IRLAB update on clinical Phase II pipeline - IRL752 and IRL790

IRLAB's two lead development programs, IRL752 and IRL790, both addressing complications in Parkinson's disease, are progressing according to communicated plans and are both evaluated in Phase II following successfully concluded Phase I-studies. The promising results give a solid foundation for continued development of the both candidate drugs. In parallel, the development of large scale synthesis of API and quality assurance has been optimized for both IRL752 and IRL790.

ISP – a unique discovery engine

IRLABs compounds in development are discovered by means of the proprietary platform ISP (Integrative Screening Platform).

The ISP is a systems biology based discovery engine designed to effectively discover new candidate drugs with novel mechanisms and improved efficacy. The discovery engine is based on IRLAB's systematically constructed *in-vivo* database built on data generated from numerous CNS active compounds. Based on chemometric methods and machine-learning algorithms, the combined chemical and biological data are converted to information that enable IRLAB to design new drugable chemical entities, which are developed to novel pharmacological treatment strategies in CNS disorders.

Preclinical results

IRL752

IRL752 is developed for the treatment of Parkinson Disease Dementia (PD-D) ultimately affecting up to 80 % of all PD patients. Effective treatments are lacking and thus, the medical need is huge. IRL752 has the ability to increase synaptic availability of the neurotransmitters norepinephrine and dopamine in the frontal cortex and also activates expression of genes modulating synaptic activity and plasticity.

IRL752 primary targets are brain 5HT7 and cortical Alpha receptors as an antagonist leading to improvement of disturbed cognitive function, antidepressant and antipsychotic effects. These are all desired properties for treatment of PD-D.

Clinical research has shown that both norepinephrine and dopamine neurotransmitters are reduced in frontal cortical brain areas in PD-D. By counteracting this reduction, treatment with IRL752 may improve cognitive and psychiatric symptoms in these patients.

IRL790

IRL790 is developed for treatment of dyskinesia in PD (PD-LIDs), i.e. involuntary movements that often follow after a number of years of treatment with L-dopa, and psychosis in Parkinson's disease (PD-P). In pre-clinical studies, IRL790 reduced involuntary movements occuring after a period of treatment with L-dopa. Additionally, in pre-clinical studies, IRL790 has shown antipsychotic properties. Thus, IRL790 has the potential for clinical treatment of both dyskinesia and psychosis in Parkinson's disease.

IRL790 acts as an antagonist at the dopamine D3 receptor. The D3 receptor was recently genetically linked to increased risk for dyskinesia in PD. In Parkinson's disease patients' basal ganglia, dopamine D3 receptor densities are elevated and in Parkinson's disease patients with LIDs, dopamine D3 receptor density is further elevated. Thus, by inhibiting brain dopamine D3 receptors, IRL790 may reduce symptoms of dyskinesia in PD.

Clinical Phase I healthy volunteer studies

Randomized, double-blind, placebo-controlled, Phase I, single and multiple dose studies were completed in 2016 and 2017 with both IRL752 and IRL790. The studies included 40 healthy volunteers each.

IRL752

IRL752 demonstrated good tolerability and very good safety profile over a wide dose range, up to 350 mg as single dose and up to 750 mg/24h as repeat dosing over 10 days which well covers the clinically anticipated patient doses. No serious adverse events were reported in the study. There were no effects on vital signs parameters nor on safety laboratory parameters. IRL752 demonstrated dose linear pharmacokinetics and concomitant food intake did not affect pharmacokinetic parameters.

The results are encouraging and indicate IRL752 to be well suited for continued clinical Phase II development.

IRL790

Up to 120 mg as single dose and up to 80 mg/24h repeated dosing for 10 days were administered. IRL790 was well tolerated and had a very good safety profile. Doses administered exceeded the planned dose levels in patients. No serious adverse events were reported in the study. There were no effects on vital signs nor on laboratory safety parameters. Also, IRL790 showed dose linear pharmacokinetics and uptake was not affected by food intake.

The encouraging results fully support continued clinical Phase II development.

Clinical studies in Parkinson disease patients - Phase Ib and Phase II

IRL752

During the fall of 2017 a randomized, double-blind, placebo-controlled and four week treatment Phase II study was initiated in 40 patients with PD-D. The study is executed in Sweden and Finland (*EU Clinical Trials Register identifier: 2017-001673-17*).

The primary objective is to study safety and tolerability of IRL752 and secondarily to study effects of IRL752 on cognitive and motor symptoms. The study will also collect data from caregivers to provide information on how the treatment affects daily living.

Top line data from this safety and tolerability study are expected in the second quarter of 2018.

IRL790

Phase Ib

To optimize the design of a Phase II study on IRL790, a randomized placebo-controlled Phase Ib study in 15 patients with PD-LIDs was performed. The primary objective was to evaluate safety and tolerability but effects on symptoms were also measured and subjected to descriptive statistics for evaluation.

PD-LID dyskinesia patients were randomized to placebo or IRL790 treatment (1:3 ratio) for 4 weeks. Average patient age was 70 years. Study drug was given as addition to the regular antiparkinsonian medication. Dosing was individually titrated during 2 weeks followed by stable dosing for another two weeks. The average dose after four weeks of IRL790 treatment was 18mg/day and for placebo 42 mg/day.

IRL790 displayed good safety. Reported side effects were mild and transient. The pharmacokinetics of IRL790 was similar to those of the healthy volunteer Phase I study.

Effects were evaluated at baseline and after 4 weeks of treatment using established and accepted rating scales; The Unified Dyskinesia Rating Scale (UDysRS) the scale accepted by regulatory bodies, Unified Parkinson's Disease Rating Scale (UPDRS) and wrist worn electronic movement devices, PKG, was used.

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 worsen the beneficial treatment effects of patients' standard anti parkinsonian treatment.

The Phase I and Phase Ib studies with IRL790 have defined a safe and tolerable dose range (10-20 mg/day) which can reduce dyskinesia without negatively affecting the parallel standard antiparkinsonian treatment.

Phase II

During the fall of 2017 IRLAB received approval from the Medicines & Healthcare products Regulatory Agency (MHRA) in the UK to conduct a Phase II study with the drug candidate IRL790 for treatment of L-dopa induced dyskinesias (LIDs) in about 74 patients *ClinicalTrials.gov Identifier: NCT03368170*).

The Phase II study aims to confirm, the Phase Ib study results and is a randomized double-blind multicentre Phase II clinical trial in Parkinson patients with LIDs. The primary objective is to investigate dyskinesia effects from day 1 to day 28 using UDysRS (the Unified Dyskinesia Rating Scale) in the dose range 10-20 mg/day. Secondary objectives are effects on the UPDRS scale plus safety and tolerability. Top line data from this study are expected in the third quarter of 2018.

Chemistry, Manufacturing and Controls (CMC)

In parallel with the clinical progress, development of manufacturing methods and quality assurance for API have been optimized for both IRL790 and IRL752. For IRL752, upscaling of production is also competed. This work fulfills authority guidelines in preparation for coming Phase IIb studies as well as other subsequent studies.

For further information

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About IRLAB

IRLAB is a research and development company, listed on Nasdaq First North Premier, focused on development of novel therapies for the treatment of neurodegenerative diseases, in particular Parkinson's disease and dementia.

IRLAB has two clinical candidate drugs, IRL752 and IRL790, focused on medical needs in Parkinson's disease. IRLAB also has additional programs in pre-clinical stages.

IRLAB's research is aimed at discovery and development of new candidate drugs addressing unmet medical need in diseases of the central nervous system, using the unique and proprietary integrative screening process, ISP.

IRLAB is based in Gothenburg, Sweden. The operations are mainly carried out through the subsidiary Integrative Research Laboratories Sweden AB.

For more information, please visit www.irlab.se.