Innovative Treatments for Central Nervous System Disorders
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## Addex Overview

| **Dipraglurant for dyskinesia in Parkinson’s disease** | Pivotal registration program ready to start but suspended due to Covid-19 pandemic, expect to dose first patient in H2 2020*  
US PD-LID market estimated at $4.2B  
FDA Orphan Drug Designation granted in PD-LID |
|------------------------------------------------|-------------------------------------------------------|
| **Validating partnerships with industry** | Indivior partnership - $330M in milestones, tiered royalties up to double digit & funded research program  
J&J deal - €109M in milestones & low double-digit royalties |
| **Leading proprietary technology platform** | “Allosteric modulators” are a validated & differentiated pharmacological approach to address drug targets  
Proprietary biological screening assays and chemical library |
| **Pipeline of in house discovered programs** | Innovative drug candidates for well validated targets  
Creating future partnership opportunities  
Driving long term growth |
| **Strong balance sheet** | Traded on the SIX Swiss Stock Exchange under ticker ADXN  
ADS representing 6 shares traded on Nasdaq under ticker ADXN  
Cash of CHF 27.1M at 31 March 2020 - Runway through 2021 |

* pending removal of governmental restrictions and lessening of the impact of the global coronavirus pandemic on the U.S. healthcare system, which delayed our previously anticipated initiation in the first quarter of 2020
Leadership Team

Tim Dyer  
CEO / CFO  
Co-Founder of Addex  
Formerly with PwC  
UK Chartered Accountant

Dr Roger Mills  
Chief Medical Officer  
Developed Nuplazid in PD Psychosis  
30 years in Pharma industry including Pfizer, Gilead and Acadia Pharmaceuticals

Dr Robert Lutjens  
Head of Discovery Biology  
Member of Addex founding team  
Formerly with Glaxo & Scripps Research Institute

Dr Jean-Philippe Rocher  
Head of Discovery Chemistry  
Member of Addex founding team  
Formerly with Pierre Fabre, GSK and Mitsubishi

Board of Directors

Vincent Lawton  
Chairman  
Former European Head of Merck & Co.  
Former MHRA Board member

Ray Hill  
Board member  
Former Executive Director Merck & Co.

Jake Nunn  
Board member  
Former Partner New Enterprise Associates

Isaac Manke  
Board member  
Former Partner New Leaf Venture Partners
• Established SAB of world-leading neuroscientists and drug discovery & development experts

• To strengthen our scientific strategy and help advance our pipeline
  • Support the execution of our clinical programs
  • Steer our unique pipeline of neurological and other diseases
  • Identify future applications of our proprietary allosteric modulation platform
## In House Discovered Pipeline

<table>
<thead>
<tr>
<th>Molecule / MoA</th>
<th>Indication</th>
<th>Partner</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Milestone</th>
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</thead>
<tbody>
<tr>
<td>Dipraglurant-IR (mGlu5 NAM)</td>
<td>PD-LID</td>
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<td>Expect topline results in Q2 2022</td>
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<td>Dipraglurant-ER (mGlu5 NAM)</td>
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<tr>
<td>ADX71149 (mGlu2 PAM)</td>
<td>Epilepsy</td>
<td>Janssen</td>
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<td>GABA&lt;sub&gt;B&lt;/sub&gt; PAM</td>
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<td>Indivior</td>
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<td>CMT1A</td>
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<tr>
<td>mGlu7 NAM</td>
<td>Post-traumatic stress disorder</td>
<td>Eurostars</td>
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<tr>
<td>mGlu2 NAM</td>
<td>Mild neurocognitive disorders</td>
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<tr>
<td>mGlu4 PAM</td>
<td>Parkinson’s disease</td>
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<tr>
<td>mGlu3 PAM</td>
<td>Neurodegenerative disorders</td>
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**Lead Program Entering US Pivotal Study and Multiple Orphan Drug Opportunities**

NAM = Negative Allosteric Modulator  
IR = Immediate Release  
PAM = Positive Allosteric Modulator  
ER = Extended Release
Dipraglurant for Parkinson’s Disease
## The Dipraglurant Opportunity in Dyskinesia associated with PD

### Clear development & regulatory path
- Pivotal study ready to dose patients but suspended due to Covid-19 pandemic, expect to dose first patient in H2 2020*
- Precedented FDA regulatory path

### Unmet need and significant commercial opportunity in PD-LID
- >1M Parkinson’s disease patients in US of which >170,000 have dyskinesia
- US LID market estimated at $4.2B
- Dipraglurant US peak sales estimated more than $1.0B
- Pricing of PD therapeutics – Nuplazid ($30K p.a.) and Gocovri ($28.5K p.a.)

### Dipraglurant: unique mechanism of action
- In house discovered, selective, orally available small molecule mGlu5 NAM
- PK profile mirrors that of L-dopa, ideal to treat LID
- Normalizes hyperglutamatergic state during L-dopa dosing

### Strong IP position
- Composition of matter through June 2025 & strong polymorph patent through 2034 (without extensions)
- US FDA orphan drug designation in PD-LID

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* pending removal of governmental restrictions and lessening of the impact of the global coronavirus pandemic on the U.S. healthcare system, which delayed our previously anticipated initiation in the first quarter of 2020
Levodopa-Induced Dyskinesia in Parkinson’s Disease (PD-LID)

| Long-term L-dopa use is invariably associated with the development of dyskinesias | ➢ Dyskinesias result from the neurodegenerative process that underlies PD  
➢ Dopamine replacement does not lead to dyskinesia per se, but lowers the triggering threshold for symptoms  
➢ LID can become as disabling as the PD symptoms themselves |
|---|---|
| LID symptoms: irregular migrating uncontrollable contractions or twisting and writhing due to dystonia, chorea, and choreoathetosis | ➢ These can be painful, lead to weight loss, fatigue and exhaustion, with increased risk for falls and injuries  
➢ Lead to withdrawal from social interaction, isolation, frustration, depression, reduced quality of life and increased burden on caregiver |
| Prevalence of LID is related to disease duration | ➢ Within 4-6 years of L-dopa treatment, LID is experienced by >40% of patients  
➢ By 9-15 years of L-dopa treatment, LID affects 90% of PD patients  
➢ Next-generation L-dopa will not negate LID |
| Over time PD drugs become less effective, exacerbated by the emergence of LID | The doctor is faced with a balancing act where treatment regimens must be continually adjusted to ensure adequate symptom control while minimizing intolerable side effects |
Dipraglurant - Overview and Mechanism of Action

**Overview and Mechanism of Action**

- Loss of substantia nigra neurons combined with the non-physiological, pulsatile stimulation of dopamine receptors with L-Dopa are at the basis of LID development.

- In the striatum, **LID is the result of:**
  
  A. *D1 receptor priming*
  B. *Excess glutamate transmission*
  C. *Loss of LTP depotentiation*

- Metabotropic glutamate receptors are attractive drug targets due to their **modulatory** action to normalize glutamatergic activity and restoration of LTP depotentiation.

- mGlu5 receptors are implicated in the control of glutamate transmission.

- Inhibition of mGlu5 decreases the excess glutamatergic tone thereby controlling dyskinesia.

- Dipraglurant is an oral, highly selective negative allosteric modulator of the mGlu5 receptor.

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**Legend:**

- **L-DOPA**: Dopamine
- **mGlu5**: Metabotropic glutamate receptors
- **D1R PRIMING**: D1 receptor priming
- **LTP = Long Term Potentiation**
- **MSN = Medium Spiny Neurons**
- **DYSKINESIA**
- **D1R PRIMING**
- **NORMALIZATION OF GLU TRANSMISSION**
- **RESTORED LTP DEPOTENTIATION**
- **REDUCTION OF DYSKINESIA**
- **DYSREGULATED DOPAMINE CLEARANCE**

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**Images:**

1. **Severe PD (advanced neuron degeneration)**
2. **Dopamine**
3. **L-Dopa (drug)**
4. **Dipraglurant**
5. **STRIATUM**
6. **MSN**
7. **mGlu5**
8. **NMDA**

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**Further Notes:**

- **DIPRAGLURANT**
- **MALADAPTIVE PLASTIC CHANGES**
- **EXCESSIVE GLU TRANSMISSION**
- **LOSS OF LTP DEPOTENTIATION**

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**References:**

10. **L-DOPA**
Dipraglurant PK is a Key Advantage for Treating LID

Pharmacokinetic Profile of Dipraglurant and L-dopa* in Humans

- Dyskinesia symptoms are correlated to peak levels of L-dopa
- PK profile of dipraglurant mirrors that of L-dopa
- Dipraglurant normalizes abnormal glutamate stimulation during peak levodopa dose

PK profile differentiates dipraglurant from other treatments

* Clinical Neuropharmacology
Vol 22 No.1 pp.24-29
Dipraglurant EU and US Phase 2a Study in LID

Multicentre study in 25 centres across US and Europe

N= 76

N= 24: Placebo

N= 52: Dipraglurant

Up-titration: 50 mg qd - 100 mg tid

Fixed dose 100 mg tid

Double-blind treatment period

Day 1

Day 14

Day 28

• **Primary objective:** safety & tolerability
• **Secondary objective:** exploratory efficacy:
  - Modified Abnormal Involuntary Movement Scale (mAIMS) on Day 1, 14 and 28
  - Unified Parkinson’s Disease Rating Scale (UPDRS)
  - Clinician Global Impression of Change (CGIC)
  - Pharmacokinetics (PK)
  - Patient diaries of “On” & “Off” time

Measuring acute effect of mid-day dose on days 1, 14 and 28

<table>
<thead>
<tr>
<th>Days</th>
<th>1-3</th>
<th>4-7</th>
<th>8-13</th>
<th>14-16</th>
<th>17-21</th>
<th>22-28</th>
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<tbody>
<tr>
<td>AM</td>
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<td></td>
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<tr>
<td>Noon</td>
<td>50</td>
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<td>PM</td>
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<tr>
<td>Daily</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
</tr>
</tbody>
</table>

Coordinating Investigator: Prof Olivier Rascol at University Hospital, Toulouse, France
R= Randomization
Dipraglurant had a statistically significant effect on the first day.

Dipraglurant reduced dyskinesia compared to placebo at all visits over the 28 days.

Placebo response resulted in significance being lost at day 28.

Dose titration contributed to placebo response (patients only on full dosage for last 7 days).

No placebo-mitigating techniques deployed in study.

**Clear dose response but need to manage placebo**
A 30% reduction in mAIMS
- One patient was able to hold & read a newspaper for the first time in years
- Another patient had improved speech and became more easily intelligible

Responder analysis reinforces robustness of dipraglurant anti-dyskinetic effect

<table>
<thead>
<tr>
<th>Responder analysis (≥30% change of peak mAIMS from baseline)</th>
</tr>
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<tbody>
<tr>
<td>Midday dose</td>
</tr>
<tr>
<td>Day 1 (50 mg)</td>
</tr>
<tr>
<td>Day 14 (100 mg)</td>
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<tr>
<td>Day 28 (100 mg)</td>
</tr>
</tbody>
</table>
Relatively simple scale reflecting everyday clinical practice

Assessment by treating physician and thus more objective than the more subjective mAIMS

Assessed at end of study compared to baseline

Clinician Rated Global Impression of Change - Dyskinesia

Dyskinesia improved with dipraglurant according to clinicians (p<0.05)
After 4-week treatment with dipraglurant:

- "On" time with dyskinesia **reduced** during the day
- "On" time without dyskinesia **increased** and maintained during the day
Dipraglurant Demonstrated Good Safety and Tolerability in PD Patients

- Adverse events were common in both treatment groups (dipraglurant 88.5%, placebo 75%)
- The majority of patients completed the dose escalation regimen
- Most common AEs:

<table>
<thead>
<tr>
<th></th>
<th>Dipraglurant</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening Dyskinesia</td>
<td>21% (15.3%*)</td>
<td>12.5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td>4%</td>
</tr>
</tbody>
</table>

* 3 of the 11 patients who reported “worsening dyskinesia” did so only in the follow up period (i.e. when not taking the drug). Thus the dyskinesia recurred only after therapy had stopped. Therefore the adjusted AE% is 15.3% for dipraglurant arm vs.12.5% for placebo arm.

- AEs caused discontinuation in 2 patients taking dipraglurant 100 mg
- AEs at the 50 mg dose level (wk 1 and 2) were less frequent – 53% vs 58% pbo than at the 100 mg dose level (wk 3 and 4) – 73% vs 63% pbo
- No treatment effects on ECG, HR, BP, haematology and biochemistry

Safety profile suitable for continued development in PD (KOLs and DSMB)
Dipraglurant PD-LID Registration Program Started

• First pivotal registration study (301) is ready to start dosing patients, but suspended due to Covid-19 pandemic
  – Study is expected to read out 18 months from first patient dosing

• 12 month Open Label Study (302) starting in parallel to study 301
  – 6 and 12 month safety data

• Primary endpoint: UDysRS – more sensitive to treatment effect than mAIMS and less prone to placebo response (Goetz, 2008 and 2013)

• Placebo mitigation is a priority

• Second pivotal registration study (303) to follow study 301 completion

• Considering Fast-Track and/or Breakthrough Therapy applications after first pivotal study readout
Dipraglurant First Pivotal PD-LID Study (301)

**Study Design**

- Primary objective is efficacy in reducing LID
  - Change over time in UDysRS at 3 months
- Secondary objectives
  - Change over time in MDS-UPDRS Part III
  - Patient diaries, on & off time
  - CGI-S
  - Safety and tolerability

**Study Design Diagram**

- **Moderate to severe PD-LID**
  - N = 140
  - Randomisation (R)
  - N = 70 Placebo
  - N = 70 Dipraglurant (100mg)
  - Double-blind treatment period
  - Primary End Point Improvement at 3 months
  - OLS = Open label study

**Key Terms**

- OLS = Open label study
Dipraglurant Confirmatory Phase 3 PD-LID Study (303)

**Study Design**

- **N = 140**
- **R = Randomisation**
- **OLS = Open label study**
- **ODS = Open label study**

**N = 70 Placebo**
- Moderate to severe PD-LID

**N = 70 Dipraglurant (100mg)**
- Double-blind treatment period

**Primary End Point**
- Improvement at 3 months

**Secondary End Point**
- Improvement at 6 months

**Primary objective efficacy in reducing LID**
- Change over time in UDysRS at 3 months

**Secondary objectives**
- Change over time in UDysRS at 6 months
- Change over time in MDS-UPDRS Part III
- Patient diaries, on & off time
- CGI-S
- Pharmacokinetics (PK)
- Safety and tolerability

*Addex Therapeutics*

R= Randomisation
OLS = Open label study
## Dipraglurant LID Opportunity

| **LID has a large unmet need and market opportunity** | ➢ > 170K LID patients in US  
➢ ~ $1B US peak sales potential for dipraglurant |
| **Limited competition – only one FDA approved medicine** | ➢ Gocovri (reformulation of generic amantadine) approved in August 2017, safety profile similar to generic  
➢ Dipraglurant is a highly selective orally available mGlu5 NAM  
➢ Improved safety profile & ideal PK profile mirrors levodopa |
| **Clear development plan with precedented regulatory path** | ➢ Two registration trials (301 and 303) with Open Label Study (302)  
➢ UDysRS is more sensitive to treatment effect & less prone to placebo response (Goetz 2008 & 2013)  
➢ Implementing measures to manage placebo response in registration program |
| **Strong patent and market exclusivity** | ➢ NCE and polymorph patent provide protection through 2034 without extensions and data exclusivity  
➢ Orphan Drug Designation – 7 years of market exclusivity |
ADX71149 (JNJ-40411813) for Epilepsy
Partnered with Janssen (JNJ)
**ADX71149 for Epilepsy - Partnership with Janssen**

- Keppra market leader with €770 million in revenue for 2019 and Briviact with €221 million
- Status of ADX71149 development:
  - Phase I complete (more than 8 studies conducted)
  - Phase II study in schizophrenia as adjunctive therapy reported positive data in negative symptoms of schizophrenia – reported 2012
  - Phase II study as adjunctive therapy for anxiety seen in major depressive disorder patients reported in Q1 2014 – signal only
- ADX71149 demonstrated synergistic efficacy with Keppra in preclinical models of epilepsy
- Plan to start Phase 2a POC in epilepsy patient as add-on to standard of care in January 2021 with topline data expected December 2021
- Strategic partnership economics:
  - To date, Addex has received €10.2 million in upfront, research funding and milestones
  - Eligible to receive €109 million in additional pre-launch milestones and low double digit royalties
ADX71149 Preclinical Efficacy in Epilepsy – 6Hz Model

- Preclinical validation in pharmacoresistant mouse Epilepsy model:
  - Keppra efficacy increased by 35 fold when administered with a low dose of ADX71149.
  - Low dose of Keppra leads to 14 fold increase in efficacy of ADX71149.
  - Similar effect observed with Briviact.
  - True synergistic effect.
GABA_B Positive Allosteric Modulators (PAM) for Addiction & Charcot-Marie-Tooth Type 1A (CMT1A) Neuropathy Collaboration with Indivior for Addiction
GABA<sub>B</sub> PAM for Addiction and CMT1A

- GABA<sub>B</sub> is the metabotropic receptor for GABA, main inhibitory neurotransmitter
  - Activation of GABA<sub>B</sub> is beneficial in alcoholism and CMT1A through use of baclofen
  - PAM is a differentiated approach, resulting in potential safety and efficacy advantages over baclofen
- Indivior partnership since 2018
  - Addex is leading a funded research program to deliver novel drug candidates
  - Addex has right to select back up compounds at clinical candidate stage for development in retained indications including CMT1A neuropathy
  - Financials: upfront of USD 5.0M, USD 5.6M research funding received to date, USD 330M of development, regulatory and commercial milestones as well as tiered royalties up to double-digit
- CMT1a is an orphan genetic peripheral polyneuropathy involving duplication of the PMP22 gene
  - Prevalence: 3 in 10,000 - upper limit of orphan classification
  - Most common inherited neurological disease
  - Regulatory path to NDA submission paved by Pharnext PX3003 (fixed dose combination of baclofen, naltrexone and sorbitol)
mGlu7 NAM for Post Traumatic Stress Disorder
(Eurostar Funded Consortium Collaboration)
mGlu7 NAM Program for Post-Traumatic Stress Disorder

• mGlu7 appears to play a central role in fear and anxiety
  — Expression, genetic and pharmacological studies have demonstrated the importance of mGlu7 receptors in anxiety disorders
  — Preclinical studies demonstrate the efficacy of mGlu7 NAMs in PTSD
  — Precise targeting of mGlu7 with NAMs should result in higher efficacy and fewer side effects

• Current treatments for PTSD (behavioral therapy, antidepressants and anxiolytics) are unspecific and largely ineffective
  — Clear unmet medical need - opportunity for improved therapies

• Supported by Eurostar funded consortium
  — €4.85M funding to deliver drug candidates
Addex Allosteric Modulation Technology Platform
Becoming an Exciting Space
What are Allosteric Modulators?

Addex is based on a leading technology platform
Potential benefits

- Novel, orally available drug class
- Superior receptor sub-type selectivity compared to orthosteric ligands
- Bind to non-competitive sites and therefore potential to address intractable targets
- Re-address well characterized and clinically validated GPCR targets
- Potential for improved safety due to selectivity and modulatory pharmacology
- Potentially superior efficacy over long term due to lack of tolerance from more modulatory pharmacology
- Clinical use in combination with competitive agonists
Financials
Financials and Stock

• Cash runway through 2021
  – Cash of CHF 27.1M at 31 March 2020

• Market capitalization: approx. CHF 45M

• No debt

• Traded on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)

• ADS representing 6 shares traded on Nasdaq: ADXN (ISIN: US00654J107; CUSIP: 00654J107)

• 32,848,635 shares outstanding 44.6M (fully diluted)
  – New Enterprise Associated - 13.91%
  – New Leaf Venture Partners - 4.86%
  – CAM Capital – 4.86%
  – Credit Suisse Asset Management - 4.87%
  – Management & board holds -14% (fully diluted basis)

• Analyst coverage:
  – Van Leeuwenhoek - Marcel Wijma
  – valuationLab - Bob Pooler
  – ZKB - Dr. Michael Nawrath
  – Baader Helvea AG – Bruno Bulic
Summary

• Leading technology Platform
• Proprietary in-house discovered pipeline
• Partnerships with Industry
• Lead asset, Dipraglurant moving into pivotal study for large unmet need and commercial opportunity with limited competition
  – Strong mechanism of action rational
  – Experienced team of drug developers
• Top tier US investors – NEA, NLV and CAM Capital
• Dual listed on Swiss SIX exchange & US NASDAQ
• Strong balance sheet
• Attractive valuation
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FOR HUMAN HEALTH

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