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

Title of study:
Phase I dose escalation study of oral administration of Pan-Histone Deacetylase (HDAC) inhibitor S 78454 given in combination with a fixed dose infusion of cisplatin in patients with advanced non-keratinising nasopharyngeal carcinoma.
Protocol No.: CL1-78454-009.
The description of the study protocol given hereafter includes the modifications of the substantial amendments to the protocol.

International coordinator:
[redacted]

Study centres:
Three centres in 2 countries included at least one patient: 6 included patients in Singapore and 2 included patients in Taiwan.

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 23 July 2012 (date of first visit first patient) Completion date: 18 October 2013 (early termination)	Phase I

Objectives:
Primary objective:
Establish the safety and tolerability of S 78454 given in combination with a fixed dose infusion of cisplatin in patients with advanced non-keratinising nasopharyngeal carcinoma in terms of the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLTs), and establish the recommended Phase II dose (RP2D).

Secondary objectives:

- Determine the overall safety profile of S 78454 given in combination with a fixed dose infusion of cisplatin.
- Determine the pharmacokinetic (PK) profile of S 78454, its main metabolites and its dose exposure relationship alone and in combination with cisplatin (see PK separate report-pooled studies).
- Measure tumour response to the oral capsule of S 78454 given in combination with a fixed dose infusion of cisplatin using revised RECIST (version 1.1) and plasma EBV DNA levels.
- Measure (optional) exploratory proteomic biomarkers potentially predictive of response to S 78454 using tumour biopsies before treatment (added by Amendment No. 1). This assessment was not done.

Methodology:
Multicentre, non-randomised, non-comparative, open-label phase I study
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: up to 30 patients in the escalation part and up to 10 patients in the confirmatory part of the study at the recommended dose level
Included: 8 patients in the escalation part of the study with early termination due to recruitment difficulties

Diagnosis and main criteria for inclusion:
Male or female patient aged ≥ 21 years in Singapore and ≥ 20 years in Taiwan, with a histologically documented, measurable or evaluable advanced non-keratinising nasopharyngeal carcinoma, 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 – 20 and 100 mg strength (expressed in base) capsules – oral route
The dose escalation followed a traditional algorithm-based design "3+3".
Cohorts of 3-6 patients were to receive a combination therapy of S 78454 oral capsules with a fixed dose of cisplatin (75 mg/m2). Planned doses were 80 mg b.i.d., 100 mg b.i.d., 120 mg b.i.d., and 140 mg b.i.d. If more than one DLT was reported at the dose level 1 (80 mg b.i.d.), a dose de-escalation was performed at dose level -1 (40 mg b.i.d.).
Due to the premature discontinuation of the study and the occurrence of two DLTs at the dose level 1, only dose level 1, *i.e*. 80 mg b.i.d., and dose-level -1, *i.e.* 40 mg b.i.d. were administered.
Patients were to receive the capsule(s) of S 78454 orally twice per day (b.i.d.) 4 hours apart on days 1-4 for 2 weeks (D1-D4, D8-D11) during 3-week cycles.

Batch Nos:

- S 78454 20 mg: L0039582
- S 78454 100 mg: L0039583

Drug in combination
Cisplatin
On D3 of each 3-week cycle, around 10h a.m., 2 hours after first S 78454 capsule(s) intake and before the second capsule(s) intake, cisplatin 75 mg/m² was to be given as a 2 h intravenous infusion.

Batch Nos:

- Cisplatin 50 mg/50 mL: L0041721, L0046064.
- Cisplatin 100 mg/100 mL: L0041719, L0046067.

Duration of treatment:
Treatment period: Treatment with S 78454 was to be initiated not later than 14 days after inclusion. Each patient was to receive at least two cycles of treatment except in case of safety concern. The maximum number of cycles for the combination treatment with cisplatin was limited to 6 cycles. Following this or in case of a premature withdrawal of cisplatin due to related toxicity, patients with response or stable disease could continue on S 78454 monotherapy at the same schedule and dose as used with combination therapy. The treatment might continue until disease progression, unacceptable toxicity, or consent withdrawal.

Withdrawal visit: up to 3 weeks after the last S 78454 capsule(s) intake.

Follow-up period: After the end of the study, a follow-up was to be performed every 3 months during a period for up to 6 months to obtain information concerning patient survival data (date of progression or the patient's survival) and to trace the ongoing adverse-events.

Criteria for evaluation:
Efficacy measurements:
Patients were evaluated for response, based on revised Response Evaluation Criteria in Solid Tumours (RECIST), at baseline within 4 weeks before the first drug administration and during day D18 to D21 of every 2 cycles beginning with cycle 2, and at the end of the study (this last tumour evaluation was at the investigator's discretion).
A response to the combination treatment was also evaluated by a plasma Epstein-Barr virus (EBV) DNA levels.

Safety measurements:

- Adverse events.
- Physical and neurological examination.
- Central QTcF interval measurement.
- Audiometric test.
- Laboratory examination.

Tolerance assessment was done according to the Common terminology criteria for adverse events (CTCAE) version v4.0.

Pharmacokinetic measurements:
Measurement of S 78454 and its metabolites were described in a separate protocol and results will be provided in a separate report.

Other measurements:
Optional exploratory proteomic biomarkers including HR23B using tumour biopsies collected before first treatment of S78454 (separate report)

Statistical methods:
Efficacy analysis (secondary objective): descriptive analysis of the best overall response.
Study outcome and safety analysis: Descriptive statistics.
Pharmacokinetic analysis: PK analyses will be described in a separate report (pooled studies).
Proteomic biomarkers analysis will be described in a separate report

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

	80 mg b.i.d.	**40 mg b.i.d.**	**All**
Included	4	4	8
Withdrawn due to	4	4	8
- lost to follow-up	-	-	-
- adverse event	3	1	4
- progressive disease	-	1	1
- non-medical reason	1	2	3
- protocol deviation	-	-	-
Completed	-	-	-
Full Analysis Set (FAS)	2	2	4
Safety set	4	4	8

Overall, patients were 57.9 ± 6.4 years old and were mainly men (62.5%).

A total of 8 patients were included in the study according to a traditional algorithm-based design "3 + 3". Four patients received S 78454 at Dose level 1, *i.e.* 80 mg b.i.d., of whom two patients presented with DLT. Four patients were included at this dose level instead of 3 as one patient withdrew consent after one week of treatment and was replaced.
Four other patients received S 78454 at Dose level -1, *i.e.* 40 mg b.i.d. of whom one patient experienced one DLT. After 3 included patients with 1 DLT, an extension to 6 patients was planned but stopped before the end due to recruitment difficulties.
As the study was stopped, the MTD could not be determined.

SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Two patients received 80 mg b.i.d. during one cycle, one patient during 3 cycles and one patient, after one cycle at 80 mg b.i.d. dose, experienced DLT and then received 40 mg b.i.d. dose during the next two cycles.

In patients who started the S 78454 treatment at 40 mg b.i.d. dose, two patients were treated for one cycle, one patient for two cycles, and one patient for four cycles.

Cisplatin was administered at 75 mg/m² dose except in one patient from the S 78454 40 mg b.i.d. group in whom the dose was reduced to 60 mg/m² as requested in the protocol when creatinine clearance was under 60 mL/min.

All patients were withdrawn from the study, due to adverse events in four patients, non-medical reason in three patients, and progressive disease in one patient.

EFFICACY RESULTS

The response to treatment was available in 4 patients.
The best overall response was a partial response in 2 patients and a stable disease in 2 patients.

SAFETY RESULTS

- **Emergent adverse events**

Overall summary of adverse events

		ALL (N = 8)
Participants having reported		
at least one emergent adverse event	n (%)	8 (100)
Of which		
- at least one S 78454 treatment-related emergent adverse event	n (%)	2 (25.0)
- at least one S 78454 or cisplatin treatment-related emergent adverse event	n (%)	7 (87.5)
- at least one cisplatin treatment-related emergent adverse event	n (%)	4 (50.0)
Participants having experienced		
at least one serious adverse event (including death)	n (%)	3 (37.5)
at least one serious emergent event (including death)	n (%)	3 (37.5)
at least one treatment-related* serious adverse event	n (%)	3 (37.5)
Participants with treatment withdrawal		
due to an adverse event	n (%)	4 (50.0)
due to a serious adverse event	n (%)	2 (25.0)
due a treatment-related adverse event	n (%)	4 (50.0)
due a treatment-related* serious adverse event	n (%)	2 (25.0)
Participants who died	n (%)	-

**relationship to S 78454 and cisplatin according to the investigator*

During the study, all patients experienced at least one EAE. The most frequently affected system organs were: General disorders and administration site conditions (8 patients), Gastrointestinal disorders (7 patients), Blood and lymphatic system disorders (5 patients), and Metabolism and nutrition disorders (4 patients).
The most frequently reported (≥ 3 patients) EAEs were fatigue (8 patients), thrombocytopenia (5 patients), nausea (4 patients), constipation (3 patients), diarrhoea (3 patients), anaemia (3 patients), and decreased appetite (3 patients).

Overall, 16/60 EAEs were severe (CTCAE grade ≥ 3) of which the most frequent were thrombocytopenia in three patients (5 cases), anaemia in two patients, neutropenia in two patients, and fatigue in two patients.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

At Cycle 1, fatigue (grade 3) was considered as a DLT in two patients at dose level 1 (80 mg b.i.d.) and renal impairment (grade 3) was a DLT in one patient at dose level -1 (40 mg b.i.d.). As the study was stopped prematurely, the MTD could not be determined.

Overall EAES were considered as related to S 78454 or cisplatin in 43/60 EAEs in 7/8 patients. Among these events, three cases of thrombocytopenia and one case of fatigue were considered by the investigator as related to S78454 only.

Five EAEs led to treatment withdrawal in four patients (2 SEAEs: anaemia and renal impairment, and 3 non-serious EAEs: 2 cases of fatigue and one case of nausea).

No patient died during the study. A total of 3 patients experienced 7 SEAEs (thrombocytopenia – 2 cases; anaemia, constipation, pyrexia, chronic osteomyelitis, renal impairment, 1 case each), 5 being considered by the investigator as related to S 78454 and to cisplatin. They led to study treatment withdrawal in 2 cases (see above). All SEAEs recovered (chronic osteomyelitis, 2 cases of thrombocytopenia, constipation, pyrexia, renal impairment) or were recovering (anaemia).

In all, 5 patients experienced 8 thrombocytopeniae. Five cases were severe (CTCAE grade $\geq$ 3), of which 2 cases were serious. All thrombocytopeniae recovered, four on treatment and four after stopping the treatment. None of them led to treatment withdrawal. Overall, the median values of nadir were lower in the 80 mg b.i.d. group (53.0 G/L) than in the 40 mg b.i.d. group (105.5 G/L), nevertheless no firm conclusion could be drawn on a dose effect due to the small sample sizes.

At baseline, all patients had a QTcF interval duration $\leq$ 450 ms. During the study, one patient had an interval duration between 450 and 480 ms with a change from baseline $\leq$ 30 ms. A change from baseline between 30 and 60 ms was observed in 3 other patients but with a QTcF interval duration $\leq$ 450 ms.

CONCLUSION

In this Phase I study, two patients experienced a DLT at S 78454 80 mg b.i.d. dose, given in combination with cisplatin, and one patient presented with a DLT at 40 mg b.i.d. dose. Due to the premature discontinuation of the study (because of difficulty in patient's recruitment), no MTD could be determined. The safety profile of S 78454 given in combination with cisplatin was in accordance with the expected safety profile of these products.

Date of the report: 07 October 2014

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