SEMINAR

PAINLESS ACD440

- A novel non-opioid analgesic with Orphan Designation

European Innovation Council

AlzeCure

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Today's presenters

EXPERIENCES

Märta Segerdahl Storck
CMO
M.D., Ph.D.

› Broad and extensive experience in global development and clinical operations Pharma industry within CNS and Pain
› Education: M.D., Karolinska Institute, Stockholm, Sweden

from GRÜNENTHAL, Karolinska Institutet, AstraZeneca, Lundbeck

Dimitrina Dimitrova
B.Sc, Master

› Experience in business development and consulting from the United Kingdom and the Nordic life science sector
› Education: B Sc in Molecular Biology from University of Aberdeen & Master student at Karolinska Master program in Bioentrepreneurship

University of Aberdeen, fios GENOMICS, Karolinska Institutet

Martin Jönsson
CEO

› Extensive experience in various senior management positions with >20 years of international experience in the industry
› Education: MSc in BA from Lund University, Ottawa, Canada & Freiburg, Germany

Roche, Lunds Universitet, FERRING PHARMACEUTICALS

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ACD440 - A novel non-opioid analgesic with Orphan Designation

- 14:00 **Welcome, brief presentation of AlzeCure Pharma & agenda** – Martin Jönsson, CEO, AlzeCure
- 14:05 **Orphan Drug Market – Past, Present & Future -** Dimitrina Dimitrova, Karolinska Institutet
- 14:20 **ACD440 – Opportunity in Erythromelalgia -** Märta Segerdahl, CMO
  - Background on **Erythromelalgia**
  - **FDA interaction & Orphan Drug Designation** (ODD)
- 14:40 **Q&A** – Moderator Martin Westerberg, FinWire
- 14:55 **Concluding remarks** – Martin Jönsson, CEO, AlzeCure and Martin Westerlund, FinWire

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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, **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					
Alzstatin®	ACD680	Gamma secretase modulator (GSM)	Alzheimer's Disease					
PainLess	ACD440	TRPV1 antagonist	Neuropathic Pain Pain in erythromelalgia					
	ACD137	Negative allosteric modulator (NAM) of TrkA-receptors	Osteoarthritic Pain & other severe pain conditions					

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

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Grant for phase 2

Selected ACD680 as lead going forwards towards clinic

Positive read-out Phase IIa
Safety, Tolerability & Pain

Selected CD
ACD137 for clinical trials

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Phase completed

Phase ongoing

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PAINLESS ACD440 – Topical TRPV1 antagonist in clinical Phase II

Neuropathic pain

> 600 million patients

Project: **ACD440**

Topical TRPV1 antagonist with positive data from clinical Phase II

Received **Orphan Designation for Pain in Erythromelalgia**

Received **positive feedback on a** potential **registration trial** in the Indication, Pain in Erythromelalgia

Orphan Drug Market - Past, Present & Future

Dimitrina Dimitrova
Master in Bioentrepreneurship
Karolinska Institutet

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dimitrina-dimitrova@outlook.com

Understanding Orphan and Rare Diseases

Rare Disease

US <200,000 people nationwide.[1]

EU <5 in 10,000 people in the population.[2]

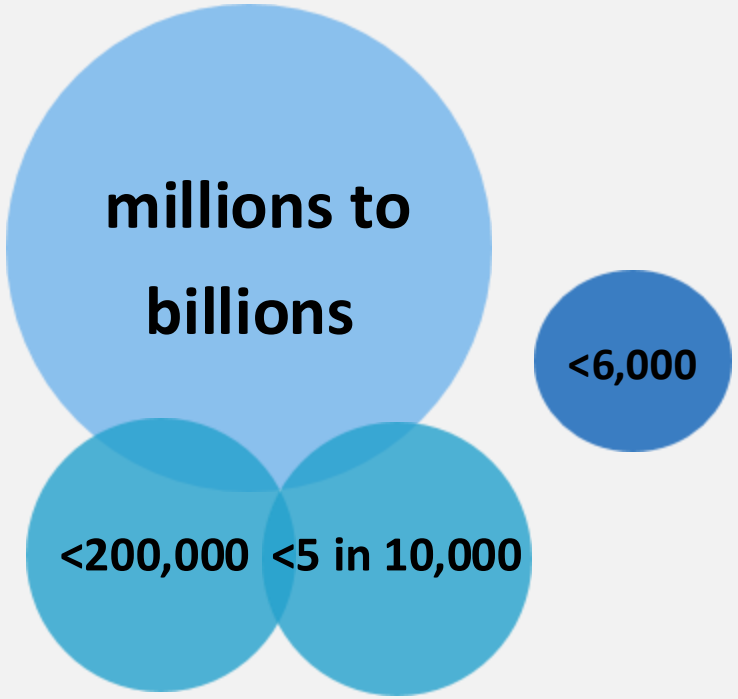
Orphan Drug

A medicine developed specifically to treat a rare disease, granted special incentives to encourage development.[1 2]

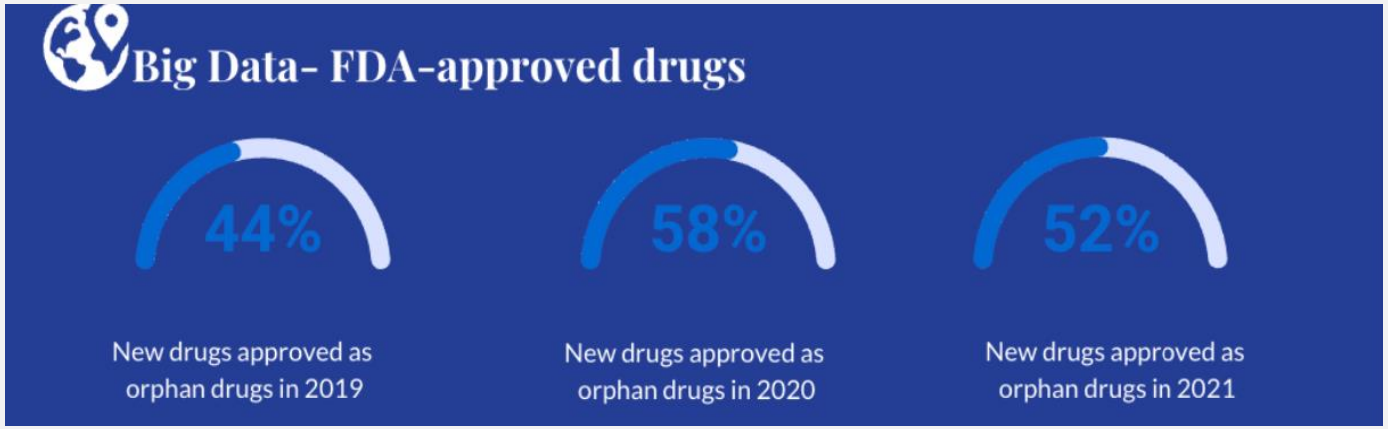
Ultra-Orphan Drug

US fewer than 6,000 patients.

UK <1 in 50,000 people in the UK.[3]



Addressing severe unmet medical needs.



1. FDA – Orphan Drug Designation: Frequently Asked Questions, 2024
2.EMA – Orphan designation: Overview, 2024
3.NICE – Highly Specialized Technologies guidance for ultra-orphan drugs, 2017
4.Orphan Pharma Report, Dimitrina Dimitrova

Orphan Market Size

$195.2 Billion[1]

60% US[2]

2x Higher CAGR[1]

1. EvaluatePharma. World Preview 2024, Outlook to 2030. 2024.
2. Grand View Research. Global Pharmaceutical Market Report 2025–2030. 2025.

Investing in Small Patient Populations
Orphan Incentives

Reaching Patients Sooner

Time to market ~5 yrs (vs. 10–12)
Patient & societal support speeds access[1].

Market Exclusivity

Long market exclusivity (7–10 years US/EU)
Strong payer acceptance for severe disease[2].

Additional FDA Support

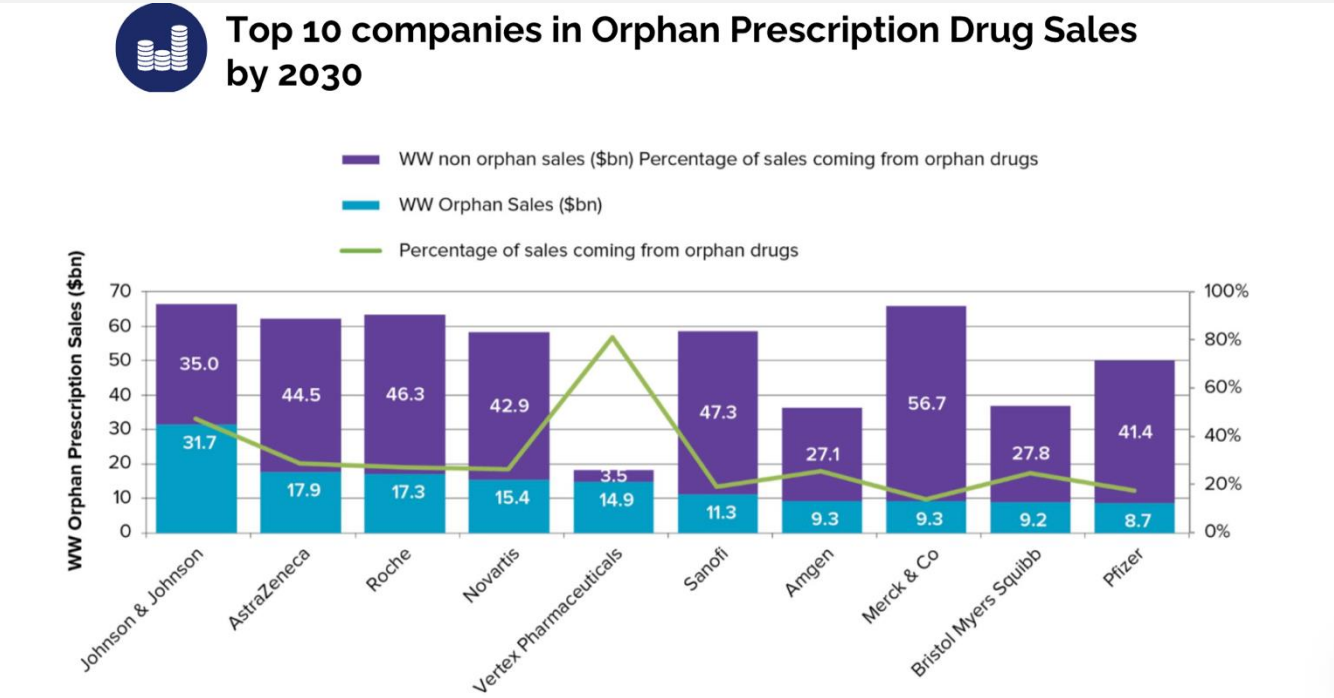
Dedicated Orphan Products Unit
FastTrack, Priority Review, waived fees[3].

Legislative Wins

Orphan Drug Act (1983)
2025 Bill expanded protections: pricing exemptions from Medicare negotiations providers[4].

1. EvaluatePharma. World Preview 2024, Outlook to 2030. 2024.
2.FDA & EMA – Orphan designation: Overview, 2024.
3.FDA – Orphan designation: Overview, 2024.
4.Jones Day. Congress Expands Orphan Drug Exemptions from Medicare Price Negotiations. July 2025.

Big Orphan Pharma



Global Pharma Revenue[1]

>50%

Sales[2]

20%

Premium Pricing[3]

17x

1. FDA – Orphan Pharma Report, 2025
2. EMA – Orphan designation: Overview, 2024
3. IQVIA Institute. Global Trends in Orphan Drug Pricing. 2022.

Active Swedish Investor in Orphan Companies

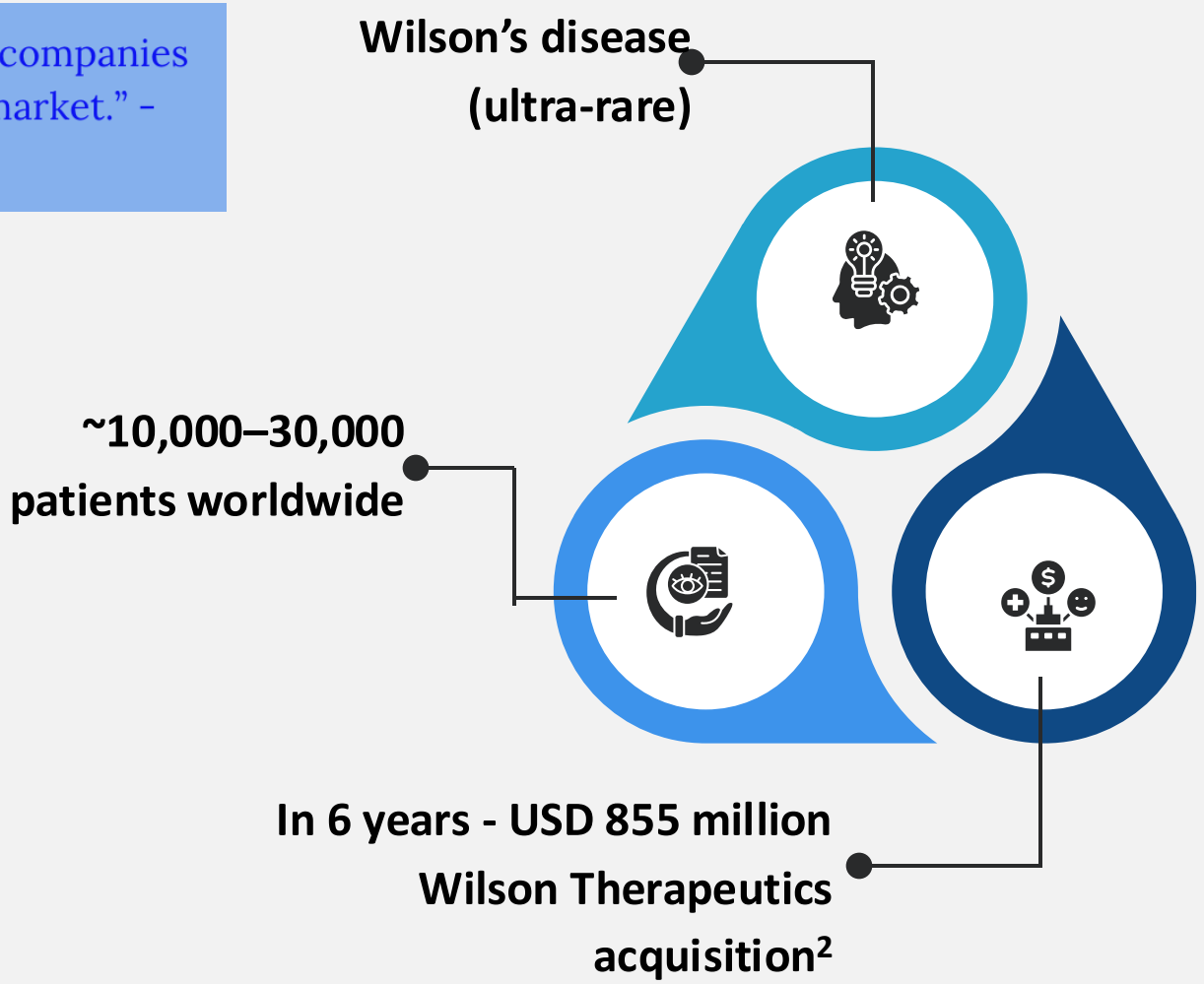
> "Exclusivity is more than IP—it's the window that gives small companies the breathing space to bring something truly meaningful to market." - Partner, HealthCap

~$86-123M

HealthCap's total orphan investments (estimates)[1]

8 Companies

WILSON THERAPEUTICS
NORDIC NANOVECTOR
oncopeptides
Vivet THERAPEUTICS
MODUS THERAPEUTICS
HEMOB Therapeutics
ultragenyx
vicore pharma



1. HealthCap. Portfolio. 2024.
2. Alexion. Alexion to Acquire Wilson Therapeutics AB. Press Release, April 2018.

The Future: Precision Medicine & Orphan Drugs

Targeted Treatments

Genomic, environmental & lifestyle data

Enhanced Diagnostics

Gender, age, disease progression, genetic makeup

3 Key Insights

Orphan drugs are the fastest-growing segment in Pharma.

Big Pharma dominance & premium pricing drive strong investment value.

They are shaping the future of precision medicine.

Thank you!

Dimitrina Dimitrova
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Access Full Report

Weblink: https://sites.google.com/view/orphandrugreport2025/home

August 27, 2025

ACD440
- An opportunity in Erythromelalgia

Märta Segerdahl, MD, PhD, CMO

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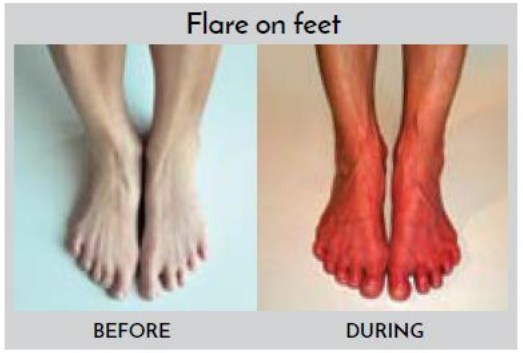
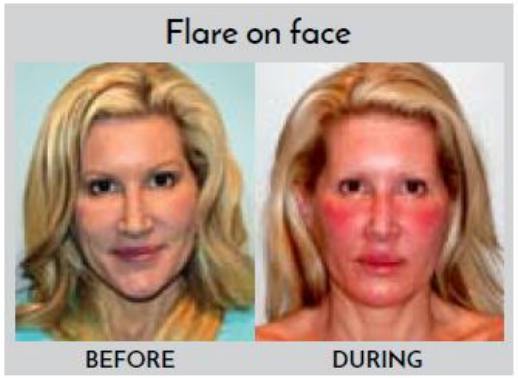
What is Erythromelalgia?

- Erythromelalgia is a **rare chronic** painful disorder - ”burning feet syndrome”
- Triad of redness, swelling and intense pain
- Pain comes in attacks, flares, **triggered by heat** or exercise
- One flare can last for an hour and up to days

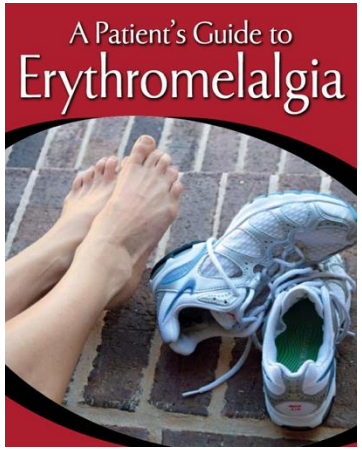


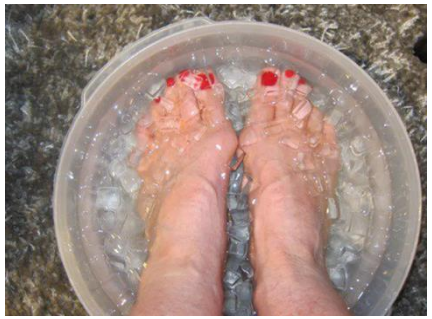


- Divided into Primary erythromelalgia, is mostly hereditary
- Secondary erythromelalgia is triggered by severe illness or by medication

How does erythromelalgia appear and how common is it?

- The prevalence of Erythromelalgia, primary and secondary together, is approximately 13/ 100,000, i.e. an orphan disease
- In the US, between 43,000 and 70,000 individuals* are estimated to have Erythromelalgia (Orphan = <200,000 patients)
- Starts in late childhood/ adolescence and up to age 25 or even later in life
  - Primary EM is mostly a **life-long, disabling** disease with many severe secondary complications
  - Secondary EM is an inflammatory microvascular disease, as a side effect to certain medications or as a co-phenomenon to different severe diseases.
- Pain attacks, flares, are felt as a very intense burning
- Mostly triggered by increased temperatures, ambient or local
- Cooling in ice water or cooling fans/ ACs are the most common reliefs





Sidiq et al, 2023 & Reed et al, 2009

Erythromelalgia – the patient story

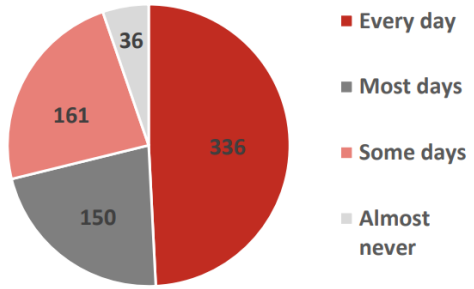
Characteristics – a 2021 patient survey by TEA*

- Symptoms in hereditary forms start by age 4-20, sporadic forms often in adult age.
- Patients are most often diagnosed by neurologists, dermatologists or rheumatologists. Rarely by primary care. >1 year from contact to diagnosis.
- Pain comes in **flares**, mostly described as **burning**, of varying duration, 1 to more than 5 hours.
- **Pain intensity** varies within individual from ”typical daily pain” as moderate (3-7/10), ”worst case pain” as **very severe** (8-10/10).
- Flares most often triggered by heat and physical stress
- Best **therapy is cooling**, which can also be damaging
- **No effective medical treatment**
- This is a life-long disease: some patient may improve over years, but most get worse over the years
- Socioeconomic impact substantial

*The Erythromelalgia Association (TEA)

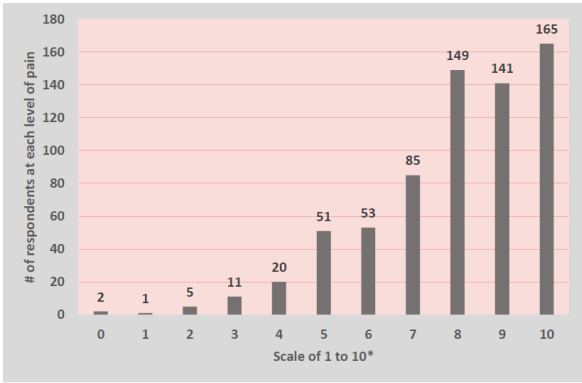
Frequency of EM flare-ups

(also known as ‘flaring’):



# of respondents for each level of frequency

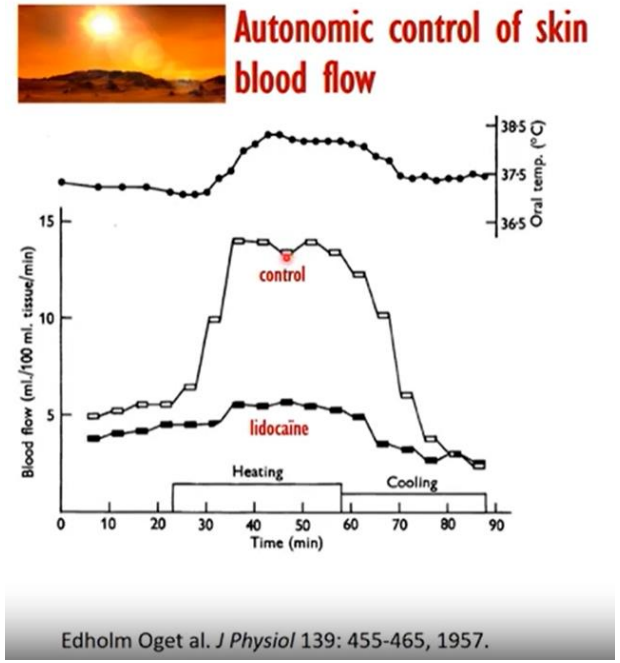
Worst case EM Pain:



The TRPV1 receptor is key in pain signalling

Professor David Julius
Nobel prize medicine laureate 2021

- The **TRPV1*** receptor was characterized in the 1990's and shown to be **central for the mediation of heat and pain.**
- The **Nobel prize 2021** was awarded to Prof. Julius for the discovery of the TRPV1 receptor



- **Heating** of the skin stimulates TRPV1 receptors and also triggers the release of the vasodilating substance from the sensory nerve endings
- Similar to capsaicin

*) TRPV1 = Transient Receptor Potential Vanilloid 1

https://www.nobelprize.org/prizes/medicine/2021/summary/

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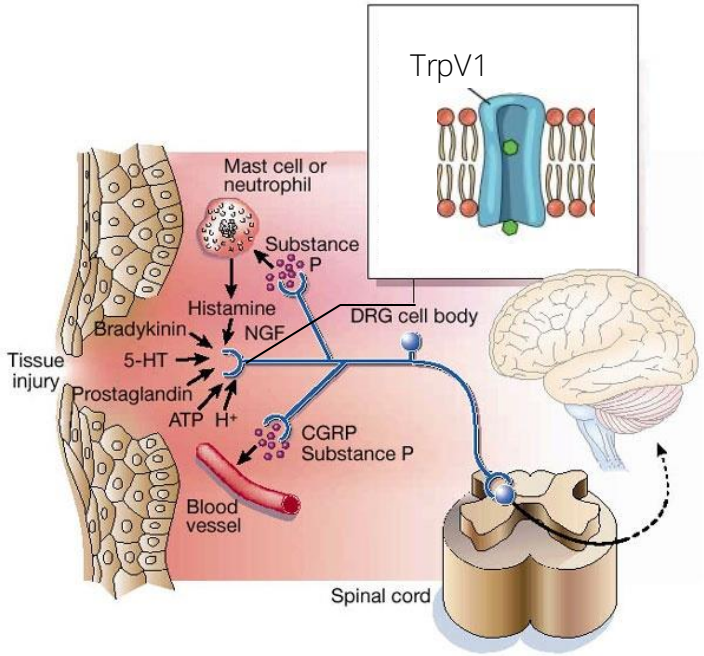
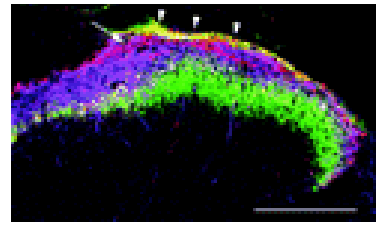
TRPV1 – Target Mechanism Central to Pain Signaling

- The transient receptor potential cation channel subfamily V member 1 (**TRPV1**), or capsaicin receptor, plays a **central role in the transduction of pain**
- It is **widely distributed** in the body, and in chronic painful conditions **TRPV1 receptors are upregulated**, as demonstrated in e.g., the skin of patients with neuropathic pain
  - Previous TRPV1 antagonists under development have been halted or changed to other topical indications, such as Novartis
  - These candidates were given orally and then challenged by systemic target effects in the form of reduced heat sensitivity, giving rise to unintended burns and scalding, or transient hyperthermia
  - By developing a **topical formulation** for ACD440, we have **circumvented** problems with **systemic side effects** such as insensitivity to heat
  - ACD440 opens up the possibility for **precision medicine** in the subpopulations of chronic pain patients with heat hyperalgesia, where current treatments are known to be ineffective, such as **erythromelalgia**



Modified from Julius & Basbaum Nature 2001:413



Tominaga et al., Neuron 1998:531

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What does an Orphan Drug Designation (ODD) add?

- ACD440 Gel is granted an Orphan Drug Designation (ODD) for the treatment of erythromelalgia by FDA
- Pre-IND meeting with the FDA took place in Q2 – FDA very supportive of our development program
- Benefits with an ODD designation
- ODD is granted for severe or life threatening diseases without currently available treatment options
  - In the US, the disorder must affect <200,000 individuals
  - In Europe, the prevalence must be ≤5/ 10,000 individuals

- Both with FDA and EMA there are several advantages, supporting the development program
- An agreement on program design and output up to NDA/ MAA; more open to some flexibility, but same requirement for efficacy
- Open to more frequent interactions along the way
- This reduces the risk – higher approval rates

ACD440 Gel effectively blocks the TRPV1 receptor reducing heat induced pain

- Two studies have been conducted
  - In healthy subjects exposed to experimental pain, ACD440 Gel reduced heat induced pain by **50%**, compared to placebo after 1 hour of application
  - In patients with chronic neuropathic pain with sensory hypersensitivity, ACD440 reduced heat induced pain by approximately **50%***

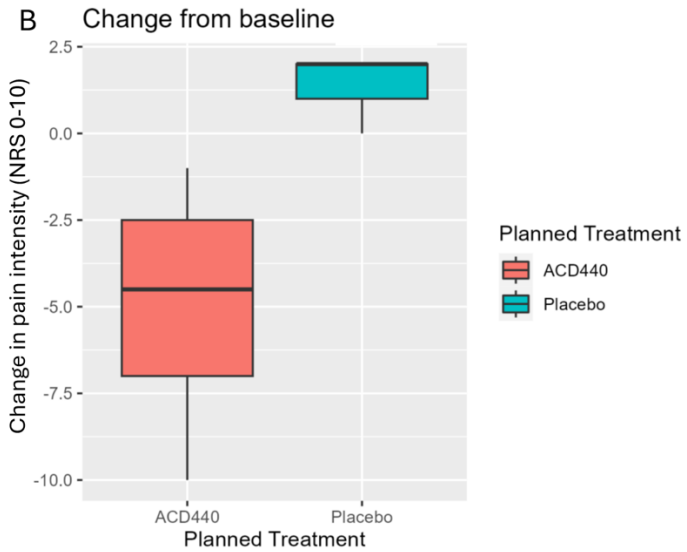
Received: 29 September 2023 | Revised: 13 May 2024 | Accepted: 25 May 2024
DOI: 10.1002/ejp.2299

EJP European Journal of Pain

ORIGINAL ARTICLE

Topically applied novel TRPV1 receptor antagonist, ACD440 Gel, reduces evoked pain in healthy volunteers, a randomized, double-blind, placebo-controlled, crossover study

M. Segerdahl[1,2] | M. Rother[1] | M. M. Halldin[1] | T. Popescu[3] | K. Schaffler[3]



DE GRUYTER Scandinavian Journal of Pain 2025; 25: 20250011

Clinical Pain Research

Adriana Miclescu, Rolf Karlsten, Ingrid Lönnstedt, Magnus M. Halldin, Märta Segerdahl*

Topically applied novel TRPV1 receptor antagonist, ACD440 Gel, reduces temperature-evoked pain in patients with peripheral neuropathic pain with sensory hypersensitivity, a randomized, double-blind, placebo-controlled, crossover study

30% reduction in pain intensity is considered clinically relevant in chronic pain

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Benefits with Orphan Drug Designation

In general, smaller programs, lower risk and shorter time to market

FDA

- Reduced cost for clinical trials – smaller programs
- Tax credits for qualified clinical trials
- No fee for marketing submission
- Exempt from Medicaid price negotiations

- Orphan drug market exclusivity for 7 years
- Pediatric study data adds 6 months to existing exclusivity or patent protection

EMA

- Free and frequent scientific advice for SMEs
- Waived fees for marketing submissions and inspections

- Orphan drugs receive 10 years of market exclusivity for each orphan-designated indication
- Pediatric study data adds 2 years for orphan-designated conditions

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Going forward from here

- After having received the supporting feedback from the FDA, and been granted the ODD, we will now continue the preparations for a full development program in Erythromelalgia
- We are focusing on optimizing the program design in all aspects
- Aiming for the shortest time to market and patients
- Pursuing Business development activities looking for the best partner to take this asset to commercialisation

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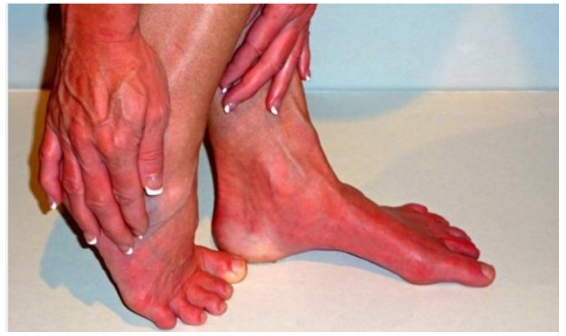
In summary



- Erythromelalgia is a rare and chronic disease of all ages
- Pain in Erythromelalgia is triggered by heat
- ACD440 Gel is effective in reducing heat induced pain
- The granted ODD shows that the FDA supports the rationale for the development of ACD440 in erythromelagia
- Orphan designation reduces development costs
- Orphan designation gives substantial market exclusivity

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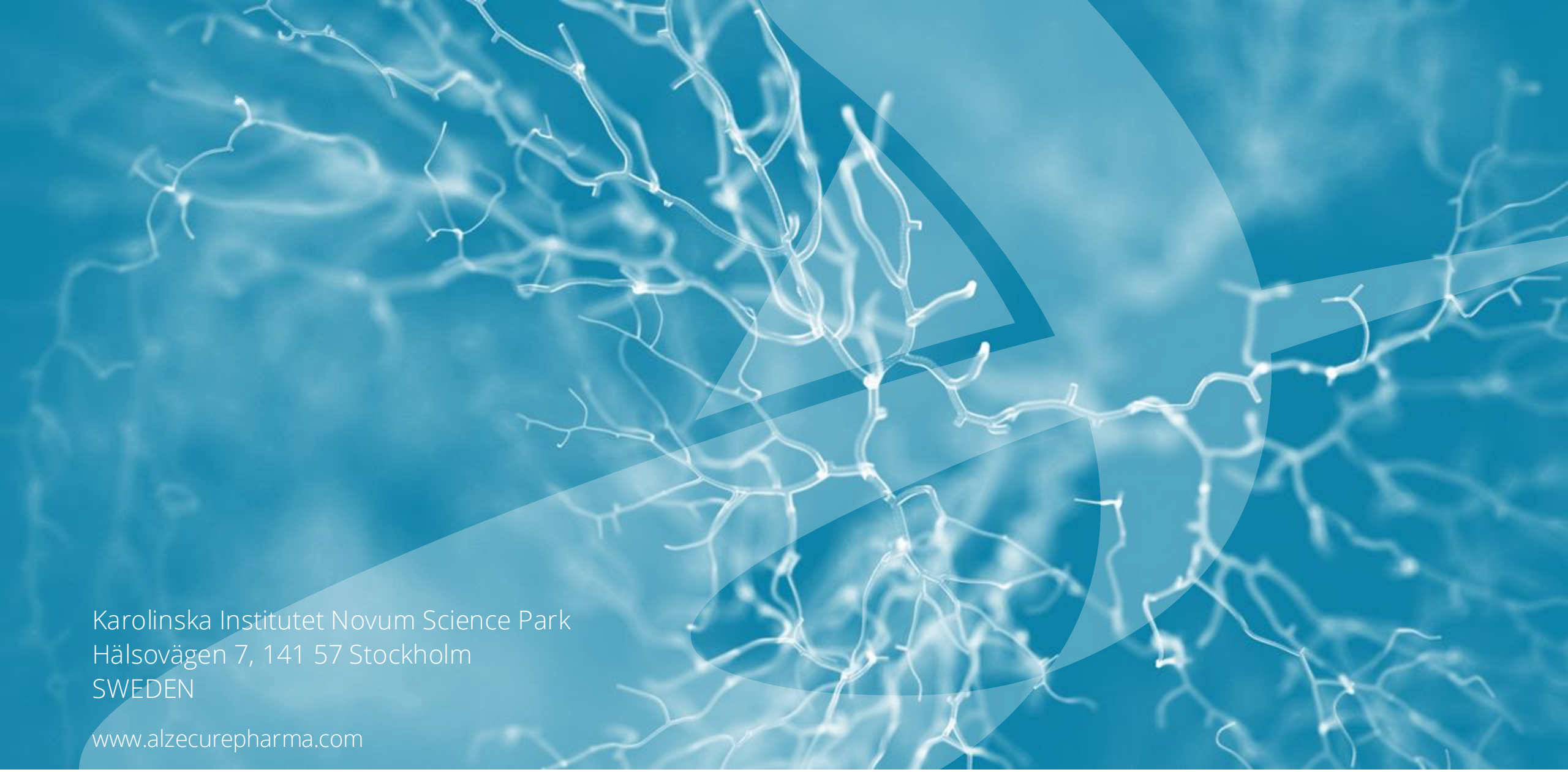

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Q&A session

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Q&A Session

EXPERIENCES

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CMO
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› Broad and extensive experience in global development and clinical operations Pharma industry within CNS and Pain
› Education: M.D., Karolinska Institute, Stockholm, Sweden

from GRÜNENTHAL, Karolinska Institutet, AstraZeneca, Lundbeck

Dimitrina Dimitrova
B.Sc, Master

› Experience in business development and consulting from the United Kingdom and the Nordic life science sector
› Education: B Sc in Molecular Biology from University of Aberdeen & Master student at Karolinska Master program in Bioentrepreneurship

University of Aberdeen, fios GENOMICS, Karolinska Institutet

Martin Jönsson
CEO

› Extensive experience in various senior management positions with >20 years of international experience in the industry
› Education: MSc in BA from Lund University, Ottawa, Canada & Freiburg, Germany

Roche, Lunds Universitet, FERRING PHARMACEUTICALS

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Final Remarks

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Key Take Home Messages

- The Orphan Drug Market grows rapidly – **twice as fast** as common drugs - and with **prices** which in general are **17 times higher** than for common drugs
- Orphan Drugs is **highly attractive** for both Big Pharma & Institutional investors
- AlzeCure's Orphan Designation for ACD440 in Erythromelalgia represents a **major opportunity** for the company, with expected **shorter time to market**
- The **unmet medical need in Erythromelalgia** is major, and today there are now approved drugs for the indication
- AlzeCure has received **positive feedback from the FDA** for a potential registration study in Erythromelalgia with ACD440
- AlzeCure's main strategy is to **outlicense ACD440**, which we now are working on, while preparing for the study

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Thank You for attending

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