STUDY REPORT'S MASTER SYNOPSIS

Name of Company: I.R.I.S., 50 rue Carnot, 92284 Suresnes Cedex - FRANCE		*(For National Authority Use only)*
Name of Finished Product: Not applicable		
Name of Active Ingredient: S95010		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study:
Safety, tolerability and pharmacokinetics of S95010 after single escalating intravenous doses in young healthy male subjects. A randomised, double-blind, placebo-controlled, monocentre, First-In-Human study.

Protocol N°.: CL1-95010-001

EudraCT N°.: 2017-004180-12

The description of the study protocol given hereafter includes the modifications of the three substantial amendments to the clinical protocol

Structures involved in the study:

- **Clinical investigator:** [redacted]
- **Pharmacokinetic interpretation:** [redacted]
- **Analytical centres:** [redacted]
- **Pharmacodynamic analyses:** Not applicable
- **Other analysis centres:** Not applicable

Publication (reference): Not Applicable

Studied period:	**Phase of development of the study:**
Initiation date: 21 February 2018 (first visit of first participant) Completion date: 10 April 2019 (last visit of last participant)	Phase I

Objectives:

Primary objective:

To assess the safety and tolerability of S95010 given by intravenous (I.V.) administration of single doses increasing from 0.01 to up to 1.5 mg/kg, in comparison with placebo, in young healthy male participants.

Secondary objectives:

To assess the pharmacokinetics (PK) of S95010 and its metabolites in plasma and urine.

Exploratory objectives:

- To identify circulating biomarkers of target engagement by investigating changes, in different blood fractions, of the expression of microribonucleic acid 92a (miR-92a) and its target messenger ribonucleic acids (mRNAs).
- To retrospectively assess the plasma concentration (and its change upon S95010 I.V. administration) of circulating biomarkers, to be selected after the study end, according to their translational interest.
- To explore the relationship between S95010 plasma concentrations and cardiovascular parameters extracted from 24-hour Holter electrocardiograms (ECGs).

Methodology:

Phase 1; monocentre, randomized, double-blind, placebo-controlled, dose-escalating study. 7 groups of 7 participants per dose (5 receiving S95010 and 2 receiving placebo) including 2 sentinel participants per dose group (1 receiving S95010 and 1 receiving placebo).

Selection period: up to 4 weeks until inclusion visit on Day 0 (INCL). Hospitalisation from INCL to Day 4 (D04) with single administration on Day 1 (D01). Ambulatory follow-up visits 2 weeks (W02) and 4 weeks (W04) after administration. Run-out (RUNO *i.e.* end of study) visit 12 weeks (W12) after administration

Decision to proceed to ascending dose taken jointly by Sponsor and Principle Investigator based on:

- all clinical and laboratory D0-W02 data of the current cohort + all available data (up to W12) of previous cohorts
- descriptive statistics of D01-D04 PK values (blinded) of current cohort + all available data (up to W12) of previous cohorts
- dose proposed by Bayesian Logistic Regression Model based on Dose Limiting Toxicity data observed during previous steps

This study was performed in strict accordance with Good Clinical Practice.

Number of subjects:

Planned: 49 completed participants (35 receiving S95010 and 14 receiving placebo) with the possibility of one additional cohort of 7 participants (maximum 56 participants) to repeat/confirm some findings.

Included: 49 completed participants (35 receiving S95010 and 14 receiving placebo).

Main criteria for inclusion:

Young healthy male participants aged between 18 and 45 years (both inclusive), with Body Mass Index (BMI) from 18.5 to 30.0 kg/m² (both inclusive) and body weight between 50.0 and 100.0 kg (both inclusive), non-smoker or ex-smoker for more than 3 months, with normal liver enzymes lab results, with normal *fundus oculi* assessment and abdominal echography examination performed between the selection and inclusion visits, and with no high myopia or history of high myopia could be included in the study.

Participants with a history of dermal/mucosal asymptomatic haemangioma (history of haemangioma resolved during infancy accepted), prior malignancies, and haemangioblastoma, could not be included in the study.

Test drug:

S95010 solution for infusion was diluted by the centre pharmacy staff from a 40 mg/mL sterile solution of S95010 [redacted] with 0.9% NaCl locally provided.
50 mL of the S95010 diluted solution was blindly administered intravenously (I.V.) as a single 10-minute infusion to 5 participants in each of the dose groups (0.01, 0.05, 0.15, 0.45, 0.90, 1.20 and 1.50 mg/kg).

Reference product or placebo:

50 mL of the 0.9% NaCl matching placebo (locally provided) was blindly administered intravenously (I.V.) as a single 10-minute infusion to 2 participants in each of the dose groups.

Duration of treatment and organisation of study visits:

Selection and inclusion visits:

One half-day assessment visit (ASSE), within 4 weeks before inclusion visit;1 half-day in the ophthalmology centre between selection and inclusion visits for *fundus oculi* assessment; 1 half-day in the radiology centre between selection and inclusion visits for abdominal echography assessment (could be on the same day as the ophthalmology visit); for participants eligible after the ophthalmology and echography assessments, one day on D0 (INCL), with hospitalisation in the phase I unit from morning for included participants.

Hospitalisation period:

Hospitalisation for 5 days and 4 nights from end of INCL to D04, with a single I.V. administration of S95010 or placebo on D01.

Ambulatory period:

Follow-up period of 12 weeks after IMP administration: week 2 visit (W02), at least two weeks (14-18 days) after IMP administration, week 4 visit (W04), at least four weeks (28-32 days) after IMP administration, and week 12 visit (W12), at least twelve weeks (84-88 days) after IMP administration, INCL, with run-out from study at the end of the visit.

Criteria for evaluation:

Safety measurements:

At each visit: Adverse event (AE) recording, physical examination, body weight, vital signs [heart rate (HR), blood pressure (BP), body temperature], 12-lead ECG (Heart rate, cardiac rhythm, ECG intervals, ECG abnormalities), blood biochemistry (fasting), and haematology. Depending on visit: coagulation test, complement activation test, blood safety biomarkers (CRP, IL1β, IL6, TNFα, cTnT, Cys C), urine biochemistry, urine chemistry: albumin, diuresis over 24 h, *fundus oculi* examination and abdominal echography.

Pharmacokinetic measurements:

For each dose group, 17 blood samples (at 17 time points) of 5 mL were collected from each participant: pre-dose (within 1 hour before infusion) and at the end of infusion, then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 h, Week (W) 02, W04, and W12 after the end of the dose infusion.

Urine samples were collected pre-dose and then 0-6 h, 6-12 h, 12-24 h, 24-48 h and 48-72 h from D01 to D04 post-injection. Additional urine samples were collected during the 12 hours prior to the follow-up visits W02, W04 and W12. All samples were collected, but measurement of urine concentrations of S 95010 were only determined for the 0.15, 0.9, 1.2 and 1.5 mg/kg dose groups.

Plasma and urine concentrations of S 95010 were analysed by validated bioanalytical methods based on proteinase K digestion and hybridization/liquid chromatography with fluorescence detection. The Lower Limit of Quantification (LLOQ) was 1.00 ng/mL in both plasma and urine. Metabolites: see stand-alone metabolism report.

Pharmacodynamic measurements: Not applicable

Exploratory genomic biomarker analysis: see stand-alone Biomarker report

Exploratory circulating biomarker analysis: not performed at time of study report

Exploratory PK/QT relationship analysis : not performed at time of study report

Statistical methods:

Included Set (IS): All participants included in the study.

Randomised Set (RS): All included and randomised participants to whom a therapeutic unit was randomly attributed.

Safety Set (SS): All participants having taken at least one dose of investigational medicinal product (IMP).

Safety analysis:

Descriptive statistics were provided by treatment groups (each S95010 dose (n=5 each) and placebo (n=14) groups) and for some parameters by pooled S95010 doses (n=35) and placebo (n=14)).

Pharmacokinetic analysis:

Individual plasma and urine concentration-time data of S 95010 were analysed by non-compartmental analysis (NCA) using Phoenix WinNonlin® Build 8.0.0.3176. The following PK parameters were determined from individual plasma and urine S 95010 concentration-time profiles: C_{inf}, ti_{nf}, C_{max}, t_{max}, C_{last}, t_{last}, $AUCl_{ast}$, AUC_{0-72}, AUC, AUC_{ext}, λ_z, $t_{1/2z}$, CL, V_{ss}, Ae_{0-t}, fe and CL_R. Descriptive statistics were calculated for plasma and urine concentrations, urine volumes and plasma and urine PK parameters.

Pharmacodynamic analysis: Not applicable

SUMMARY - CONCLUSIONS

DISPOSITION OF PARTICIPANTS AND ANALYSIS SETS

	S95010							Placebo (N = 14)	All (N = 49)
	0.01 mg/kg(N = 5)	0.05 mg/kg (N = 5)	0.15 mg/kg (N = 5)	0.45 mg/kg (N = 5)	0.90 mg/kg (N = 5)	1.20 mg/kg (N = 5)	1.50 mg/kg (N = 5)		
Included	5	5	5	5	5	5	5	14	49
Randomised	5	5	5	5	5	5	5	14	49
Withdrawn	-	-	-	-	-	-	-	-	-
Completed	5	5	5	5	5	5	5	14	49
Safety Set	5	5	5	5	5	5	5	14	49

N: number of participants per group

A total of 49 healthy male participants were included in the study, and all 49 participants completed the study.

There was a total of 7 deviations in 7 participants (14.3%) at or before inclusion, concerning non-fulfilment of inclusion criteria (3 participants) or selection criteria (1 participant), a missing biological parameter (1 participant), a clinically significant abnormal urinalysis result (1 participant), and a *fundus oculi* examination not performed between the selection and inclusion visits (1 participant).

During the study period, after inclusion, 7 participants (14.3%) had a total of 12 protocol deviations, of which 5 deviations in 5 participants concerned missing parameters or a time interval not respected, 5 deviations in 2 participants concerned unauthorised concomitant treatment, and 2 deviations in 2 participants concerned wrong IMP volume administered (48.0 mL and 56.0 mL instead of the planned volume of 50.0 mL). Among these deviations, only one concerned a participant in the placebo group (missing parameter)

BASELINE CHARACTERISTICS

All participants in the Randomised Set were male; they were 20 to 45 years old with a BMI ranging from 18.8 to 29.3 kg/m². All participants except four were Caucasian. There was no difference in demographic characteristics between treatment groups.

EXTENT OF EXPOSURE

As planned, 35 participants received a single I.V. administration of S95010 (*i.e.* 5 participants per dose group: 0.01 mg/kg, 0.05 mg/kg, 0.15 mg/kg, 0.45 mg/kg, 0.90 mg/kg, 1.20 mg/kg and 1.50 mg/kg); and 14 participants received a single I.V. administration of placebo.

PHARMACOKINETIC RESULTS

Population

The NCA was performed on the PK set with 35 male participants receiving S 95010 (5 subjects per dose group). The PK Set was defined as all included participants having at least one administration of study treatment without any major deviation or event affecting the PK interpretation. The mean ± SD age, weight, height, body mass index (BMI) and creatinine clearance (CRCL) of the participants were 31 ± 7.7 years old, 78 ± 9.3 kg, 179 ± 5.7 cm, 24 ± 2.8 kg/m^2 and 8.2 ± 1.5 L/h, respectively. Demographics were similar across all dose groups.

Pharmacokinetic results

The summary PK parameters of S 95010 obtained after administration of 0.01 to 1.5 mg/kg of S 95010 are presented in the tables below:

Mean (CV%), median pharmacokinetic parameters of S 95010 after single administration of 0.01 to 1.5 mg/kg of S 95010 in healthy male participants

PK Parameter	S 95010 Dose (mg/kg)			
(unit)	0.01	0.05	0.15	0.45
N	5	5	5	5
C_{inf} (ng/mL)	167 (17), 164	828 (7.0), 793	2812 (25), 3170	8912 (12), 9310
t_{inf} (h)	0.17 [0.17-0.22]	0.17 [0.17-0.18]	0.17 [0.17-0.18]	0.17 [0.17-0.17]
C_{max} (ng/mL)	167 (17), 164	828 (7.0), 793	2812 (25), 3170	8912 (12), 9310
t_{max} (h)	0.17 [0.17-0.22]	0.17 [0.17-0.18]	0.17 [0.17-0.18]	0.17 [0.17-0.17]
C_{last} (ng/mL)	1.5 (25), 1.35	2.6 (110), 1.29	1.6 (21), 1.74	1.5 (30), 1.42
t_{last} (h)	4.17 [3.17-4.17]	6.17 [3.17-6.18]	8.17 [8.17-12.2]	24.2 [12.2-72.2]
AUC_{last} (h.ng/mL)	110 (14), 113	544 (10), 512	2708 (28), 2805	15667 (21), 16143
AUC_{0-72} (h.ng/mL)	112 (13), 115	547 (10), 518	2711 (28), 2808	15672 (21), 16151
AUC (h.ng/mL)	112 (13), 115	547 (10), 518	2711 (28), 2808	15693 (21), 16151
AUC_{ext} (%)	1.6 (49), 1.3	0.53 (70), 0.35	0.11 (31), 0.098	0.23 (190), 0.039
$t_{½,z}$ (h)	0.769 (19), 0.757**	0.963 (24), 1.06**	1.22 (28), 1.1**	12.9 (170), 3.7**
CL (L/h)	6.4 (8.1), 6.4	6.9 (16), 6.7	4.5 (18), 4.3	2.2 (9.6), 2.2
V_{ss} (L)	4.65 (13), 4.37	4.62 (14), 4.7	4.01 (18), 3.75	4.04 (40), 3.37
Ae_{0-72} (mg)	-	-	0.12 (28), 0.10	-
fe (%)	-	-	1.0 (20), 1.0	-
CL_R (L/h)	-	-	0.045 (21), 0.043	-
CL_R (mL/min)	-	-	0.75 (21), 0.71	-

PK Parameter	S 95010 Dose (mg/kg)		
(unit)	0.9	1.2	1.5
N	5	5	5
C_{inf} (ng/mL)	16620 (21), 17300	22440 (12), 21600	26300 (20), 27100
t_{inf} (h)	0.17 [0.17-0.17]	0.17 [0.17-0.17]	0.17 [0.17-0.18]
C_{max} (ng/mL)	19780 (26), 19200	24060 (9.2), 24000	30800 (5.1), 31500
t_{max} (h)	0.42 [0.17-0.82]	0.42 [0.17-0.67]	0.42 [0.38-0.67]
C_{last} (ng/mL)	1.8 (46), 1.39	2.0 (35), 1.99	1.4 (24), 1.35
t_{last} (h)	72.2 [48.2-335]	72.2 [72.2-335]	337 [337-432]
AUC_{last} (h.ng/mL)	47617 (20), 47878	71907 (19), 65315	94533 (11), 94157
AUC_{0-72} (h.ng/mL)	50825 (22), 47877*	71824 (19), 65314	93719 (11), 93454
AUC (h.ng/mL)	-	77239 (22), 69335*	94838 (11), 94437
AUC_{ext} (%)	-	0.30 (47), 0.35*	0.33 (38), 0.30
$t_{½,z}$ (h)	-	111 (85), 68.3*/***	151 (11), 145
CL (L/h)	-	1.3 (23), 1.4*/	1.3 (7.1), 1.3
V_{ss} (L)	-	4.62 (26), 4.54*	8.12 (17), 8.27
Ae_{0-72} (mg)	1.6 (23), 1.7	2.7 (16), 2.6*	4.2 (19), 4.2
fe (%)	2.2 (25), 2.4	2.3 (27), 2.4	3.4 (17), 3.4
CL_R (L/h)	0.033 (23), 0.030*	0.041 (18), 0.041*	0.045 (10), 0.044
CL_R (mL/min)	0.55 (23), 0.50*	0.68 (18), 0.69*	0.74 (10), 0.73

N=3, ** Due to low number of S 95010 concentrations above the LLOQ for terminal phase, any derived λ_z and $t_{1/2,z}$ for this dose level may not reflect the true $t_{1/2,z}$ * Due to low number of S 95010 concentrations above the LLOQ for terminal phase, most of the derived λ_z and $t_{1/2,z}$ for this dose level may not reflect the true $t_{1/2,z}$ Mean (CV%), median except for t_{inf}, t_{max} and t_{last}, where median [min-max] presented*

Metabolites: see stand-alone Metabolism report

PHARMACODYNAMIC RESULTS

Not applicable

SAFETY RESULTS

- **Emergent adverse events (EAEs)**

Overall summary of adverse events in the Safety Set

		S95010							Placebo (N=14)
		0.01 mg/kg(N = 5)	0.05 mg/kg (N = 5)	0.15 mg/kg (N = 5)	0.45 mg/kg (N = 5)	0.90 mg/kg (N = 5)	1.20 mg/kg (N = 5)	1.50 mg/kg (N = 5)	
Participants having reported at least one:									
EAE	n (%)	1 (20%)	1 (20%)	3 (60%)	4 (80%)	2 (40%)	2 (40%)	1 (20%)	5 (35.7%)
Treatment-related EAE	n (%)	-	-	-	-	-	-	-	1 (7.1%)*

** Headache*

There were no deaths or serious AEs reported nor AE leading to treatment withdrawal.

In the Safety Set, the percentage of participants with at least one EAE was similar in the pooled-dose S95010 group (40.0%) and in the placebo group (35.7%).

The 2 system organ classes (SOCs) most frequently affected in the pooled-dose S95010 group were Nervous system disorders (7 participants, 20.0%), including mainly headache (4 participants, 11.4%), and Infections and infestations (5 participants, 14.3%), including mainly nasopharyngitis (3 participants, 8.6%). EAEs affecting these 2 SOCs and with the same preferred terms were reported in 1 participant each (7.1%) in the placebo group.

No dose-related effect was apparent.

No EAE was rated of severe intensity during the study. Five (5) EAEs in participants in the S95010 group were of moderate intensity; all other EAEs (in S95010 and placebo groups) were mild.

One EAE (headache of moderate intensity) was considered related to the treatment in the placebo group.

All EAEs in all groups had resolved at the end of the study.

No AE defined in the list of dose-limiting toxicities occurred in the S95010 groups, and dose-escalation progressed as planned in the protocol without any limitation of dose due to EAEs.

- **Laboratory tests, other safety evaluation**

Concerning biological parameters, few participants who received S95010 presented emergent potentially clinically significant abnormal (PCSA) values:

- 2 participants (5.7%) in the S95010 group had high emergent PCSA values for creatine kinase *versus* 1 (7.1%) in the placebo group, likely to be related to physical activity.
- 2 participants (5.7%) in the S95010 group had emergent PCSA low values for high-density lipoprotein cholesterol *versus* none in the placebo group, with no clinical relevance.
- 4 participants (11.4%) in the S95010 had had emergent PCSA high values for urinary albumin *versus* 1 (7.1%) in the placebo group, likely to be due to the participants lying in bed for 5 days.
- 4 participants (11.4%) in the S95010 group had emergent PCSA low values for prothrombin ratio *versus* 1 (7.1%) in the placebo group; however, no PCSA values were observed for International Normalised Ratio and this difference was not clinically significant.

Potassium, protein and triglycerides PCSA values were reported in participants of the placebo group but not for participants of the S95010 groups.

With regards to haematology parameters, no participant on S95010 experienced a PCSA value, whereas 2 placebo participants had emergent PCSA low values for leucocytes and neutrophils, respectively. The low neutrophil value was not considered clinically significant by the investigator while the low leucocyte value, also not considered clinically significant by the investigator ,was however reported as an EAE.

Twelve (12) participants (34.3%) who received S95010 had high emergent out-of-reference-range values for prothrombin time compared to 2 participants (14.3%) in the placebo group but no PCSA value was reported for this parameter.

With the only exception of the PCSA leukopenia values, reported as an EAE (although not considered as clinically significant by the investigator), no participant presented an abnormality following study treatment for biochemistry, haematology, urine chemistry, urine biochemistry or coagulation that was reported as an EAE or considered as clinically significant by the investigator.

No dose effect of S95010 was observed on 24 h diuresis.

No clinically significant abnormality and no EAE were reported during the study either for vital signs, ECG, *fundus oculi* or abdominal ultrasound scan examinations.

With regards to ECG parameters, 3 participants (8.6%) in the S95010 group had high abnormal values for PR duration *versus* none in the placebo group; and 4 participants (11.4%) *versus* 2 (14.3%), respectively had high abnormal values for QTcF. None of these values were considered as clinically significant by the investigator.

Concerning vital signs, 3 participants (8.6%) who received S95010 had abnormal (high or low) values for BP during the study *versus* 4 participants (28.6%) who received placebo. None of these values were considered as clinically significant by the investigator.

Safety biomarker analysis showed a higher percentage of participants with high abnormal values of IL6 and TNFα in the pooled-dose S95010 group than in the placebo group at different visits including baseline. The increases in IL-6 and TNFα were observed, independently of the dose or the visit No abnormal value was considered as clinically significant by the investigator. Consistent inflammatory status (i.e. concomitant increase of IL6 and CRP or TNF) appeared in only 3 cases in the S95010 group among which two were explained by concomitant infectious AE. It can thus be excluded that S95010 has a systemic pro-inflammatory action at the tested doses.

Safety biomarker analyses also showed no evidence of an effect on:

- Cardiomyocytes, as shown by circulatory the cTnT levels, which remained under detectable levels at all times and for all doses.
- Renal function, as shown by the circulatory CysC levels with only one patient in the S95010 group presenting an emerging abnormal high value after treatment, which was not considered as clinically significant by the investigator.

EXPLORATORY ANALYSES RESULTS

Genomic biomarker: see standalone Biomarker report

Circulating biomarker retrospective analysis: not applicable

Exploratory PK/QT relationship analysis: not applicable

CONCLUSION

The primary objective of the study was to assess the safety and tolerability of S95010 given by I.V. administration of single doses increasing from 0.01 to up to 1.5 mg/kg, in comparison with placebo, in young healthy male participants.

Single I.V. administration of S95010 at 0.01, 0.05, 0.15, 0.45, 0.90, 1.20 and 1.50 mg/kg to healthy male participants was safe and well tolerated compared to placebo in this First-In-Human study. There was no dose-related effect on the occurrence of EAEs, and no clinically significant abnormal values after S95010 administration for biochemistry, haematology, coagulation, complement activation, safety (circulatory) biomarkers, urine chemistry, urine biochemistry, vital signs, or ECG.

Furthermore, there was no effect of S95010 at any dose on the vascularisation of the retina, as assessed by *fundus oculi* at W02 and W04, nor on the emergence of liver or visceral haemangioma as assessed by abdominal echography at W12, which suggests the absence of any undesirable pro-angiogenic effect of S95010, administered as a single I.V. dose, in these monitored non-target organs.

The secondary objective of the study was to assess the pharmacokinetics (PK) of S95010 and its metabolites in plasma and urine.

After single IV administration of 0.01 to 1.5 mg/kg S 95010,

- peak exposure (Cmax) increased in a dose proportional manner with increasing dose.
- the overall exposure increased greater than proportionally with dose in the range 0.01 to 0.90 mg/kg, and proportionally with dose from 0.90 to 1.5 mg/kg S 95010.
- variability on PK parameters (AUC, C_{max}, CL, V_{ss}) was low at all doses and for all parameters (except at 0.45 mg/kg at which variability on Vss was moderate).
- based on the highest dose level (1.5 mg/kg), the mean $t_{1/2z}$ of S 95010 is estimated to be 151 hr.
- on average, 1.0 to 3.4% of the S 95010 dose was recovered unchanged in the urine across the range of doses evaluated.
- the maximum exposure defined in the clinical protocol was not reached

Date of the study report: 12 December 2019

Signature of the study report

S95010 Clinical Development Leader: [redacted]

[redacted]