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:** S49076 Associated agent: gefitinib		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Phase I/II study of oral administration of S49076 given in combination with gefitinib in patients with EGFR mutated advanced non-small-cell lung cancer who have progressed after treatment with EGFR tyrosine kinase inhibitor.

Protocol No CL1-49076-003

EudraCT No.: 2015-002646-31

The description of the study protocol given hereafter includes the modifications of the 5 substantial amendments to the protocol.

International coordinator or **National coordinator** or **Investigator**

[redacted]

Study centres:

Phase I: dose escalation part:

17 centres in 6 countries pre-screened a total of 92 patients of which 22 EGFR/T790M-negative were screened for MET/AXL dysregulations, and 14 were included: Italy (3 centres, 10 patients pre-screened, 3 included), Japan (4 centres, 10 patients pre-screened, 0 included), Korea (3 centres, 24 patients pre-screened, 2 included), Singapore (2 centres, 19 patients pre-screened, 3 included), Spain (3 centres, 16 patients pre-screened, 3 included), and Taiwan (2 centres, 13 patients pre-screened, 3 included).

Phase II part: not performed.

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 26-January-2016 (date of First Visit First Patient) Completion date: 07 November 2018 (date of last follow-up)	Phase I/II

Objectives:

The aim of this study was to evaluate the safety and activity of S49076 in combination with gefitinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring activating Epidermal Growth Factor Receptor (EGFR) mutations, who had received clinical benefit and then progressed on an EGFR tyrosine kinase inhibitor (TKI) (erlotinib, gefitinib, icotinib, afatinib or dacomitinib).

This phase I/II international, multicenter, single-arm, open-label, non-randomised and non-comparative study was divided in two parts:

- **Phase I part**: dose-escalation study of S49076 in combination with gefitinib. The purpose of the dose escalation part was to determine the Recommended Phase II Dose (RP2D) of S49076 in combination with standard dose of gefitinib, based on the assessment of the Dose-Limiting Toxicities (DLTs).
- **Phase II part**: activity study of S49076 in combination with gefitinib. The purpose of the phase II part was to evaluate the anti-tumour activity in several biomarker populations, of S49076 given at the RP2D defined in the dose escalation part with standard dose of gefitinib.

Phase I: dose escalation part

Primary objectives

- Determine the safety and tolerability profile of S49076 given in combination with a fixed dose of gefitinib by assessment of DLTs (assessed during cycle 1) and the adverse events (assessed at each study visit).
- Establish the RP2D of S49076 given in combination with a fixed dose of gefitinib.

Secondary objectives

- Evaluate the pharmacokinetic profile of S49076 and gefitinib combination.
- Evaluate the response to S49076 and gefitinib in 3 subgroups of patients with MET and/or AXL deregulation using archived tumour or newly performed biopsy.
- Measure tumour response to S49076 in combination with gefitinib by using Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1).

Phase II: activity part
Due to feasibility challenges, the phase II part of the study was not carried out (Sponsor decision, letter dated 3 July 2018).

Methodology:
The study was divided into two successive parts: a dose-escalation part (phase I) and an activity part (phase II).

Patients were selected according molecular profile, presence of the activating EGFR T790M-negative mutation with at least one of the following molecular status: MET amplification or MET overexpression, or AXL overexpression.
A modified version of the Continual Reassessment Method (mCRM) was used for the dose allocation process in phase I.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: a maximum of 21 patients in the Phase I.
Included: 14 patients (4 patients in the 500 mg group, 10 patients in the 600 mg group).

Diagnosis and main criteria for inclusion:
Principal inclusion criteria:

- Male or female patient aged ≥ 18 years old, or legal age of the majority in the country.
- Histologically or cytologically confirmed stage IIIB/IV NSCLC (locally advanced or metastatic, non-eligible for radical chemoradiotherapy or surgery with curative intention).
- Progression on single agent EGFR TKI treatment (erlotinib, gefitinib, icotinib, afatinib or dacomitinib) in the 1st line setting or in the 2nd line (after a first line of chemotherapy).
- Measurable tumour disease according to RECIST v1.1 (at least one measurable lesion).
- Estimated life expectancy > 12 weeks.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
- Presence of EGFR Mutation without T790M mutation (T790M); Tyrosine-protein kinase receptor (UFO) (AXL) over expression or *MET* amplification and/ or MET overexpression

Principal non-inclusion criteria:

- Foreseeable poor compliance to the study procedures.
- Legally incapacitated person under guardianship or trusteeship.
- Pregnant or breast-feeding women.
- Unable to undergo computed tomography (CT) scans or magnetic resonance imaging (MRI).
- Having received more than 1 line of chemotherapy and more than 1 line of EGFR TKI.
- Blood transfusion within 2 weeks prior to the inclusion.
- Major surgery within 4 weeks prior to the inclusion.
- Patients treated by strong inhibitors and/or inducers cytochrome P450 3A4 or by BCRP, OCT1, OATP1B1 and OATP1B3 transporter substrates within 5 half-lives prior to the inclusion.
- Cardiovascular disorders, central nervous system (CNS) metastases, uncontrolled infection disorder, serious or unstable systemic disorder.

Test drug:
S49076 IMP was given orally once daily (*q.d.*) in combination with gefitinib 250 mg on a continuous schedule of 28-day cycles, in fasting conditions.
S49076 was supplied as tablets of 100 mg.
Patients took either 5 or 6 tablets of S49076 per day in combination with one tablet of gefitinib 250 mg per day.
Batch Nos.: [redacted].

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

Duration of treatment:
Patients continued treatment as long as they appeared to be receiving clinical benefit, and unless occurrence of unacceptable toxicity, or investigator's/patient's decision of withdrawal. The maximum number of cycles was at the discretion of the investigator.

Post withdrawal follow-up period: After discontinuation of the study drug and its associated agent, a follow-up was performed every 3 months and up to 9 months to follow on-going adverse event, and to collect survival data. The participant received another treatment, and/or had access to other appropriate care by his/her doctor, which was at the investigator discretion. Following protocol amendment No. 5, this post-withdrawal follow-up period was cancelled for the one remaining patient (n = 1).

Criteria for evaluation:
The primary objective of phase I part was safety.
Efficacy measurements:
Antitumor activity based on the RECIST v1.1.

Safety measurements:
Determination of DLT, Maximum Tolerated Dose (MTD), RP2D.
AEs, toxicity grading according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE V4.0), any change or addition of a new concomitant treatment, physical examination, vital signs, ECOG status, laboratory tests (biochemistry, haematology, cardiac Tn, coagulation, urinalysis), 12-lead-electrocardiogram (ECG), Left Ventricular Ejection Fraction (LVEF) from echocardiography were collected.

Pharmacokinetic (PK) measurements: *See PK report.*
Blood concentration of S49076, its metabolites, and gefitinib.
[redacted]

Statistical methods:

Analysis Set:
Safety Set (SS): all patients having taken at least one dose of S49076 or one dose of gefitinib.
Full Analysis Set (FAS): All included patients who had taken at least one dose of S49076 or one dose of gefitinib.
DLT Evaluable Set (DLTES): All patients from safety set who were evaluable for DLT according to the DLT assessment at end of cycle 1.
Molecular Status groups: patients either *MET* amplified and/or MET over-expressed, AXL over-expressed and MET amplified and/or MET over-expressed and AXL over-expressed.

Study outcome:
Descriptive statistics by dose level and overall were provided for characteristics at baseline [demography, disease history, previous therapies, medical and surgical history, initial tumour assessment, vital signs, Left Ventricular Ejection Fraction (LVEF) and ECG] in patients of the IS. Concomitant treatments were described in patients of the SS.
The extent of exposure and treatment duration were provided during the treatment period by dose level and overall in patients of the SS and the FAS.

Efficacy analysis:
Efficacy analyses were carried out on the FAS by molecular status, recommended dose (RD) and on overall.
The following criteria were analysed:

- Best overall response (BOR).
- Objective Response Rate (ORR).
- Clinical Benefit Rate (CBR).
- Overall response (OR).
- Duration of response.
- Progression-free survival (PFS).
- Relative change from (baseline/nadir) of the sum of the lesions diameters.
- Best relative change from baseline of the sum of the lesions diameters.

Safety analysis: Descriptive statistics were provided of the DLTs on the DLTES, and of emergent adverse events (EAEs) and serious AEs (SAEs), death, biology parameters, vital signs, ECG and LVEF in patients of the SS by dose level and overall.

Pharmacokinetic analysis: PK analyses were described in a separate report.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

	500 mg (N = 4)	**600 mg (N = 10)**	**All (N = 14)**
Included	4	10	**14**
Withdrawn due to			
- adverse event	0	2	**2**
- progressive disease	3	8	**11**
- non-medical reason	1	0	**1**
FAS	4	10	**14**
DLT Evaluable Set	3	7	**10**
Safety set	4	10	**14**

BASELINE CHARACTERISTICS

92 patients were pre-screened, among them 22 patients were screened who met the molecular status criteria, having positive EGFRm and negative *T790M*.
A total of 14 patients with EGFR mutant NSCLC without *T790M* were included in the study: 4 patients in the 500 mg group and 10 patients in the 600 mg group.

14 patients reported NSCLC stage IV with a mean duration of the disease of 1.3 years. The majority of included patients were MET dysregulated (4 *MET* amplified, 11 MET overexpressed), and 2 were AXL-only overexpressed.

The population was composed of 8 females (57%) and 6 males (43%); 8 Asians (57%) and 6 Caucasians (43%). Both groups were comparable in terms of demographic characteristics, clinical examination, history of the NSCLC, 12 lead-ECG, LVEF, except for ethnicity, smoking habits and weight. Most of the patients were non-smokers: all 4 patients in the 500 mg group (100%) and 5 patients in the 600 mg group (50%).

The median weight was lower in the 500 mg group (50.1 kg; mean 54.7 ± 14.2 kg) than in the 600 mg group (69.7 kg; mean 64.3 ± 17.1 kg). The progression-free interval of the NSCLC before the study was slightly longer in the 500 mg group (13.4 months) than in the 600 mg group (11.1 months). An ECOG Performance Status equal to 1 was reported for the 4 patients (100%) of the 500 mg group and for 6 patients (60%) in the 600 mg group. An ECOG PS equal to 0 was reported for 4 patients (40%) in the 600 mg group. As NSCLC with targetable EGFR mutation are more frequent in Asian, female and non-smoker population, this population distribution regarding sex, ethnicity, smoking habits was in accordance with the disease frequency.

Overall, the observed frequency of MET dysregulation in the population of patients with locally advanced or metastatic NSCLC was comparable to those already reported in the literature, whereas AXL over expression was lower than expected.

EXTENT OF EXPOSURE

Patients were treated during a median number of cycles of 8.5 in the 500 mg group and of 3 cycles in the 600 mg group.

Overall, 3 patients had a poor compliance for both S49076 and gefitinib, with both Relative Dose Intensity (RDI) < 80%.

Of note, the groups were different in term of number of patients and duration of study participation, leading difficulties in the interpretation of the results. Five patients were treated for more than 6 cycles: 3 in the 500 mg group and 2 in the 600 mg group; one patient of the 500 mg group withdrew from the study during cycle 18.

EFFICACY RESULTS

Analyses were carried out on the FAS, and it should be noted that two patients of the 600 mg group were not evaluable.

The BOR was confirmed partial response in 2/14 patients (14.3%) and stable disease in 8/14 (57.1%). The ORR was 14.3% (2 patients) with a median duration of response of 29.3 weeks. The clinical benefit rate was 33.3% including 4 patients with PR/SD ≥ 6 months (all MET dysregulated). Among the two patients with confirmed PR, one presented moderate MET amplification, and MET3+ and AXL2+ over-expression, and the other a MET high over-expression only. No objective response was observed in patients with AXL-only over-expression. As a consequence, it did not allow the identification of AXL over expression as an oncogenic driver of acquired resistance to EGFR TKI therapy.

The median PFS was 24.6 weeks for all patients, and 15.7 weeks at RD 600 mg.

SAFETY RESULTS

- **Dose-escalation, RP2D and PK findings**

DLT was assessed during cycle 1 according to a mCRM and stopping rules. The doses tested were 500 mg and 600 mg of S49076.

One DLT was described: one patient among 6 of the 600 mg group had an oral mucositis grade 3 on Day 11 of Cycle 1 (C1D11), leading to a dose reduction of S49076 at 500 mg. At the end of dose escalation, no MTD was reached.

[redacted]

Concomitant intake of gefitinib did not appear to modify the S49076 PK profile and gefitinib concentrations in co-administration of S49076.

On available safety data, the RP2D was defined as 600 mg of S49076 per day given in combination with 250 mg of gefitinib in patients with EGFR mutated advanced NSCLC.

- **Emergent adverse events (EAEs)**

Main results for AE reported during the treatment period in the Safety Set are described in the table below.

Patients having reported during treatment period at least one		**500 mg (N = 4)**	**600 mg (N = 10)**	**All (N = 14)**
EAE	n (%)	4 (100)	10 (100)	14 (100)
Treatment-related EAE				
S49076	n (%)	4 (100)	8 (80)	12 (86)
gefitinib	n (%)	1 (25)	7 (70)	8 (57)
S49076 and gefitinib	n (%)	1 (25)	7 (70)	8 (57)
Serious AE (including death)	n (%)	3 (75)	6 (60)	9 (64)
Treatment related serious EAE				
S49076 EAE	n (%)	3(75)	2 (20)	5 (36)
Gefitinib EAE	n (%)	1 (25)	1 (10)	2 (14)
S49076 and gefitinib EAE	n (%)	1 (25)	1 (10)	2 (14)
EAE leading to treatment withdrawal	n (%)	0 (0)	3 (30)	3 (21)
Serious EAE	n (%)	0 (0)	1 (10)	1 (7)
Treatment-related EAE leading to treatment withdrawal				
S49076-related EAE	n (%)	0 (0)	2 (20)	2 (14)
Treatment-related serious EAE leading to treatment withdrawal				
S49076-related serious EAE	n (%)	0 (0)	0 (0)	0 (0)
Patients who died during the treatment period	n (%)	0 (0)	1 (10)	1 (7)

During the study, 224 EAEs were reported in 14 patients Among them, the most frequently reported were diarrhoea (50%), paronychia (50%), asthenia (43%), nausea (43%), decreased appetite (36%), oedema peripheral (43%), AST increased (36%), ALT increased (36%), hypoalbuminaemia (36%).

One death in the 600 mg group occurred during the treatment period due to malignant neoplasm progression, and respiratory distress, and was not considered as related to the study drug.

5 patients (36%) died during the post-withdrawal follow-up period, 4 patients due to progressive disease, and 1 patient due to another reason (cardiovascular event).

Overall, 126/224 EAEs were considered by the investigators to be related to S49076 and/or gefitinib, of which 9.5% (12/126) were of grade 3:

- 122 EAES in 12 patients (86%) were considered to be related to S49076. Those S49076-related EAEs and reported in more than 2 patients were: diarrhoea (6 patients), paronychia (6 patients), asthenia (5 patients), nausea (5 patients), decreased appetite (4 patients), alanine aminotransferase increased (4 patients), aspartate aminotransferase increased (3 patients), stomatitis (3 patients), yellow skin (3 patients), oedema peripheral (3 patients), anaemia (3 patients). The EAEs of grade 3 considered as related to S49076 were 3 stomatitis, 2 asthenia, 2 diarrhoea, 1 ALT increase, 1 GGT increase, 1 febrile neutropenia, 1 neutrophil count decrease.
- 56 EAEs in 8 patients (57%) were considered as related to gefitinib. The most common gefitinib related EAEs (> 2 patients) were: diarrhoea (4 patients), paronychia (4 patients), asthenia (3 patients), and anaemia (3 patients). The EAEs of grade 3 considered as related to gefitinib were 3 stomatitis, 2 diarrhoea, 1 febrile neutropenia, 1 AST increased.
- 52 EAEs in 8 patients (57%) were considered as related to S49076 and gefitinib. The most common S49076 and gefitinib related EAEs (> 2 patients) were diarrhoea (4 patients), paronychia (4 patients), asthenia (3 patients), and anaemia (3 patients). The EAEs of grade 3 considered as related to S49076 and gefitinib were 3 stomatitis, 2 diarrhoea, 1 febrile neutropenia.

None of the patients had a serious treatment-related EAE of grade 4 or 5.
In the Safety Set, 4 EAE in 3 patients (30%) of the 600 mg group led to treatment withdrawal (pulmonary embolism, one respiratory failure, generalised oedema, peripheral swelling). 6 emergent adverse events in 6 patients (43%) led to study drug dose reduction (S49076 or gefitinib): 2 generalised oedema, 1 asthenia, 2 stomatitis, 1 pruritus.

Overall 33 SAEs were reported during the study in 9 patients (64%). 14 SEAEs occurred in 3 patients of the 500 mg group whereas 19 SEAE occurred in 6 patients of the 600 mg group.
Two SEAEs in 1 patient led to study drug withdrawal: those SEAEs were pulmonary embolism and respiratory failure (both serious and not related).
2 SEAEs were considered as related to S49076: atrial fibrillation, and asthenia, and 3 SEAEs were considered as related to both S49076 and gefitinib: febrile neutropenia, diarrhoea and stomatitis.

- **Laboratory tests**

Biochemistry parameters presented only sparse, emergent severe abnormal values and all of grade 3. Among them, single value of high AST, high ALT value and hypokalaemia were observed. Among non-gradable parameters, the most frequent emergent out-of-range worst values were detected for the low total protein (9 patients, 64%).
Haematology parameters presented six emergent severe abnormal values of grade 3: one anaemia, two low neutrophil events, three low white blood cell count (WBC) events. Overall the most frequent emergent out-of-range worst values were reported for low haematocrit (6 patients, 43%), and low red blood cell count (RBC) (5 patients, 36%).

- **Other safety evaluation**

ECOG performance status (PS) was good: During the study, the worst ECOG PS scores reached above 1 were "2" for 2 patients (14.3%) and "3" for 2 patients (14.3%, 1 patient in each treatment group). The median of the worst ECOG PS was "1" (range 0-3).

The median change in weight from baseline to the highest post-baseline value was 7.05 kg in the 500 mg group and 3.30 kg in the 600 mg group. There were no relevant changes in SBP/DBP or heart rate during the study.
The maximum Fridericia corrected QT interval (QTcF) change from baseline was ≤ 30 ms for all patients.
One clinically significant emergent ECG abnormality was a QTcF prolonged in a female patient in the interval [450 ms; 480 ms[, concomitant to an emergent atrial fibrillation.
Two LVEF decreases greater than 10% were measured on treatment in two patients. One of them was reported as an AE (non serious).

Except for paronychia (no case in monotherapy) and diarrhoea (less frequent in monotherapy), these EAEs were in line with the known safety profile of S49076.

CONCLUSION

CL1-49076-003 was a phase I/II international, multicenter, single-arm, open-label, non-randomised and non-comparative study. The aim of this study was to evaluate the safety and activity of S49076 in combination with gefitinib in Epidermal Growth Factor Receptor (EGFR)-mutated locally advanced or metastatic non-small cell lung cancer patient, who progressed on an EGFR tyrosine kinase inhibitor.
This study also explored the relevance of targeting MET and/or AXL biomarkers dysregulation to overcome acquired EGFR-T790M mediated resistance to EGFR-TKI first or second generation.

In all, 92 patients were pre-screened, 22 patients EGFR/T790M-negative were screened for MET/AXL dysregulations, and 14 patients were treated in this phase I. The majority of included patients were MET dysregulated (4 MET amplified, 11 MET overexpressed), and 2 were AXL-only overexpressed.
The dose-escalation phase I was to establish the Recommended Phase II Dose (RP2D) of S49076 given in combination with a fixed dose of gefitinib and to determine the safety and tolerability profile of this association by assessment of Dose-Limiting Toxicities (DLTs) during cycle 1 and the adverse events.

The S49076 dosages tested were 500 mg and 600 mg *q.d.* One patient reported a DLT at 600 mg *q.d.*, an oral mucositis grade 3. Based on safety and PK data, the RP2D was defined as 600 mg of S49076 per day given in combination with 250 mg of gefitinib in patients with EGFR mutated advanced non-small-cell lung cancer who have progressed after treatment with EGFR tyrosine kinase inhibitor.

The most frequent emergent adverse events considered as related to S49076 were diarrhoea, paronychia, asthenia and nausea. Except for paronychia (no case in monotherapy) and diarrhoea (less frequent in monotherapy), these EAEs were in line with the known safety profile of S49076. Safety of S49076 in combination with gefitinib appeared consistent with the known safety profiles of the individual drugs, and no new safety signals were identified with the combination.

Preliminary antitumor activity showed confirmed partial response in 14.3% patients, and stable disease in 57.1% patients. The objective response rate was 14.3%, and the clinical benefit rate was 33% with a median duration of 27.7 weeks. During phase I, the observed low frequency of AXL-only overexpression and the absence of objective response in this subgroup did not allow demonstration of the role of AXL as an oncogenic driver of acquired resistance to EGFR TKI therapy. Additionally, the global anti-tumoral preliminary data did not suggest an increase of activity by adding S49076 to gefitinib.
Following to the preliminary clinical data from the phase I part and due to feasibility challenges, the Sponsor decided to not initiate the phase II part.

Date of the report: 12 June 2019

Version of the report: Final version