CONFIDENTIAL

A prospective, single-centre, randomised, double-blind, placebo-controlled, phase I, First-In-Human (FIH) trial evaluating the safety and tolerability of single and multiple ascending oral doses of IRL757 in healthy volunteers.

PROTOCOL

Version:	4.0
Version date:	27-NOV-2024
Superseded version:	Not applicable
Sponsor:	Integrative Research Laboratories Sweden AB (IRLAB)
Product:	IRL757 [redacted]
Trial Number(s):	IRL757C001
	EU trial no: 2024-511426-31-00

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PROTOCOL APPROVAL PAGE

A prospective, single-centre, randomised, double-blind, placebo-controlled, phase I, First-In-Human (FIH) trial evaluating the safety and tolerability of single and multiple ascending oral doses of IRL757 in healthy volunteers.

IRL757C001 protocol version 4.0 dated 27-NOV-2024

"I agree to the terms of this Clinical Trial Protocol."

Signature:	**Joakim Tedroff, MD, PhD** **Chief Medical Officer** **IRLAB**
Date:	

INVESTIGATOR PROTOCOL APPROVAL PAGE

A prospective, single-centre, randomised, double-blind, placebo-controlled, phase I, First-In-Human (FIH) trial evaluating the safety and tolerability of single and multiple ascending oral doses of IRL757 in healthy volunteers.

IRL757C001 protocol version 4.0 dated 27-NOV-2024

I, the undersigned, have read and understood the protocol and am aware of my responsibilities as an Investigator. I agree to conduct the trial in accordance with this protocol and any subsequent amendments, the Declaration of Helsinki, ICH GCP guidelines, and the laws and regulations of the country in which the trial is being conducted.

Investigator Name: **Investigator Title:** **Investigator Address:**	[redacted]

Investigator Signature: **Date:**	

AMENDMENT HISTORY

Protocol version	Change	Justification
V1.0 08-FEB-2024	Initial version	Not applicable.
V2.0 12-APR-2024	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
V3.0 14-OCT-2024	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

	[redacted]	
	[redacted]	[redacted]
	[redacted]	[redacted]
V4.0 27-NOV-2024	[redacted]	[redacted]

TRIAL SYNOPSIS

Trial Title A prospective, single-centre, randomised, double-blind, placebo-controlled, phase I, First-In-Human (FIH) trial evaluating the safety and tolerability of single and multiple ascending oral doses of IRL757 in healthy volunteers.	
Trial code IRL757C001	**EU trial no** 2024-511426-31-00
Trial period Estimated date of first subject enrolled: Q2 2024 Estimated date of last subject completed: Q1 2025	**Phase of development** Phase I, FIH
Trial background IRL757 [redacted] is a novel small molecule compound developed for the treatment of apathy in neurodegenerative disorders. This is a FIH trial of IRL757 with the aim to study safety, tolerability and PK following single oral ascending doses and subsequent repeated dosing of the compound administered to healthy volunteers.	
Trial design and trial population Single Ascending Dose (SAD) part: A randomised, double-blind, placebo-controlled single ascending dose trial in healthy volunteers. Multiple Ascending Dose (MAD) part: A randomised, double-blind, placebo-controlled multiple dosing trial in healthy volunteers.	
Objectives Primary objective: To evaluate the safety and tolerability of IRL757 after single and repeated dosing in healthy volunteers. Secondary objectives: 1. To determine the single and multiple dose pharmacokinetic (PK) characteristics of IRL757 and its 3 main metabolites in healthy volunteers. 2. To evaluate the interaction with food after single oral dosing of IRL757 on its PK characteristics and its 3 main metabolites in healthy volunteers. Exploratory objective: To characterize the metabolite profile in human plasma and urine and compare metabolite exposures between human and the safety species rat and dog.	

Endpoints

Primary endpoints: Safety assessments

- Frequency, seriousness and intensity of Adverse Events (AEs)
- Physical examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Electrocardiogram (ECG) recordings
- Telemetry (SAD part of the trial only)
- Vital signs (blood pressure, heart rate and body temperature)
- Safety laboratory measurements

Secondary endpoints: PK assessments

- SAD part: Area under the plasma concentration-time curve $AUC_{0->\infty}$, AUC_t, AUC_{0-24h}, maximum concentration (C_{max}), time to maximum concentration (T_{max}), terminal elimination rate constant ($lambda_z$), terminal half-life ($T_{1/2}$), total apparent clearance of drug from plasma (CL/F), volume of distribution (V_z/F), amount excreted in urine (Ae), fraction of the dose excreted in urine (Fe) (for IRL757), renal clearance CL_R.
- Relative bioavailability after fed and fasting conditions determined from AUC_t and $AUC_{0-\infty}$, and C_{max}.
- MAD part, Day 1: AUC_{0-tau}, C_{max}, T_{max}, $lambda_z$, $T_{1/2}$, Day 10: AUC_{0-tau}, C_{max}, T_{max}, $lambda_z$, $T_{1/2}$, CL/F, V_z/F, fraction of the dose excreted in urine (Fe) (for IRL757) for the last dose interval in the morning of Day 10, renal clearance CL_R.
- Dose proportionality after single dose based on $AUC_{0->\infty}$ and C_{max}.
- Dose proportionality after multiple doses based on AUC_{0-tau} and C_{max}.
- Accumulation ratio (AR) after multiple doses based on C_{max} ratio and ratio AUC_{0-tau} (Day 10) to AUC_{0-tau} for the first dose interval on Day 1.

Exploratory endpoints

- Metabolite In Safety Testing (MIST) analysis of the metabolite profile in plasma in comparison with the metabolite profile in plasma from non-clinical safety studies.
- Profile of excreted metabolites in the urine.

Number of subjects planned

In the SAD part of the trial, forty (40) healthy subjects will be included (5 cohorts, 8 subjects in each cohort, randomised 3:1). Six (6) additional subjects will be included in a food interaction sub-study.

In the MAD part of the trial, up to 36 healthy subjects will be included in 2-3 cohorts with twelve (12) subjects in each cohort (up to 3 cohorts depending on the results of the SAD part of the trial, 12 subjects in each cohort, randomised 3:1).

If indicated by emerging data and recommended by the internal safety review committee (iSRC), 1 optional cohort (8 subjects) may be added to the SAD part of the trial, and 1 optional cohort (12 subjects) to the MAD part of the trial.

Diagnosis and main eligibility criteria

Healthy volunteers 18-55 years of age inclusive, 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. Female volunteers of childbearing potential must agree to use a highly effective method of contraception during the trial period to prevent pregnancy. Male volunteers must agree to use adequate contraception during the trial period to prevent pregnancy of a female partner.

Methodology

The SAD part of the trial will be a parallel group design with up to five (5) pre-defined ascending dose levels of IRL757 (see Table 1 below). Intermediary dose levels may be considered if recommended by the iSRC.

Forty (40) eligible and consenting subjects will be included in one (1) of five (5) cohorts, eight (8) subjects in each cohort. At each dose level, two (2) subjects will be given placebo, and six (6) subjects will be given IRL757.

Table 1 SAD Dosing cohorts/groups

Sequence No / Group		Cohort 1 (n=8)		Cohort 2 (n=8)		Cohort 3 (n=8)		Cohort 4 (n=8)		Cohort 5 (n=8)	
1	n=2	Placebo (1)	[redacted] (1)	Placebo (1)	[redacted] (1)	Placebo (1)	[redacted] (1)	Placebo (1)	[redacted] (1)	Placebo (1)	[redacted] (1)
2	n=3	Placebo (1)	[redacted] (5)	Placebo (1)	[redacted] (5)	Placebo (1)	[redacted] (5)	Placebo (1)	[redacted] (5)	Placebo (1)	[redacted] (5)
3	n=3										

* tentative dose that may change upon iSRC recommendation.

The eight (8) subjects in a cohort will be divided into at least three (3) groups with two (2) subjects in the first group and three (3) subjects in the following two (2) groups. In the first group at each dose level, a "sentinel group" of two (2) subjects (one [1] active drug/ one [1] placebo) will be dosed first and closely observed for 24 hours before proceeding to dose the remaining subjects, in two (2) groups with three (3) subjects in each with an interval of at least 30 minutes between subjects. The subsequent groups will be dosed approximately 24 hours apart.

There will be an interval of at least one (1) week between each dose level to allow time for PK and safety data to be analysed, evaluated and reviewed by the iSRC. The iSRC will have the choice to recommend to escalate the dose as planned, reduce or increase the dose escalation step, repeat the dose, reduce the dose or terminate the trial. Should dose adjustments be recommended the adjusted dose increments will remain in a somewhat similar design as in Table 1.

Screening (Visit 1) will take place between Day -28 and Day -1.

Eligible subjects will be confined to the research clinic from the evening before each dosing (Day -1) until 48 hours post-dose (Day 3). The subjects should be fasting overnight (10 hours) before dose administration on Day 1. During the in-clinic period, PK blood sampling and urine sampling will be performed, from IMP administration until 48 hours post-dose and until 24 hours post-dose respectively.

A Follow-up Visit will be performed 5-10 days after administration of Investigational Medicinal Product (IMP).

The food interaction sub-study will include six (6) additional subjects. The six subjects will be administered IRL757 in fasted and fed conditions. A standardized breakfast meal will be consumed within 30 minutes prior to IMP administration, in order to study potential food interactions. After the completion of cohort 4, safety and PK data will be evaluated to determine which dose level will be used for the food interaction sub-study. For each administration, the subjects will be confined to the research clinic from the evening before dosing (Day -1) until at least 48 hours after administration (Day 3).

In the MAD part of the trial, 24 or 36 eligible and consenting subjects will be allocated to one of two (2) or three (3) cohorts; IRL757 Dose Level 1, IRL757 Dose Level 2, and IRL757 Dose Level 3 if applicable, with 12 subjects in each cohort. Within each cohort subjects will be randomly assigned to treatment with placebo or IRL757; three (3) subjects will be given placebo, and nine (9) subjects will be given IRL757.

The 12 subjects in a cohort will be divided into four (4) groups; a sentinel group, two (2) groups of three (3) subjects each and one (1) group of four (4) subjects. In each cohort, the "sentinel group" of two (2) subjects (one [1] active drug/ one [1] placebo) will be dosed first and closely observed for 24 hours before starting the dosing in the following group. Subsequent groups in the cohort will be dosed approximately 24 hours apart. In each group the subjects will be dosed with an interval of at least 30 minutes between subjects. It is foreseen that subjects will be treated with two (2) daily oral doses of IRL757 or placebo administered at the same time during ten (10) consecutive days (the dosing interval is subject to change and will be confirmed depending on the results from the SAD part of the trial).

There will be an interval of at least one (1) week between last administration in a cohort and initiation of next cohort to allow time for PK and safety data to be analysed, evaluated and reviewed by the iSRC. The iSRC will have the choice to recommend to escalate the dose as planned, reduce or increase the dose escalation step, repeat the dose, reduce the dose or terminate the trial.

The decision on dose levels will be done following the SAD part of the trial and a cautious selection of dose will be done if dosing is expected to approach the exposure limit.

Screening (Visit 1) will take place between Day -28 and Day -1.

Eligible subjects will be confined to the research clinic from the evening before first dosing (Day -1) until Day 11 and will come back to the clinic on Day 12 for extended PK and safety samples (including 48 hours post the last morning dose). The subjects should be fasting overnight (10 hours) before dose administration on Day 1 and Day 10. A Follow-up Visit will be performed 5-10 days after last administration of IMP.

An additional third cohort (IRL757 Dose Level 3), with twelve (12) additional subjects may be implemented following the review of data of the SAD part of the trial. The cohorts are described in Table 2.

Table 2 MAD dosing groups

Cohort	Dose	Groups	
Cohort 1 (n=12)	Dose Level 1	2 + 3 + 3 + 4	Sentinel group (n=2): 1 active, 1 placebo Subsequent groups (n=3+3+4): 8 active, 2 placebo
Cohort 2 (n=12)	Dose Level 2	2 + 3 + 3 + 4	
Cohort 3 (n=12)	*Dose Level 3*	*2 + 3 + 3 + 4*	

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

IRL757 half-life is expected to be 2-7 hours.

IRL757 capsules [redacted]

Placebo capsules: [redacted]

Duration of treatment

Subjects included in the SAD part will be treated with one (1) single oral dose of IRL757 or placebo (see Table 1).

Subjects included in the food interaction sub-study will be treated with two (2) oral doses of IRL757.

Subjects included in the MAD part will receive two (2) daily oral doses of IRL757 or placebo for ten (10) consecutive days. The number of daily doses in the MAD part of the trial will be confirmed following review of PK data from the SAD part of the trial.

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 four (4) weeks prior to start of IMP administration.

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

In the food interaction sub-study, each subject's involvement duration will also depend on how soon the second dose will be given after the first IMP administration (may vary between 5 half-lives and 14 days).

Total duration of involvement per subject:

- SAD part of the trial: from 7 days up to 39 days
- food interaction sub-study: up to 54 days
- MAD part of the trial: from 16 days up to 48 days

Statistical methods

No formal sample size calculation has been performed for this trial. The size of the cohorts/dose groups 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 program (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 treatment and dose group. The data for subjects receiving placebo will be presented pooled across groups.

Continuous data will be summarised by treatment and dose group using number of observations, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarised by treatment and 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 randomised treatment with IMP and have available data. Evaluations will be done according to actual treatment regardless of randomisation. A dose group will consist of all subjects treated with that dose

regardless of dose panel. Similarly, the placebo group will consist of all subjects treated with placebo regardless of dose panel. The Full Analysis Set (FAS) data set will be used for the safety and tolerability assessments.

The Per Protocol Analysis Set (PPAS) comprises data from all subjects randomised and treated with evaluable PK parameter data, and no major protocol deviations with an impact on PK data. The PPAS set will be used for presentation of PK endpoints.

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

Table 3 Schedule of events, SAD part of the trial (fasted condition)

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	X				X
Height	X					
Pregnancy test[10]	X	X				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
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
Telemetry[5]			X	X		
Randomisation			X[1]			
IMP administration			X			
Blood sampling (PK and MIST analysis)			X[7]	X[8]	X[8]	
PK urine sampling[9]			X	X		
Baseline symptoms	X	X				
AE reporting			X	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] Cardiac surveillance up to 24 hours 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. The sample for MIST analysis is only applicable from dose level 2 and onwards.
[8] 24 hours (±1 hour) post-dose and 48 hours (±1 hour) post-dose. The sample for MIST analysis is only applicable from dose level 2 and onwards.
[9] Urine collection in fractions 0-6, 6-12 and 12-24 h post-dose. For SAD cohort 5 also 24-48 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 from dose level 2 and onwards.
[10] Serum at screening, urine at Day -1 and Follow-up.

Table 4 Detailed schedule of events, SAD part of the trial, in-clinic Day -1 to Day 3 (fasted condition)

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
Weight, BMI	X															
Pregnancy test	X[7]															
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
Drugs of abuse	X															
Alcohol screen	X															
ECG	X[2]	X[3]					X	X	X		X			X	X	X
Telemetry		X	X													
Randomisation		X														
IMP administration			X													
Blood sampling[4, 6] (PK and MIST analysis)		X		X		X	X	X	X	X	X	X	X	X	X	X
PK urine sampling[5]		X	X													
Baseline symptoms	X	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 and 12-24 h post-dose. For SAD cohort 5 also 24-48 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 two aliquots for metabolite pattern analysis from dose level 2 and onwards.

[6] Plasma obtained at each time point will be divided into two samples, one for PK analysis and one for MIST analysis. Each of these samples will be separated into two aliquots. The sample for MIST analysis is only applicable from dose level 2 and onwards.
[7] Urine test.

Table 5 Schedule of events, SAD part of the trial, food interaction sub-study

Visit	Visit 1	Visit 2				Visit 3[1]				Follow-up Visit
	Screening	In-clinic				In-clinic				Ambulatory
Day	-28 to -1	-1	1	2	3	-1 fed	1 fed	2 fed	3 fed	5-10 days after last dose
Informed consent	X									
Demographics and medical/surgical history	X									
Inclusion/exclusion criteria	X		X[2]							
Physical examination	X		X[2]		X[3]		X[3]		X[3]	X
C-SSRS	X				X				X	X
Weight, BMI	X	X				X				X
Height	X									
Pregnancy test[10]	X	X				X				X
Blood pressure, heart rate, respiratory rate	X	X	X[4]	X[4]	X	X	X[4]	X[4]	X	X
Body temperature		X		X	X	X		X	X	
Haematology, clinical chemistry, coagulation	X	X			X	X			X	X
HIV, Hepatitis B and C	X									
Drugs of abuse	X	X				X				
Alcohol screen	X	X				X				
ECG	X	X[11]	X	X	X	X[11]	X	X	X	X
Standardized breakfast meal[8]							X			
IMP administration[9]			X				X			
PK blood sampling			X[5]	X[6]	X[7]		X[5]	X[6]	X[7]	
Baseline symptoms	X	X								
AE reporting			X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Admission to clinic		X				X				

[1] Visit 3 is performed after a minimum of 5 half-lives of the IMP and no later than 14 days after the first IMP administration.
[2] Pre-dose.
[3] Symptom-driven physical examination.
[4] Pre-dose and 30 min,1, 2, 4, 8, 12 and 24 hours post-dose.
[5] 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.
[6] 24 hours (±1 hour) post-dose.
[7] 48 hours (±1 hour) post-dose.
[8] Standardized breakfast meal is provided to the subject within 30 min prior to IMP administration.
[9] The dose used for the food interaction sub-study will be determined after completion of Cohort 4 (Dose Level 4) in the SAD part of the trial.
[10] Serum at screening, urine at Day -1 and Follow-up.
[11] Triplicate ECGs separated by at least 1 min.

Table 6 Detailed schedule of events, SAD part of the trial, food interaction sub-study, in-clinic Day -1 to Day 3

	In-clinic															
Visit No.	**Visit 2 (fasted condition)/Visit 3 (fed condition)**															
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**	**10 h**	**12 h**	**24 h**	**48 h**
Inclusion/exclusion criteria		X														
Physical examination		X[8]														X[9]
C-SSRS																X
Weight, BMI	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
Pregnancy test	X[7]															
Drugs of abuse	X															
Alcohol screen	X															
ECG	X[1]	X[2]					X	X	X		X			X	X	X
Standardized breakfast meal		X[3]														
IMP administration			X													
PK blood sampling[4]		X		X		X	X	X	X	X	X	X	X	X	X	X
Baseline symptoms	X[5]	X[5]														
AE reporting	X[6]	X[6]	X													
Concomitant medications	X	X	X													

[1] Triplicate ECGs separated by at least 1 min at Day -1.
[2] Within 60 min prior to dose at Pre-dose.
[3] Meal to be started within 30 min prior to administration of IMP. Applicable only to Visit 3 (fed condition).
[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] Applicable only to Visit 2 (fasted condition).
[6] Applicable only to Visit 3 (fed condition).
[7] Urine test.
[8] Full physical examination at Visit 2. Symptom-driven physical examination at Visit 3.
[9] Symptom-driven physical examination.

Table 7 Schedule of events MAD part of the trial

	Screening	In-clinic							Ambulatory	Follow-up
Visit	**Visit 1**	**Visit 2**							**Visit 3**	**Visit 4**
Day	**Day -28 to -1**	**-1**	**1**	**2, 3, 4**	**5, 6**	**7**	**8, 9**	**10**	**11**	**12**	**5-10 days after last dose**
Informed consent	X										
Demographics and medical/surgical history	X										
Inclusion/exclusion criteria	X		X[1]								
Physical examination	X		X[1]	X[2]		X[2]		X[2]			X[2]
C-SSRS	X					X			X		X
Weight, BMI	X	X						X			X
Height	X										
Pregnancy test[16]	X	X									X
Blood pressure, heart rate, respiratory rate	X	X	X	X[18]	X[18]	X[18]	X[18]	X[18]	X	X	X
Body temperature		X	X[18]			X[18]		X[18]		X	
Haematology, clinical chemistry, coagulation[3]	X		X[4]	X[5]		X		X[4]		X	X
HIV, Hepatitis B and C	X										
Drugs of abuse	X	X									
Alcohol screen	X	X									
ECG	X	X[6]	X[6]	X[7]	X[7]	X[7]	X[7]	X[7]	X	X	X
Randomisation			X[1]								
IMP administration[8]			X	X	X	X	X	X			
PK blood sampling[17]			X[9]	X[10]	X[10]	X[11]	X[13]	X[9]	X[12]	X[12]	
MIST blood sampling[14, 17]			X	X				X	X	X	
PK urine sampling			X[1]					X[15]	X[15]		
Baseline symptoms	X	X									
AE reporting			X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X

[1] Pre-dose.
[2] Symptom-driven physical examination.
[3] Coagulation parameters at Screening, Day 1, Day 7, Day 10 and Follow-up only.
[4] Pre-dose and Day 10 safety samples taken in fasted condition.
[5] At Day 2 and 4 only.

[6] Triplicate ECGs separated by at least 1 min on Day -1. Within 60 min prior to morning dose on Day 1 and at 1, 2, 3, 6 and 12 hours post dose.
[7] 2-4 hours post morning dose on Day 2-10.
[8] Twice daily. Only 1 dose on Day 10, in the morning.
[9] Day 1 and Day 10, first dose of the day: pre-dose (within 10 min), 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, and 14 hours (±30 min). Timepoints for PK sample collection are subject to change according to results from the SAD part of the trial and dose regimen. 12-, 24- and 48-hour samples are taken within 10 min pre-dose.
[10] Days 2, 3, 4, 5 and 6: pre-dose (within 10 min prior morning dose of the day).
[11] Day 7, first dose of the day: pre-dose (within 10 min prior morning dose), 20 (±2) min, 40 (±4) min, 1 (±6 min), 2 (±12 min), 4 hours (±24 min) post-dose. Timepoints for PK sample collection are subject to change according to results from the SAD part of the trial and dose regimen.
[12] Day 11: 24 hours post last morning dose (on Day 10) and Day 12: 48 hours post last morning dose (on Day 10).
[13] Days 8 and 9: pre-dose (within 10 min prior morning dose of the day).
[14] Same samples/timepoints as for PK blood sampling at Day 1 and Day 10 (up to 48 hours) will be used for MIST analysis.
[15] Urine collection 0-24h in fractions 0-8h, 8-12h and 12-24h from morning dose on Day 10. Time interval for the fractions can be revised according to dose regimen chosen. A sample from each fraction will also be kept for metabolite pattern analysis.
[16] Serum at screening, urine at Day -1 and Follow-up.
[17] Each plasma sample obtained will be separated into two aliquots.
[18] Once daily, within 1 hour post morning dose.

Table 8 Detailed schedule of events, MAD part of the trial, in-clinic period (Day -1 – Day 7)

	In-clinic period																			
Visit No.	**Visit 2**																			
Day	**Day -1**	**Day 1**														**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Time /assessment	**Admission**	**Pre-dose**	**0**	**20min**	**30min**	**40min**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**12 h**	**14 h**	**24 h**	**48 h**				
Inclusion/exclusion criteria		X																			
Physical examination		X														X[1]	X[1]	X[1]			X[1]
C-SSRS																					X
Weight, BMI	X																				
Pregnancy test	X[11]																				
Blood pressure, heart rate, respiratory rate	X	X			X		X	X		X		X		X		X[12]	X[12]	X[12]	X[12]	X[12]	X[12]
Body temperature	X	X																			X[12]
Haematology, clinical chemistry, coagulation[2]		X[3]														X		X			X
Drugs of abuse	X																				
Alcohol screen	X																				
ECG	X[4]	X[4]					X	X	X		X			X		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Randomisation		X																			
IMP administration			X											X		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
PK blood sampling[7]		X[8]		X		X	X	X	X	X	X	X	X	X	X	X[10]	X[10]	X[10]	X[10]	X[10]	X[9]
MIST blood sampling		X[8]		X		X	X	X	X	X	X	X	X	X	X	X	X				
PK urine sampling		X																			
Baseline symptoms	X	X																			
AE reporting			X																		
Concomitant medications	X																				

[1] Symptom driven physical examination.
[2] Coagulation parameters at Day 1 and Day 7 only.
[3] In fasted condition.
[4] Triplicate ECGs separated by at least 1 min on Day -1. Within 60 min prior to morning dose on Day 1.
[5] 2-4 hours post morning dose on Day 2-7.
[6] Twice daily.
[7] PK blood sampling timepoints are subject to change, depending on results from the SAD part of the trial and dose regimen.
[8] Within 60 min prior to IMP administration.
[9] First dose of the day: pre-dose (within 10 min prior IMP administration), 20 min, 40 min, 1, 2, 4 hours post-dose. Timepoints for PK sample collection are subject to change according to results from the SAD part of the trial and dose regimen.
[10] First dose of the day: pre-dose (within 10 min prior IMP administration) for trough plasma concentration.
[11] Urine test.
[12] Once daily, within 1 hour post-morning dose.

Table 9 Detailed schedule of events, MAD part of the trial, in-clinic period (Day 8 - 11)

	In-clinic period															Ambulatory
Visit No.	**Visit 2**															**Visit 3**
Day	**Day 8**	**Day 9**	**Day 10**												**Day 11**	**Day 12**
Time /assessment			**Pre-dose**	**0**	**20min**	**40min**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**12 h**	**14 h**		
Physical examination			X[1]														
C-SSRS																X	
Weight, BMI			X[1]														
Blood pressure, heart rate, respiratory rate	X[10]	X[10]					X									X	X
Body temperature							X										X
Haematology, clinical chemistry, coagulation[3]			X[2]														X
ECG[4]	X	X						X								X	X
IMP administration	X[5]	X[5]		X													
PK blood sampling[6]	X[7]	X[7]	X[7]		X	X	X	X	X	X	X	X	X	X	X	X[8]	X[8]
MIST blood sampling			X[7]		X	X	X	X	X	X	X	X	X	X	X	X	X
PK urine sampling[9]				X													
AE reporting	X	X	X													X	X
Concomitant medications	X	X	X													X	X

[1] Performed at any time during Day 10.
[2] In fasted condition.
[3] Coagulation parameters at Day 10 only.
[4] ECG 2-4 hours post morning dose on Day 8-10 (time confirmed based on the results from the SAD part of the trial).
[5] Twice daily. Only 1 morning dose on Day 10.
[6] PK blood sampling timepoints are subject to change, depending on results from the SAD part of the trial.
[7] First dose of the day: pre-dose (within 10 min prior IMP administration) for trough plasma concentrations.
[8] 24-hour PK sample after last morning dose and 48-hour PK sample after last morning dose.
[9] Urine collection 0-24h in fractions 0-8h, 8-12h and 12-24h from morning dose on Day 10. Time interval for the fractions can be revised according to dose regimen chosen. A sample of approx. 2 mL from each fraction will also be kept for metabolite pattern analysis.
[10] Once daily after Day 1, within 1 hour post-morning dose.