CONFIDENTIAL

A single-centre, open-label, phase I trial evaluating the pharmacokinetics of single ascending oral doses of IRL757 in healthy elderly volunteers.

PROTOCOL SYNOPSIS

Version:	2.1
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Superseded version:	Not applicable
Sponsor:	Integrative Research Laboratories Sweden AB (IRLAB)
Product:	IRL757 [redacted]
Trial Number(s):	IRL757C002
	EU trial no: 2024-515124-36-00
	NCT no: NCT06699628

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TRIAL SYNOPSIS

Trial Title A single-centre, open-label, phase I trial evaluating the pharmacokinetics of single ascending oral doses of IRL757 in healthy elderly volunteers.	
Trial code IRL757C002	**EU trial no** 2024-515124-36-00
Trial period Estimated date of first subject enrolled: Q3 2024 Estimated date of last subject completed: Q4 2024	**Phase of development** Phase I
Trial background IRL757 [redacted] is a novel small molecule compound developed for the treatment of apathy in neurodegenerative disorders. This is a trial of IRL757 with the aim to study safety, tolerability and PK following single oral doses to healthy elderly volunteers.	
Trial design and trial population An open label single oral dose trial in elderly healthy volunteers.	
Objectives Primary objective: • To determine the single oral dose pharmacokinetic (PK) characteristics of IRL757 and its 3 main metabolites in healthy elderly volunteers. Secondary objectives: • To evaluate the safety and tolerability of IRL757 after single oral dosing in healthy elderly volunteers. Exploratory objective: • To characterize the metabolite profile in plasma and urine of healthy elderly volunteers.	
Endpoints Primary endpoints: PK assessments • AUC_{0-t}, AUC_{0-24h}, $AUC_{0->\infty}$, C_{max}, T_{max}, $lambda_z$, $T_{1/2}$, amount excreted in urine (Ae), CL/F, V_z/F, fraction of the dose excreted in urine (Fe) (for IRL757), renal clearance CL_R. • Dose proportionality after single doses based on AUC_{0-t}, $AUC_{0->\infty}$ and C_{max}. Secondary endpoints: Safety assessments • Frequency, seriousness and intensity of Adverse Events (AEs) • Physical examination	

- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Electrocardiogram (ECG) recordings
- Vital signs (blood pressure, heart rate and body temperature)
- Safety laboratory measurements

Exploratory endpoints:

- Metabolite profile in plasma
- Profile of excreted metabolites in urine

Number of subjects planned

12 healthy subjects will be included in two dose groups.

Diagnosis and main eligibility criteria

Healthy elderly volunteers ≥65 and <90 years of age, with a weight of 50 to 110 kg, who are willing to comply with trial procedures and who have given written consent, will be considered eligible for participation in the trial.

Methodology

Twelve (12) eligible and consenting subjects will be allocated to two dose groups. All subjects will be assigned to a single dose treatment with IRL757, 6 subjects to dose 1 and 6 subjects to dose 2.

Eligible subjects will be confined to the research clinic from the evening before first dosing (Day -1) until 48 hours following dosing. The subjects should be fasting overnight (10 hours) before dose administration on Day 1. A Follow-up Visit will be performed 5-10 days after administration of IMP.

Investigational Medicinal Products (IMP), dosage and mode of administration

IRL757 half-life is expected to be 4-10 hours.

IRL757 capsules [redacted]

Duration of treatment

Subjects included in the study will receive one dose of IRL757.

Duration of each subject's involvement in the trial

Subjects will be screened for eligibility according to trial-specific inclusion/exclusion criteria at Visit 1 (Screening visit) within 28 days prior to IMP administration.

A Follow-up Visit will be performed for all subjects 5-10 days after last administration of IMP.

Statistical methods

No formal sample size calculation has been performed for this trial. The size of the dose group is considered sufficient to provide adequate information on the safety and PK parameters for the purpose of this trial.

All statistical calculations will be performed using the SAS® version 9.4 or later (SAS Institute Inc., Cary, NC, USA). The statistical analyses will only include descriptive statistics reflecting the explorative nature of the trial. In general, the data will be presented by dose group.

Continuous data will be summarised by dose group using number of observations, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarised by dose group using the number and percentage of subjects in each category.

Unless otherwise stated, statistical evaluations will be based on all subjects who have received treatment with IMP. The Full Analysis Set (FAS) data set will be used for the safety, tolerability assessments and description of trial population.

The Pharmacokinetic Analysis Set (PKAS) comprises data from all subjects who received IMP, who provided an evaluable plasma concentration profile and who have no AEs or protocol deviations judged to affect the PK analysis. Individual PK values may be excluded from the analysis as specified in the SAP.

The PK parameters will be calculated by non-compartmental analysis (NCA) using the software Phoenix WinNonlin® version 8.3 or later (Certara, USA).

Table 1 Schedule of events

Visit	Visit 1	Visit 2				Follow-up Visit
	Screening	In-clinic				Ambulatory
Day	-28 to -1	-1	1	2	3	5-10 days after IMP administration
Informed consent	X					
Demographics and medical/surgical history	X					
Inclusion/exclusion criteria	X		X[1]			
Physical examination	X		X[1]		X[2]	X
C-SSRS	X				X	X
Weight, BMI	X					
Height	X					
Blood pressure, heart rate, respiratory rate	X	X	X[3]	X[3]	X	X
Body temperature		X		X	X	
Haematology, clinical chemistry, coagulation	X	X			X	X
Urinalysis		X				
HIV, Hepatitis B and C	X					
Drugs of abuse	X	X				
Alcohol screen	X	X				
ECG	X	X[6]	X[4]	X[4]	X[4]	X
IMP administration			X			
Blood sampling (PK and metabolite pattern)			X[7]	X[8]	X[8]	
PK urine sampling[9]			X	X	X	
Baseline symptoms	X	X	X[1]			
AE reporting			X[5]	X	X	X
Concomitant medications	X	X	X	X	X	X
Admission to clinic		X				

[1] Pre-dose.
[2] Symptom-driven physical examination
[3] Pre-dose and 30 min, 1, 2, 4, 8, 12 and 24 hours post-dose.
[4] Pre-dose, 1, 2, 3, 6, 12, 24 and 48 hours post-dose.
[5] Post dose.
[6] Triplicate ECGs separated by at least 1 min.
[7] Within 60 min pre-dose and 20 (±2) min, 40 (±4) min, 1 hour (±6 min), 2 hours (±12 min), 3 hours (±18 min), 4 hours (±24 min), 6 hours (±30 min), 8 hours (±30 min), 10 hours (±30 min), and 12 hours (±30 min) post-dose.
[8] 24 hours (±1 hour) post-dose and 48 hours (±1 hour) post-dose.
[9] Urine collection in fractions 0-6, 6-12, 12-24, 24-36 and 36-48 h post-dose. Subjects to empty their bladder prior to dose for urine collection (a pre-dose sample will be retained). A sample (approx. 2mL) from each fraction will also be kept for metabolite pattern analysis.

Table 2 Detailed schedule of events

Visit No.	Visit 2														
Day	Day -1	Day 1												Day 2	Day 3
Time /assessment	Admission	Pre-dose	0	20min	30min	40min	1 h	2 h	3 h	4 h	6 h	8 h	10h	12 h	24 h	48 h
Inclusion/exclusion criteria		X														
Physical examination		X														X[1]
C-SSRS																X
Blood pressure, heart rate, respiratory rate	X	X			X		X	X		X		X		X	X	X
Body temperature	X														X	X
Haematology, clinical chemistry, coagulation	X															X
Urinalysis	X															
Drugs of abuse	X															
Alcohol screen	X															
ECG	X[2]	X[3]					X	X	X		X			X	X	X
IMP administration			X													
Blood sampling[4, 6] (PK and metabolite pattern analysis)		X		X		X	X	X	X	X	X	X	X	X	X	X
PK urine sampling[5]		X	X													
Baseline symptoms	X	X														
AE reporting									X							X
Concomitant medications	X	X							X							X

[1] Symptom-driven physical examination.
[2] Triplicate ECGs separated by at least 1 min at Day -1.
[3] Within 60 min prior to dose at Pre-dose.
[4] Within 60 min pre-dose and 20 (±2) min, 40 (±4) min, 1 hour (±6 min), 2 hours (±12 min), 3 hours (±18 min), 4 hours (±24 min), 6 hours (±30 min), 8 hours (±30 min), 10 hours (±30 min), 12 hours (±30 min), 24 hours (±1 hour) and 48 hours (±1 hour) post-dose.
[5] Urine collection in fractions 0-6, 6-12, 12-24, 24-36 and 36-48 h post-dose. Subjects to empty their bladder prior to dose for urine collection (a pre-dose sample will be retained). A sample of approx. 2 mL from each fraction will also be kept and divided into 2 aliquots for metabolite pattern analysis.
[6] Plasma obtained at each time point will be divided into two samples, one for PK analysis and one for metabolite pattern analysis. Each of these samples will be separated into two aliquots.