SYNOPSIS

Name of Company: Tiziana Life Sciences, PLC **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC); named **Milciclib** throughout this document	*(For National Authority Use only)*
Title of Study: Phase II study of oral Milciclib Maleate (PHA-848125AC) in patients with thymic carcinoma previously treated with chemotherapy	
Protocol Number: CDKO-125a-006	
Investigators: 1) Silvia Novello; 2) Maria Chiara Garassino; 3) Benjamin Besse; 4) Julien Mazières; 5) Glen J. Weiss; 6) G. Giaccone/Rajan Arun; 7) Daren Kocs; 8) J. Mark Barnett.	
Study Centers: 1) Coordinating Site: Azienda Ospedaliero-Universitaria San Luigi Gonzaga S.S.D, Orbassano (TO) Italy ; 2) Fondazione IRCCS Istituto Nazionale dei Tumori Milano (MI) Italy; 3) Institut Gustave Roussy, Villejuif Cedex, France; 4) CHU Toulouse Hopital Larrey, Toulouse Cedex, France; 5) Scottsdale Clinical Research Institute, Scottsdale, USA; 6) National Cancer Institute Center for Cancer Research, Bethesda, USA; 7) Texas Oncology Austin, Austin, USA; 8) Rocky Mountain Cancer Center, Longmont, USA.	
Publication Reference:	
Studied Period (Years): 22 February 2010 13 June 2017	**Phase of Development:** Phase II
Objectives: **Primary:** Assessment of the antitumor activity of milciclib as second-line treatment in patients with recurrent or metastatic, unresectable thymic carcinoma previously treated with chemotherapy. Antitumor activity has been evaluated on the basis of the progression-free survival status at 3 months. **Secondary:** Assessment of additional measures of tumor control to further characterize the efficacy profile of milciclib in recurrent or metastatic, unresectable thymic carcinoma patients previously treated with chemotherapy **Exploratory objective:** Relationship of baseline molecular features in tumor biopsies of p53, p21, p27, cyclin D1, p75, TRKA and other genes/proteins involved in the milciclib mechanism of action with treatment efficacy.	
Methodology: This was a single-arm, 2-stage, open-label, multicentre phase II clinical trial of milciclib administered to patients with recurrent or metastatic, unresectable thymic carcinoma previously treated with chemotherapy (only one prior systemic therapy allowed).	
Number of Subjects (Planned and Analyzed): A sample size of 60 evaluable patients was anticipated for the primary efficacy analysis of this study (20 in case the trial would have stopped at the end of the 1st stage). Overall, 72 patients were enrolled and treated.	
Diagnosis and Main Criteria for Inclusion: **Subject Inclusion Criteria** 1. Signed and dated IRB/IEC-approved Informed Consent	

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2. Histologically or cytologically proven diagnosis of unresectable B3 thymoma or thymic carcinoma recurrent or progressing after prior chemotherapy (only one prior systemic therapy allowed)
3. Presence of measurable disease defined as at least one lesion that could be accurately measured by CT scan in at least one dimension, as > 10 mm for non nodal lesions (longest diameter to be recorded) and ≥ 15 mm for lymph nodal lesions (short axis to be recorded). (CT scan was the desirable method for lesion measurement. Other measurement techniques [*eg* MRI] were acceptable [but not for lung lesions] provided that the size of the measurable lesion is twice the slice thickness of the MRI).
   Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, were usually not considered measurable unless progression in the lesion had been demonstrated.
4. Age ≥ 18 years
5. ECOG (WHO) performance status 0-1
6. Estimated life expectancy of at least 3 months
7. Negative pregnancy test (if female in reproductive years)
8. Agreement upon the use of effective contraceptive methods (hormonal or barrier method of birth control, or abstinence) prior to study entry and for the duration of study participation, if men and women of child producing potential
9. Adequate liver function:
   - Total Serum Bilirubin ≤ 1.5 x upper limit of normal (ULN)
   - Transaminase AST (SGOT), ALT (SGPT) ≤2.5 ULN (if liver metastases were present, then ≤ 5 ULN was allowed)
   - Alkaline phosphatase ≤ 2.5 ULN (if liver and/or bone metastases were present, then ≤ 5 ULN was allowed)
10. Adequate renal function:
    - Serum creatinine ≤ ULN
    or
    - Creatinine Clearance calculated by Cockcroft and Gault's formula > 60 mL/min
11. Adequate hematologic status:
    - ANC ≥ 1,500 cells/mm^3
    - Platelet count ≥ 100,000 cells/mm^3
    - Hemoglobin ≥ 9.0 g/dL
12. At the time of treatment start, at least 2 weeks must had elapsed since completion of prior chemotherapy, minor surgery and radiotherapy (provided that no more than 25% of bone marrow reserve had been irradiated)
13. With the exception of alopecia, resolution of all acute toxic effects of any prior surgery, radiotherapy or chemotherapy to NCI CTC (Version 3.0) grade ≤ 1 and to the baseline laboratory values as defined in Inclusion Criteria Number 9, 10, 11
14. Able and willing to comply with scheduled visits, therapy plans, and laboratory tests required in this protocol
15. Capability to swallow capsules intact (without chewing, crushing, or opening).

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Subject Exclusion Criteria

1. Any of the followings in the past 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis
2. Grade >1 retinopathy as determinated by an ophtalmologist
3. Known brain metastases
4. Major surgery, other than diagnostic surgery, within 4 weeks prior to treatment
5. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy
6. Known infection with HIV, active hepatitis B or hepatitis C
7. Pregnant or breast feeding women
8. Previous (within the last 5 years) or current malignancies at other sites, except for adequately treated basal cell or squamous cell skin cancer or in situ carcinoma of the cervix uteri
9. Current enrollment in or participation in another therapeutic clinical trial within 4 weeks preceding treatment start
10. Diabetes mellitus uncontrolled
11. Gastrointestinal disease (e.g. Crohn's disease, ulcerative colitis, or short gut syndrome) that would have impacted on drug absorption
12. Patients under treatment with anticoagulants or with coagulation disorders or with signs of hemorrhage at baseline
13. Patients with previous history or current presence of neurological disorders, including epilepsy (although controlled by anticonvulsant therapy), Parkinson's disease and extra-pyramidal syndromes
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that might have increased the risk associated with study participation or might have interfered with the interpretation of study results and, in the judgment of the Investigator, would have made the patient inappropriate for entry into this study or could have compromised protocol objectives in the opinion of the Investigator and/or the Sponsor.

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Test Product, Dose and Mode of Administration, Batch Number:

Milciclib is formulated as oral 10 mg, 50 mg and 100 mg capsules to be swallowed intact (without chewing, crushing or opening). The compound was administered once daily at the flat dose of 150mg/day for 7 days on / 7 days off in a 2-week cycle. The batch numbers used for this study were:

N0901764, N1000070, N1000175, N1000658, N1001080, N1001085, N1001690, N1001740, N1001781, N1001787, N1001793, N1100001, N1100157, N1101772, N1200173, N1200175, N1200212, N1200484, N1200486, N1200490, N1200769, N1200773, N1200792, N1201102, N1300264, N1300266, N1300741, N1300743, N1301056, N1301497, N1400147, N1400163, N1400686, N1401101, N1500619, N1500688, N1500764, N1500966, N1501698, N1600181, N1600266, N1600439, N1600574, N1700075, N1700099, N1700245, N1700554, N1700597, N1700611 (50 mg caps),

N0901765, N1000071, N1000176, N1000659, N1001691, N1001741, N1001782, N1001788, N1001794, N1100002, N1100158, N1101773, N1200174, N1200176, N1200213, N1200485, N1200487, N1200491, N1200770, N1200772, N1200774, N1201103, N1300265, N1300267, N1300742, N1300744, N1301057, N1301263, N1301498, N1301499, N1400148, N1400163, N1400687, N1400724, N1401102, N1402168, N1500620, N1500689, N1500766, N1500968, N1501699, N1501803, N1600034 (100 mg caps).

No batches of 10 mg strength were used.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.

Duration of Treatment: Patients were to continue on study treatment until disease progression, patient refusal or withdrawal of patient consent, or the occurrence of unacceptable toxicity and were to be followed up for survival up to the end of the study and in any case for no more than 2 years from the end of treatment.

Enrollment was completed on April 2016. On March 2017 an amendment was implemented stipulating a target data cut-off date on 31 May 2017 followed by clinical database closure and the preparation of this Clinical Study Report. The Sponsor has guaranteed the continued supply of the investigational compound for all patients who were on study drug at the time of clinical data cut-off and are deemed benefiting per their respective treating physician (PI).

Endpoints and Criteria for Evaluation:
Primary endpoint was based on progression-free survival rate at 3 months (PFS-3 rate). The PFS-3 rate was defined as the proportion of evaluable patients known to be alive and progression-free at ≥ 3 months since study treatment start, out of the total number of evaluable patients.
Secondary endpoints:
-Confirmed objective tumor response according to RECIST [Therasse P. et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000; 92 (3):205-216];
- Disease Control Rate (Confirmed Objective Response Rate + ≥ 6 weeks SD rate);
- Progression-free survival, calculated as the time from the date of treatment start to the date of first documentation of objective progression or of death due to any cause, whichever came first;
- Duration of Response measured from the time measurement criteria were first met for CR/PR (whichever was first recorded) until the first date that recurrent or progressive disease was objectively documented (taking as reference for progressive disease the smallest measurements recorded on study);
- Overall Survival (OS), i.e. the time from the date of treatment start to the date of death from any cause;
- Overall safety profile, evaluated on the basis of laboratory and clinical safety parameters (i.e. hematology and blood chemistry, urinalysis, vital signs, ophthalmologic examinations and adverse events emerging during the trial). The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

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Version 3.0 was used for the severity grading of adverse events and hematological and blood chemistry abnormalities.
Exploratory endpoint:
Baseline characterization of selected biomarkers (p53, p21, p27, cyclin D1, p75, TRKA and other genes/proteins involved in the milciclib mechanism of action) in tumor tissue of consenting patients. Assessments was to be done on paraffin embedded blocks, obtained from all patients before study entry, by IHC and other possible techniques, such as FISH and PCR.

Statistical Methods:
In consideration of the exploratory nature of the study, a Simon's optimal two-stage design was adopted.

The primary endpoint of the study was the progression-free survival status at 3 months and the primary efficacy analysis was to be performed on the proportion of successes (i.e. patients alive and in a progression-free status at 3 months since treatment start) out of the total number of evaluable patients (PFS-3 rate).

Considering a 33% PFS-3 rate as clinically interesting, against a clinically uninteresting hypothesis of a PFS-3 rate no higher than 17%, the system of hypotheses to be tested was:

H_0: $p \leq p_0$, $p_0 = 0.17$ vs. H_1: $p \geq p_1$, $p_1 = 0.33$

The analysis was to be performed at the overall level $\alpha = 0.05$ (1-sided).
The design below outlined would have provided 80% power (1-β) not to reject the treatment as insufficiently effective, if the true PFS-3 rate would have been 33% or higher.

In the first stage, 17 evaluable patients were to be assessed. If ≤ 3 successes were observed, the study treatment was to be considered as providing insufficient evidence of efficacy and the trial would have been terminated. If at least 4 successes had observed in the 1st stage, patients' enrollment would have proceeded up to an overall enrollment of 54 evaluable patients.
Accounting for a 10-15% proportion of non evaluable patients, up to 20 patients could have been required in the 1st stage of the study and up to 60 patients for completing the trial (1st and 2nd stage).

At the final analysis, ≥ 14/54 successes (PFS-3 rate ≥ 25.9%) were to be required to reject the null hypothesis and suggest that the drug might have been an interesting level of efficacy. The progression free survival at 3 months would have been evaluated based on the antitumor activity evaluated during the oncologic assessment at 3 months after first drug administration. As per Amendment 3, the oncologic assessment was to be performed between 92-98 days from treatment start, but all patients with assessments performed up to 134 days were considered evaluable for the primary end-point.

H0 vs. H1	α (1-sided)	power (1-β)	1st Stage (*)		2nd Stage		
			Patients	STOP and Reject drug	Patients	Reject drug	Do not reject drug
p0 ≤ 0.17 vs. p1 ≥ 0.33 (PFS-3 rate)	0.05	0.80	17 evaluable patients	≤ 3 / 17 successes	54 evaluable patients	≤ 13 / 54 succ. (PFS-3 rate ≤24.1%)	≥ 14 / 54 succ. (PFS-3 rate ≥ 25.9%)
(*) Probability of Early Termination: PET=0.675, if the drug is actually ineffective; Probability to continue the trial > 0.863, if the true PFS-3 rate is at least 33%:							
Expected sample size assuming ineffective drug: 29							
No. of enrolled patients: ≤20 patients in the 1st stage, ≤60 patients overall (if 10%-15% inevaluable patients)							

Supportive analyses of the primary endpoint would have included the estimation of the PFS-3 rate together with its exact, two-tail, 95% confidence interval and the estimation of the PFS curve by the Kaplan-Meier

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method in both the evaluable and the treated patient population. The other efficacy endpoints including the confirmed objective response rate, the disease control rate, the duration of response, and the overall survival were descriptively analyzed in both the evaluable and the treated patient populations. Kaplan-Meier estimates were generated and plotted for the overall survival endpoint.

Patient Populations: *Screened Patients*: This population included all patients who were screened for potential eligibility for the trial, regardless of whether or not they were enrolled in the study. This population was to be evaluated in the analysis of patients' disposition.
Enrolled Patients: This population included all the enrolled patients, regardless of whether they received or not the study drug. This population was to be evaluated in the analysis of patients' disposition.
Treated Patients: The treated patient population consisted of all enrolled patients who had actually received at least one study drug administration. This population was to be evaluated in the analysis of patient disposition, baseline characteristics, treatment efficacy and safety and treatment exposure.
Patients Evaluable for Efficacy Analysis: This definition included the patient population for the primary efficacy analysis of 12-week PD-free rate and consisted of all treated patients who had fulfilled the following additional conditions: a) They had received at least 80% of drug in the first two cycles overall; b)They had undergone baseline and ≥1 on-treatment tumor/oncologic assessments or had died before tumor re-assessment.

SUMMARY OF RESULTS:

Disposition of Patients and Baseline Characteristics:

In the present trial 72 patients (37 females and 35 males, with median age of 55.0 years) with thymic carcinoma were enrolled and treated with a flat dose of 150 mg/day of milciclib once daily for 7 consecutive days (Days 1 to 7) followed by 7 days of rest (Days 8 to 14) for a total of a 14 days period (2-week cycle). All patients had at least one prior systemic therapy and, in addition, 16 patients underwent surgery, 10 patients had radiotherapy and 36 patients underwent both surgery and radiotherapy. Seventy-one patients had metastatic disease at study entry and the most frequent sites of metastases were lung (54%), lymph nodes (40%), liver (24%) and bones (22%). ECOG PS was reported in all patients and scored 0 (46 patients) and 1 (23 patients). The main reasons for treatment discontinuation (*off –treatment* reasons) were progression of disease in 56 patients (78%), adverse events in 8 patients (11%); the *off-study* reasons were death (37 patients, 51.4%), FU completed as per protocol and sponsor's decision (15 patients each, 20.8% each). When more than the 14 successes required by protocol were achieved, collected data were considered sufficient for the primary efficacy endpoint; therefore the Sponsor decided to stop collecting data in CRF and to just guarantee the supply of investigational compound (until patients still on treatment would have benefit from the therapy), and safety monitoring, in order to close the database, prepare the present CSR and plan for further investigations. To this aim, Amendment 4 was released and at the cut-off date of 31 May 2017, data from patients still on treatment or in the 2-year follow up, were no longer collected in the CRFs but only in the patients' medical notes. Four patients were still on treatment at that time; all the related information was censored at the cut-off date and these patients were considered off-study, as reported in all tables and listings. Two out of these four patients were, later on, shifted on a "compassionate use" protocol, approved on December 2018. **Treatment exposure**: milciclib maleate was administered for 7 days on/7 days off in a 2-week cycle at the flat dose of 150 mg/day with a median dose intensity of 95.8 mg/week (min-max: 214.6 – 544.4 mg/week). A total of 1256 cycles were administered, and the median number of cycles per patient was 7.5 (min-max: 1–135). *Treatment modifications* (interruption/reduction) were implemented at cycle start or intra-cycle and occurred due to *hematological toxicity* (mainly neutropenia and anemia) in 14 patients (19%), *non hematological toxicity* (mainly nausea, diarrhoea and vomiting) in 48 patients (67%) and modifications due to *other reasons* (i.e: logistic reasons) in 48 patients (67%). *Treatment compliance*: over a total number of 1256 cycles, the percentage of the administered *vs* scheduled dose by cycle was 95% in 455 cycles (36%), between 80% and

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95% in 24 cycles (2%), between 50% and 80% in 760 cycles (61%) and less than 50% in 17 cycles (1%).

Efficacy Results:
The primary endpoint of the study, i.e., the progression free survival status at 3 months, has been achieved in 24 out of the 54 evaluable patients (44.4%), with median *PFS* of 6.83 months with upper and lower 95% confidence limits of 4.11 and 8.71 months, respectively.
Evaluable patients had median OS of 24.18 months with upper and lower 95% confidence limits of 16.89 and 36.57 months, respectively.
Two PR and 39 SD were observed among the evaluable patients as best confirmed response, with a disease control rate of 75.9%.
Biomarkers,
The exploratory analysis on selected biomarkers was conducted in tumor samples from 56 patients with B3 thymomas and C thymic carcinoma enrolled in the study and indicates that there was a significant difference between B3/C success and B3/C failure groups for p53, cyclin D1 and p21 biomarkers.

Safety Results:
All the 72 treated patients experienced at least 1 AE in the first or subsequent cycles and 71 patients presented drug related events. The safety data from this study are consistent with milciclib toxicological profile from the previous clinical experience. These are mainly mild/moderate gastrointestinal toxicity, and only sporadically severe, asthenia and fatigue, neurological effects reversible upon drug discontinuation or dose reduction and ocular effects.

The findings reported in haematology and blood chemistry were unremarkable, except for abnormalities in lymphocytes (one CTC Grade 4), occurrence of ALT increase and lipase increase (CTC Grade 4 in one case).

Two deaths on study (i.e. occurring within 28 days from the last administered dose) were reported to the Sponsor and considered not related to the study treatment; drug-related SAEs occurred in 10 patients.

Pharmacokinetic Results:
No Pharmacokinetics analysis was performed in this study

CONCLUSIONS:
Data obtained from the present study demonstrated that treatment with milciclib administered at the adopted dose-schedule (i.e.: 150 mg/day for 7-day on/ 7-day off q2wks) have met the primary endpoint of progression free survival at 3 months.

The overall safety profile of milciclib was manageable supporting the adopted dose-schedule is well tolerated in these patients with no new emerging safety issues, and therefore could be further evaluated in other tumor types.

Date of the Report:
04 March 2019