IRLAB Therapeutics
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Developing novel treatments in Parkinson’s disease

The Integrative Screening Process (ISP)
- Proprietary technology platform. A unique systems pharmacology discovery approach

Two leading programs in Phase II
- IRL790 to treat PD-LIDs and PD-P
- IRL752 to treat Postural Instability/falls in PD

Company listed on Nasdaq Stockholm
First North Premier (IRLAB-A)
- In transit to Nasdaq Stockholm Main Market
Addressing Top Priorities in the Management of PD

**BMJ Open** Priority setting partnership to identify the top 10 research priorities for the management of Parkinson’s disease

Katherine H O Deane,1 Helen Flaherty,1 David J Daley,1 Roland Pascoe,1 Bridget Penhale,1 Carl E Clarke,2,3 Catherine Sackley,4 Stacey Storey5

1. Postural instability (balance) and falls → IRL752
2. …
3. Reducing dyskinesias (LIDs) → IRL790
4. …
5. Dementia → IRL752
6. Cognitive problems → IRL752
<table>
<thead>
<tr>
<th>COMMENT</th>
<th>DISCOVERY</th>
<th>PRE-CLINICAL</th>
<th>IND-ENABLING</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PHASE III</th>
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<tr>
<td>Parkinson’s disease – L-dopa Induced Dyskinesia</td>
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<td>Follow-on to IRL790</td>
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<td>Parkinson’s disease – Postural instability/Falls in PD Dementia-population</td>
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<td>IRL752</td>
<td>PFC enhancer</td>
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<tr>
<td>Dementias</td>
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<td>IRL752</td>
<td>PFC enhancer</td>
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<td>Neurodegenerative disorders / ageing</td>
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<td>P003</td>
<td>Dopamine substitution</td>
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</table>

- **IRL790**, a dopamine D3 receptor antagonist with psychomotor stabilizing properties for the treatment of L-dopa induced dyskinesias in Parkinson’s Disease (PD-LIDs) and Parkinson’s Disease psychosis (PD-Psychosis)
- **IRL752**, a "cortical enhancer" (5-HT7 and Alpha receptor antagonist) for the treatment of postural instability & falls in Parkinson’s Disease (PD-D population)
**IRL790**

**Phase Ib Trial Outcomes**

**IRL790 reduced dyskinesia without changes in mobility**

<table>
<thead>
<tr>
<th></th>
<th>IRL790</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>UDysRS Baseline</td>
<td>33</td>
<td>23*</td>
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<tr>
<td></td>
<td>Week 4</td>
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<tr>
<td>UPDRS 4 q 32-35</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PKG, dyskinesia</td>
<td>6.8</td>
<td>3.9</td>
</tr>
<tr>
<td>PKG, bradykinesia</td>
<td>25.5</td>
<td>24.6</td>
</tr>
<tr>
<td>UPDRS part 1 (Mentation, behavior, mood)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>UPDRS part 2 (ADL)</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>UPDRS part 3 (Motor)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>UPDRS part 4 (Complications)</td>
<td>9</td>
<td>6</td>
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</table>

Descriptive statistics of efficacy assessments in IRL790 Phase 1b trial; ITT population. *p<0.01 vs. Baseline

- On the UDysRS scale a median reduction of 11.5 points vs placebo and a mean reduction of 8.2 points vs placebo was observed for the IRL790 treated group (ITT) during the 4 week study.

- The UPDRS scale and the PKG indicated that IRL790 did not affect the beneficial treatment effects of patients’ standard anti parkinsonian treatment.

- PKG assessments (bradykinesia score) showed a mean relative change from baseline of 6.47% after treatment with IRL790, and 12.6% for placebo treatment.

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## IRL790

**Development path to proof of concept**

First in class To treat Levodopa Induced Dyskinesias (PD-LID) and Psychosis (PD-P)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment duration</th>
<th>Design</th>
<th># subjects</th>
<th>Outcomes</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Ph I: SAD+ MAD</td>
<td>Healthy male volunteers</td>
<td>SAD+MAD 10 days</td>
<td>DB placebo controlled</td>
<td>16 (SAD) 24 (MAD)</td>
<td>PK, safety, tolerability</td>
<td>Finalized</td>
</tr>
<tr>
<td>Ph Ib: MAD (patients)</td>
<td>PD-LIDs (dyskinesia)</td>
<td>4 weeks</td>
<td>DB placebo controlled</td>
<td>15 (3:1 allocation)</td>
<td>Tolerability, PK, safety, UDysRS, PKG (actigraph), UPDRS</td>
<td>Finalized</td>
</tr>
<tr>
<td>Ph IIa</td>
<td>PD-LIDs (dyskinesia)</td>
<td>4 weeks</td>
<td>DB placebo controlled</td>
<td>74</td>
<td>UDysRS, CGI, MDS-UPDRS, Hauser diary</td>
<td>Ongoing</td>
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<tr>
<td>Ph II</td>
<td>PD-Psychosis</td>
<td>6 weeks</td>
<td>DB placebo controlled</td>
<td>Ca 150</td>
<td>Primary: SAPS-PD Secondary: UPDRS II+III, CGI-S</td>
<td>Planned</td>
</tr>
</tbody>
</table>
Advanced PD - Widespread Cortical Involvement

- Extranigral neuronal degeneration in PD affect noradrenergic, serotoninergic and cholinergic systems. Cortical pathology also follows

- Unlike the motor networks, impairments in cortical networks in PD (the cortical control networks, CCN) are poorly responsive to levodopa therapy or DBS

- Postural instability and falls (balance impairment) are strongly linked to impaired executive function and attention in PD

- Dopaminergic treatment (levodopa) is unable to alleviate balance impairment and prevent falls

*Literature

1) Huang C et al., Neuroimage. 2007;34:714-23.
2) Hausdorff et al., Exp Aging Res. 2006;32:411-29
3) Debu et al., Current Neurology and Neuroscience Reports (2018) 18:23
5) Robbins and Cools, Movement Disorders, Vol. 29, No. 5, 2014

- Sommerauer et al., BRAIN 2018: 141; 496–504
**IRL752**

**Improvement of Postural Stability**

**IRL752 postural stability and falls**

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**Phase IIa data; Change from baseline (%) in sum score of UPDRS items 13, 14 and 30**

**Phase IIa data; UPDRS item 13 in fallers.**

1. Rare falling
2. Occasionally falls; less than once daily
3. Falls an average of once per day
4. Falls more than once daily

* *p=0.0011 vs. baseline

**UPDRS items**

- Item 13  Falling unrelated to freezing
- Item 14  Freezing when walking
- Item 30  Postural stability (Retropulsion pull test)

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IRL752

Phase I and IIa Conclusions

- Well tolerated in healthy volunteers and in Parkinson disease patients

- **IRL752 shows promising *improvements in executive function* in PD**
  - Axial motor symptoms /Postural stability/Falls
  - Apathy
  - Cognitive impairment*

- **Effects suggest cortical mode of action of IRL752**
  - Targets clinical domains *not* treated by regular dopaminergic treatments

- **Results predicted by ISP – good translation**

**Note:**
- Efficacy assessments are exploratory
- Study not designed or powered for efficacy
# IRL752 Development path to proof of concept

## First in Class - Postural Instability & Falls

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Phase I: SAD+MAD</td>
<td>Healthy male volunteers</td>
<td>SAD+MAD 10 days</td>
<td>Double blind placebo controlled</td>
<td>16 (SAD) 24 (MAD)</td>
<td>PK, safety, EEG (MAD part)</td>
<td>Finalized</td>
</tr>
<tr>
<td>Phase IIa</td>
<td>PD-D (MMSE11-26)</td>
<td>4 weeks</td>
<td>Double blind placebo controlled</td>
<td>40 (3:1 allocation)</td>
<td>Primary: Tolerability, safety, PK Secondary: CANTAB battery, NPI-12, UPDRS, FOGQ, TUG, EEG, CIBIC-plus</td>
<td>Finalized</td>
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<tr>
<td>Phase IIb</td>
<td>PD-MCI/PD-D (MoCa ≤26) with a history of falls</td>
<td>12 weeks</td>
<td>Double blind placebo controlled</td>
<td>Ca 150 (placebo, 300mg, 600mg)</td>
<td>Primary: Falls diary Secondary: MoCA, UPDRS-Postural dysfunction, FES-I, NPI-12, ESS, CGI-S</td>
<td>Planned</td>
</tr>
</tbody>
</table>
Key Major Milestones

- **2017**
  - Phase I programme IRL752 and IRL790 completed
  - Start Phase Ila IRL752
  - Start Phase Ila IRL790
  - US and EU institutional investors

- **2018**
  - New candidate drugs
  - Phase Ila top-line data IRL752

- **2019**
  - Study report Phase Ila IRL752
  - Top-line Phase Ila IRL790
  - Initiation of Phase IIb with IRL752
  - Initiation of Phase II PDP with IRL790
  - Listing on Main Market
  - US INDs
  - IRL752 Phase Ila publication
  - IRL790 & IRL752 pharmacology publications