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Key Takeaways

- Leading a breakthrough in **Combination Drug** development

- **Pleotherapy™ R&D Platform**
  - Universal, efficient, safer, faster and more affordable
  - Synergistic combinations of repositioned therapies at low doses
  - Smart small efficient clinical trials

- **Orphanext – Late-stage pipeline of orphan drugs**
  - Pivotal Phase 3: **PXT3003** for orphan indication CMT1A
  - Phase 1: **PXT864** with a novel MOA for neurodegenerative orphan diseases

- **Strong partnering opportunities pursuing common indications**
  - Tasly strategic partnership
  - Galapagos R&D collaboration
  - Other active ongoing discussions: **PXT864** in AD (Phase 2a completed) and other common diseases

- **Multiple near-term milestones** expected for PXT3003 Phase 3 trial

Abbreviations: CMT1A, Charcot-Marie-Tooth disease type 1A; MOA, Mechanism Of Action; AD, Alzheimer's Disease.

• Synergistic drug combinations improve therapeutic selectivity and reduce toxicities (Lehar et al 2009, Nat Biotech 27(7):659)

• Known drug target genes are often associated to disease (Nelson et al 2015, Nat Gen 47(8):856)

• Combination therapy increases the chance of success of drug repositioning (Sun et al 2016, Drug Disc Today 21(7):1189 2016)
“The clinical trials system is “broken” and there needs to be new ways to collect and utilize patient data. [...] trials that look

• at multiple therapies in a single disease
• or a single treatment in multiple diseases
• and the development of new clinical trial networks
  need to be the future.”

Janet Woodcock, Director of FDA’s Center for Drug Evaluation and Research
Workshop at the National Academies of Sciences, Engineering, and Medicine today September 20, 2017

“Drug combinations must be considered even in the earliest stages of pre-clinical drug development”

Russel Katz, Former Director of the Division of Neurology Products at FDA
Experienced Management Team

Prof. Daniel Cohen, MD, PhD
CEO & Founder

Catherine Chalandon
Vice-President

René Goedkoop, MD
Chief Medical Officer

Rodolphe Hajj, Ph.D.
Chief Pharmacology Officer

Serguei Nabirotchkin, PhD
Chief Biology Officer & Co-Founder

Xavier Paoli
Chief Commercial Officer
Pleotherapy™ Universal R&D Platform
Starting with Big Data, High-Science & Analytics

- > 2,000 approved drugs
- 6-12 mo
- In Silico Proprietary AI & Expert System

- 50 candidate drugs (filtered for PK, toxicity, safety, IP)
- ≈ 2 years
- Preclinical

- 1 Pleodrug™
- ≈ 7 years
- Clinical

Knowledge Integration
Disease Network
Virtual Screening

- In Vitro Screening
- In Vivo Test

25 Positive Drugs 4 synergistic combos

Phase 1 (not always mandatory)
Phase 2A/B
Phase 3

Approval
Pleotherapy™: Universal & Efficient R&D Platform

28 molecular disease networks already mapped

<table>
<thead>
<tr>
<th>Repurposed</th>
<th>Standards of Care</th>
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</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>Donepezil</td>
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<tr>
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<td>L-Dopa</td>
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<td>Sorbitol</td>
<td>Memantine</td>
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<tr>
<td>Other</td>
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Pharnext Patent Portfolio – Key Facts

700 Patents: 460 Granted
240 pending

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<tbody>
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<td>PXT864</td>
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Naltrexone
Baclofen
Sorbitol
Acamprosate
Baclofen

Synergy

+Supplementary Protection Certificate in Europe
## Expected Upcoming Milestones

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<td>PXT3003 (adult) Ph 3 adaptive design analysis</td>
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<td>PXT3003 (pediatric) Launch Ph 3 trial</td>
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<td><strong>Other Indications</strong></td>
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<td>Selection of Additional Indications</td>
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<table>
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<tr>
<th>Results</th>
<th>Other milestone</th>
<th>Timeframe Estimate for Milestone</th>
<th>Blue color = orphan indication. Pink color = common indication.</th>
</tr>
</thead>
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* CMT1A: Charcot-Marie-Tooth disease type 1A
Various Diseases Share Drug Targets
Preclinical Pipeline In Multiple Indications to be selected with 4 pre-existing patented compounds

- Preclinical pipeline includes Pleodrugs combining Baclofen, Acamprosate, Naltrexone, Sorbitol, other compounds and Standards Of Care
- Pipeline targets orphan and common diseases and is protected by robust IP

**Orphanext**
Orphan Diseases
- Amyotrophic Lateral Sclerosis
- Acute idiopathic demyelinating polyneuropathy
- Autism subtypes
- Best vitelliform macular dystrophy
- Chronic inflammatory demyelinating polyneuropathy
- Charcot-Marie-Tooth type 2
- Cortical-basal ganglionic degeneration
- Creutzfeldt-Jacob disease
- Dysphasia
- Frontotemporal dementia
- Huntington’s disease
- Multiple system atrophy
- Primary lateral sclerosis
- Progressive bulbar palsy
- Progressive supranuclear palsy
- Rett syndrome
- Spinal muscular atrophy
- Tuberous sclerosis

**Partnerships**
Common Diseases
- Alzheimer’s disease
- Parkinson’s disease
- Age-related macular degeneration
- Alcohol addiction
- Alcohol withdrawal
- Alcoholic neuropathy
- Anosmia
- Anxiety
- Apraxia
- Bipolar disorder
- Chemo-induced peripheral neuropathies
- Diabetic neuropathies
- Diabetic retinopathies
- Dyspraxia
- Epilepsy
- Fibromyalgia
- Lewy body dementia
- Metabolic syndrome
- Mild cognitive impairment
- Multiple sclerosis
- Obesity
- Pain
- Parkinson’s-dementia
- Peripheral nerve injury
- Schizophrenia
- Spinal cord injury
- Stroke
- Traumatic brain injury
- Type 1 diabetes
- Type 2 diabetes
- Vascular dementia
- Attention Deficit - hyperactivity disorder
Various Diseases Share Drug Targets
Preclinical Pipeline In Multiple Indications to be selected with 4 pre-existing patented compounds

- Preclinical pipeline includes Pleodrugs combining Baclofen, Acamprosate, Naltrexone, Sorbitol, other compounds and Standards Of Care
- Pipeline targets orphan and common diseases and is protected by robust IP

Optimally, 5-6 indications from this list of candidates will be selected for further clinical trials based on:

- Shortest trial duration
- Optimal well-defined efficacy endpoints
- Cost
- Competition
- Expected peak sales

Orphan diseases:
- Amyotrophic Lateral Sclerosis
- Acute idiopathic demyelinating polyneuropathy
- Alzheimer's disease
- Alcohol addiction
- Anosmia
- Anxiety
- Apraxia
- Bipolar disorder
- Peripheral neuropathies
- Dyspraxia
- Epilepsy
- Fibromyalgia
- Lewy body dementia
- Metabolic syndrome
- Multiple sclerosis
- Obesity
- Pain
- Parkinson’s-dementia
- Peripheral nerve injury
- Schizophrenia
- Spinal cord injury
- Stroke
- Traumatic brain injury
- Type 1 diabetes
- Type 2 diabetes
- Vascular dementia
- Attention Deficit - hyperactivity disorder

Common diseases:
- Charcot-Marie-Tooth type 2
- Cortical-basal ganglionic dystrophy
- Frontotemporal dementia
- Huntington’s disease
- Lewy body dementia
- Metabolic syndrome
- Multiple sclerosis
- Obesity
- Pain
- Parkinson's-dementia
- Peripheral nerve injury
- Schizophrenia
- Spinal cord injury
- Stroke
- Traumatic brain injury
- Type 1 diabetes
- Type 2 diabetes
- Vascular dementia
- Attention Deficit - hyperactivity disorder
Pharnext Business Model

**Orphanext**

Internal pipeline for **orphan indications**:

- **PXT3003** for Charcot-Marie-Tooth Disease Type 1A
- **PXT864** for rare neurodegenerative diseases

**Partnerships**

Common indications:

- **TASLY** (Oncology, cardiovascular and neurovascular disorders)
- **Galápagos** (Immunoinflammatory and neurodegenerative disorders)
Tasly Strategic Partnership

### Tasly Key Financials (2016)
- Top 10 Chinese pharmaceutical company
- Revenue: €2B
- 20,000 employees
- Market cap (Shanghai Stock Exchange): €6B

### Tasly Business Activities
- Development, manufacturing and distribution of pharmaceutical products
- Focus on Modernized Traditional Chinese Medicine (M-TCM)
- Lead Asset Dantonic® On Path to FDA Approval

### Strategic Partnership Highlights
May 10th 2017: Signature of 3 agreements
1. €20M financial investment by Tasly in Pharnext
2. Joint Venture Company in China
3. Licensing agreement for PXT3003 for treatment of CMT in China
PXT3003
What is Charcot-Marie-Tooth Disease Type 1A?

<table>
<thead>
<tr>
<th>Characteristics/Symptoms</th>
<th>Chronic, severe, debilitating inherited neuropathy leading to muscle atrophy in extremities: walking and hand disabilities up to handicap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>~100,000 people affected with mild to moderate CMT1A in US and EU5</td>
</tr>
<tr>
<td>Treatment Options</td>
<td>No drug approved or in clinical development, only supportive care</td>
</tr>
<tr>
<td>Barriers to entry</td>
<td>In addition to robust IP until at least 2030, orphan drug status in US and EU5 provides also market exclusivity</td>
</tr>
<tr>
<td>Expected Peak Sales</td>
<td>Approx. &gt; $1 billion (U.S. +EU5)</td>
</tr>
</tbody>
</table>
Targeting Both Cause & Consequences of Genetic Impairment in CMT1A with PXT3003

Disease at-a-glance

Genetic Defect: PMP22 duplication

The CMT network

Muscarinic receptor

GABA receptor

Opioid receptor

Naltrexone

Baclofen

Sorbitol

Improving

- Myelin
- Axon
- Muscle
- Inflammation

“Polytherapy with a combination of three repurposed drugs (PXT3003) down-regulates Pmp22 over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy”

Chumakov et al., Orphanet Journal of Rare Diseases 2014, 9:201
Phase 2A Trial in CMT1A
Unique Combination of Small Doses

• Assessment Measures / Endpoints
  - Safety and tolerability
  - 11 exploratory efficacy endpoints
  - No Phase 1 needed

• Phase 2A Trial Design
  - 12-month treatment in 6 French reference centers
  - Placebo-controlled, randomized and double-blind
  - Oral liquid low dose formulation given twice daily

• Dosing
  - Same fixed ratio of 3 different doses ranging from 1/1,000 to 1/20 of approved dose
Phase 2A Trial of PXT3003 in CMT1A
Promising & Significant Efficacy Results

Positive efficacy results on composite z-score*

High dose
Significant improvement vs placebo (p = 0.007)
vs baseline (p = 0.0006)

Intermediate dose

Placebo

Low dose

Significant dose effect
(p = 0.003)

*Z-score summing all objective measures: clinical measures (CMTES, ONLS, PEG test, walk test, QMT) and electrophysiology variables. Abbreviations: LD, Low Dose; ID, Intermediate Dose; HD, High Dose.
Phase 2A Efficacy Results on ONLS: Disability
Previously used for approvals of Tegeline®, Octagam® and Privigen® in similar diseases

Main Efficacy Criteria (ONLS) for FDA and EMA
ITT population

- **High dose**: 18.6% (0.4 point) improvement vs placebo*
- **Intermediate dose**: (0.3 point increase vs placebo)
- **Low dose and Placebo**: Significant dose effect (p < 0.01)

*Attarian et al., Orphanet Journal of Rare Diseases 2014, 9:199
Abbreviations: ONLS, Overall Neuropathy Limitations Scale.
Phase 3 Trial in CMT1A: Fully Enrolled FDA/EMA Approved Design; Top-line Results H2 2018

• **Endpoints defined with FDA & EMA**
  - Primary endpoint: ONLS
  - Clinical and EMG endpoints: consistency with ONLS

• **PLEO-CMT Trial Design**
  - Pivotal, randomized, 15-month, double blind, placebo-controlled
  - 30 centers across the U.S., EU and Canada
  - 9-month open-label extension study initiated (PLEO-CMT-FU)
  - Formulation: oral liquid solution given twice a day

Abbreviations: ONLS, Overall Neuropathy Limitation Scale; EMG, electromyography.
*Partially open-label, amended protocol to address formulation solubility in 2x Phase 2 high dose arm.
PXT864
New Mechanism of Action: 
Restoring a Chemical Disbalance\(^1\) - Common & Orphan diseases

**Disease at-a-glance**

Alzheimer and other diseases  
Rare & Common

Healthy brain  
Diseased brain

\[ \text{Glu: Glutamate} \]

\[ \text{Aβ, Tau, αSyn,…} \]

**AD, ALS, PD Network analysis**

GABA receptor  
Glutamate receptor

**Design of PXT864**

Acamprosate  
Baclofen  
GABA receptor


AD: Alzheimer’s Disease; ALS: Amyotrophic Lateral Sclerosis; PD: Parkinson’s Disease
Phase 2A Trial of PXT864 in Alzheimer’s Disease (2015)
Significant improvement then stabilization

- Total duration: 9 months
  - 3 months, single-blind crossover including full 2nd month with placebo
  - 6 months open extension ITT
- Mild patients: 45 ITT, 32 PP
- 12 clinical efficacy endpoints
- 3 doses: ranging per day
  - Baclofen: 12 – 30 mg (1/10)
  - Acamprosate: 1 – 40 mg (1/50)

Abbreviations: ADAS-cog, Alzheimer’s Disease Assessment Scale-cognitive.

*p = 0.027
Phase 2A Trial of PXT864 in Alzheimer’s Disease (2015)
Additional double blind analysis based on both drug’s C Max

- All the same posology but different blood concentration (Cmax) from Low (L) to High (H)

+ trend at 15%
* significant at 5%

A\textsubscript{L}B\textsubscript{L} (n = 10)
A\textsubscript{H}B\textsubscript{L} (n = 7)
A\textsubscript{L}B\textsubscript{H} (n = 7)
A\textsubscript{H}B\textsubscript{H} (n = 7)
Phase 2A Trial of PXT864 in Alzheimer’s Disease (2015)
Additional double blind analysis based on both drug’s C Max

• Higher response in patients with higher blood concentration for both drugs ($A_H / B_H$)

**Cognitive test on Alzheimer patients**

After 3 months of treatment

- **A_L B_L** (n = 10)
- **A_H B_H** (n = 7)
- **A_L B_H** (n = 7)
- **A_H B_H** (n = 7)
- **All - A_H B_H** (n = 24)

+ trend at 15%
* significant at 5%

1 data presented on n=31 patients – PP population with available blood dosage
Cognitive test = ISAACS test after 3 months of treatment
Phase 2A Trial of PXT864 in Alzheimer’s Disease (2015)
Additional double blind analysis based on both drug’s C Max

Strong confirmation of efficacy even with small sample size

- All the same posology but different blood concentration (Cmax) from Low (L) to High (H)
- Higher response in patients with higher blood concentration for both drugs ($A_H / B_H$)

Data presented on n=31 patients – PP population with available blood dosage
Cognitive test = ISAACS test after 3 months of treatment
Towards personalized Blood Concentration

Phase 2A Trial of PXT864 in Alzheimer’s Disease (2015)
Additional double blind analysis based on both drug’s C Max

Abbreviations: ADAS-cog, Alzheimer’s Disease Assessment Scale-cognitive; $A_{HHB_H}$: highest Acamprosate blood dosage amongst $A_{HB_H}$. 

* $p = 0.027$
Phase 2A Trial of PXT864 in Alzheimer’s Disease (2015)
Additional double blind analysis based on both drug’s C Max

Meta-Comparison with Aducanumab

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive.

*p = 0.027
Abbreviations: Zscore, standardized sum of all endpoints; [HH]-, all treated excluding HH patients; H, high drug concentration; L, low drug concentration; CMT1A, Charcot-Marie-Tooth disease Type 1A; AD, Alzheimer’s Disease.
Potential of PXT864 in Other Neurodegenerative Diseases

Networks confirm similar imbalance in ALS and PD

PXT864 could be developed in ALS, ADHD and PD

Patents granted for PXT864 plus Standards of Care: donepezil and levodopa

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; PD, Parkinson’s Disease; ADHD, Attention Deficit Hyperactivity Disorder.

Patents granted for PXT864 plus Standards of Care: donepezil and levodopa.
# Expected Upcoming Milestones

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<th>Year</th>
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## CMT1A*

- PXT3003 (adult)
  - Ph 3 adaptive design analysis
- PXT3003 (adult)
  - Ph 3 futility analysis
- PXT3003 (adult)
  - Top-line Ph 3 results
- **PXT3003 (adult)**
  - Potential market approval US/EU

## Other Indications

- **Selection of Additional Indications**
- **Pursuing partnerships for AD and other common diseases**
- **Launch other Ph 2A (orphan)**

### Repurposed Standards of Care

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*CMT1A: Charcot-Marie-Tooth disease type 1A

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Appendix
Interim Financial Statements
## H1 2017 Financial Results

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<th>as €K (1) – IFRS at 30 June</th>
<th>H1 2017</th>
<th>H1 2016</th>
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<tr>
<td>Other income</td>
<td>1,216</td>
<td>1,993</td>
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<tr>
<td>Research &amp; development expenses</td>
<td>(7,610)</td>
<td>(5,740)</td>
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<tr>
<td>Administrative costs</td>
<td>(2,936)</td>
<td>(1,927)</td>
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<tr>
<td><strong>Operating income</strong></td>
<td>(9,330)</td>
<td>(5,674)</td>
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<td>Financial income</td>
<td>(767)</td>
<td>(2,295)</td>
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<tr>
<td><strong>Net income</strong></td>
<td>(10,098)</td>
<td>(7,969)</td>
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<tr>
<td>Net cash flows generated from (used in) operating activities</td>
<td>(12,108)</td>
<td>(3,692)</td>
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<td>Net cash generated from (used in) investment activities</td>
<td>(152)</td>
<td>(296)</td>
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<td>Net cash generated from (used in) financing activities</td>
<td>1,740</td>
<td>5,907</td>
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<tr>
<td>Change in cash and cash equivalents</td>
<td>(10,521)</td>
<td>1,919</td>
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<tr>
<td>Cash and cash equivalents</td>
<td>6,149</td>
<td>5,008</td>
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<tr>
<td><strong>Pro forma cash after Tasly investments</strong></td>
<td>26,149</td>
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(1) In €K as at 30 June
Pharnext on the Stock Market
Pharnext’s Shareholder Structure
as of 23 October 2017 – based on 11,184,615 shares

- Kotys: 22.73%
- Founders & Employees: 16.21%
- Industrials: 10.87%
- Tasly: 10.51%
- Truffle: 3.93%
- CBLux: 3.57%
- Public: 32.18%
Stock History

Stock information

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<tr>
<td>Number of securities</td>
<td>11,192,615</td>
</tr>
<tr>
<td>Share price on 01 March 2018</td>
<td>€8.20</td>
</tr>
<tr>
<td>Market cap. at 01 March 2018</td>
<td>€87m</td>
</tr>
<tr>
<td>12-month high</td>
<td>€10.7 (16/05/2017)</td>
</tr>
<tr>
<td>12-month low</td>
<td>€7.53 (02/03/2017)</td>
</tr>
</tbody>
</table>

Source: Euronext - figure at 01/03/2018

Change in stock price and volumes
(Since 18 July 2016)
Lowering PMP22 overexpression improves signaling in CMT1A Schwann cells

Network controlling PMP22 gene expression

ATP/glutamate pro-inflammatory cytokines

Muscle cells

Neurons

Immune cells

Global effect

Schwann Cells

- genes mutated in CMT disease
- therapeutic target of baclofen
- therapeutic target of naltrexone
- therapeutic targets of sorbitol
- activation
- inhibition