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: FINESSE – An open, 3-cohort, Phase II trial testing oral administration of lucitanib in patients with FGFR1-amplified or non-amplIfied oestrogeN rEceptor poSitive metaStatic breast cancEr

Protocol No.: BIG 2-13/CL2-80881-001
EudraCT No.: 2013-000288-10
The description of the study protocol given hereafter includes the modifications of the 6 substantial amendments to the protocol.

International lead investigators: [redacted] France [redacted] Spain [redacted]

Study centres:
17 centres in 9 countries included at least one patient: Australia (2 centres, 12 patients included), Belgium (2 centres, 9 patients included), Canada (1 centre, 4 patients included), France (2 centres, 8 patients included), Italy (2 centres, 16 patients included), Spain (3 centres, 11 patients included), UK (2 centres, 11 patients included), Hungary (1 centre, 3 patients included), Germany (2 centres, 2 patients included).

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 3 December 2013 (FVFP) Completion date: 5 April 2017 (LVLP)	II

Objectives:

- ***Primary objective:*** To evaluate the objective response rate (ORR) of single agent lucitanib in metastatic breast cancer patients with FGFR1-amplified, FGFR1-non-amplified with 11q amplification, or FGFR1-non-amplified without 11q amplification.
- ***Secondary objectives:***
  - To determine the clinical benefit rate (CBR) of single agent lucitanib in metastatic breast cancer patients with FGFR1-amplified, FGFR1-non-amplified with 11q amplification, or FGFR1-non-amplified without 11q amplification. CBR was defined as the proportion of patients for whom a confirmed CR or a confirmed PR or a prolonged SD (disease had remained stable (SD according to RECIST criteria) during treatment for at least 24 weeks from inclusion) was observed during the treatment.
  - To evaluate the progression-free survival (PFS) in metastatic breast cancer patients with FGFR1-amplified, FGFR1-non-amplified with 11q amplification, or FGFR1-non-amplified without 11q amplification, receiving single agent lucitanib.
  - To evaluate the duration of response in metastatic breast cancer patients with FGFR1-amplified, FGFR1-non-amplified with 11q amplification, or FGFR1-non-amplified without 11q amplification, receiving single agent lucitanib.
  - To evaluate the safety of lucitanib.
  - To evaluate the pharmacokinetics of lucitanib.
- ***Exploratory objective:*** To determine the pharmacodynamics (PD) profile of lucitanib:
  - By characterising biological activity of lucitanib on soluble growth factors of interest.
  - By characterising biological activity of lucitanib on tumour cells obtained from metastatic tumour biopsies.
  - By exploring biomarkers potentially predictive for lucitanib response in blood samples and in primary archived and metastatic tumours.

Methodology:
This was a Phase II multicentre, open-label, Simon two stages study of lucitanib given as single agent in 3 cohorts: patients with FGFR1-amplified (Cohort 1), FGFR1-non-amplified with 11q amplification (Cohort 2), or FGFR1-non-amplified without 11q amplification (Cohort 3). Following Amendment No. 5, lucitanib was given at the starting dose of 10 mg orally (instead of 15 mg orally) on a daily basis until unacceptable toxicity according to the investigator, disease progression or withdrawal of consent.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

During the FINESSE trial it was decided to prematurely and definitively halt the recruitment of patients. This decision was based on an analysis by the Sponsor of all available data from the lucitanib breast cancer clinical development program. The analysis showed that lucitanib was not likely to be superior than standard of care therapy in patients with advanced breast cancer. [redacted] Therefore all the planned patients were not included and the present CSR is abbreviated.

Number of patients:
Planned: 21 patients in each cohort with measurable disease at baseline were to be assessed at the end of stage 1. If at least 2 patients showed evidence of response as per the pre-specified criteria, this cohort was to continue to enrol additional 20 patients (stage 2). Therefore, up to 123 patients could have been included in the study.

Included: 76 patients. 32 patients in Cohort 1, 18 patients in Cohort 2 and 26 patients in Cohort 3.
In each of the Cohorts 1 and 3, 2 responses were observed during stage 1, so additional patients were enrolled (stage 2). No response was observed in Cohort 2 after 18 patients included.

Diagnosis and main criteria for inclusion:
Patients with ER+ and HER2- metastatic breast cancer. These patients should have been treated with first line anticancer therapy in the metastatic setting, but no more than two lines of chemotherapy with or without targeted therapy. There was no limit of lines of endocrine therapy and targeted therapy.

Test drug:
Lucitanib was administered orally, once daily, on a continuous administration schedule in fasting conditions (at least 2 hours prior to and 2 hours after a meal). The starting dose of lucitanib had been reduced from 15 mg to 10 mg per protocol Amendment No. 5. Patients enrolled prior to the protocol Amendment No. 5 who had already started on the 15 mg daily dose were permitted to continue receiving lucitanib at their current dose if the investigator deemed it appropriate. Otherwise, the dose of lucitanib was to be reduced to 10 mg daily when starting the following cycle. Newly enrolled patients from protocol amendment No. 5 were not allowed to receive doses >10 mg daily and dose reductions below 5 mg daily were not allowed.

Comparator:
Not applicable.

Duration of treatment:
Screening period: 28 days without treatment.
Treatment period: no time-limit was defined. Patients were to continue on study drug until unacceptable toxicity according to the investigator, disease progression or withdrawal of consent.
Follow-up period: up to 4 weeks after last dose intake for patient withdrawn for disease progression and until progression, death or loss of follow-up for patient withdrawn for reasons others than disease progression.

Criteria for evaluation:

Activity assessments:
The primary endpoint was the Objective Response Rate (ORR: CR and PR as best overall response during treatment, according to Response Evaluation Criteria In Solid Tumours [RECIST] criteria version 1.1).

Secondary endpoints:
Secondary endpoints were Clinical Benefit Rate (CBR), duration of response among responders (confirmed CR or PR), Progression Free Survival (PFS).

Safety assessments:
Adverse events, SAEs, clinical laboratory evaluation (biochemistry including LFTs, haematology, coagulation and thyroid function parameters, urinalysis), vital signs and clinical examination (ECOG, weight, height, SBP, DBP, HR, respiratory rate, temperature), cardiac evaluation (12-lead ECG, LVEF by ECHO or MUGA scan).

Pharmacodynamics assessments:

Analysis of predictive and pharmacodynamic biomarkers:

- FGFR1 genomic amplification (FISH and ddPCR).
- FGFR1 protein over-expression (IHC).
- CCND1 (11q13) genomic amplification (FISH).
- FGFBF/CD31 protein co-expression (dual IHC).
- Ki67/CD31 protein co-expression (dual IHC).
- Six circulating protein levels: FGFBF, FGF23, MCSF, PDGF-AA, PDGF-BB and VEGFA.

Statistical methods:
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 having taken at least one dose of study treatment.
- **Per Protocol Set (PPS):** Patients of the FAS without any relevant deviation which could affect the evaluation of the anti-tumoral activity and who were evaluable for tumour response.

Activity analysis: main analysis was carried out in the FAS.
The primary endpoint was the ORR. Other criteria analysed were Best Overall Response (BOR), CBR, duration of clinical benefit, duration of response, time to response and PFS. Results were provided by Cohort and overall.
There was no statistical test intended to compare cohorts / dose levels between them, the analyses were descriptive. The 95% Wilson's confidence interval for rates was computed based on inverting the normal test that uses the null proportion in the variance (the score test). Median duration and 95% confidence interval for time-dependent parameters were estimated using the Kaplan-Meier method.

Patients' disposition, baseline characteristics and treatment exposure analysis: Descriptive statistics were provided in the IS and in the FAS (for treatment exposure), by Cohort and overall.

Safety analysis: Descriptive statistics were provided in the SS, by Cohort and overall.

PD analyses: Analyses are detailed in a separate report (Appendix 16.4).

SUMMARY - CONCLUSIONS
DISPOSITION OF PATIENTS AND BASELINE CHARACTERISTICS

A total of 76 patients were included in the study: 32 patients in Cohort 1 (FGFR1-amplified), 18 patients in Cohort 2 (FGFR1-non-amplified with 11q amplification) and 26 patients in Cohort 3 (FGFR1-non-amplified without 11q amplification). During the stage 1, at least 2 patients in Cohorts 1 and 3 showed evidence of response as per the pre-specified criteria. Consequently, these two cohorts continued to enrol additional patients (stage 2). No response was observed in Cohort 2 after 18 patients included.

All of the 76 included patients were withdrawn from the study, due to progressive disease in 58 patients (76.3%), adverse events in 16 patients (21.1%) and other reason in 2 patients (2.6%: "in view of the repeated hospitalizations and daily intake of the study drug" and "patient decided to stop the treatment", one patient each).

Demographic and baseline characteristics of patients in the Included Set were in line with the inclusion criteria defined for the study. Women enrolled in the study had a mean age of 54.9 ± 10.3 years (78.9% of them were aged 65 years old or younger).

All but 3 patients included in the study had breast cancer of *ER+/HER2-* phenotype, and 27 out of 43 cases with a known status (35.5%) were progesterone receptor positive. Overall, the median disease duration from diagnosis was 6.7 years. At the time of inclusion, most of the patients (54 patients, 71.1%) had breast cancer for over 4 years. The overall median progression free interval (PFI *i.e.,* interval between the start of last therapy and last progression) was 241 days, ranging from 13 to 1884 days. For 44 patients (57.9%), the time since latest progression was longer than 180 days. The overall median time since the diagnosis of metastatic disease was 2.4 years, ranging from 0.2 to 12.6 years.

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND BASELINE CHARACTERISTICS (Cont'd)

All the patients included in this study received systemic therapy for their breast cancer, while 86.8% received previous surgery and 80.3% received previous radiotherapy.
As required by the protocol, no patient was included with an ECOG performance status ≥ 2.

At baseline, mean SBP, DBP, and heart rate were 124.2 ± 14.7 mmHg, 77.7 ± 9.8 mmHg, and 78.6 ± 11.9 bpm, respectively. All but one patient had QTcF below 450 ms (mean was 406.6 ± 20.7 ms).

EXTENT OF EXPOSURE

In the FAS, 59 patients (77.6%) received lucitanib at the starting dose of 15 mg daily and 17 patients (22.4%) received lucitanib at the starting dose of 10 mg daily (following Amendment No. 5). The overall median global treatment duration was 79.5 days, ranging from 2 to 565 days. The mean lucitanib relative dose intensity per patient was 76.6 ± 19.0% (reflecting the treatment interruptions and dose reductions proposed for the management of toxicities described in the study protocol). The mean cumulative dose of lucitanib was 1148.2 ± 1034.1 mg and the mean dose intensity was 10.5 ± 2.7 mg/day overall. Of note, in case of an adverse event occurring on lucitanib 15 mg, doses reductions to 10 mg, 7.5 mg and 5 mg daily could be considered. In case of an AE on lucitanib 10 mg, doses reductions to 7.5 mg and 5 mg daily could be considered. Daily dosing below 5 mg was not authorised.

ACTIVITY RESULTS

Overall, in the FAS the ORR was 13.2% (10 patients). Similarly, in the PPS, the ORR was 14.3% (9 patients).
For these 10 patients in the FAS, the median time to first response was 89.5 days and the median duration of response was 129 days.
Overall, in the FAS, the Best Overall Response (BOR) was PR in 10 patients (13.2%), while BOR was SD in 33 patients (43.4%), Non CR/Non PD in 1 patient (1.3%) and PD in 24 patients (31.6%). Eight patients were NE (10.5%).
The CBR (defined as confirmed CR or PR, or SD ≥ 24 weeks) was 28.9% (22 patients).
The overall median PFS was 113 days.

- **Biomarkers analysis**

Weak trends of association were observed between FGFR1 amplification and objective response, BRC and PFS in FINESSE cohort, especially for patients with high FGFR1 amplification (5/23 = 21.7% responders). By contrast, 11q amplification might be associated with poor response (2/29 = 6.9% responders). The FGFR1 membrane over-expression was weakly associated with objective response (5/20 = 25.0% responders) and patients with FGFR1 membrane overexpression had in average 3-month longer PFS than other patients. However, 4/10 responder patients did not exhibit any FGFR1 alteration. Those clinical responses were most probably due to the anti-angiogenic action of the compound (targeting VEGFR).

Due to an analytical issue, pharmacodynamic analyses were solely reliable for FGF23. A significant increase of circulating FGF23 levels was detected after 14 days of treatment for both lucitanib doses (p-value = $1.74e^{-}$ 06). No significant difference in FGF23 changes could be identified between responders and non-responders (p-value = 0.39). A high inter-individual variability was detected at both timepoints.

FGFR1 genomic amplification determined using ddPCR and FISH technologies showed good consistency (p = 0.79). FGFR1 over-expression was mostly detected for patients with FGFR1 amplification, both from amplified and highly amplified classes (24/27 patients with over-expression exhibit amplification). No strong correlation could be detected between FGFR1 FISH signals or ddPCR copy numbers and IHC H-score (p = 0.71). As expected, FGFR1 genomic amplification was not necessarily associated with FGFR1 protein over-expression (60% of amplified patients show over-expression in FINESSE).

In FINESSE cohort, FISH and ddPCR FGFR1 amplification measures were overall consistent between metastases and primary tumors (out of the 13 FGFR1 amplified patients at baseline, 11 already exhibited the amplification in the primary tumor). The FGFR1 expression in metastatic biopsies was partially consistent with matched primary tumors (p = 0.75).

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

Overall summary of safety results – Safety Set

		All (N = 76)
Patients having reported at least one		
Emergent Adverse Event (EAE)	n (%)	76 (100)
Treatment-related EAE	n (%)	74 (97.4)
Severe EAE	n (%)	69 (90.8)
Patients having reported at least one		
Serious EAE	n (%)	38 (50.0)
Treatment-related emergent SAE	n (%)	20 (26.3)
Patients who discontinue the treatment due to		
EAE	n (%)	16 (21.1)
SAE	n (%)	11 (14.5)
Treatment-related EAE	n (%)	14 (18.4)
Treatment-related emergent SAE	n (%)	9 (11.8)
Patients who died during the treatment period	n (%)	1 (1.3)
Patients who died during the follow-up period	n (%)	8 (10.5)

During the study, all patients reported at least one EAE. The most frequent affected **System Organ Classes (SOCs)** were vascular disorders (68 patients, 89.5%), gastrointestinal disorders (59 patients, 77.6%), and general disorders and administration site conditions (56 patients, 73.7%).

Overall, the most frequently reported **EAEs** were hypertension (67 patients, 88.2%), hypothyroidism and nausea (36 patients, 47.4% for each event). Of note, a total of 162/212 (76.4%) EAEs "hypertension" resolved and 3 were resolving at the end of the study.

One case of Posterior Reversible Encephalopathy Syndrome (PRES) was reported in a [redacted] patient treated with lucitanib at 15 mg daily. Treatment was stopped. This patient completely recovered from all symptoms (detailed narrative of this patient is provided in Section 12.1.1).

During the treatment period, most of the patients (59 patients, 77.6%) experienced at least one EAE of **grade 3** as worst grade, while 9 patients (11.8%) reported at least one EAE rated **grade 4** as worst grade.
In addition, one patient reported 1 EAE of **grade 5**: death of unknown cause.

Overall, 74 patients (97.4%) had at least one EAE considered **related to the treatment**. The most common EAEs related to lucitanib (reported in more than 30% of patients) were hypertension (66 patients, 86.8%), hypothyroidism (34 patients, 44.7%), nausea (25 patients, 32.9%), and proteinuria (24 patients, 31.6%). Among these most common EAEs related to lucitanib, the following EAEs were judged severe (grade ≥ 3): hypertension (in 50/66 patients, 75.8%) and nausea (1/25 patients, 4%).

A total of 16 patients (21.1%) had 38 EAEs that led to **premature treatment discontinuation.** Overall, 13 EAEs of hypertension were reported in 6 patients (7.9%). All the other events leading to premature treatment discontinuation were reported only in one patient.

In all, 38 patients (50.0%) experienced a total of 83 emergent **serious adverse events** during the treatment period. A total of 48 emergent SAEs were considered related to the study drug in 20 patients (26.3%), and were mainly hypertension (7 patients, 9.2%).

Nine patients (11.8%) died during the study: 1 died during the treatment period, due to unknown cause and 8 (10.5%) died during the follow-up period, all due to breast cancer progression.

- **Laboratory tests**

For **biochemical parameters**, the most frequently observed emergent abnormal gradable value was high GGT in 16 patients (21.8%).
Among non-gradable biochemical parameters, the most frequently reported emergent abnormal value was high TSH in 52 patients (72.2%). This was consistent with the EAE hypothyroidism reported on treatment (36 patients [47.4%]).
For **haematological parameters**, the incidence of reported emergent abnormal values gradable and non-gradable was low, reported in no more than 7.0% of patients.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Other safety evaluations**

Most patients (59 patients, 77.6%) had an **ECOG performance status** that remained ≤ 1 during the treatment period. Concerning **weight** loss, the average relative loss in weight from baseline to lowest value was -3.8 ± 4.2 %.

Regarding **blood pressures**, the mean changes from baseline to highest SBP and DBP values were 28.4 ± 17.5 mmHg and 18.2 ± 11.6 mmHg, respectively. A total of 47 patients (61.8%) had a highest SBP value ≥ 140 mmHg during the treatment period while the baseline value was < 140 mmHg. For DBP, 44 patients (57.9%) had a highest value ≥ 90 mmHg during the treatment period while the baseline value was < 90 mmHg.

The mean change in heart rate from baseline to highest value was 11.4 ± 13 bpm. In all, 18 patients (23.7%) had a highest HR value ≥ 100 bpm during the treatment period while the baseline value was < 100 bpm.

Emergent **ECG abnormalities** were considered as clinically significant in 2 patients (ST depression localized, T wave inversion and complete left bundle branch block). Regarding **QTc Fridericia interval** (QTcF), 4 patients experienced maximum QTcF prolongation during the treatment period between 451 ms and 480 ms. Four patients (5.3%) had a maximum increase of QTcF interval from baseline > 60 ms.

CONCLUSION

This study was a Phase II trial to determine the activity of lucitanib in patients with FGFR1-amplified or non-amplified oestrogen receptor positive metastatic breast cancer.

During the FINESSE trial it was decided to prematurely and definitively halt the recruitment of patients. This decision was based on an analysis by the Sponsor of all available data from the lucitanib breast cancer clinical development program. The analysis showed that lucitanib was not likely to be superior than standard of care therapy in patients with advanced breast cancer. [redacted]

With the early termination of enrolment, a total of 76 patients were included and received the study treatment: 32 patients in Cohort 1 (FGFR1 amplified, irrespective of 11q amplification status), 18 patients in Cohort 2 (FGFR1 non-amplified, 11q amplified) and 26 patients in Cohort 3 (FGFR1 and 11q non-amplified). All patients were evaluated for activity. Regarding clinical activity, the ORR was 13.2% overall (10 patients, all had PR). The CBR (defined as confirmed CR or PR, or SD ≥ 24 weeks) was 28.9% (22 patients). The overall median PFS was 113 days. As regards to biomarkers analysis, weak trends of association were observed between FGFR1 amplification and efficacy, especially for patients with high FGFR1 amplification (ORR 21.7%). Biomarker modulations were consistent with lucitanib's mechanism of action.

The safety assessment showed that, despite a reduction of lucitanib starting dose from 15 mg to 10 mg daily, a substantial number of patients experienced hypertension or hypertension-related events. Measures to manage cases of hypertension were implemented and most patients recovered. The other most frequent EAEs considered as treatment-related by the investigators were in line with the known safety profile of lucitanib, and were hypothyroidism, nausea and proteinuria, which appeared to be manageable through dose interruption and dose reduction. No patient had QTcF interval > 480 ms.

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