**DISRUPTIVE COMBINATION**
AGAINST NEUROLOGICAL DISORDERS

# INVESTOR PRESENTATION

NEURONAL NETWORK
GLIAL NETWORK

Theranexus

# YOUR CONTACTS

**Franck MOUTHON**

Co-founder and Chairman and CEO

- Franck Mouthon holds a degree in life sciences from the École Normale Supérieure
- Joined the Life Sciences Department of the French Alternative Energies and Atomic Energy Commission (CEA) in 1995
- Founded CEA spin-off Theranexus in March 2013 with Mathieu Charvériat
- Board member of France Biotech

**Thierry LAMBERT**

CFO

- Thierry Lambert holds a degree in business administration from Birmingham University and an MBA from INSEAD
- 4 years of experience in syndicated and corporate finance
- 5 years as Chief Financial Officer for listed companies Naturex and then Safe Orthopaedics
- Joined Theranexus in 2017

# A DIVERSIFIED PIPELINE

Clinical trials

| | Candidate selection | Pre-clinical trials | Phase I | Phase II | Phase III | |
|---|---|---|---|---|---|---|
| THN 102 (BREVET DEPOSE) | | | **Ph2 results Q1-2020** | | | Excessive Daytime Sleepiness linked to Parkinson's disease **No treatment to date** |
| THN 201 (BREVET DEPOSE) | | | **Ph1b results Published** | | | Neurocognitive disorders linked to Alzheimer's disease **$3.2 billion** |
| THN 101 (BREVET DEPOSE) | | | | **Ph2 under preparation** | | Neuropathic pain **$3 billion** |
| BBDF 101 (BREVET DEPOSE) | | | | **Ph1-3 (pivotal) under preparation** | | Batten disease * **No treatment to date** |
| THN XX | | | | | | New indications |

*All figures are derived from Datamonitor reports (ND, dementia); company annual reports (Jazz Pharmaceuticals, Teva)

# THERANEXUS PLATFORM: PROPRIETARY, SCALABLE & VERSATILE

## CNS DRUGS

**DRUG SEEN AS THE 1ST LINE-TREATMENT**

Condition with a strong unmet need for improved efficacy (with the current therapeutics arsenal)

*CNS drugs 1st line- treatment for CNS* conditions*

Action on the neuron

## GLIAL CELL MODULATOR

**DRUG REPOSITIONED AS A MODULATOR**

Optimization of the glial network

*Theranexus library of 27 glial cell modulators*

PATENTED

**THN XXX**

## 3 major advantages

- **Ambition to achieve superiority at all stages (*Best in class*)**
- **New monopoly on use (patent)**
- **Higher probability of success, greater flexibility and shorter time-to-market**

**Central Nervous System*

# NEUROLEAD :STRENGTHENING THE LEAD GENERATION PLATFORM

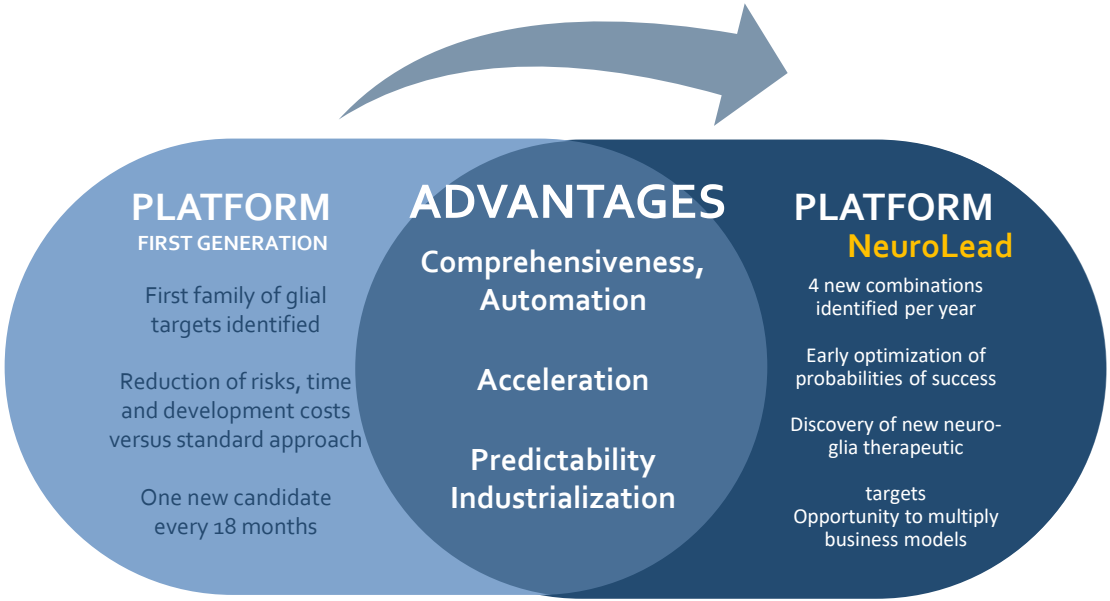
## NeuroLead

- Development of a drug candidate generating platform based on neuron-glia interactions
- Prestigious partners:

- Capacity to build on the latest innovations in neuroscience and Deep Learning

- Funding package of €6.2m from BpiFrance, for the consortium managed by Theranexus

A NEW PLATFORM FOR DRUG CANDIDATE GENERATION FOCUSED ON MEDICAL AND INDUSTRIAL VALUE




FROM PIONEER TO REFERENCE PLAYER IN NEUROLOGY

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# THN102: A DRUG CANDIDATE TO COMBAT SLEEPINESS RELATED TO PARKINSON'S

**MODAFINIL** | FLECAINIDE

THN 102

## Parkinson's disease

Sleepiness, attention, cognition

Almost **1 million patients** (G7)
**30-50%** of Parkinson's sufferers

NO TREATMENT

**No drug approved to date**
**6.1 million Parkinson's sufferers[1] – 40%[2] affected by sleepiness…**

4 drug candidates are at a clinical stage, all targeting only neurons

## Phase II clinical trial underway

**Design:**
Double-blind study comparing 2 doses of THN102 with a placebo in a three period cross-over format: each patient receives either THN102 or the placebo, chosen at random, over three periods of 2 weeks

**Efficacy criteria**: sleepiness, attention, alertness, cognition

Study carried out on **60 Parkinson's patients** (including one group in the United States)

**Last patient included 24/09/2019**

IND authorization for clinical trial in the United States

Eligible for 505(b)(2) regulatory pathway (opportunity to benefit from existing data for reference drugs)

**Results expected in Q1 2020**

[1]: European Parkinson's Disease Association
[2] Market research study performed by LSA Partnering & Analytics

# THN201: A HIGH-POTENTIAL CANDIDATE FOR DEMENTIA

**DONEPEZIL** | **MEFLOQUINE**

THN 201

## Neurocognitive disorders linked to **Alzheimer's disease**

Impaired memory, reasoning and orientation

**15 million patients** in 2015 (G7)
**19 million** by 2030
**45%** of patients undiagnosed

DONEPEZIL

**$3.2 billion**
(annual cost of treatment per patient €4,000-5,000)

**23 drug candidates at clinical trial stage**

## Launch of Phase Ib clinical trial

Under the CX-COG project funded by the French **"Fonds Unique Interministériel"** (FUI AAP22)

**Double-blind randomized study comparing placebo and standard of care drug** (Donepezil)

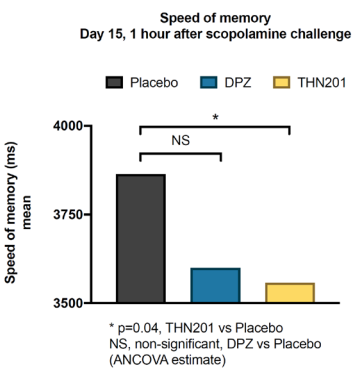
**Trial conducted on three parallel groups** evaluating the cognitive activity, tolerability and pharmacokinetic profile of THN201

**Key efficacy criteria:** measurement of pro-cognitive activity through a scopolamine test

**Results published 15/01/2020**
Trial conducted on 152 healthy volunteers in a parallel group design in 10 centers in France and abroad

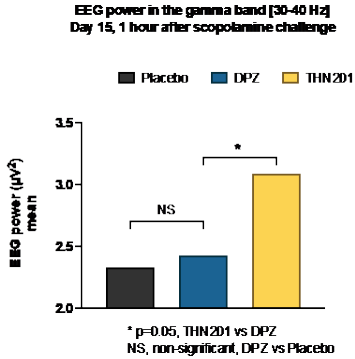
# THN201 :KEY RESULTS

Significant increase of speed of memory by THN201 vs Placebo (p=0.04) at 1 h post scopolamine challenge
No significant effect of DPZ vs Placebo




Composite endpoint of the CDR assessment ; this endpoint is typically considered to be one of the most sensitive to decline in AD patients over time (Wesnes et al, 2010).

Significant increase of EEG power on gamma band by THN201 vs DPZ (p=0.05) at 1 h post scopolamine challenge




EEG gamma band is recognized as a marker of cognitive activity (Herrmann et al, 2001 ; Fitzgibbon et al, 2004) ; an increase in this band is considered as beneficial for AD patients (Herrmann et al, 2005).

Similar profile to Donepezil on other pharmacodynamic parameters

➔ ENLARGEMENT OF THE EFFECT OF DONEPEZIL BY MEFLOQUINE IN FAVOUR OF A REINFORCEMENT OF EXECUTIVE PROCESSES

➔ THE TOLERANCE PROFILE OF THN201 IS SIMILAR TO THAT OF DONEPEZIL

# THN101: DRUG CANDIDATE READY FOR PHASE II TRIALS: PAIN

**AMITRIPTYLINE** | **MEFLOQUINE**

**THN 101**

| Neuropathic pain | Preparation stage for Phase II clinical trial |
|---|---|
| Chronic pain with occasional stabbing pain, sensations of burning or electric shocks | **Key efficacy criteria:** pain scale |
| **70 million patients** (Europe, USA, Japan) | **Double-blind randomized study comparing placebo with standard of care drug** (Amitriptyline) |
| AMITRIPTYLINE | **Trial conducted on three parallel groups:** Amitriptyline 25 mg/day and mefloquine 10 mg/day vs. Placebo and vs. active comparator (amitriptyline). Regular evaluation of pain and analysis of multiple secondary markers and tolerability. |
| **$3 billion** (annual cost of treatment per patient $3,000-4,000) | Patients suffering from neuropathic pain caused by diabetes or post-herpetic neuralgia (following shingles) |
| **32 drug candidates at clinical trial stage** | Multi-center international trial conducted on **370 patients** Conducted in parallel at **40-45 centers in Europe**. |

**Phase II trial program at preparation stage**

# THN102: PARTNERSHIP STRATEGY FOR THN102

Candidate selection | Pre-clinical trials | Clinical trials: Phase I | Phase II | Phase III

THN 102 — BREVET DÉPOSÉ

Market and dimension

Excessive Daytime Sleepiness linked to Parkinson's disease
**No treatment to date**

Specialists in EDS or CNS

Jazz Pharmaceuticals
SK biopharmaceuticals
Sumitomo Dainippon Pharma
Zambon
Lundbeck
ucb Pharma

Generalists and "big pharma"

NOVARTIS PHARMACEUTICALS
Boehringer Ingelheim
Mitsubishi Tanabe Pharma

**MULTIPLE OPPORTUNITIES FOR PARTNERSHIPS:**

+ INTRINSIC COMMERCIAL POTENTIAL OF PRODUCT

+ OPTIMIZATION OF SALES FORCES USED FOR PARKINSON'S

+ POSSIBILITY TO REACH NEW MARKET FOR EDS SPECIALISTS

BLOCKBUSTER POTENTIAL FOR AN INDICATION WITH A GROWING BUT UNTREATED NEED

# STRONG INTEREST AMONG INDUSTRY PLAYERS FOR THE FIRST 3 CONDITIONS TARGETED

| CONDITION | DATE | SELLER | BUYER | PROFILE | DEVELOPPEMENT STAGE | UP FRONT (M$) | MILESTONES (M$) | ROYALTIES (M$) |
|---|---|---|---|---|---|---|---|---|
| **Parkinson's disease** | 2018 | Prexton | Lundbeck | NCE | Phase II | **123** | **993** | - |
| | 2016 | Cynapsus | Sunovion | LCM | Phase III | **624** | - | - |
| **Neuropathic pain** | 2015 | Convergence | Biogen | NCE | Phase II | **200** | **475** | NC |
| | 2015 | Spinifex | Novartis | NCE | Phase II | **200** | **500** | NC |
| **Alzheimer's disease** | 2017 | Lyndra | Allergan | LCM | Préclinique | **15** | **90** | NC |
| | 2016 | Chase Pharma | Allergan | Combination | Phase I/II | **125** | **875** | NC |
| **Other neurological disorders** | 2014 | Avanir | Otsuka | Combination | Market | **3,500** | - | - |

TURNING POINT IN VALUE AT THE END OF PHASE II
(BETTER RATIO OF DEVELOPMENT COSTS
TO IMMEDIATE AND SUBSEQUENT REVENUES)

[1] *New Chemical Entity*

[2] *Life Cycle Management*

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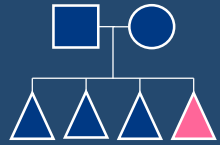
# Batten disease or juvenile neuronal ceroid lipofuscinosis (NCL3)
# A rare genetic disease that is fatal between the ages of 20 and 30

## EPIDEMIOLOGY AND PHYSIOPATHOLOGY OF NCL3

c. 3,000 patients
(all NCL types)



Autosomal recessive

Diagnosis in children
aged 4 to 8

Blindness

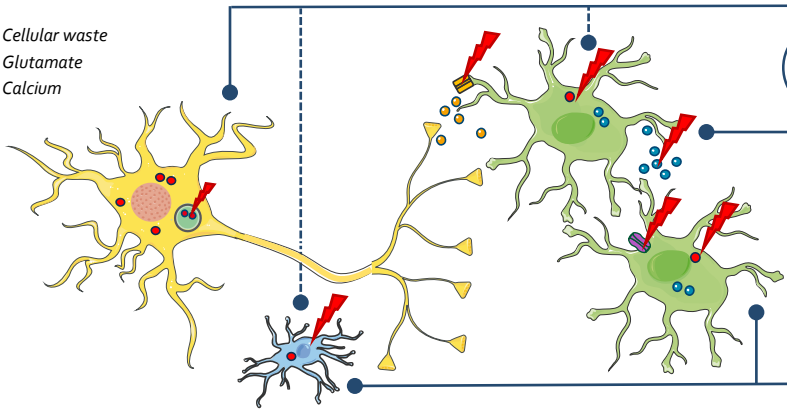
Cognitive decline

Loss of motor skills

No registered
treatment

## ROLE OF NEURON-GLIA INTERACTION IN NCL3

- *Cellular waste*
- *Glutamate*
- *Calcium*



Lysosomal and autophagic signaling pathway deficiency

Defective glutamate recycling pathway
Disruption of calcium pathways
Dysfunctions in hemichannel activity

Neuroinflammation

**ASTROCYTE FUNCTIONS ARE SEVERELY IMPAIRED, LEADING TO THE NEURONAL DEFICIENCY RESPONSIBLE FOR THE SYMPTOMS**

# The product – BBDF 101 - miglustat-trehalose combination

**FOUNDATION**

BEYOND BATTEN DISEASE FOUNDATION

Created in 2008 by Craig Benson
**USD 30 million** R&D investment leading to identification of **BBDF101**

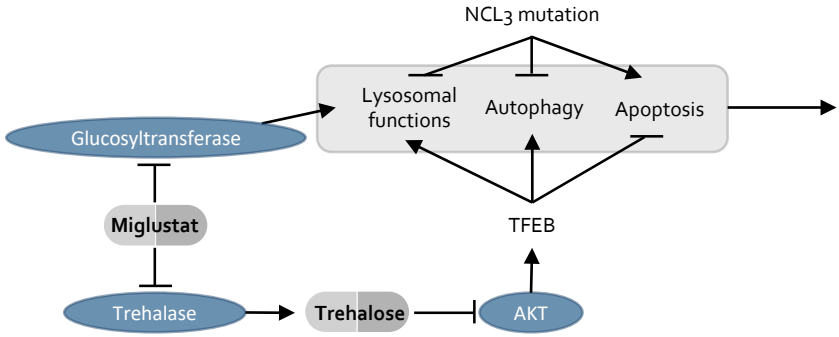
**BBDF101** **Trehalose + Miglustat combination**

Pre-IND meeting – Strong support from FDA

- Eligible for **Fast Track** procedure (MA in 6 months)
- Eligible for **pediatric ODD** Exclusivity for 7.5 years in USA and 12 years in EU
- Patent grant underway in USA, valid until 2036

→ Ready to enter Phase I/III , pre-registration, open label, **against historical data**

**MECHANISM OF ACTION**




**PRECLINICAL DEMONSTRATION**

*NCL3 transgenic mice*

- ↑ Cell survival
- ↓ Neuroinflammation
- ↓ Lysosomal signaling pathway deficiency

STRONG IMPACT ON MECHANISMS RESPONSIBLE FOR NCL3 SYMPTOMS

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# Competitive environment and market opportunity

## COMPARABLES

| ZAVESCA 100 mg (miglustat) capsules | Myozyme (alglucosidase alfa) | elaprase (idursulfase) | Brineura (cerliponase alfa) |
|---|---|---|---|
| 6,000 cases USA<br>5,000 cases EU | 5,000 cases USA<br>1,800 cases EU | 500 cases USA<br>400 cases EU | 500 cases USA<br>250 cases EU |
| Gaucher disease | Pompe disease | Hunter syndrome | NCL2 |
| $240,000/yr/patient<br>€55,000/yr/patient | $300,000/yr/patient | $375,000/yr/patient | $700,000/yr/patient |
| Peak (2014): $113m | Peak (2018): $947m | Peak (2018): $634m | Peak (2027): $359m (f) |

*Notes: All drugs have 'Orphan Drug Designation' status and Brineura obtained a pediatric voucher (sold for $120m)*

## COMPETITION IN CLINICAL DEVELOPMENT

NCL3 AAV9 **gene therapy**
Amicus Therapeutics

Phase I/II: Recruitment underway

Duration: 36 months' control
Completion due in December 2022

Design: n=7

## MARKET ACCESS

**Access to patients highly structured – Direct sales force of limited size**

USA: Two main associations (BBDF and BDSRA)
and 18 hospitals taking care of Batten patients
EU: 7 primary centers (France, UK, Germany, Norway)

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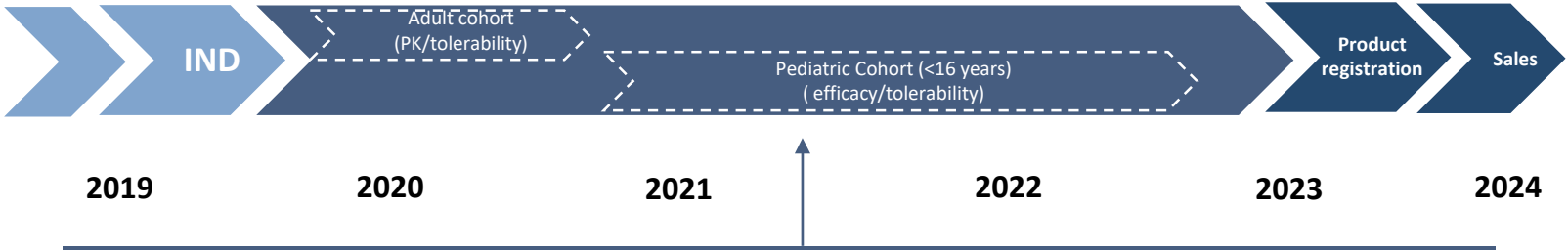
# BBDF 101 development plan

Signing of definitive licensing agreement between BBDF and Theranexus in December 2019

Application for IND (authorization to enter clinical trial phase) from the FDA (US Food and Drug Administration)- h12020

Registration of product – the FDA has already confirmed that the product would be eligible for fast-track registration (rare pediatric disease)

Theranexus plans to market the product directly. The limited number of specialist doctors and therefore of potential prescribers limits the required marketing expenditure.




## Clinical trials:

- Phase I-III (leading directly to product marketing)
- On 36 patients in the USA :
  - adolescent/adult cohort of six patients over a period of 5 month
  - pediatric cohort of 30 patients over a period of two years with an intermediate assessment at 12 month
- Open label
- The evaluation is based on comparing the disease progression in patients recruited for the trial against the natural course of the disease as described by several existing groups of NCL3 patients – similar to the trials conducted by Biomarin for Brineura™

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# P&L H1 2019

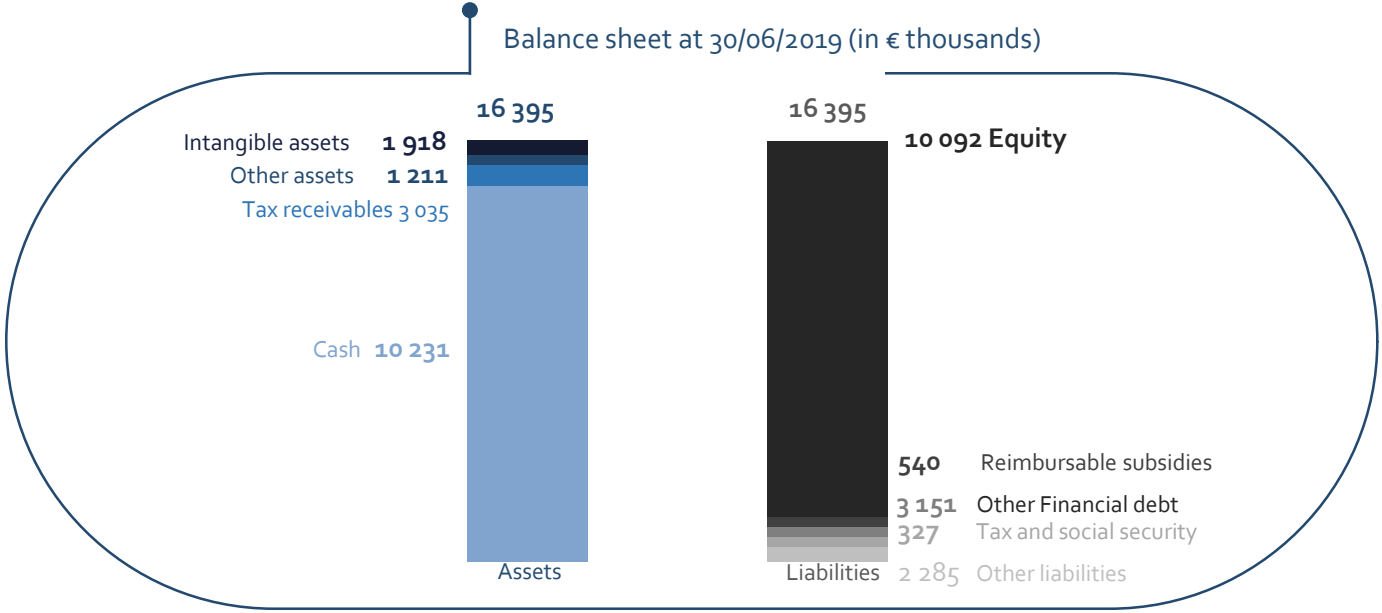
| In K€ (French GAAP) | H1 2018 | H1 2019 |
|---|---|---|
| **Operating income** | **101** | **574** |
| Other purchases and external charges | 2 2024 | 2 897 |
| Salaries and benefits | 992 | 1 215 |
| Depreciation and amortization | 21 | 30 |
| Other operating expenses | 10 | 18 |
| Operating result | (2 947) | (3 587) |
| Net financial income | - | (132) |
| Corporate tax | 893 | 941 |
| Net income | (2 054) | (2 778) |

GOOD CONTROL OVER EXPENSES IN A CONTEXT OF ACCELERATED CLINICAL DEVELOPMENTS

MAINLY RESEARCH TAX CREDIT

CASH AS AT DECEMBER 31ST 2019: 9.5 M€

# BALANCE SHEET STRUCTURE



# INVESTORS RELATIONS AND SHAREHOLDERS

## FINANCIAL DATA

**ISIN :** FR0013286259 - **Mnemo:** ALTHX

**Listed on** Euronext Growth

**Stock price :** 2.5 € (on January. 21st 2019)

**Market Cap :** 9 M€

**Liquidity contract** : Portzamparc

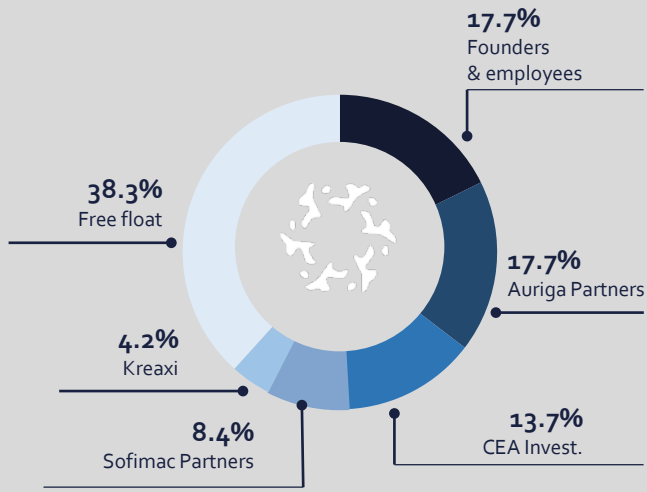
ALTHX EURONEXT GROWTH

ENTREPRISE INNOVANTE bpifrance

ELIGIBLE PEA PME

## SHAREHOLDERS

**Total shares:** 3 622 413

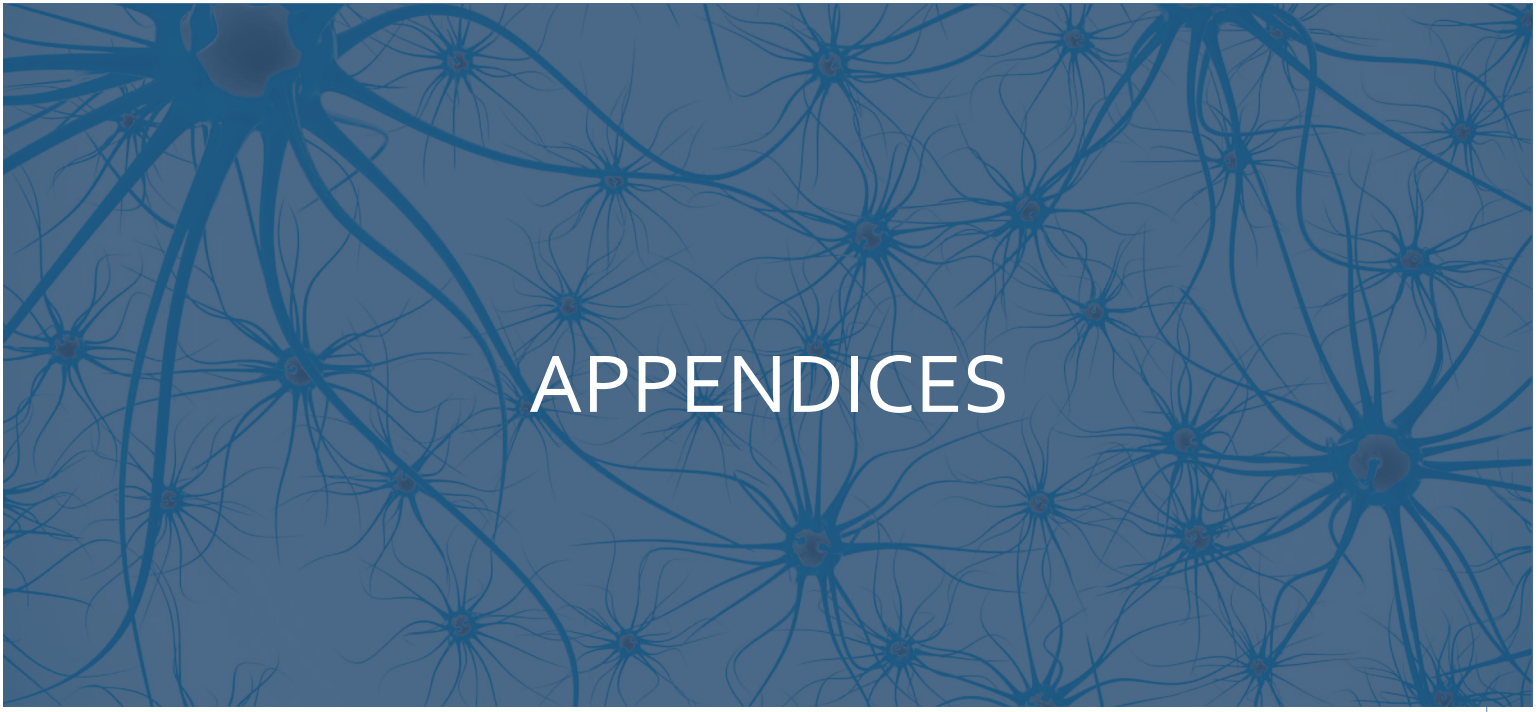


# PUBLICATION SCHEDULE FOR 2020

Results P2 : Q1-2020


IND authorization for BBDF 101 in Batten disease H1-2020
ODD Granting for BBDF 1010 in Batten disease : H1-2020
Inclusion of the first patient : H2-2020


Preparation P2: pain H1-2020



# APPENDICES

# Clinical development – Example: Brineura (BioMarin) for CLN2

**CLN2**
500 CLN2 cases US – 250 cases EU
Diagnostic between 2 and 4 years old
Autosomal recessive
Dementia, motor deficit,
vision loss
Mortality between 8 and 12 years old

Phase I/II Pre- registration
Duration: **2 years** –extension study on going
n=23 patients (Enrolment in six months)

**ICV Administration** – 4h30
infusion every two weeks


**Natural history control group**
DEM-CHILD database –
Comparing the language and
motor scores

Price: US$ **700 000** /year/patient
MAA 2017, Revenue 2027(f) US**$ 359 M**
Priority Review Voucher ~ US**$ 100 M**

ODD in Europe and in the US
European MAA; FDA approval

BioMarin – pioneer in enzymatic therapy for rare genetic diseases
Market Capital: US$ 15 B (Nasdaq)

# TRANSFORMING RESEARCH INTO INNOVATION

**PRINCIPLE:**
Enhance neuron action with the modulation of glial cells

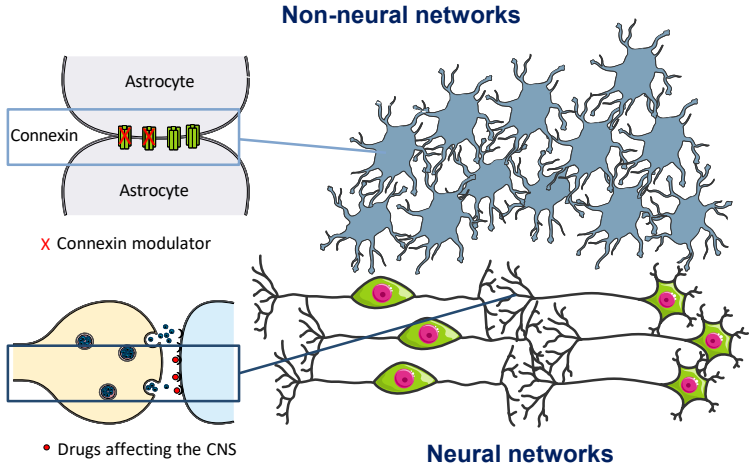
**APPLICATION:**
Combine medication that targets neurons with a medication that optimizes neuroglial interaction

**Connexin modulator**

**CNS drug**

**(Psychostimulant, antidepressant, anxiolytic, etc.)**

Action on neurotransmitter systems




The modulation of glial connexins optimizes the neuroglial interface to **improve the way in which neurons react to CNS drugs**


*Giaume et al., Nat Rev Neurosci, 2010*
*Rouach et al., Science, 2008*
*Picoli et al., J Biomol Screen, 2012*
*Duchêne et al., Sleep, 2016*
*Charvériat et al. Front Cell Neuro, 2017*


**THE CHALLENGE:** MAXIMISE NEURON RESPONSE TO EXISTING DRUGS BY TARGETING THE ENVIRONMENT

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# Strategic interest of BBDF101 for Theranexus

**SCIENTIFIC CONVERGENCE**

- Disease involving neuron/glia interactions
- A pharmacology acting on both cell types in the brain

**CONSISTENCY AND COMPLEMENTARITY OF THE PORTFOLIO**

- A rare terminal paediatric neurological disease
- A combination of 2 repositioned drugs
- An accelerated clinical development benefiting from FDA incentives for rare paediatric severe diseases

**MARKET OPPORTUNITY**

- 1st treatment in this orphan indication
- Light commercial structure
- Increased visibility in the US market

**CAPITALISING ON OUR PLATFORM**

- Partnership to include applying the Neurolead platform to research of Lysosomal storage diseases

- **Theranexus will market the product**
- **The foundation will have an interest in the additional value created in the form of milestones and royalties on future sales**

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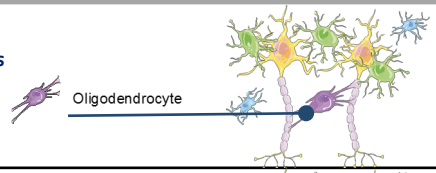
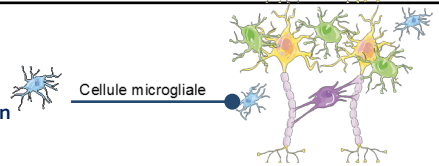
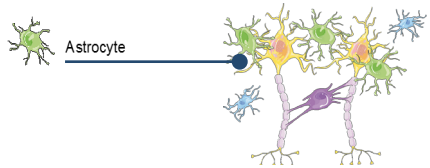
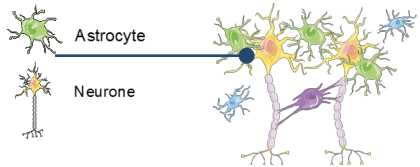
# TARGETING GLIAL CELLS : A SOARING APPROACH

| APPROACH | MECHANISM OF ACTION | SOCIETIES |
|---|---|---|
| Oligodendrocytes & remyelination |   | Biogen, ACØRDA THERAPEUTICS, astellas |
| Microglia & neuroinflammation |   | DENALI THERAPEUTICS, Daiichi-Sankyo, IONIS PHARMACEUTICALS |
| Astrocytes & metabolism |   | Astrocyte Pharmaceuticals Inc., NEURACLE SCIENCE, GliaPharm, GliaCure |
| Interactions neurons / Glia |   | Theranexus |

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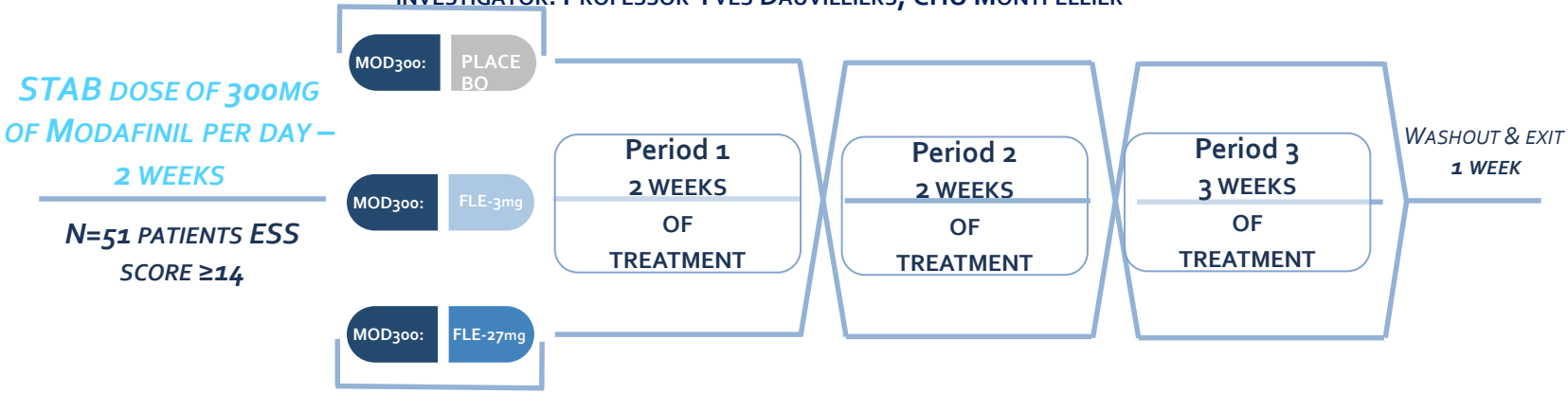
# Phase IIa trial: NARCOLEPSY

**SAFETY AND EFFICACY OF THN102 IN SLEEPINESS IN NARCOLEPTIC PATIENTS**

**DOUBLE-BLIND MULTICENTER STUDY COMPARING 3 TREATMENTS OVER 5 SITES IN FRANCE AND ONE IN BELGIUM**

**INVESTIGATOR: PROFESSOR YVES DAUVILLIERS, CHU MONTPELLIER**




| Key efficacy criteria | Results | Discussion |
|---|---|---|
| THN102 sleepiness much less than Modafinil sleepiness | No significant statistical difference<br>excellent tolerability profile | Patient sleepiness on Modafinil equivalent to patients without treatment[1]<br>Too high proportion of patients not responsive to Modafinil in the study |



(1): Thorpy et al. 2019 / (2): Bogan et al. 2015 / (3): Dauvilliers et al. 2013 / (4): Fry et al. 1998

# THN201 P1B STUDY ENDPOINTS – EXTRACT FROM THE SYNOPSIS

**THN 201-101 ENDPOINTS**

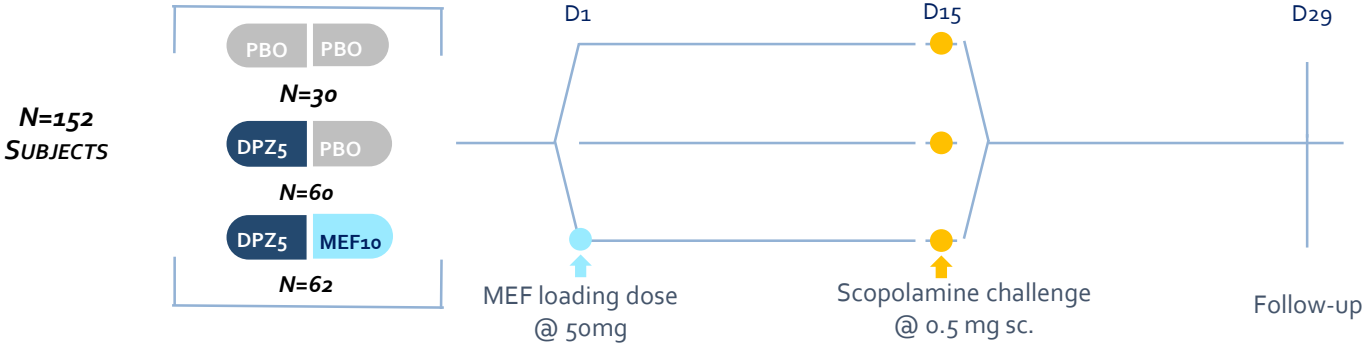
| | Objective | Endpoint |
|---|---|---|
| **Primary** | - To quantify the efficacy of THN201 versus donepezil and placebo to improve cognition impairment induced by scopolamine. | - Comparison before and after scopolamine challenge using cognitive test evaluation: Cognitive Drug Research (CDR) battery. |
| | - To assess the effects of THN201 versus donepezil and placebo on electroencephalograms (EEGs) after a scopolamine challenge. | - Comparison before and after scopolamine challenge: quantitative EEG (qEEG) and event-related potential (P300). |
| **Secondary** | - To assess the safety and tolerability of THN201 in healthy male volunteers. | - Adverse events (AEs);<br>- Physical examination;<br>- Laboratory results;<br>- Vital signs;<br>- Digital 12-lead electrocardiogram (ECG; triplicate recordings);<br>- Columbia-Suicide Severity Rating Scale (C-SSRS). |
| | - To determine the plasma levels of mefloquine and donepezil at steady state. | - Plasma concentrations of mefloquine and donepezil. PK time points (trough) will be used to confirm participant compliance. |

# THN201-101 :STUDY DESIGN

## A Pharmacodynamics, Safety, and Pharmacokinetics Study of THN201 Versus Donepezil (DPZ) in Healthy Male Subjects

A double-blind, randomized, parallel-Group, placebo & active controlled study

*(10 sites in Europe - PI: Prof. Regis Bordet, Lille)*




**Pharmacodynamic endpoints :**

Cognitive function: Cognitive Drug Research (CDR) computerized assessment

EEG: quantitative EEG (qEEG), event related potentials (P300).

**Safety and PK endpoints**

# A COMPLEMENTARY TEAM IN AN AGILE ORGANIZATION

**Franck Mouthon** CHAIRMAN & CEO

**Werner Rein** CMO

**Mathieu Charvériat** CSO

**Julien Veys** CBDO

**Thierry Lambert** CFO

High profile partners

18 EMPLOYEES DEDICATED TO KEY FUNCTIONS

# CASH FLOW STATEMENT

Cash flow statement (in € thousands )

| Data in K€- Audited -French GAAP | 30.06.18 | 30.06.19 |
|---|---|---|
| Gross cash flow | (2 024) | (2 629) |
| Others | - | 11 |
| Change in net working capital | (862) | (1 019) |
| Investments | (2 072) | **(942)** |
| **FREE CASH FLOW** | **(3 158)** | **(4 579)** |
| Borrowings and financial debts | (10) | (36) |
| Repayments | (113) | (325) |
| **CASH FLOW FROM FINANCING ACTIVITIES** | **(123)** | **(361)** |
| **CASH (END OF PERIOD)** | **14 945** | **10 231** |