Innovative Treatments for Central Nervous System Disorders

May 2019
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<table>
<thead>
<tr>
<th>Addex Overview</th>
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<tr>
<td><strong>Dipraglurant for dyskinesia in Parkinson’s disease</strong></td>
<td>➢ Pivotal registration program on track to start in Q4 2019</td>
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<td></td>
<td>➢ US PD-LID market estimated at $4.2B</td>
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<td>➢ FDA Orphan Drug Designation granted in PD-LID</td>
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<tr>
<td><strong>Validating partnerships with industry</strong></td>
<td>➢ Indivior partnership - $330m in milestones, tiered royalties up to double digit &amp; funded research program</td>
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<td>➢ J&amp;J deal - €109m in milestones &amp; low double digit royalties</td>
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<tr>
<td><strong>World leading technology platform</strong></td>
<td>➢ “Allosteric modulators” are a validated &amp; differentiated pharmacological approach to address drug targets</td>
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<td>➢ Proprietary biological screening assays and chemical library</td>
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<td><strong>Deep pipeline of first / best in class programs</strong></td>
<td>➢ Creating future partnership opportunities</td>
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<td></td>
<td>➢ Driving long term growth</td>
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<tr>
<td><strong>Strong balance sheet</strong></td>
<td>➢ 28.6M shares traded on the SIX Swiss Stock Exchange – ADXN</td>
</tr>
<tr>
<td></td>
<td>➢ Cash of CHF41.7m at 31 December 2018</td>
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<td>➢ Runway through 2021</td>
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</table>
Experienced 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  
Partner New Enterprise Associates

**Isaac Manke**  
Board member  
Partner New Leaf Venture Partners

Experienced Board of Directors
Pipeline with Lead Program Entering US Pivotal Study

<table>
<thead>
<tr>
<th>Molecule / MoA</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>Dipraglurant-IR (mGlu5 NAM)</td>
<td>Parkinson’s disease levodopa-induced dyskinesia</td>
<td></td>
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</tr>
<tr>
<td>Dipraglurant-ER (mGlu5 NAM)</td>
<td>Focal cervical dystonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADX71149 (mGlu2 PAM)</td>
<td>Epilepsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; PAM</td>
<td>Addiction</td>
<td></td>
<td></td>
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</table>

NAM = Negative Allosteric Modulator  
PAM = Positive Allosteric Modulator

Multiple orphan drug opportunities
# Extensive Discovery Stage Pipeline Driving Long-Term Growth

<table>
<thead>
<tr>
<th>Molecule / MoA</th>
<th>Hit to Lead</th>
<th>Lead Optimization</th>
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</thead>
<tbody>
<tr>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; PAM</td>
<td>Charcot-Marie-Tooth GABA&lt;sub&gt;B&lt;/sub&gt; PAM</td>
<td></td>
</tr>
<tr>
<td>mGlu7 NAM</td>
<td>Psychiatric Disorders (PTSD &amp; Hearing Loss)</td>
<td></td>
</tr>
<tr>
<td>mGlu2 NAM</td>
<td>Mild Cognitive Impairment</td>
<td></td>
</tr>
<tr>
<td>mGlu4 PAM</td>
<td>Parkinson’s Disease</td>
<td></td>
</tr>
<tr>
<td>mGlu3 PAM</td>
<td>Neurodegenerative Disorders</td>
<td></td>
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<tr>
<td>TrkB PAM</td>
<td>Neurodegenerative Disorders</td>
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</tbody>
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PAM = Positive Allosteric Modulator  

Promising pipeline of potential drug candidates
Dipraglurant in Parkinson’s Disease
## The Dipraglurant Opportunity in Dyskinesia Associated with PD

### Clear Development & Regulatory Path
- Pivotal studies on track to start in Q4 2019
- Manufacturing and planning ongoing
- 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 at $1.4B

### Dipraglurant: Unique Mechanism of Action
- First-in-class, selective, oral small molecule mGluR5 NAM
- PK profile mirrors that of L-dopa, making it ideal to treat LID
- Normalizes abnormal glutamate stimulation 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
### 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>
<th>Dopamine replacement does not lead to dyskinesia per se, but lowers the triggering threshold for symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>LID symptoms: irregular migrating uncontrollable contractions or twisting and writhing due to dystonia, chorea, and choreoathetosis</td>
<td>Dyskinesias result from the neurodegenerative process that underlies PD</td>
</tr>
<tr>
<td>Prevalence of LID is related to disease duration</td>
<td>LID can become as disabling as the PD symptoms themselves</td>
</tr>
<tr>
<td>Over time PD drugs become less effective, exacerbated by the emergence of LID</td>
<td>This can be painful, lead to weight loss, fatigue and exhaustion, with increased risk for falls and injuries</td>
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<td></td>
<td>Leading to withdrawal from social interaction, isolation, frustration, depression, reduced quality of life and increased burden on caregiver</td>
</tr>
<tr>
<td></td>
<td>Within 4-6 years of L-dopa treatment, LID is experienced by &gt;40% of patients</td>
</tr>
<tr>
<td></td>
<td>By 9 -15 years of L-dopa treatment, LID affects 90% of PD patients</td>
</tr>
<tr>
<td></td>
<td>Next-generation L-dopa will not negate LID</td>
</tr>
<tr>
<td>The doctor is faced with a balancing act where drug and dosing regimens must be continually optimized in order to ensure adequate symptom control while minimizing intolerable side effects</td>
<td></td>
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Dipraglurant - Overview & Mechanism of Action

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

- In the striatum, **LID is the result of:**
  - **A** D1 receptor priming
  - **B** Abnormal 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 mGluR5 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.
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

Dipraglurant PK/PD profile is ideal for treating LID
Dipraglurant EU and US Phase 2a Study in LID

Multicentre study in 25 centres across US and Europe

Coordinating Investigator: Prof Olivier Rascol at University Hospital, Toulouse, France
N= number of patients; R= randomization

Day 1

Day 14

Day 28

Up-titration: 50 mg qd -100 mg tid

Fixed dose 100 mg tid

Double-blind treatment period

N= 24: Placebo
N=52: Dipraglurant
N=76

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 and Patient Global Impression of Change (CGIC & PGIC)
– Pharmacokinetics (PK)
– Patient diaries of ON & OFF time

Days 1-3 4-7 8-13 14-16 17-21 22-28

Dose/mg
AM
50
50
50
50
50
100

Noon
50
50
100
100
100

PM
50
50
50
100
100

Daily
50
100
150
200
250
300

Measuring acute effect of mid-day dose on days 1, 14 and 28
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 confounded significance 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:
- No centralized raters
- No independent raters
- Rater not blinded to visit number
- Patients were more moderate than severe

Mean % change of peak mAIMS from baseline

<table>
<thead>
<tr>
<th>Midday dose</th>
<th>Dipraglurant (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (50 mg)</td>
<td>19.9%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Day 14 (100 mg)</td>
<td>32.3%</td>
<td>12.6%</td>
</tr>
<tr>
<td>Day 28 (100 mg)</td>
<td>31.4%</td>
<td>21.5%</td>
</tr>
</tbody>
</table>

Clear dose response but need to manage placebo.
Responder Analysis Demonstrates Dipraglurant Significant Benefit

### Cumulative % of Patients Showing ≥ 30% Change of Peak mAIMS from Baseline

<table>
<thead>
<tr>
<th>Day</th>
<th>Dipraglurant</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (50 mg)</td>
<td>n=13 26.0%</td>
<td>n=3 12.5%</td>
<td>0.2377</td>
</tr>
<tr>
<td>Day 14 (100 mg)</td>
<td>n=29 56.9%</td>
<td>n=6 25.0%</td>
<td>0.0132</td>
</tr>
<tr>
<td>Day 28 (100 mg)</td>
<td>n=27 55.3%</td>
<td>n=7 29.2%</td>
<td>0.0474</td>
</tr>
</tbody>
</table>

- A 30% reduction in mAIMS is clinically meaningful
  - 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 - Dyskinesia

- 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
- Greater 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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</thead>
<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>

CGIC PBO
CGIC DIP
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 50 and 100 mg Doses Demonstrated Safety and Satisfactory Tolerability in PD Patients

- Adverse events were common in both treatment groups (dipraglurant 88.5%, pbo 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>
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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)
The Phase 3 trial is fully funded and expected to report out in Q3 2021
- Considering Fast-Track and/or Breakthrough Therapy applications after first pivotal study readout
- Management of placebo response is a priority:

<table>
<thead>
<tr>
<th>Objective</th>
<th>Strategy</th>
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<tbody>
<tr>
<td>Minimize rater variability (across and within sites)</td>
<td>➢ Use independent (centralized) raters</td>
</tr>
<tr>
<td>Reduce expectancy bias</td>
<td>➢ Raters blinded to visit and do not rate the same patient at baseline and study endpoint</td>
</tr>
<tr>
<td>Exclude patients with minimal symptoms (as more likely to respond to placebo)</td>
<td>➢ Ensure that symptom score reflects moderate to severe symptoms that warrant therapy</td>
</tr>
<tr>
<td></td>
<td>➢ Ensure occur frequently enough for scale sensitivity</td>
</tr>
<tr>
<td>Exclude potential investigator rating inflation</td>
<td>➢ Independent oversight of screening and use of centralized rater baseline visit score as study entry gate</td>
</tr>
<tr>
<td>Draw placebo response ahead of randomization</td>
<td>➢ Consider non-pharmacologic intervention during screening period</td>
</tr>
<tr>
<td>Ensure no geographic bias</td>
<td>➢ Only include countries / sites where centralized rating is feasible</td>
</tr>
</tbody>
</table>
Dipraglurant pivotal registration studies

1st Pivotal LID Study (301)

N=200
Moderate to severe PD-LID

N=100 Dipraglurant (100mg)
Fixed dose
Double-blind treatment period

N=100 Placebo
End of 3 months ⇒ OLE

2nd Pivotal LID Study (302)

N=200
Moderate to severe PD-LID

N=100 Dipraglurant (100mg)
Fixed dose
Double-blind treatment period

N=100 Placebo
End of 3 months
End of 6 months ⇒ OLE

The Primary and Secondary endpoints for both trials are the same:

- **Primary objective**
  - efficacy in reducing LID
  - ✓ Change over time in UDysRS (wk13 from baseline)

- **Secondary objectives**
  (Safety & tolerability, additional efficacy parameters, PK)
  - ✓ Change over time in MDS-UPDRS Part III
  - ✓ Patient diaries, on & off time
  - ✓ CGI-S
  - ✓ Pharmacokinetics (PK)
  - ✓ Safety and tolerability

N= number of patients; R= randomisation; LID= L-Dopa induced dyskinesia; OLE = open label extension
## Dipraglurant LID Opportunity

| LID has a large unmet need and market opportunity | ➢ > 170K LID patients in US  
➢ ~$1.4bn US market opportunity for dipraglurant |
|-----------------------------|--------------------------------------------------------------------------------|
| Limited competition – only one FDA approved medicine | ➢ Gocovri (reformulation of generic amantadine): Approved on 24th August 17 – safety profile similar to generic  
➢ Dipraglurant 1st in class highly selective oral monotherapy –  
➢ Improved safety profile  
➢ Ideal PK profile mirrors levodopa – recognized by KOLs as key advantage |
| Clear development plan with precededented regulatory path | ➢ Precedented regulatory path paved by Gocovri (Adamas)  
➢ Two registration trials (301 and 302) with Open Label extension |
| 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 |
Promising Preclinical Pipeline
GABA_B PAM Program for Charcot-Marie-Tooth 1A Neuropathy

• Rationale:
  – GABA_B is the metabotropic receptor for GABA, main inhibitory neurotransmitter
  – Activation of GABA_B is validated through the use of baclofen (GABAB orthosteric agonist)
    • Clinical efficacy in Charcot-Marie-Tooth type 1A (CMT1A)
  – Positive Allosteric Modulator (PAM) is a differentiated pharmacological approach
    • Preclinical validation of efficacy of ADX71441 in rodent model of CMT1A
    • Potential safety and efficacy advantages – lack of tolerance and less side effects
• Status:
  – Lead optimization ongoing – progressing towards IND-enabling studies
  – Novel chemical series with potent, selective, orally bioavailable and brain penetrant compounds
  – Significant novel IP in the field
mGlu7 PAM Program for PTSD & Hearing Loss

• Rationale:
  – Based on mGlu7 receptor knockout mice phenotype & mGlu7 receptor pharmacological inhibition studies, negative allosteric modulators show strong potential for anxiety related disorders such as PTSD
  – In addition, other potential indications include pain, neuroprotection, schizophrenia, ADHD, age-related hearing impairment, tinnitus…

• Status:
  – Late lead optimization – progressing towards IND-enabling studies
  – Two main chemical series with potent, selective, orally bioavailable and brain penetrant compounds
  – Preclinical proof-of-concept efficacy in rodent PTSD model; inner ear studies ongoing
  – Significant novel IP in the field
mGlu2 NAM Program for Mild Cognitive Impairment

• Rationale:
  – Potential to treat medical conditions linked to lowered glutamate levels in the brain via restoration of a normalized glutamatergic tone
    • Alzheimer’s Disease (AD): cognitive deficits and possible disease-modifying effect (slowing disease progression via reduction of build-up of amyloid β induced by mGluR2 activation (Kim et al) and reducing chromogranin A-induced microglial neurotoxicity (Taylor et al)
    • Major Depressive Disorder: ketamine-like antidepressant efficacy in depressed patients whilst avoiding the NMDA associated negative effects of ketamine.

• Status:
  – Late lead optimization – 12 month program leading to IND-enabling studies
  – Several novel chemical series with potent, selective, orally bioavailable and brain penetrant compounds
  – Significant novel IP in the field
mGlu4 PAM Program for Parkinson’s Disease

• **Rationale:**
  – Novel non-dopaminergic approach to treat Parkinson’s disease with potential to treat both motor and non-motor symptoms, disease modifying neuroprotective potential:
    • Motor functions: in acute and chronic preclinical models of PD, mGluR4 PAM demonstrated improvement
    • Neuroprotection: effect in MPTP mice model demonstrated with mGluR4 PAM
    • Non-motor (anxiety): mGluR4 activators demonstrated anxiolytic-like response in preclinical rodent models
  – Potential to treat a broad range of debilitating autoimmune disorders linked to aberrant TH17 responses, including rheumatoid arthritis, psoriasis, inflammatory bowel disease and uveitis
  – Raised interest in field following recent acquisition of Prexton Therapeutics by Lundbeck

• **Status:**
  – Late lead optimization – progressing towards IND-enabling studies
  – Several novel chemical series with potent, selective, orally bioavailable and brain penetrant compounds with significant novel IP potential
mGlu3 PAM Program for Neurodegenerative Diseases

• Rationale:
  – Novel mechanism of action for treatment of neurodegenerative disorders & schizophrenia
  – Strong rational and preclinical validation through:
    • Schizophrenia: studies demonstrate GRM3 gene variants association; mGlu3 receptor KO mice exhibit a “schizophrenia-like” phenotype
    • Neurodegenerative diseases: demonstrated neuroprotective effects, with “dual” action: reduction of glutamate release, potentially lowering excitotoxic insult; and stimulation of production of growth factors such as GDNF & TGFβ1

• Status:
  – Lead generation stage
  – Several novel chemical series identified from internal screening of corporate library with proprietary screening tools – two series prioritized
  – Most potent and selective mGlu3 PAMs ever described – first in class potential
  – Significant novel IP in the field
TrkB PAM Program for Neurodegenerative Diseases

• Overview:
  – TrkB is the receptor for BDNF (brain-derived neurotrophic factor)
  – TrkB activation is preclinically validated
    • neurodegenerative diseases - Alzheimer's, Parkinson's, or Huntington's disease
    • potential for both disease-modifying and symptomatic treatment
  – PAM approach enabled identification of novel chemistry

• Status:
  – Lead generation stage
  – Supported with grants from Michael J Fox Foundation and InnoSuisse
  – Collaboration with University of Geneva access to complex in vitro, ex vivo and in vivo models
to probe neuroprotective and neurogenesis potential of TrkB PAMs
Allosteric Modulation
Becoming an Exciting Space
What are Allosteric Modulators?

Addex is based on a world leading technology platform
Allosteric Compounds Provide Unique Opportunity

- Allosteric drugs bind to a position away from the orthosteric (primary) binding site of a target protein
- Allosteric sites can be targeted with great selectivity by allosteric modulators
- When bound by an allosteric drug, the target protein subtly changes in shape either having a positive or negative effect on the biochemical activity induced by the natural ligand
- In addition, an allosteric drug may change the affinity of the target protein for its natural ligand, either increasing or decreasing it. This induces an up/down regulation of the signalling
- This is particularly useful in neurological disorders where fully blocking the target site may be undesirable. Importantly, allosteric drugs are more modulatory, respecting the natural rhythm of receptor activation
- Allosteric modulators therefore have the potential to unlock undruggable targets

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907734/
Hitting previously undruggable targets is an increasingly exciting space with the vast majority of well understood drug targets currently being undruggable.

There is an opportunity for allosteric compounds to find hits for well-validated targets which have no approved drugs because traditional orthosteric approaches have failed to deliver.

Allosteric sites are largely unexplored for drug discovery although it is an increasingly hot area.

There are a number of proprietary technologies that Addex has developed to identify new allosteric approaches in addition to many years of “know-how” held by the employees of the company.

Allosteric approaches are also interesting as the IP landscape is less crowded so there may be greater freedom to operate.

Allosteric Modulators Could Unlock Multiple “Undruggable” Targets

- Hitting previously undruggable targets is an increasingly exciting space with the vast majority of well understood drug targets currently being undruggable.
- There is an opportunity for allosteric compounds to find hits for well-validated targets which have no approved drugs because traditional orthosteric approaches have failed to deliver.
- Allosteric sites are largely unexplored for drug discovery although it is an increasingly hot area.
- There are a number of proprietary technologies that Addex has developed to identify new allosteric approaches in addition to many years of “know-how” held by the employees of the company.
- Allosteric approaches are also interesting as the IP landscape is less crowded so there may be greater freedom to operate.
Allosteric Approach Gathering Momentum

• Academic research into allosteric receptor modulators is increasing – as shown by chart on right

• Ongoing research into identifying structural information about alternative binding sites in proteins are a boon for Addex
  – Addex is well positioned to benefit from the explosion in knowledge in this field and in biology more broadly. As we understand more about underlying cellular biology, the number of potential allosteric targets should increase rapidly
  – Some scientists are taking a lead from nature – which commonly uses allosteric sites for enzyme regulation – as one can be sure such sites are important (e.g. Hotspot therapeutics)
  – Relay therapeutics has developed a system to model protein movement over time to uncover potential new binding sites that would not be visible in static X-ray crystallography

Source: Google Scholar search for “allosteric modulator”

Number of Protein Structures Deposited in Protein Data Bank

Source: Protein Data Bank
Allosteric Approach Gathering Momentum
Multiple examples of allosteric modulators opening up new treatment possibilities

- Novartis’ ABL001 is an allosteric modulator, and demonstrated strong anti-tumour responses as monotherapy in heavily pre-treated patients with Chronic Myeloid Leukemia (including those resistant to Glivec/Tasigna)

- Gilead’s allosteric candidate GS-0976 (acquired as lead asset from its acquisition of Nimbus Apollo for $400m upfront and $800m of milestones) recorded a **positive P2 readout in NASH** in October 2017

- KRAS - a molecular on/off switch implicated in up to 30% of cancers, but there is no obvious blocking site: this “**undruggable**” target **naturally lends itself towards an allosteric approach**. In March 2018, a joint research team from Wellspring and J&J reported the first small molecule KRas inhibitor that worked in animal models. It targeted a mutated cysteine in an allosteric pocket of KRas.
**Allosteric Space Heating Up**

- **HotSpot Therapeutics** was co-founded by Nimbus employees who developed allosteric modulator GS-0976, which was acquired by Gilead for $1.2bn as part of Nimbus Apollo
  - HotSpot looks for natural regulatory sites on proteins, on the basis that evolution has perfected these sites as regulatory switches over millions of years – they claim to have identified over 100 sites to date
  - They completed a $45m series A financing in July 2017, but have yet to IPO
- **Revolution Medicines** try to discover new oncology drugs targeting currently undrugged proteins
  - They specialise looking at atypical binding sites, including (but not exclusively) allosteric sites; they are yet to IPO
- **Cadent Therapeutics** recently raised $40m & signed a deal with Novartis for their NMDA NAM in P2

- In addition, several Big Pharma companies have developed or in-licensed allosteric drugs:

<table>
<thead>
<tr>
<th>Company</th>
<th>Allosteric Drug</th>
<th>Target</th>
<th>Dev Phase</th>
<th>Primary Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche</td>
<td>RG7816</td>
<td>GABA_A alpha5</td>
<td>Ph1-2</td>
<td>Autism Spectrum Disorder</td>
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<tr>
<td>Sanofi</td>
<td>RMC-4630</td>
<td>SHP2</td>
<td>Ph1-2</td>
<td>Solid tumours</td>
</tr>
<tr>
<td>Astellas</td>
<td>ASP-4345</td>
<td>D1R</td>
<td>Ph2</td>
<td>Cognitive Impairment in SCZ</td>
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<tr>
<td>Eli Lilly</td>
<td>LY3154207</td>
<td>D1R</td>
<td>Ph2</td>
<td>Dementia in PD</td>
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<tr>
<td>AstraZeneca</td>
<td>Selumetinib</td>
<td>MEK1/2</td>
<td>Ph2</td>
<td>Liver cancer</td>
</tr>
</tbody>
</table>
What Differentiates Addex’s Allosteric Platform?

- Addex library of ~80k compounds is drug-like, but occupies distinct chemical space (see charts right)
- Fast-hit library is used to validate the initial hit – increasing quality of candidates and saving on cost
- Addex hit confirmation rate of 70-95% vs industry average of 10-30%
- Over 150 proprietary biological assays
- Non-calcium proximal assays are more sensitive and have greater fidelity – leading to fewer false positives and negatives
- Proven track record, with a Phase 3 candidate and collaborations with major Pharma companies
Addex Platform Already Validated – Indivior Partnership Case Study

• **The alliance with Indivior** focusing on discovery of GABA$_{B}$ Positive Allosteric Modulators (PAMs) for addiction

• 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)

• Positive Allosteric Modulator (PAM) is a differentiated pharmacological approach
  — Potential safety and efficacy advantages – lack of tolerance and less side effects

• Worldwide license and collaboration on GABA$_{B}$ PAM

• 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

• Financial terms:
  — Upfront of USD 5 million & USD 4 million research funding over 2 years
  — USD 330 million of development, regulatory and commercial milestones
  — Tiered royalties up to double-digit royalties
Financials
Financials and Stock

- Cash runway through 2021
  - Cash of CHF41.7M at 31 December 2018
  - Fully funded through dipraglurant study 301 readout

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

- 28,564,031 shares outstanding (37.7M fully diluted)
  - New Enterprise Associated – 16%
  - New Leaf Venture Partners – 5.6%
  - CAM Capital – 5.6%
  - Credit Suisse Asset Management – 5.5%
  - Management & board holds - 15% (fully diluted basis)

- Analyst coverage:
  - Van Leeuwenhoek – Marcel Wijma

- Market capitalization: approx. CHF50M

- No debt
## Upcoming Major Development Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipraglurant – LID Phase 3 Registration Program</td>
<td></td>
</tr>
<tr>
<td>Complete manufacturing of Drug Product</td>
<td>Q3 2019</td>
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<tr>
<td>Study 301 – start dosing</td>
<td>Q4 2019</td>
</tr>
<tr>
<td>Study 301 – Top line data</td>
<td>Q3 2021</td>
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</table>
ALLOSTERIC MODULATORS FOR HUMAN HEALTH

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