October 11, 2023

Developing therapies for Alzheimer's & Pain

Martin Jönsson, CEO

AlzeCure

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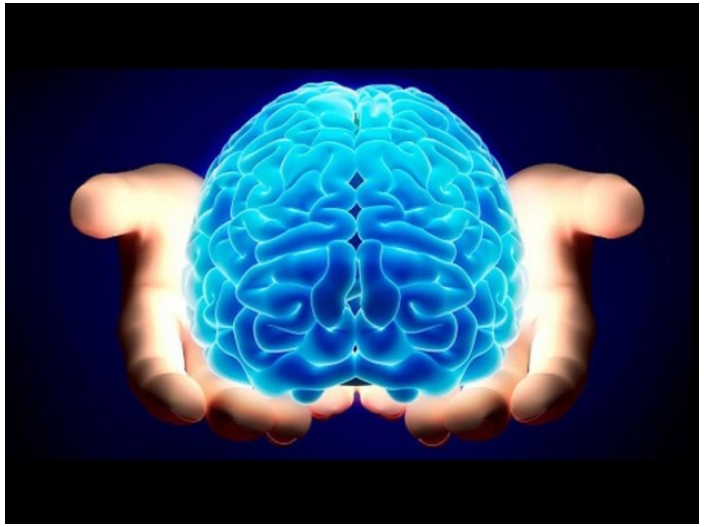
Agenda

- Who we are
- Focus areas
- Pipeline & the science
  - Progress, plans & goals



EVENTFUL LAST MONTHS

New Positive Phase 2 data, several new publication, and progress in our projects & categories

+ additional data release in the coming month

AlzeCure

AlzeCure Pharma – in brief

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

- Three project platforms with multiple **small molecule** candidates with **first-in-class properties**
  - **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 since Nov. 2018 (Ticker: ALZCUR)
- Market cap: **SEK 246m** (Oct 9, 2023)
- Cash position: **SEK 45m** (Q2 2023 interim report)

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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, Sleep disorders, Traumatic brain injuries Parkinson's disease, 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 1 trial
Safety, Tolerability & Target engagement

Selected new additional CD
ACD680

Positive read-out Phase 2a
Safety, Tolerability & Pain

Phase completed

Phase ongoing

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Close cooperation with leading KOLs & Institutions

Professor Bengt Winblad
Karolinska Institute

Professor Maria Eriksdotter
Karolinska Institute

Professor Henrik Zetterberg
Sahlgrenska and UCL

Karolinska Institutet

GÖTEBORGS UNIVERSITET
SAHLGRENSKA AKADEMIN

UCL

AlzeCure

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**

AlzeCure

Alzstatin®

MOA: Gamma-Secretase Modulator

Preventive Disease Modifying therapy against Alzheimer's

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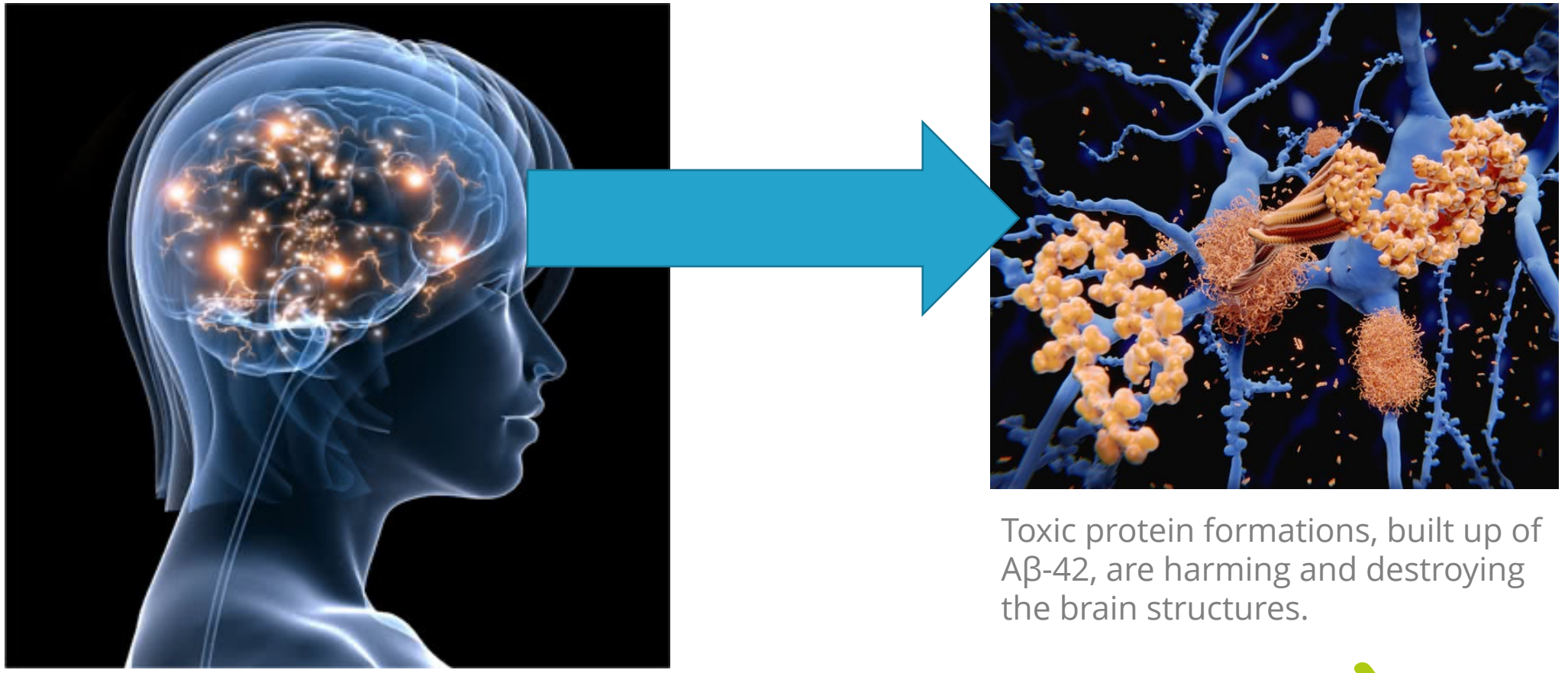
The Alzheimer's brain and its destruction

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

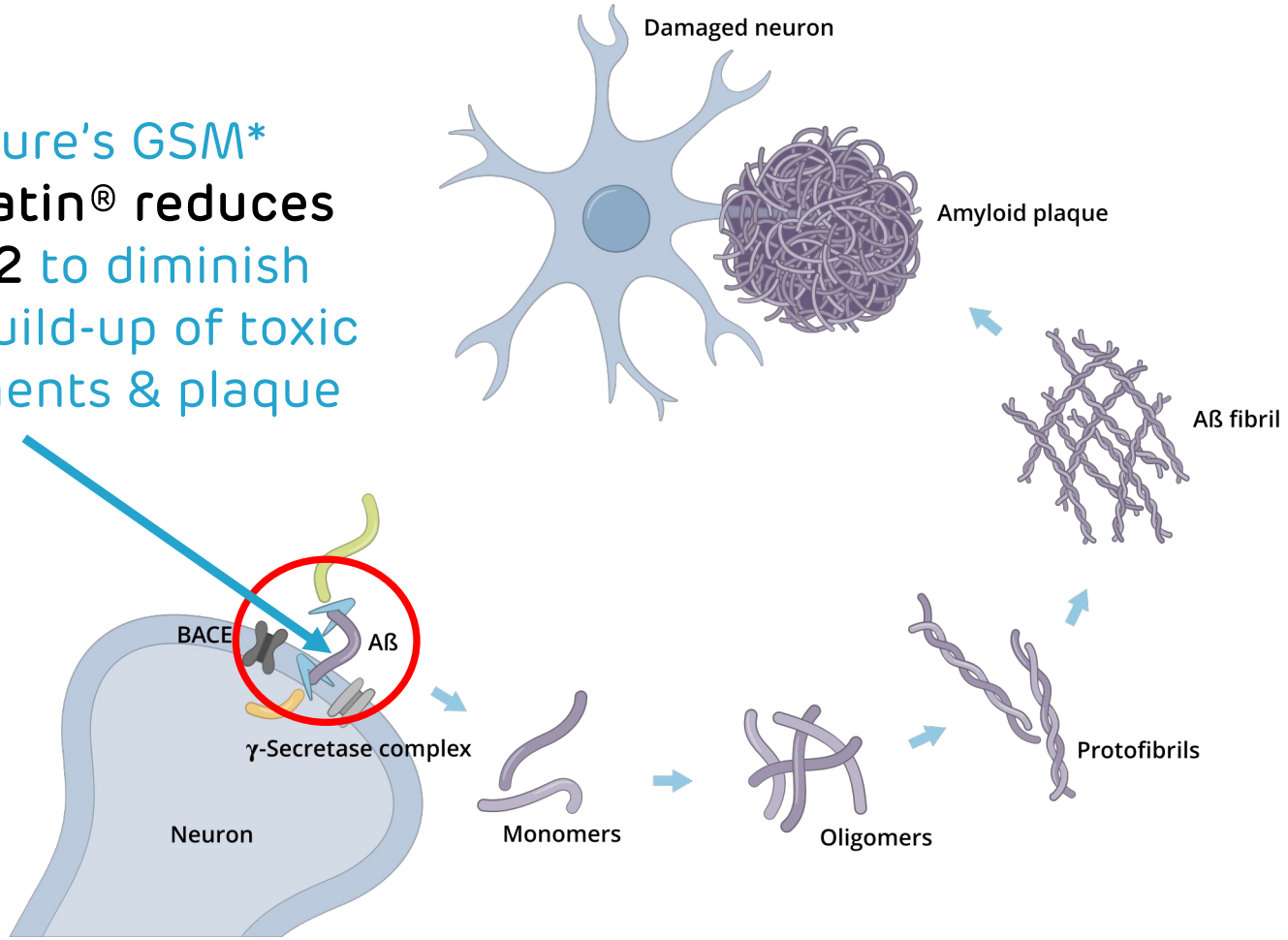


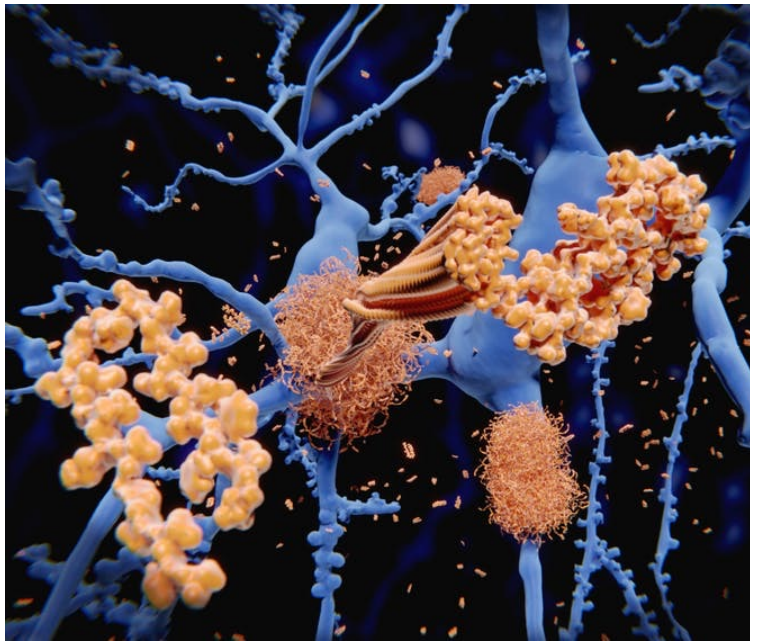
Toxic protein formations, built up of Aβ-42, are harming and destroying the brain structures.

AlzeCure

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-Secretase Modulator

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Increasing interest support for GSMs, such as Alzstatin, to treat & prevent Alzheimer's

Luo and Li *Cell & Bioscience* (2022) 12:2
https://doi.org/10.1186/s13578-021-00738-7

Cell & Bioscience

REVIEW Open Access

Turning the tide on Alzheimer's disease: modulation of γ-secretase

Joanna E. Luo[1,2*] and Yue-Ming Li[1,2*]

Abstract

Alzheimer's disease (AD) is the most common type of neurodegenerative disorder. Amyloid-beta (Aβ) plaques are integral to the "amyloid hypothesis," which states that the accumulation of Aβ peptides triggers a cascade of pathological events leading to neurodegeneration and ultimately AD. While the FDA approved aducanumab, the first Aβ-targeted therapy, multiple safe and effective treatments will be needed to target the complex pathologies of AD. γ-Secretase is an intramembrane aspartyl protease that is critical for the generation of Aβ peptides. Activity and specificity of γ-secretase are regulated by both obligatory subunits and modulatory proteins. Due to its complex structure and function and early clinical failures with pan inhibitors, γ-secretase has been a challenging drug target for AD. γ-secretase modulators, however, have dramatically shifted the approach to targeting γ-secretase. Here we review γ-secretase and small molecule modulators, from the initial characterization of a subset of NSAIDs to the most recent clinical candidates. We also discuss the chemical biology of γ-secretase, in which small molecule probes enabled structural and functional insights into γ-secretase before the emergence of high-resolution structural studies. Finally, we discuss the recent crystal structures of γ-secretase, which have provided valuable perspectives on substrate recognition and molecular mechanisms of small molecules. We conclude that modulation of γ-secretase will be part of a new wave of AD therapeutics.

Keywords: γ-secretase, Alzheimer's disease, Inhibitor, Modulator, Mechanism

Introduction

Alzheimer's disease (AD) is the most common cause of dementia affecting more than 6 million Americans. In 2021, AD and other dementias cost $355 billion in healthcare, and these costs could exceed $1 trillion by 2050 [1]. Early symptoms include memory loss and behavioral changes; in late stages of AD cognitive decline interferes with most everyday activities. While acetylcholinesterase inhibitors and N-methyl-D-aspartic acid (NMDA) antagonists alleviate cognitive and behavior symptoms [2], there are no treatments which delay or stop disease progression. Earlier this year the FDA approved aducanumab, the first novel therapy for AD in almost two decades. Aducanumab, a human monoclonal antibody which targets aggregated amyloid-beta (Aβ), reduced amyloid plaques in the brain, and is expected to delay cognitive decline [2, 3].

AD pathology is characterized by the deposition of Aβ plaques in brain tissue [4]. While the underlying disease mechanisms are complex and still being elucidated, multiple lines of evidence support the "amyloid hypothesis," which posits that the accumulation of Aβ peptides initiates a chain of pathological events, including formation of neurofibrillary tangles and inflammatory responses, leading to widespread neurodegeneration and ultimately AD [5, 6]. The gene encoding the amyloid precursor protein (APP) was identified on chromosome 21, which corresponded with Down's syndrome individuals who consistently exhibited AD [7, 8]. Mutations in *APP*, *Presenilin-1* (PS1), and *Presenilin-2* (PS2) have been linked to

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Abstract

Alzheimer's disease (AD) is the most common type of neurodegenerative disorder. Amyloid-beta (Aβ) plaques are integral to the "amyloid hypothesis," which states that the accumulation of Aβ peptides triggers a cascade of pathological events leading to neurodegeneration and ultimately AD. While the FDA approved aducanumab, the first Aβ-targeted therapy, multiple safe and effective treatments will be needed to target the complex pathologies of AD. γ-Secretase is an intramembrane aspartyl protease that is critical for the generation of Aβ peptides. Activity and specificity of γ-secretase are regulated by both obligatory subunits and modulatory proteins. Due to its complex structure and function and early clinical failures with pan inhibitors, γ-secretase has been a challenging drug target for AD. γ-secretase modulators, however, have dramatically shifted the approach to targeting γ-secretase. Here we review γ-secretase and small molecule modulators, from the initial characterization of a subset of NSAIDs to the most recent clinical candidates. We also discuss the chemical biology of γ-secretase, in which small molecule probes enabled structural and functional insights into γ-secretase before the emergence of high-resolution structural studies. Finally, we discuss the recent crystal structures of γ-secretase, which have provided valuable perspectives on substrate recognition and molecular mechanisms of small molecules. We conclude that modulation of γ-secretase will be part of a new wave of AD therapeutics.

Keywords: γ-secretase, Alzheimer's disease, Inhibitor, Modulator, Mechanism

" We conclude that modulation of γ-secretase will be part of a **new wave of AD* therapeutics**."

https://doi.org/10.1186/s13578-021-00738-7

*) AD = Alzheimer's disease

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Roche CTAD 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)

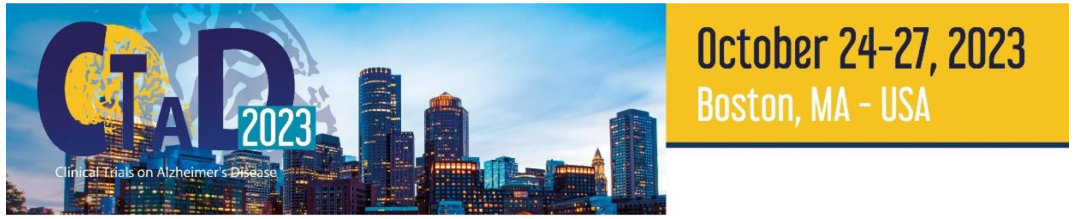
Time: Oct. 27 at 3.15 pm

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

Early Value Driving Proof-of-Mechanism in Phase I

- **BBB-penetrant small molecule for oral use**
  - Not expected to cause brain oedema (ARIA-E) and brain microbleeds (ARIA-H) associated with mAb therapies*

- **PoM & Central Target Engagement established - already in ph 1**
  - Phase I- SAD/MAD studies
    - Evaluation of safety and tolerability after single and repeated administration
  - Possibility to explore biomarker effects **showing central target engagement**
    - Aβ42/40 – show **reduction of toxic Aβ-species**
    - Aβ37/38 – show **increase of shorter protective Aβ-species**, establishing gamma-secretase involvement and MoA
    - Measurements done both in CSF & plasma utilizing already **available biomarker kits**

* E.g. antibodies (mAb) like Leqembi ™ (lecanumab) & donanemab

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Multiple Target Populations - Maintenance to Preventive Therapy

Maintenance therapy in patients with established Alzheimer's

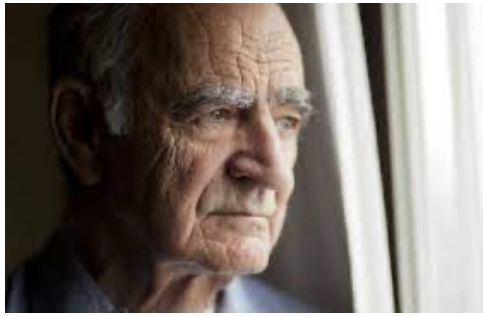
- Treatment after initial plaque clearance by monoclonal antibody treatment (as initially proposed by Lilly) e.g., with: Lecanemab (Eisai/Biogen/Bioarctic), Donanemab (Lilly), Remternetug (Lilly)

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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NeuroRestore® ACD856

MoA: Trk-PAM

A Cognitive & Neural Regenerant

with Broad Neuroprotective Disease Applications

AlzeCure

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.

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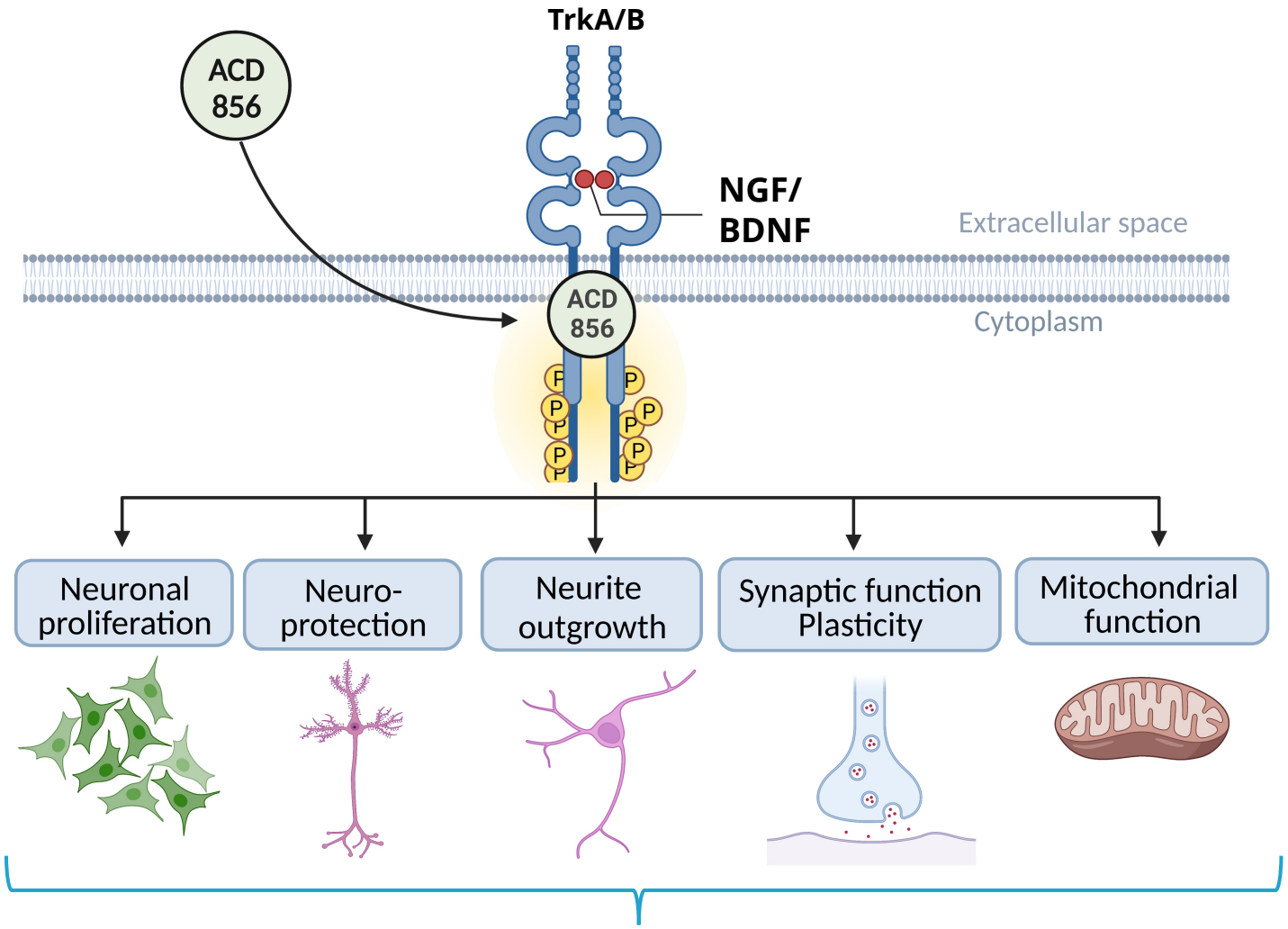
NEW RESULTS

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**



Potential for Disease Modifying Effect +

Improved Learning, Memory & Depression

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

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)

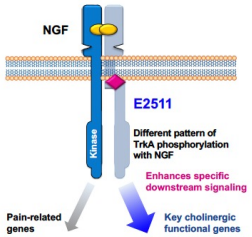
Pau Aceves[1], Nancy Hall[2], Cuiyuan Cai[3], Jagadeesh Aluri[2], Satish Dayal[1], Takuya Yagi[2], Julia Chang[2], Masaki Mikamoto[3], Garth E. Ringheim[2], Tomioka Takesuya[3], Naoki Hiramatsu[3], Robert Gordon[1], Luigi Giorgi[1]

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



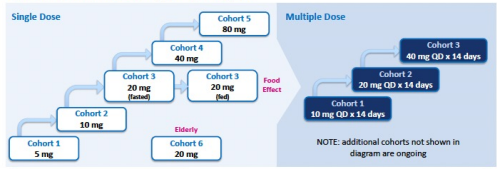
- Activation of NGF-induced trophic signaling via TrkA has potential as a disease modifying therapy to restore cholinergic innervation in neurodegenerative diseases, including AD[5-8]
- E2511 is a novel orally bioavailable small molecule TrkA biased PAM that has shown reinnervative effects on cholinergic 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

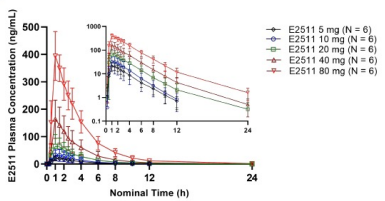
- Single and multiple oral (PO) doses of E2511 were safe and well-tolerated across the investigated doses in adult and elderly healthy subjects
- Most common (≥2) treatment-emergent adverse event (TEAE) in the SAD was contact dermatitis (same incidence in active and placebo-treated subjects [10%])
- 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)

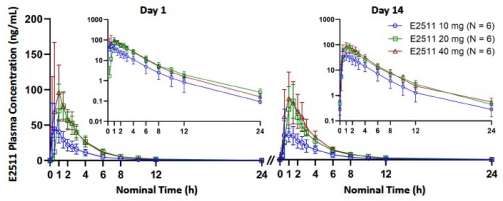
Geometric mean (%CV) values shown unless otherwise noted.
1: Median (range)

- 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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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**

Presenting new data at CTAD in Boston, end of October

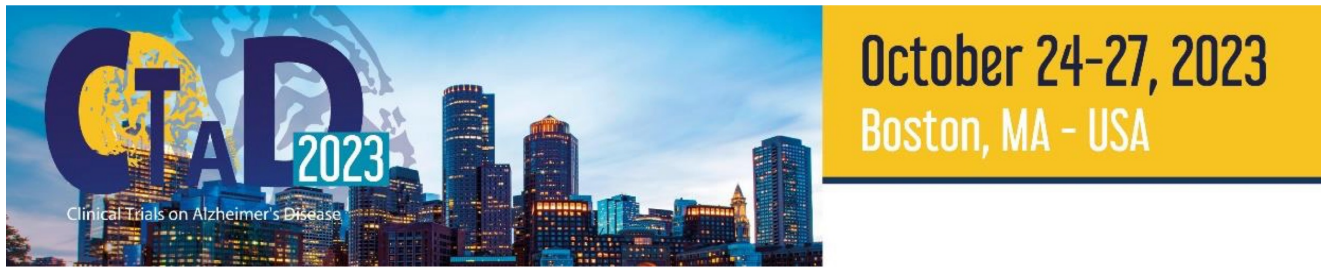
" These results support further development of E2511 as a disease-modifying therapy for neurodegenerative diseases"

NeuroRestore ACD856 data release at CTAD in October

- New data further supporting Disease Modifying Abilities

TITLE

NeuroRestore ACD856, a Trk-PAM in clinical development for Alzheimer's disease shows neuroprotective and neurorestorative effects



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

AlzeCure

Our platform PAINLESS – Targeting Unmet Medical Needs within Pain

Osteoarthritis & severe pain conditions

> 300 million patients

Project: **TrkA-NAM**

Negative allosteric modulator of TrkA-receptors in research phase

Neuropathic pain

600 million patients

Project: **ACD440**

Topical TRPV1 antagonist in clinical Phase II

AlzeCure

ACD440 – Novel TRPV1 Antagonist in Clinical Phase 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

VR1 – 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

- 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 received & released **positive phase 2a data**

AlzeCure

NEW RESULTS

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

- Demonstrate **Positive Proof-of-Mechanism** (PoM) results **in patients** with chronic **peripheral neuropathic pain** induced by cold and heat.

- 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**

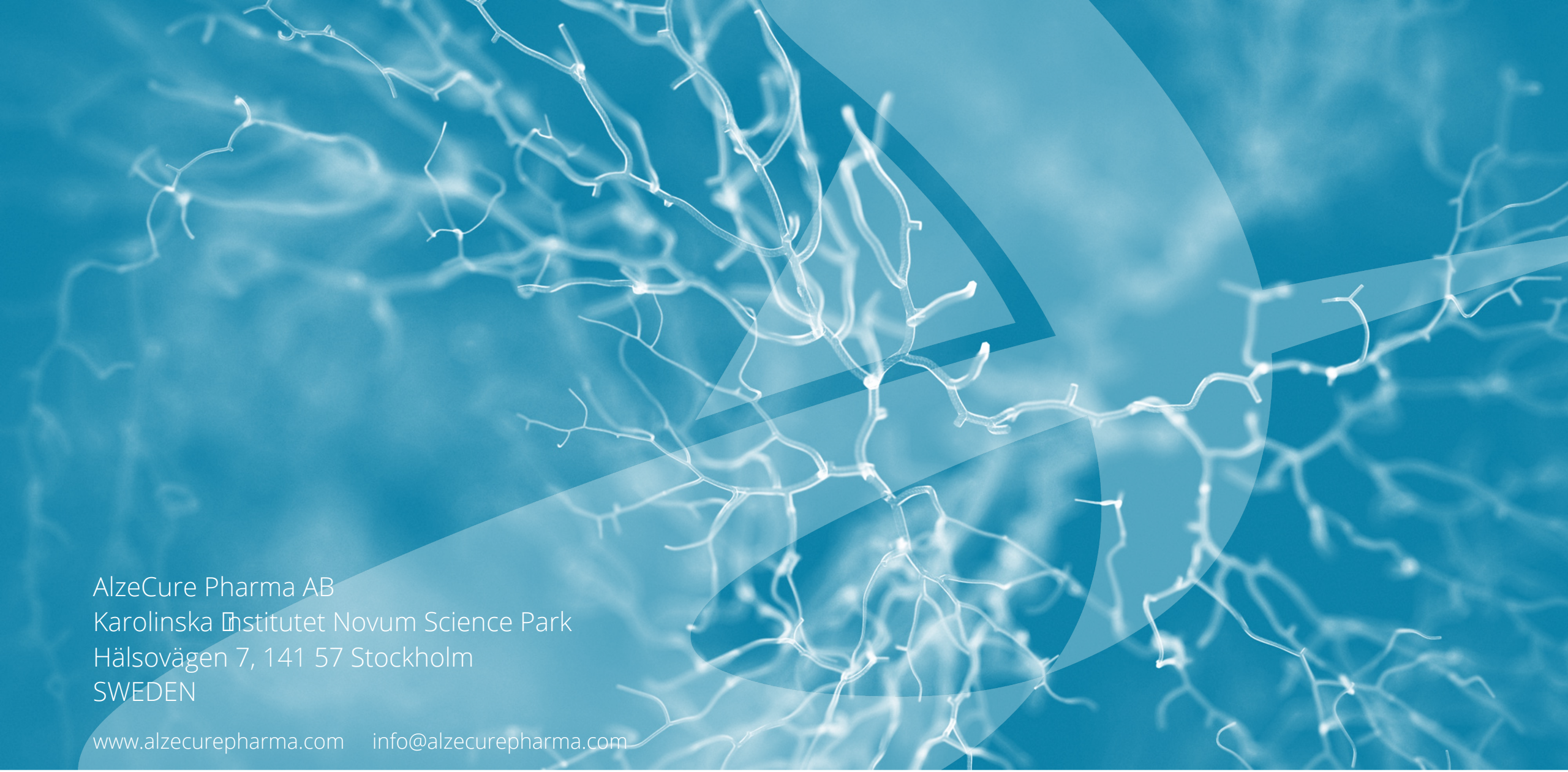
- **Well tolerated** as a topical gel on the skin, which shows **suitability for continued clinical development**

AlzeCure

Key Investment Highlights in AlzeCure

- Targeting areas of **significant unmet medical needs**
- **Strong team** with extensive experience and track record – from idea to clinic
- **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 from a discovery into a **phase II company**

AlzeCure



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