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:** S 78454 (abexinostat)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Phase I dose-escalation study of oral administration of S 78454 given with a fixed dose infusion of doxorubicin administered weekly 3 out of 4 weeks in patients with solid tumour.

Protocol No.: CL1-78454-005
EudraCT No.: 2010-020954-33

The description of the study protocol given hereafter includes the modifications of the four substantial amendments to the protocol.

International coordinator: [redacted]

Study centres:
Three centres located in two countries included 35 patients: two centres in France (24 patients included), one in Belgium (11 patients included)

Publication (reference): Not Applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 28 January 2011 (date of first visit first patient) Completion date: 17 December 2013 (date of last visit last patient). Amendment No. 4 applicable in France and Belgium postponed the completion date from November 2012 to November 2013.	Phase I

Objectives:

Primary objective:

- To assess the safety and tolerability of the oral capsule form of S 78454 (abexinostat) given in combination with doxorubicin in patients with solid tumour in terms of the Maximum Tolerated Dose (MTD) and the Dose-Limiting Toxicities (DLTs).
- To establish the recommended Phase II dose (RP2D) in combination with doxorubicin.

Secondary objectives :

- To measure the tumour response to the oral capsule of S 78454 in association with doxorubicin using the revised Response Evaluation Criteria In Solid Tumors (RECIST) guideline (version 1.1).
- To determine the pharmacokinetic (PK) profile of the oral capsule form of S 78454 and its main metabolites alone and in association with doxorubicin.
- To determine the pharmacokinetic (PK) profile of doxorubicin and its main metabolite in association with S 78454.
- To assess the influence of the food on the PK of S 78454 and its metabolites.
- To determine the pharmacodynamic effects of S 78454 alone or given in combination therapy with doxorubicin:
  - To monitor pharmacological effects of S 78454 alone on Histone Deacetylase (HDAC) inhibition on peripheral blood mononuclear cells (PBMCs) by exploring the acetylation state of proteins before and after treatment.
  - To characterize biological activity of S 78454 using tumour cells obtained from tumour biopsies before and after treatment in terms of expression of RAD51, acetylation, genomic and proteomic analysis.

Methodology:
Multicentre, international, non-randomised, non-comparative, dose escalation, open Phase I study. Dose escalation followed a traditional algorithm-based design "3+3".
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: up to 36 patients.
Included: 35 patients.

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

Test drug: S 78454 (hard gelatine oral capsules at 20 mg and 100 mg)
Cohorts of 3-6 patients received orally the capsules of S 78454 b.i.d. daily 4 hours apart on days 1-4 (D1-D4) weekly 3 out of 4 weeks at the following four level doses planned to determine the MTD:

- Dose Level 1: 30 mg/m² b.i.d. (60 mg/m²/day).
- Dose Level 2: 45 mg/m² b.i.d. (90 mg/m²/day).
- Dose Level 3: 60 mg/m² b.i.d. (120 mg/m²/day).
- Dose Level 4: 75 mg/m² b.i.d. (150 mg/m²/day).

Three patients who met the eligibility criteria were enrolled at the initial dose level 1 and observed for acute toxicity for one cycle of treatment before any more patients were entered. If none of the 3 patients experienced a DLT, then the next cohort of 3 patients was treated at the next higher dose level. If one of the first 3 patients experienced a DLT, 3 additional patients were treated at the same dose level.

The dose escalation continued until at least 2 patients among a cohort of 3 to 6 patients experienced DLTs and the MTD was defined at that dose level. If the MTD was not reached at the dose level of 75 mg/m² b.i.d., additional cohorts were to be enrolled, increasing the dose by 20% per cohort until the MTD was reached.
Manufacturing batch numbers: L0032902, L0032905, L0036983.

Other drug : Doxorubicin (solution for intravenous infusion at 2 mg/ml)
On D3, weekly 3 out of 4 weeks, doxorubicin 25 mg/m^2 was administered intravenously (IV) over ~ 15 minutes via a central venous catheter, 2 hours after the second intake of S 78454.
Manufacturing batch numbers: L0035261; L0036459; L0043067; L0046639.

Comparator (Reference product and/or placebo):
None.

Duration of treatment: From 2 cycles (except in case of safety concerns) to 6 cycles of doxorubicin or until the patients had received a maximum lifetime cumulative dose of 550 mg/m² of doxorubicin.
Run-in period: None.
Treatment period: S 78454 had to be initiated no later than 15 days after inclusion. S 78454 capsules were taken b.i.d. during the first 4 days on the weeks 1, 2 and 3 of the doxorubicin cycle (4 weeks). Doxorubicin infusion was performed on D3 of weeks 1, 2 and 3 of the cycles.
Wash-out / Follow-up period**:** Every 3 months with a maximum duration of 6 months for non-progressive patients.

Criteria for evaluation:

Efficacy measurements:

- Tumour assessment was performed based on the revised RECIST criteria (version 1.1). Baseline tumour assessment was performed within 4 weeks before the first drug administration. Tumour assessments during the treatment were performed during cycle 2 (between D24 and D28), then every 2 cycles, and at the withdrawal visit (this last tumour evaluation was at the investigator's discretion).

Safety measurements:

- Recording of adverse events (AEs).
- Toxicity assessment according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
- Physical examination, ECOG status, body weight, vital signs (temperature, blood pressure, heart rate, respiratory rate), electrocardiogram (ECG), cardiac function assessment (left ventricular ejection fraction, LVEF) by echocardiography/multi-gated acquisition scan (MUGA).

Criteria for evaluation (Cont'd):
Safety measurements (Cont'd)°:

- Laboratory examination:
  - Haematology: White Blood Cells (WBC) and differential count, Red Blood Cells (RBC), Haemoglobin (Hb), haematocrit, platelets.
  - Biochemistry: albumin, bicarbonate, ionogram (Na, K, Cl, Ca, Mg), urea, serum creatinine (creatinine clearance), proteins, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin.
  - Coagulation: prothrombin time, international normalized ratio (INR), activated partial thromboplastin time (aPTT).

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

Pharmacodynamic:

- Acetylation status of the proteins in the PBMCs is provided in a separate report in Appendix 16.4.
- Acetylation, genomic and proteomic approach on tumour biopsies: Biopsies were optional. No biopsies were performed due to medical reasons or because the patients did not choose the option**.**

Statistical methods:

Analysis Sets:

- Screened Set: This set corresponded to all screened patients.
- Included Set (IS): This set corresponded to all included patients.
- Safety Set (SS): This set corresponded to patients having taken at least one dose of study treatment.
- Full Analysis Set (FAS): Based on the intention-to-treat principle, this set corresponded to included patients who had taken at least one dose of study treatment and who had at least one baseline and one post-baseline tumour evaluation.
- DLT Evaluable Set (DLTES): All patients from safety set who were evaluable for DLT according to the DLT assessment at end of cycle 1. Patients were considered evaluable if:
  - They discontinued during first cycle because of a DLT, or
  - They received at least 20 of 24 S 78454 capsules and underwent a DLT assessment before beginning the second cycle.

Study outcome: Descriptive statistics were provided for the status and disposition of the patients and for the main baseline characteristics.

Efficacy analysis:
The Best Overall Response (BOR), defined as best response across all time points from the start of the study treatment until Progressive Disease (PD) or the end of the treatment period, was provided for each dose level and overall on the FAS. The Objective Response Rate (ORR, proportion of patients with a complete response [CR] or a partial response [PR] as best overall response) and the Clinical Benefit Rate (CBR; proportion of patients with CR, PR or stable disease [SD] prolonged for 3 months at least as BOR), the duration of clinical benefit (time elapsed between the first drug intake and PD or death among patients having CR, PR or SD prolonged for 3 months at least), the duration of response (time elapsed between the first CR or PR assessment and PD or death), the time to first response, and the Progression Free Survival (PFS, time elapsed between the first drug intake and PD or death) were provided for the recommended dose and overall**.**
The overall response was evaluated according to the investigators. The survival functions of time-dependent parameters (duration of clinical benefit, duration of response, time to first response and PFS) were estimated via Kaplan-Meier curves.

Safety analysis: Descriptive statistics were provided.
The safety was assessed with a description of DLTs on the DLT Evaluable Set. Adverse events (AEs) (serious and emergent), death, laboratory parameters (biochemistry, haematology and coagulation) using the NCI-CTCAE classification, vital signs (including blood pressure, heart rate, respiratory rate, temperature, body weight and ECOG performance status), echocardiography or MUGA (LVEF) and ECG parameters were described on the Safety Set.

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

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Summary of Patient Disposition

		30 mg/m² b.i.d. (N = 4)	45 mg/m² b.i.d. (N = 3)	60 mg/m² b.i.d. (N = 20)	75 mg/m² b.i.d. (N = 8)	All (N = 35)
Screened	**n**					**39**
Included	n					35
Not included	n					4
TREATMENT PERIOD						
Included	**n**	**4**	**3**	**20**	**8**	**35**
In compliance with protocol	n	1	1	5	1	8
With protocol deviation before or at inclusion	n	3	2	15	7	27
Withdrawn due to	**n**	**1**	**2**	**15**	**6**	**24**
Progressive disease	n	-	1	9	1	11
Adverse events	n	1	1	5	3	10
Non-medical reason	n	-	-	1	1	2
Protocol withdrawal other than AE and non-medical reason	n	-	-	-	1	1
AFTER TREATMENT PERIOD	**n**	**4**	**2**	**20**	**8**	**34**
Follow-up 1 (3 months after last treatment administration)	**n**	**4**	**2**	**20**	**8**	**34**
On going	n	2	2	12	7	23
Withdrawn due to	n	2	-	8	1	11
Death	n	2	-	8	1	11
Follow-up 2 (3-6 months after last treatment administration)	**n**	**2**	**2**	**12**	**7**	**23**
Completed follow-up	n	1	1	7	3	12
Withdrawn due to	n	1	1	5	4	11
Death	n	1	1	5	4	11

N: total number of patients by schedule; n: number of patients.

A total of 35 patients were included in the study. Patients received S 78454 treatment according to the protocol in association with doxorubicin infusion. After reaching the MTD at 75 mg/m^2 b.i.d., subsequent cohorts of patients received S 78454 treatment at the recommended 60 mg/m^2 b.i.d. dose. Finally, 4 patients were treated at 30 mg/m^2 b.i.d., 3 patients at 45 mg/m^2 b.i.d., 20 patients at 60 mg/m^2 b.i.d. and 8 patients at 75 mg/m^2 b.i.d. Twenty-four (24) patients were withdrawn from the study mainly for PD (11 patients). Moreover, 10 patients were withdrawn for AEs, 2 patients for non-medical reason and 1 for a reason other than AE or non-medical reason. One patient died during the treatment period from a septic shock. The 34 other patients were followed-up after the treatment period. A total of 23 patients completed the Follow-Up 1 (FU1) and 11 patients died during FU1. Among the 23 patients who attended the Follow-Up 2 (FU2), 12 completed FU2 and 11 died.

EXTENT OF EXPOSURE

In the FAS (N = 25), the total treatment duration of S 78454 ranged from 4 to 28 weeks, with a mean of 16.0 ± 8.5 weeks (median = 14.0 weeks). The mean number of cycles received was 3.8 ± 2.0 cycles (median = 3.0 cycles). The mean relative dose intensity (RDI) per patient (*i.e.* compliance) was 84.9 ± 13.0% and the mean cumulative dose received by patient was 4628 ± 2809 mg/m².

In the SS (N = 35), the total treatment duration of S 78454 ranged from 4 to 28 weeks, with a mean of 13.2 ± 9.1 weeks (median = 9.0 weeks). The mean number of cycles received was 3.1 ± 2.1 cycles (median = 2.0 cycles). The mean RDI per patient (*i.e.* compliance) was 82.7 ± 17.4% and the mean cumulative dose received by patient was 3818 ± 2945 mg/m².

The dose of 75 mg/m^2 b.i.d. (approximately 140 mg b.i.d.) was considered as the MTD and the recommended dose (RP2D) was 60 mg/m^2 b.i.d. (approximately 120 mg b.i.d.).

SUMMARY - CONCLUSIONS (CONT'D)

EFFICACY RESULTS

Among the 25 patients co-treated with S 78454 and doxorubicin in the FAS, the BOR was PR in 3 patients (2 patients treated at 60 mg/m² b.i.d. [adenoid cystic carcinoma and pleural malignant mesothelioma], 1 patient treated at 75 mg/m² b.i.d. [nasopharyngeal squamous cell carcinoma]) and SD in 5 patients (2 patients treated at 30 mg/m² b.i.d. [pleural malignant mesothelioma and lung neuroendocrine carcinoma], 1 patient treated at each other doses: 45 mg/m² b.i.d.[papillary transitional cell carcinoma of bladder], 60 mg/m² b.i.d. [small cell lung cancer] and 75 mg/m² b.i.d. [pleural malignant mesothelioma]), whereas 15 patients had PD and 2 patients were non-evaluable. All patients with PR or SD completed 6 cycles of treatment.

The measurement of the lesions showed as best relative change from baseline a decrease from -3% to -62% of the sum of the lesions diameters in 11 patients. There was an increase as best relative change from baseline of the sum of the lesions diameters ranging from 1 to 70% in 14 patients.

Overall, the ORR was 3/25 patients (12.0%) and the CBR was 8/25 patients (32.0%). At the recommended dose of 60 mg/m² b.i.d., the ORR was 2/15 patients (13.3%) and the CBR was 3/15 patients (20.0%).

The median duration of clinical benefit was 35.5 weeks overall (8 patients) and 35.6 weeks in the 3 patients treated at the 60 mg/m² b.i.d. recommended dose. The median duration of the response was 18.4 weeks overall and 17.8 weeks in the 2 patients treated at the 60 mg/m² b.i.d. recommended dose. The median PFS was 16.1 weeks overall and 8.4 weeks at the 60 mg/m² b.i.d. recommended dose.

SAFETY RESULTS

- **Emergent adverse events and DLTs**

Summary of safety results

		All (N = 35)
Patients having reported at least one		
EAE	n (%)	35 (100)
Treatment-related EAE	n (%)	33 (94.3)
Patients having reported at least one		
Serious EAE	n (%)	17 (48.6)
Treatment-related emergent SAE	n (%)	8 (22.8)
Patients who discontinue the treatment due to		
EAE	n (%)	10 (28.6)
SAE	n (%)	5 (14.3)
Treatment-related EAE	n (%)	5 (14.3)
Treatment-related emergent SAE	n (%)	2 (5.7)
Patients who died during the treatment period	n (%)	1 (2.8)
Patients who died during the follow-up period	n (%)	22 (62.9)

EAE: emergent adverse event; SAE: serious adverse event.

All 35 patients reported at least one emergent adverse event (EAE) for a total of 524 EAEs. The most frequently affected system organ classes (SOCs) (> 30% of patients) were gastrointestinal disorders (32 patients, 91.4%), blood and lymphatic system disorders (31 patients, 88.6%), and general disorders and administration site conditions (26 patients, 74.3%). The most frequently reported EAEs were thrombocytopenia (25 patients, 71.4%), anaemia (22 patients, 62.9%), and neutropenia (21 patients, 60.0%).

Most of the EAEs resolved or were resolving/improving (79.6%) at the end of the study.

During the study, EAEs were mainly rated Grade 3 (16 patients including 10 patients having anaemia), or Grade 4 (10 patients including 5 patients having thrombocytopenia), or Grade 2 (8 patients). One patient treated at 45 mg/m^2 b.i.d. died during the treatment period from a septic shock considered as not related to the study treatment.

EAEs reported as treatment-related according to investigators' opinion occurred in 33 patients (94.3%). They were mostly thrombocytopenia (49 events in 24 patients, including 5 patients having Grade 4 thrombocytopenia as DLTs, neutropenia (38 events in 20 patients) and anaemia (25 events in 15 patients).

At the end of cycle 1, the following adverse events were considered as DLTs:

- Grade 4 thrombocytopenia or thrombocytopenia associated with a bleeding episode requiring platelets transfusion in 3 patients treated at 60 mg/m^2 b.i.d. and in 2 patients treated at 75 mg/m^2 b.i.d.
- Failure to restart S 78454/doxorubicin administration within 1 week of the first missed dose due to delayed recovery from drug-related toxicity in 1 patient treated at 60 mg/m^2 b.i.d. and in 1 patient treated at 75 mg/m^2 b.i.d.
- Any Grade ≥ 3 non-haematologic toxicity, according to the CTCAE classification, except alopecia, nausea or vomiting in 1 patient (fatigue) treated at 60 mg/m^2 b.i.d.

SAFETY RESULTS (CONT'D)

The dose of 75 mg/m^2 b.i.d. was considered as the MTD and 60 mg/m² b.i.d. as the RP2D.

EAEs led to the study drug discontinuation in 10 patients. Five of these EAEs were considered by the investigators as related to the study treatment: Grade 4 neutropenia, Grade 3 asthenia and Grade 2 vomiting in 3 patients treated at 60 mg/m^2 b.i.d.; Grade 3 thrombocytopenia, and Grade 2 neutropenia in 2 patients treated at 75 mg/m^2 b.i.d.

One patient died during the treatment period from a septic shock and 22 patients died during the follow-up period from progressive disease.

Emergent serious adverse events were reported in 17 patients for 25 events. The most frequently reported emergent SAEs were anaemia (5 patients), thrombocytopenia (3 patients) and pulmonary embolism (2 patients). Eight of these events were considered as treatment-related: 3 cases of anaemia, 3 cases of thrombocytopenia, 1 case of vomiting, and 1 case of parotitis. Emergent SAEs led to the study treatment discontinuation in 5 patients having atrial fibrillation, septic shock, vomiting, pulmonary embolism and thrombocytopenia.

- **Laboratory tests**

Regarding the biochemistry parameters rated according to the CTCAE grading, the overall incidence of emergent severe abnormal values (CTCAE Grade ≥ 3) was low. Five Grade 3 or 4 abnormal values were reported in 4 patients for sodium, potassium, calcium, or transaminases. One of the 5 severe abnormal values reported (Grade 3 decrease in blood potassium) was reported as an AE of hypokalaemia by one investigator. Regarding the biochemistry parameters not gradable according to the CTCAE, the most frequently emergent abnormal values were reported for urea, total protein and chloride. None of these emergent out-of-range values was reported as AEs by the investigators.

Regarding the haematological parameters rated according to the CTCAE grading, emergent severe abnormal values were detected for low amount of the following parameters:

- Lymphocytes, 12 patients graded 3 (1 patient at 30 mg/m^2 b.i.d., 9 patients at 60 mg/m^2 b.i.d. and 2 patients at 75 mg/m^2 b.i.d.) and 5 patients graded 4 (4 patients at 60 mg/m^2 b.i.d. and 1 patient at 75 mg/m^2 b.i.d.).
- WBC, 10 patients graded 3 (1 patient treated at 30 mg/m^2 b.i.d., 8 patients at 60 mg/m^2 b.i.d. and 1 patient at 75 mg/m^2 b.i.d.) and 3 patients graded 4 (2 patients at 60 mg/m^2 b.i.d. and 1 patient at 75 mg/m^2 b.i.d.).
- Platelets, 7 patients graded 3 (6 patient at 60 mg/m^2 b.i.d. and 1 patient at 75 mg/m^2 b.i.d.) and 5 patients graded 4 (3 patients at 60 mg/m^2 b.i.d. and 2 patient at 75 mg/m^2 b.i.d.).
- Haemoglobin, 9 patients graded 3 (1 patient treated at 30 mg/m^2 b.i.d., 1 patient at 45 mg/m^2 b.i.d., 6 patients at 60 mg/m^2 b.i.d. and 1 patient at 75 mg/m^2 b.i.d.) and 1 patient treated at 60 mg/m^2 b.i.d. graded 4.
- Neutrophils, 7 patients graded 3 (6 patients at 60 mg/m^2 b.i.d. and 1 patient at 75 mg/m^2 b.i.d.) and 3 patients graded 4 (1 patient at 60 mg/m^2 b.i.d. and 2 patients at 75 mg/m^2 b.i.d.).

Among these patients, a Grade 4 thrombocytopenia was reported in 5 patients and considered as a DLT. During the treatment period, considering all cycles, the median nadir value for platelets was observed at 64.0 giga/L (G/L) overall and 54.5 G/L for the 20 patients treated at the RP2D (60 mg/m² b.i.d.). The median time to nadir was 15.0 days for the 35 patients included in the study and 16.0 days for the 20 patients treated at 60 mg/m² b.i.d.

- **Other safety evaluation**

According to ECG central reading, 20 patients had at least one emergent ECG abnormality. Four patients had ECG abnormalities considered as clinically significant that occurred in the context of atrial fibrillation or transient ischaemic event. Regarding corrected Fridericia QT interval (QTcF), four patients treated at 60 mg/m² b.i.d. had a QTcF interval > 450 ms including 3 patients having a QTcF interval between 450 and 480 ms and 1 patient having a QTcF interval between 480 ms and 500 ms. Four patients had an absolute change of QTcF interval from baseline > 60 ms and 12 patients an absolute change of QTcF interval from baseline between 30 and 60 ms. No patients presented a maximum QTcF interval value > 500 ms. The mean (±SD) of the worst LVEF post-baseline value during the treatment period was 60.7 (±5.7)%, ranging from 50 to 73%.

CONCLUSION

In this open dose-escalation Phase I study with oral doses of S 78454 (abexinostat) administered in association with doxorubicin, a total of 35 patients were included. Thirty five patients received the study treatment and 25 were evaluable for efficacy. The administration schedule of S 78454 consisted in a b.i.d. administration, 4 days on/ 3 days off during 3 weeks, 1 week off up to 6 cycles with an infusion of doxorubicin on days 3, 10 and 17 of each cycle. The maximum tolerated dose (MTD) was determined at 75 mg/m² b.i.d. and the recommended dose at 60 mg/m² b.i.d. The most common dose limiting toxicity (DLT) was Grade 4 thrombocytopenia. This DLT was recorded in 5 patients: 3 patients at 60 mg/m² b.i.d. and 2 patients at 75 mg/m² b.i.d.

Anticancer clinical activity was reported for 8 patients; 3 patients had partial response and 5 patients had stable disease for ≥ 24 weeks. A partial response was obtained for 2 patients treated at 60 mg/m² b.i.d. (adenoid cystic carcinoma and pleural malignant mesothelioma) and 1 patient treated at 75 mg/m² b.i.d. (nasopharyngeal squamous cell carcinoma). Stable disease was obtained for 2 patients treated at 30 mg/m² b.i.d. (pleural malignant mesothelioma and lung neuroendocrine carcinoma), 1 patient treated at 45 mg/m² b.i.d. (papillary transitional cell carcinoma of bladder), 1 patient treated at 60 mg/m² b.i.d. (small cell lung cancer) and 1 patient treated at 75 mg/m² b.i.d. (pleural malignant mesothelioma).

The safety profile of abexinostat in this trial in combination with doxorubicin was consistent with our knowledge of the drug.

The most frequent emergent adverse events considered treatment-related by the investigators were thrombocytopenia, neutropenia, anaemia, asthenia, vomiting, nausea, decreased appetite, fatigue and leukopenia. No patient had QTcF interval > 500 ms, according to central reading procedure.

Date of the report: 08 December 2014

Version of the report: Final version