23 de octubre de 2024

# CTH120, first-in-class neuroplasticity modulator for neurodevelopmental disorders

CONNECTA THERAPEUTICS

*Jordi Fàbrega*

MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
AGENCIA ESTATAL DE INVESTIGACIÓN
MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española
farmaindustria

# Content

# CONNECTA Therapeutics

## Developing Innovative treatments to respond to unmet CNS medical needs



**2019** Founded as a Spin-off of Prous Institute for Biomedical Research

**2020** Initial Seed VC Round secured

**2021** Launch of nonclinical studies, CTH120

Orphan drug status for CTH120 in FXS (nr EU/3/21/2432)

**2022** Favourable nonclinical results, CTH120

**2023** Phase I for FXS leading program, CTH120

Extension to additional indications and new compounds

**2024** Phase I results, CTH120


**STRATEGIC PARTNERS**

PROUS INSTITUTE for Biomedical Research · inveready · CDTI · ASSOCIACIÓ CATALANA SÍNDROME X FRÀGIL · Federación Española Síndrome X Frágil · nfxf NATIONAL FRAGILE X FOUNDATION · CRG Centre for Genomic Regulation · Hospital del Mar Research Institute Barcelona · Parc Taulí Institut d'Investigació i Innovació I3PT · UCDAVIS MIND INSTITUTE

# CONNECTA`s team - Expertise & Motivation

Experienced team backed up with top advisors in drug development and in CNS/FXS clinicals trials



## MANAGEMENT & GOVERNANCE TEAM

**Jordi Fàbrega,**
**Pharmacist, MBA**
**CEO / Co-Founder / Board Member**

**Dr Josep Prous Jr.,**
**Chemist Ph.D., MBA**
**CSO / Co-Founder / Board Member**

**Sara Secall**
**Chemist, MBA**
**Board Member**

## SCIENTIFIC ADVISORY BOARD

**Dr Mara Dierssen**
**Neurobiologist, Ph.D.**
**Research Advisor**

**Dr Randi Hagerman**
**Pediatrician, M.D.**
**Clinical Advisor**

**Dr Joseph Horrigan**
**Paediatric neuropsychiatrist, M.D.**
**Medical Advisor**

## PROJECT MANAGEMENT TEAM

**Dr Marta Pascual**
**Chemist, Ph.D., MSc.**
**Director of R&D**

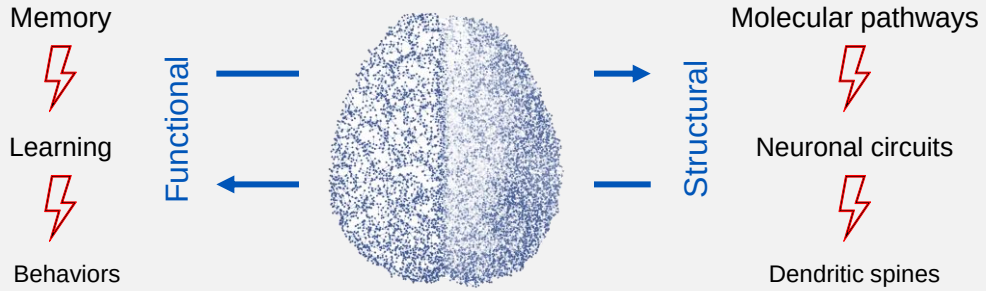
**Irene Domingo**
**Biologist, MSc.**
**Project Manager**

# Neurodevelopmental disorders as a major healthcare challenge

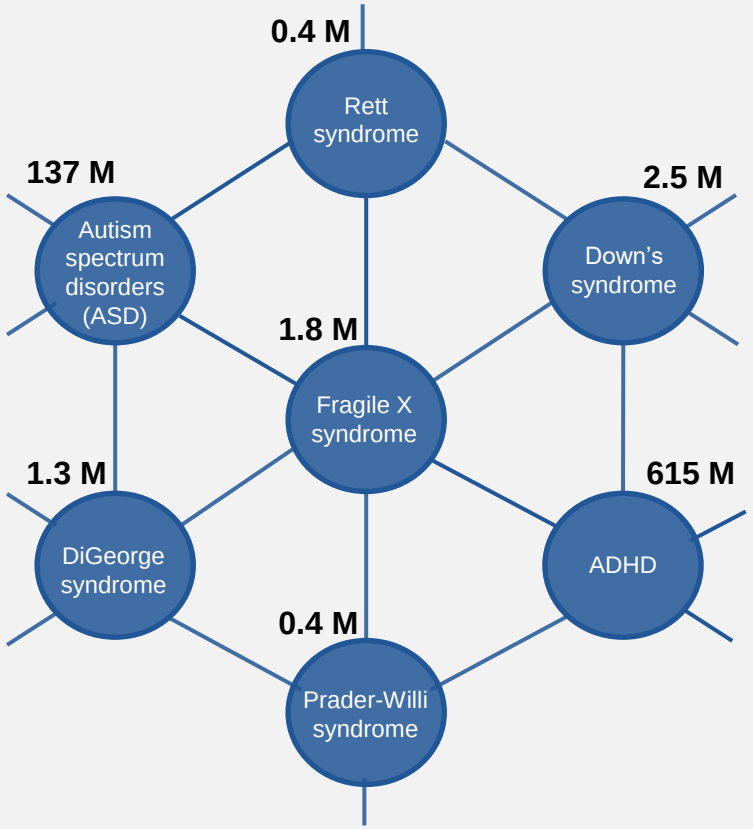
## Neuroplasticity modulation as an innovative approach for therapeutic intervention

Target indication

**Neuroplasticity imbalance impact** in neurodevelopmental disorders




**~ 1 Bn people affected worldwide**, 15% children




Adapted from: M. Toricelli et al. Mechanisms of neuroplasticity and brain degeneration: strategies for protection during the aging process. Neural Regen Res 2021;16:58-67

Own estimations based on Orpha.net and Carlsson et al. Early environmental risk factors for neurodevelopmental disorders - a systematic review of twin and sibling studies. Dev Psychopathol. 2021;33(4):1448-1495

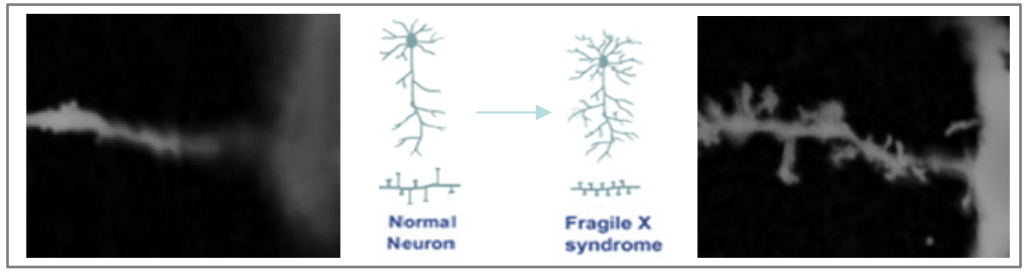
# Neuroplasticity imbalance in Fragile X syndrome

## Fragile X syndrome (FXS), the most common cause of inherited intellectual disability

Target indication

- Genetic disorder (FMR1 gene)
- Rare disease (3/10,000), estimated 1.8 M worldwide
- Paediatric onset disease affecting all genders
- Expensive patient care (59 K€ in Europe)*
- No cure (only symptomatic treatment with limited efficacy and significant negative side effects)
- High unmet medical need

- Higher density and immature ratio of dendritic spines




- Severe impairment in cognition with behavioral manifestations

| Fragile X manifestations | | Males | Females |
|---|---|---|---|
| Cognition | Developmental delay or intellectual disability | 96% | 64% |
| Behavioral | Attention problems | 84% | 67% |
| | Anxiety | 70% | 56% |
| | Hyperactivity | 66% | 30% |
| | Autism | 46% | 16% |
| | Self Injury | 41% | 10% |
| | Aggressiveness | 38% | 14% |
| | Seizures | 18% | 7% |
| | Depression | 12% | 22% |

(*) Chevreul et al.. Social/economic costs and health-related quality of life in patients with fragile X syndrome in Europe. Eur J Health Econ. 2016

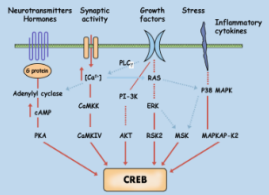
Source: Adapted from Centres for Disease Control and Prevention (CDC)

# CONNECTA's *in silico* discovery approach

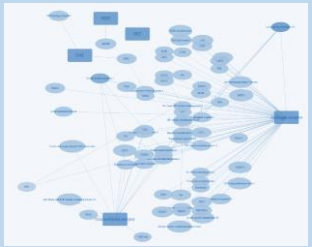
## From *in silico* to *in vivo* PoC

Innovative mechanism of action

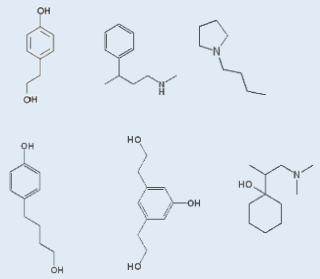
Disease process modeling



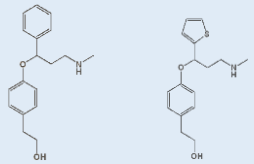

Systems Biology
Target identification



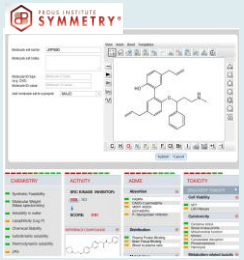
Privileged fragment selection

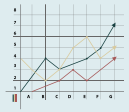


*In silico* library construction



*In silico* efficacy profiling

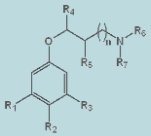


ADME & safety optimization

Patentability studies

Focused library



Synthesis

Pharmaco-logical Evaluation

*In vivo* efficacy in animal model

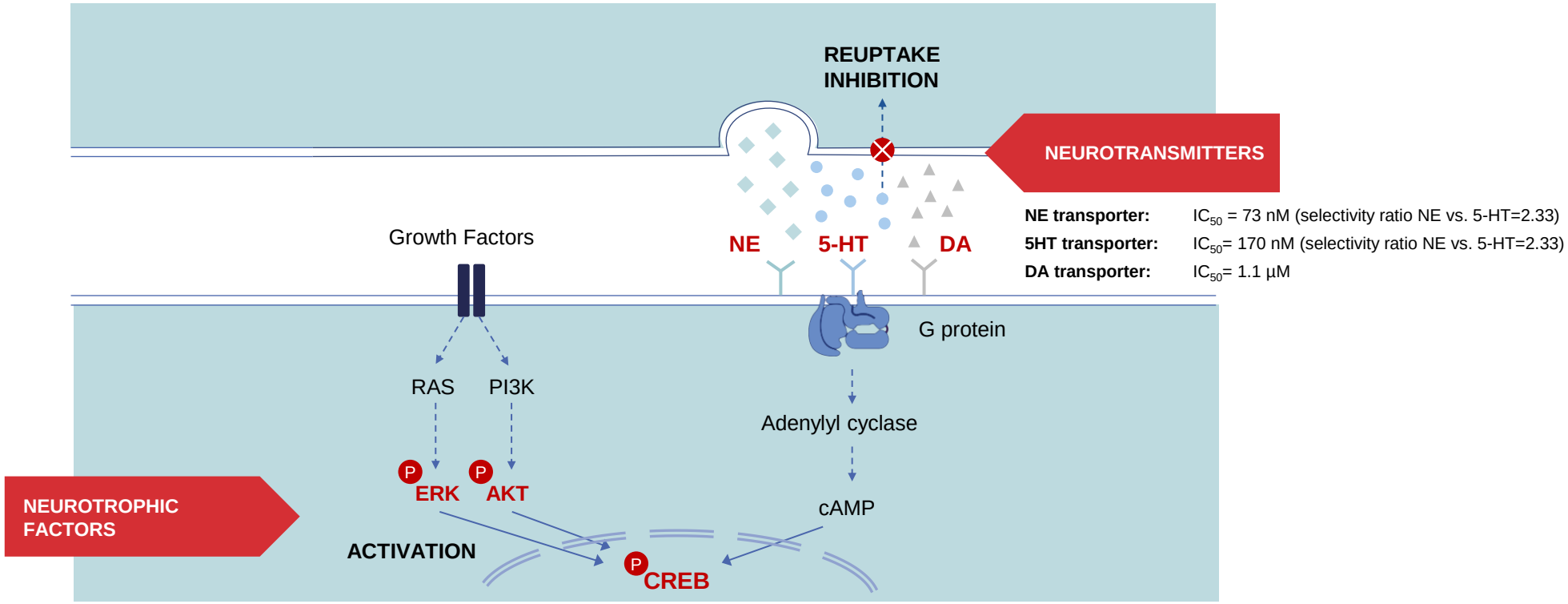
NCE preclinical candidates

# CTH120, an innovative neuroplasticity modulator

## With a novel mechanism of action based on network pharmacology

Innovative mechanism of action

**NETWORK PHARMACOLOGY**
***Polypharmacological activity***




**NE transporter:** $IC_{50}$ = 73 nM (selectivity ratio NE vs. 5-HT=2.33)
**5HT transporter:** $IC_{50}$= 170 nM (selectivity ratio NE vs. 5-HT=2.33)
**DA transporter:** $IC_{50}$= 1.1 µM

**Increase of p-Erk and p-Akt:** obtained at 1 h after oral administration of 30 mg/kg i.p. in mouse hippocampus

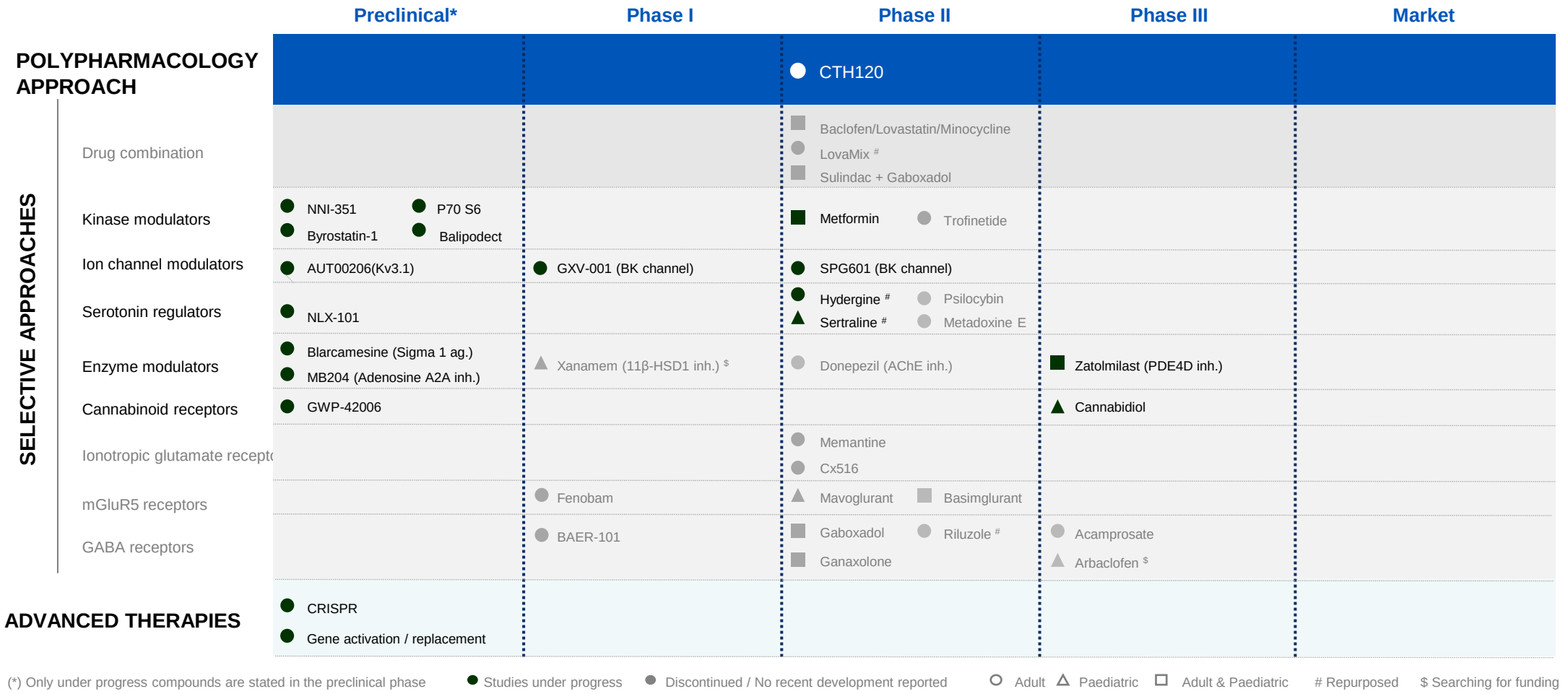
**Increase of pCREB:** obtained at 0.5 µM in SN56 and T48 cells

NE: Norepinephrine 5-HT: Serotonin DA: Dopamine

# CTH120, competitive advantage & value proposition

## Unique polypharmacology approach and mechanism of action vs competitors

Differential features facing the market




(*) Only under progress compounds are stated in the preclinical phase

Studies under progress

Discontinued / No recent development reported

Adult

Paediatric

Adult & Paediatric

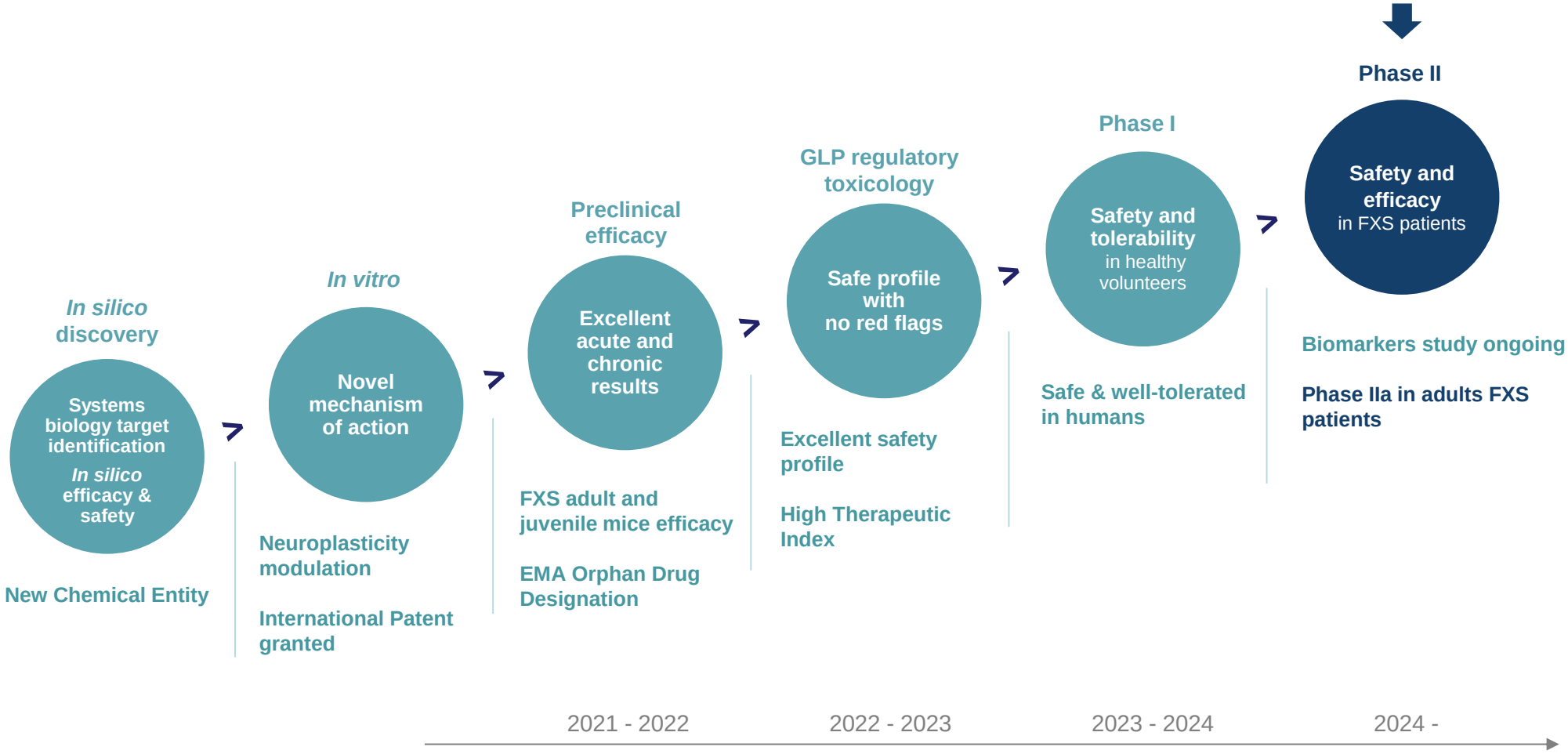
# Repurposed

$ Searching for funding

# CTH120, ready for phase II clinical trial in FXS adult patients

## Chronic oral administration of CTH120 as a disease-modifying treatment for FXS

Current status of development



# CTH120, a disease-modifying treatment

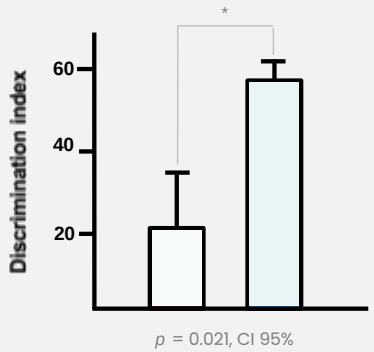
## Demonstrated efficacy in multiple *Fmr1-KO* mice model studies

Current status of development

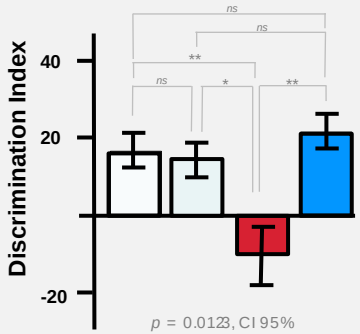
### Improves COGNITIVE ABILITY

*Novel Object Recognition test*

**Single injection i.p. 30 mg/kg** - C57 mice



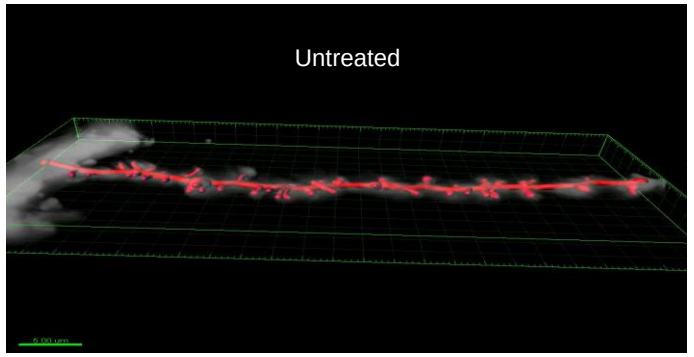

**3-month p.o. 10 mg/kg/day** - *Fmr1*-KO mice

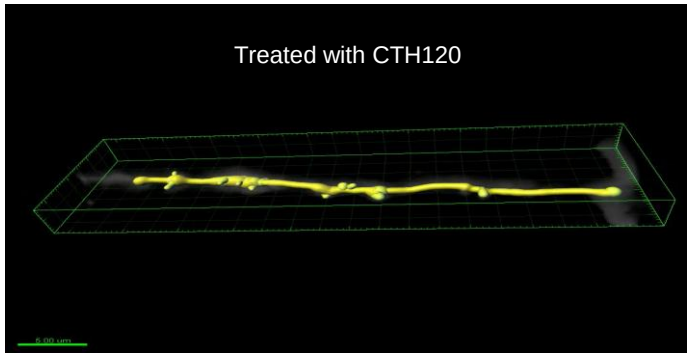



### Rescues FXS DENDRITIC SPINE PATHOLOGY

*Spine analysis layer III-IV of medial prefrontal cortex*

**3-month p.o. 10 mg/kg/day** - *Fmr1*-KO mice

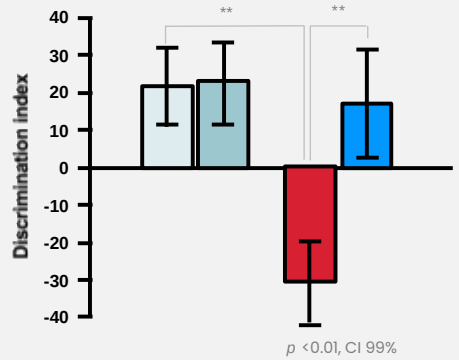


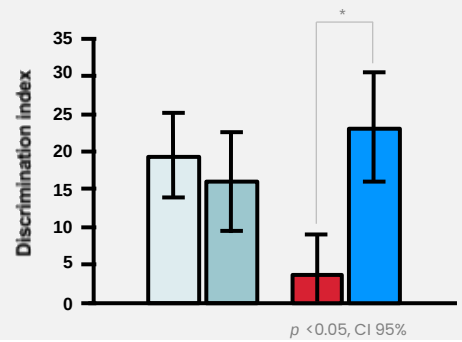

### Restores SOCIAL ABNORMALITIES

*Social Recognition assay*

**Single injection i.p. 30 mg/kg** - *Fmr1*-KO mice




**3-month p.o. 10 mg/kg/day** - *Fmr1*-KO mice




Discrimination index expressed (time exploring the novel stimulus – time exploring the familiar stimulus / total exploration time x 100).

WT untreated | WT CTH120 | *Fmr1*-KO untreated | *Fmr1-KO* CTH120

# CTH120, a disease-modifying treatment

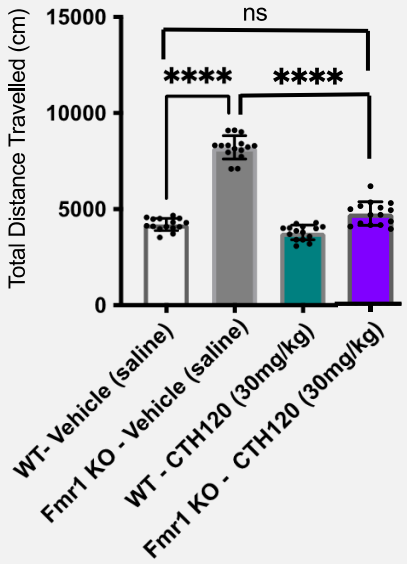
## Demonstrated efficacy in multiple *Fmr1-KO* mice model studies

Current status of development

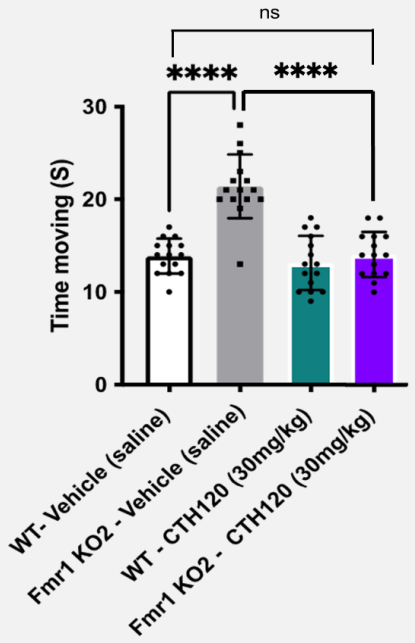
**Single injection i.p. 30 mg/kg**

### 1 HYPERACTIVITY *Open field test*

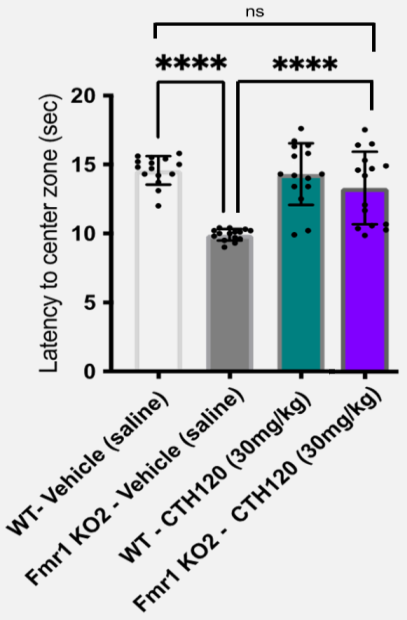
Distance travelled



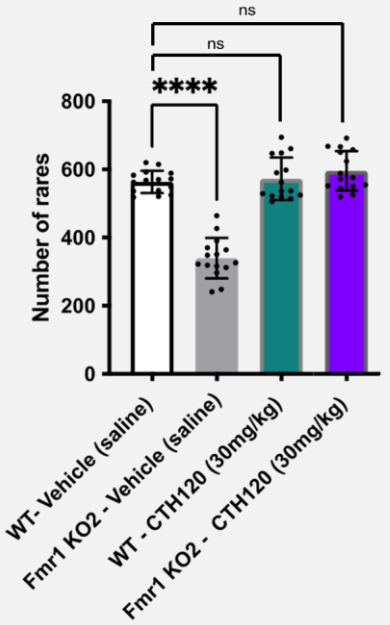

Movement




Latency to center




Number of rares



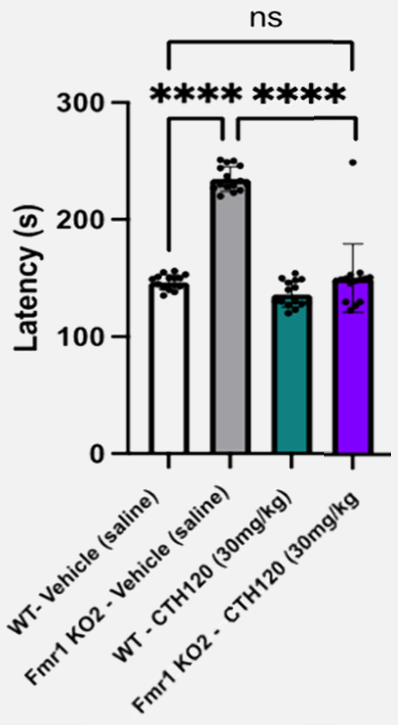
# CTH120, a disease-modifying treatment

## Demonstrated efficacy in multiple *Fmr1-KO* mice model studies

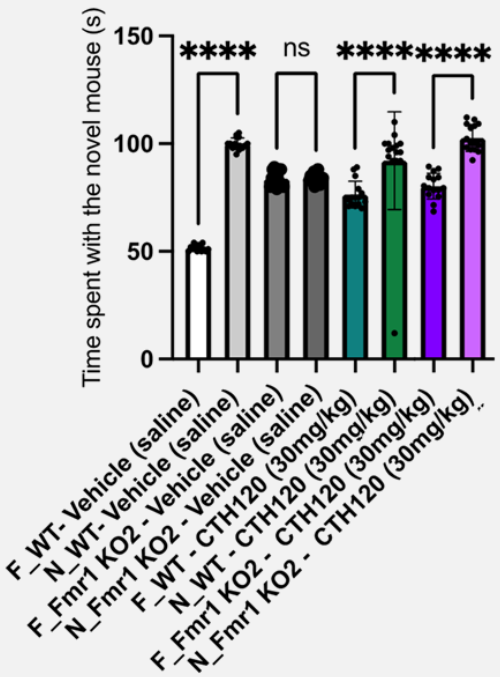
Current status of development

**Single injection i.p. 30 mg/kg**

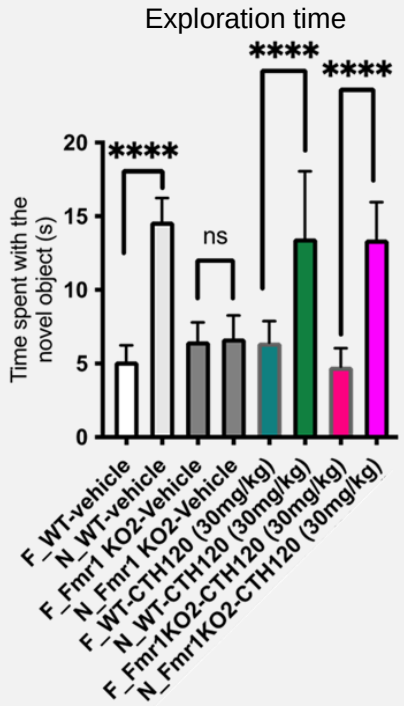
### 2 ANXIETY *Hyponeophagia test*

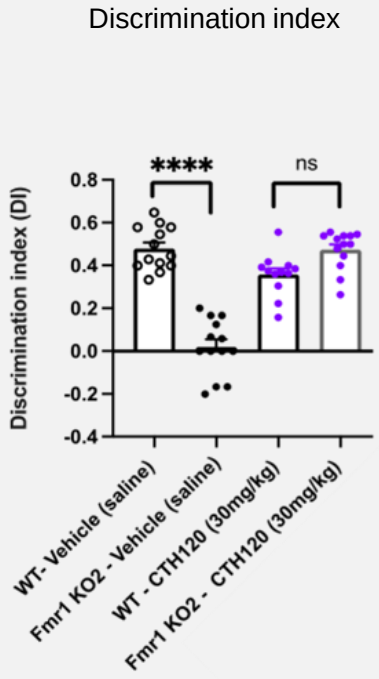



### 3 SOCIABILITY *Three chamber partition test*




### 4 MEMORY AND LEARNING *Novel Object Recognition test*



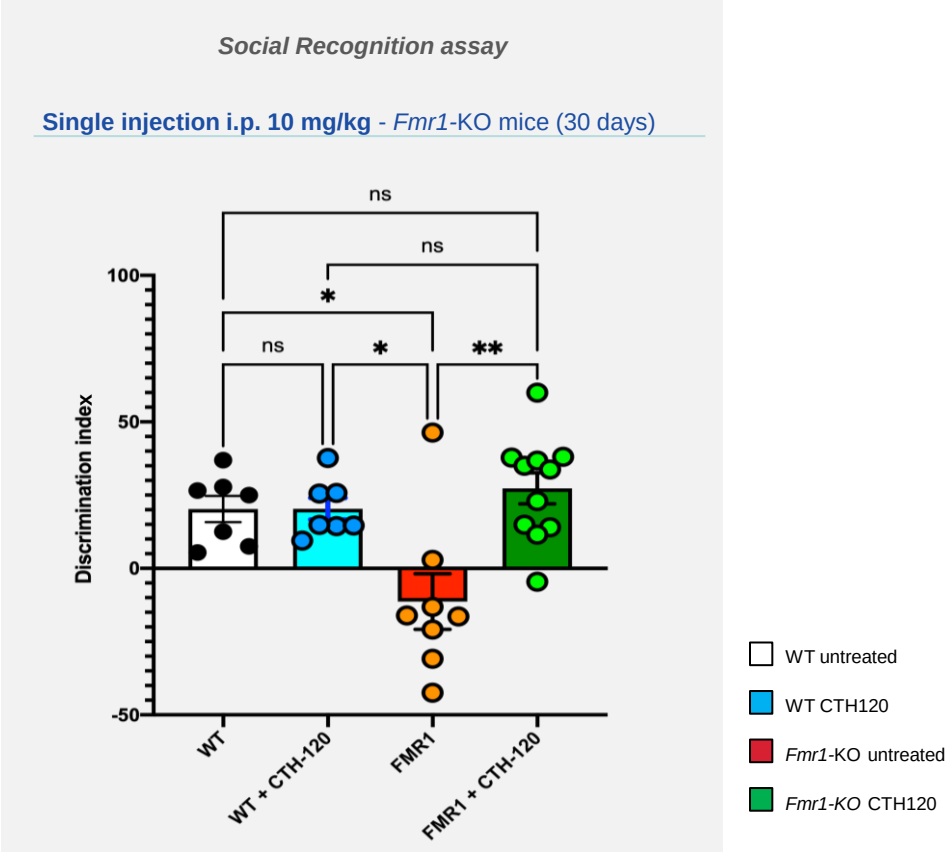



# CTH120, favorable preclinical results in juvenile mice

## Demonstrated efficacy in *Fmr1-KO* juvenile mice model and proteomics validation

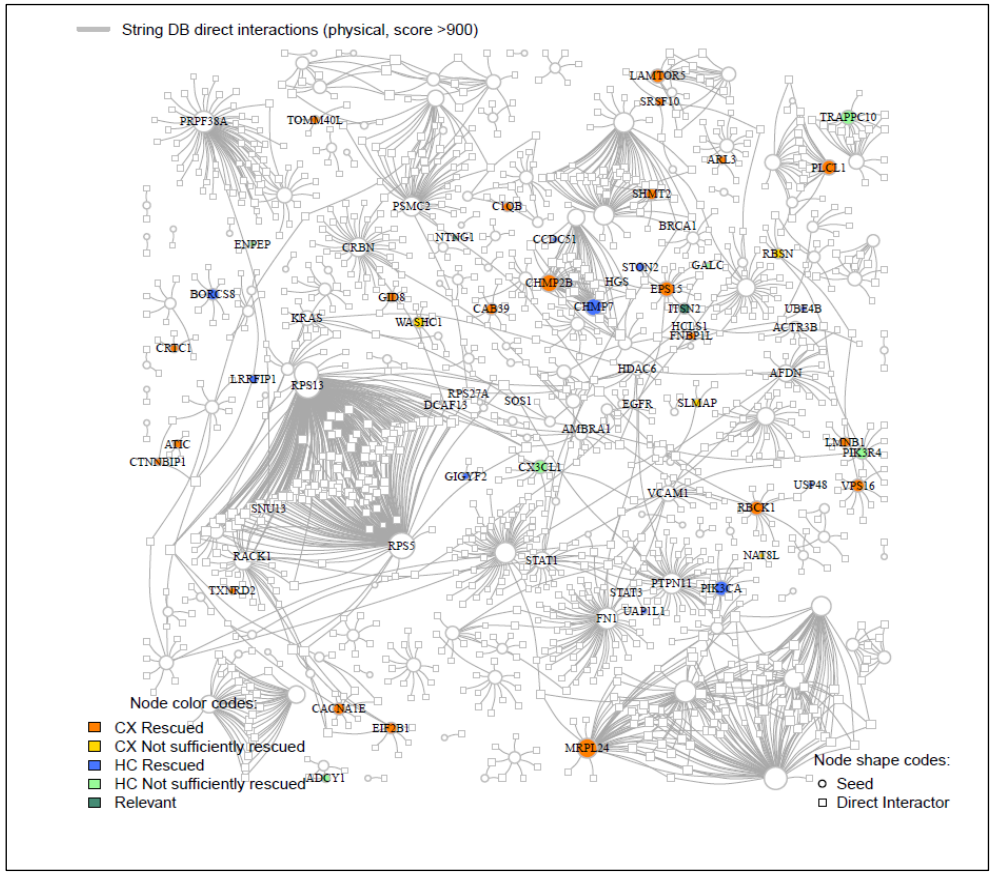
Current status of development

### Restores SOCIAL ABNORMALITIES in Juvenile mice




Discrimination index expressed (time exploring the novel stimulus – time exploring the familiar stimulus / total exploration time x 100).

### Confirmed NETWORK PHARMACOLOGY APPROACH IN PROTEOMICS ANALYSIS




Cortex and hippocampal proteomics analysis after 3-month treatment in FXS mice

# CTH120, safe and well tolerated in humans

## Without any treatment-related serious adverse event reported in FIH

Current status of development

**FIH-CTH120** **Safety and tolerability of CTH120, first-in-human phase I study**

ClinicalTrials.gov NCT06480968


- **76 healthy adult males and females, 60 administered with CTH120 once daily orally**

## SAD

| | |
|---|---|
| **5 cohorts:** | 40 healthy volunteers |
| **Intervention Model:** | Parallel Assignment (Placebo or treatment arms) |
| **Masking:** | Double (Participant, Investigator) |

## MAD (7-day treatment)

| | |
|---|---|
| **3 cohorts:** | 24 healthy volunteers |
| **Intervention Model:** | Parallel Assignment (Placebo or treatment arms) |
| **Masking:** | Double (Participant, Investigator) |

## FI

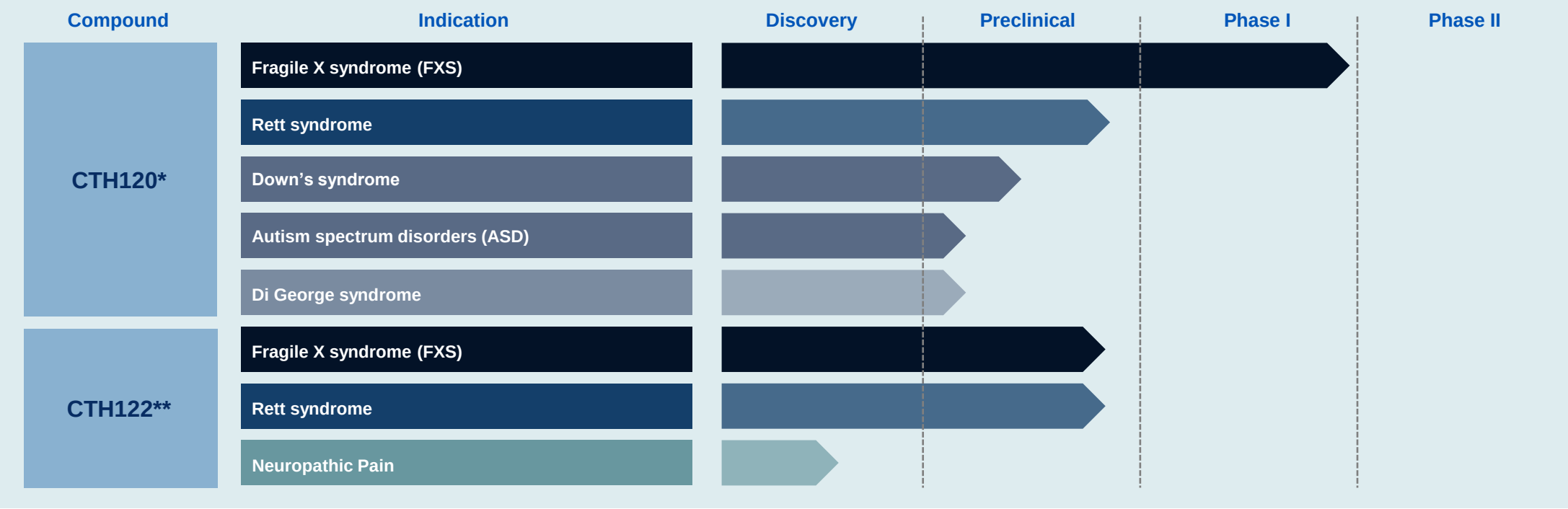
| | |
|---|---|
| **1 cohort:** | 12 healthy volunteers |
| **Intervention Model:** | Two-condition (fed vs fasting), two sequences, crossover design |
| **Masking:** | Open-label |

agencia española de medicamentos y productos sanitarios

# CTH120, a First-in-class NCE

## International patent protection & Scalability to other diseases

IPR protection




**IPR protection**

* CTH120: International patent family granted from: EP20120382527 - WO2014096377 A1

Patent in force in: Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Luxemburg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK, Japan, Australia, Canada and USA

Protection up to 12/2033 (+5 years extension: 12/2038)

Orphan drug extension EU +10 years / USA +7 years / Extension for paediatric studies +6 months

abg Intellectual Property

** CTH122: (July 2024) New patent application EP24382738.3

**Orphan drug designation**

The EMA has granted orphan drug status for CTH120 in FXS, as orphan medicinal product nr EU/3/21/2432 (May 2021)

Planned to apply for FDA ODD

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# CTH120, assessing its efficacy in a Phase IIa clinical trial

## Well-designed clinical protocol as a key success factor

Pitfalls & Risks to be considered

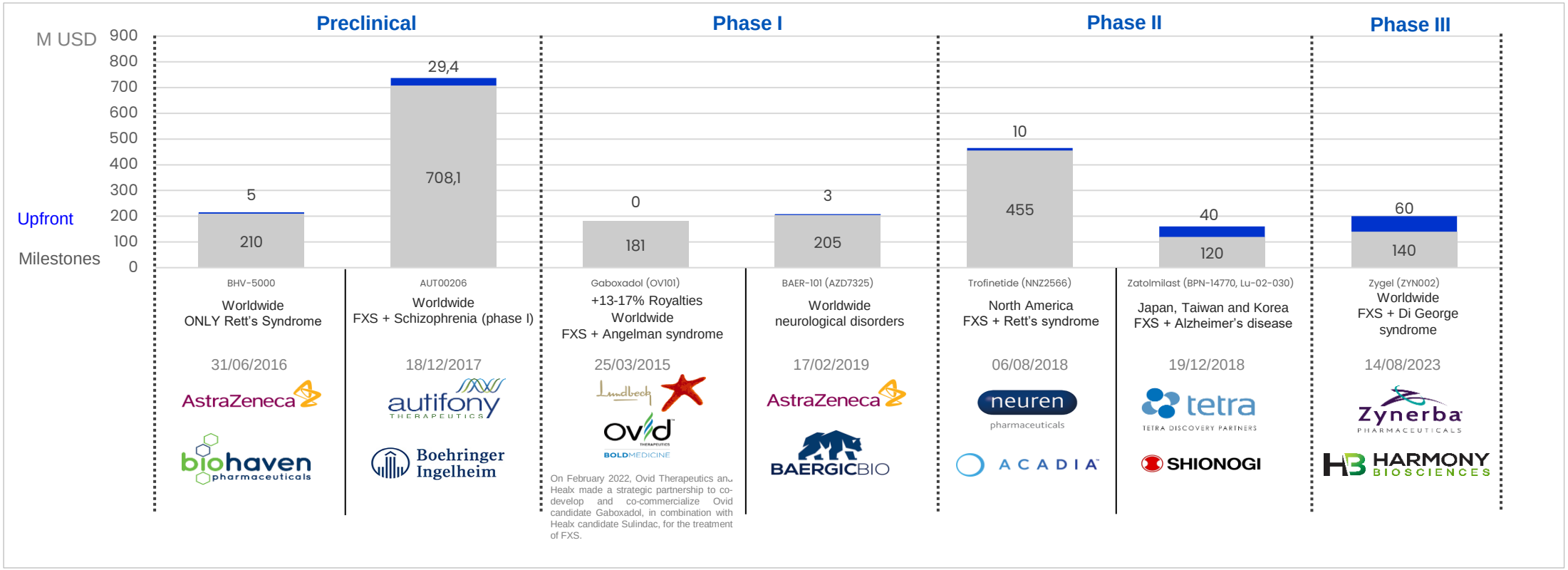
| Description of risk | Likelihood | Severity | Risk mitigation measures |
|---|---|---|---|
| **Technological (Phase II)** | | | |
| No significant efficacy | Medium | High | • Robust preclinical data package that demonstrates the efficacy of CTH120 both in adult and juvenile animal models of cognition and behaviour.<br>• Preclinical studies performed in different research centers with two FXS mice models.<br>• Maximum tolerated dose will be tested in Phase IIa.<br>• Validated neurodevelopmental scales in several efficacy domains will be tested in a previous biomarkers observational study.<br>• Protocol defined to disentangling the placebo effect.<br>• Adequate sample size defined using power analysis. |
| Unexpected related adverse events | Low | High | • No safety red flags found during safety studies in animals.<br>• No serious adverse effects found during Phase I clinical trial in healthy volunteers. |
| Inadequate recruitment ratio | Medium | Medium | • Spanish Patient Associations already engaged.<br>• Largest FXS clinical unit in Spain involved in Phase IIa. |
| Regulatory issues and decision delays | Low | Medium | • Strategic regulatory partners that defined the regulatory roadmap.<br>• Trusted advisors with extensive knowledge of EMA and National Medicines Agencies' procedures, as their experience dates to former positions in these institutions. |
| **Financial & Commercial** | | | |
| Run-out of cash | Low | High | • Strong support of shareholders. |
| Small market share | Medium | Medium | • No initiative in clinical development with the therapeutic approach of CTH120.<br>• Dual-activity in cognition and behaviour, unlike competitors acting in a single aspect.<br>• Continued surveillance monitoring to adapt the development plan, if necessary.<br>• Scalable assets to other neurodevelopmental disorders. |

# Seeking partnerships to accelerate and expand its programs

## Open to different modalities of collaboration in an attractive market opportunity

Partnering opportunities

- **Co-development or Licensing-out formulas (upfront + milestones) for CTH120/CTH122 programs are the modalities that are being most actively considered.**
- **The acquisition of the company by a pharmaceutical firm is considered a secondary alternative.**



# HIGHLIGHTS

- **Neurodevelopmental disorders, a major healthcare challenge**, ~ 1 Bn people affected worldwide, 15% children
- **Neuroplasticity, affected in neurodevelopmental disorders** such as Fragile X syndrome (FXS)
- **FXS, the most common cause of inherited intellectual disability**, 1.8 M patients with no cure

- **CTH120, a neuroplasticity modulator with a novel mechanism of action** based on a unique network pharmacology approach
- **CTH120, demonstrated efficacy** in multiple preclinical studies of neurodevelopmental disorders, also in juvenile mice
- **CTH120, safe and well tolerated in humans** as demonstrated in Phase I clinical trial

- **CONNECTA, ready for Phase IIa adult FXS patient clinical trial**
- **CONNECTA, lead by experienced team** backed up with strategic partners and top advisors in the field

# CONTACT DETAILS


Jordi Fàbrega
Co-Founder & CEO
*jfabrega@connectatherapeutics.com*

Dr. Josep Prous
Co-Founder & CSO
jprous@prousresearch.com

www.connectatherapeutics.com