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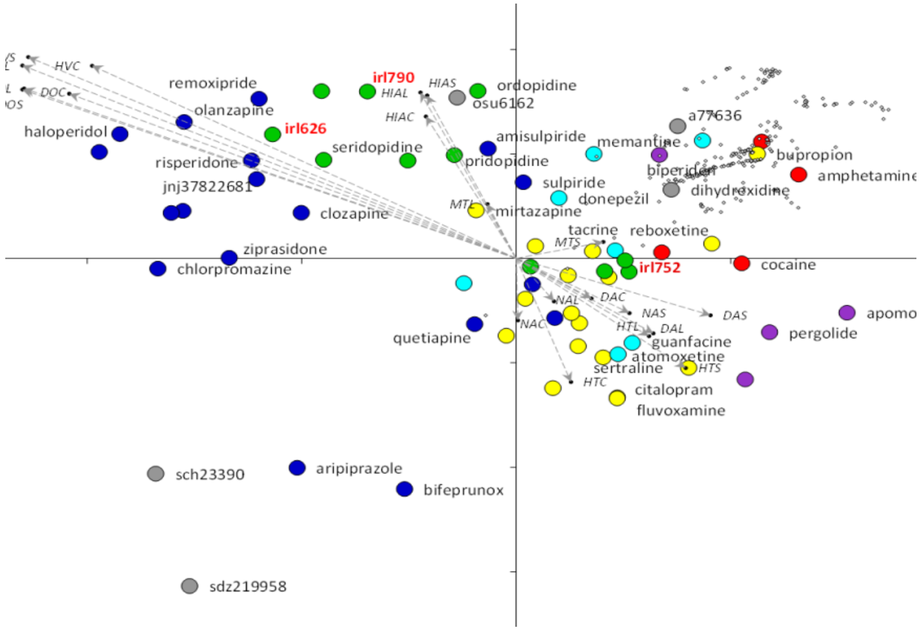
IRLAB Therapeutics



Pareto Securities' 11th Annual Healthcare Conference, September 2020

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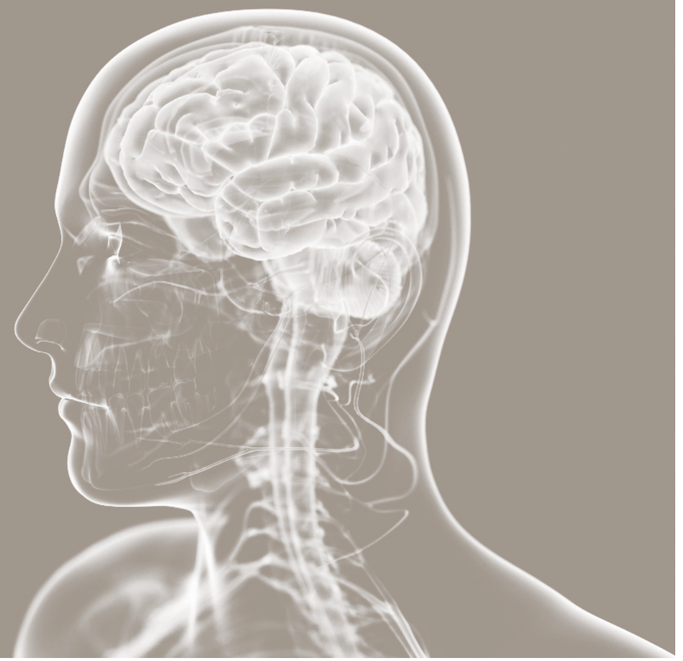
In short

Swedish biotech working for a better future for patients affected by Parkinson's disease

- **Developing novel treatment in Parkinson's disease**
- **Two leading clinical programs in Phase II**
  - Mesdopetam is under development for the treatment of levodopa induced dyskinesias in PD (**PD-LIDs**), aiming to improve motor function by reducing dyskinesia, and thereby increasing daily **Good ON-time**.
  - Mesdopetam is also in development for the treatment of psychosis in PD (**PD-P**).
  - Pirepemat (IRL752) is under development for the treatment of postural dysfunction and falls in PD (**PD-Falls**), a major unmet medical need.
- **Preclinical pipeline candidates in age-related CNS diseases**
- **Company listed on Nasdaq Stockholm First North (IRLAB-A)**

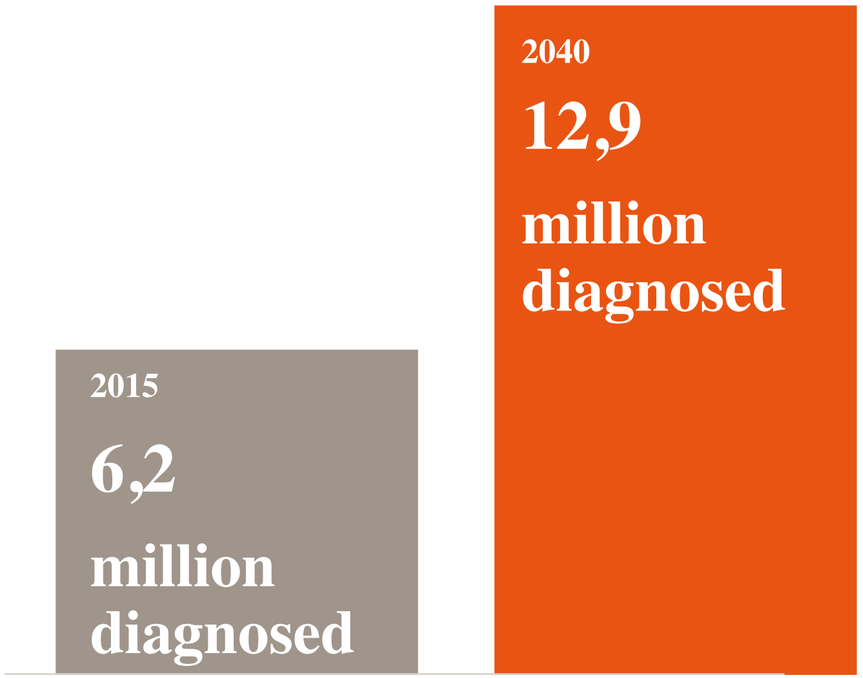
"The dopamine independent symptoms e.g., balance, falls, and dementia, … is very challenging as they don't answer on the treatment available today."

– Key Opinion Leader, Europe (GlobalData)



Top priorities for management of Parkinson's

Parkinson's is one of the fastest growing disorders



The burden of society from PD in the US alone translates to $51,800 per year per patient with Parkinson[1]

Identified top priorities include treatments for:

- Impaired balance and falls
- Cognitive decline
- Motor complications: levodopa induced dyskinesias (LIDs)
- Non-motor symptoms, e.g. psychosis, anxiety

thebmj

Priority setting partnership to identify the top 10 research priorities for the management of Parkinson's disease

Deane KHO, et al. BMJ Open 2014;4:e006434. doi:10.1136/bmjopen-2014-006434

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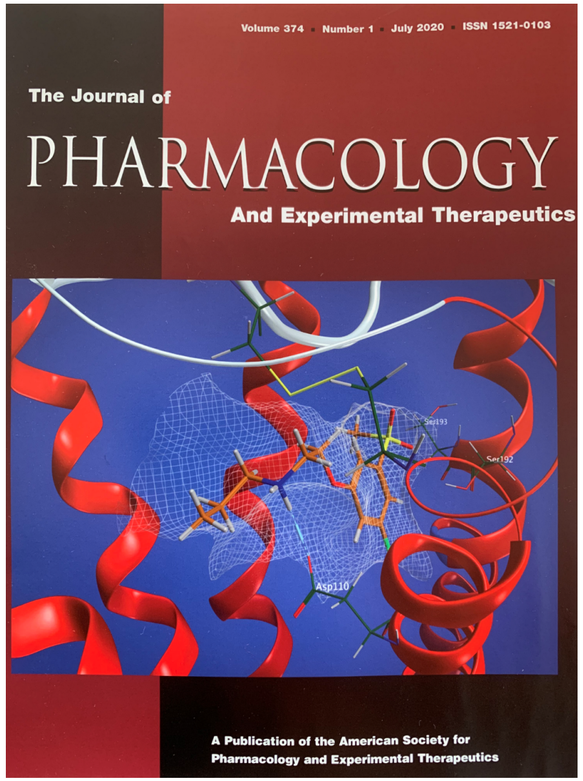
1. Yang, G. et al. (2017). Report: Economic Burden and Future Impact of Parkinson's Disease. Lewin Group.

Pipeline generated by proprietary technology platform: ISP

The Integrative Screening Process (ISP)

- **Advanced systems biology strategy**
- **Extensive, world unique, standardized database on CNS compounds and classes collected over 25 years**
- **ISP database**
  - Describes CNS drug property space
    > 1250 diverse compounds characterized
  - Physiologically relevant, uniform and comparable high-quality data
  - Captures **patterns & connectivity**
  - Utilizing machine learning techniques
- **Translational aspects**
  - Supports mapping of clinical effects vs. properties in animal models



About the cover: IRL790 docked into the binding site of the dopamine D3 receptor crystal structure.
Waters ES et al., (2020) Journal of Pharmacology and Experimental Therapeutics,
DOI: https://doi.org/10.1124/jpet.119.264226.

Reference: In Vivo Systems Response Profiling and Multivariate Classification of CNS Active Compounds: A Structured Tool for CNS Drug Discovery. *ACS Chemical Neuroscience* 2017;8(4):785-97.

Portfolio transforming treatment of patients with Parkinson's disease

Clinical phase II

- **Mesdopetam (IRL790):** To treat debilitating involuntary movements occurring upon long-term treatment with levodopa (PD-LIDs)
- **Pirepemat (IRL752):** To improve reactive postural dysfunction and reduce the risk of falls in PD (PD-Falls)

Preclinical phase

- **IRL942 & IRL1009:** To treat psychiatric, cognitive and motor symptoms associated with neurodegenerative and age-related CNS-diseases

Discovery phase

- **P003:** Compounds being developed for the treatment of early stages of PD

The NCE mesdopetam (IRL790)

NCE in new CNS compound class

WHO-INN proposes new INN, Mesdopetam

Globally issued patent, patent life up to 2037

Dose range defined & highly predictable PK properties

Safe and well tolerated in Phase I and in PD patient Phase Ib and Phase IIa studies

Solid translational evidence in PD-LIDs

- Validated D3 receptor MOA
- Preclinical efficacy
- Clinical efficacy (Phase Ib and Phase IIa)
- Efficacious plasma concentration @ D3 receptor affinity

Potential additional indications linked to D3

- Parkinson disease psychosis (PD-P)
- Tardive dyskinesia (TD)
- Ser9Gly D3 variant related disorders (i.e. D3 “gain of function” disorders)

Phase IIb/III and Phase III program under development with scientific advisors and regulatory experts

Levodopa-induced dyskinesia (PD-LIDs)

PD-LIDs

- PD-LIDs refers to involuntary movements that may occur from long-term use of anti-PD drugs and remains an unmet clinical need since the introduction of levodopa in the 1970s
- The reason why LIDs develop is not fully understood, however, it is believed that a number of brain neurotransmitters, including dopamine, serotonin and glutamate and their respective neuroreceptors and signaling pathways are involved
- About 30% of PD patients develop LIDs, which can involve the whole body
- **Once present, LID limits the optimization of levodopa therapy**

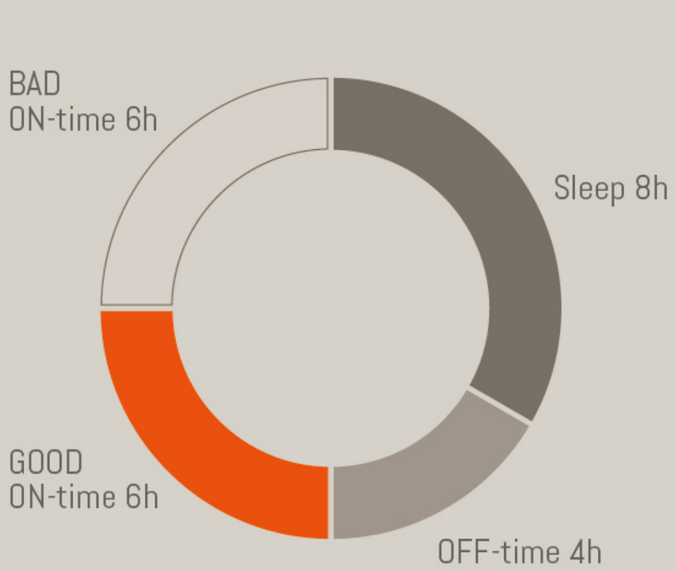
PD-LIDs patient population	
Geography	Population
US	172,000
EU5	181,000
Japan	72,000

References: 1. Turcano et al 2018 Neurology. 91:1-6; 2. Van Gerpen et al, Arch Neurol 2006,63:205-9; 3. Dorsey et al, JAMA Neurology 2018;75:9-10; 4. Michael J. Fox Foundation for Parkinson's disease (n.d.) Dyskinesia; 5. Turcano et al 2018, GBD 2018 The Lancet. 17: 939 – 953;

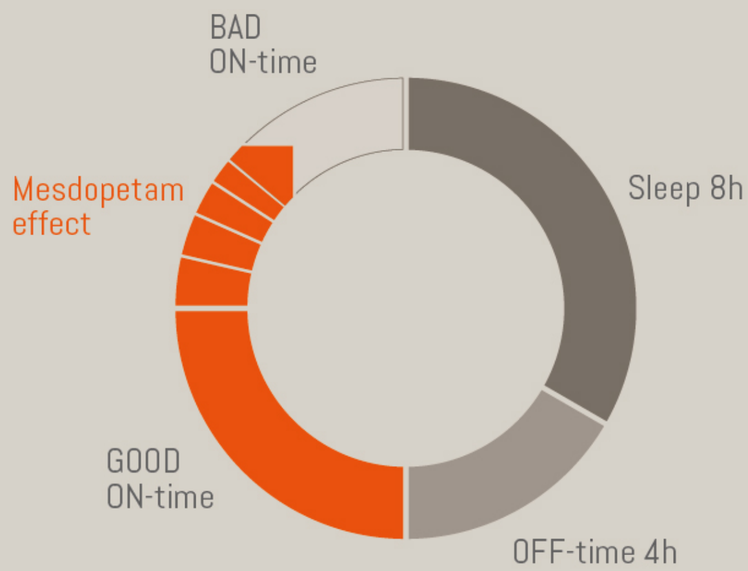
Mesdopetam

Objective to increase Good ON

Increase daily Good ON through targeted reduction of daily Bad ON (ON with dyskinesia)



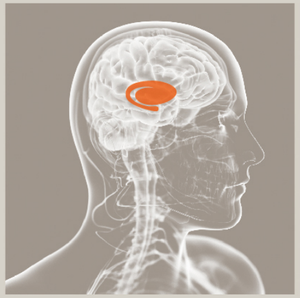
Levodopa-treated LIDs patient



Levodopa + mesdopetam treated LIDs patient

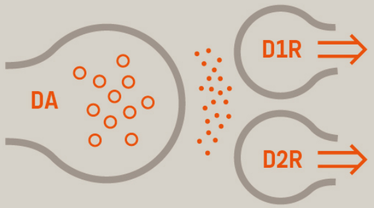
Illustration of patients' motor function during a 24-hour cycle

Mechanism of action



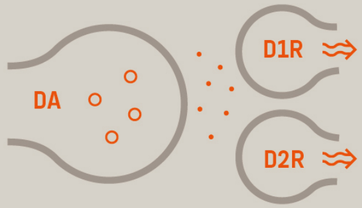
Reducing dyskinesia by targeting dopamine D3 receptors

1.
HEALTHY



NORMAL NERVE ACTIVITY
BALANCED AND HIGH STIMULATION
OF D1R AND D2R

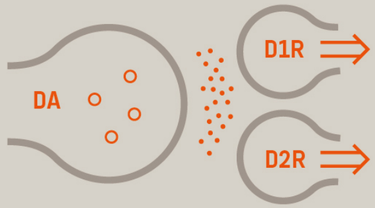
2.
PARKINSON'S DISEASE DIAGNOSIS



LOW NERVE ACTIVITY
DUE TO LOSS OF DOPAMINE
LOW STIMULATION OF D1R AND D2R

PD SYMPTOMS APPEAR

3.
PARKINSON'S DISEASE + L-DOPA TREATMENT



INTRODUCTION OF L-DOPA TREATMENT
L-DOPA INCREASES DOPAMINE
RESTORED HIGH STIMULATION OF D1R AND D2R

PD SYMPTOMS UNDER CONTROL

4.
PARKINSON'S DISEASE + L-DOPA TREATMENT L-DOPA INDUCED DYSKINESIAS

CONTINUOUS L-DOPA TREATMENT
DOPAMINE D3R OCCUR AND ENHANCE D1R ACTIVITY.
IMBALANCE BETWEEN [D1R+D3R] AND D2R STIMULATION

DYSKINESIAS EMERGE

5.
PARKINSON'S DISEASE + L-DOPA TREATMENT + MESDOPETAM TREATMENT ~~L-DOPA INDUCED DYSKINESIAS~~

CONTINUOUS L-DOPA TREATMENT
MESDOPETAM TREATMENT BLOCKS OUT D3R
RESTORED BALANCE BETWEEN D1R AND D2R STIMULATION

PD SYMPTOMS UNDER CONTROL WITHOUT DYSKINESIAS

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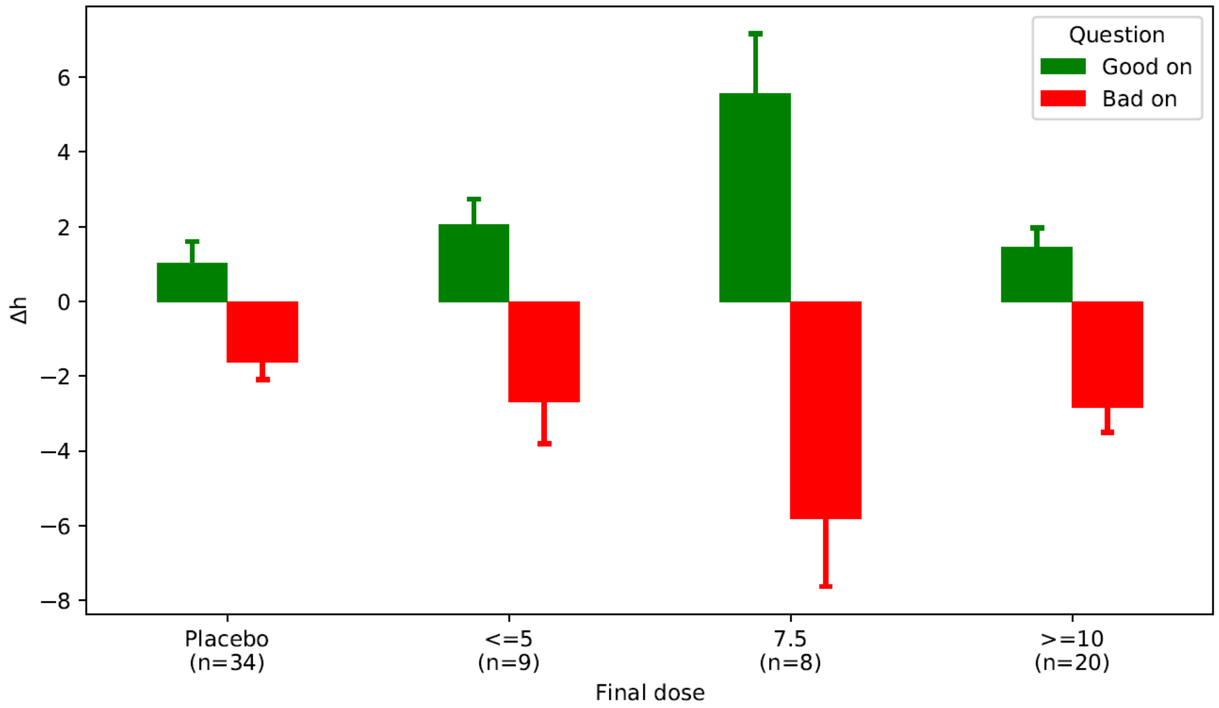
References: 1. Bordet, R. et al., (1997) Proc Natl Acad Sci U S A 94(7): 3363-3367; 2. Marcellino, et al., (2008) J Biol Chem 283(38): 26016-26025; 3. Bezard, et al., (2003) Nat Med 9(6): 762-767; 4. Payer,et al., (2016) Neurology 86(3): 224-230, 5. Waters ES et al., (2020) Journal of Pharmacology and Experimental Therapeutics, DOI: https://doi.org/10.1124/jpet.119.264226.

Mesdopetam

Clinical Phase IIa dose response analyses: Good ON-time vs dose



Supportive analysis of Phase IIa data

- Support for dose dependent efficacy
- Peak benefit appears at 7.5 mg b.i.d.
- No added benefit above 7.5 b.i.d.
- **Relevant dose range identified**

LS mean; adjusted change from baseline; Good ON-time
@ ≤ 7.5 mg b.i.d (aggregated dose groups) vs. placebo, **p<0.002**

Data support dose dependent efficacy @ ≤ 7.5 mg/kg b.i.d.

Clinical Phase IIa: Key conclusions

Phase IIa in PD

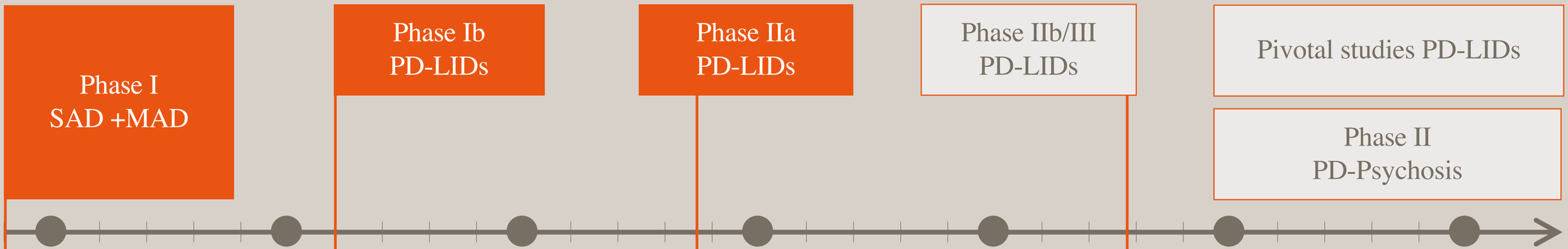
- Clinically meaningful & quantitatively impressive effects on dyskinesias assessed by Hauser diaries and by UPDRS dyskinesia assessments
- Patients reported functional improvements
- Qualitative shift in ON-time towards more daily ”**Good ON-time**” without troublesome dyskinesia
- Dose- and plasma concentration dependent efficacy
- No safety concerns
- Side effect profile on par with placebo
- Linear, highly predictive PK
  - Allows for excellent control of exposure, and greatly facilitates dosing in the PD population

Mesdopetam can offer a marked qualitative shift towards more ‘Good ON hours’ without troublesome dyskinesia or adverse effects

Mesdopetam

First-in-class to increase daily “Good ON-time”

Overview of the clinical studies



- Well tolerated
- Safe
- Very good pharmacokinetic properties

- Well tolerated
- Efficacy on LIDs indicated (several scales)
- Doses defined

- Clinically meaningful & quantitatively impressive effects on dyskinesias
- Mesdopetam offers a marked qualitative shift towards more “Good ON-time”
- Side effects on par with placebo

- ***Next study***:
  Effects of mesdopetam on daily “Good ON-time” without troublesome dyskinesia

Why mesdopetam?

- Mechanism
  - D3 receptor central for manifestation of LIDs and;
  - D3 receptor central for development of LIDs
- Efficacy (Phase Ib & IIa studies) highly clinically relevant (at least 50% up vs. competition)
- Outstanding side effect profile vs competition
- No competition with D3 mechanism in global clinical pipeline, we are 4-5 years ahead
- IRL790 has the potential to be a first-in-class treatment

Falls in Parkinson's disease is a major issue

- To reduce falling is the greatest medical need in Parkinson's disease
- Reasons why people with Parkinson's fall[1,2]:

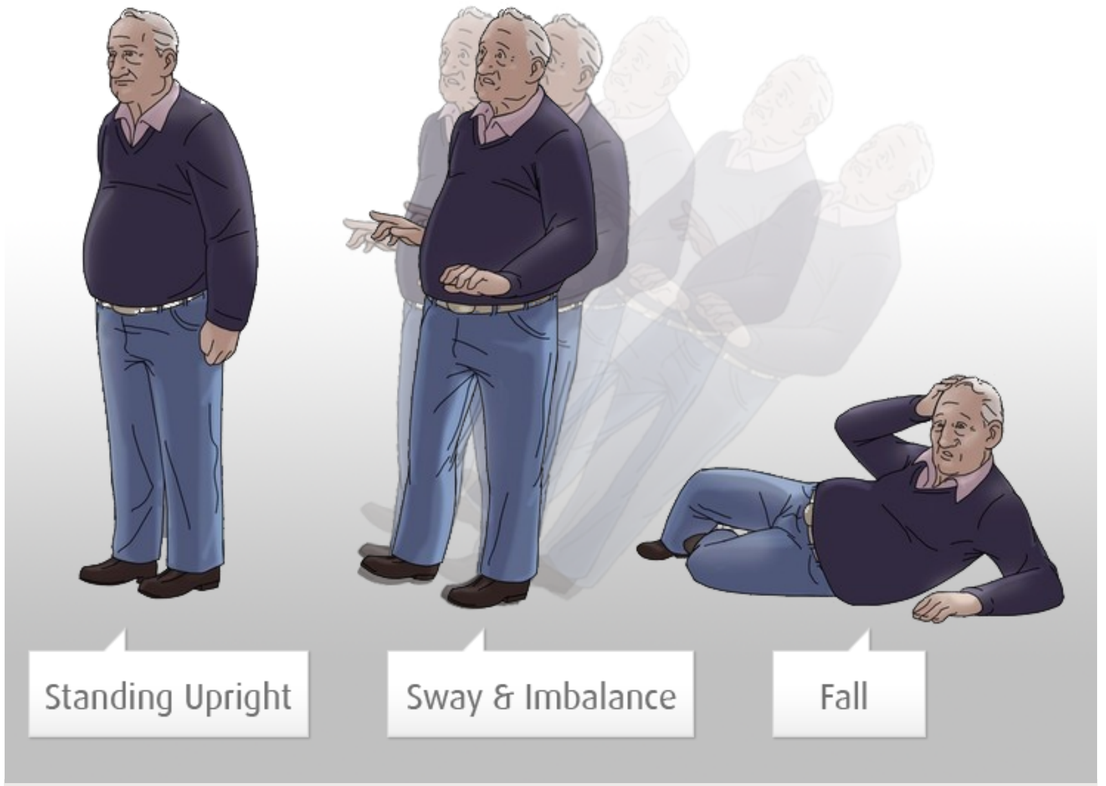
Cognitive decline
↓
Impaired balance
↓
Falls

- "An intervention that demonstrates a 25% relative reduction in falls rate would be clinically meaningful"[3]

The minimum clinically important difference (MCID) for a falls intervention in Parkinson's: A delphi study

Emily J. Henderson[a,b,*], Gemma S. Morgan[a], Jigisha Amin[c], Daisy M. Gaunt[d], Yoav Ben-Shlomo[a]

[a] *Department of Population Health Sciences, Bristol Medical School, University of Bristol, 39 Whatley Road, Bristol, BS8 2PS, United Kingdom*
[b] *Royal United Hospitals NHS Foundation Trust Bath, BA1 3NG, United Kingdom*
[c] *Faculty of Health Sciences, Bristol Medical School, University of Bristol, Bristol, BS8 2PS, United Kingdom*
[d] *Bristol Randomised Trials Collaboration (BRTC), Department of Population Health Sciences, Bristol Medical School, University of Bristol, 39 Whatley Road, Bristol, BS8 2PS, United Kingdom*



Fall injuries are the dominant cause of hospitalization for Parkinson's sufferers.

Reference: 1. Shrag et al (2015) npj Parkinson's Disease. 15011; **2**. Ibarrientos, (2019) Thesis for: BS Materials Science and Engineering **3**. Parkinsonism Relat Disord. 2019 Apr;61:106-110. doi: 10.1016/j.parkreldis.2018.11.008

Pirepemat (IRL752)

The NCE pirepemat

NCE, new mode of action candidate

Patent issued in all major markets, ultimate case exclusivity > 2040

WHO-INN recommends new INN, pirepemat

Well tolerated in healthy volunteers and in Parkinson's disease patients

IRL752 shows promising improvements in postural stability and potential to reduce falls in PD

Efficacy profile indicates cortical mode of action - good translation from preclinical to clinical

- Targets clinical domains not addressed by regular Parkinson's disease treatments

Phase IIb program developed with expert regulatory and clinical advisors

IRL752 targets a large untapped market

- About 50% of patients with PD in Hoehn&Yahr stage ≥ 3
- Early phase health economic modeling indicate treatment benefits in the form of reduced health care resource use and QALY gains combined with a favorable pricing opportunity

Postural dysfunction or falls in Parkinson's disease

What is falls in Parkinson's?

- Postural dysfunction is strongly linked to cognitive decline
- Associated with increased risk of falls and corresponding complications such as fractures
- Approximately 60% of Parkinson's patients fall every year with around 70% of fallers falling recurrently
- The risk of falling in Parkinson's patients compared to non-Parkinson's patients is 2-3 times higher
- US CDC: Average hospital cost for a fall injury is estimated to $30,000 in elderly > 65 years

PD-Falls population		
Geography	Population (risk of falls)	Population (recurrent falls)
US	460,000	320,000
EU5	485,000	340,00
Japan	195,000	135,000

IRLAB targets an untapped market

- Postural dysfunction in Parkinson's has high prevalence
- Represents unmet needs; and
- No approved treatment
- Pirepemat is the only compound in clinical development, worldwide
- **In the US**, falls among adults age 65 and older cause an estimated $50 billion/year spend on non-fatal fall injuries and $754 million is spent on fatal falls

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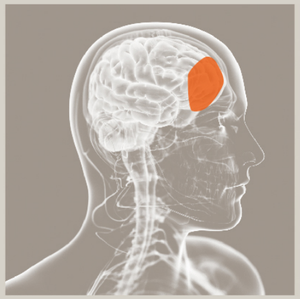
References: Crouse J. et al. (2016) Rev. Neurosci. 0002: 1-5; GBD (2016) Lancet Neurol 2018; 17: 939–53; Kalilani (2016) PLoS One. 2016; 11(9): e0161689; Kim et al (2018) Handbook of Clinical Neurology. 159 (3): 173 – 193; https://www.cdc.gov/homeandrecreationalsafety/falls/fallcost.html. Florence CS, et al., Medical Costs of Fatal and Nonfatal Falls in Older Adults. Journal of the American Geriatrics Society, 2018 March

Pirepemat (IRL752)

Mechanism of action

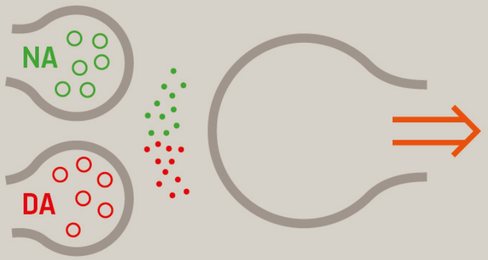


Pirepemat is intended to be used as an adjunct treatment in Parkinson's to improve postural dysfunction and reduce falls

Improves balance & reduce risk of falls through regio-specific increases of NA & DA in frontal cortex

1.

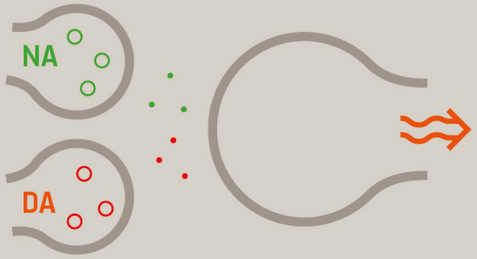
HEALTHY



NORMAL NERVE ACTIVITY IN FRONTAL CORTEX
BALANCED AND HIGH ACTIVITY OF NA AND DA

2.

ADVANCED PARKINSON'S DISEASE

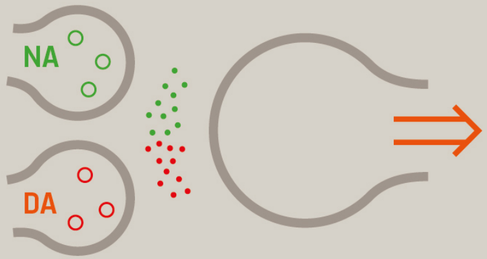


LOSS OF NA AND DA IN FRONTAL CORTEX
IMPAIRED COGNITIVE FUNCTION WHICH LEADS TO

POOR BALANCE AND FALLS

3.

ADVANCED PARKINSON'S DISEASE + IRL752 TREATMENT



NA AND DA ACTIVITY INCREASES IN FRONTAL CORTEX

BALANCE IMPROVED AND FALLS REDUCED

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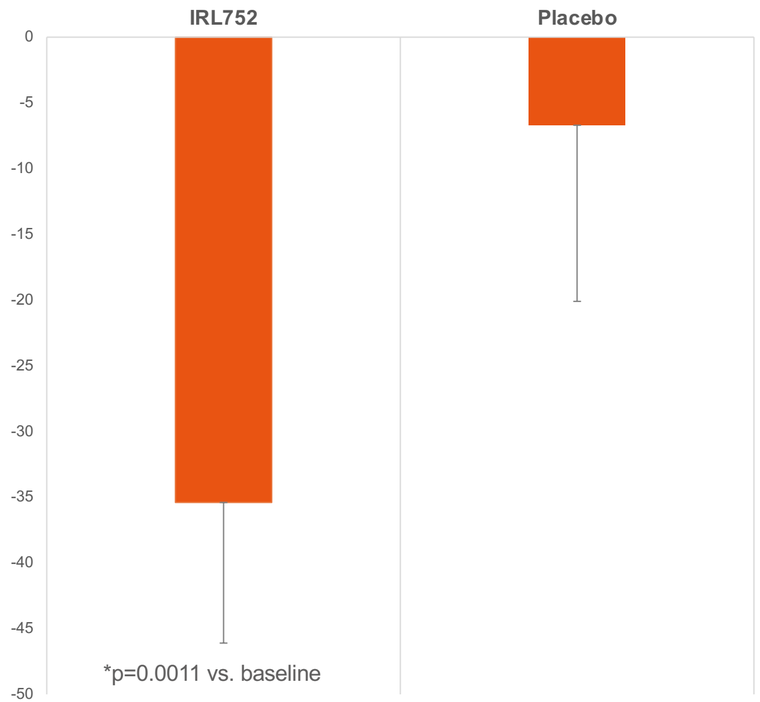
References: 1. Huang C et al., Neuroimage. 2007;34:714-23; 2. Hausdorff et al., Exp Aging Res. 2006;32:411-29; 3. Debu et al., Current Neurology and Neuroscience Reports (2018) 18:23; 4. Fasano, A. et al., Nat. Rev. Neurol. 11, 98–110 (2015); 5. Robbins and Cools, Movement Disorders, Vol. 29, No. 5, 2014
6. Hjort et al (2020) Journal of Pharmacology and Experimental Therapeutics, DOI: 10.1124/jpet.120.000037...

Pirepemat (IRL752)

Clinical Phase IIa data: Improvement of Postural dysfunction and Falls

Balance

Change from baseline (%) in sum score of UPDRS items 13, 14 and 30

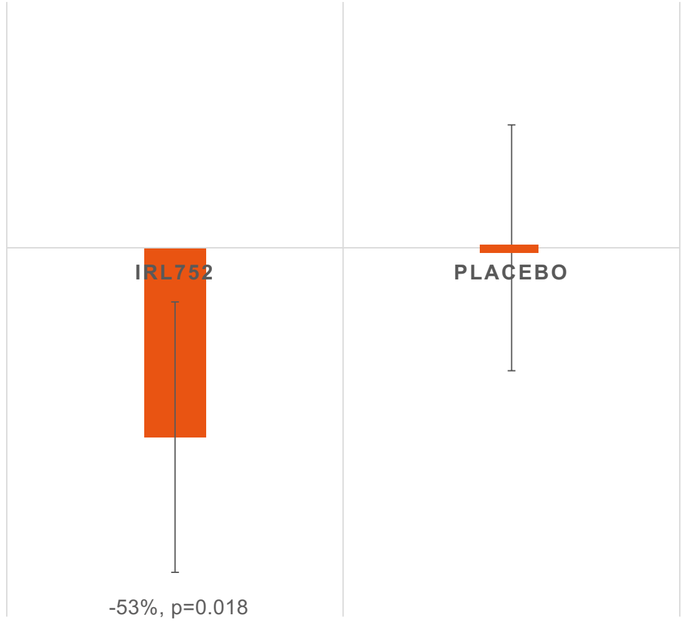


UPDRS items

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

Falls

Absolute change with 95% conf. intervals for UPDRS q13 (Falling unrelated to freezing) 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

IRL752:
8/13 improved ≥1 point
1/13 1 point worse

Placebo:
1/6 1 point worse
1/6 1 point improved

Pirepemat (IRL752)

Clinical Phase I and IIa: Key conclusions

- Well tolerated in young healthy volunteers and in PD patients
- IRL752 shows promising *improvement potential* in PD:
  - Postural stability / Balance
  - Reduced fall frequency
  - Apathy
  - Cognitive impairment
- Effects suggest cortical mode of action of IRL752
  - Targets clinical domains *not* treated by regular antiparkinsonian treatments
- **Results predicted by ISP – good translation**

Movement Disorders

Official Journal of the International Parkinson and Movement Disorder Society

Movement Disorders, 2020

Published online 00 Month 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28020

Check for updates

RESEARCH ARTICLE

A Phase 2a Trial Investigating the Safety and Tolerability of the Novel Cortical Enhancer IRL752 in Parkinson's Disease Dementia

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[9]*Clinical Trial Consultants, Uppsala, Sweden*
[10]*Integrative Research Laboratories AB, Göteborg, Sweden*

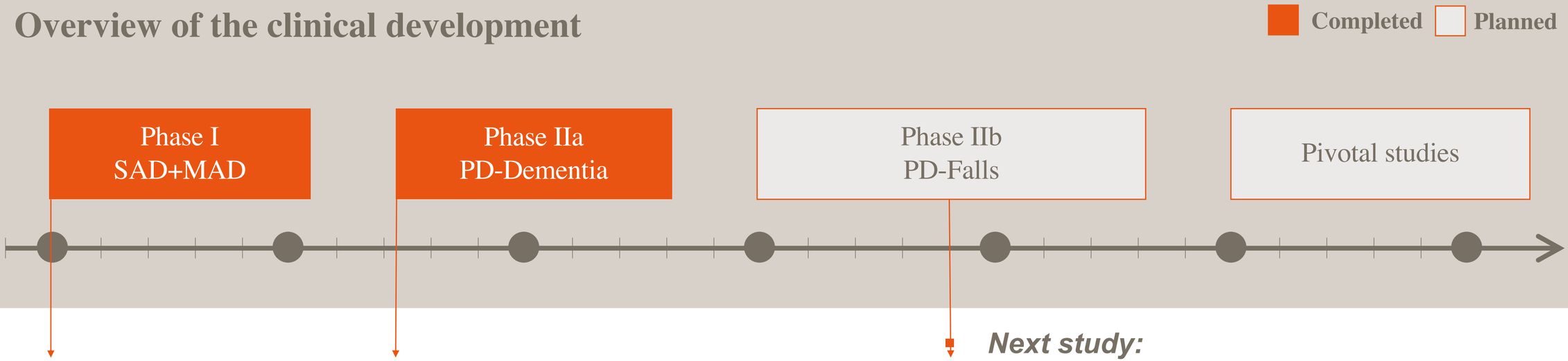
Note:
- Efficacy assessments are exploratory
- Study not designed or powered for efficacy

Pirepemat can offer an improvement in balance and reduce risk of falls

Pirepemat (IRL752)

First-in-class to treat Postural dysfunction/Falls

Overview of the clinical development



- Well tolerated in dose range studied
- Very good pharmacokinetic properties

- Well tolerated
- Promising improvements:
  - Balance
  - Reduced falls frequency
  - Less Apathy
  - Cognitive tests

Next study:
A Phase IIb to evaluate the effects of pirepemat on falls frequency as compared to placebo:

- Falls frequency
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Balance and postural dysfunction
- Effects on cognitive functions as compared to placebo

Why pirepemat?

- Mechanism
  - Pirepemat acts by antagonism at 5HT7 and alpha 2 receptors leading to frontal cortical increase of NA and DA improving cognitive function and reactive postural responses (i.e. balance)
  - Frontal cortical increase of NA and DA central for reactive postural responses (i.e. balance)
  - Frontal cortical increase of NA and DA central for reactive postural responses (i.e. balance) and cognitive improvement
- Efficacy (Phase IIa study) highly clinically relevant (50% reduction in fall frequency)
- Excellent side effect profile
- No competition with the pirepemat mechanism in global clinical pipeline, we are 4-5 years ahead
- IRL752 has the potential to be a first-in-class treatment

Focus during 2020

Key milestones 2020

- [x] WHO-INN recommends **mesdopetam** for IRL790
- [x] WHO-INN recommends **pirepemat** for IRL752
- [x] Financing round of ca 215 MSEK
- [ ] Move to Nasdaq Stockholm Main Market
- [ ] Initiation Fas IIb/III study with mesdopetam
- [ ] Initiation Fas IIb study with IRL752
- [ ] US INDs
- [x] Pirepemat Fas IIa published in *Movement disorders*
- [x] Mesdopetam published in *JPET*
- [x] Pirepemat published in *JPET*

Positioning of the mesdopetam *and* pirepemat programs

- First-in-class drug candidates
- Novel mechanisms of action
- 4-5 years ahead of competitors
- Large markets with unmet needs

Integrative
Research
Laboratories

Q&A

Contact: Nicholas Waters, CEO, nicholas.waters@irlab.se

IRLAB is a Swedish research and development company focused on developing novel treatments for Parkinson's disease. The company's two lead drug candidates, mesdopetam (IRL790) and pirepemat (IRL752), which both have cleared Phase IIa-studies, intends to treat some of the most difficult symptoms related to Parkinson's disease: involuntary movements (PD-LIDs), psychosis (PD-P) and symptoms related to cognitive decline such as impaired balance and increased risk of falls (PD-Falls). Through the proprietary research platform ISP (Integrative Screening Process), IRLAB discovers and develops drug candidates for central nervous system (CNS) related diseases where growing unmet medical needs exist. In addition to the clinical candidates, the ISP platform has also generated several CNS programs that are now in preclinical phase.