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:** **Name of Active Ingredient:** Lucitanib (S 80881)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: An Open-Label, Dose-escalation, Phase I/IIa Study to Determine the Maximum Tolerated Dose, Recommended Dose, Efficacy, Pharmacokinetics and Pharmacodynamics of the dual VEGFR-FGFR Tyrosine Kinase Inhibitor, E-3810, Given Orally as Single Agent to Patients With Advanced Solid Tumours

The initial Phase I study had been amended regarding the study design to introduce a formal efficacy objective through the addition of a Part IIa.

Protocol No.: CL1-80881-007 / E-3810-I-01

EudraCT No.: 2010-019121-34

The description of the study protocol given hereafter includes the modifications of the 14 substantial amendments to the protocol.

National investigators: [redacted]

Study centres:

Four centres in 3 countries included at least one patient: Spain (1 centre, 37 patients included), France (2 centres, 85 patients), Italy (1 centre, 12 patients).

Publication (reference): Soria JC, DeBraud F, Bahleda F, *et al*. Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of Lucitanib in advanced solid tumors. Ann Oncol. 2014 Nov;25(11):2244-51.

Studied period:	**Phase of development of the study:**
Initiation date: 23 July 2010 (first visit first patient) Last patient included: 2 September 2014 Last visit/contact of the last patient: 04 May 2017	I/IIa (added by Amendment No. 6)

Objectives:

- ***Primary objectives:***
  - *Phase I:* To determine the MTD of S 80881 when administered orally, once daily for 28 consecutive days.
  - *Phase II:* To evaluate the objective response rate and the rate of non-progressive disease at 24 weeks in patients with tumours bearing *FGFR1* amplification (added by Amendment No. 6).
- ***Secondary objectives:***
  - To establish the safety profile and define the Dose-Limiting Toxicities (DLT) of S 80881.
  - To select the Recommended Dose (RD) and the optimal dosing schedule of S 80881.
  - To characterise the pharmacokinetic (PK) profile of S 80881 following single and multiple daily oral administrations.
  - To evaluate the effect of S 80881 treatment on tumour perfusion by Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) and Dynamic Contrast Enhanced Ultra Sounds (DCE-US)
  - To evaluate the effects of S 80881 on circulating pharmacodynamic (PD) markers of angiogenesis, including soluble Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) and VEGFR1, VEGF, Collagen IV, Basic Fibroblast Growth Factor (bFGF), Placental Growth Factor (PIGF, added by Amendment No. 6), FGF23 (added by Amendment No. 7), Circulating Endothelial Cells (CEC), Circulating Endothelial Progenitor cells (CEP) and Circulating Tumour Cells (CTC).
  - To identify genetic events that may be associated with response to S 80881 and with cancer disease (added by Amendment No. 10).
  - To preliminarily evaluate the antitumour activity of S 80881.
  - To correlate the occurrence of hypertension with the PK of S 80881 and/or the antitumour activity.

Methodology:
This was a Phase I/IIa multicentre, open-label, uncontrolled dose escalation study in patients with histologically or cytologically confirmed locally advanced or metastatic solid tumour, relapsed or refractory to standard therapy (Phase I), followed by dose-expansion at the identified RD with evaluation of efficacy (Phase IIa, added by Amendment No. 6).
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Following Amendment No. 15, the study was closed with a definition of the end of trial. Ongoing patients were permitted to continue lucitanib within the context of a compassionate use program, although it was decided to stop lucitanib development. Therefore, the present CSR is abbreviated.
Results of patients having completed at least 6 cycles of treatment had been presented in an intermediate clinical study report (CSR) (NP35410). At this time, 9 patients were still on-going. Therefore, the aim of the present CSR is to present overall data once all patients had discontinued the study.

Number of patients:
Planned: 60 patients in total amended to 130 patients in total, including at least 14 patients with tumours bearing *FGFR1* amplification for the phase IIa part of the study.
Included: 134 patients, including 35 patients FGF+.

Diagnosis and main criteria for inclusion:
For the dose-escalation phase, patients were to have histologically or cytologically confirmed locally advanced or metastatic solid tumour, relapsed or refractory to standard therapy.
For the dose-expansion phase, patients were to have:

- Histologically or cytologically confirmed locally advanced or metastatic solid tumours (*e.g.:* breast cancer, squamous or small cell lung cancer) and with Fibroblast Growth Factor Receptor 1 (FGFR1) amplification. Patient with breast cancer should have had at least one prior endocrine therapy in the metastatic setting if ER+, and at least one chemotherapy line otherwise. (Modified by Amendments No. 4 and 6), *or*
- Histologically or cytologically confirmed locally advanced or metastatic solid tumour who received as their prior therapy an approved or investigational antiangiogenic drug as a single agent or in a chemotherapy combination and were progressing after having experienced SD (lasting for at least six month) or PR as best response to such antiangiogenic treatment. Suitable tumours might include hepatocellular, non-FGFR1-amplified breast, colorectal, non-squamous Non-Small Cell Lung Carcinoma (NSCLC) and renal cancer (this list was not limitative).

  Patients with tumour types known to be potentially sensitive to antiangiogenic treatments (*e.g.* thyroid cancer, thymic carcinoma) could be recruited even in absence of pre-treatment provided no antiangiogenic agents were approved and\or available for that specific condition (added by Amendment No. 6).

Test drug:
During the dose-escalation phase, S 80881 was administered orally, once daily (q.d.), on a continuous administration schedule in fasting conditions (at least 2 hours prior to and 2 hours after a meal) for an initial 28-day cycle.
Both continuous and intermittent dosing schedules (*e.g.* 5 days on/2days off [5/2] or 21 days on/7 days off [21/7]) were explored in the expansion phase (as per Amendment No. 8).

During the dose-escalation phase, four doses were tested: 5, 10, 20 and 30 mg.
During the dose-expansion phase, four doses were tested: 20, 15, 12.5 and 10 mg.
Overall during the study, 3 patients received 5 mg, 11 patients received 10 mg, 25 patients received 12.5 mg, 71 patients received 15 mg, 17 patients received 20 mg and 7 patients received 30 mg.

Comparator:
Not applicable.

Duration of treatment:
Screening period: 30 days without treatment.
Treatment period: up to 6 cycles (including the first one) of 4 weeks. *In exceptional cases, in the best interest of patients who showed continued clinical benefit according to their doctor, treatment beyond cycle 6 could be allowed (added by Amendment No. 3).*
Follow-up period: one month post-treatment, with an end-of-study visit scheduled one month after the last drug administration, regardless of the reason for treatment discontinuation. The end-of-study visit (*i.e.:* Follow-up visit) was omitted for patients continuing lucitanib within the context of a compassionate use program, and the end of the trial was defined as the date of the last visit of the last patient (as added by Amendment No. 15).

Criteria for evaluation:

Efficacy assessments:

The primary endpoints, for the Phase IIa part of the study (as per Amendment No. 6), were the objective response rate (CR and PR according to Response Evaluation Criteria In Solid Tumours [RECIST version 1.1]) and the rate of non-progressive disease at 24 weeks according to RECIST.

The criteria were Best Overall Response (BOR), Objective Response Rate (ORR), Clinical Benefit Rate (CBR), duration of clinical benefit, duration of response, time to response and Progression Free Survival (PFS).

Safety assessments:

Determination of the MTD, defined as the dose level at which at least 2 out of 3-6 patients experienced DLT, was the primary objective of the Phase I study.

The other safety criteria were DLTs, adverse events, death, clinical laboratory evaluations (biochemistry, haematology, coagulation and thyroid function parameters, cardiac troponin I and BNP, urinalysis), vital signs and clinical examination (ECOG, weight, SBP, DBP, HR), 12-lead ECG, LVEF (ECHO or MUGA scan).

Pharmacokinetic assessments:

See separate report.

Pharmacodynamics assessments:

- For all patients of the continuous administration schedule excluding dose 12.5 mg:
  - Tumour Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) parameters.
  - Tumour Dynamic Contrast Enhanced UltraSonography (DCE-US) for measurement of tumour blood flow.
  - Soluble VEGFR-2 and sVEGFR-1, VEGF, bFGF, PIGF (added by Amendment No. 6), FGF-23 (added by Amendment No. 7), and Collagen IV (ELISA).
  - Mature Circulating Endothelial Cells (CEC) and Circulating Endothelial Progenitor (CEP), measured by flow cytometry.
  - Circulating tumour Cells (CTC) measured by CellSearch method.
- For patients with a dose level of 12.5 mg continuous administration schedule:
  - Analysis of soluble growth factors, including but not limited to FGF-23, FGF-2 and VEGF.
  - Analysis of free tumour circulating DNA.
  - Analysis of genomic background in circulating normal cells.

Statistical methods:

The analysis performed once all patients had completed at least 6 cycles of treatment (at the cut-off date of 31 August 2015) was presented in the intermediate CSR (NP35410). The present abbreviated CSR include the analysis (at the cut-off date of 17 July 2017) of overall patients once all of them had discontinued the study (including the 9 patients on-going at the cut-off date of 31 August 2015).

Analysis Set:

- **Included Set (IS):** All included patients.
- **Safety Set (SS):** Patients having taken at least one dose of study treatment.
- **Full Analysis Set (FAS):** Included patients who had taken at least one dose of study treatment.
- **Response Evaluable Set (RES):** All patients in the FAS who had at least one baseline and one post-baseline tumour evaluation.
- **DLT evaluable Set (DLTES):** All patients included in the dose-escalation phase. A patient was not considered evaluable if:
  - He/she discontinued during first cycle without DLT or
  - He/she did not receive at least 21 of 28 doses during first cycle unless patients presented a DLT.

Efficacy analysis

Descriptive statistics by dose level, genomic abnormality, tumour type and overall, as well as the 95% confidence interval for both the objective response and the clinical benefit were provided in the FAS and the RES.

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 the FAS.

Statistical methods (Cont'd)

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

Pharmacodynamic analyses:
Circulating pharmacodynamic biomarkers were studied separately between patients with a dose level of 12.5 mg/d and patients with continuous schedule excluding dose level of 12.5mg/d as the matrix and the time points studied were different and not measured in the same laboratory. No biomarker assessment was performed for intermittent schedule.

The evolution between baseline (C1D1) and post baseline visits was evaluated using the paired Wilcoxon signed rank test and the Hodges-Lehmann's estimator for related sample.
The changes from baseline to post baseline visits were compared between the dose levels (only for patients with continuous schedule excluding dose level of 12.5mg/d) by a Kruskal-Wallis test.
These changes were also compared between responders and non-responders (defined by ORR with confirmation of responses) by a non-parametric approach based on the Hodges-Lehmann's estimator for independent samples and a Wilcoxon test.
Finally, for the circulating proteins with interesting results in non-parametric tests and showing a gaussian distribution, a longitudinal analysis based on mixed model was performed as a sensitivity analysis.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND BASELINE CHARACTERISTICS

Patients withdrew the study mainly for progressive disease (96 patients, 71.6%) or adverse event (30 patients, 22.4%).

Demographic and baseline characteristics of patients in the Included Set (N = 134) were globally in accordance with the inclusion criteria defined for the study. Patients had a median age of 55.0 years old (mean = 55.2 ± 10.5 years), and most of them were 65 years old or younger (80.6% overall). More than half of the patients were female (55.2% overall).

At inclusion in the study, patients had a solid tumour for a median of 4.1 years (mean = 5.7 ± 5.4 years). The most frequent diagnoses were breast cancer in 34 patients (25.4%), colon cancer in 24 patients (17.9%), thyroid cancer in 19 patients (14.2%) and thymoma or thymic carcinoma in 16 patients (11.9%).

The median duration between relapse and the inclusion visit was 1.1 months (mean = 1.7 ± 2.9 months). Patients received their last therapy (chemotherapy, radiotherapy and/or surgery) for their tumour disease for a median of 43.0 days before inclusion (mean = 91.8 ± 182.2 days). The majority of patients had received three (24.8%) or more than three (46.3%) lines of prior systemic therapy.

At baseline, 125 patients (96.6%) had measurable target lesions.

At baseline, the ECOG performance status was ≤ 1 for 132 patients (98.5%) and 2 for two patients (a protocol deviation was reported for these patients).

EXTENT OF EXPOSURE

In the Full Analysis Set (N = 134), the total duration of S 80881 treatment ranged from 1.0 to 278.0 weeks, with a median of 16.0 weeks (mean = 34.4 ± 50.5 weeks). The median number of cycles received was 4.0 cycles (mean = 8.7 ± 12.4 cycles). The mean relative dose intensity (RDI) per patient was 82.6 ± 22.2% and the mean cumulative dose received by patient was 2295.2 ± 2837.9 mg.

After reaching the MTD at 30 mg, subsequent cohorts of patients received S 80881 treatment at the recommended 20 mg dose. However, due to safety concerns (hypertension and proteinuria), the RD was reduced to 15 mg and then to 10 mg. The additional dosing of 12.5 mg was also tested, based on PK/PD modeling and simulation. Finally, three patients were treated at 5 mg, 11 patients at 10 mg, 25 patients at 12.5 mg, 71 patients at 15 mg, 17 patients at 20 mg and seven patients at 30 mg as a starting dose, respectively.

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Overall, among patients treated with S 80881 in the Response Evaluable Set (RES), the confirmed BOR was CR in 2 patients (1.6%, both patients were antiangiogenic sensitive with thyroid cancer) and PR in 17 patients (13.7%), while for 69 patients (55.7%) the BOR was SD.

Other parameters measuring antitumour activity of S 80881 are described in the following table.

Other parameters measuring antitumour activity in the overall patients and in the FGF+ and antiangiogenic sensitive groups of patients - RES (N = 124)

		FGF+ (N = 33)	Antiangiogenic sensitive (N = 83)	All (N = 124)
ORR[1]	n (%)	6 (18.2	12 (14.5)	19 (15.3)
	95% CI [4]	[8.61;34.39]	[8.91;24.70]	[10.38;23.41]
Duration of response (weeks)				
Number of censors	Nobs	1	4	5
Number of events	Nobs	5	8	14
	Median	39.0	75.0	48.7
	Min ; Max	5.6;136.9	16.1;226.7	5.6;226.7
Clinical Benefit Rate[2]	n (%)	12 (36.4)	30 (36.1)	45 (36.3)
	95% CI [4]	[22.19;53.38]	[28.07;49.00]	[29.35;46.42]
Disease Control Rate[3]	n (%)	23 (69.7)	60 (72.3)	88 (71.0)
	95% CI [4]	[52.66;82.62]	[61.84;80.77]	[62.44;78.23]
PFS (weeks)				
Number of censors	Nobs	3	14	19
Number of events	Nobs	30	69	105
	Median	15.6	20.1	18.3
	Min ; Max	3.6;177.6	0.6; 274.1	0.6;274.1

[1] Objective Response Rate with confirmation (Best overall response with confirmation of responses = CR or PR)
[2] Clinical Benefit Rate with confirmation (Best overall response with confirmation of responses = CR or PR or stabilization (SD or Non CR /Non PD) > 24 weeks);
[3] Disease Control rate with confirmation of responses (complementary analysis) Best overall response with confirmation (= CR or PR) and SD of any duration
[4] 95% Confidence Interval of the estimate using Wilsons' method

According to the FGF+ status or antiangiogenesis sensitivity, the following results were observed:

- FGF+ patients: 6/33 patients (18.2%) had a PR. The ORR was 18.2% (n = 6 patients), the CBR was 36.4% (n = 12 patients) and the DCR (complementary analysis) was 69.7% (n = 23 patients).
  In FGF+ patients with breast cancer, the ORR was 25.0% (n =5 patients), the CBR was 45.0% (n = 9 patients) and the DCR was 80.0% (n = 16 patients).
- Antiangiogenesis sensitive group: 2/83 patients (2.4%) achieved a CR (both patients had a thyroid cancer) and 10/83 patients (12.1%) had a PR. The ORR was 14.5% (n = 12 patients), the CBR was 36.1% (n = 30 patients) and the DCR was 72.3% (n = 60 patients).
  In antiangiogenesis sensitive patients with:
  - Breast cancer, the ORR was 20.0% (n = 2 patients), the CBR was 20.0% (n = 2 patients) and the DCR was 60.0% (n = 6 patients).
  - Thyroid cancer, the ORR was 27.8% (n = 5 patients), the CBR was 55.6% (n = 10 patients) and the DCR was 94.4% (n = 17 patients).
  - Thymic carcinoma & thymoma, the ORR was 12.5% (n = 2 patients), the CBR was 50.0% (n = 8 patients) and the DCR was 87.5% (n = 14 patients).

With respect to biomarkers assessed in the FAS restricted to patients with a continuous administration schedule excluding 12.5 mg, statistically significant increases in PlGF, VEGF-A levels and decreases in sVEGFR1 and sVEGFR2 were observed as early as C1D7.
The modulation of sVEGFR2, VEGF-A and PlGF from baseline to C1D7 and sVEGFR2 from baseline to C1D28 appeared to slightly increase with the increased doses, however the unequal and low number of samples in each dose limit the interpretation of these results.
From baseline to C1D7 and from baseline to C1D28, no statistical relationship with the ORR (considering adjusted p-value) was evidenced in the modulation of biomarkers.

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Similarly, in the FAS restricted to patients at the dose of 12.5 mg, statistically significant increases in FGF23 (p = 0.0202), PlGF (p = 0.0005), VEGF-A (p = 0.0006) and VEGF-D (p = 0.0005) serum levels were observed at C1D15, as well as a decrease of sVEGFR1 (p = 0.0024). The highest size effect was observed for PlGF (about 392% of increase at C1D15 compared to median at baseline).

Altogether, those biomarker modulations were consistent with S 80881 mechanism of action, *i.e.* targeting VEGFRs (significant increase of VEGF-A and PlGF, significant decrease of soluble VEGFR1 and 2) and FGFR1 (significant increase of FGF23).

SAFETY RESULTS

Initially, four dose levels (*i.e.* 5, 10, 20, and 30 mg) were tested during the dose-escalation part of the study. At the end of Cycle 1, at the dose of 30 mg once daily, three DLTs (one case of Grade 4 depressed level of consciousness and two cases of Grade 3 thrombotic microangiopathy confirmed by renal biopsy in one patient) were observed in the six patients assessable for DLT. The dose of 30 mg was therefore considered as the MTD and the RD for the next phase was 20 mg once daily. However, the RD was reduced to 15 mg for more than half of the patients due to recurrent toxicities (hypertension and proteinuria), and then to 10 mg for some patients. Treatment at 12.5 mg q.d. was also tested based on PK/PD modelling and simulation data.

- **Emergent adverse events**

Overall summary for adverse events in the Safety Set

	All (N = 134) n (%)
Patients having reported at least one	
EAE	134 (100)
Treatment-related EAE	134 (100)
Severe EAE	120 (89.6)
Patients having reported at least one	
Serious EAE	67 (50.0)
Treatment-related emergent SAE	26 (19.4)
Patients who discontinue the treatment due to	
EAE	37 (27.6)
SAE	16 (11.9)
Treatment-related EAE	21 (15.7)
Treatment-related emergent SAE	7 (5.2)
Patients who died during the treatment period	20 (83.3)
Patients who died during the follow-up period	4 (3.0)

During the study, all patients reported at least one EAE. The most frequently affected **system organ classes** (SOCs) were Gastrointestinal disorders (n = 126 patients, 94.0%), General disorders and administration site conditions (n = 125 patients, 93.3%) and Vascular disorders (n = 120 patients, 89.6%). The most frequently reported **EAEs** were hypertension (n = 119 patients, 88.8%), asthenia (n = 105 patients, 78.4%) and proteinuria (n = 94 patients, 70.1%).
Most of the EAEs resolved (77.9%) according to last information available.

During the study, 93 patients (69.4%) experienced at least one grade 3 EAE (including 79 patients [59.0%] experiencing hypertension), 18 patients (13.4%) experienced at least one grade 4 EAE and 13 patients (9.7%) at least one grade 2 EAE. In all, 10 EAEs were fatal in n = 9 patients: respiratory failure (2 patients, both in 10 mg group), general physical health deterioration (2 patients, 10 mg and 12.5 mg), tricuspid valve disease (15 mg), acute respiratory distress syndrome (12.5 mg), bronchospasm (12.5 mg), non-cardiac chest pain (15 mg), neoplasm progression (15 mg), and tracheal haemorrhage (15 mg). None of these fatal EAEs were considered as related to the study treatment.

EAEs reported as **treatment-related** according to investigators' opinion occurred in all 134 patients (100%). They were mostly hypertension (n = 118 patients [88.1%], including 79 patients [59.0%] having Grade 3 hypertension), proteinuria (n = 94 patients [70.1%], including 17 patients [12.7%] having Grade 3 proteinuria) and asthenia (n = 83 patients [61.9%], including 17 patients [12.7%] having Grade 3 asthenia).

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

A total of 37 patients (27.6%) experienced at least one emergent adverse event **leading to treatment withdrawal**. The most frequently reported were thrombotic microangiopathy (n = 6 patients, 4.5%), proteinuria and asthenia (each in n =3 patients, 2.2%). In 21 patients (15.7%) these EAEs were considered as related to S 80881.

A total of 67 patients (50.0%) experienced 120 emergent **SAEs**. The most frequent emergent SAEs were thrombotic microangiopathy in n = 15 patients (11.2%), dyspnea in n = 10 patients (7.5%), pleural effusion and general physical health deterioration (each reported in n = 4 patients [3.0%]). Emergent SAEs were considered as related to the study treatment according to the investigator in 26 patients (19.4%), and were mainly thrombotic microangiopathy (n = 15 patients [11.2%]), proteinuria (n = 3 patients, [2.2%]), angina pectoris and left ventricular dysfunction (each in n = 2 patients [1.5%]). Emergent SAEs led to study drug withdrawal in 16 patients (11.9%), mostly due to thrombotic microangiopathy (n = 5 patients [3.7%]).

Twenty-four patients (17.9%) **died** during the study and 20 (14.9%) during the treatment period: due to disease progression (n = 11 patients), adverse event not considered as treatment-related by the investigator (n = 6 patients), or other reason (n = 2 patients from respiratory failure and n = 1 from sigma perforation due to neoplasic disease). Four patients (3.0%) died during the follow-up period: n = 3 due to disease progression and n = 1 classified as other reason: health deterioration.

- **Laboratory tests**

Regarding the **biochemistry parameters** rated according to the CTCAE grading, overall incidence of emergent severe abnormal values (CTCAE Grade ≥ 3) was low. The most frequently observed emergent Grade ≥ 3 laboratory abnormalities were high GGT (n = 24 patients [17.9%]), low sodium (n = 14 patients [10.4%]) and low albumin (n = 10 patients [7.5%]). Regarding the biochemistry parameters not gradable according to the CTCAE, the most frequently reported emergent abnormal values were high TSH (n = 80 patients [59.7%]), high total protein (n = 41 patients [30.6%]), high chloride (n = 39 patients [29.1%]) and high cortisol (n = 36 patients [26.9%]).

For **haematology parameters**, the most frequently observed emergent CTCAE Grade ≥ 3 were low haemoglobin (n = 7 patients [5.2%], all Grade 3) and low lymphocytes (n = 6 patients [4.5%], all Grade 3). Among non-gradable parameters, the most frequent observed emergent abnormal values was high haematocrit (n = 21 patients [15.7%]).

Regarding **coagulation parameters**, a total of 3 patients (2.2%) presented an emergent Grade 3 abnormal activated partial thromboplastin time (APTT). No emergent Grade ≥ 3 were reported for international normalized ratio (INR) during the study.

A total of 92 patients (68.7%) had a **urinary test** positive and significant for albumin during the study while it was negative, non-significant positive or missing at baseline.

- **Other safety evaluation**

Regarding **blood pressure**, 103 patients (76.9%) had a highest SBP value ≥ 140 mmHg during the treatment period while the baseline value was < 140 mmHg, and 106 patients (79.1%) had a highest DBP value ≥ 90 mmHg during the treatment period while the baseline value was < 90 mmHg. These finding are in line with the reported EAEs and with the mechanism of action of S 80881 (class effect). For HR, a total of 33 patients (24.6%) had a highest HR value ≥ 100 bpm during the treatment period while the baseline value was between 60 bpm (inclusive) and 100 bpm (exclusive).

During the study, patients had an average **body weight** decrease of -7.0 ± 6.2 % between baseline and the lowest value reported during the treatment period. Emergent adverse event of "weight decreased" was reported in 52 patients (38.8%) and "decreased appetite" in 74 patients (55.2%).

The majority of patients had an ECOG PS of 1 as worst post-baseline value during the study (91 patients, 67.9%). Overall, 2 patients (1.5%) had change of **ECOG PS** from 2 at baseline to 4 (*i.e.* completely disabled) as worst post-baseline value, and 13 patients (9.7%) from ≤ 2 at baseline to 3 (*i.e.* capable of limited selfcare) as worst post-baseline value.

A total of 86 patients (69.9%) had at least one emergent **ECG** abnormality, which was considered as clinically significant in two patients: atrial fibrillation and non-specific T wave abnormalities in one patient, and T wave inversion localized in antero-septal leads [V1 - V4] in one patient. Regarding **QTc** Fridericia interval (QTcF), none of the patients had a QTcF interval > 480 ms during the treatment period and seven patients had a QTcF interval in the 450 ms (exclusive) to 480 ms (inclusive) range. The mean (± SD) relative change from baseline to the lowest **LVEF** post-baseline value on treatment was -8.7% (± 10.4%), ranging from -50 % to 21%.

CONCLUSION

In this open dose-escalation Phase I/IIa study with oral doses of S 80881 (lucitanib), a total of 134 patients were included and received the study treatment, and 124 were evaluated for efficacy. The maximum tolerated dose (MTD) was determined at 30 mg once daily and the recommended dose at 20 mg once daily. Due to recurrent toxicities (hypertension and proteinuria), the RD was reduced to 15 mg and then to 10 mg. An additional dose level of 12.5 mg was also tested.

Concerning clinical activity, 2 patients (1.6%) had complete response (both patients had thyroid cancer) and 17 patients (13.7%) had partial response.

In the FGF aberrant pathway population, 6/33 patients (18.2%) displayed a partial response, the CBR was 36.4% (12 patients) and the DCR was 69.7% (23 patients). In FGF+ patients with breast cancer, the ORR was 25.0% (5 patients), the CBR was 45.0% (9 patients) and the DCR was 80.0% (16 patients).

Among antiangiogenesis sensitive patients, 2/83 (2.4%) achieved a complete response, 10/83 (12.1%) displayed a partial response, the ORR was 14.5% (12 patients), the CBR was 36.1% (30 patients) and the DCR was 72.3% (60 patients). In antiangiogenesis sensitive patients with breast cancer, the ORR was 20.0% (2 patients), the CBR was 20.0% (2 patients) and the DCR was 60.0% (6 patients). In those with thyroid cancer, the ORR was 27.8% (5 patients), the CBR was 55.6% (10 patients) and the DCR was 94.4% (17 patients). In those with thymic carcinoma & thymoma, the ORR was 12.5% (2 patients), the CBR was 50.0% (8 patients) and the DCR was 87.5% (14 patients).

Biomarker modulations were consistent with lucitanib's mechanism of action.

The safety profile of lucitanib was consistent with the expected effect of a potent inhibitor of the VEGF axis. The most frequent EAEs considered as treatment-related by the investigators were hypertension, proteinuria and asthenia. No patient had QTcF interval > 480 ms.

Date of the report: 19 January 2018

Version of the report: Final version