2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product: Not Applicable** **Name of Active Ingredient: S81694**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study:
Phase I dose-escalation study of S81694 administered intravenously in adult patients with dvanced/metastatic solid tumours

Protocol No.: CL1-81694-001
EudraCT No.: 2014-002023-10
The description of the study protocol given hereafter includes the modifications of the five substantial amendments to the protocol.

International coordinator
[redacted]

Study countries:
Total number of countries: 2 (Belgium, The Netherlands)
Total number of centres: 3 (two in Belgium and one in the Netherland)
Two countries included 39 patients overall: 26 patients in Belgium and 13 patients in the Netherlands

Publication (reference):
Not applicable

Studied period: Initiation: date: 29 September 2015 Completion date: 03 July 2019	**Phase of development of the study:** Phase I

Objectives:
Primary Objective:
To determine the maximum tolerated dose (MTD) and the associated dose-limiting toxicities (DLTs) of S81694 administered in adult patients with advanced/metastatic solid tumours failing or refractory to available therapy
Secondary Objectives:
- To define the safety and tolerability profile of S81694;
- To define the recommended phase II dose (RP2D) based on the safety and tolerability profile;
- To determine the pharmacokinetics (PK) profile of S81694 and its metabolite(s) in plasma and urine;
- To explore the relationship between PK and selected adverse events;
- To explore any potential exposure-response relationship for safety, efficacy and pharmacodynamics;
- To explore early signs of antitumor efficacy;
- To identify potential predictive biomarkers of efficacy.

Methodology:
Phase I, multicentre, open-label, non-randomised, non-comparative study.
This study was performed in strict accordance with Good Clinical Practice.
Due to strategic reorientation, this first in-human phase I study was discontinued.

Number of patients:
Planned: up to 72 patients
Included: 39

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Diagnosis and main criteria for inclusion:

Inclusion criteria:

- Male or female patients with age ≥ 18 years;
- Histologically or cytologically confirmed diagnosis of advanced/metastatic solid tumour in patients for whom no effective standard therapy is available anymore or standard therapy is considered unsuitable;
- For patients participating to the expansion cohort at RP2D, acceptance of pre- and post-treatment biopsies;
- At least 4 weeks must have elapsed or, in absence of toxicity, 5 half-lives, between S81694 first administration and the completion of the prior antineoplastic therapy (6 weeks for nitrosoureas or mitomycin C), including biologic, immunologic or targeted anticancer therapy;
- Prior radiotherapy is allowed provided that no more than 25% of bone marrow reserve has been irradiated (see Appendix 5);
- Patients with controlled CNS involvement are accepted as long as therapy with corticosteroids and/or anticonvulsant is not required;
- Resolution (return to baseline) or return to NCI CTCAE Grade ≤ 1 of all acute toxicities due to prior anticancer therapy except alopecia, grade 2 paraesthesia, grade 2 hyper- or hypothyroidism and other non- clinically significant adverse events;
- ECOG (WHO) performance status 0-1;
- Patients must use effective contraception:
  Within the frame of this study, female patients of childbearing potential must be on a highly effective method of birth control defined as those which result in a low failure rate (i.e. less than 1% per year) such as implants, injectable, combined oral contraceptives, intra-uterine devices (IUDs), vasectomized partner or true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient).
  Male patients with partners of childbearing potential must be either vasectomized or agree to use a condom in addition to having their partners using another method of contraception resulting in a highly effective method of birth control defined as those which result in a low failure rate (i.e. less than 1% per year) such as implants, injectable, combined oral contraceptives, or IUDs.
  Birth control methods should be used ≤7 days prior to receive investigational drug for female, for the duration of study participation and up to 3 months following the last dose of investigational drug for all participants.
  The investigator must inform the patient about the risks not to use an effective method of birth control during the course of the study.
- Baseline laboratory values fulfilling the following requirements:

Absolute neutrophils count (ANC)	≥ 1,500/mm^3 (≥ 1.5 x 10^9/L)
Platelets (PLT)	≥ 100,000/mm^3 (≥ 100 x 10^9/L)
Haemoglobin (Hb)	≥ 10.0 g/dL
Serum creatinine or Creatinine clearance*	≤ 1.5 x ULN > 60 mL/min
Total serum bilirubin	≤ 1.5 x ULN
Liver transaminases (AST/ALT)	≤ 3.0 x ULN; ≤ 5 x ULN if liver metastasis are present
Alkaline phosphatase (ALP)	≤ 2.5 x ULN; ≤ 5 x ULN if liver and/or bone metastasis are present
Direct Coombs test	Negative
Cold agglutinins	Negative (titers < 64)
Serum pregnancy test, if female childbearing potential	Negative within 7 days of starting treatment
ULN = upper limit of normal; * As per local standard method of measurement	

- Available original informed consent form completed

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Non-inclusion criteria

- Unlikely to cooperate in the study;
- Pregnancy, breastfeeding or possibility of becoming pregnant or fathering during the study;
- Participation in another interventional study at the same time;
- Patient already enrolled in the study (informed consent previously signed and screening failure or intolerance/progression on treatment);
- Blood transfusion ≤ 3 weeks before treatment start;
- Episode(s) of clinically relevant active bleeding in the past 3 weeks;
- Known history of haemolytic anaemia (including G6PD deficiency), thrombotic thrombocytopenic purpura (TTP), microangiopathic haemolytic anaemia (MAHA), haemolytic uremic syndrome (HUS)
- Major surgery within 4 weeks before the first day of investigational drug administration without recovery of ECOG 0-1;
- Any of the following in the past 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis or thrombolysis;
- Clinically significant respiratory or metabolic diseases uncontrolled by medication;
- Patients with uncontrolled high blood pressure (systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 95 mmHg despite treatment on ≥ 2 out of 3 determinations done in case that the first one meets the criterion for exclusion);
- Presence of risk factors for torsade de pointes (e.g. heart failure, hypokalaemia, family history of long QT syndrome);
- Patients who have undergone treatment with high-dose chemotherapy requiring progenitor cell transplantation;
- Known active or uncontrolled infections (bacterial, fungal, viral including HBV and HCV infections); patients who are seropositive following HBV vaccine are eligible as well as patients HBV and HCV seropositive, but negative for viral DNA by RT-PCR;
- Known HIV seropositive patients;
- Patients with known history of allergic reactions to polysorbate 80;
- Any known organ dysfunction, serious illness, medical condition, or other medical history, including laboratory abnormalities, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study or with the interpretation of the results;
- Any condition (e.g., known or suspected poor compliance, psychological instability, geographical location, etc.) that, in the judgment of the Investigator, may affect the patient's ability to understand and sign the informed consent and fully comply with all study procedures;
- Patients who, within 7 days prior to the first S81694 intake, are receiving or received strong inducers of Flavin containing Mono Oxygenase (FMO1 and FMO3)
- Patients who are receiving sensitive cytochrome P3A4 (CYP3A4) substrates, CYP3A4 and breast cancer resistant protein (BCRP) substrates with narrow therapeutic index (NTI)

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Test drug:
S81694: 30 mg powder for solution for infusion formulated in Mannitol 4%, polysorbate 80 0.5%. The product was reconstituted in 10 ml of water for injection (WFI) for a solution of 3 mg/ml. The solution was then diluted to 250 or 375 mL (according to the dose of S81694) with saline solution, and then delivered over 1 hour or 1 hour and 30 minutes infusion per local hospital standard practices for infusion.
Schedule: S81694 administered IV as single agent once a week for three consecutive weeks (Day 1, 8, 15) in a 28-day cycle.

Dose allocation methodology
This study was designed with inter-individual dose-escalation in cohorts of at least 3 patients each (dose escalation phase). At the beginning of the study the dose escalation followed a 3+3 design; once the 4th amendment was applicable, a Bayesian Logistic Regression Model (BLRM) guided the dose escalation to determine the MTD. Increments of no more than 100% of the dose of previous cohort were allowed, providing the proposed dose satisfied the Escalation With Overdose Control (EWOC) criterion.
The starting dose of Schedule 1 was 4 mg/m^2/week (12 mg/m^2 per cycle).

Mode of administration
At each administration, the number of vials of S 81694 to be reconstituted was calculated to achieve the amount of S 81694 foreseen based on the patient BSA and the cohort dose level. According to the dose of S 81694, the amount of S 81694 to be administered to the patient was injected into a 250 mL infusion bag of a saline solution after having withdrawn with a syringe an equivalent volume from it so that the final volume of the bag remained 250 mL (if the dose is ≤ 255 mg) or injected into a 500 mL infusion bag of a saline solution after having withdrawn with a syringe the necessary volume of solution (125 ml + an equivalent volume of S 81694) from it so that the final volume of the bag was 375 mL (if the dose > 255 mg and < 480 mg).

Comparator (Reference product and/or placebo):
Not applicable

Duration of treatment:
Inclusion period: up to 28 days before treatment start day
Treatment period: from day 1 of treatment administration until disease progression, patient refusal to continue investigational drug, withdrawal of patient consent, or the occurrence of unacceptable toxicity, major protocol deviation, and any medical event requiring administration of unauthorized concomitant treatments.
Follow-up period: 30 days after the study drug discontinuation

Criteria for evaluation:
Efficacy measurements:
There was no efficacy measurement with regard to primary endpoint of the phase I part of the study.

Determination of DLT, MTD, RP2D.

Dose Limiting Toxicity (DLT) was defined as any of the following events for which the relationship to S81694 could not be definitely excluded. Toxicities were to be graded according to the NCI CTCAE version 4.03.

Haematological toxicity

- Grade 4 neutropenia (ANC < 500/mm^3) lasting > 7 days
- Febrile neutropenia Grade ≥ 3
- Neutropenic related infection (i.e., infection documented clinically or microbiologically with grade ≥ 3 neutropenia)
- Grade 4 thrombocytopenia (platelet count < 25,000/mm^3)
- Grade 3 thrombocytopenia (platelet count < 50,000-25,000/mm^3) lasting > 7 days or associated with Grade ≥ 2 bleeding

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- Haemolyses Grade ≥ 3
- Grade ≥ 3 anaemia with or without evidence of haemolysis (LDH increased and/or presence of schistocytes in the blood smear and/or haptoglobin decreased and/or unconjugated bilirubin increase and/or urine dips positive for haemoglobinuria (positive for blood without red cells in the sediment)

Nausea or vomiting
- Grade ≥ 3 nausea or vomiting

Diarrhoea
- Grade ≥ 3 diarrhoea

Injection site reaction
- Grade > 3 (Ulceration or necrosis that it is severe; operative intervention indicated)

Other non-haematological toxicity
- Grade ≥ 3 toxicities attributable to investigational drug and representing a shift by at least 2 CTC grades from baseline
- Failure to recover (except alopecia, peripheral neuropathy and hypo/hyperthyroidism)
- Failure to recover to Grade ≤ 1 toxicity at day 35

Omission of dosing
- If, because of the toxicity due to S81694, a patient did not receive at least 66% of the intended total dose during Cycle 1, this patient was considered to have had a DLT. No replacement of this patient was required.

The maximum tolerated dose (MTD) was defined as the highest drug dose unlikely (<25% posterior probability) to cause DLT in more than 33% patients in the first cycle of S 81694.The recommended phase II dose (RP2D) would have corresponded to the dose with the highest probability to be in the target toxicity interval [16;33%]. The final selection of the RP2D would have taken into account also the whole safety profile of all the patients.

Due to premature accrual discontinuation, the MTD was not reached and the RP2D not identified.

Safety measurements:

- Vital signs:

Clinical examination; Blood pressure and heart rate (in supine position); Body temperature; Weight (in kg); ECOG performance status; Height (in cm);

- ECG (12-lead triplicate);
- Laboratory tests

Haematology: Hb, RBC, reticulocytes, PLT and WBC with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils, reticulocytes and other cells differentials).
Blood chemistry: electrolytes (Na, K, Ca, P), Blood Urea Nitrogen (BUN) or urea, serum creatinine, creatinine clearance/glomerular filtration rate, total protein, albumin, AST, ALT, GGT, conjugated and unconjugated bilirubin, ALP.
Coagulation parameters: International Normalized Ratio (INR) of prothrombin.
Haemolysis parameters: *in blood* (cold agglutinins and Coombs test [at baseline only], LDH, haptoglobin, unconjugated bilirubin and peripheral blood smear [search of schistocytes]) and *in urine*: Hb (dipstick acceptable) and search of red cells in the sediment
Urinalysis (excluding Hb and sediment): pH, glucose and protein (qualitative, dipstick accepted).
Serum pregnancy test was indicated only for women of reproductive potential.

Pharmacokinetic measurements:
A full pharmacokinetic profile was defined by collecting blood samples from all patients for evaluation of S81694 and its N-oxyde metabolite (M1). PK assessments were performed on D1, D2, D3, D4, D8, D15, D16, D17, D18, D22 of cycle 1; on D1 and D15 of cycle 2.

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Statistical methods:

Analysis Sets:

The following populations are identified in the Statistical analysis plan:

Treated patients (Safety Set): All enrolled patients who received at least one dose of S81694.

PK Set: All patients who had baseline and sufficient on-study sampled material to provide interpretable results.

Evaluable Patients for DLT: All treated patients who received at least 66% of S81694 in the first cycle and for whom a DLT assessment was available, unless the reason for non-compliance was drug-related toxicity.

Evaluable Set for Efficacy: For exploring antitumor activity, the evaluable population consisted of all patients who had a measurable disease documented at baseline and at least one tumour assessment while on treatment. Patients discontinuing from treatment for progressive disease prior to the scheduled time for the first on treatment tumour assessment were classified as early PD and were described separately.

Study patients: disposition, baseline characteristics and treatments analysis, and safety analysis:

Patients' disposition and reasons for ending the study were presented in frequency distribution tables and individual data listings. The patients not meeting the eligibility criteria, and considered protocol violators were also described.

Descriptive statistics of the baseline characteristics were generated on treated patients and patients evaluable for efficacy. Frequency distributions were presented for the categorical/categorized variables. Summary statistics including mean, standard deviation (SD), median, minimum, maximum and the number of assessed patients were calculated, as appropriate, for the quantitative variables. Individual data were presented in listings

Efficacy analysis:

There was no efficacy measurement with regard to primary endpoint (DLT) of the phase I study. Objective tumour responses were determined based on Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in patients with at least one baseline and one on treatment valid assessment. Tumour assessment data were documented in data listings.

Additional efficacy analysis were planned, but they were not performed due to premature accrual discontinuation.

Safety analysis :

Number and percentage of DLTs were reported breaking in haematological and non haematological ones. Descriptive analyses of safety data were performed considering adverse events, laboratory parameters and vital signs. Adverse Events were coded according to the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI-CTCAE) version 4.03. AEs were evaluated at pre-treatment (≤ 7 days from treatment start), at every treatment cycle (within 24 h before the first infusion), at the end of last cycle, at safety follow-up (30 days after discontinuation of the drug). The analysis focused on all adverse events reported after the start of treatment (treatment emergent adverse events). Adverse event incidence by dose level and by whole treatment period was calculated.

Pharmacokinetic and PK/PD analyses: S81694 and its metabolite(s) plasma concentrations were analysed by population approach, described in a separate Data Analysis Plan, in order to assess the PK of S81694 and its metabolite(s) and to investigate potential sources of variability through a covariate analysis. Any potential PK/PD relationships with activity, efficacy and safety were to be investigated through an exploratory analysis, and if relevant, a PK/PD Data Analysis Plan was to be set up. Due to the premature interruption of patients' accrual, no exploratory analyses were performed.

SUMMARY OF RESULTS:

Disposition of Subjects and Baseline Characteristics

Out of 39 enrolled patients, 38 patients (20 males and 18 females) were treated with S81694 at nine different dose levels: 4 (6 patients), 6(3 patients), 13.5 (4 patients), 20 (6 patients), 30 (3 patients), 45 (3

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patients), 67.5 (4 patients), and 135 mg/m^2/wk (7 patients). The median age at study entry was 58.5 years (range 44-73), ECOG performance status was 0 in 16 patients (42.1%) and 1 in 22 (57.9%). Patient weight and height median 74.0 Kg (range 47-119.3) and 171.0 cm (range 150-191).
The most frequent cancer types at study entry were: cancer of the gastrointestinal tract (23.7%), lung cancer (13.2%), head and neck cancer (10.5%), sarcoma of the soft tissue and bone (7.9%), mesothelioma, breast cancer and cancer of the endocrine system (5.3% each).
Prior to study entry all patients received at least one line of prior systemic therapy for their disease.
The most frequent reason for study discontinuation was disease progression in 30 patients (78.9%), adverse event in 7 patients (18.4%) and consent withdrawal for one patient (2.6%).
Treatment Exposure: a total of 144 cycles of S81694 were administered. The median number of cycles per patient was 2 (range 1-32 cycles). Treatment modifications were implemented in 22 patients over 49 cycles
One patient was not treated due to a worsening in hepatic parameters (AST and ALP > 5ULN) on the day planned for the first S81694 administration.

Efficacy results:

Thirty-six patients were evaluable for efficacy, but 35 only were assessed for a best overall response (1 patient died before his first on treatment oncologic assessment) :
- 1 patient (treated at 4 mg/m^2/wk) had a Complete Response (CR) lasting 112.7 weeks;
-13 patients had SD with median duration of 24.29 weeks (95%CI: 12.29-67.29); out of the 13 Stable Disease (SD), 1 patient (treated at 135 mg/m^2/wk) had a transient Partial Response (PR) at Cycle 5 and therefore classified as SD;
- 21 patients had Progressive Disease (PD) as best response

Safety results:

Thirty-eight patients were evaluable for safety and 36 patients (out of 38) were evaluable for DLT. (two patients were not evaluable for DLT evaluation due to discontinuation without completing Cycle 1 for reasons other than DLT [one patient died before completion of first treatment cycle] and for violation of eligibility criteria [one patient had positive test for cold agglutinins, not meeting exclusion criterion 11]).

Three first-cycle DLTs (primary study endpoint) were observed: Grade 3 anemia at 4 mg/m^2/wk, Grade 4 hypertensive crisis at 20 mg/m^2/week and Grade 3 fatigue at 135 mg/m^2/week (one case each): in the first cohort (4 mg/m^2/wk) the first patient enrolled reported Grade 3 anemia during Cycle 1, considered a DLT by the investigators; the cohort was then expanded to 6 patients and no additional DLTs were reported; in the following cohorts the dose was increased of no more than 50%. Three additional cohorts of patients were treated at 6, 9, and 13.5 mg/m^2/wk, respectively, with no further DLTs. At the fifth dose level (20 mg/m^2/wk) a second DLT (Grade 4 hypertensive crisis) was reported and the cohort was expanded to six patients. Again, an increment of ≤ 50% of the previous dosage was applied to the following cohorts. No DLTs were observed at 30, 45 and 67.5 mg/m^2/wk. The third DLT (Grade 3 fatigue) was observed at 135 mg/m^2/wk dose level, the cohort was therefore expanded (7 patients instead of 6 since one patient was considered not evaluable for DLT and replaced). No further DLTs were reported. Due to strategic reorientation, the accrual for this FIH phase I study was discontinued and no additional cohorths were opened, without reaching the maximum tolerated dose and defining the recommended Phase 2 dose.

All patients experienced at least one treatment-emergent adverse event (TEAE).

Overall, 30 patients (78.9%) experienced a TEAE related to S81694. The most affected (>50 %) drug related SOCs were General disorders and administration site conditions (84.2%), Gastrointestinal disorders (65.8%) and Blood and lymphatic system disorders (52.6%).

The most frequent EAEs reported in at least 15% of overall patients were fatigue (22 patients; 57.9%), anaemia (17 patients; 44.7%); nausea (12 patients, 31.6%), decreased appetite (11 patients; 28.9%), constipation, pain, vomiting (9 patients, 23.7% each), cough (8 patients; 21.1%); diarrhoea (7 patients; 18.4%); dyspnoea (6 patients, 15.8%).

The most frequent (>5 patients) drug related TEAEs were anemia (14 patients), fatigue (11 patients), nausea (8 patients), decreased appetite (6 patients) and neutropenia (5 patients).

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Overall 18 patients experienced a SAE, which was considered related to S81694 in 3 cases, namely Grade 4 hypertensive crisis, Grade 3 keratitis and Grade 2 diarrhoea, the last two occurred at the highest dose level (135 mg/m^2/wk).

Five patients died during the study due to cancer progression.

No major abnormalities were reported in biochemistry except for Grade 3 increase in ALT and AST in two patients and Garde 3 Gamma GT increase in 11 patients (28.9%). The majority of patients with increase in liver enzymes had liver metastases.

Anaemia was observed at all dose levels. Grade 3 anemia was observed in only four patients, one case, reported as DLT), occurred at the first dose level, one other case at 13.5 mg/m^2/wk and the two cases at 135 mg/m^2/week. Neutropenia was not observed or was negligible at all dose levels up to until 67.5 mg/m^2/week. At 135 mg/m^2/week, out of seven patients with baseline neutrophils within normal limits, four patients experienced Grade 3 neutropenia during treatment and 3 remained within the normal limits.

CONCLUSION

Study CL1-81694-001 did not meet the primary endpoint of defining the MTD of S81694 given weekly for 3 weeks every 4 weeks, due to premature discontinuation of patient enrollment.

The safety profile of S81694 was however characterized in this study, with haematological toxicity, general disorders and gastro-intestinal symptoms reported as the main toxicities. The observed safety profile is overall in line with the expected profile based on preclinical studies. Effects on the hemolymphopoietic and gastro-intestinal systems were in fact observed in animals, along with transient haemolytic effects and local effects at the site of injection.

In this study, anaemia without concomitant signs of haemolysis occurred across dose levels, with some apparent increase in frequency and/or severity with higher doses, whereas clinically relevant neutropenia was observed only at the highest dose level tested of 135 mg/m^2/wk.

No relevant effect was seen on platelets, except for a single instance of transient Grade 3 thrombocytopenia. These hematologic effects were always manageable with supportive therapy (e.g. blood transfusion) or dose adjustments and only in one case led to treatment discontinuation.

Haemolysis was reported in very limited number of patients. Also effects at the injection site were reported, and were managed by prolonging the infusion time.

As expected in a Phase 1 trial in cancer patients who have exhausted effective therapies, most of the patients had disease progression as best response and only seven patients remained on study for at least six cycles, and two of them are on the 135 mg/m^2/wk dose level.

One patient with metastatic clear renal cell carcinoma, previously treated with four lines of antitumour treatments (surgery and targeted therapies), achieved a long-lasting CR, although at the lowest dose level tested. One patient with histological diagnosis of hepatocellular carcinoma had a transient decrease in the target lesions. The patient had received 3 lines of prior systemic therapy and was treated with S81694 at the highest dose of 135 mg/m^2/wk.

Overall the safety profile of S81694 administered IV on day 1, 8 and 15 every 4 weeks appears manageable and adequate for further clinical studies.

Date of the report: 17 March 2020

Version of the report: Final version