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:** S787454		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Phase I dose-escalation study of oral administration of the Histone Deacetylase (HDAC) Inhibitor S78454 given in combination with a fixed dose infusion of Cisplatin in patients with advanced solid tumours.
Protocol No.: CL1-78454- 008
EudraCT No.: 2011-002606-69
The description of the study protocol given hereafter includes the modifications of the only substantial amendment to the protocol.

National coordinator

[redacted]

Study centres:
National, multicentre study = 3 centres located in France included at least one patient.

Publication (reference): Not Applicable

Studied period: Initiation date: 16/04/2012 (date of first visit first patient) Completion date: 07/03/2014 (date of last visit last patient)	**Phase of development of the study:** Phase I

Objectives:
Primary Objectives

- Assess the safety and tolerability of the oral capsule form of S78454 given in combination with a fixed dose infusion of cisplatin in patients with advanced solid tumours in terms of the Maximum Tolerated Dose (MTD) and the Dose Limiting Toxicities (DLTs).
- Establish the recommended Phase II dose (RP2D) of S78454 given in combination with a fixed dose of cisplatin.
- Evaluate the global safety and toxicity profile of the combination.

Secondary Objectives

- Determine the pharmacokinetic (PK) profile of S78454 and its main metabolites, alone and in combination with cisplatin.
- Determine the PK profile of cisplatin in combination with S78454.
- Determine the pharmacodynamic (PD) profile of S78454 alone and given in combination with cisplatin:
  - Monitor effects of S78454 in combination with cisplatin on Circulating Tumour Cells (CTC) in peripheral blood as a potential biomarker of efficacy. This dosage was to be performed for the patients of the confirmatory cohort.
- Measure the tumour response to the oral capsule of S78454 in combination with a fixed dose of cisplatin using the revised RECIST guideline (version 1.1) in terms of:
  - Overall Response Rate (ORR).
  - Duration of Stable Disease (SD).
  - Progression Free Survival (PFS).

Methodology:
Phase I dose-escalation, national, multicentre, open-label, non-randomised, non-comparative study.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
The study being prematurely discontinued, after the dose-escalation part and before initiation of the confirmatory part, due to difficulties in the management of the specific schedule of administration in this study in terms of haematological, biological and clinical re-administration criteria, an abbreviated clinical report is presented.

Number of patients:
Planned: up to 50 patients overall in the study of which up to 20 patients in the confirmatory cohort at the recommended dose.
Included: 19 patients in the escalation part with early termination.

Diagnosis and main criteria for inclusion:
Male or female aged ≥ 18 years, with a histologically confirmed diagnosis for advanced solid tumours that had relapsed or was refractory to conventional standard forms of therapy and that might respond to cisplatin therapy, having an evaluable or measurable disease according to RECIST criteria, having an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, an estimated life expectancy > 12 weeks, adequate haematological, renal and hepatic functions and coagulation parameters in normal limit.

Test drug:
S78454: 20 and 100 mg strength (expressed in base) capsules
Administered orally twice a day *(b.i.d.)* 4 hours apart for 4 consecutive days, during the first two weeks (D1-D4, D8-D11), during 3-week cycles, with a glass of water, at least 30 minutes before eating and at least 2 hours after a meal.
The dose escalation of S78454 followed a traditional algorithm-based design "3+3". Cohorts of 3-6 patients were to receive a combination therapy of S78454 with a fixed dose of cisplatin. The starting dose of S78454 was 80 mg *b.i.d.* (dose level 1). The other planned doses were: 60 mg *b.i.d.* (dose level -1)/40 mg *b.i.d.* (dose level -2) in the de-escalation part, and 100 mg *b.i.d.* (dose level 2)/120 mg *b.i.d.* (dose level 3)/140 mg *b.i.d.* (dose level 4)/160 mg *b.i.d.* (dose level 5) in the escalation part. Due to the occurrence of DLTs, only the dose levels 1, -1 and -2 were administered.
Batch No.: L0039582 and L0039583

Drug in combination:
Cisplatin: 100 mL vial
Administered intravenously on D3 every 3-week cycle, at a fixed dose of 75 mg/m^2 over 2 hours by central venous catheter, 2 h after the first intake of S78454 and before the second one, up to a maximum of 6 cycles.
Batch N°.: L0041027

Duration of treatment:
Treatment period: Treatment with S78454 was to be initiated not later than 14 days after inclusion. Each patient was to receive at least 2 cycles of treatment except in case of safety concerns. If the disease did not progress and if the drug was sufficiently well tolerated, patients could continue to receive the treatments with a tumour evaluation every 2 cycles. Cisplatin was to be administered for up to 6 cycles. After 6 cycles of cisplatin administration or if cisplatin was to prematurely stopped, S78454 could be maintained for patients with response or stable disease, if safety criteria were fulfilled, until disease progression or until investigators/patient's decision of withdrawal.
Withdrawal visit: Up to 3 weeks after the last intake of study treatment.
Follow-up period: After the end of the participation in the study, the date of progression or the patient's survival was to be recorded.

Criteria for evaluation:
Efficacy measurements:
The Response Evaluation Criteria in Solid Tumour (RECIST - Eisenhauer, 2009) was used to define lesions and the criteria for objective tumour response. Tumour assessment was to be available at baseline within 4 weeks before inclusion. The CT/MRI scans of all target and non-target lesions were to be performed during cycle 2 between D18 and D21, then every 2 cycles, and at the withdrawal visit (this last tumour evaluation was at the investigator's discretion).
The efficacy criteria were the best overall response, the objective response rate, the clinical benefit rate, the time to first response and the best relative change of the sum of the lesions diameters from baseline.

Safety measurements:

- DLTs
- Adverse events: emergent and serious.
- Deaths
- ECG measurements centrally reviewed: emergent ECG abnormalities and QTcF.
- Laboratory tests: biochemistry, haematology, coagulation and urinalysis.
- Physical examination and vital signs: weight, BSA, ECOG performance status, heart rate and blood pressure.
- Neurological examination
- Audiometric test

The toxicity was graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse events and version 4.03 for biological data.

Pharmacokinetic measurements:
Bioanalytical results are provided in a separate report in Appendix 16.4.
Concentration individual data (S78454 and its metabolites and cisplatin) are provided in Appendix 16.2.6.1.4.

Statistical methods:
Analysis Set:

- **Safety Set (SS)**: This set corresponds to patients having taken at least one dose of study treatment.
- **Full Analysis Set (FAS)**: Based on the intention-to-treat principle, this set corresponds to included patients who have taken at least one dose of study treatment and who have at least one baseline and one post-baseline tumour evaluation.
- **DLT Evaluable Set (DLTES):** All patients from Safety Set who are evaluable for DLT according to the DLT assessment at end of Cycle 1. A patient is considered evaluable if:
  - He/she had a DLT during first cycle or
  - He/she received at least 14 of 16 S78454 and he/she underwent a DLT assessment before beginning the second cycle.

Efficacy analysis (secondary objective):
Descriptive statistics by dose level and overall as well as the 95% Wilson's confidence interval for both the objective response rate and the clinical benefit rate were provided in the FAS.

Study outcome: Descriptive statistics were provided in the Included Set, except treatment duration and extent of exposure which were described in the Safety Set and FAS.

Safety analysis: Descriptive statistics were provided in the Safety Set for each dose level and overall. DLTs were assessed in the DLT evaluable Set.

Pharmacokinetic analyses: Concentration individual data (S78454 and its metabolites and cisplatin) are provided in Appendix 16.2.6.1.4.

SUMMARY - CONCLUSIONS

Disposition of patients and analysis sets

		All
Included	n	**19**
Withdrawn due to	n	**19**
- lost to follow-up	n (%)	-
- adverse event	n (%)	11 (57.9)
- progressive disease	n (%)	7 (36.8)
- non-medical reason	n (%)	1 (5.3)
- cure, remission, improvement	n (%)	-
- protocol deviation	n (%)	-
Safety set	n (%)	**18 (94.7)**
DLT Evaluable Set	n (%)	**18 (94.7)**
FAS	n (%)	**15 (78.9)**

This study was to enroll up to 50 patients, but it was prematurely stopped on 5 March 2014, after the dose-escalation part and before initiation of the confirmatory part, due to difficulties in the management of the specific schedule of administration in this study in terms of haematological, biological and clinical re-administration criteria. Consequently, the second part of the study, i.e. the extension phase to confirm the recommended dose for phase II, was not performed.

Overall, a total of 19 patients were included in the study according to a traditional algorithm-based "3+3" design. Eighteen patients received at least one dose of study drug (corresponding to the Safety Set) and one patient was not treated:

- 7 patients received S78454 at the dose of 80 mg *b.i.d.*, the dose was reduced to 60 mg *b.i.d.* at the end of C001 in 2 patients.
- 5 patients at the dose of 60 mg *b.i.d.*, the dose was reduced to 40 mg *b.i.d.* at the end of C001 in one patient.
- 6 patients at the dose of 40 mg *b.i.d.*

The patients of Safety Set cumulatively received from 400 to 8000 mg of S78454 with a mean of 3017.78 ± 2168.00 mg and from 72.3 to 455.5 mg/m^2 of cisplatin with a mean of 220.17 ± 140.56 mg/m^2.
The relative dose intensity was in average 87.8% for S78454 and 91.2% for cisplatin, in the Safety Set.

In the Safety Set, treatment duration ranged between 3.0 and 24.1 weeks with a mean (± SD) of 10.23 ± 6.21 weeks (median = 7.05 weeks).
The patients received in average 3.3 ± 2.1 cycles (range from 1 to 8 cycles, median = 2.0 cycles). One patient in the 40 mg *b.i.d.* cohort had 3 delayed cycles and 8 patients (1 in the 40 mg *b.i.d.* cohort, 2 in the 60 mg *b.i.d.* cohort and 5 in the 80 mg *b.i.d.* cohort) had one delayed cycle.

In the FAS, the treatment duration ranged from 5.9 to 24.1 weeks and the mean (11.68 ± 5.78 weeks) and the median (12 weeks) were higher than in the Safety Set. The patients of FAS cumulatively received from 1260 to 8000 mg of S78454 with a mean of 3484.00 ± 2072.71 mg and from 75.0 to 455.5 mg/m^2 of cisplatin with a mean of 249.38 ± 136.03 mg/m^2.

Included patients were in average 51.4 ± 13.3 years old, all except one were women. All patients had advanced solid tumours with the breast (7/19 patients) and the ovary (7/19 patients) as main sites and all except one had metastatic tumour. The disease duration from diagnosis ranged from 0.9 to 22.9 years with a mean of 5.73 ± 5.69 years (median = 4 years). Sixteen out of 19 patients were in relapse, the duration from relapse diagnosis ranged from 0.4 to 3.2 months with a mean of 1.41 ± 0.86 months. In the 19 patients receiving chemotherapy, the number of lines was on average 6.8 ± 4.1 lines (range from 2 to 16 lines).

All included patients were withdrawn from the study: 11 for adverse events, 7 for progressive disease and 1 for non-medical reason. No patient was lost to follow-up.

EFFICACY RESULTS

Among the 15 patients of the FAS, the clinical benefit rate was 40% (6/15 patients) with as best overall response:

- Partial response in one patient in the 60 mg *b.i.d.* cohort (No. 008 250 002 00013: adenocarcinoma of the cervix). The best relative change of the sum of the lesions diameters from baseline was -36% and the time to first response was 5.9 weeks.
- Stable disease during at least 3 months in 3 patients (one in the 40 mg *b.i.d.* cohort, No. 008 250 0002 00023: invasive ductal breast carcinoma and 2 in the 80 mg *b.i.d.* cohort: No. 008 250 0001 00003: adenocarcinoma pancreas and No. 008 250 003 00008: serous cystadenocarcinoma ovary). Among them, 2 patients (one in the 40 mg *b.i.d.* cohort and 1 in the 80 mg *b.i.d.* cohort) had a progressive disease afterwards (evaluated during C006 and C008, respectively).
- Non complete response/non-progressive disease during at least 3 months in the 2 patients considered with non-measurable disease at baseline (1 in the 40 mg *b.i.d.* cohort: No 008 250 0002 00020 neuroendocrine carcinoma and 1 in the 60 mg *b.i.d.* cohort: No 008 250 0001 00014 breast cancer). Both had a progressive disease afterwards (evaluated during C005 and C006, respectively).

For the 9 other patients:

- 5 had a progressive disease with the onset of at least one new lesion under treatment (2 patients in the 80 mg *b.i.d.* cohort, 2 in the 60 mg *b.i.d.* cohort and 1 in the 40 mg *b.i.d.* cohort).
- 4 had a best overall response considered as non-evaluable (3 patients in the 80 mg *b.i.d.* cohort and 1 in the 40 mg *b.i.d.* cohort) because they had a stable disease only up to C002 but no other assessment afterwards.

SAFETY RESULTS

- **Emergent adverse events**

Overall summary for adverse events in the Safety Set

		40 mg *b.i.d.* (N = 6)	60 mg *b.i.d.* (N = 5)	80 mg *b.i.d.* (N = 7)	ALL (N = 18)
Patients having reported					
at least one emergent adverse event	n (%)	6 (100)	5 (100)	7 (100)	18 (100)
at least one S78454 only-related emergent adverse event	n (%)	3 (50.0)	4 (80.0)	4 (57.1)	11 (61.1)
at least one cisplatin only-related emergent adverse event	n (%)	3 (50.0)	3 (60.0)	6 (85.7)	12 (66.7)
at least one S78454 and cisplatin-related emergent adverse event	n (%)	6 (100)	5 (100)	7 (100)	18 (100)
Patients having experienced					
at least one serious adverse event (including death)	n (%)	3 (50.0)	4 (80.0)	4 (57.1)	11 (61.1)
at least one serious emergent event (including death)	n (%)	2 (33.3)	4 (80.0)	4 (57.1)	10 (55.6)
at least one S78454 only-related serious adverse event	n (%)	-	1 (20.0)	-	1 (5.6)
at least one cisplatin only-related serious adverse event	n (%)	-	1 (20.0)	1 (14.3)	2 (11.1)
at least one S78454 and cisplatin-related serious adverse event	n (%)	1 (16.7)	2 (40.0)	2 (28.6)	5 (27.8)
Patients with treatment withdrawal					
due to an emergent adverse event	n (%)	4 (66.7)	3 (60.0)	3 (42.9)	10 (55.6)
due to an emergent serious adverse event	n (%)	1 (16.7)	3 (60.0)	2 (28.6)	6 (33.3)
due a S78454-related emergent adverse event (regardless of relationship to cisplatin)	n (%)	2 (33.3)	2 (40.0)	2 (28.6)	6 (33.3)
due a S78454-related emergent serious adverse event (regardless of relationship to cisplatin)	n (%)	-	2 (40.0)	2 (28.6)	4 (22.2)
Patients who died during the study*	n (%)	-	-	-	-

** After the end of the participation in the study, 13 patients died during the follow-up period.*

Overall, all patients experienced at least one emergent adverse event.

The **most frequently affected system organ classes** (SOC) were Gastrointestinal disorders (18 patients [100%]), General disorders and administration site conditions (18 patients [100%]), Blood and lymphatic system disorders (16 patients [88.9%]) and Metabolism and nutrition disorders (13 patients [72.2%]).

SAFETY RESULTS (Cont'd)

The **most frequently reported emergent adverse events** of any grade (> 3 patients) were nausea (18 patients), asthenia (18 patients), anaemia (13 patients [72.2%]), thrombocytopenia (13 patients [72.2%]), vomiting (12 patients [66.7%]), decreased appetite (10 patients [55.6%]), diarrhoea (9 patients [50.0%]), constipation (6 patients [33.3%]), GGT increased (5 patients [27.8%]), neutropenia (4 patients [22.2%]) and tinnitus (4 patients [22.2%]).
All these events except constipation and tinnitus are adverse drug reactions known of S78454.
Nausea, vomiting, decreased appetite, anaemia, thrombocytopenia, neutropenia and tinnitus are also adverse drug reactions known under cisplatin.

Overall, 38/266 EAEs (14.3% of the total number of EAEs) were rated as **severe** (CTCAE grade ≥ 3) of which the most frequent (> 3 patients) were thrombocytopenia (9 patients [50.0%]) and neutropenia (4 patients [22.2%]).

A **DLT**, assessed at the end of Cycle 1, according to investigator's opinion, was reported in 5 patients: 2 in the 80 mg *b.i.d.* cohort (hepatocellular injury grade 3 and thrombocytopenia grade 4), 2 in the 60 mg *b.i.d.* cohort (ECG repolarisation abnormality grade 3 and thrombocytopenia grade 4) and 1 in the 40 mg *b.i.d.* cohort (ALAT increase grade 3).

The dose level 60 mg *b.i.d.* corresponded to the Maximum Tolerated Dose. The dose level-2, 40 mg *b.i.d.*, was considered as the Recommended Dose (RP2D) according to the protocol for the schedule of administration D1-D4, D8-D11 during the first 2 weeks of 3-week cycle in combination with a D3 infusion of cisplatin at 75 mg/m^2. This RP2D could not be confirmed as the confirmatory part of the study was not performed

Overall, 202/266 emergent adverse events were considered by investigators to be **related to S78454 or cisplatin**:

- 17 emergent adverse events in 11 patients (61.1%) were considered as related to S78454 only. The most frequent (> 3 patients) were diarrhoea (4 patients).
- 47 emergent adverse events in 12 patients (66.7%) were considered as related to cisplatin only. The most frequent (> 3 patients) were nausea (5 patients) and tinnitus (4 patients).
- 138 emergent adverse events in 18 patients (100%) were considered as related to S78454 and cisplatin. The most frequent (> 3 patients) were asthenia (16 patients), nausea (13 patients), thrombocytopenia (12 patients), anaemia (10 patients), vomiting (9 patients), decreased appetite (9 patients), neutropenia (4 patients) and GGT increased (4 patients).

The investigators mainly rated the S78454 or cisplatin-related EAEs in grade 1 (49.5% of all S78454 or cisplatin-related EAEs) or grade 2 (35.6%).

Overall, 10 patients (55.6%) experienced at least one **adverse event leading to treatment withdrawal**, all being emergent during the treatment period. These EAEs were sparse within the different PTs, the most frequent ones being thrombocytopenia and malignant neoplasm progression (in 2 patients each). They were serious in 6 patients and non-serious in 4 patients. They were considered by the investigator as related to both S78454 and cisplatin in 5 patients.

A total of 11 patients (61.1%) experienced 18 **serious adverse events** during the study: 15 serious emergent adverse events during the treatment period in 10 patients (55.6%) and 3 SAEs after the treatment period in 1 patient (5.6%).

The most frequent emergent serious adverse events were thrombocytopenia (3 patients) and malignant neoplasm progression (2 patients).

Overall, one SEAE "ECG repolarisation abnormality" was considered as only related to S78454, 2 SEAEs "hyponatremia" and "hydronephrosis" were considered as only related to cisplatin and 5 SEAEs "thrombocytopenia (3 cases)", hepatocellular injury" and "posterior reversible encephalopathy syndrome" were considered related to S78454 and cisplatin.

Eight SEAEs in 6 patients led to study drug withdrawal: malignant neoplasm progression (2 cases), thrombocytopenia, atelectasis, small intestinal haemorrhage, hepatocellular injury, ECG repolarisation abnormality and posterior reversible encephalopathy syndrome (1 case each).

SAFETY RESULTS (Cont'd)

No **death** was reported during the study.
After the end of the participation in the study, 13 patients died during the follow-up period, due to the progression of studied cancer.

- **Laboratory tests**

Regarding the **analysed haematological parameters**, emergent abnormal values grade ≥ 3 according to CTCAE grade from baseline to worst post-baseline value were detected: 8 patients with platelets low values, 3 with haemoglobin low values, 5 with neutrophils low values and 6 with lymphocytes low values.
The mean nadir for platelets tended to remain stable during the different cycles (from Cycle 1 to 6), around 100-120 G/L except for the Cycle 4 (mean = 158.1 ± 72.0 G/L). The time to nadir tended also to remain stable during the different cycles, around 14-16 days.
The mean nadir for haemoglobin tended to remain stable during the different cycles (from Cycle 1 to 6), between 93 and 103 g/L. The time to nadir tended also to remain stable during the different cycles, between 18 and 21 days.

Emergent abnormal values grade ≥ 3 were also detected for the **analysed biochemical parameters**: 2 patients with ALAT high values, 1 patient with ASAT high value and 2 patients with GGT high values. Concerning the creatinine clearance, 3 patients presented at least one value < 50 mL/min during the treatment period.

- **Other safety evaluation**

Concerning **ECOG performance status**, no patient was rated grade > 2 as worst value during the treatment period.
Regarding **vital signs**, no patient had a gain or a loss of weight ≥ 20% between baseline and the worst value during the treatment period.

Six patients had SBP increases > 20 mmHg and 3 patients had DBP increases > 20 mmHg. Two patients had SBP decreases > 20 mmHg and no patient had DBP decreases > 20 mmHg.
Overall, from baseline to worst value during the treatment period, the mean increase of HR was 15.9 ± 7.2 bpm and the mean decrease was -16.6 ± 8.7 bpm.

Regarding **ECG** and according to central reading, 4 patients had emergent ECG abnormalities but not considered as clinically significant: flat T waves, T wave inversion and isolated atrial premature beat.

During the treatment period, one patient presented a maximum absolute prolongation of QTcF equal to 455 ms (mean of triplicate ECG) at C001 Day 3 Tinf + 2h30 after cisplatin infusion, and 5 patients presented a maximum change of QTcF > 30 ms (1 patient in the 40 mg *b.i.d.* cohort, 2 in the 60 mg *b.i.d.* cohort and 2 in the 80 mg *b.i.d.* cohort).
A DLT concerning a grade 3 ECG repolarisation abnormality was reported in one patient. For this diagnosis "unknown/persistent ECG changes in postero lateral repolarisation pattern (negative T wave)", the cardiologist hypothesised that this ECG pattern evoked more a neuro-metabolic trouble than a coronary syndrome and he had no explanation regarding this ECG modification. A myocardial scintigraphy with thallium was performed and showed no sign of infarction. The patient recovered after withdrawal from the study. During the central ECG review, the qualitative analysis performed on the whole patient did not show any more this abnormality.

CONCLUSION

This phase I dose-escalation study, conducted in 18 treated patients, was prematurely stopped on 5 March 2014, after the dose-escalation part and before initiation of the confirmatory part, due to difficulties in the management of the specific schedule of administration of abexinostat administered in combination with cisplatin in terms of haematological, biological and clinical re-administration criteria. Five patients experienced a DLT: 2 at S78454 80 mg *b.i.d.* dose (hepatocellular injury grade 3 and thrombocytopenia grade 4), 2 at 60 mg *b.i.d.* (ECG repolarisation abnormality grade 3 and thrombocytopenia grade 4) and 1 at 40 mg *b.i.d.* (ALAT increase grade 3). The dose level 60 mg *b.i.d.* corresponded to the Maximum Tolerated Dose. The dose level-2, 40 mg *b.i.d.*, was proposed as the Recommended Dose for phase II (RP2D) of S78454 according to the protocol for the schedule of administration D1-D4, D8-D11 during the first 2 weeks of 3-week cycles in combination with a D3 infusion of cisplatin at 75 mg/m^2.

Concerning early signs of clinical activity, one patient in the 60 mg *b.i.d.* cohort had a partial response and 3 patients (1 in the 40 mg *b.i.d.* cohort and 2 in the 80 mg *b.i.d.* cohort) had stable disease during at least 3 months.

Date of the report: 20 November 2014

Version of the report: Final version