Nordic American Healthcare Conference
NYC, USA

December 6 - 7, 2023

Developing therapies for Alzheimer's & Pain

Martin Jönsson, CEO

AlzeCure

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Our Primary Focus Area

Alzheimer's Disease

- EVERY FIVE SECOND a new person is diagnosed with Alzheimer's
- Costs the society more than oncology & cardiovascular diseases TOGETHER
- The patient population & costs are expected to TRIPLE in the next 30 years

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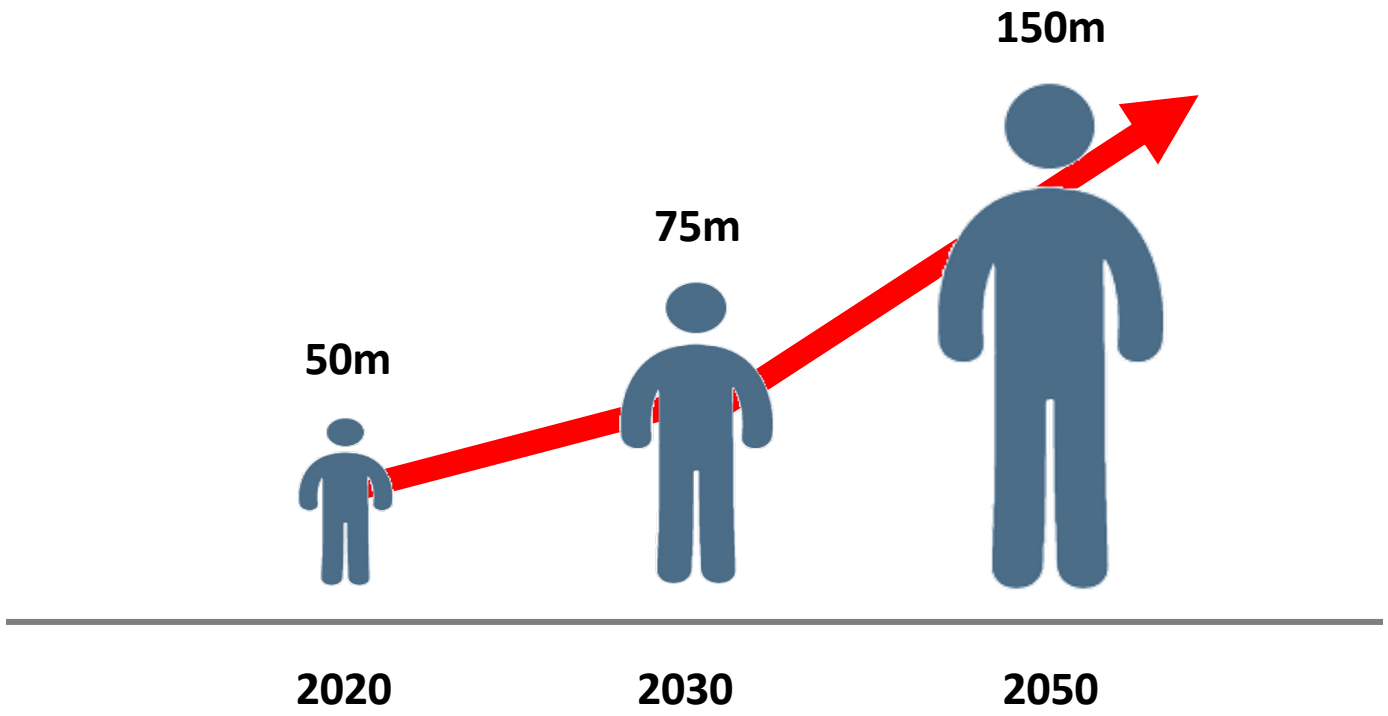
Tripling Alzheimer's Patient Population – due to aging population



- **50 million** people worldwide live with dementia …
- … and **doubling every 20 years**
- Alzheimer's accounts for 60 - 80% of all dementia cases

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Progress & Increased Activity in the Alzheimer's field

De-risking

- Validation of treatment approach: - Amyloid protein targeting
- Positive out-comes in clinical trials, - incl in phase III + approvals
- Vastly improved biomarkers & diagnostics identifying patients => increased probability of success in future studies

Increased investments

- Additional Big Pharma companies entering the field
- More funds and private equity investment in companies and projects

However …

No Curative & Cognitive Enhancing Treatment Against Alzheimer's has so far not been developed

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AlzeCure Pharma – in brief

- Working in **Alzheimer's Disease** (AD) and **Pain** – Hugh unmet medical need
- Spin-out from **AstraZeneca** as the left the CNS field
- Founded in **2016**, out of a research foundation sponsored by Alzheimerfonden
- Based at Novum Science Park, **Karolinska Institute**, Stockholm, Sweden

- **Three platforms** with multiple **small molecule** and **first-in-class** candidates
  - **Alzstatin®** – An innovative preventive & disease-modifying treatment against Alzheimer's (AD)
  - **NeuroRestore®** – A novel symptomatic treatment for cognitive disorders, e.g. AD, with disease modifying potential
  - **Painless** – Innovative projects for osteoarthritic & neuropathic pain
- Listed on **Nasdaq** First North Premier Growth Market in **Sweden** since Nov. 2018 (Ticker: ALZCUR)

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Our Business Model

- We are a **Research & Development** company
- Research & **develop through early clinical phase** and then to **out-license** or partner on our projects
- Gain incomes through:
  - **Upfront payments**
  - **Milestone payments**
  - **Royalties** on sold products

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A pipeline of small-molecule programs

– Multiple candidates increase chance of success

Platform	Candidate	Target	Indication	Research phase	Preclinical phase	Phase I	Phase II	Phase III
NeuroRestore®	ACD856	Positive allosteric modulator (PAM) of Trk-receptors)	Alzheimer's Disease, TBI - Traumatic brain injuries Parkinson's disease, Sleep disorders, Depression					
	ACD857	Positive allosteric modulator (PAM) of Trk-receptors	Alzheimer's Disease					
Alzstatin®	ACD679	Gamma secretase modulator (GSM)	Alzheimer's Disease					
	ACD680	Gamma secretase modulator (GSM)	Alzheimer's Disease					
PainLess	ACD440	TRPV1 antagonist	Neuropathic Pain					
	TrkA-NAM	Negative allosteric modulator (NAM) of TrkA-receptors	Osteoarthritic Pain & other severe pain conditions					

Positive read-out Phase I trial
Safety, Tolerability & Target engagement

Selected new additional CD
ACD680

Positive read-out Phase IIa
Safety, Tolerability & Pain

Phase completed

Phase ongoing

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Two Alzheimer's platforms - 1st-in-class properties & potential game-changers

MEETING NEEDS OF AD PATIENTS – ADRESSING SHORT TERM NEEDS WITH LONG-TERM BENEFITS

Preventive Disease-modifying therapy

Alzstatin®

Gamma-secretase modulator

Targeting Amyloid Production

- *Novel Oral Small Molecule*

Symptomatic & pot. Disease-modifying therapy

NeuroRestore®

Trk-PAM

Improving Neuronal & Cognitive Function

- *Novel Oral Small Molecule*

Two fast followers to **Roche**, **Eisai** respectively → Provides Concept **Validation**

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Preventing or delaying Alzheimer's

Alzstatin®

MoA: Gamma-Secretes-Modulator

Targeting Toxic Amyloid Production

- *Novel Oral Small Molecule*

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Alzstatin – Gamma-Secretase Modulator (GSM) for the Prevention & Treatment of Alzheimer's Disease

PROJECT OVERVIEW

Emanates from Big Pharma	› Renewed big pharma activity – Alzstatin is the **most advanced biotech** GSM program › Approximately **$15M USD** historical **investment** › **ACD679** – a novel candidate with **strong IP protection**
Strong linkage to Alzheimer's	› Gamma-secretase is a **key enzyme** producing **toxic Aβ42** › **Genetic linkage to Alzheimer's** - Majority of all familial mutations are linked to the gamma-secretase complex causing early onset of disease › GSM **reduces production** of Aβ42 **without toxicity** of gamma-secretase inhibition
Positive preclinical data	› Compounds developed with **potent reduction of Aβ42 production** - up to 60% *in vivo* › Alzstatin **reduces amyloid oligomer** formation *in vivo* › GSMs also **increase shorter Aβ peptides** with protective potential

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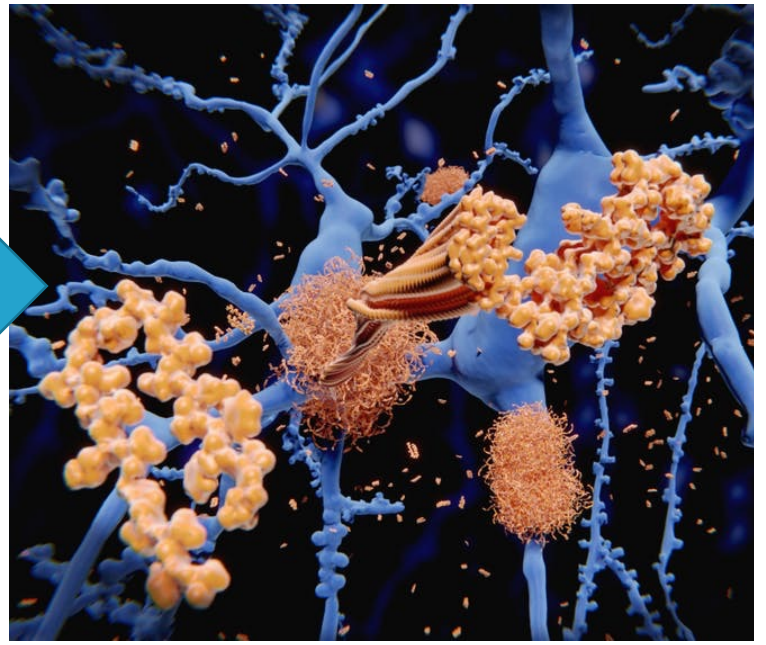
The Alzheimer's brain and its destruction

Toxic protein formations – **Aβ-42** amyloid pathology & plaque – are harming and destroying the brain. The formation process is called the **Amyloid Cascade**



Toxic protein formations, built up of Aβ-42, are harming and destroying the brain structures.

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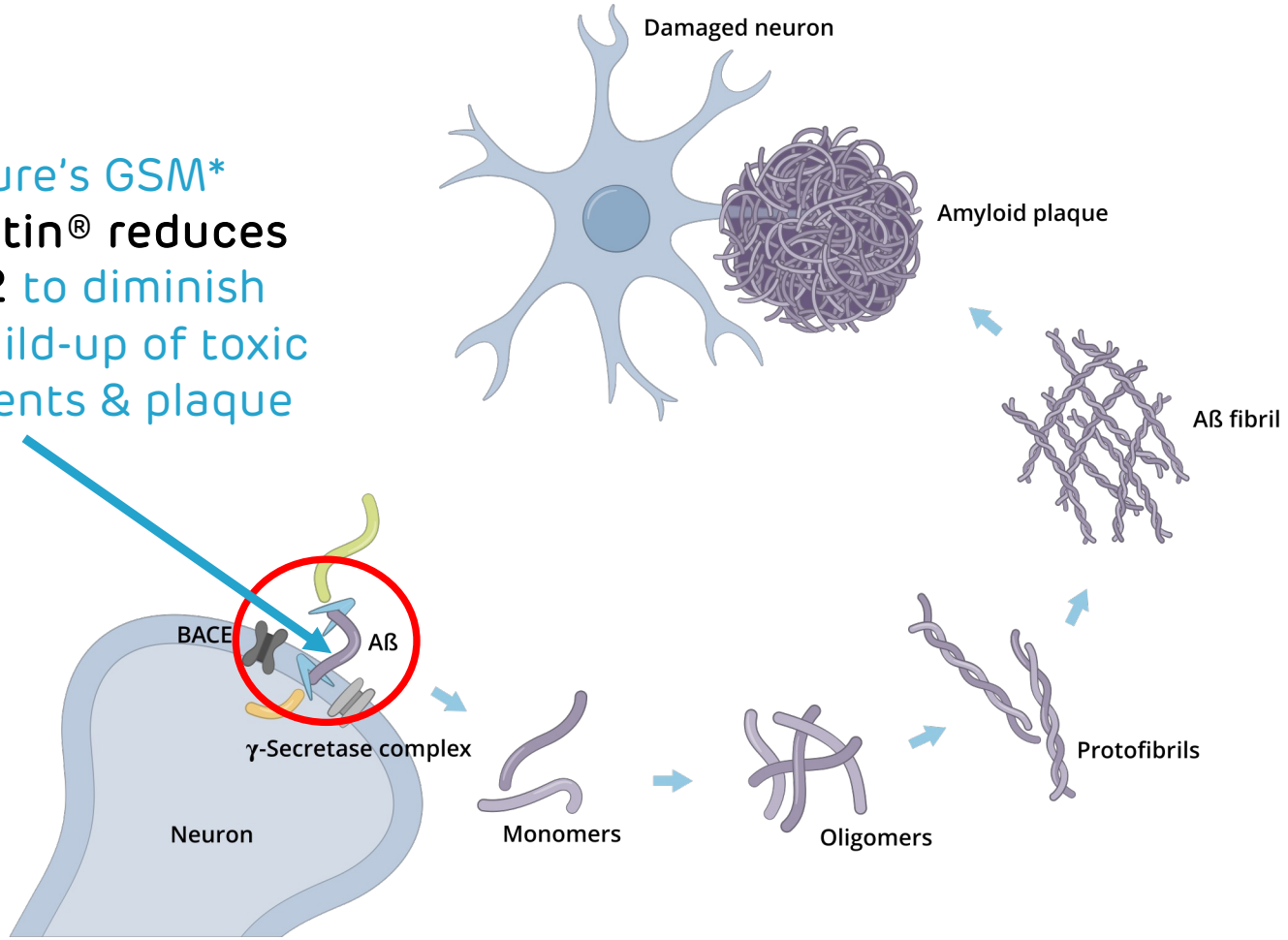
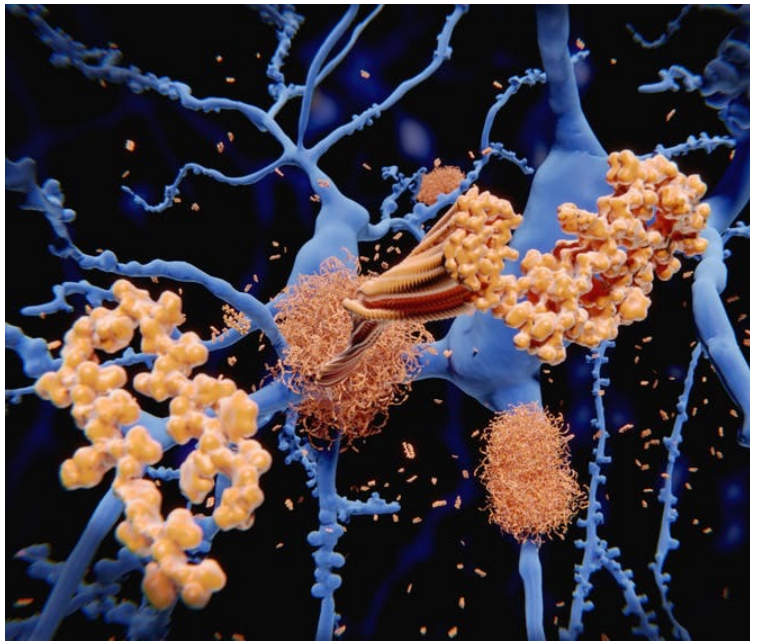
The Amyloid Cascade - Generates toxic & damaging fragments, including plaques, destroying neurons & brain structures

AlzeCure's GSM*
Alzstatin® reduces
Aβ -42 to diminish
the build-up of toxic
fragments & plaque

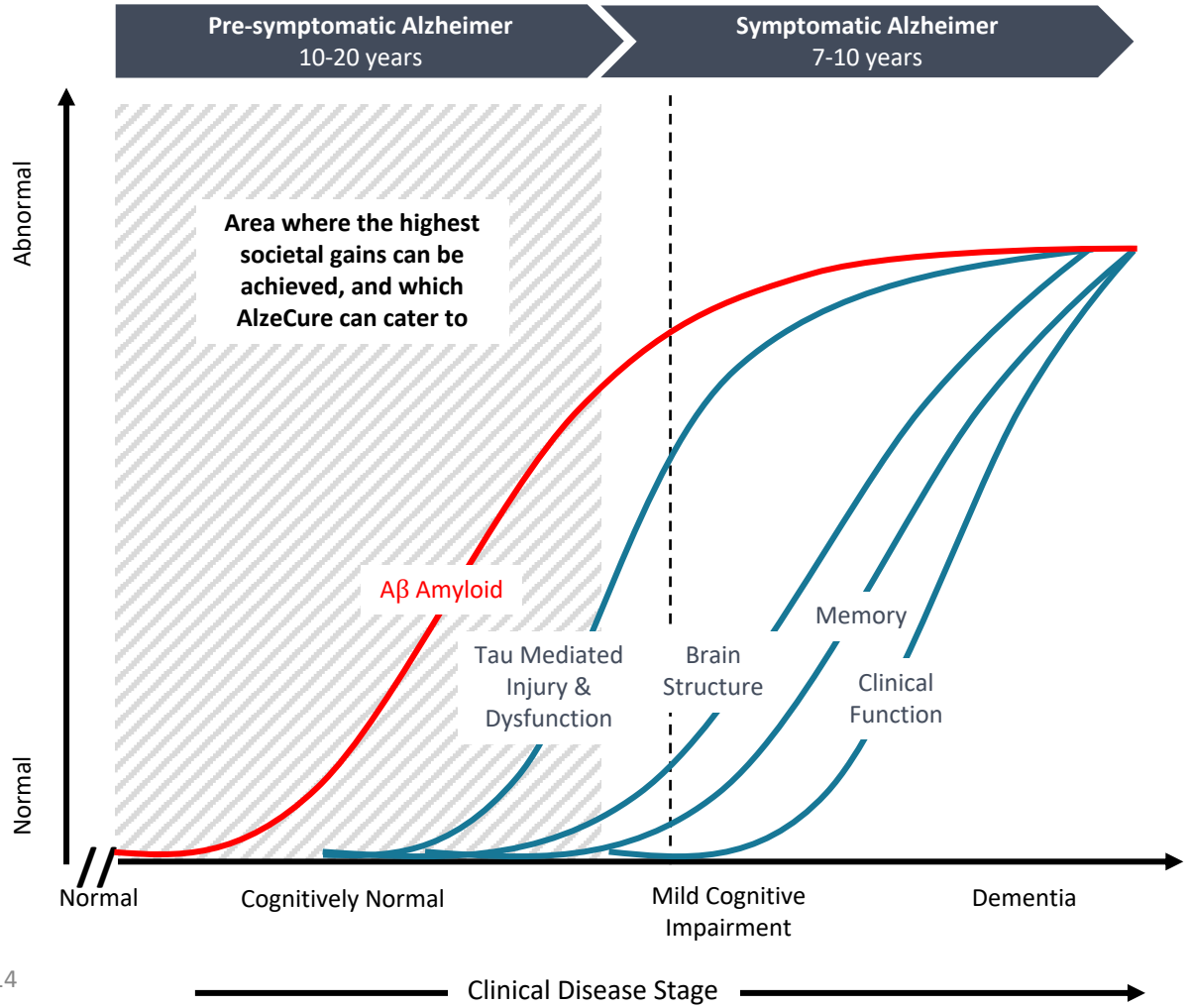




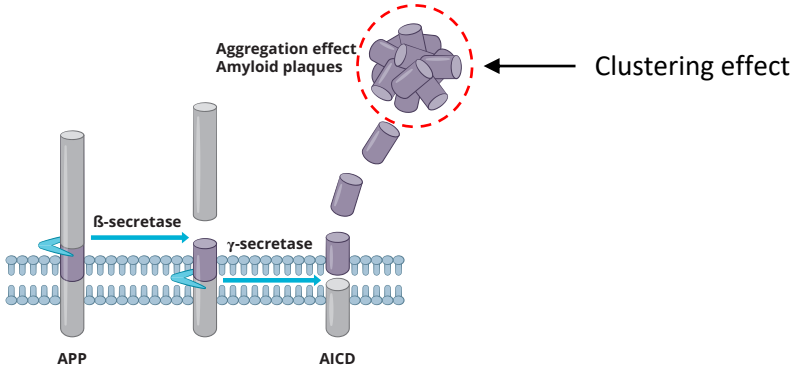
*) GSM = Gamma Secretes Modulator

Alzheimer's Disease Modifier – Preventing or delaying Disease Progression

ALZHEIMER'S DISEASE PROGRESSION

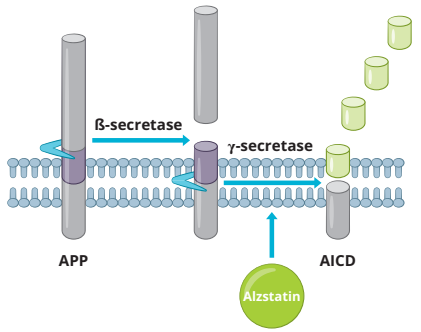


Aβ-42 - main culprit in Alzheimer progression



Found a way to limit Aβ–42 clustering

Alzstatin® modulates the enzyme and thereby **limits the clustering effect**



*Alzstatin® **targets the g-secretase***

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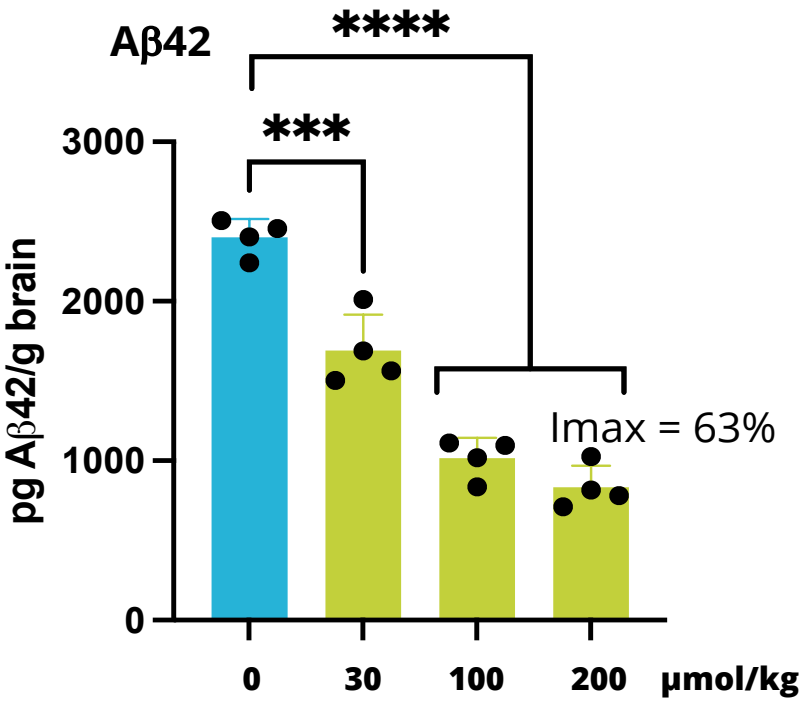
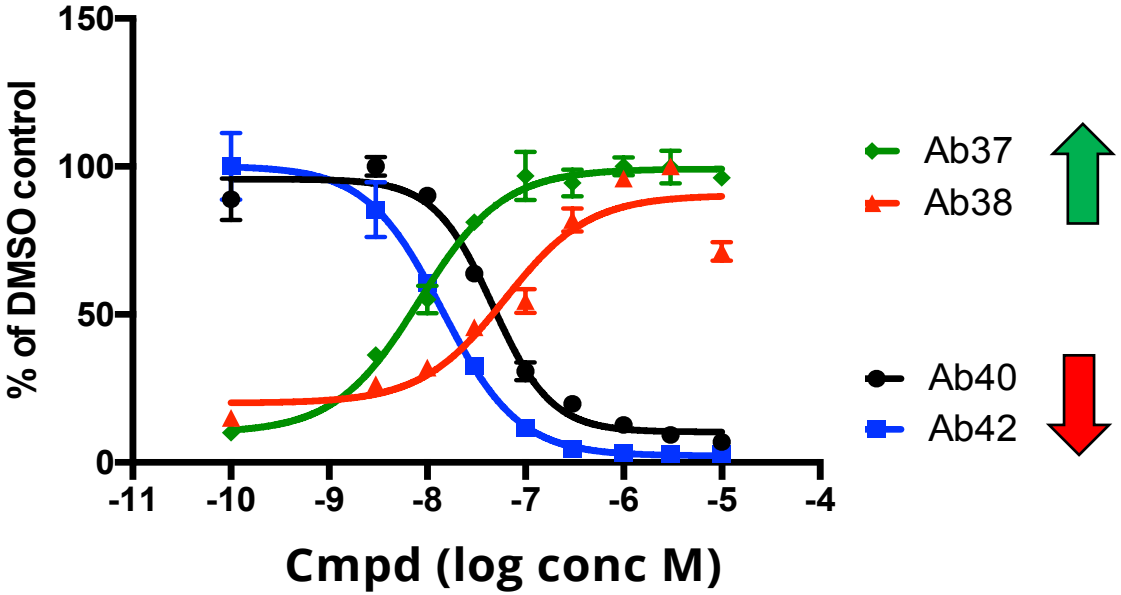
Potent reduction of toxic Aβ42 & increasing protective Aβ37 & 38



Alzstatin potently reduces the amount of toxic brain protein Aβ42 in mice



Alzstatin reduces toxic Aβ42 and Aβ40, while increasing protective Aβ38 and Aβ37 peptides

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Multiple target populations - maintenance and preventive therapy

Maintenance therapy in patients with established Alzheimer's

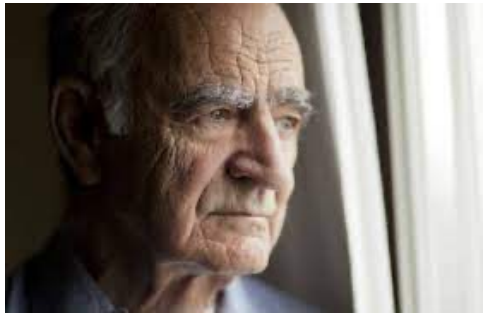
- Treatment after initial plaque clearance by monoclonal antibody treatment (as initially proposed by Lilly) e.g., with: Lecanemab (Eisai/Biogen/Bioarctic), Donanemab (Lilly), Remternetug (Lilly)

Combination therapy together with monoclonal antibody treatment - early AD

- Combine plaque clearance by monoclonal antibody treatment and reduction of Aβ42 production by GSM

Preventive therapy based on genetic risk factors* and biomarkers

- Early stand-alone treatment before onset of symptoms and any major neurodegeneration occurs (prior to rapid increase in Tau pathology)
- Prevents build-up of amyloid – an early pathological feature of AD
- Familiar forms of the disease (incl. Downs syndrome) suitable for initial proof of concept clinical studies



*) E.g. ApoE4

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Roche CTAD 2023 Presentation on their GSM project - Phase 1 data & preparation for phase 2

OC31 - RG6289, a new γ-secretase modulator for the treatment of Alzheimer's disease: Results from a phase I healthy volunteer study

Stefan Sturm 1, Agnes Portron 1, Annamarie Vogt 2, Agnes Poirier 1, Tianxu Yang 3, Adnan Mohamed Abdi 1, Gwendlyn Kollmorgen 4, Cory Simmons 5, Kalbinder Mahil 6, Lothar Lindemann 2, Karl-Heinz Baumann 2, Thomas Mueggler 2, Taner Vardar 7, Rosanna Tortelli 2, Irene Gerlach 2 1Pharmaceutical Sciences, Roche Pharma Research and Early Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 2Neuroscience and Rare Diseases, Roche Pharma Early Research and Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 3Product Development Safety Risk Management (PDS), F. Hoffmann-La Roche Ltd - Beijing (China), 4Roche Diagnostics GmbH - Penzberg (Germany), 5Product Development Data Sciences, F. Hoffmann-La Roche Ltd - Mississauga (Canada), 6Roche Innovation Center Welwyn, Roche Pharma Research and Early Development, Roche Products Limited - Welwyn (United Kingdom), 7Product Development Safety Risk Management (PDS), F. Hoffmann-La Roche Ltd - Basel (Switzerland)

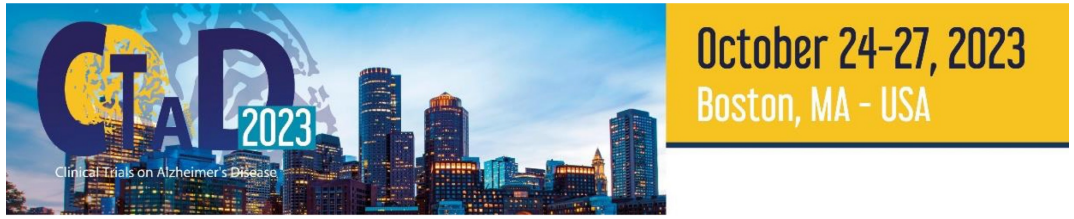
Time: Oct. 27 at 3.15 pm

Validating, de-risking & giving guidance to our Alzstatin project

RG6289, a new γ-secretase modulator for the treatment of Alzheimer's disease: Dose selection for a phase II trial based on population PK/PD modeling

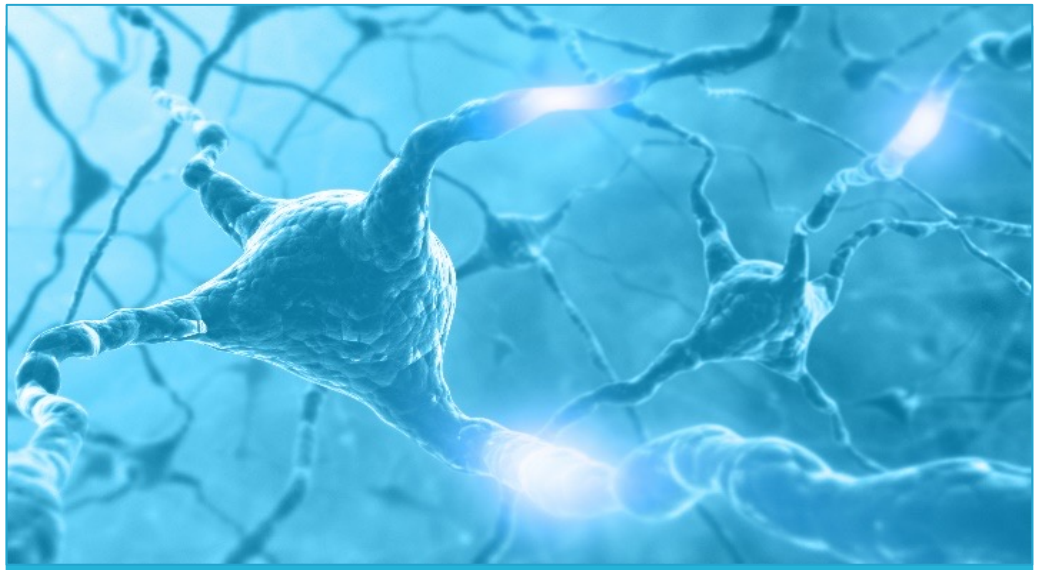
Dominik Lott [1], Agnes Portron [1], Mizan Alam [1], Carina Cantrill [1], Ruth Croney [2], Fabien Alcaraz [3], Rosa Maria Rodríguez Sarmiento [4], Lothar Lindemann [3], Lutz Mueller [1], Thomas Mueggler [3], Taner Vardar [5], Rosanna Tortelli [3], Stefan Sturm [1], Irene Gerlach [3]

[1]Pharmaceutical Sciences, Roche Pharma Research and Early Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), [2]Roche Innovation Center Welwyn, Roche Pharma Research and Early Development, Roche Products Limited - Welwyn (United Kingdom), [3]Neuroscience and Rare Diseases, Roche Pharma Early Research and Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), [4]Medicinal Chemistry, Roche Pharma Early Research and Development, F. Hoffmann-La Roche Ltd - Basel (Switzerland), [5]Product Development Safety Risk Management (PDS), F. Hoffmann-La Roche Ltd - Basel (Switzerland)



https://www.ctad-alzheimer.com/files/files/Final%20Program%20CTAD2023_October%201-Poster%20presentations.pdf

Improving Learning & Memory Capabilities



NeuroRestore®

Trk-PAM

Improving Neuronal Function & Cognition

- *Novel Oral Small Molecule*

Shown safety, tolerability & target engagement in clinical trial phase 1

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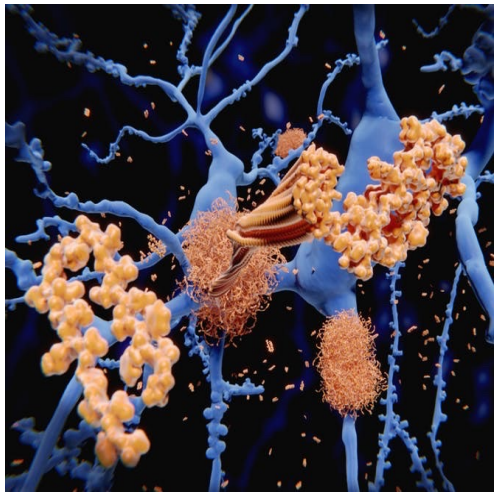
The Relevance of BDNF & NGF Signaling in Alzheimer's

- The neurotrophins Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) are **key for brain health and cognition**
- BDNF& NGF bind to their respective receptors, TrkB and TrkA
- BDNF& NGF signaling are implicated in several key neuronal functions, including **cholinergic function**, hippocampal neurogenesis and **synaptic plasticity**
- **Loss of NGF-dependent cholinergic neurons** in the basal forebrain and hippocampal atrophy are early hallmarks of Alzheimer's disease and **correlates with cognitive decline**
- **Certain genetics** in man, like the BDNF-Val66Met polymorphism, leads to **lower levels of BDNF**, and is associated with **more rapid cognitive impairment** and **increased disease progression** in Alzheimer's



Reduced BDNF and/or NGF-levels could limit the brain's ability to withstand pathological conditions and **enhance disease progression**

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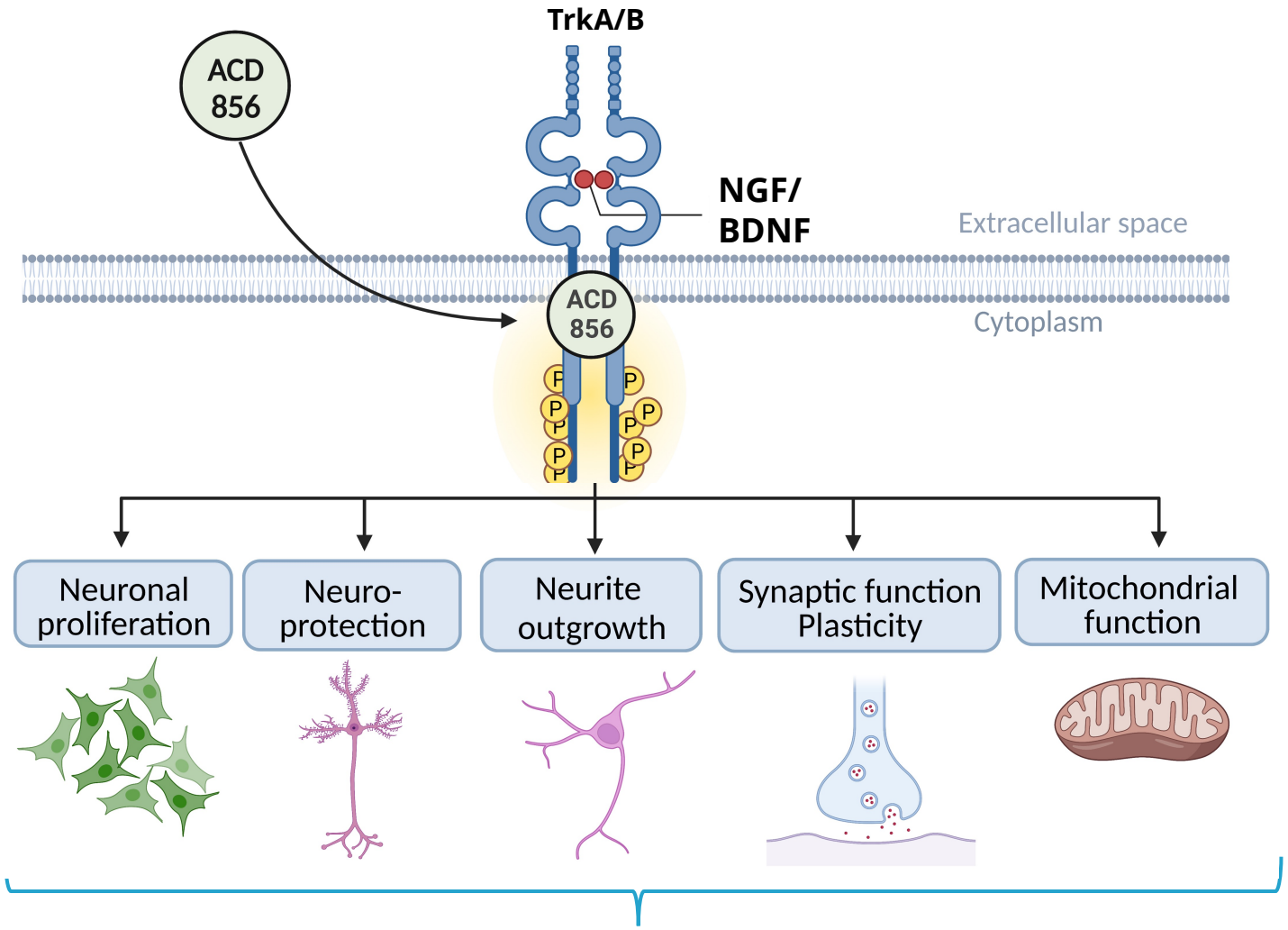
ACD856 - MoA & data supports Disease Modifying Potential

- ACD856 is a novel small molecule positive modulator of Trk-receptors **enhancing the signaling** of neurotrophins such as **NGF** & **BDNF**
- The enhanced signaling leads to immediate **symptomatic effects** & with potential **long-term benefits**
- The long-term effects of ACD856 could include **improved neuronal function, increased mitochondrial function & enhanced cognition, etc**



Parrado Fernandez C et al. Int J Mol Sci. 2023 Jul 6;24(13):11159.
https://doi.org/10.3390/ijms241311159

Potential for Disease Modifying Effect +
Improved Learning, Memory & Depression

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TrkA-PAM by Eisai: Disease-Modifying Therapy for Neurodegenerative Diseases

FIRST-IN-HUMAN (FIH), SINGLE- AND MULTIPLE-ASCENDING-DOSE (SAD/MAD) STUDIES IN HEALTHY SUBJECTS OF E2511, A NOVEL TROPOMYOSIN RECEPTOR KINASE A (TrkA) POSITIVE ALLOSTERIC MODULATOR (PAM)

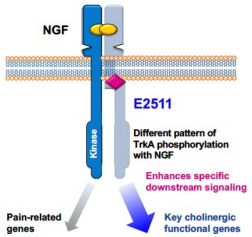
Pau Aceves[1], Nancy Hall[2], Cuiyuan Cai[3], Jagadeesh Aluri[2], Satish Dayal[1], Takuya Yagi[2], Julia Chang[2], Masaki Mikamoto[3], Garth E. Ringheim[2], Tomioka Takesuya[3], Naoki Hiramatsu[3], Robert Gordon[1], Luigi Giorgi[1]

1. Eisai Ltd., Hatfield, United Kingdom. 2. Eisai Inc., Nutley, NJ, USA. 3. Eisai Co, Ltd., Tsukuba, Japan.

Introduction

- Cholinergic innervation is affected early in multiple neurodegenerative diseases and correlates with cognitive dysfunction[1-3]
  - The progressive senescence and eventual loss of cholinergic neurons in Alzheimer's disease (AD) is correlated with cognitive impairment
- Nerve growth factor (NGF) plays a major role in the maintenance and function of cholinergic neurons[4] (see Figure 1)

Figure 1. Activation of specific trophic signaling of TrkA



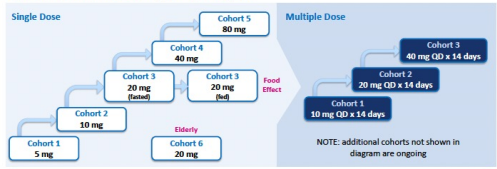
- Activation of NGF-induced trophic signaling via TrkA has potential as a disease modifying therapy to restore cholinergic innervation in neurodegenerative diseases, including AD[5-8]
- E2511 is a novel orally bioavailable small molecule TrkA biased PAM that has shown reinnervative effects on cholinergic neurons in nonclinical studies without NGF-associated hyperalgesia

Methods

- The main objectives of the E2511 FIH Phase 1 studies (SAD [completed] and MAD [ongoing]) are to evaluate the safety, tolerability and pharmacokinetics (PK) in healthy subjects
- Both SAD and MAD are randomized, double-blind and placebo-controlled studies
- The SAD evaluated 5 cohorts in adults and one cohort in elderly subjects (Figure 2); food effect was also evaluated in Cohort 3
- Repeat dosing with E2511 (once daily for 14 days) is currently under evaluation in the MAD study (3 cohorts completed; Figure 2)
- Safety was evaluated through the review of adverse events, physical examinations, clinical laboratory tests, vital signs, electrocardiogram and electroencephalograms
- Serial blood samples were collected for determination of plasma E2511 concentrations
- In MAD Cohorts 1 to 4, CSF was collected via lumbar puncture (LP) for PK/PD assessments in two occasions (1 predose and 1 postdose)

Methods *(continued)*

Figure 2. SAD and MAD Study Design Diagram



Results

Subjects

- A total of 40 and 24 healthy adult subjects have been dosed in the SAD and MAD studies, respectively (Table 1); and 5 Elderly subjects (3 E2511: 2 placebo) in the SAD

Table 1. SAD and MAD Baseline Subject Characteristics

	Single Dose								Multiple Dose					
		E2511								E2511				
	Placebo N=10	5 mg N=6	10 mg N=6	20 mg N=6	40 mg N=6	80 mg N=6	E2511 Total N=30	Total N=40	Placebo N=6	10 mg N=6	20 mg N=6	40 mg N=6	E2511 Total N=18	Total N=24
Age, mean years (SD)	34 (9)	38 (13)	40 (13)	34 (8)	35 (9)	36 (9)	36 (10)	36 (10)	45 (5.8)	27 (4)	36 (9)	32 (5)	32 (7)	35 (8)
Female, %	40	50	33	17	33	33	33	35	0	33	50	33	39	29
Race, %														
White	70	67	67	33	67	100	67	68	33	50	67	17	44	42
Black or African American	20	33	33	50	17	0	27	25	67	17	0	67	28	38
Asian	10	0	0	0	17	0	3	5	0	33	17	17	22	17
American Indian or Alaska Native	0	0	0	17	0	0	3	3	0	0	17	0	6	4
Weight, mean kg (SD)	71 (12)	73 (14)	75 (14)	71 (13)	76 (14)	72 (9)	73 (12)	72 (12)	84 (13)	76 (16)	74 (12)	73 (10)	74 (13)	77 (13)
BMI, mean kg/m², (SD)	25 (3)	25 (2)	25 (3)	24 (4)	26 (1)	25 (4)	25 (3)	25 (3)	26 (3)	25 (4)	25 (4)	25 (3)	25 (14)	25 (14)

Safety

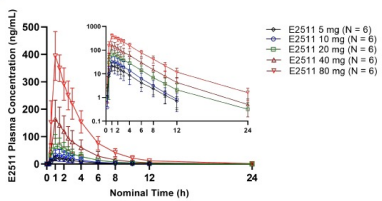
- Single and multiple oral (PO) doses of E2511 were safe and well-tolerated across the investigated doses in adult and elderly healthy subjects
- Most common (≥2) treatment-emergent adverse event (TEAE) in the SAD was contact dermatitis (same incidence in active and placebo-treated subjects [10%])
- Most common (≥2) TEAEs in the MAD were post-LP syndrome, headache, back pain and nausea; generally thought to be related to the LP procedures
- No subjects were withdrawn due to drug-related safety events
- There were no dose dependent, serious or severe TEAEs
- There were no clinically significant changes in the evaluated safety parameters (safety laboratory, vital signs, ECG, EEG and physical exam) on E2511 compared to placebo
- SAD exposure-response analyses confirmed no effects on the Holter ECG parameters, including HR, cardiac repolarization (QTcF), and cardiac conduction (PR, QRS)

Results *(continued)*

SAD: E2511 Clinical Pharmacokinetic Results

- Rapidly absorbed (t_{max}: 1 hour); with a plasma half-life of 3.19 hours (Figure 3)
- Plasma exposures (C_{max} and AUC) increased dose proportionally over the dose range of 5 to 80 mg (power model exponent [90% CI]: 1.09 [0.92, 1.25] for C_{max} and 1.08 [0.91, 1.25] for $AUC_{(0\text{-}inf)}$)

Figure 3. SAD: E2511 Plasma Concentration-Time Profiles and PK Parameters



Parameter (SD)	5 mg/kg (n=6)	10 mg/kg (n=6)	20 mg/kg (n=6)	40 mg/kg (n=6)	80 mg (n=6)
C_{max}, ng/mL	21.5 (40.8)	29.1 (98.0)	63.7 (51.8)	156 (50.8)	402 (18.2)
t_{max}, hours[1]	1.0 (1.0, 1.5)	1.0 (1.0, 2.0)	1.3 (1.0, 3.1)	1.0 (0.6, 1.5)	1.1 (1.0, 1.5)
$AUC_{(0\text{-}24h)}$, h·ng/mL	75.6 (43.9)	97.5 (91.8)	222 (55.7)	497 (55.1)	1400 (23.5)
$AUC_{(0\text{-}inf)}$, h·ng/mL	75.9 (44.1)	97.8 (92.2)	223 (55.9)	500 (55.2)	1410 (23.6)
CL/F, L/h	65.9 (44.0)	102 (92.2)	89.7 (55.9)	80.2 (55.2)	56.8 (23.7)
V_z/F, L	248 (42.9)	401 (57.2)	420 (37.1)	407 (52.4)	314 (26.5)
$t_{1/2}$, hours	2.61 (39.6)	2.72 (40.5)	3.25 (29.4)	3.52 (8.38)	3.83 (8.79)

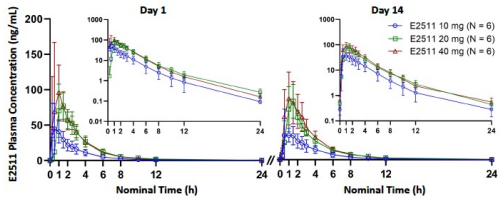
Geometric mean (%CV) values shown unless otherwise noted.
1: Median (range)

- Food (standardized high-fat, high calorie meal) led to a decrease of 19% in C_{max} and 15% in AUC compared to fasted conditions (at a dose of 20 mg)
- Plasma exposures in elderly and younger adult subjects were deemed comparable (at a dose of 20 mg), as Elderly plasma PK exposures (N=3) were fully contained within the observed range of younger adults (N=6, at same dose)

MAD: E2511 Clinical Pharmacokinetic Results

- There was little or no accumulation observed following 14 days of dosing (Figure 4)
- There was no evidence of time dependent-kinetics

Figure 4. MAD: E2511 Plasma Concentration-Time Profiles and PK Parameters



Parameter (SD)	10 mg QD		20 mg QD		40 mg QD	
	Day 1 (n=6)	Day 14 (n=6)	Day 1 (n=6)	Day 14 (n=5)	Day 1 (n=6)	Day 14 (n=6)
C_{max}, ng/mL	47.4 (88)	81.7 (50.2)	86.1 (32.3)	91.8 (22.3)	110 (59.9)	95.0 (35.9)
t_{max}, hours[1]	1.0 (0.3, 1.5)	1.0 (0.5, 2.5)	1.3 (1.0, 1.5)	1.0 (0.5, 1.5)	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)
$AUC_{(0\text{-}24h)}$, ng·h/mL	116 (57.1)	140 (24.6)	247 (22.7)	271 (16.2)	276 (34.6)	309 (30.8)
CL/F, L/h	85.7 (57.4)	71.7 (24.6)	80.4 (22.8)	73.7 (16.2)	145 (34.7)	129 (30.8)
V_z/F, L	355 (43.3)	478 (26.7)	431 (20.7)	448 (20.9)	682 (25.4)	792 (39.0)
$t_{1/2}$, hours	2.87 (46.9)	4.63 (19.2)	3.72 (20.8)	4.21 (12.7)	3.27 (31.0)	4.25 (17.8)
R_{ac}, C_{max}[2]	N/A	1.06 (132)	N/A	0.997 (48.3)	N/A	0.863 (34.9)
R_{ac}, AUC[3]	N/A	1.2 (37.8)	N/A	1.03 (25.2)	N/A	1.12 (19.1)
Rss[4]	N/A	1.2 (38.1)	N/A	1.02 (25.1)	N/A	1.12 (19.2)

Geometric mean (%CV) values shown unless otherwise noted. N/A: not applicable.
1: Median (range);
2: R_{ac}, C_{max}: Accumulation ratio determined based on C_{max} [Day 14]/ C_{max} [Day 1];
3: R_{ac} AUC: Accumulation ratio determined based on $AUC_{(0\text{-}24h)}$ [Day 14]/ $AUC_{(0\text{-}24h)}$ [Day 1];
4: R_{ss}: Time dependency ratio was determined based on $AUC_{(0\text{-}24h)}$ [Day 14]/ / $AUC_{(0\text{-}inf)}$ [Day 1]

Conclusions

- E2511 presents an adequate single and multiple dose safety profile in healthy adults up to the currently highest evaluated doses (80 mg PO in SAD; 40 mg QD PO in MAD)
- E2511 has shown predictable single and multiple dose PK with a short plasma half-life that is consistent with human PK projections based on non-clinical data
  - Dose-proportional plasma PK over the dose range of 5 to 80 mg (in the SAD) and time-invariant PK (up to at least 40 mg QD in the MAD)
  - Mild effect of food on rate and extent of plasma E2511 exposure supports dosing without regards to food
  - Plasma E2511 exposures (C_{max}, AUC) in a small group of elderly subjects suggest there is no need for dose adjustment in the target population
- These results support further development of E2511 as a disease-modifying therapy for neurodegenerative diseases

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Acknowledgments

We thank the subjects and the sites who participated in these studies. Editorial support, funded by Eisai Inc, was provided by Mayville Medical Communications. Funding for the studies and analyses was provided by Eisai.

Presented at the 2022 Alzheimer's Association International Conference (AAIC) Annual Meeting. Poster #66208

If you have any questions about this poster, please email or call Eisai Medical Information at ESI_MedInfo@eisai.com or 888-274-2378

The data is **validating & increasing interest in NeuroRestore**

" These results support further development of E2511 as a Disease-Modifying Therapy for Neurodegenerative Diseases"

NeuroRestore - Cognitive Enhancer Improving Learning and Memory Ability

Stages of memory formation

LEARN

Transforming information into a form that can be stored in memory

STORE

Maintaining the encoded information in memory

REMEMBER

Re-accessing the information from the past which has been encoded and stored

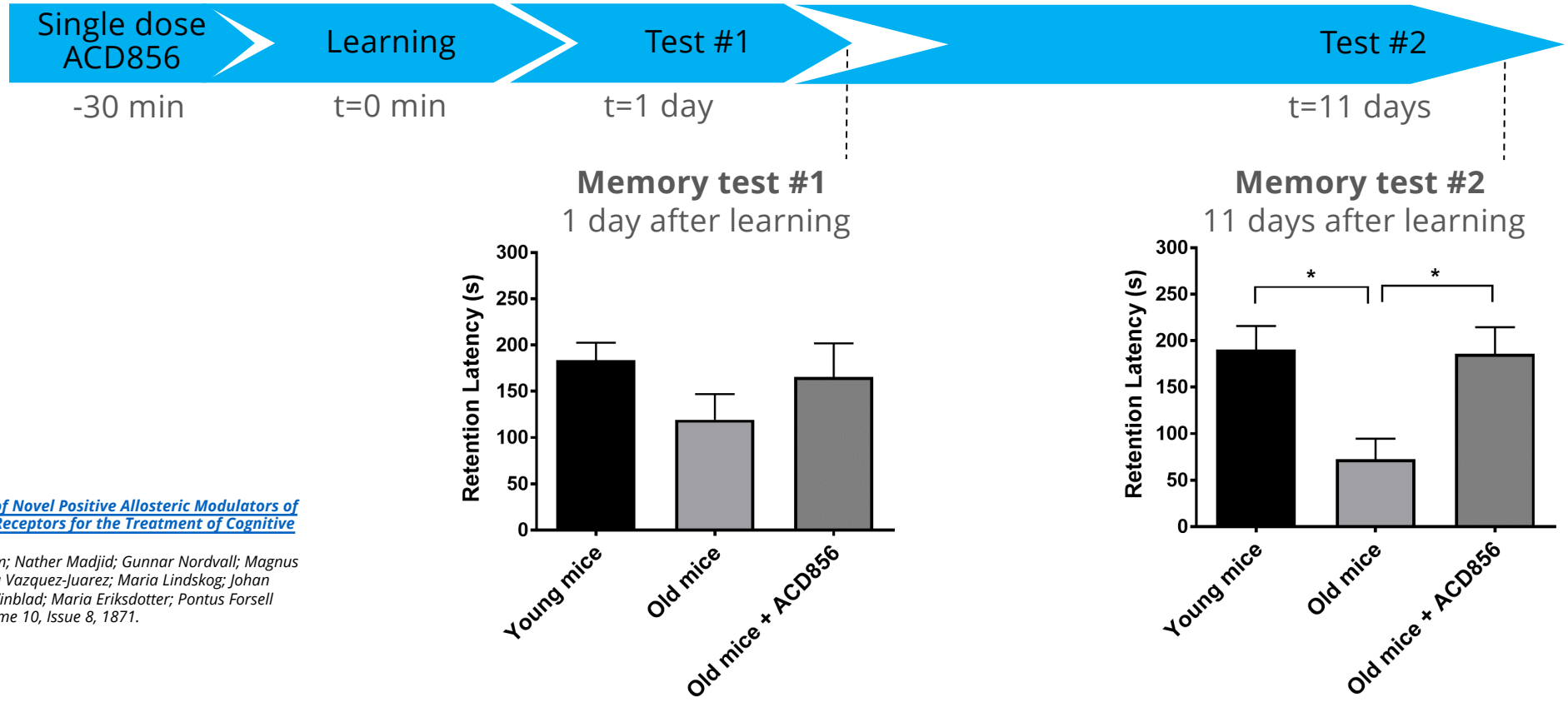
NeuroRestore has in pre-clinical models shown that it can improve the ability to **learn** and **remember** information, so the information is accurately recollected when needed.

- Phase II ready - focusing on Alzheimer's

AlzeCure

ACD856 Improves Aged-induced Memory Impairment

- 18-months old animals were used to study effects on age-induced memory impairment and compared to young animals
- Two memory tests were performed 1 or 11 days after learning



Identification of Novel Positive Allosteric Modulators of Neurotrophin Receptors for the Treatment of Cognitive Dysfunction
Märta Dahlström; Nather Madjid; Gunnar Nordvall; Magnus M. Halldin; Erika Vazquez-Juarez; Maria Lindskog; Johan Sandin; Bengt Winblad; Maria Eriksdotter; Pontus Forsell Cells 2021, Volume 10, Issue 8, 1871.

Fully revert the memory impairment in old animals to the level in young animals

AlzeCure

NeuroRestore ACD856 – Candidate in Clinical Phase

- Patent in the US, Japan and Europe to 2039

AlzeCure receives US patent for NeuroRestore ACD856

Long Patent Time

AlzeCure Pharma AB (publ) (FN STO: ALZCUR), a pharmaceutical company that develops a broad portfolio of small molecule candidate drugs for diseases affecting the central nervous system, with projects in both Alzheimer's disease and pain, today announced that the United States Patent Office (USPTO) has issued a patent covering ACD856, which is being developed against Alzheimer's disease and other disorders with cognitive impairment.

USPTO has announced that they have now approved the company's patent application in the US, which refers to ACD856, the leading drug candidate in the NeuroRestore platform, which is being developed against Alzheimer's disease. The patent number is US 11,352,332 and the patent is valid until 2039.

ACD856 and other substances in the NeuroRestore platform stimulate several important signaling systems and signaling molecules in the brain such as BDNF (Brain Derived Neurotrophic Factor) and NGF (Nerve Growth Factor), which can lead to improved cognition. Previous preclinical studies have shown that AlzeCure's drug candidates strengthen communication between nerve cells and improve cognitive ability, including learning and memory functions. New preclinical results also show potential neuroprotective and disease-modifying effects with these substances. The biological mechanism behind NeuroRestore enables several indications, such as Alzheimer's and Parkinson's disease, but also depression.

=> In addition, being a NCE, there is 5 years of expected market exclusivity in the US => 2039 + 5 years = **2044**

https://www.alzecurepharma.se/en/alzecure-receives-us-patent-for-neurorestore-acd856/
https://www.alzecurepharma.se/en/alzecure-is-granted-european-patent-for-neurorestore-acd856/

AlzeCure

Our second Focus area

Chronic Pain

- Suicide due to chronic pain is as common as due to depression
- Most common cause for sick leaves, creating misery & high societal costs
- Opioid crisis in the US - is huge & reversing the mean average lifespan of Americans

Huge need for more efficacious and safer treatments

AlzeCure

Our platform PAINLESS – Targeting unmet medical needs within pain

Osteoarthritis & severe pain conditions

> 300 million patients

Project: **TrkA-NAM**

Neuropathic pain*

600 million patients

Project: **ACD440**

AlzeCure

*) Neuropathic pain = Pain initiated or caused by a primary lesion or dysfunction in the somatosensory nervous system

ACD440 – Novel TRPV1 antagonist in phase 2 for neuropathic pain

PROJECT OVERVIEW

Emanates from Big Pharma

- Approximately **20M USD** already **invested** on project development
- **Mode of action confirmed** in several Phase 1 clinical trials
- Synthesized compound and formulation developed

TRPV1 – **Optimized for local delivery**

- The vanilloid receptor subtype 1 (TRPV1) is expressed in nociceptive sensory neurons
- TRPV1 is upregulated in the skin of patients with neuropathic pain
- **Strong scientific support** for peripheral/local treatment with TRPV1 antagonists

Positive clinical trial results in 1b & 2a

- Developed **topical formulation to avoid AEs** associated with systemic TRPV1 blockade
- **Clinical trial** with topical formulation was initiated and **successfully finalized**
- Phase 1b study addressed **safety, tolerability & efficacy – POSITIVE OUTCOMES**

Now presented detailed **positive phase 2a data**

AlzeCure

Positive Phase 2a Results for first-in-class ACD440

- Demonstrate **Positive Proof-of-Mechanism** (PoM) results **in patients** with chronic **peripheral neuropathic pain** in a placebo cross-over trial

- The patients have had **chronic pain** for many years & were on **concomitant medication**
  - A **significant analgesic effect** on pain induced by cold and heat.
    - The data are **in line with previously** reported phase Ib **results**
  - Pain reduced by appr. 50%, - a **clinically significant magnitude**

- **Well tolerated** as a topical gel on the skin, which shows **suitability for continued clinical development**

AlzeCure

Neuropathic pain - Fast growing market

- The most valuable segment within the pain indications
- Poorly served patients
- Huge demand for better drugs

2020
$11 billions

CAGR to 2027
12.9% => **$25 billions**

The Neuropathic Pain market was valued at $10,8 billion in 2020 globally and is forecast to reach $25,2 billions by 2027, at a Compound Annual Growth Rate (CAGR) of 12,9%

GlobalData, Global Pain Therapeutics Market Overview, May 2021

AlzeCure

Key investment highlights in AlzeCure

- Targeting areas of **huge unmet medical needs**
- **Strong team** with extensive experience and track record
- **Platforms with first-in-class properties** and potential **game-changers**
- **Parallel investments** in several candidates and potent **follow-up programs**
- **Multi-billion dollar** market **opportunities**
- Evolved into a **phase II company**

AlzeCure

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Hälsovägen 7, 141 57 Stockholm
SWEDEN

www.alzecurepharma.com

AlzeCure

Alzstatin publications

- **Gamma-secretase modulators: a promising route for the treatment of Alzheimer's disease**
  Gunnar Nordvall1,2* Johan Lundkvist1,2,3 Johan Sandin1,2
  1AlzeCure Pharma AB, Huddinge, Sweden, 2Department of Neurobiology, Care Sciences, and Society, Division of Neurogeriatrics, Center for Alzheimer Research, Karolinska Institutet, Stockholm, Sweden, 3Sinfonia Biotherapeutics AB, Huddinge, Sweden
- **In vitro and in vivo profile of AC-0027875 (Alzstatin ACD680), a novel gamma-secretase modulator for the prevention and treatment of Alzheimer's disease**
  Authors : Märta Dahlström, Lotta Agholme, Maria Backlund, Veronica Lidell, Azita Rasti, Pontus Forsell, Sanja Juric, Magnus M. Halldin, Johan Sandin, Johan Lundkvist, Henrik Zetterberg, Gunnar Nordvall.
  AD/PD 2023, March 28 – April 1, 2023.
- **AC-0027875, a novel gamma-secretase modulator**
  Authors : Johan Sandin[1], Märta Dahlström[1], Veronica Lidell[1], Azita Rasti[1], Pontus Forsell[1], Sanja Juric[1], Magnus Halldin[1], Maria Backlund[1], Gunnar Nordvall[1]
  [1]AlzeCure Pharma AB- Huddinge (Sweden) CTAD 29 nov–2 dec 2022.
- **γ-Secretase modulators show selectivity for γ-secretase–mediated amyloid precursor protein intramembrane processing** Tobias A. Weber, Johan Lundkvist, Johanna Wanngren, Hlin Kvartsberg, ShaoBo Jin, Pia Larssen, Dan Wu, Daniel V. Oliveira, Karolina Minta, Gunnar Brinkmalm, Henrik Zetterberg, Kaj Blennow, Gunnar Nordvall, Bengt Winblad, Erik Portelius, Helena Karlström., Journal of Cellular and Molecular Medicine, 20 December 2021.
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- **Second generation γ-secretase modulators exhibit different modulation of Notch β and Aβ production**
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- **Alzheimer's disease: Presenilin 2-sparing γ-secretase inhibition is a tolerable Abeta peptide lowering strategy**
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Links above available in presentation mode

NeuroRestore publications

- Safety, Tolerability, Pharmacokinetics and Quantitative Electroencephalography Assessment of ACD856, a Novel Positive Allosteric Modulator of Trk-Receptors Following Multiple Doses in Healthy Subjects
  Önnestam, K., Nilsson, B., Rother, M. Rein-Hedin E., Bylund J., Anderer P., Kemethofer M., Halldin, M., Sandin J., Segerdahl M. J Prev Alzheimers Dis (2023).
- Antidepressant effects of novel positive allosteric modulatorsof Trk receptor mediated signaling – a potential therapeutic concept?
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- Neuroprotective and Disease-Modifying Effects of the Triazinetrione ACD856, a Positive Allosteric Modulator of Trk-Receptors for the Treatment of Cognitive Dysfunction in Alzheimer's Disease
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  Authors : Johan Sandin, Sanja Juric, Cristina Parrado-Fernández, Nather Madjid, Gunnar Nordvall, Maria Backlund, Märta Dahlström, and Pontus Forsell,
  AD/PD 2023, March 28 – April 1, 2023.
- Preclinical characterization of ACD856
  Authors : Cristina Parrado-Fernández[1], Gunnar Nordvall[1], Sanja Juric[1], Nather Madjiid[1], Maria Backlund[1], Märta Dahlström[1], Johan Sandin[1], Pontus Forsell[1]
  [1]AlzeCure Pharma AB- Huddinge (Sweden) CTAD 29 nov–2 dec 2022.
- Quantitative EEG results from a multiple ascending dose study
  Authors : Martin Jönsson[1], Kristin Önnestam[1], Boel Nilsson[1], Matthias Rother[1], Erik Rein- Hedin[2], Peter Anderer[3], Manuel Kemethofer[3], Magnus Halldin[1], Pontus Forsell[1], Gunnar Nordvall[1], Johan Sandin[1], Märta Segerdahl[1].
  [1]AlzeCure Pharma AB- Huddinge (Sweden) [2]CTC Clinical Trial Consultants AB- Uppsala (Sweden) [3]The Siesta Group Schlafanalyse GmbH- Vienna (Austria) CTAD 29 nov–2 dec 2022.
- The Trk-pam Acd856 Improves Mitochondrial Function And Increases Bdnf Levels In Primary Cortical Neurons Cristina Parrado, Sanja Juric, Märta Dahlström1, Johan Sandin, Pontus Forsell, AlzeCurePharma AB, Hälsovägen7, Huddinge, Sweden.
- Neurotrophin targeted therapeutics – a gateway to cognition and more? Dr. Gunnar Nordvall, Head of Chemistry, Dr. Pontus Forsell, Head of Research and Discovery and Dr. Johan Sandin, CSO, Aug 16, 2022.
- Results From a Multiple Ascending Dose Study in Healthy Volunteers of ACD856, a Positive Modulator of Neurotrophin Trk-Receptors, AAIC, July – Aug., 2022
  Kristin Önnestam[1] MSc, Matthias Rother[1] MD, PhD, Erik Rein-Hedin[2] MD, Johan Bylund[2] PhD, Magnus M Halldin[1] PhD, Boel Nilsson[1] MSc, Pontus Forsell[1] PhD, Gunnar Nordvall[1] PhD, Johan Sandin[1] PhD, Märta Segerdahl[1] MD, PhD. AlzeCure Pharma AB, Hälsovägen 7, Huddinge, Sweden 2. CTC Clinical Trial Consultants AB, Dag Hammarskjölds väg 10B, Uppsala, Sweden.
- Characterization of positive allosteric modulators of TrkB for the treatment of depression Sandin, J., Nordvall, G., Madjid, N., Dahlström, M., Parrado, C., Backlund, M., Lidell, V., Halldin, M. and Forsell, P., ECNP 2021, October 2-5.
- ACD856, a novel cognitive enhancer targeting neurotrophin signaling for the treatment of Alzheimer's Disease Forsell, P., Halldin, M., Dahlström, M., Madjid, N., Rother, M., Van Es-Johansson, A., Lundkvist, J., Eriksdotter, M., Jönsson, M., Winblad, B. and Sandin, J., CTAD 2020, Nov 4-7.
- Identification of Novel Positive Allosteric Modulators of Neurotrophin Receptors for the Treatment of Cognitive Dysfunction
  Märta Dahlström; Nather Madjid; Gunnar Nordvall; Magnus M. Halldin; Erika Vazquez-Juarez; Maria Lindskog; Johan Sandin; Bengt Winblad; Maria Eriksdotter; Pontus Forsell Cells 2021, Volume 10, Issue 8, 1871.
- ACD856, a positive modulator of neurotrophin signaling reverses scopolamine- or age-induced cognitive deficits
  Pontus Forsell, Gunnar Nordvall, Nather Madjid, Märta Dahlström, Magnus Halldin, Johan Lundkvist, Bengt Winblad, Prof Maria Eriksdotter, Prof Johan Sandin, Martin Jönsson., 2020 April 2-5; AAT-ADPD.
- ACD856 – a novel positive allosteric modulator of Trk-receptors in clinical development for the treatment of Alzheimer's disease
  Nordvall, G., Madjid, N., Backlund, M., Halldin, M., Rother., M., Nilsson, B., Sandin, J.* and Forsell, P., AAIC 2021, July 26-30.
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AlzeCure

Painless publications

ACD440

- **AlzeCure ACD440 TRPV1 antagonist_ Ph 2 data, EFIC 2023** Adriana Miclescu2, MD, PhD, M. Halldin1, MSc Pharm, PhD, Karin Ellström3, MSc Pharm, Rolf Karlsten2, MD, PhD, Märta Segerdahl1,4, MD, PhD, Assoc Prof.
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TrkA-NAM

- **Negative allosteric modulators of TrkA for the treatment of pain; Scientific presentation at IASP** Nordvall, G., Dahlström, M., Parrado, C., Backlund, M., Lidell, V., Halldin, M., Sandin, J. and Forsell, P., 2021 June 27-July 1.

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