Innovative Treatments for Central Nervous System Disorders
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### Dipraglurant for dyskinesia in Parkinson’s disease
- Pivotal registration program ready to start but suspended awaiting resolution of Coronavirus 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
- ADR representing 6 shares traded on Nasdaq under ticker ADXN
- Cash of CHF 31.5M at 31 December 2019 - Runway through 2021

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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
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

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

Board of Directors

addex therapeutics
### 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>
</tr>
</thead>
<tbody>
<tr>
<td>Dipraglurant-IR (mGlu5 NAM)</td>
<td>PD-LID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Expect topline results in Q2 2022</td>
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<tr>
<td>Dipraglurant-ER (mGlu5 NAM)</td>
<td>Dystonia</td>
<td></td>
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<tr>
<td>ADX71149 (mGlu2 PAM)</td>
<td>Epilepsy</td>
<td>Janssen</td>
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<tr>
<td>GABA(_B) PAM</td>
<td>Addiction</td>
<td>Indivior</td>
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<tr>
<td>mGlu7 NAM</td>
<td>Post-traumatic stress disorder</td>
<td>Eurostars</td>
<td></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 in Parkinson’s Disease
### The Dipraglurant Opportunity in Dyskinesia associated with PD

| Clear development & regulatory path | ➢ Pivotal study ready to dose patients but start suspended awaiting resolution of Coronavirus Covid-19 pandemic, expect to dose first patient in H2 2020*  
| | ➢ Precedent 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  
| Dipraglurant: unique mechanism of action | ➢ In house discovered, selective, orally available small molecule mGlu5 NAM  
| | ➢ PK profile mirrors that of L-dopa, making it ideal to treat LID  
| | ➢ Inhibits 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 |

* 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)**

<table>
<thead>
<tr>
<th>Long-term L-dopa use is invariably associated with the development of dyskinesias</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Dopamine replacement does not lead to dyskinesia per se, but lowers the triggering threshold for symptoms</td>
</tr>
<tr>
<td>➢ Dyskinesias result from the neurodegenerative process that underlies PD</td>
</tr>
<tr>
<td>➢ LID can become as disabling as the PD symptoms themselves</td>
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</tbody>
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<table>
<thead>
<tr>
<th>LID symptoms: irregular migrating uncontrollable contractions or twisting and writhing due to dystonia, chorea, and choreoathetosis</th>
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<tbody>
<tr>
<td>➢ This can be painful, lead to weight loss, fatigue and exhaustion, with increased risk for falls and injuries</td>
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<tr>
<td>➢ Leading to withdrawal from social interaction, isolation, frustration, depression, reduced quality of life and increased burden on caregiver</td>
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<table>
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<tr>
<th>Prevalence of LID is related to disease duration</th>
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<tbody>
<tr>
<td>➢ Within 4-6 years of L-dopa treatment, LID is experienced by &gt;40% of patients</td>
</tr>
<tr>
<td>➢ By 9 -15 years of L-dopa treatment, LID affects 90% of PD patients</td>
</tr>
<tr>
<td>➢ Next-generation L-dopa will not negate LID</td>
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<tr>
<th>Over time PD drugs become less effective, exacerbated by the emergence of LID</th>
</tr>
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<tbody>
<tr>
<td>Physicians are faced with a balancing act where drug and dosing regimens must be optimized in order to ensure adequate PD symptom control</td>
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"addex therapeutics"
Dipraglurant - 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

• Preclinical and clinical data show that mGlu5 blockade controls dyskinesia

• Dipraglurant is an oral small molecule active as a highly selective negative allosteric modulator at the mGlu5 receptor with the potential to treat LID

LTP = Long Term Potentiation
MSN = Medium Spiny Neurons

Dipraglurant - Overview and Mechanism of Action

Severe PD
(advanced neuron degeneration)

STRIATUM

L-DOPA

Dopamine

Dipraglurant

mGlu5

D1R PRIMING

MALADAPTIVE PLASTIC CHANGES

EXCESSIVE GLU TRANSMISSION

LOSS OF LTP DEPOTENTIATION

DYSKINESIA

DIPSYCHICPAE

DYSFUNCTIONAL

DOPAMINE CLEARANCE

A

B

C

RESTORING LTP DEPOTENTIATION

NORMALIZATION OF GLU TRANSMISSION

REDUCTION OF DYSKINESIA

A

B

C

Dipraglurant

mGlu5

NMDA

D1R PRIMING

MALADAPTIVE PLASTIC CHANGES

EXCESSIVE GLU TRANSMISSION

LOSS OF LTP DEPOTENTIATION

DYSKINESIA

DIPSYCHICPAE

DYSFUNCTIONAL

DOPAMINE CLEARANCE

A

B

C

RESTORING LTP DEPOTENTIATION

NORMALIZATION OF GLU TRANSMISSION

REDUCTION OF DYSKINESIA

A

B

C
Dipraglurant PK is a Key Advantage for Treating LID

- Dyskinesia symptoms are correlated to peak levels of levodopa therapy
- PK profile of dipraglurant mirrors that of levodopa
- Dipraglurant inhibits abnormal glutamate stimulation during peak levodopa dose but releases the receptor during normal glutamate activity

PK profile differentiates dipraglurant from other treatments

![Pharmacokinetic Profile of Dipraglurant and L-Dopa* in Humans](image)

* 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=24: Placebo**
- **N=52: Dipraglurant**

**Up-titration:** 50 mg qd - 100 mg tid

**Fixed dose:** 100 mg tid

### Days 1-3
- **AM:** 50 mg
- **Noon:** 50 mg
- **PM:** 50 mg
- **Daily:** 150 mg

### Days 4-7
- **AM:** 50 mg
- **Noon:** 50 mg
- **PM:** 50 mg
- **Daily:** 100 mg

### Days 8-13
- **AM:** 50 mg
- **Noon:** 50 mg
- **PM:** 50 mg
- **Daily:** 150 mg

### Days 14-16
- **AM:** 50 mg
- **Noon:** 100 mg
- **PM:** 50 mg
- **Daily:** 200 mg

### Days 17-21
- **AM:** 50 mg
- **Noon:** 100 mg
- **PM:** 100 mg
- **Daily:** 250 mg

### Days 22-28
- **AM:** 50 mg
- **Noon:** 100 mg
- **PM:** 100 mg
- **Daily:** 300 mg

**R**

---

**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

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**Coordinating Investigator:** Prof Olivier Rascol at University Hospital, Toulouse, France

**N= Number of patients; 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.

MMRM analysis of the effect of dipraglurant on the peak mAIMS score reported as reduction from baseline.

- Day 1 (50 mg): Dipraglurant 19.9%, Placebo 4.1%
- Day 14 (100 mg): Dipraglurant 32.3%, Placebo 12.6%
- Day 28 (100 mg): Dipraglurant 31.4%, Placebo 21.5%

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
Clinician rated global impression of change in LID patients after administration of dipraglurant and placebo

- Relatively simple scale that reflects everyday clinical practice
- Assessment by treating physician and thus is a more objective assessment than the more subjective mAIMS
- Assessment performed at end of study compared to baseline

Improvement in dyskinesia with dipraglurant according to clinicians (p<0.05)

<table>
<thead>
<tr>
<th></th>
<th>Dipraglurant</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Improved (p&lt;0.05)</td>
<td>71.2%</td>
<td>49.9%</td>
</tr>
<tr>
<td>No change</td>
<td>17.3%</td>
<td>45.8%</td>
</tr>
</tbody>
</table>
Patient Diaries – Improvement Throughout the Waking Day

Pattern of motor complications of dipraglurant patients over the course of a day, as reported in patients’ diaries

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>
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<th>Dipraglurant</th>
<th>Placebo</th>
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<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>
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</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 any safety monitoring variables (ECG, HR, BP, haematology and biochemistry)

Safety profile suitable for continued development in PD (KOLs and DSMB)
First pivotal registration trial (301) is ready to start dosing patients, but start has been suspended awaiting resolution of Coronavirus Covid-19 pandemic
   - Study is expected to ready out 18 months from first patient dosing

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 (Goetz, 2008) and less prone to placebo response (Goetz, 2013)

Implementing measures to manage placebo response is a priority

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

**Primary objective**
- 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**
- **N= Number of patients**
- **R= Randomisation**
- **LID= L-Dopa induced dyskinesia**
- **OLS = Open label study**

- **Moderate to severe PD-LID**
  - **N=140**
    - **Fixed dose**
    - **Double-blind treatment period**
    - **Primary End Point**
      - End of 3 months
    - **N = 70 Placebo**
    - **N = 70 Dipraglurant (100mg)**
    - **OLS**
**Study Design**

**N=** Number of patients  
**R=** Randomisation  
**LID=** L-Dopa induced dyskinesia  
**OLS=** Open label study  

- **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
## Dipraglurant LID Opportunity

<table>
<thead>
<tr>
<th>Limited competition – only one FDA approved medicine</th>
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<tbody>
<tr>
<td>➢ &gt; 170K LID patients in US</td>
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<tr>
<td>➢ ~ $1B US peak sales potential for dipraglurant</td>
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<tr>
<th>LID has a large unmet need and market opportunity</th>
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<tbody>
<tr>
<td>➢ Gocovri (reformulation of generic amantadine)</td>
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<tr>
<td>➢ Approved on 24th August 17, safety profile similar to generic</td>
</tr>
<tr>
<td>➢ Dipraglurant is a highly selective orally available mGlu5 NAM</td>
</tr>
<tr>
<td>➢ Improved safety profile &amp; Ideal PK profile mirrors levodopa</td>
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<tr>
<th>Clear development plan with precededented regulatory path</th>
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<tbody>
<tr>
<td>➢ Precedented regulatory path paved by Gocovri (Adamas)</td>
</tr>
<tr>
<td>➢ Two registration trials (301 and 303) with Open Label Study (302)</td>
</tr>
<tr>
<td>➢ Managing placebo response in registration trials is key for success:</td>
</tr>
<tr>
<td>➢ UDysRS is more sensitive to treatment effect &amp; less prone to placebo response (Goetz 2013)</td>
</tr>
<tr>
<td>➢ Implementing measures to manage placebo response in registration program</td>
</tr>
</tbody>
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<tr>
<th>Strong patent and market exclusivity</th>
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<tbody>
<tr>
<td>➢ NCE and polymorph patent provide protection through 2034 without extensions and data exclusivity</td>
</tr>
<tr>
<td>➢ Orphan Drug Designation – 7 years of market exclusivity</td>
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Addex Allosteric Modulation Technology Platform
Becoming an Exciting Space
What are Allosteric Modulators?

Addex is based on a leading technology platform
Using Allosteric Modulation to Discover Novel CNS Drug Candidates

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
- Potentially 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

The alliance with Indivior focusing on discovery of GABA_B Positive Allosteric Modulators (PAMs) for addiction

- Positive Allosteric Modulator (PAM) is a differentiated pharmacological approach
  - Potential safety and efficacy advantages – lack of tolerance and less side effects
- Addex leading funded research effort to deliver drug candidates for preclinical / clinical development
  - Addex has right to select back up compounds at clinical candidate stage for development in retained indications including CMT1A neuropathy

- Worldwide license and collaboration on GABA_B PAM
- GABA_B is the metabotropic receptor for GABA, main inhibitory neurotransmitter
  - Activation of GABA_B is validated through the use of baclofen (GABA_B orthosteric agonist)
    - Approved for the treatment of spasticity
    - Clinical efficacy in alcoholism and Charcot-Marie-Tooth type 1A (CMT1A)

- Financial terms:
  - Upfront of USD 5.0M & USD 5.6M research funding over 2 years
  - USD 330M of development, regulatory and commercial milestones
  - Tiered royalties up to double-digit
Financials
Financials and Stock

- Cash runway through 2021
  - Cash of CHF 31.5M at 31 December 2019

- Market capitalization: approx. CHF 55M

- 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
ALLOSTERIC MODULATORS FOR HUMAN HEALTH