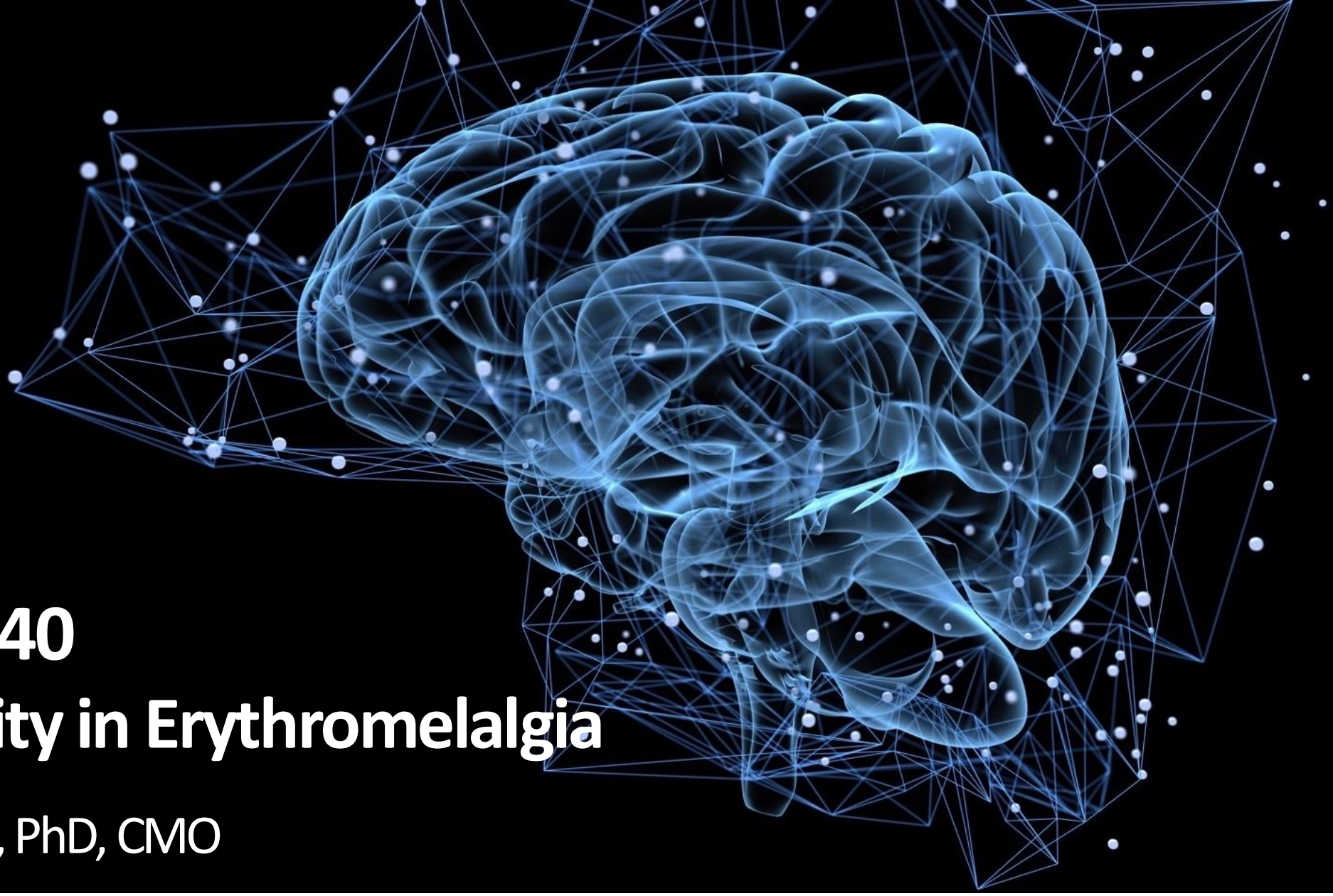
August 27, 2025



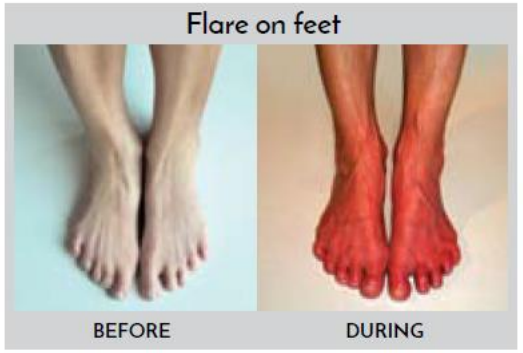
Painless ACD440
- An Opportunity in Erythromelalgia

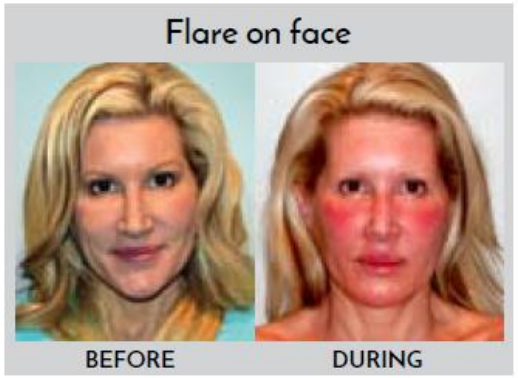
Märta Segerdahl, MD, PhD, CMO

AlzeCure

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

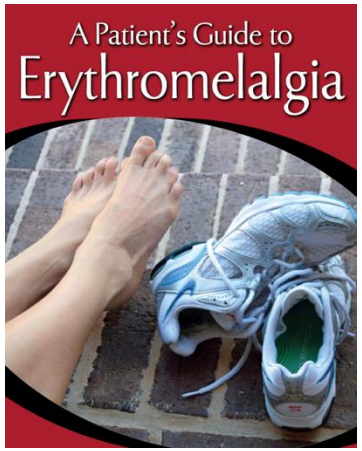


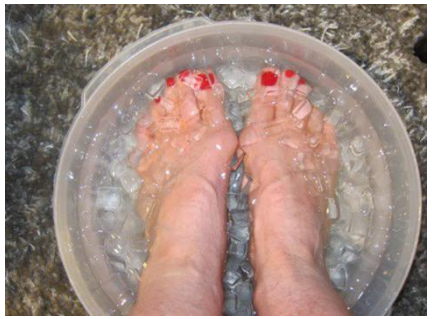


- Divided into Primary erythromelalgia, is mostly hereditary
- Secondary erythromelalgia is triggered by severe illness or by medication

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

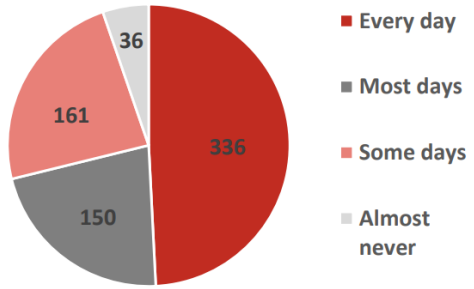
Characteristics – a 2021 patient survey by TEA*

- 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)

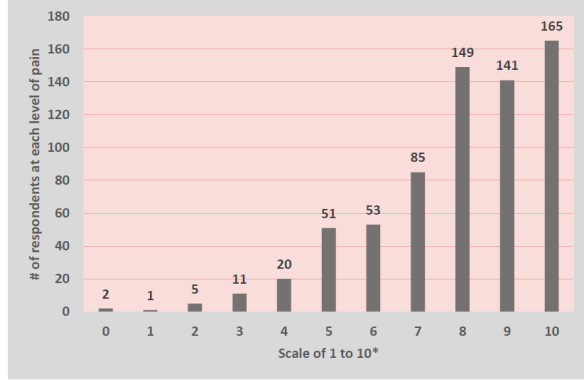
Frequency of EM flare-ups

(also known as ‘flaring’):



# of respondents for each level of frequency

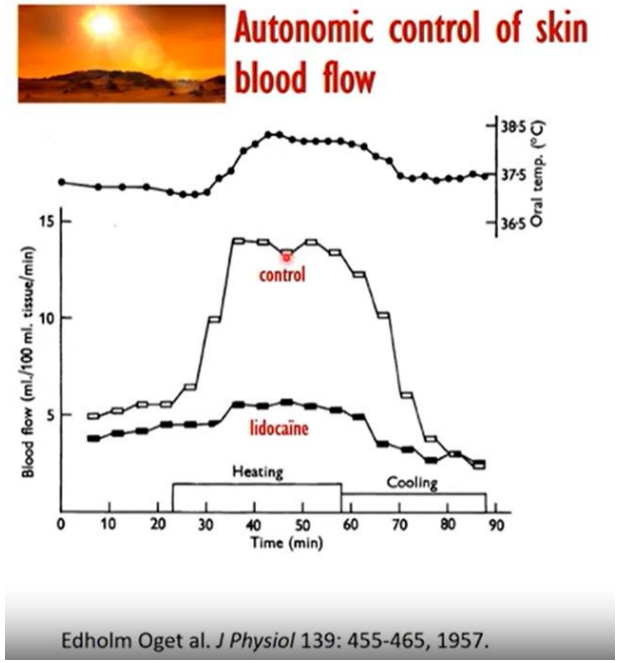
Worst case EM Pain:



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

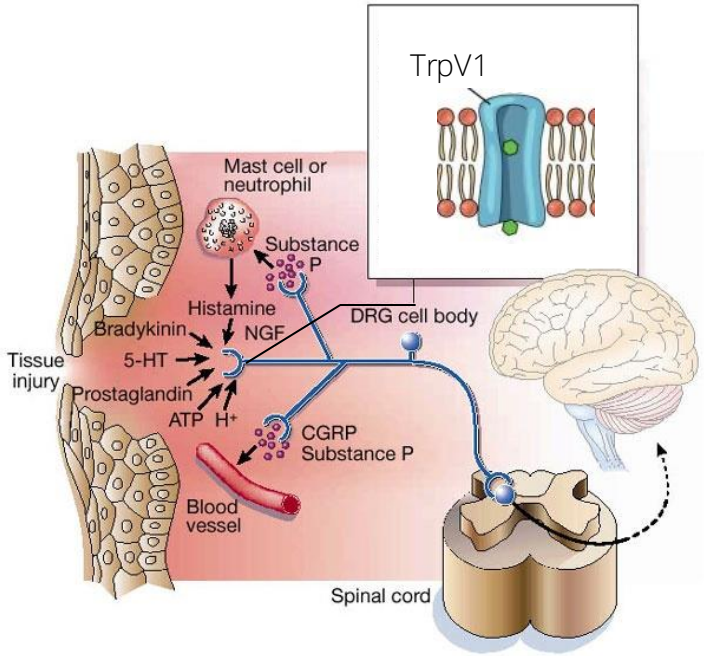
*) TRPV1 = Transient Receptor Potential Vanilloid 1

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

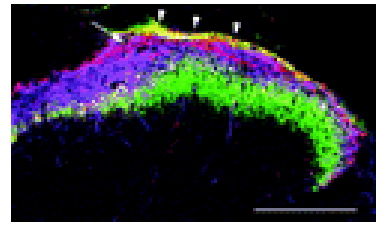
AlzeCure

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

AlzeCure

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%***

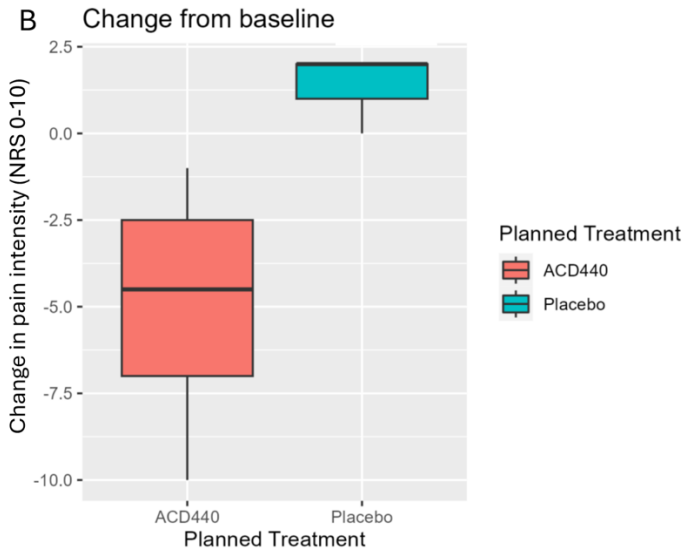
Received: 29 September 2023 | Revised: 13 May 2024 | Accepted: 25 May 2024
DOI: 10.1002/ejp.2299

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

AlzeCure

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

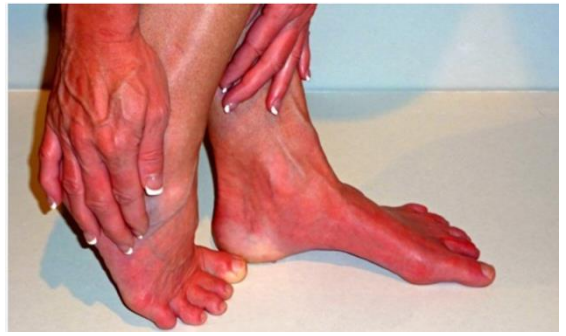
AlzeCure

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

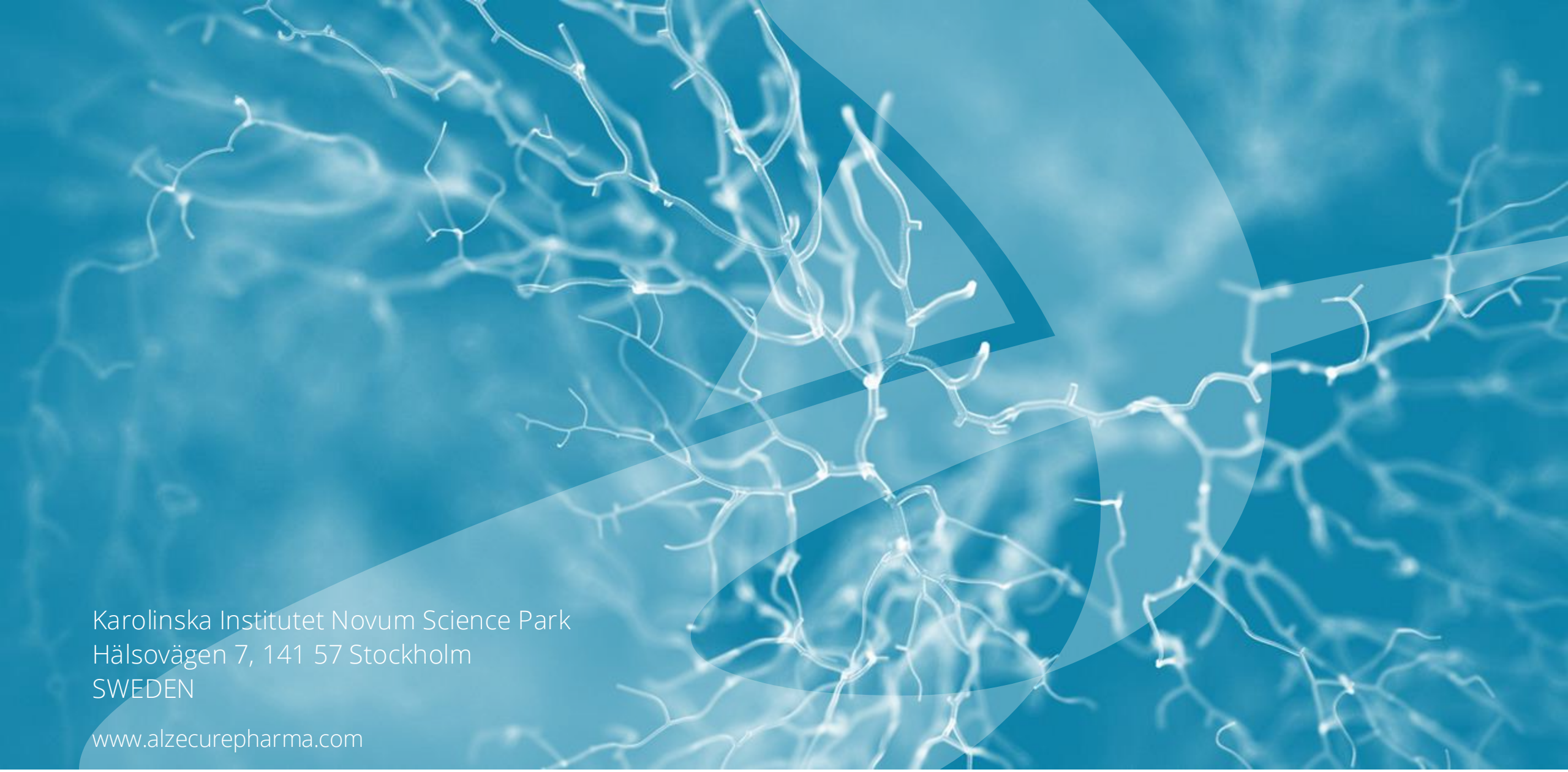
AlzeCure

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

AlzeCure



Karolinska Institutet Novum Science Park
Hälsovägen 7, 141 57 Stockholm
SWEDEN

www.alzecurepharma.com

AlzeCure