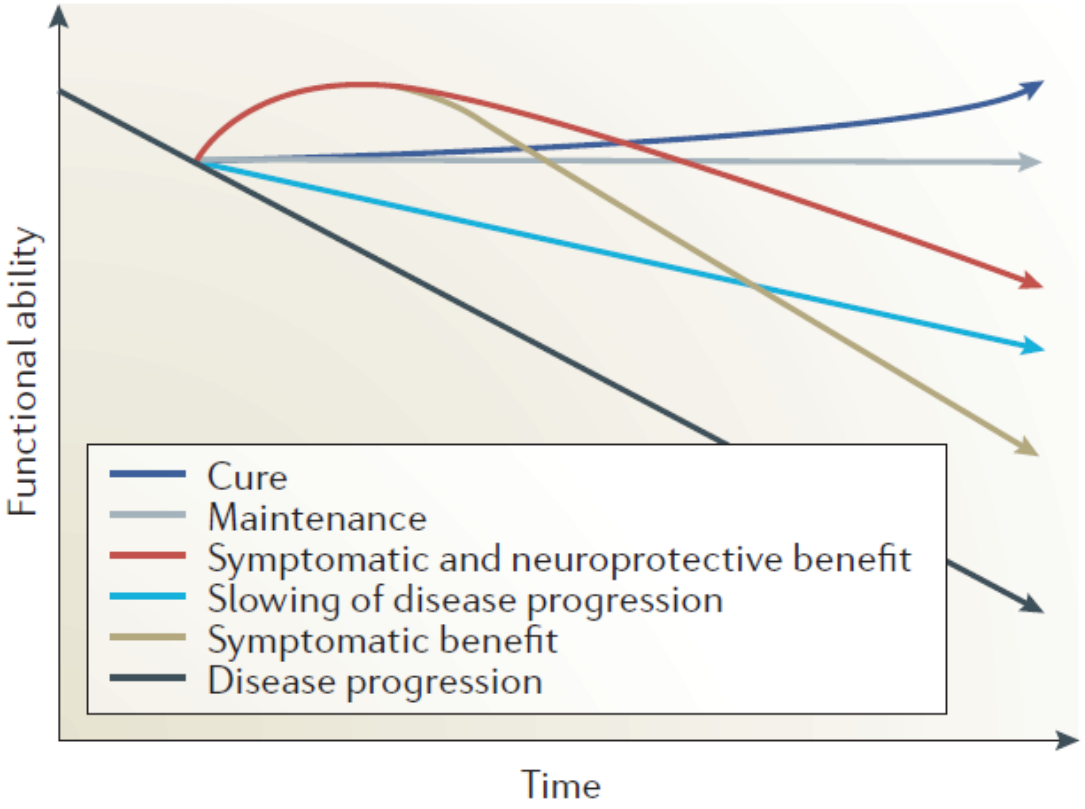
Anti Amyloïd Therapie een doorbraak ?

Ook voor Belgen?

Prof Dr Peter Paul De Deyn

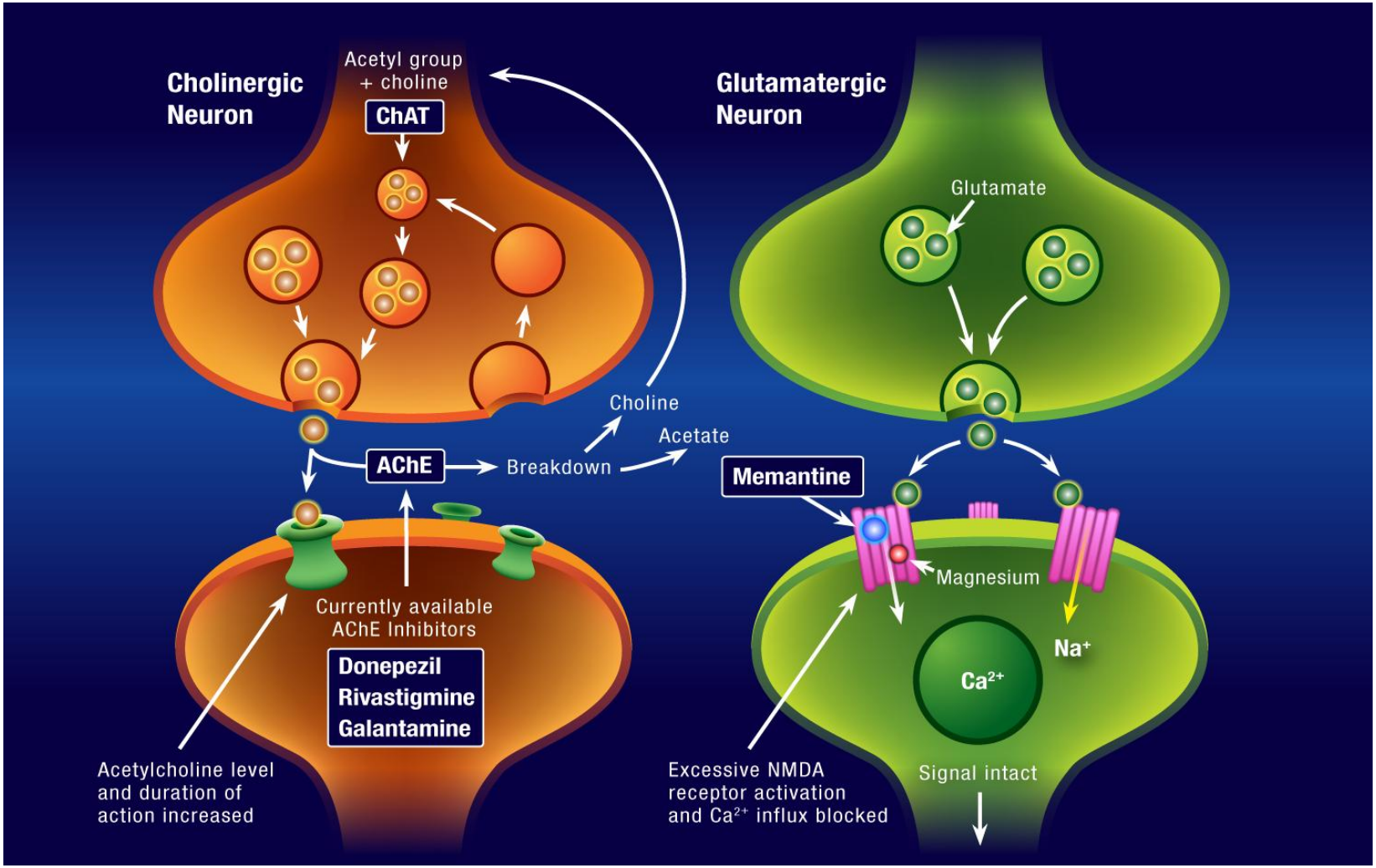
Universiteit Antwerpen

Theoretische mogelijkheden van AD behandeling



Van Dam & De Deyn (2006) Nat. Rev. Drug Discov.

Van Symptomatische Behandeling: Neurotransmitter-gerichte benadering

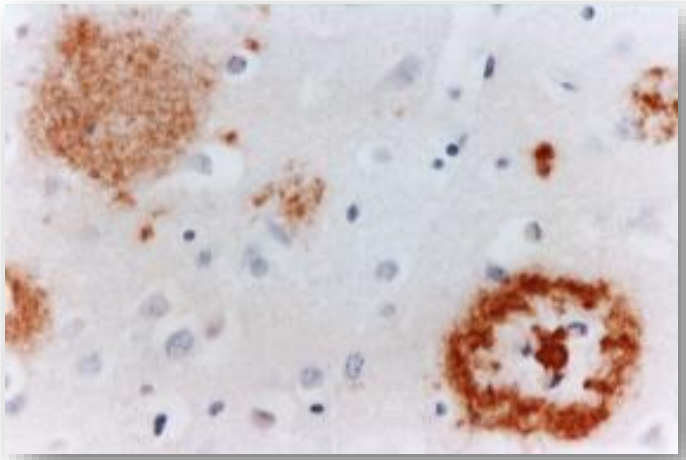


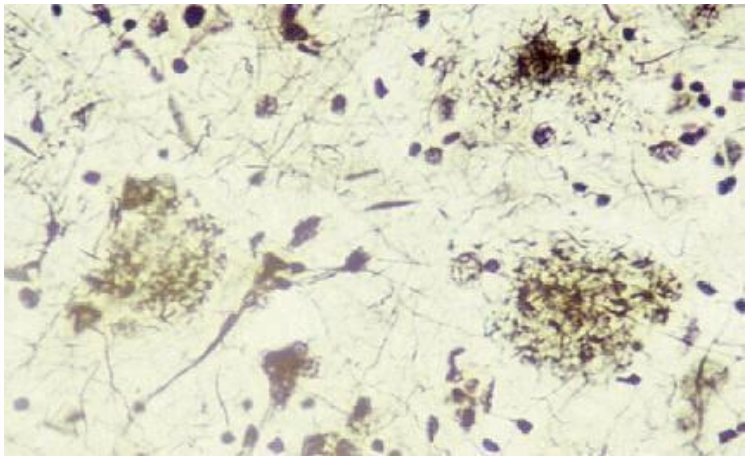
Naar een ziekteproces modificiërende aanpak

Universiteit Antwerpen

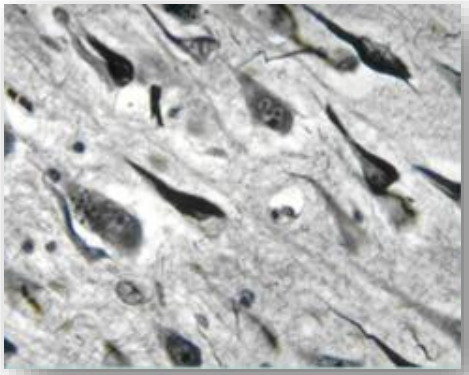
Neuropathologie dementie

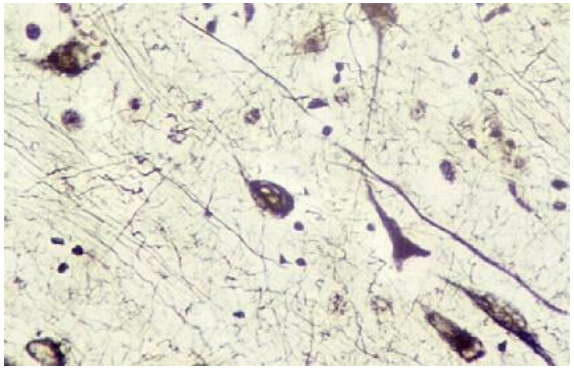
Amyloid plaques





Neurofibrillaire kluwens





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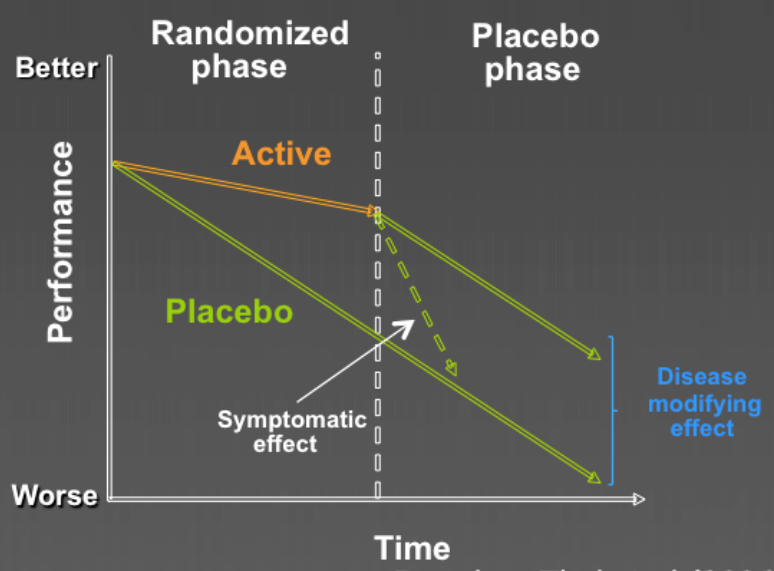
Ziekteproces beïnvloedende trials

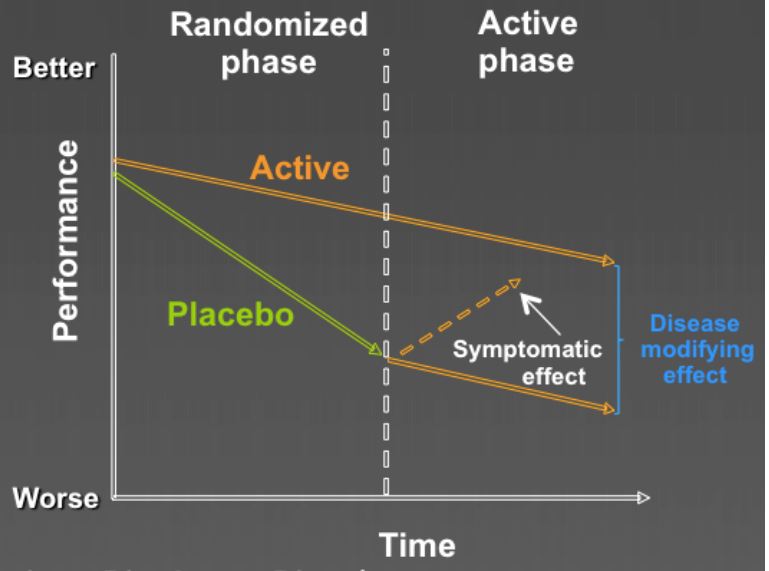
Randomized Withdrawal design

Include a wash-out period and see if any effects are maintained over placebo



Randomized Start design

Do patients treated for a longer time maintain some benefit over newly treated patients?

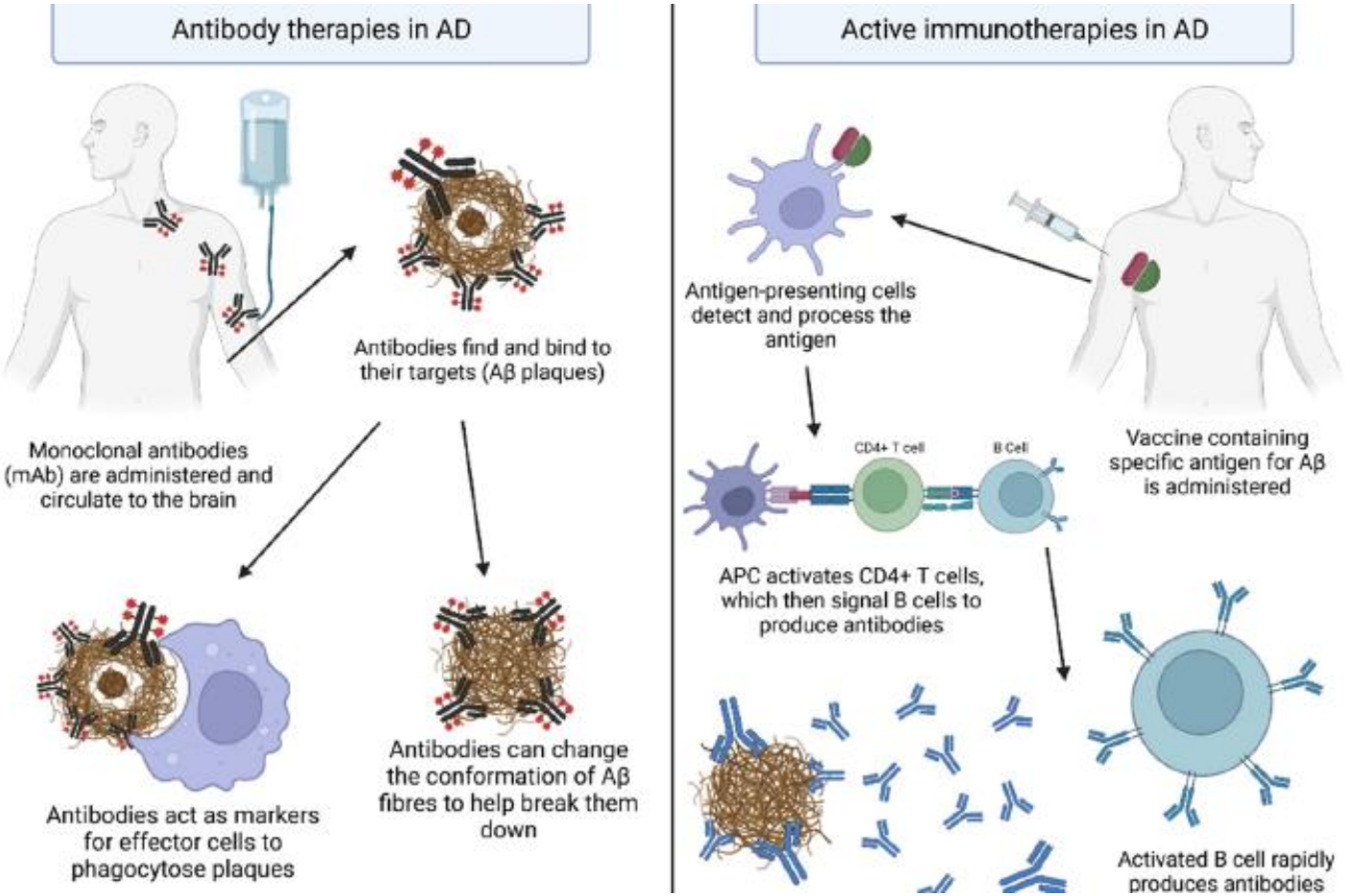


Based on Thal et al (2006) Alzheimer Dis. Assoc. Disord.

AD pipeline focussing on Aβ

Strategy	Categories	Examples / Current phase
Decrease formation Aβ monomer	Secretase inhibitors Anti-monomer immunotherapy	**LY450139 = Semagacestat (Ph III)** **AAB-001 = Bapineuzumab (Ph III)** LY2062430 = Solanezumab (Ph III)
Increase $A\beta_{1-40}/A\beta_{1-42}$	Secretase modulators	MPC-7869 = r-flurbiprofen = flurizan™ (Ph III=negative)
Inhibit Aβ aggregation	Intercalators Metal-protein attenuating agents	3APS=homotaurine=Vivimind™(Ph III) PBT-2 (Ph II)
Off-pathway stabilization	Aggregation inhibitors	**ELND005 = Scyllo-inositol™ (Ph III)**
Anti-oligomer agents	Small molecule inhibitors Anti-oligomer immunotherapy	Curcumin=Longvida™ (Ph II) **IGIV (Ph III)**

Vaccinatie versus passieve immunotherapy



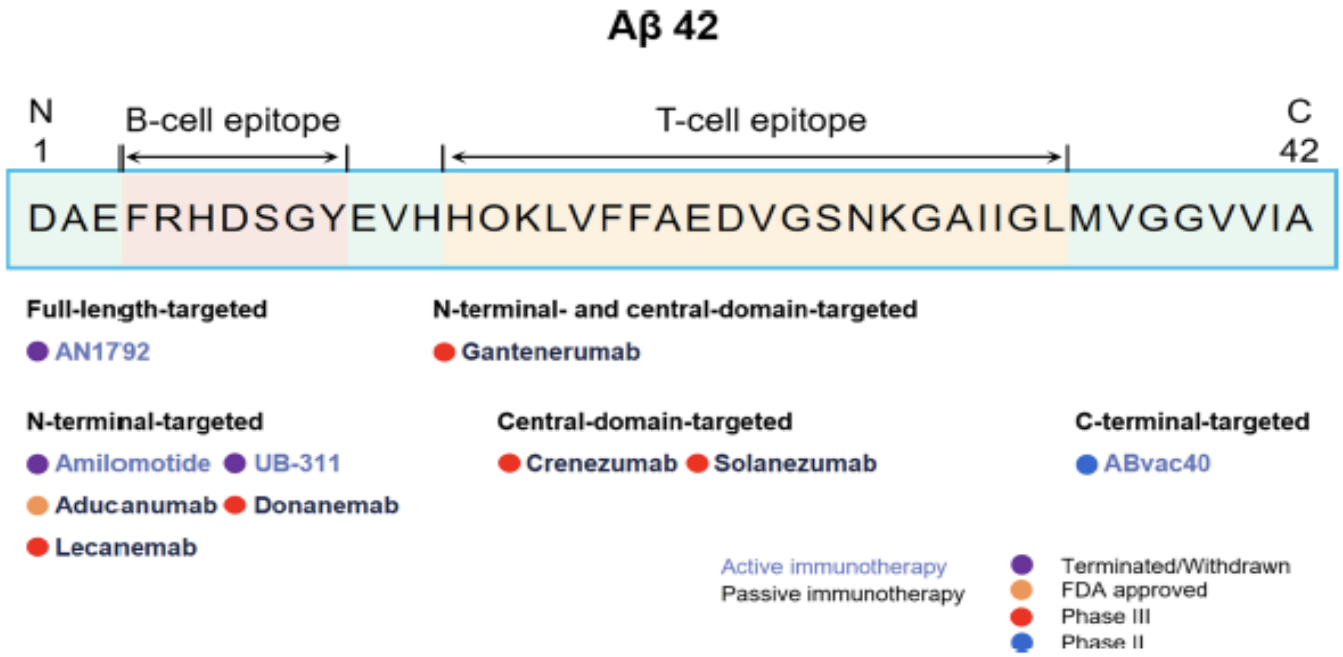
Vaccins

- **Active Vaccines:**
  - compound AN1792 seemed to have promising effects against β-amyloid and slowing down functional decline
  - however too many potential side effects from the treatment (since it requires the body to produce anti-bodies)

- **Monoclonal Antibodies:** potentially safer since using laboratory or harvested from human blood antibodies
  - **Bapineuzumab** (Salloway et al., 2014) and **Solanezumab** (Doody et al., 2014) = good safety profiles but no significant effect seen.
  - Ongoing trials include patients in very early AD and MCI due to AD stages, while others just include individuals that are at risk to develop AD in the future.
    - **Aducanumab** (By Biogen): All phases completed- On August 2020, granted priority review by the FDA to expedite the approval of the medication
    - Gantenerumab (By Roche)
    - En extreme reeksen van inmiddels andere geteste en momenteel onderzochte substanties

Passieve Immunisatie

- Monoclonal antibodies in development are designed to target 1 of 3 domains of the Aβ protein: the n-terminus, the middle portion, or the c-terminus.
  - It is possible that efficacy, safety, or both may be substantially different depending on the binding domain.



Recent onderzochte mABs

tinued)

Drug	Mechanism	Sponsor	Study population	Admin	Phase	Results	Clinical Trial Identifier	Start date	Estir
Aducanumab (BIIB037)	Monoclonal antibody	Biogen	Early AD	IV	III	Terminated	NCT02484547	2015 Sept	2019
			Early AD		III	Terminated	NCT02477800	2015 Aug	2019
			Early AD		III	Active, not recruiting	NCT04241068	2020 Mar	2023
Crenezumab (RG7412)	Monoclonal antibody	Roche/AC Immune SA	Prodromal to mild AD	IV	III	Terminated	NCT02670083	2016 Mar	2019
			Prodromal to mild AD		III	Terminated	NCT03114657	2017 Mar	2019
			Prodromal to mild AD		III	Terminated	NCT03491150	2018 Apr	2019
Lecanemab (BAN2401)	Monoclonal antibody	Biogen /Eisai	Early AD	IV	III	Recruiting	NCT03887455	2019 Mar	2024
			Preclinical AD		III	Recruiting	NCT04468659	2020 Jul	2027
Donanemab (LY3002813)	Monoclonal antibody	Eli Lilly	Early symptomatic AD	IV	III	Recruiting	NCT04437511	2020 Jun	2023
			Preclinical AD		III	Recruiting	NCT05026866	2021 Aug	2027

isease; Admin, Route of administration; SC, subcutaneous; IM, intramuscular; IV, intravenous

Recente data en een FDA goedgekeurd product in 2021

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

50 | NATURE | VOL 537 | 1 SEPTEMBER 2016

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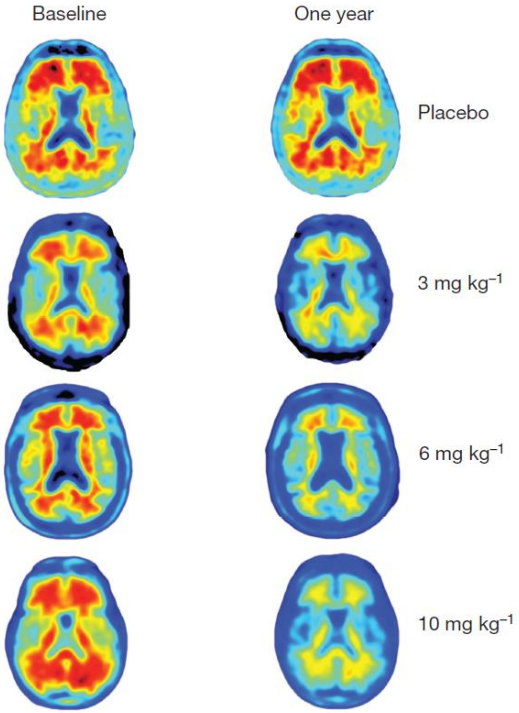

Figure 1 | Amyloid plaque reduction with aducanumab

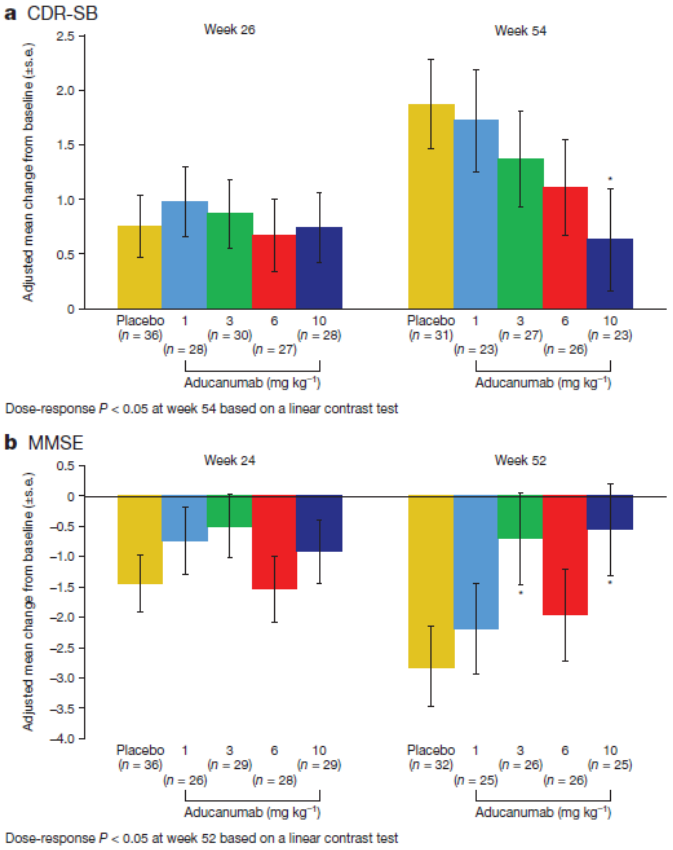

Table 2 | Summary of adverse events and most common adverse events

		Aducanumab			
Adverse event (*n* (%))	Placebo (*n* = 40)	1 mg kg^{-1} (*n* = 31)	3 mg kg^{-1} (*n* = 32)	6 mg kg^{-1} (*n* = 30)	10 mg kg^{-1} (*n* = 32)
Any adverse event	39 (98)	28 (90)	27 (84)	28 (93)	29 (91)
Serious event	15 (38)	3 (10)	4 (13)	4 (13)	12 (38)
Discontinuing treatment due to an adverse event	4 (10)	3 (10)	2 (6)	3 (10)	10 (31)
Common adverse events					
ARIA	2 (5)	2 (6)	4 (13)	11 (37)	15 (47)

ACS Chemical Neuroscience

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Editorial

FDA Approval of Aducanumab Divided the Community but Also Connected and United It

Cite This: *ACS Chem. Neurosci.* 2021, 12, 2716−2717

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Aduhelm (aducanumab) was approved on June 7, 2021, and the chemical neuroscience community, which had been debating the clinical trial data and eagerly awaiting the FDA decision, came alive. Scientists from across the community were, to say the least, divided. Part of the division stems from the unique FDA pathway used for approval. The Accelerated Approval pathway, which is based on surrogate end points (https://pubs.acs.org/doi/10.1021/acschemneuro.0c00238) that are reasonably likely to predict a clinical benefit for a serious or life-threatening illness, in this case Alzheimer's disease, was used in a remarkable move.

Why remarkable? There have been 42 clinical trials that aimed to lower amyloid burden through several mechanisms. Of these, approximately three-quarters of therapeutics definitively lowered amyloid load! In all of them, the lower amyloid plaque burden was not associated with a positive change, relative to placebo, in the primary efficacy end point. The challenge here is that amyloid plaques are present decades

to solving the enormous challenge of neurogenerative diseases and who have made fundamental contributions to our current understand of Alzheimer's disease. It took me a while to understand this.

After reading and rereading the comments and opinions, I found that despite the side someone falls on of the debate, scientists are unified in a very meaningful way. The passion that has been expressed is visceral and in all cases comes from a deep, very deep emotional desire to do what is right for people suffering from Alzheimer's disease and their families and friends that are also impacted. The justification of each opinion or position fundamentally boils down to how one predicts or estimates what comes next: the impact to patients at all levels from the individual to the healthcare system (and economics thereof) and the impact the decision will have on future science that *WILL* undoubtedly lead to therapies with greater efficacy.

Aducanumab (Aduhelm) is niet meer op de markt

Biogen heeft de ontwikkeling en de verkoop ervan gestaakt

Dit gebeurde wereldwijd in januari 2024, nadat het gebruik in de VS al minder werd vanwege de controverses rond het medicijn, zoals twijfelachtige werkzaamheid en bijwerkingen, en het feit dat het in Europa nooit werd goedgekeurd

Europa: Het medicijn is in Europa nooit goedgekeurd door het Europees medicijnagentschap (EMA)

Verenigde Staten: In de VS werd aducanumab in 2021 via een versneld traject goedgekeurd, maar de verkoop en het gebruik namen daarna sterk af

VS versus Europa

VS versus Europa: niet alleen qua farma beleid

Verschillen in bescherming van architecturaal erfgoed

De ZvA Disease Modifying Nieuwkomers

- Lecanemab – Leqembi ®

  Biogen & Eisai

- Donanemab – Kisunla ®

  Eli Lilly and Company

Lecanemab

Swanson *et al. Alzheimer's Research & Therapy* (2021) 13:80
https://doi.org/10.1186/s13195-021-00813-8

Alzheimer's Research & Therapy

RESEARCH Open Access

A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody

Lecanemab

The NEW ENGLAND JOURNAL of MEDICINE

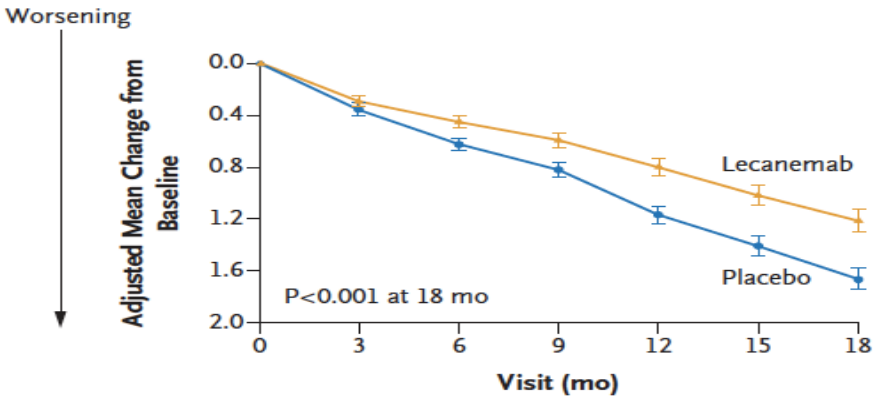
ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

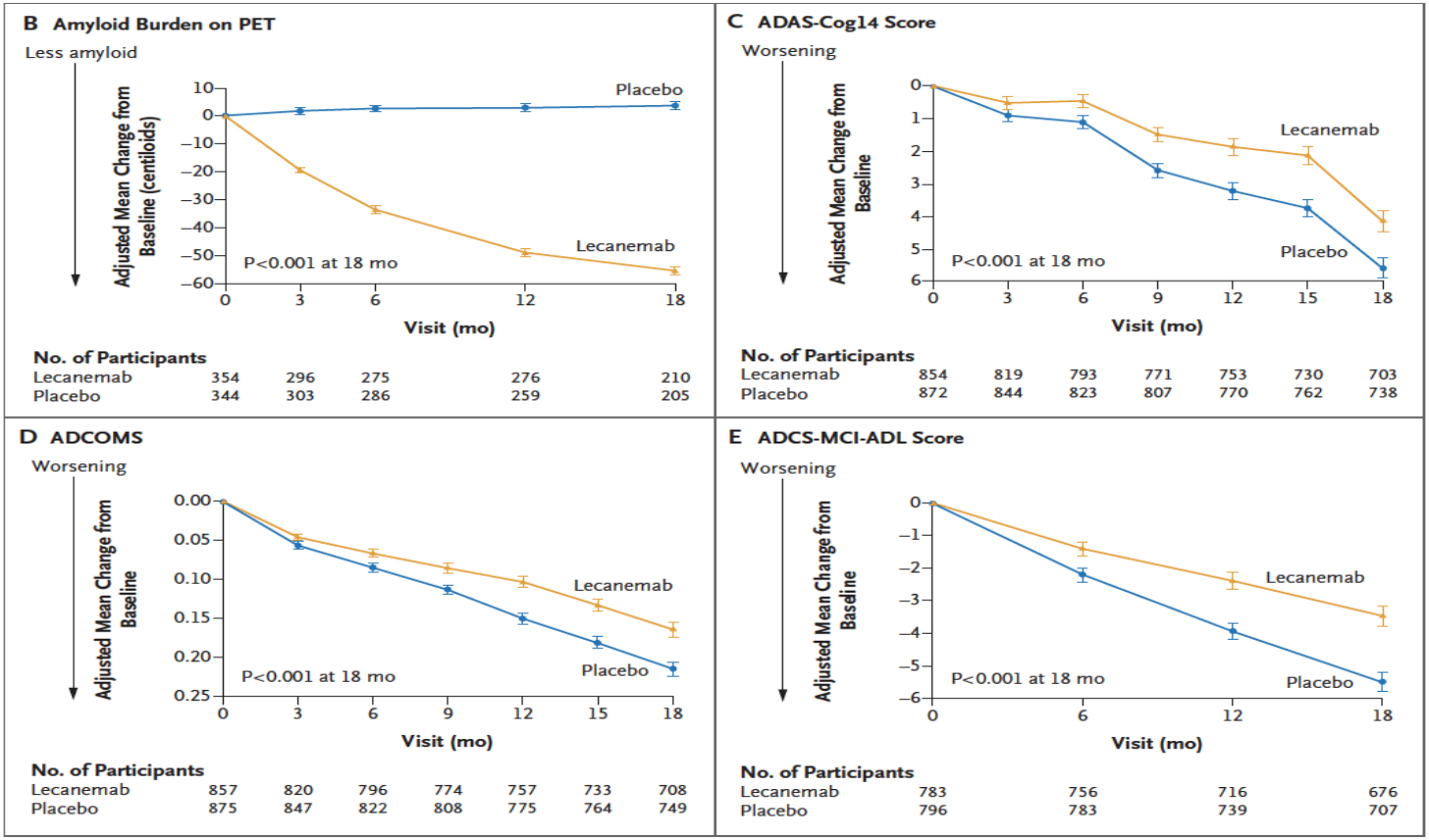
Ziekteproces beïnvloedend effect

A CDR-SB Score



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Ziekteproces beïnvloedend effect



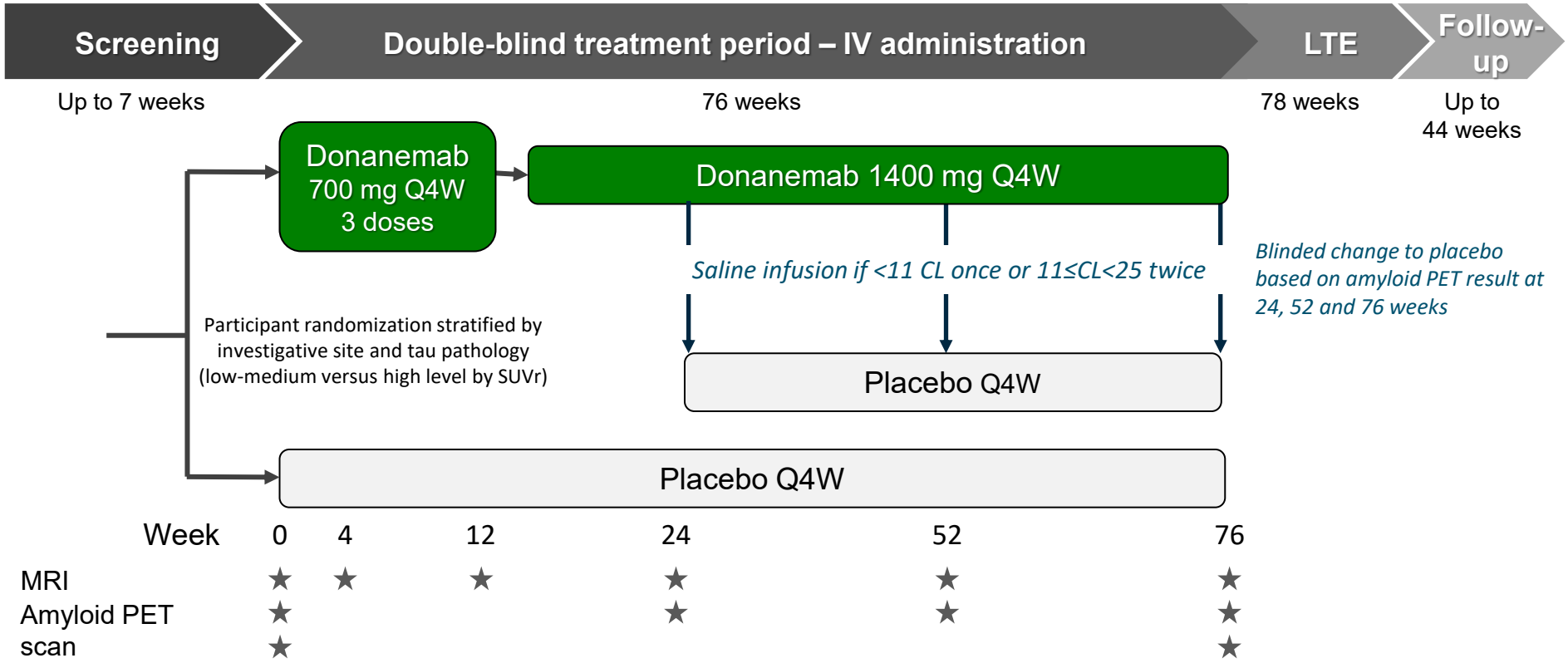
Nevenwerkingen in actieve en placeobo groep

	Actief	Placebo
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)

Nevenweringen in actieve en placeobo groep

	Actief	Placebo
ARIA‡		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

Donanemab:
TRAILBLAZER-ALZ 2 study



Abbreviations: CL=centiloid unit; IV=intravenous; LTE=long term extension; PET=positron emission tomography; Q4W=every 4 weeks; SUVr=standardized uptake value ratio

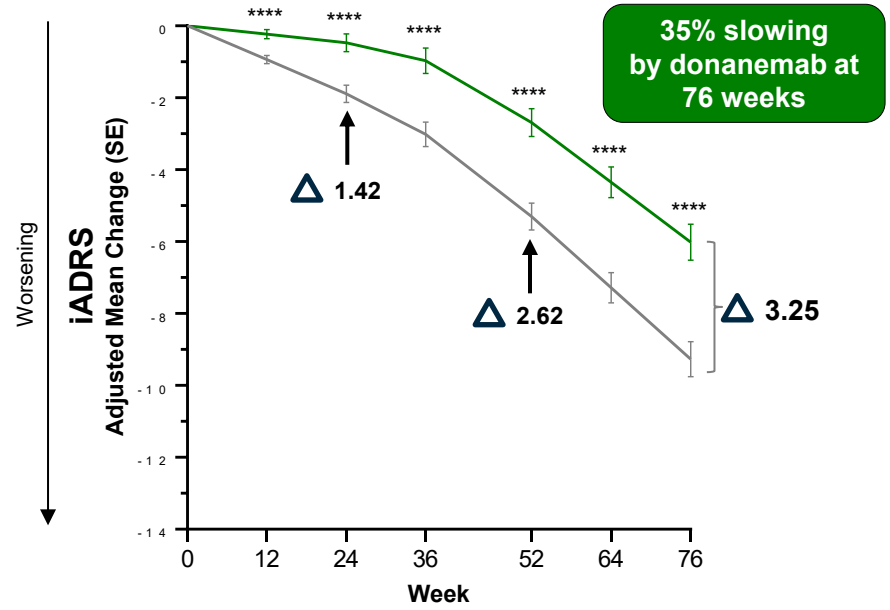
Gebruikte schalen en biomerkers

Primary Outcome	Gated Clinical Outcomes	Gated Biomarker Outcomes
iADRS Integrated assessment of cognition and daily function comprised of items from the ADAS-Cog_{13} and the ADCS-iADL, measuring global AD severity across the AD continuum [scores range from 0-144 with lower score=greater impairment] • Change from baseline to Week 76 in either low-medium tau pathology population or combined population	**CDR-SB** **ADCS-iADL** **ADAS-Cog_{13}** **CDR-G**	**Amyloid PET** **Plasma P-tau217** **Tau PET**

Abbreviations: AD=Alzheimer's disease; ADAS-Cog_{13}=Alzheimer's Disease Assessment Scale–13-item Cognitive subscale; ADCS-iADL=Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory; CDR-G=Clinical Dementia Rating-global; CDR-SB=Clinical Dementia Rating Scale-Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; PET= positron emission tomography; P-tau217=phosphorylated tau 217

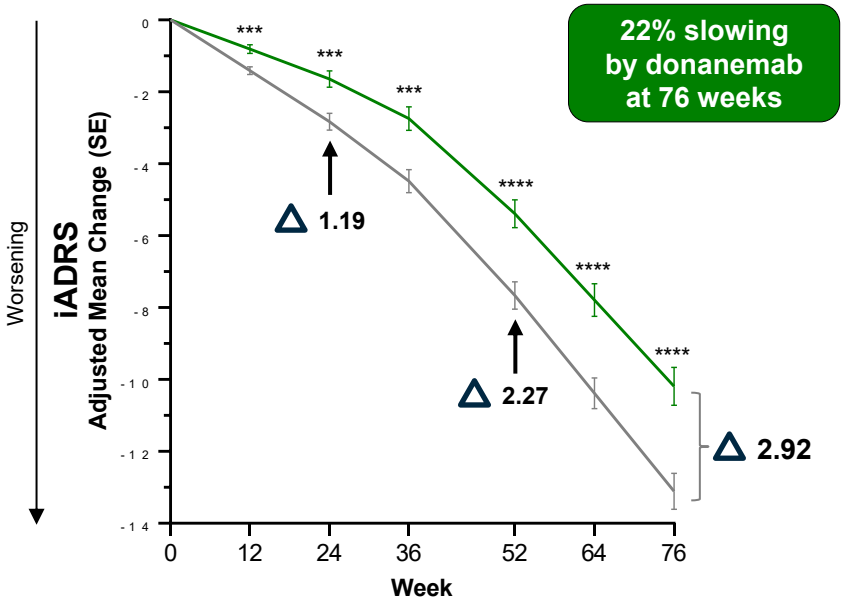
Phase 3 primair eindpunt: iADRS

iADRS: Low-medium Tau Population



Placebo	560	549	526	506	474	447	444
Donanemab	533	517	487	459	441	406	418

iADRS: Combined Tau Population

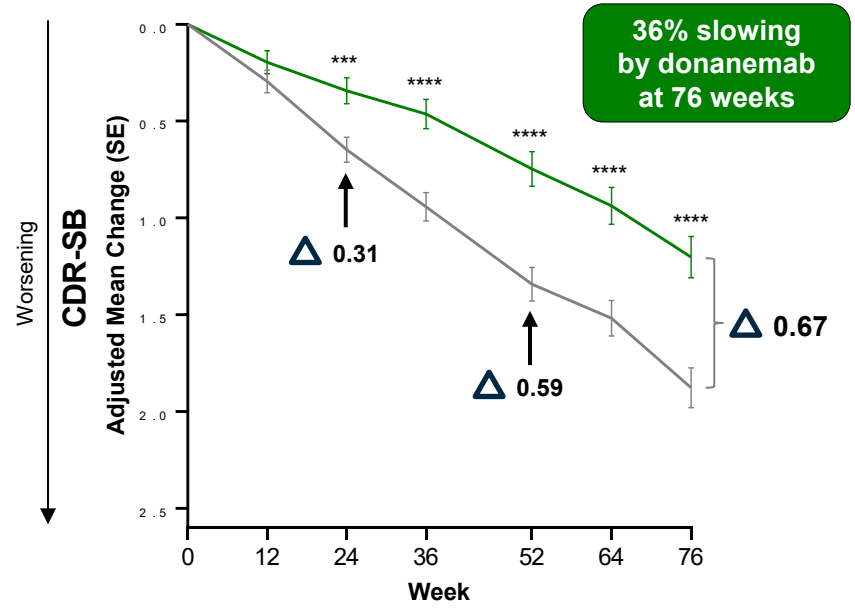


Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

TRAILBLAZER-ALZ 2 primary analysis (iADRS) used the natural cubic spline (NCS) model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level (Combined model only), and baseline acetylcholinesterase inhibitor/memantine use. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: iADRS = Integrated Alzheimer's Disease Rating Scale; n = number of participants; SE = Standard Error

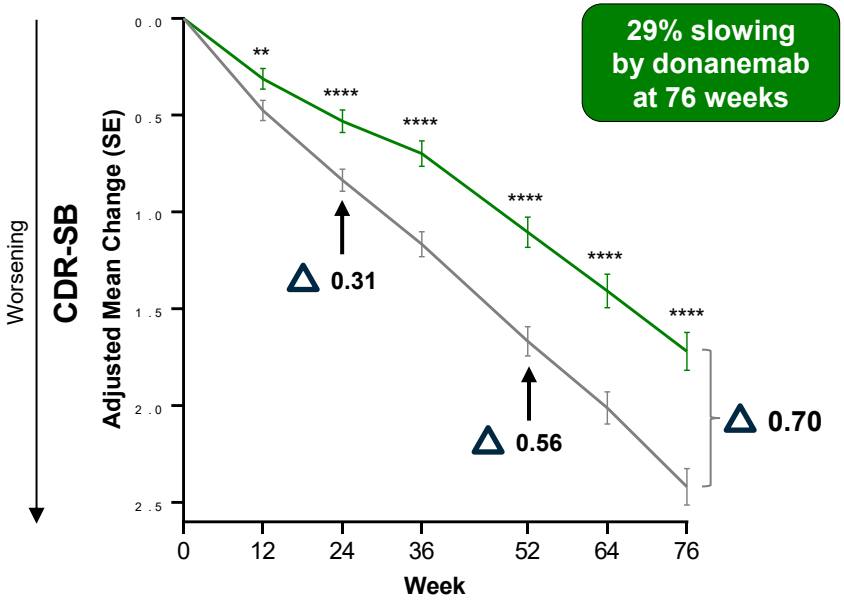
Secundaire eindpunten : CDR-SB

CDR-SB: Low-medium Tau Population



Placebo	569	561	540	516	486	461	459
Donanemab	546	530	499	471	451	418	424

CDR-SB: Combined Tau Population



Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

For CDR-SB: adjusted mean change from baseline, SE, 95% CI and p-value are derived using pre-specified mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, pooled investigator, baseline acetylcholinesterase inhibitor/memantine use and baseline tau level (Combined model only). ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: CDR-SB = Clinical Dementia Rating – Sum of Boxes n = number of participants; SE = Standard Error

Hoe in de praktijk te implementeren ?

If approved of course

In- en exclusie criteria

- **Inclusiecriteria**
- Amyloïd-bèta-pathologie
- De aanwezigheid van amyloïd-bèta-pathologie moet worden bevestigd door middel van een geschikte test voordat de behandeling wordt gestart
- Personen met MCI due to AD of milde ziekte van Alzheimer (MMSE scores ≥ 22/30.

In- en exclusie criteria

- **Exclusiecriteria:**

- MRI-bevindingen bij baseline van eerdere intracerebrale bloedingen, meer dan 4 microbloedingen, oppervlakkige siderose of vasogeen oedeem (ARIA-E), of andere bevindingen, die wijzen op cerebrale amyloïdangiopathie (CAA)
- bloedingsstoornissen die niet voldoende onder controle zijn
- Doorlopende behandeling met anticoagulantia
- Ernstige wittestofletsels
- slecht gecontroleerde hypertensie
- Aandoeningen waardoor een MRI-onderzoek niet mogelijk is, waaronder claustrofobie of de aanwezigheid van metalen (ferromagnetische) implantaten/pacemaker

- (*APOE*) ε4 homozygotie

Noodzakelijke voorzieningen specifieke centra ??

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Special Article

Donanemab: Appropriate use recommendations

G.D. Rabinovici[a,*], D.J. Selkoe[b], S.M. Greenberg[b], S.B. Hendrix[i], [illegible]

[a] Memory & Aging Center, Department of Neurology, [illegible]
[b] Ann Romney Center for Neurologic Diseases, Departmen[illegible]
[c] Department of Neurology, Washington University School[illegible]
[d] Alzheimer's Treatment Research Institute, University of [illegible]
[e] Departments of Neurology, Radiology, Medical and Mol[illegible]
[f] Banner Sun Health Research Institute, Banner Health, S[illegible]
[g] Center for Brain/Mind Medicine, Department of Neurol[illegible]
[h] Department of Neurology, Massachusetts General Hospi[illegible]
[i] Pentara Corporation, Millcreek UT, USA
[j] Department of Neurology, Mayo Clinic, Rochester, MN, [illegible]
[k] Departments of Radiology and Biomedical Imaging, Med[illegible]
[l] Butler Hospital and Warren Alpert Medical School of Br[illegible]
[m] Chambers-Grundy Center for Transformative Neuroscie[illegible]
Vegas, NV, USA

J Prev Alz Dis 2023;3(10):362-377
Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

Review

Lecanemab: Appropriate Use Recommendations

J. Cummings[1], L. Apostolova[2], G.D. Rabinovici[3], A. Atri[4], P. Aisen[5], S. Greenberg[6], S. Hendrix[7], D. Selkoe[8], M. Weiner[9], R.C. Petersen[10], S. Salloway[11], For the Alzheimer's Disease and Related Disorders Therapeutics Work Group

1. Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV), Las Vegas, NV; USA; 2. Departments of Neurology, Radiology, Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA; 3. Memory and Aging Center, Department of Neurology, Weill Institute for Neurosciences and Department of Radiology and Biomedical Imaging; University of California, San Francisco, San Francisco, CA, USA; 4. Banner Sun Health Research Institute, Banner Health, Sun City, AZ; Center for Brain/Mind Medicine, Harvard Medical School, Boston, MA, USA; 5. Alzheimer's Treatment Research Institute, University of Southern California, San Diego, CA, USA; 6. Deparment of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; 7. Pentara Corporation, Millcreek Utah, USA; 8. Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; 9. Departments of Radiology and Biomedical Imaging, Medicine, Psychiatry and Neurology, University of California San Francisco, San Francisco, CA, USA; 10. Department of Neurology, Mayo Clinic, Rochester, MN, USA; 11. Butler Hospital and Warren Alpert Medical School of Brown University, Providence RI, USA

Corresponding Author: Jeffrey Cummings, MD, ScD, 1380 Opal Valley Street, Henderson, NV 89052, USA, jcummings@cnsinnovations.com, T: 702-902-3939

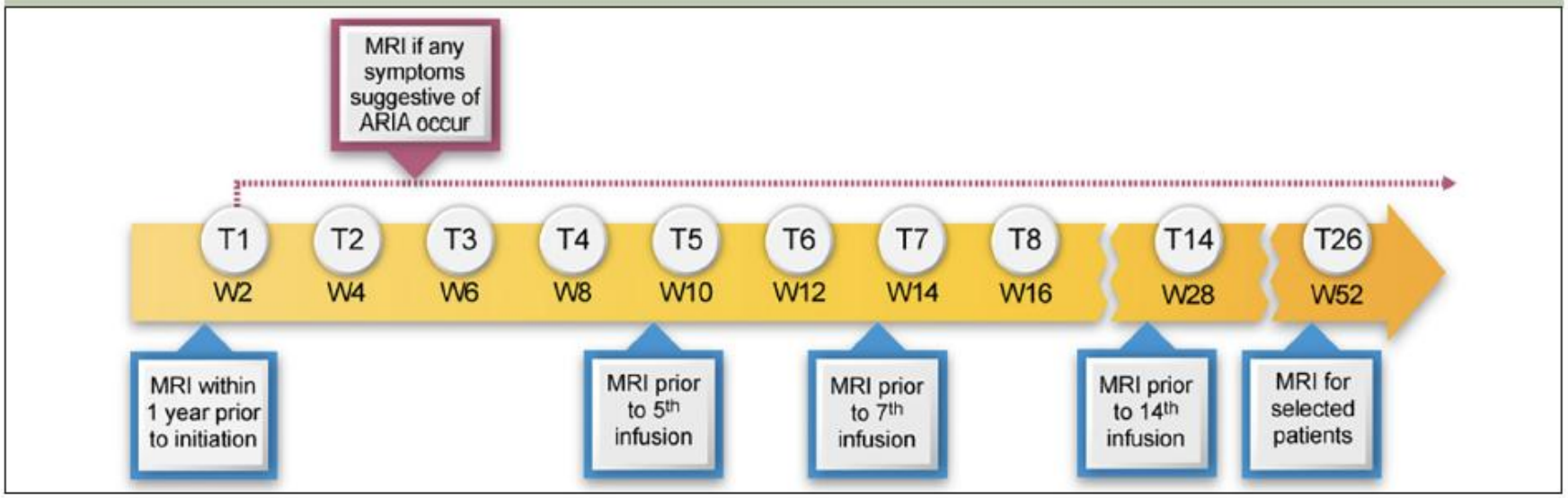
Repetitieve IV toedieningen

- Daghospitalisatie
- Personele omkadering
- Voorzieningen in geval complicaties
- Trainingen neuroradiologen voor evaluaties ARIA's
- Ervaringen met opvolgen en managen ARIA's

- Opvolging met amyloid pet imaging ?
- Snelle toegangkelijkheid tot expert MRI acquisitie/analyse

Noodzakelijke voorzieningen specifieke opvolgingen ??

Figure 1. MRI monitoring for lecanemab



Hoe zit het met de terugbetaling ?

- De vraag tot vergoeding van **lecanemab** is op 23 juni 2025 bij het RIZIV ingediend, dat 90 dagen de tijd had om een eerste oordeel te vellen en vragen te stellen. Eisai ontving dit eind september en kreeg 60 dagen om te reageren.

- Een definitief besluit zou binnen 180 dagen na de indiening moeten worden genomen (rond Kerstmis), maar het kan zeer goed zijn dat dit wordt uitgesteld.

- **Lecanemab** wordt sinds 1 september 2025 vergoed in Duitsland en Oostenrijk

- De aanvraag tot vergoeding **donanemab** wordt in 2026 bij het RIZIV ingediend. Eind januari of februari vindt er een overleg met het RIZIV plaats vóór de indiening. EMA heeft het op 25 september 2025 goedgekeurd

Min. Vandenbroucke komt met versnelde procedure voor (gratis) innovatieve geneesmiddelen

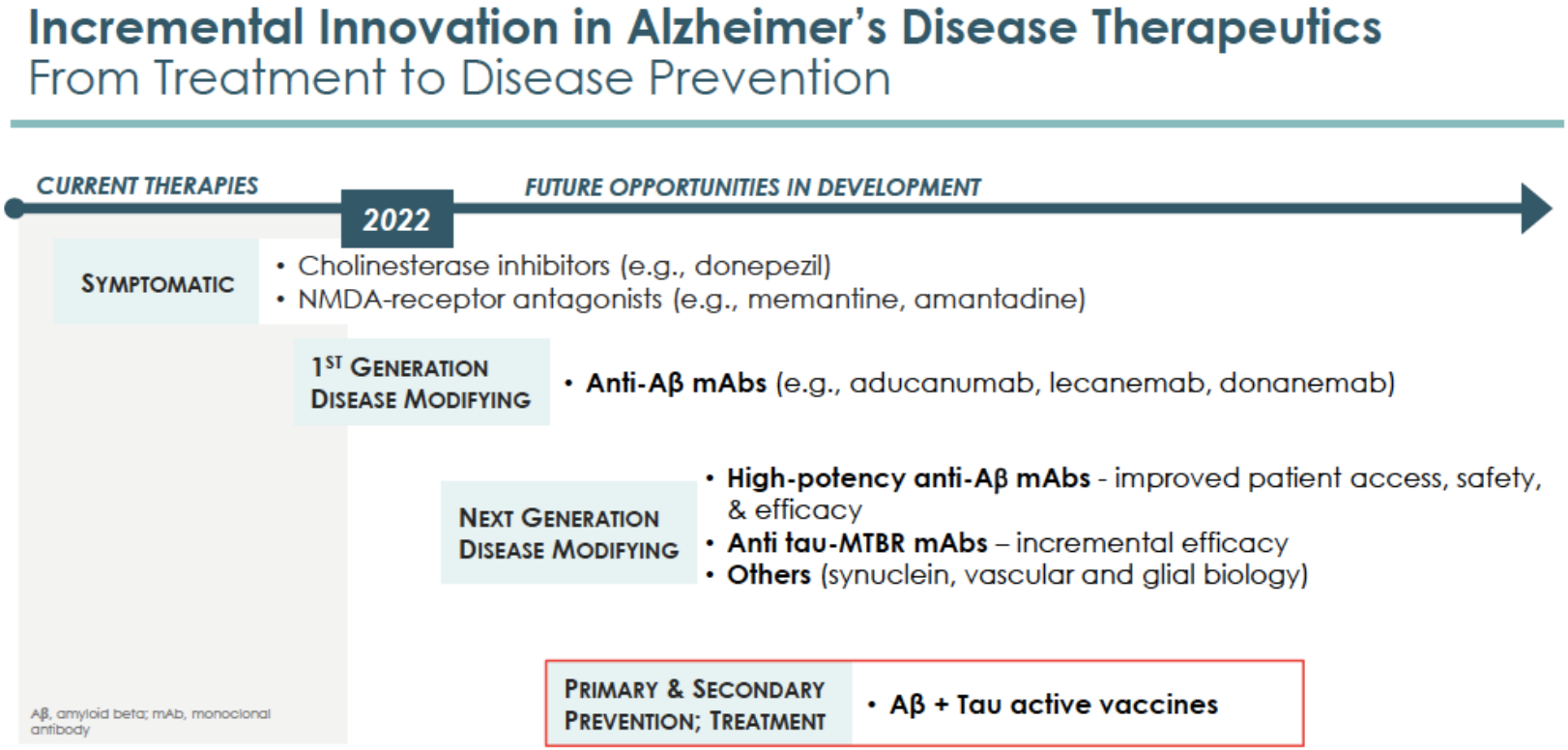
- **Vanaf 1 januari zullen geneesmiddelen die beloftevolle resultaten halen in klinische studies, sneller terugbetaald worden, nog voor ze officieel zijn goedgekeurd. Patiënten met ernstige of zeldzame aandoeningen zullen zo sneller toegang krijgen tot experimentele behandelingen.**

Epiloog

- Combinatie therapieën voor AD zijn mogelijks de toekomst

- Er zijn natuurlijk naast de ziekte van Alzheimer nog meer etiologische entiteiten onderliggend aan dementie

Gecombineerd anti amyloid/tau



nature International weekly journal of science

Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21

Marc Cruts[1,2,5], Ilse Gijselinck[1,2,5], Julie van der Zee[1,2,5], Sebastiaan Engelborghs[3,5,6], Hans Wils[1,2,5], Daniel Pirici[1,2,5], Rosa Rademakers[1,2,5], Rik Vandenberghe[7], Bart Dermaut[9], Jean-Jacques Martin[4,5], Cornelia van Duijn[10], Karin Peeters[1,2,5], Raf Sciot[8], Patrick Santens[9], Tim De Pooter[1,2,5], Maria Mattheijssens[1,2,5], Marleen Van den Broeck[1,2,5], Ivy Cuijt[1,2,5], Krist'l Vennekens[1,2,5], Peter P. De Deyn[3,5,6], Samir Kumar-Singh[1,2,5] & Christine Van Broeckhoven[1,2,5]

Vol 442|24 August 2006|doi:10.1038/nature05017

Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17

Matt Baker[1]*, Ian R. Mackenzie[2]*, Stuart M. Pickering-Brown[5,6]*, Jennifer Gass[1], Rosa Rademakers[1], Caroline Lindholm[3], Julie Snowden[6], Jennifer Adamson[1], A. Dessa Sadovnick[3,4], Sara Rollinson[5], Ashley Cannon[1], Emily Dwosh[4], David Neary[6], Stacey Melquist[1], Anna Richardson[6], Dennis Dickson[1], Zdenek Berger[1], Jason Eriksen[1], Todd Robinson[1], Cynthia Zehr[1], Chad A. Dickey[1], Richard Crook[1], Eileen McGowan[1], David Mann[6], Bradley Boeve[7], Howard Feldman[3] & Mike Hutton[1]

Vol 442|24 August 2006|doi:10.1038/nature05016

Behandeling voor FTD patienten – met progranuline mutaties

- **Vesper Bio announces positive Phase Ib/IIa topline results for lead candidate VES001 for frontotemporal degeneration**

- Phase Ib/IIa study found VES001 (selective sortilin inhibitor) , the first oral therapy being tested in FTD, led to >95% mean increase in progranulin levels in CSF, compared to baseline

- VES001 normalises levels of progranulin in people who have a shortage of this vital protein for genetic reasons, potentially stopping them developing symptomatic frontotemporal dementia (FTD)
- Results support progressing VES001 into Phase IIb/III trials in people with FTD-GRN, the variant of FTD caused by genetically low progranulin levels