NEUROCHLORE

PAR YEHEZKEL BEN-ARI

# Treating autism spectrum disorders (ASD) with NKCC1 inhibitors

NEUROCHLORE
Prof. Yehezkel BEN-ARI
ben-ari@neurochlore.fr
https://www.neurochlore.fr/
Marseille, France

# PURSUING A BREAKTHROUGH IN ASD CARE

## THE CURRENT ASD TREATMENT LANDSCAPE IS INADEQUATE

There are **no FDA-approved therapies addressing the core symptoms of Autism Spectrum Disorder**. Current treatment approaches focus on managing associated symptoms like irritability and hyperactivity but leave the underlying challenges of social communication and repetitive behaviors unaddressed. This gap leaves patients, families, and healthcare systems struggling to cope with the diverse needs of those on the spectrum.

## ASD IS A GROWING GLOBAL HEALTH CHALLENGE

ASD affects over **28 million people globally**, with prevalence rates rising sharply. In the United States alone, **1 in 36 children is diagnosed with ASD**, and the **direct and indirect costs of care exceed $270 billion annually**. As awareness and diagnostic capabilities improve, the number of identified cases continues to grow, placing immense pressure on healthcare systems to meet these unmet needs.

IT IS TIME TO TRANSFORM ASD CARE. WE NEED TO SHIFT THE PARADIGM BY FOCUSING ON INNOVATIVE SOLUTIONS THAT ADDRESS THE CORE SYMPTOMS OF ASD WHILE REDUCING THE ADVERSE EFFECTS ASSOCIATED WITH EXISTING TREATMENTS. NOW IS THE TIME TO DELIVER TARGETED, EFFECTIVE THERAPIES THAT IMPROVE QUALITY OF LIFE AND REDEFINE STANDARDS OF CARE FOR INDIVIDUALS WITH ASD AND THEIR FAMILIES.

# NEUROCHLORE

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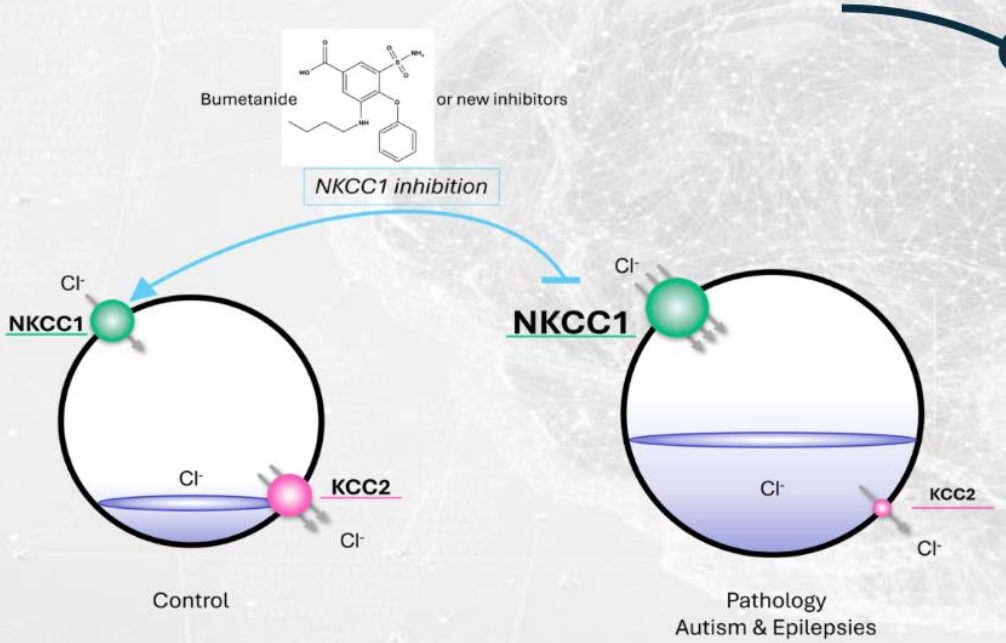
MEET NEUROCHLORE'S ASD SOLUTION: AT THE CUTTING EDGE OF AI POPULATION IDENTIFICATION AND USING NKCC1 INHIBITORS TO ATTENUATE BRAIN DISORDERS.

# NKCC1 inhibitors, a ground-breaking approach to autism treatment




An innovative therapeutic product for the treatment of autism in children and adolescents (between 2 and 18 years old).

The equilibrium between NKCC1 (importer) & KCC2 (exporter) regulates GABAergic inhibition & cell volume.

NKCC1 activity is increased (and KCC2 activity decreased) in Autism, epilepsies, Fragile X, brain trauma, and Huntington disease (Ben-Ari TINS 2021).

Inhibiting NKCC1 activity restores GABAergic inhibition & has been shown to attenuate the severity of Autism, Fragile X & epilepsies (Savardi et al TIPS et al 2021, Ben-Ari TINS 2021).

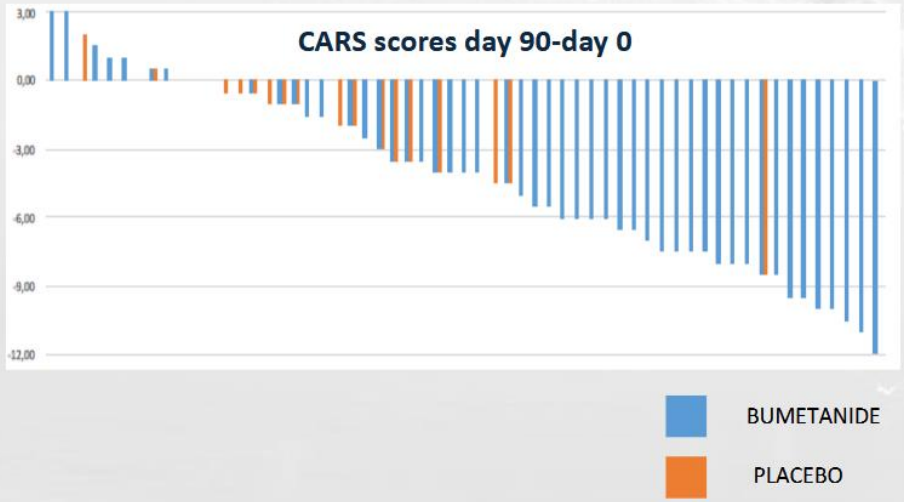
# Neurochlore is adopting a dual pathway approach, ensuring the chances of success

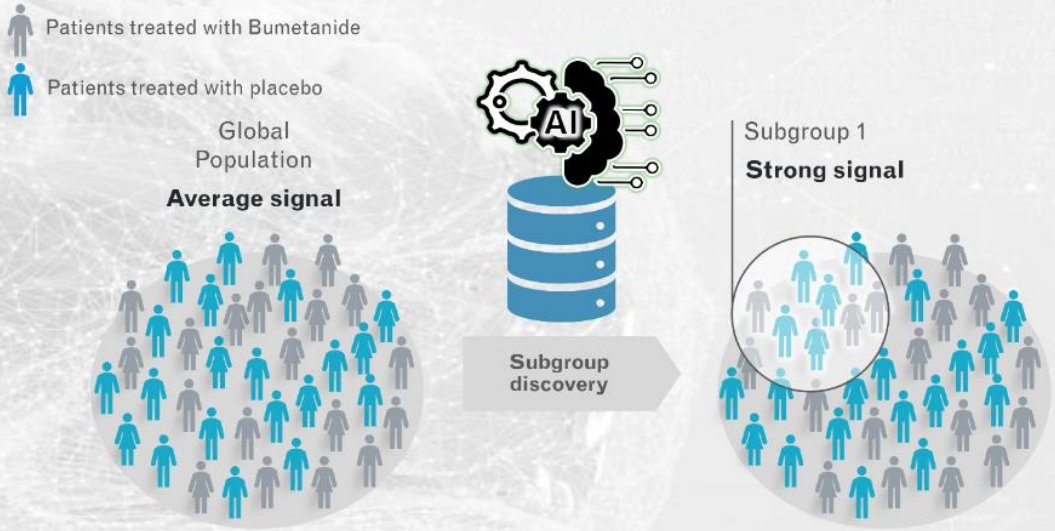

Neurochlore is adopting **a dual approach** to revolutionizing Autism Spectrum Disorder (ASD) treatment by focusing on both the **second-generation application of bumetanide** and the development of patented novel NKCC1 inhibitors. The second-generation strategy leverages bumetanide's well-established safety and efficacy profile, supported by extensive clinical data, while using advanced analytics to identify responsive subgroups, making the treatment more targeted and impactful.

Simultaneously, the **development of novel NKCC1 inhibitors** offers a pathway for breakthrough innovation, targeting broader patient populations with enhanced efficacy and safety profiles. Pursuing both strategies ensures a balanced pipeline that combines near-term commercialization potential with long-term growth opportunities, making Neurochlore's portfolio both scientifically robust and commercially attractive.

# A phase 3 exploring bumetanide as a second generation treatment is likely to succeed

- Bumetanide shown to attenuate autism severity in our 2 trials; and in 7 other Phase 2 trials (>1030 children) performed in many different countries (e.g. NCT01078714, NCT03156153, NCT04766177, NCT03715166, NCT03715153)
- Bumetanide ameliorates visual interactions, identification of emotive figures and functional MRI alterations.
- A Phase III trial using as a principal criterion CARS2 (a sum of 15 different items) failed because it did not consider the heterogeneity of autism…
- …but we learnt that bumetanide responders can be predicted from EEG or immunological parameters, suggesting **different biological features of responders and non-responders.**



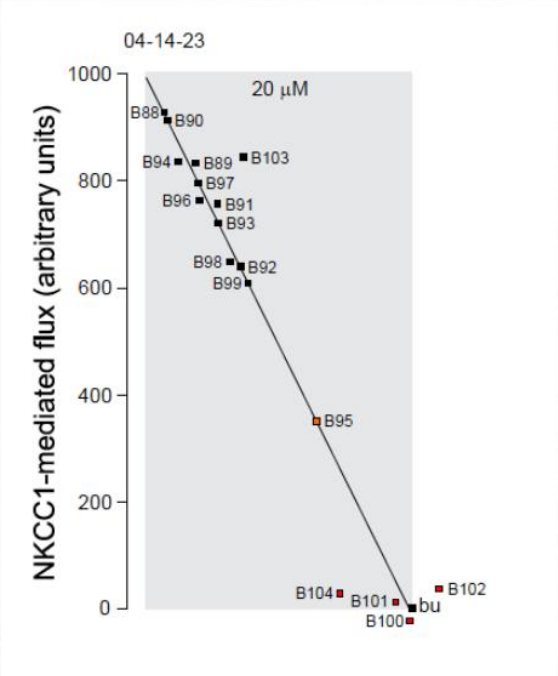




- We re-analysed all Phase III data using multiple items of rating subscales of the scales used to determine autism severity (SRS (65 items), CARS (15 items), DSM (4 items)).
- **Using machine learning**, we succeeded to identify **20% to 40% responder subgroups** relying on dual combinations of rating subscales

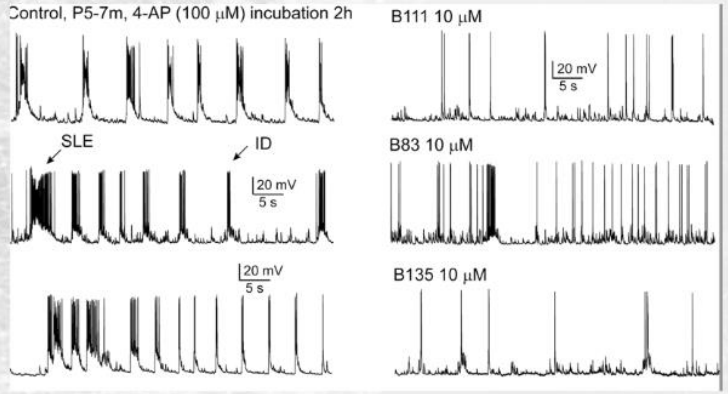
A PHASE III RELYING ON THESE INCLUSION CRITERIA WILL MOST LIKELY SUCCEED.

PATENT PROTECTION: "Treating clinically identified subpopulations of children & adolescents with Autism" with inclusion parameters restricted to the 30-40% of children having special clinical combination of 2 sub-parameters of conventional criteria –SRS, CARS, DSMV – that we have identified by machine learning.

# We are well advanced in our pursuit of novel inhibitors for ASD treatment




We have synthetized over 120 novel inhibitors some with 75 to 120% efficacy when compared to Bumetanide (US application number 18/361,284)




Our novel inhibitors reinforce GABAergic inhibition in rodent hippocampal brain slices thereby also attenuating seizures and hyperexcitability

PATENT PROTECTION: "We have a worldwide patent on treating children with autism with Bumetanide valid until January 2026"

A novel patent on treating a subpopulation of children with autism (having the clinical criteria selected in our machine learning process from the failed Phase III responders) has been applied for. This patent determines inclusion criteria for phase 2/3 relying on the parameters determined by our Machine learnng analysis of the phase 3

# ASD is affecting over 28M people globally, the US has one of the highest prevalence rates

ASD appears to be more prevalent in males than females in a ratio of 3:1

Approximately 1/100 children are diagnosed with ASD around the world. Prevalence is higher in the US, with 1 in 36 8 year olds likely to have ASD

Direct and indirect costs of caring for ASD suffers in the United States are estimated at over $270 billion

The cost of education, health care, and other lifelong services for an autistic patient varies from $1.4 million to $2.4 million per year

CURRENT STANDARD OF CARE NECESSITATES A COMPLEX, INDIVIDUALISED APPROACH TO DEAL WITH THE HETEROGENEITY OF ASD, WITH NO CURATIVE TREATMENT AVAILABLE. There is currently no single or combination of treatments that is able to reverse ASD. The standard of care for ASD involves a comprehensive, individualized approach aimed at maximizing functioning and quality of life. Effectiveness varies from person to person. Early treatment is critical—starting as soon as possible after diagnosis can significantly reduce challenges and help individuals build on their strengths and acquire new skills. In some cases, early intervention leads to such progress that children may no longer meet the criteria for being on the autism spectrum as they grow older. However, **there remains significant unmet needs in ASD care and treatment.**

# Market perspective of Neurochlore

ASD is a **highly heterogeneous disorder**, and while there are numerous treatment options, the **lack of FDA-approved drugs for core symptoms** represents a crucial gap in therapeutic options. This, coupled with the **adverse events linked to current treatments** for irritability, demonstrates **a significant opportunity for innovation in this space.**

The global ASD treatment market was valued at $34.1 billion in 2023 and is projected to grow at a CAGR of 4.8% from 2024 to 2032, potentially reaching $52 billion by 2032. Looking specifically at the sales for the 8 major markets of the US, Germany, France, Italy, the UK, and Japan the market potential is significant with an estimated increase in sales of over 300% across a ten-year period from 2021 to 2031. Across these countries the US accounts for the majority of total global sales given the high prevalence and high costs for treatment.

Treatment market valued at **€34** billion in 2023

Growth in ASD treatment has been strongly driven by improvements in diagnostic tools. As these technologies advance, they allow for earlier and more accurate identification of ASD, resulting in an increase in diagnosed cases. This, in turn, has led to a higher demand for treatment options. Additionally, greater awareness among healthcare providers and parents, along with better diagnostic capabilities, has prompted more people to seek screenings and receive diagnoses for ASD, further contributing to market expansion.

**Awareness** Leads to more diagnoses

The ASD market is composed of medications that address symptoms like irritability and hyperactivity, many of which are generics. Two of the most commonly prescribed FDA-approved drugs for managing irritability in ASD are Janssen's Risperdal (risperidone) and Otsuka's Abilify (aripiprazole).

Available treatments however associated with concerning side effects, including extrapyramidal symptoms (EPS), metabolic changes, nausea, drowsiness and weight gain.

A significant unmet need remains for treatments targeting the core symptoms of ASD, safely and effectively.

Current **Treatments** Have significant side effects

**The competitive landscape: no direct competing solutions on the market (yet).**

Indirect competitors include:

- Antipsychotics (Otsuka Pharmaceutical's Aripiprazole; Janssen's Risperidone; Sanofi's Chlorpromazine hydrochloride and Periciazine; Binnopharm's Haloperidol)
- Anticonvulsant (Sandoz' Sulpiride; Sunrise Remedies' Levetiracetam)
- Sleep controls (Algen Healthcare's melatonin)

# Stalicla, a Swiss company, is also pursuing NKCC1 inhibitors for ASD treatment. Its financial track record shows fundability in this space

Stalicla's three pipeline products:

- STP1 has completed phase 1b trials showing safety and tolerability, improvements in brain function for executive function and memory and improved autism severity scores. STP1 is being progressed into Phase 2 trials in 2025
- STP2 (a stabilized synthetic form of sulforaphane) is being advanced as a precision medicine treatment candidate for a subgroup of patients with ASD called Phenotype 2. Phase 1 data is currently being evaluated to support phase 2 trials
- STP7 is the most clinically advanced negative allosteric modulator of the glutamate receptor 5 (mGluR5 NAM). It has been administered for up to 2 years in over 1800 patients in Phase 2 trials and STALICLA will advance it in two formulations, 100mg MR for a subgroup of patients with ASD'

**Our points of difference**

- Neurochlore targets children not adults – a major population of interest as **early treatments are pivotal**
- Stalicla identifies subpopulations based on a list of criteria (EEG and blood measures) that have been shown to fail
- The Stalicla molecule has failed to show a statistically significant action (see Erikson et al 2024 biomedicine)
- Yet to be proven that STP1 provides additional benefit to Bumetanide, casting doubt as to its relevance to the treatment
- 9 successful phase 2 Bumetanide trials in France, China, England, Holland, Tunisia, Egypt and Iran). Stalicla have none at this stage

# Strong track record

Highlights deal potential in this space

| Deal type | Deal stage | Deal value | Description |
|---|---|---|---|
| 16 Jan 2024 | Venture Financing | $17.4M | Completed the first closing of its Series B financing round, securing $17.4 million for its neurodevelopmental disorder-specific precision medicine platform, the two assets quoted are STP1 and STP2 which are in clinical development. |
| 9 Jan 2023 | Licensing Agreement | $270M | Stalicla entered into an exclusive in-licensing agreement with Novartis to develop mavoglurant as a treatment for substance-use disorder and neurodevelopmental disorders. |
| 10 Oct 2022 | Licensing Agreement | $187M | Evgen Pharma a clinical stage drug development company developing sulforaphane-based medicines for the treatment of cancer and other indications, licensed the global rights for lead asset SFX-01 in neurodevelopmental disorders and schizophrenia to Stalicla. |
| 3 Feb 2020 | Venture Financing | $8M | Second tranche of series A funding from a consortium of Swiss, European and US private equity and Biotech experienced investors, for the development of its lead ASD precision medicine candidate - STP1 - into Phase Ib clinical trials and its second program, STP2, into IND enabling pre-clinical studies, and to support the scale-up of its first in class neurodevelopmental disorder focused discovery platform |

# Additional benchmark deals display strong exit potential for Neurochlore

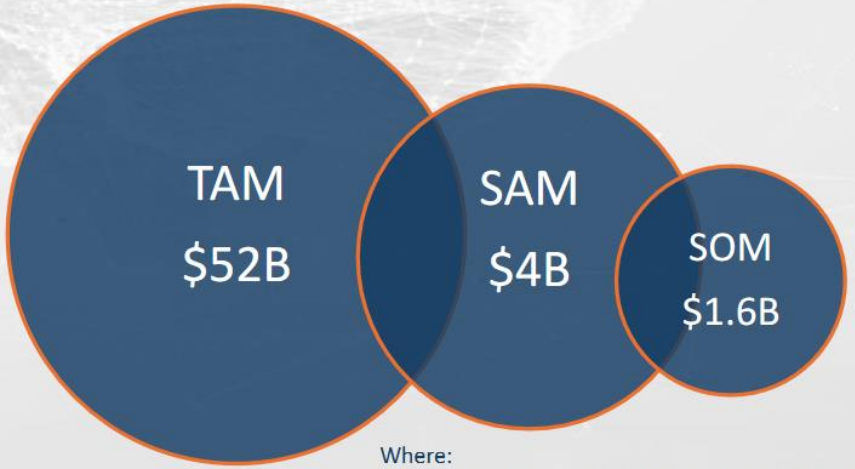
| Licensor/Target | Licensee/Acquirer | Date | Deal type | Deal stage | Deal value | Description |
|---|---|---|---|---|---|---|
| Monument Therapeutics Ltd | The Forster Foundation | 15 Oct 2024 | Minority Acquisition (Europe) | Preclinical | $2M | Monument (a precision neuroscience company), invested over $2M for minority equity in the Forster Foundation. This investment builds on equity and non-dilutive funding announced in April 2024 and supports the clinical development of MT1988, a novel treatment for the cognitive symptoms of schizophrenia and ASD. |
| Zynerba Pharmaceuticals Inc | Harmony Biosciences Holdings Inc | 11 Oct 2023 | Acquisition (North America) | Phase III | $200M | Harmony, a pharmaceutical company that develops and commercialises therapies for patients with neurological diseases, acquired Zynerba Pharmaceuticals Inc, a leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for neuropsychiatric disorders, including ASD and Fragile X syndrome (FXS). |
| Yissum Research Development Company of the Hebrew University of Jerusalem Ltd | Beyond Air Inc | 15 June 2023 | Licensing Agreement (Middle East and Africa) | Preclinical | Unknown | Deal for Beyond to license the rights for multiple neuronal nitric oxide synthase (nNOS) inhibitor candidates, under development for the treatment of autism spectrum disorder and other neurological conditions. |
| Kinoxis Therapeutics Pty Ltd | Boehringer Ingelheim International GmbH | 5 May 2023 | Licensing Agreement (Asia-Pac) | Preclinical | $181M | Kinoxis, a clinical-stage biotechnology company which develops a variety of novel therapeutic small-molecule compounds for the treatment of neurological and psychiatric disorders, entered into a strategic partnership and licensing agreement with Boehringer for the development of first-in-class oxytocin targeting autism spectrum disorder and social anxiety disorder. |
| Italian Institute of Technology | IAMA Therapeutics Srl | 31 Jan 2022 | Licensing Agreement (Global) | Phase I | Unknown | IAMA Therapeutics, a pharma focusing on emerging advances in drug discovery and neurobiology is building a next-generation neuroscience pipeline, and entered into agreement with for an exclusive, worldwide license to **research, develop, manufacture, and commercialize a class of selective NKCC1-inhibitors**. |

Recent deal making activity suggests there is **diverse investor appetite** for innovative breakthroughs **at early stages in ASD.**

# The unique value proposition of Neurochlore...

- Treat the core symptoms
- Minimal side effects
- Low cost of production
- Non-toxic, liquid formula
- Exclusive licenses

## ...ensures significant penetration of a $52B market by 2031




Where:
- TAM = world-wide market for ASD treatments
- SAM = Initial focus on **US** and **European** markets
- SOM = 30 - 40% predicted penetration

# Neurochlore's distinguished leadership and experience sets it apart

## Our CEO & Founder

**Prof. Yehezkel Ben-Ari** has extensive knowledge in neurobiology, physiology, and biophysics.

- He has made seminal discoveries on brain developmental sequences, epilepsies and anoxic insults. He has 5 decades of research on ionic currents in development health and disease and has discovered the well know GABA developmental shift that has been preserved throughout evolution.
- He is the author of >500 scientific publications and widely cited by others with close to 60,000 citations (ranking as the 5th French neuroscientist and amongst the 200 most quoted neuroscientists around the world).
- He directed a major INSERM unit in France, and founded and directed the Mediterranean Institute of Neurobiology.
- For his discoveries, he has also received many important awards including the INSERM Grand prix (the most prestigious French biomedical award) and the European and US grand prix of the Epilepsy foundations.

## Partners and network

As a small company we access specific knowledge from our industry partners, while also having a strong advisor/consultant basis available through our excellent international network. Of particular mention are:

- **Prof. Eric Delpire (Vanderbilt University, US)** is the world expert regarding NKCC1 that he has contributed to its cloning, structure in crystallography and the effects of knocking it out in mice. He has extensive experience in human cell lines preparations to investigate the structural function of NKCC1.
- **Dr. Denis Ravel** is the founder of Initial R&D Consulting that specialises in (pre)clinical development of small biopharmaceutical molecules. He has more than 25 years of experience in pharmaceutical R&D (Servier, Genset-Merck-Serono, and Diatos).
- **Dr. Pascal George**, accomplished his industrial career at Synthelabo (1978-1999), Sanofi-Synthelabo (2000-2005), Sanofi-Aventis (2005-2010), as the global Director of CNS medicinal chemistry. His most known achievements are the design of Zolpidem (aka, Stilnox and Ambien) a blockbuster sleep disorder drug.
- **Servier Group**, French pharmaceutical manufacturing partner.
- **Expert patent companies, including ICOSA, Mundel, and local finance experts /lawyers such as P Marenghi** are dedicated to strengthen our development
- **Expert accountants - IODA and auditors** ensure all our financial expenditures are in check

# Our business strategy adopts a common approach for the Life Sciences industry

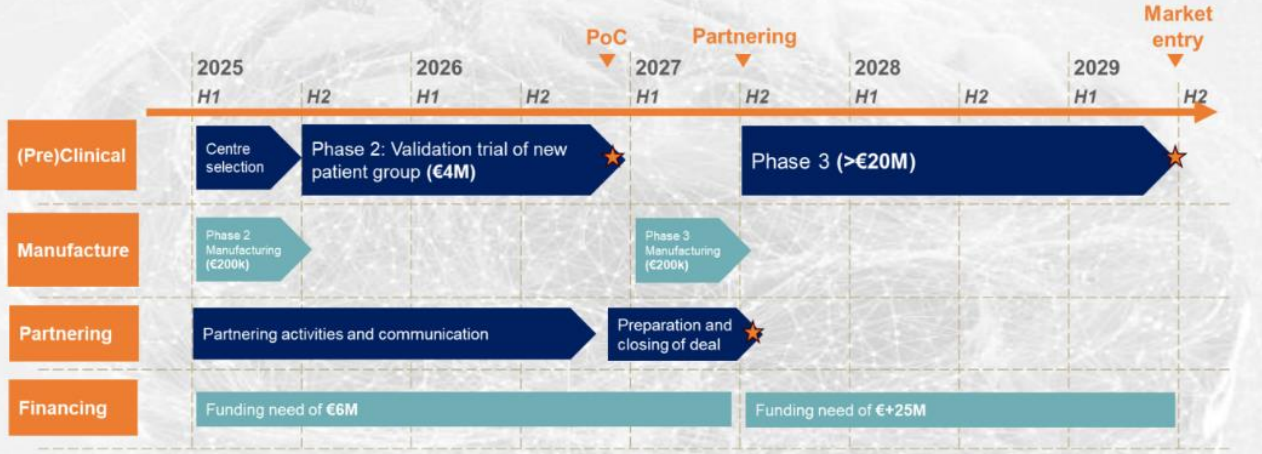

To bring our NKCC1 treatments to market and ensure widespread implementation by healthcare professionals and their patients, we aim to follow a common strategy in the Life Sciences industry by partnering with established companies who have the resources and infrastructure to realize this. The most feasible and attractive option is to enter a strategic partnership through an out-licence agreement or an acquisition.

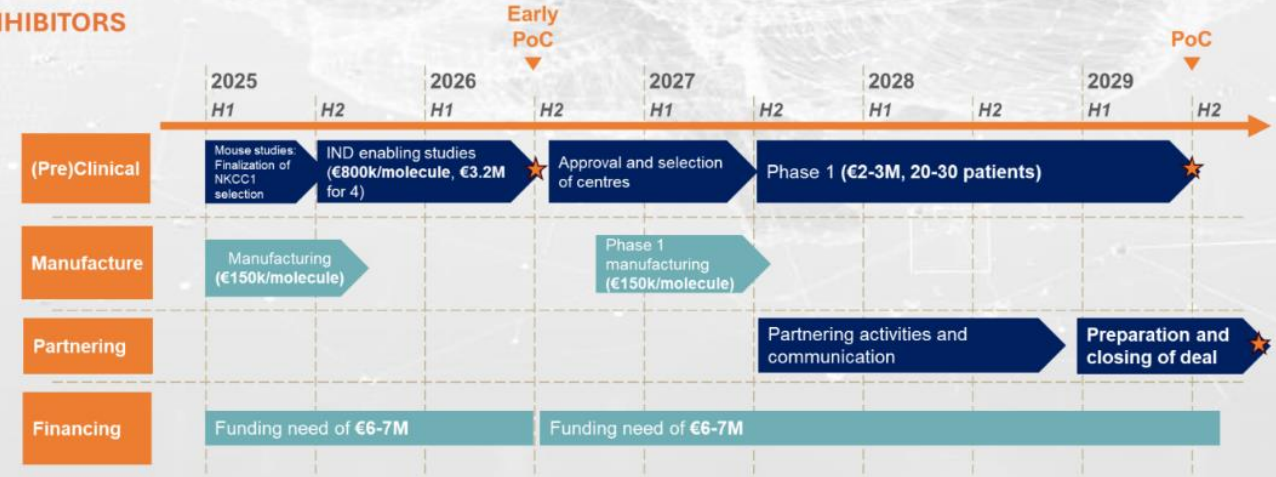
**Out-licensing** to a pharmaceutical partner for Phase 3 trials—or earlier—offers a strategic pathway to accelerate development while optimizing resource allocation. This model de-risks late-stage development for Neurochlore by leveraging the partner's expertise in clinical trial management, regulatory navigation, and global commercialization. Large pharma benefits from accessing an innovative asset with strong clinical potential, thus diversifying their pipeline without bearing the full cost of early-stage. This approach, enables faster time-to-market.

**Acquisition** In the life sciences sector, acquisitions are a common strategy alongside out-licensing partnerships. In this way the acquiring company can incorporate our innovation into their portfolio without directly investing in the initial R&D. Neurochlore would either be fully integrated into the new parent company or operate independently as a subsidiary.

**Investors are currently being sought to finance Phase II clinical validation.**

# We will fully transition into a clinical-stage company working towards commercial partnership for both programs


## Out-licensing

can be for one or both programs.

# Financial projections based on a clear funding need

Cost Estimations 2025-2028:

- €5M Phase II validation (in 2 to 3 French centres)
- In addition, €2M local fees (salaries, operation fees, patent experts, lawyers, EMA and FED discussions  etc.)
- Once results are validated, a large Phase III will be pursued throughout Europe and the US

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