# I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

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| *Document title* | **Clinical Study Report** |
| *Study title* | **Phase I dose-escalation study of oral administration of Pan-Histone Deacetylase (HDAC) Inhibitor S 78454 in patients with solid tumour** |
| *Study drug* | **Abexinostat (S 78454)** |
| *Studied indication* | **Solid tumors** |
| *Development phase* | **Phase I** |
| *Protocol code* | **CL1-78454-002** |
| *Study initiation date* | **22 February 2010** |
| *Study completion date* | **07 May 2012** |
| *Main coordinator* | [redacted] **France** |
| *Company / Sponsor* | **Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**50 rue Carnot**<br>**92284 Suresnes cedex - France** |
| *Responsible medical officer* | [redacted] |
| *GCP* | **This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.** |
| *Date of the report* | **Final version of 15 April 2013** |

**~~CONFIDENTIAL~~**

## 2. SYNOPSIS

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**Title of study:**
Phase I dose-escalation study of oral administration of Pan-Histone Deacetylase (HDAC) Inhibitor S 78454 in patients with solid tumour.
Protocol No.: CL1-78454-002 – EudraCT Number: 2009-013692-22

**Investigator:**
[redacted] France.

**Study centre:**
[redacted] France.

**Publication (reference):** Not applicable

| | |
|---|---|
| **Studied period:**<br>Initiation date: 22 February 2010 (date of first visit)<br>Completion date: 07 May 2012 (date of last visit) | **Phase of development of the study:** Phase I |

**Objectives:**
**Primary Objective:** Establish the safety and tolerability of the oral capsule form of S 78454 in patients with solid tumour in terms of the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLTs), and establish the optimal administration schedule and its associated (according to Amendment No. 2) recommended Phase II dose (RP2D).

**Secondary Objectives:**
- Determine the pharmacokinetic (PK) profile of the oral capsule form of S 78454, its main metabolites and its dose exposure relationship.
- Determine the pharmacodynamic (PD) profile of the oral capsule form of S 78454:
  - Monitor pharmacological effects of S 78454 on HDAC inhibition on peripheral blood mononuclear cells (PBMC) by exploring the acetylation state of proteins (tubulin and histones) before and after treatment.
  - Characterize biological activity of S 78454 using blood samples and tumour cells obtained from tumour biopsies before and after treatment by genomic and proteomic analysis (according to Amendment No. 2).
  - Monitor S 78454 effects on circulating tumour cells in peripheral blood as a potential biomarker of efficacy.
- Measure tumour response to the oral capsule of S 78454.

**Methodology:**
Monocentre, non-randomised, non-comparative, open phase I study.

**Number of patients:**
Planned: 50 patients increased to 60 patients (Amendment No. 2).
Included: 39 patients, 18 patients (schedule 1) and 21 patients (schedule 2).

**Diagnosis and main criteria for inclusion:**
Male or female patient aged ≥ 18, with an 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 estimated life expectancy > 12 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and adequate haematological, renal and hepatic functions.

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**Study drug:**
**Schedule 1**
5 cohorts of 3-6 patients received orally the capsule of S 78454 twice daily (*bis in die*, BID) 4 hours apart over 14 consecutive days (D1-D14) during a 3-week cycle (schedule 1) at the following doses, following a traditional algorithm-based design "3+3":

- Dose Level 1: 30 mg/m² BID (60 mg/m²/day).
- Dose Level 2: 45 mg/m² BID (90 mg/m²/day).
- Dose Level 3: 60 mg/m² BID (120 mg/m²/day).
- Dose Level 4: 75 mg/m² BID (150 mg/m²/day).
- Dose Level 5: 90 mg/m² BID (180 mg/m²/day).

Each patient of a considered cohort received the same dose level and was to perform at least 2 cycles of treatment except in case of safety concerns. Three patients who met the eligibility criteria were enrolled at the initial dose level 1 and were observed for acute toxicity for one 3-week cycle of treatment before any more patients were entered. If none of these patients experienced dose limiting toxicity (DLT), then the next cohort was treated at the next higher dose. If any DLT was observed in one of these patients, 3 additional patients were included at this dose level. If DLT was observed in at least 2/3 or 2/6 patients, the dose escalation was stopped and the MTD1 was defined at that dose level. If the MTD was not reached at a dose level of 90 mg/m² BID, additional cohorts were enrolled, increasing the dose by 20% per cohort until the MTD1 was reached.
**Schedule 2** (added by Amendment No. 2)
Then, subsequent cohorts of patients received S 78454 BID 4 hours apart on a revised schedule (schedule 2) on days 1-4 of each week during 3-week cycles. The starting dose of schedule 2 was the recommended dose of schedule 1 (RP2D1), defined as one dose level below MTD1. The dose escalation followed the same design "3+3" as in the original schedule 1 with the same pre-defined dose levels until MTD2 was reached.
Once the RP2D was determined (defined as one dose step below MTD of the optimal schedule, *i.e.* the schedule among the two tested allowing the administration of the highest dose with acceptable toxicity), up to 10 patients (according to Amendment No. 3, instead of the 24 patients initially planned) were included and treated at this dose level to confirm the RP2D and to better evaluate cumulative toxicity if any.

**Reference product:** Not applicable.

**Duration of treatment:**
**Treatment period**: S 78454 had to be initiated not later than 15 days after inclusion. The total number of cycles (at least 2 cycles except in case of safety concerns) and the maximum treatment duration were at the discretion of the investigator (instead of treatment duration limited to 12 months, according to Amendment No. 2).
**Withdrawal visit**: up to 3 weeks after the last capsule intake.
**Follow-up period:** after the last capsule intake in order to trace ongoing adverse events, treatments received since the withdrawal visit and patient's survival at three month intervals, for up to six months.

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**Criteria for evaluation:**

**Activity measurements**:

Tumour assessment, based on revised Response Evaluation Criteria in Solid Tumors (RECIST), was available at baseline within 4 weeks before the first drug administration and was performed every 2 cycles (between D18 and D21) beginning with cycle 2, and at the end of the study (this last tumour evaluation is at the investigator's discretion). After the treatment period, a follow-up was performed every 3 months with a maximum duration of 6 months, with a tumour assessment planned at each follow-up visit.

**Safety measurements**:

- Recording of adverse events and toxicity (grading according to the Common Terminology Criteria for Adverse Event (CTCAE) v3.0) at each visit.
- Records of any change or addition of a new concomitant treatment at each visit.
- Laboratory tests.
- Electrocardiogram (ECG).
- Physical examination, performance status: Eastern Cooperative Oncology Group (ECOG), and vital signs.

**Pharmacokinetic measurements:**

Concentrations of S 78454 were determined in plasma and in urine. Concentrations of its two major metabolites (S 78730 and S 78731) were determined in plasma. The method for measurement of S 78454 and its metabolites, and results will be provided in the separate pharmacokinetic report.

**Pharmacodynamic measurements:**

The pharmacodynamic assessments included the acetylation state of proteins in PBMCs, the biological activity of S 78454 through genomic and proteomic approach, and the presence of circulating tumour cells. Results will be presented in a separate report.

**Statistical methods**:

**Study outcome***:* Descriptive analysis.

**Efficacy analysis**: the overall response rate, the best overall response rate (defined as the best response obtained for each patient during the treatment period), the sum of lesions diameters, the clinical benefit rate, and the clinical progression were analysed. The objective response rate analysis initially planned was not provided as no patient had a complete or a partial response as best overall response. The number and percentage of patients per overall response was reported for each visit. The overall distribution per best overall response was also provided. The sum of lesions diameters was provided at each visit and the relative change from baseline to each post-baseline value was provided. The clinical benefit rate was evaluated according to the investigator assessments. The corresponding exact binomial 95% confidence interval was provided. The survival functions for the duration of stable disease and time to progression were estimated via Kaplan-Meier curves. In addition, 95% confidence intervals for median duration were computed and the number and type of events/censored were provided.

**Safety analysis**: Descriptive statistics were provided for toxicity (according to the CTCAE v3.0 grading), adverse events, ECG parameters, physical examination, performance status (ECOG), vital signs and laboratory tests.

**Pharmacokinetic analysis**:

Descriptive statistics were provided for S 78454 and its main metabolites concentration and for pharmacokinetic parameters.

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**SUMMARY - CONCLUSIONS**

STUDY POPULATION AND OUTCOME

**Disposition of patients**

| | | | S 78454 | | | | |
|---|---|---|---|---|---|---|---|
| **SCHEDULE 1** | | **Not treated (N = 2)** | **30 mg/m² (N = 3)** | **45 mg/m² (N = 3)** | **60 mg/m² (N = 3)** | **75 mg/m² (N = 7)** | **All (N = 18)** |
| **Screened** | **n** | | | | | | **20** |
| Included | **n** | | | | | | 18 |
| Not included | **n** | | | | | | 2 |
| **TREATMENT PERIOD** | | | | | | | |
| **Included** | **n** | **2** | **3** | **3** | **3** | **7** | **18** |
| In compliance with the protocol | n | 1 | 2 | 2 | - | 2 | 7 |
| With protocol deviation before or at inclusion | n | 1 | 1 | 1 | 3 | 5 | 11 |
| **Lost to follow-up** | **n** | **-** | **-** | **-** | **-** | **-** | **-** |
| **Withdrawn due to** | **n** | **2** | **3** | **3** | **3** | **7** | **18** |
| Progressive disease | n | 1 | 3 | 3 | 2 | 5 | 14 |
| Adverse event | n | 1 | - | - | 1 | 1 | 3 |
| Non-medical reason | n | - | - | - | - | 1 | 1 |
| **AFTER TREATMENT PERIOD** | | **-** | **3** | **3** | **3** | **6** | **15** |
| **Follow-up 1** **Performed the visit** | **n** | **-** | **3** | **1** | **3** | **3** | **10** |
| **Did not perform the visit due to** | **n** | **-** | **-** | **2** | **-** | **3** | **5** |
| Death | n | - | - | 2 | - | 2 | 4 |
| Lost to follow-up | n | - | - | - | - | 1 | 1 |
| Non-medical reason | n | - | - | - | - | - | - |
| **Follow-up 2** **Performed the visit** | **n** | **-** | **1** | **-** | **1** | **1** | **3** |
| **Did not perform the visit due to** | **n** | **-** | **2** | **1** | **2** | **2** | **7** |
| Death | n | - | 2 | 1 | 1 | - | 4 |
| Lost to follow-up | n | - | - | - | - | 2 | 2 |
| Non-medical reason | n | - | - | - | 1 | - | 1 |

| **SCHEDULE 2** | | **Not treated (N = 1)** | **60 mg/m² (N = 3)** | **75 mg/m² (N = 4)** | **90 mg/m² (N = 10 *)** | **105 mg/m² (N = 3)** | **All (N = 21)** |
|---|---|---|---|---|---|---|---|
| **Screened** | **n** | | | | | | **23** |
| Included | n | | | | | | 21 |
| Not included | n | | | | | | 2 |
| **TREATMENT PERIOD** | | | | | | | |
| **Included** | **n** | **1** | **3** | **4** | **10** | **3** | **21** |
| In compliance with the protocol | n | - | 1 | 3 | 6 | 2 | 12 |
| With protocol deviation before or at inclusion | n | 1 | 2 | 1 | 4 | 1 | 9 |
| **Lost to follow-up** | **n** | **-** | **-** | **-** | **-** | **-** | **-** |
| **Withdrawn due to** | **n** | **1** | **3** | **4** | **10** | **3** | **21** |
| Progressive disease | n | - | 2 | 4 | 5 | 2 | 13 |
| Adverse event | n | 1 | - | - | 3 | 1 | 5 |
| Non-medical reason | n | - | 1 | - | 2 | - | 3 |
| **AFTER TREATMENT PERIOD** | n | - | 3 | 4 | 10 | 3 | 20 |
| **Follow-up 1** **Performed the visit** | **n** | **-** | **1** | **1** | **8** | **1** | **11** |
| **Did not perform the visit due to** | **n** | **-** | **2** | **3** | **2** | **2** | **9** |
| Non-medical reason | n | - | 1 | 2 | 1 | - | 4 |
| Death | n | - | - | 1 | 1 | 1 | 3 |
| Lost to follow-up | n | - | 1 | - | - | 1 | 2 |
| **Follow-up 2** **Performed the visit** | **n** | **-** | **1** | **-** | **6** | **-** | **7** |
| **Did not perform the visit due to** | **n** | **-** | **-** | **1** | **2** | **1** | **4** |
| Death | n | - | - | - | 1 | 1 | 2 |
| Lost to follow-up | n | - | - | 1 | - | - | 1 |
| Non-medical reason | n | - | - | - | 1 | - | 1 |

*N total number of patients by schedule; n number of patients; Schedule 1 S 78454 BID received from D1 to D14 during a 3-week cycle; Schedule 2 S 78454 BID received from D1 to D4 of each week during a 3-week cycle; * including 3 patients added at this RP2D dose according to Amendment No. 3.*

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**SUMMARY - CONCLUSIONS (Cont'd)**

STUDY POPULATION AND OUTCOME (Cont'd)

A total of 43 patients were screened and 39 patients were included in the study. Patients were to receive S 78454 treatment according to schedule 1 (S 78454 BID from D1 to D14 during 3-week cycles). After reaching MTD1, subsequent cohorts of patients were to receive S 78454 treatment according to schedule 2 (S 78454 BID from D1 to D4 of each week during 3-week cycles), starting from the recommended dose obtained for schedule 1 (one dose level below MTD1). Finally, 36 patients were treated with the study drug, and among them, 28 patients had at least one baseline and one post-baseline tumour evaluation.

All included patients were withdrawn from the study, mainly for progressive disease (27 patients: 14 patients in schedule 1 and 13 patients in schedule 2). Protocol deviations at inclusion (23 in 20 patients, 51.3%) were mainly due to patients having not reported using an efficient method of contraception (5 in 5 patients, 12.8%), and those detected after inclusion (79 in 27 patients, 69.2%) were mainly due to ECG not carried out or non-analysable (27 in 18 patients, 46.2%). No patient was lost to follow-up and no patient died during the treatment period.

After treatment period, 21 out 35 patients performed the first follow-up (FU) visit, and among these 21 patients, 10 performed the second FU visit. The patients did not perform FU visits for non-medical reason (6 patients), or because they were lost to follow-up (6 patients), or deceased (13 patients).

**Demographic and baseline characteristics**

In the Included Set (N = 39), patients were on average 54.1 ± 10.1 years, ranging from 37 years to 76 years, and males were more represented than females: 77.8% in schedule 1 and 57.1% in schedule 2. All patients had an effective method of contraception or were menopausal, and/or hysterectomised, or sterile, except 5 males considered as having a protocol deviation. At inclusion in the study, all patients had a solid tumour since on average 5.6 ± 4.5 years (median = 3.9 years, 3.8 years in schedule 1 and 4.0 years in schedule 2), and received their last therapy (chemotherapy, hormonotherapy or immunotherapy) for their tumour disease about 110 days before inclusion (median = 49 days, 45.5 days in schedule 1 and 54.5 days in schedule 2). At inclusion, all patients but one in relapse in schedule 2, were refractory to previous conventional treatment.

At baseline, 33 patients had measurable target lesions and 27 patients had presence of non-target lesions. ECOG performance status was ≤ 1 for all patients (grade 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature). Regarding ECG, the mean QTcF was 392.2 ± 19.8 ms (ranging from 353 to 429 ms), and none of the ECG abnormalities detected was considered as clinically significant.

In the Safety Set (N = 36), the mean total treatment duration was 61.8 ± 33.7 days (median = 47.5), ranging from 21 to 154 days, and the number of cycles received was on average 2.9 ± 1.6 cycles (median = 2.0) with a maximum of 6 cycles in schedule 1 and 7 cycles in schedule 2 (one patient in each schedule). The mean relative dose intensity per patient (*i.e.* compliance) was 78.3 ± 18.1% (ranging from 30.5 to 105.3%) with a higher percentage in schedule 1 (81.5 ± 19.6%) than in schedule 2 (75.8 ± 16.9%).

For schedule 1, the dose of 75 mg/m² BID was considered as the MTD1 and the recommended dose (RP2D1) was 60 mg/m² BID (*i.e.* one step below the MTD1). For schedule 2, the dose of 105 mg/m² BID was considered as the MTD2, and the RP2D2 was 90 mg/m² BID.

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EFFICACY RESULTS

In the Full Analysis Set (N = 28), the best overall response was stable disease observed for 4 cycles in 2 patients (1 patient at dose of 75 mg/m² BID in each schedule, one patient having colon cancer and one a colorectal cancer), and 21 patients had progressive disease (11 patients in schedule 1 and 10 patients in schedule 2), whereas 5 patients were non-evaluable. No clinical benefit was observed in patients treated at the recommended dose in each schedule. Clinical progression was observed in 7/8 patients, with a time for clinical progression of 11.8 weeks (median) at RP2D1 and 10.8 weeks (median) at RP2D2.

SAFETY RESULTS

**Summary of safety results**

| | | **Schedule 1 (N = 16)** | **Schedule 2 (N = 20)** |
|---|---|---|---|
| Patients having reported at least one | | | |
| EAE | n (%) | 16 (100) | 20 (100) |
| treatment-related EAE | n (%) | 15 (93.8) | 19 (95.0) |
| Patients having experienced at least one | | | |
| SEAE | n (%) | 4 (25.0) | 10 (50.0) |
| treatment-related SEAE | n (%) | 2 (12.5) | 7 (35.0) |
| Patients having experienced a treatment discontinuation due to | | | |
| EAE | n (%) | 2 (12.5) | 6 (30.0) |
| SEAE | n (%) | 1 (6.3) | 4 (20.0) |
| Treatment-related EAE | n (%) | 1 (6.3) | 5 (25.0) |
| Treatment-related SEAE | n (%) | 1 (6.3) | 3 (15.0) |
| Patients who died during the follow-up period | n (%) | 8 (50.0) | 5 (25.0) |

*N total number of exposed patients in the considered treatment group; n number of patients affected; % (n/N) x 100.*
*EAE emergent adverse event; SEAE serious emergent adverse event.*

All patients reported at least one **emergent adverse event** (EAE): 16 patients reported 186 emergent adverse events in schedule 1 and 20 patients reported 280 emergent adverse events in schedule 2. The most frequently affected SOCs were Gastrointestinal disorders (16 patients in schedule 1 and 19 patients in schedule 2), and General disorders and administration site conditions (15 patients and 18 patients, respectively). Moreover, Blood and lymphatic system disorders were frequently reported in both schedules (14 patients and 15 patients, respectively). The most frequently reported EAEs were for both schedules: asthenia (15 patients in each schedule), thrombocytopenia (14 patients and 15 patients, respectively), and nausea (11 patients and 15 patients, respectively).

Most of the EAEs **recovered or were recovering/improving** (81.2% of the total EAEs in schedule 1 and 77.5% in schedule 2).

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SAFETY RESULTS (Cont'd)

During the study, EAEs were mainly rated **grade 1** (all patients reported at least one in each schedule) or 2 (15 patients in schedule 1 and 19 patients in schedule 2). EAEs were rated grade 3 in 8 patients in schedule 1 and 10 patients in schedule 2. EAEs grade 4 affected 6 patients in each schedule, including thrombocytopenia for 5 patients in schedule 1 and 4 patients in schedule 2. One patient in schedule 2 had a neoplasm progression grade 5 (*i.e.* leading to death).

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

- In schedule 1:
  - Thrombocytopenia grade 4, in 4 patients receiving the 75 mg/m² BID dose. This dose was considered the MTD1.
- In schedule 2:
  - Drug-induced liver injury grade 4, in one patient at 90 mg/m² BID dose, that did not recover. Of note this patient with a breast cancer, had liver and bone metastasis, and was included with baseline values rated grade 2 for ASAT, ALAT and GGT. This patient reported liver cytolysis in her medical history, still ongoing at the time of inclusion in the study.
  - Thrombocytopenia grade 4, in 2 patients at 105 mg/m² BID dose. This dose was considered the MTD2.

These thrombocytopenia showed a rapid recovery while the treatment was stopped.

EAEs led to **premature S 78454 discontinuation** in 8 patients: 2 patients in schedule 1 and 6 patients in schedule 2, including the patient in schedule 2 having a grade 4 drug-induced liver injury as DLT, serious, and considered related to S 78454 and 4 patients having thrombocytopenia rated grade ≥ 3 (one serious EAE of grade 4 considered as a DLT in schedule 1, and 3 EAEs including one serious in schedule 2). All these thrombocytopenia were considered as treatment-related according to the investigator's opinion.

EAEs considered as **treatment-related** according to investigator's opinion occurred in 15 patients (93.8%) in schedule 1 and 19 patients (95.0%) in schedule 2. They were mostly thrombocytopenia in both schedules: 31 events in 13 patients in schedule 1, and 26 events in 15 patients in schedule 2 (including 4 patients in schedule 1 and 2 patients in schedule 2 having thrombocytopenia of grade 4 as DLT), asthenia (13 EAEs in 13 patients and 14 EAEs in 14 patients respectively), and nausea (10 EAEs in 10 patients and 21 EAEs in 15 patients, respectively).

**Emergent serious adverse events** (SEAEs) were reported in 14 patients (9 SEAEs in 4 patients in schedule 1 and 20 SEAEs in 10 patients in schedule 2). The most frequently reported SEAEs were: thrombocytopenia (2 patients in schedule 1 and 3 patients in schedule 2), anaemia (2 patients in schedule 2), neoplasm progression (2 patients in schedule 2), and vomiting (1 patient in schedule 1 and 2 patients in schedule 2). Most of these SEAEs were considered as treatment-related by the investigator: 6 EAEs in 2 patients in schedule 1, mainly thrombocytopenia (3 EAEs in 2 patients), and 12 events in 7 patients in schedule 2, mainly thrombocytopenia (4 EAEs in 3 patients) and vomiting (2 EAEs in 2 patients). SEAEs led to S 78454 discontinuation in one patient in schedule 1 due to 3 SEAEs (thrombocytopenia, rectal haemorrhage and skin haemorrhage), and 4 patients in schedule 2 one having thrombocytopenia, one having vomiting, one having drug-induced liver injury, and one patient having both neoplasm progression and pleural effusion.

None of the patients died during the treatment period while **13 patients died** during the follow-up period due to disease progression: 8 patients in schedule 1 and 5 patients in schedule 2.

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**Laboratory results**

Regarding **biochemistry**, no clinically relevant change over time at each cycle was detected for all parameters recorded. Emergent severe abnormal values according to CTCAE grading *i.e.* emergent abnormal values rated ≥ 3 (from baseline to worst post-baseline value) were detected for the following parameters: albumin low values (1 patient in each schedule), sodium low values (2 patients and 4 patients, respectively), glucose high values (1 patient in schedule 2), GGT high values (1 patient and 4 patients, respectively), ASAT high values (2 patients in schedule 2), ALAT high values (1 patient in schedule 2 having also high severe emergent values for ASAT and GGT), and bilirubin high values (1 patient in schedule 2). In schedule 1, none of these severe abnormal values were reported as an adverse event or a DLT, or considered as clinically relevant by the investigator. In schedule 2, severe emergent abnormal values were reported as adverse event for 5 patients: hyponatremia (2 patients), hyperbilirubinaemia (1 patient), bile duct obstruction (1 patient), and drug-induced liver injury grade 4 that was a DLT at the end of cycle 1 in one patient (having ASAT, ALAT, and GGT increased).

Regarding **haematology**, emergent severe abnormal values according to CTCAE grading (from baseline to worst post-baseline value) were detected for the following parameters: haemoglobin (2 patients in schedule 1 and 3 patients in schedule 2, including 1 patient having grade 4), neutrophils (2 patients in schedule 1), lymphocytes (2 patients in schedule 1 and 4 patients in schedule 2, including 2 patients having grade 4), and platelets (8 patients, including 5 patients having grade 4 in schedule 1 and 9 patients, including 4 patients having grade 4 in schedule 2). Among these patients, 6 (4 in schedule 1 and 2 in schedule 2) had severe abnormal values of platelets occurring at the end of cycle 1, for which a grade 4 thrombocytopenia was reported and considered as a DLT. During the treatment period, considering all cycles, the lowest mean nadir value for platelets was observed at the highest doses for both schedules: 24.7 ± 20.7 G/L (median = 18.0) at 75 mg/m² BID dose in schedule 1, and 24.0 ± 23.6 G/L (median = 21.0) at 105 mg/m² BID dose in schedule 2.

**Vital signs**, **ECOG performance, and ECG**

Patients had a weight decrease of -3.3 ± 3.7 kg on average in schedule 1 and of -2.2 ± 3.4 kg in schedule 2 (from baseline to End), in the Safety Set. Regarding ECOG performance status at post-baseline, all patients were rated grade ≤ 1 in schedule 1 (grade 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), while the worst grade encountered was 3 (capable of only limited self-care) for 2 patients in schedule 2.

According to ECG central reading, 22 patients (11 patients in each schedule) had at least one emergent ECG abnormality. Among them, none had ECG abnormalities considered as clinically significant in schedule 1, while one patient in schedule 2 (60 mg/m² BID dose) had a non-pathological U wave and a non-specific T wave abnormalities considered as clinically significant (using Minnesota classification). Regarding QT corrected Fridericia (QTcF), no patient had a maximum absolute prolongation in QTcF value > 500 ms in both schedules. No patient in schedule 1 had a QTcF change from baseline > 60 ms, while 2 patients in schedule 2 had a QTcF change from baseline > 60 ms associated for one patient each with: a QTcF between ]450-470] ms (*i.e.* grade 1), or ]470-500] ms (*i.e.* grade 2). For these patients, QTcF values returned into normal range (< 450 ms) at the last post-baseline visit under treatment, and none of them had ECG abnormalities considered as clinically significant by the investigator.

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|---|---|---|
| **Name of Company:**<br>**I.R.I.S.**<br>**50 rue Carnot**<br>**92284 Suresnes Cedex - France** | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>Not applicable | **Volume:** | |
| **Name of Active Ingredient:**<br>Abexinostat (S 78454) | **Page:** | |

**CONCLUSION**

**In the open dose-escalation phase I study with oral doses of S 78454, a total of 39 patients were included, 36 received the study treatment, and 23 were evaluable for the response. After reaching the maximum tolerated dose (MTD1) of 75 mg/m$^2$ BID in schedule 1 (14 day on/7 days off during 3-week cycles), subsequent cohorts of patients received the treatment on the revised schedule 2 (4 days on/3 days off during 3-week cycles) until reaching MTD2 of 105 mg/m$^2$ BID.**

**The schedule 2, with its associated recommended dose of 90 mg/m$^2$ BID, was considered the optimal schedule administration because it allowed an increase by two more dose levels beyond the MTD obtained in schedule 1 with a smaller platelet decrease.**

**As expected, based on pre-clinical findings and due to mechanism of action, the dose limiting toxicity (DLT) consistently observed across both schedules, was thrombocytopenia with rapid recovery while the treatment stopped.**

**Concerning early signs of clinical activity, 2 patients had stable disease for 4 cycles of treatment (one patient having colon cancer and one a colorectal cancer, both patients at 75 mg/m² BID dose, one in each schedule).**

**The safety profile was acceptable with most of emergent adverse events rated grade 1 or 2. The most frequent emergent adverse events considered treatment-related by the investigator were thrombocytopenia, asthenia, nausea, decreased appetite, vomiting, diarrhoea, neutropenia, anaemia, stomatitis, muscle spasms, and dysgeusia. No patient had QTcF > 500 ms, according to central reading procedure. No cumulative toxicity was detected.**

**Date of the report: 15 April 2013**