-2,27	-6,25	-3,07	3,05
Total shares	0,00	7,53	7,53	7,53	7,53

VALUATION	2016	2017	2018E	2019E	2020E
EV	N/A	N/A	N/A	N/A	N/A
P/E	N/A	N/A	N/A	N/A	N/A
P/E diluted	N/A	N/A	N/A	N/A	N/A
P/Sales	N/A	N/A	N/A	N/A	N/A
EV/Sales	N/A	N/A	N/A	N/A	N/A
EV/EBITDA	N/A	N/A	N/A	N/A	N/A
EV/EBIT	N/A	N/A	N/A	N/A	N/A
P/BV	N/A	N/A	N/A	N/A	N/A

SHARE PERFORMANCE		GROWTH/YEAR	16/18E
1 month	35,4 %	Net sales	0,0 %
3 month	17,3 %	Operating profit adj	0,0 %
12 month	78,3 %	EPS, just	0,0 %
Since start of the year	29,1 %	Equity	36,5 %

SHAREHOLDER STRUCTURE %	CAPITAL	VOTES
Avanza Pension	12,3 %	12,3 %
GU Ventures	11,5 %	11,5 %
Nordnet Pensionsförsäkring	7,1 %	7,1 %
Torleif Härd	2,5 %	2,5 %
Ola Hermansson	2,5 %	2,5 %
Anders Sandberg	2,4 %	2,4 %
Moll Invest AB	1,5 %	1,5 %
Jan Löngårdh	1,4 %	1,4 %
Asperö Handels AB	1,1 %	1,1 %
David Bendz	1,0 %	1,0 %

SHARE INFORMATION	
Reuters code	ALZ.SS
List	First North
Share price	29.7
Total shares, million	7.5
Market Cap, MSEK	223.6

MANAGEMENT & BOARD	
CEO	Per Wester
CFO	-
IR	
Chairman	Björn Larsson

FINANCIAL INFORMATION	
FY 2018 Results	February 26, 2019

ANALYSTS	Redeye AB
Anders Hedlund	Mäster Samuelsgatan 42, 10tr
anders.hedlund@redeye.se	111 57 Stockholm
Klas Palin	
klas.palin@redeye.se	

Redeye Rating and Background Definitions

The aim of a Redeye Rating is to help investors identify high-quality companies with attractive valuation.

Company Qualities

The aim of Company Qualities is to provide a well-structured and clear profile of a company's qualities (or operating risk) – its chances of surviving and its potential for achieving long-term stable profit growth.

We categorize a company's qualities on a ten-point scale based on five valuation keys; 1 – Management, 2 – Ownership, 3 – Profit Outlook, 4 – Profitability and 5 – Financial Strength.

Each valuation key is assessed based a number of quantitative and qualitative key factors that are weighted differently according to how important they are deemed to be. Each key factor is allocated a number of points based on its rating. The assessment of each valuation key is based on the total number of points for these individual factors. The rating scale ranges from 0 to +10 points.

The overall rating for each valuation key is indicated by the size of the bar shown in the chart. The relative size of the bars therefore reflects the rating distribution between the different valuation keys.

Management

Our Management rating represents an assessment of the ability of the board of directors and management to manage the company in the best interests of the shareholders. A good board and management can make a mediocre business concept profitable, while a poor board and management can even lead a strong company into crisis. The factors used to assess a company's management are: 1 – Execution, 2 – Capital allocation, 3 – Communication, 4 – Experience, 5 – Leadership and 6 – Integrity.

Ownership

Our Ownership rating represents an assessment of the ownership exercised for longer-term value creation. Owner commitment and expertise are key to a company's stability and the board's ability to take action. Companies with a dispersed ownership structure without a clear controlling shareholder have historically performed worse than the market index over time. The factors used to assess Ownership are: 1 – Ownership structure, 2 – Owner commitment, 3 – Institutional ownership, 4 – Abuse of power, 5 – Reputation, and 6 – Financial sustainability.

Profit Outlook

Our Profit Outlook rating represents an assessment of a company's potential to achieve long-term stable profit growth. Over the long-term, the share price roughly mirrors the company's earnings trend. A company that does not grow may be a good short-term investment, but is usually unwise in the long term. The factors used to assess Profit Outlook are: 1 – Business model, 2 – Sale potential, 3 – Market growth, 4 – Market position, and 5 – Competitiveness.

Profitability

Our Profitability rating represents an assessment of how effective a company has historically utilised its capital to generate profit. Companies cannot survive if they are not profitable. The assessment of how profitable a company has been is based on a number of key ratios and criteria over a period of up to the past five years: 1 – Return on total assets (ROA), 2 – Return on equity (ROE), 3 – Net profit margin, 4 – Free cash flow, and 5 – Operating profit margin or EBIT.

Financial Strength

Our Financial Strength rating represents an assessment of a company's ability to pay in the short and long term. The core of a company's financial strength is its balance sheet and cash flow. Even the greatest potential is of no benefit unless the balance sheet can cope with funding growth. The assessment of a company's financial strength is based on a number of key ratios and criteria: 1 – Times-interest-coverage ratio, 2 – Debt-to-equity ratio, 3 – Quick ratio, 4 – Current ratio, 5 – Sales turnover, 6 – Capital needs, 7 – Cyclicality, and 8 – Forthcoming binary events.

Redeye Equity Research team

Management

Björn Fahlén
bjorn.fahlen@redeye.se

Håkan Östling
hakan.ostling@redeye.se

Technology Team

Jonas Amnesten
jonas.amnesten@redeye.se

Henrik Alveskog
henrik.alveskog@redeye.se

Dennis Berggren
dennis.berggren@redeye.se

Havan Hanna
havan.hanna@redeye.se

Kristoffer Lindström
kristoffer.lindstrom@redeye.se

Fredrik Nilsson
fredrik.nilsson@redeye.se

Tomas Otterbeck
tomas.otterbeck@redeye.se

Eddie Palmgren
eddie.palmgren@redeye.se

Viktor Westman
viktor.westman@redeye.se

Editorial

Jim Andersson
jim.andersson@redeye.se

Eddie Palmgren
eddie.palmgren@redeye.se

Ludvig Svensson
ludvig.svensson@redeye.se

Life Science Team

Anders Hedlund
anders.hedlund@redeye.se

Arvid Necander
arvid.necander@redeye.se

Klas Palin
klas.palin@redeye.se

Mathias Spinnars
mathias.spinnars@redeye.se

Jakob Svensson
jakob.svensson@redeye.se

Erik Nordström (Trainee)
erik.nordstrom@redeye.se

Disclaimer

Important information
Redeye AB ("Redeye" or "the Company") is a specialist financial advisory boutique that focuses on small and mid-cap growth companies in the Nordic region. We focus on the technology and life science sectors. We provide services within Corporate Broking, Corporate Finance, equity research and investor relations. Our strengths are our award-winning research department, experienced advisers, a unique investor network, and the powerful distribution channel redeye.se. Redeye was founded in 1999 and since 2007 has been subject to the supervision of the Swedish Financial Supervisory Authority.
Redeye is licensed to; receive and transmit orders in financial instruments, provide investment advice to clients regarding financial instruments, prepare and disseminate financial analyses/recommendations for trading in financial instruments, execute orders in financial instruments on behalf of clients, place financial instruments without position taking, provide corporate advice and services within mergers and acquisition, provide services in conjunction with the provision of guarantees regarding financial instruments and to operate as a Certified Advisory business (ancillary authorization).

Limitation of liability
This document was prepared for information purposes for general distribution and is not intended to be advisory. The information contained in this analysis is based on sources deemed reliable by Redeye. However, Redeye cannot guarantee the accuracy of the information. The forward-looking information in the analysis is based on subjective assessments about the future, which constitutes a factor of uncertainty. Redeye cannot guarantee that forecasts and forward-looking statements will materialize. Investors shall conduct all investment decisions independently. This analysis is intended to be one of a number of tools that can be used in making an investment decision. All investors are therefore encouraged to supplement this information with additional relevant data and to consult a financial advisor prior to an investment decision. Accordingly, Redeye accepts no liability for any loss or damage resulting from the use of this analysis.

Potential conflict of interest
Redeye's research department is regulated by operational and administrative rules established to avoid conflicts of interest and to ensure the objectivity and independence of its analysts. The following applies:

- For companies that are the subject of Redeye's research analysis, the applicable rules include those established by the Swedish Financial Supervisory Authority pertaining to investment recommendations and the handling of conflicts of interest. Furthermore, Redeye employees are not allowed to trade in financial instruments of the company in question, effective from 30 days before its covered company comes with financial reports, such as quarterly reports, year-end reports, or the like, to the date Redeye publishes its analysis plus two trading days after this date.
- An analyst may not engage in corporate finance transactions without the express approval of management, and may not receive any remuneration directly linked to such transactions.
- Redeye may carry out an analysis upon commission or in exchange for payment from the company that is the subject of the analysis, or from an underwriting institution in conjunction with a merger and acquisition (M&A) deal, new share issue or a public listing. Readers of these reports should assume that Redeye may have received or will receive remuneration from the company/companies cited in the report for the performance of financial advisory services. Such remuneration is of a predetermined amount and is not dependent on the content of the analysis.

Redeye's research coverage
Redeye's research analyses consist of case-based analyses, which imply that the frequency of the analytical reports may vary over time. Unless otherwise expressly stated in the report, the analysis is updated when considered necessary by the research department, for example in the event of significant changes in market conditions or events related to the issuer/the financial instrument.

Recommendation structure
Redeye does not issue any investment recommendations for fundamental analysis. However, Redeye has developed a proprietary analysis and rating model, Redeye Rating, in which each company is analyzed and evaluated. This analysis aims to provide an independent assessment of the company in question, its opportunities, risks, etc. The purpose is to provide an objective and professional set of data for owners and investors to use in their decision-making.

Redeye Rating (2019-01-22)

Rating	Management	Ownership	Profit outlook	Profitability	Financial Strength
7,5p - 10,0p	47	46	19	11	21
3,5p - 7,0p	91	86	120	40	53
0,0p - 3,0p	13	19	12	100	77
Company N	151	151	151	151	151

Duplication and distribution

CONFLICT OF INTERESTS

Anders Hedlund owns shares in Alzinova: No
Klas Palin owns shares in Alzinova: No
Redeye performs/have performed services for the Company and receives/have received compensation from the Company in connection with this.