Name of Sponsor/Company: *Grupo Español de Investigación en Sarcomas (GEIS)*	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	***(For National Authority Use Only)***
Name of Finished Product: *Pazopanib*		
Name of Active Ingredient: *444731-52-C/Pazopanib/based on MPD record: SUB29175*		

Title of Study:	Phase II Clinical Trial of Pazopanib to evaluate the activity and tolerability in patients with advanced and/or metastatic liposarcoma who have relapsed following standard therapies or for whom no standard therapy exists	
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Publication (reference):	*Interim analysis:* DOI: 10.1200/JCO.2016.34.15_suppl.11039 Journal of Clinical Oncology 34, no. 15_suppl (May 20 2016) 11039-11039.	
Studied period (years):	5	***Phase of development:*** *Therapeutic exploratory (II)*
Date of first enrolment:	29-jan.-2013 (first informed consent signature) 05-feb.-2013 (first enrolment)	
Date of last completed:	02-mar.-2018	
Objectives:	*Primary:* To evaluate the activity of Pazopanib in patients with advanced and/or metastatic liposarcoma by means of progression-free survival (PFS) assessed 12 weeks after start of treatment. (According the RECIST criteria 1.1 and	

	central radiology review). *Secondaries:* ● Median progression-free survival (median PFS) ● Objective tumor response (confirmed complete response [CR] and partial response [PR] using modified Response Evaluation Criteria in Solid Tumors [RECIST] 1.1). ● Time to onset of response. ● Duration of response. ● Overall survival (OS). ● Clinical benefit rate (CBR). ● Growth Modulation Index (GMI). ● Safety profile (according CTCAE, version 4.0).
Methodology:	The drug was separately investigated in the following liposarcoma subtypes: ● Well-differentiated liposarcoma/dedifferentiated liposarcoma (ALT-WD) - (Cohort A). ● Myxoid/round cell liposarcoma (Cohort B) *Sample size:* The following design characteristics and decision rules were applied separately to each stratum. The Simon optimal one sample two stages testing procedure (optimal design) was used with the following hypotheses: ● Success in 20% of the cases or less in one of the strata will be considered as unacceptable, and would not warrant further investigation (null hypothesis). Therefore, the value of P0 was taken as 20%. ● Success in 40% of the cases or more in one of the strata was considered as an acceptable result warranting further investigation of the drug in this histology (alternative hypothesis). Therefore, the value of P1 was taken as 40%. These two reference values are based on a retrospective analysis of the EORTC STBSG database of patients treated with 2nd line therapy. Under those hypotheses, a total of 37 eligible and treated patients were needed to be recruited in each stratum and followed for at least 12 weeks. The size of the type I and type II errors is 10% (alpha=beta=0.1). A total of 17 eligible and treated patients will be included (in each stratum) in the first step of the study. 1. If ≤ 3 successes are observed in a stratum, the trial will be stopped in this stratum with the conclusion that the drug should not be further investigated in this histology. 2. Else, patients will continue to be accrued until 37 eligible patients have been recruited and have started therapy. If 11 or more successes are observed in those 37 patients, we will conclude that the results of this trial warrant further investigation in this histology. *Analyses for results* Results presented here correspond to stage 2 of the trial

	(please see protocol for more information) and are calculated based on the intent-to-treat sample (for efficacy outcomes); safety, on the other hand, has been analysed considering all patients with at least one dose of the investigational product. Data has been considered from first patient's inclusion to study close-out (13 December 2017). Safety was evaluated based on type, frequency, and intensity of adverse events related to the combination treatment.
Number of patients	
● Planned:	74* **Inclusion for the myxoid liposarcoma cohort (B) was concluded when 15 patients were recruited.*
● Analysed:	52 (Cohort A: 37 patients; Cohort B: 15 patients).
Diagnosis:	Advanced and/or metastatic liposarcoma
Main criteria for inclusion:	1. Subjects must provide written informed consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow-up. 2. Age > 18 years or legal age of consent if greater than 18 years. 3. Histological confirmed diagnosis of high or intermediate grade malignant liposarcoma with metastatic or locally advanced disease. Formalin fixed paraffin embedded tumour block and/or representative H/E (haematoxylin/eosin) slides must be available for central pathologic review. 4. Patient must have documentation of disease progression within 6 months prior to study entry. 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. 6. Measurable disease by RECIST v1.1 criteria. At least one measurable lesion located outside of a previously irradiated area. If the only measurable lesion is in a previously irradiated area, RECIST progression should be documented after radiotherapy, in the previous 6 months before study entry. 7. The patient should not be considered eligible for surgery or radical radiotherapy. e.g. Patients to whom surgery/radiotherapy can not be performed with a curative intent due to the extension of the disease. In the case of radiotherapy, it may also be limited due to a previous treatment with radiotherapy in the same area. 8. The patient must have either been considered ineligible for systemic chemotherapy or received at least one previous regimen for relapsed, refractory or metastatic disease. A maximum of three previous lines for advanced/metastatic disease are allowed.

	9. The patient should be able to swallow and retain study drug. 10. Adequate organ system function as defined in Table 1 of protocol. 11. A subject is eligible to enter and participate in this study if she/he is following the contraceptive indication detailed in protocol. 12. LVEF above the lower limit of normal for the institution, based on ECHO or MUGA.
Test product	
● **Dose:**	Pazopanib 800 mg (2x400mg or 4x200 mg) given as a single agent administered once daily.
● **Mode of administration:**	Oral use
● **Batch number:**	Not applicable
● **Duration of treatment**	Until progression of disease, according to study protocol
Reference therapy	Not applicable
● Dose:	Not applicable
● Mode of administration:	Not applicable
● Batch number:	Not applicable
Criteria for evaluation	
● Efficacy	● Progression free survival 12 weeks after start of therapy ● Overall progression free survival (median PFS) ● Overall survival (OS) ● Clinical benefit rate ● Growth Modulation Index (GMI)
● Safety	● Safety profile (according CTCAE, version 4.0)
Statistical methods:	All results are presented using intention-to-treat analysis. Patients fulfilling all eligibility criteria were included in the efficacy analysis, that was primarily aimed to assess progression free survival 12 weeks after start of therapy, measured as a binary variable and based on the disease evaluation performed 12 weeks after start of treatment with central radiology review. Patients who are alive and progression free at this time will be considered as successes. Patients who have progressed or are dead at this time will be considered as failure. Patients with an unknown progression status will be considered as failure. The diagnosis of progression was based on tumor measurements, according to the RECIST 1.1 criteria and based on radiological imaging performed throughout the study and assessed by central reviewer.

	For continuous variables, mean, standard error (for efficacy variables), standard deviation (for other measurements), median, minimum and maximum, were considered. Categorical variables are presented using frequencies and percentages. Survival was assessed with two-sided confidence intervals (CI 95%s) Kaplan–Meier curves. Comparison on results of progression-free survival among cohorts were performed using the Log-rank test (%) and with u-Mann Whitney test (median, min-max comparison). Safety data were analysed throughout the entire study and is presented as number and proportion of each event.
SUMMARY CONCLUSIONS	
EFFICACY RESULTS	Median follow-up was 61.5 (2.3-217.3) months for the total population, 69.7 (5.0-217.3) months for Cohort A and 46.4 (2.3-163.6) months for cohort B. To highlight the good tolerance of the treatment, only 3 patients were reported to have had dose reductions throughout the study period. ***Objective Tumor Response and clinical benefit rate*** Evaluation of response at 6 weeks resulted in 8.1% and 6.7% of patients with partial response in Cohort A and Cohort B, respectively. When the 12-weeks evaluation was analysed, these proportions were 5.4% and 0.0%, respectively. No patients with complete response were reported. Clinical benefit rate (in this case patients reaching partial response or stable disease) was 54.1% and 32.4% at 6- and 12-weeks these proportions corresponded to 40% and 6.7%, respectively.(Cohort A) and 40% (Cohort B) of patients obtained clinical benefit from treatment. The 12-weeks evaluation showed 32.4% and 6.7%). ***PFS-12 weeks after start of therapy*** As per RECIST 1.1, PFS at 12 weeks was 54.1% (CI 95%: 38-70.2%) for Cohort A and 40% (CI 95%: 15.2-64.8%) for Cohort B. Cohort B did not reached the predefined >40% PFS-12, and therefore the recruitment in this cohort was interrupted after the first 15 patients were analysed. ***Progression free survival (median PFS)*** Median PFS (as per RECIST 1.1) was 15 weeks (CI 95%: 8.19 - 21.81) for cohort A and 8.71 weeks (CI 95%: 4.93 a 12.5) for Cohort B. In the total population, 9 patients (17.3%) did not progress (17.3%) after a median follow up of 162 weeks. This included 6 out of 37 patients (16.2%) in the Cohort A and 3 out of 15 patients (20%) in the Cohort B; p=0.706). For those patients with PD (n=43), time to progression in Cohort A (median; range) was 9.7 weeks (2.3-178.7), 11.6

	weeks (5.3-178.7) for Cohort A and 7.5 weeks (2.3-95.7) for Cohort B. and ***Overall survival (OS)*** Median OS for this study was similar: 70.43 weeks (CI 95% de 42.69 - 98.17) for cohort A and 71.29 weeks (CI 95% de 31.21 - 111.36) for cohort B, (p=0.711). Thirty-five patients (67.3%) have died at the end of follow up: 26 of 37(70.3%) for cohort A and 9 out of 15 (60%) for cohort B, p=0.135). Among this 35 patients, 30 had a PD-related death and this occurred after a median of 45.9 weeks after start of treatment, with no differences between cohorts (45.1 and 46.4 weeks, respectively; p=0.821). ***Growth Modulation Index (GMI)*** Considering GMI as the ratio between time to PD with pazopanib (TTPp) divided by the time to PD with the previous line of treatment (TTPp-1), an analysis of all patients with information on both progressions (n=39) was performed. A median GMI of 0.4 was observed, with significant differences between cohorts: 0.7 in Cohort A and 0.2 in Cohort B, p=0.022). When GMI was categorized into groups (<1, 1-1.33 and >1.33), however, differences were not reported (p=0.223). The GMI was also considered in further analysis related to efficacy based on local evaluations of disease. The GMI/PFS analysis showed a larger median PFS for the GMI>1.33 group (33.86 weeks), particularly higher than for the GMI <1 group (8.43 weeks, p=0.001). These differences were also observed when cohort A was evaluated, not so for the rest of patients (Cohort B) for whom results were comparable (GMI <1: 7 weeks; GMI 1-1.33: 12.71 weeks). Overall survival did not show differences for global sample depending on the GMI (p=0.329) nor for each cohort (p= 0.329 and p=0.662, cohort A and B, respectively).
SAFETY RESULTS	***Safety profile (according CTCAE, version 4.0)*** During treatment, all participants reported at least one adverse event (of any grade) and 88.5% of the 52 patients reported at least one toxicity/event of any grade which was associated with treatment. These findings did not differ between cohorts (89.2% vs 86.7%, p=1.000). 26 (50.0%) reported at least one ≥G3 event. The most common G3 reported events were: Hypertension (n=7; 13.5%), diarrhea (n=4; 7.7%), neutropenia (n=3; 5.8%) and ALT increased (n=3; 5.8%). No differences between cohorts (45.9% vs 60.0%, p=0.358) were observed. When ≥G3 events were associated with treatment (toxicities) this proportion was 30.8%, and without particular differences among groups (29.7% vs 33.3%, p=1.000). During the whole follow-up, severe adverse events (SAEs) were observed in 14 patients (26.9%) and 11 of the

	reported SAEs occured while on treatment, and 4 of them were considered related to the IMP: ALT increased (n=1) Myocardial infarction (n=1), ALT increased (n=1), increase of bilirubin (n=1), all these events were graded as 3 according to severity. After treatment, frequency of adverse events of any grade was 23.1%, again without differences (27% vs 13.3%, p=0.470). At that time, 15.4% patients (n=8) reported at least one toxicity of any grade (Cohort A: 16.2% vs Cohort B 13.3%, p=1.000) and ≥G3 events related to treatment were reported in 3 patients (5.8%).
CONCLUSION	This study corroborates pazopanib 800mg is well tolerated and is potentially active for the treatment of Well-differentiated/Dedifferentiated LPS as it is in other sarcoma subtypes, but not in Myxoid/Round Cell LPS. Safety profile is comparable to previous reports. The prognostic value of GMI when progression free survival was analyzed is of clinical interest and can be considered as a potential prognostic factor in this clinical situation. Further analysis in larger populations (ex. in countries were pazopanib is approved in this setting) should be considered.
Date of report	03-dic.-2018