2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot, 92284 Suresnes Cedex – France Laboratorios Servier S.L., 33 avenida de los Madroños, 28043 Madrid, Spain	*(For National Authority Use only)*
Name of finished product: Not applicable	
Name of active ingredient: S64315	
Title of study: Phase I/II, international, multicentre, open-label, non-randomised, non-comparative study evaluating the safety, tolerability and clinical activity of intravenously administered S64315, a selective Mcl-1 inhibitor, in combination with azacitidine in patients with acute myeloid leukaemia (AML) Protocol No.: CL1-64315-004 EudraCT No.: 2019-004896-38 CT.gov No: NCT04629443 The description of the study protocol given hereafter includes the modifications implemented through the 5 substantial amendments to the protocol.	
International Coordinator: [redacted]	
Number of patients and countries: Seventeen patients were included in 4 countries: Australia (2 patients), France (3 patients), Spain (10 patients) and USA (2 patients).	
Studied period: Initiation date: 17 February 2021 (first visit first patient) Completion date: 25 August 2023 (last visit last patient)	**Phase of development of the study:** Phase I/II
Publication (reference): Not applicable	
Background and rationale for the study: In this study, S64315 and azacitidine were administered in combination to patients with AML to characterize their safety and tolerability, and to determine a recommended Phase II dose (RP2D) for future clinical studies. The Sponsor decided to discontinue the recruitment for the study based on strategic considerations due to the limited efficacy seen with this treatment in most patients. This decision was not a consequence of any safety concerns. The discontinuation of recruitment was effective as of 28 November 2022. The study was discontinued during the dose escalation Phase I part, and the expansion Phase II part of the study was not initiated. In this context, an abbreviated clinical study report was written.	

Objectives and endpoints:

Objectives	Endpoints
Primary objective: - To determine the safety profile (including dose-limiting toxicities [DLTs] and maximum tolerated dose [MTD]) and tolerability of S64315 in combination with azacitidine in patients with AML	Primary endpoints: - Incidence of DLTs starting from the Lead-in Dose (LID) period to the end of the first cycle of treatment of S64315 in combination with azacitidine - Incidence and severity of adverse events (AEs) and serious AEs according to National Cancer Institute Common Terminology Criteria for Adverse Event v5.0 - Recording of any change or addition of a new concomitant treatment - Laboratory tests: haematology with differential, blood biochemistry, thyroid function, blood coagulation, urinary analysis, hepatitis markers, tumour lysis syndrome monitoring, cardiac markers follow-up - Complete physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs measurements - Electrocardiogram (ECG) parameters, cardiac function assessment - Left ventricular ejection fraction (LVEF) - Dose interruptions, reductions and dose intensity

Study design:

This was an international, open-label, multicentre, non-randomised, non-comparative Phase I/II study of S64315 in combination with azacitidine administered in patients with AML.

This study was originally designed as 2 phases: Phase I for dose escalation and Phase II for dose expansion. Furthermore, the dose escalation Phase I part was further planned to have 2 arms: Arm A evaluating the combination of S64315 with azacitidine, and Arm B evaluating [redacted] However, the Phase I (Arm B) and Phase II (dose expansion) were not conducted due to recruitment discontinuation during the dose escalation Phase I of Arm A.

This study was performed in strict accordance with Good Clinical Practice.

Number of patients (Planned and Analysed):

Planned:

- Arm A
  - Dose escalation Phase I part: approximately 30 patients
  - Expansion Phase II part: approximately 50 patients per sub-arm (up to 100, overall)

Analysed: 17 patients.

A total of 17 patients were included in the study in the dose escalation Phase I part:

- Safety Set (SS): 17 patients.
- DLT-Evaluable Set (DLTES): 13 patients.

Diagnosis and main criteria for inclusion/exclusion:

- Male or female patients aged ≥ 18 years.
- Patients with cytologically confirmed and documented de novo, secondary or therapy-related AML as defined by World Health Organization 2016 classification excluding acute promyelocytic leukaemia (APL, French-American-British M3 classification):
  - With relapsed or refractory disease and without established alternative therapy or
  - Secondary to myelodysplastic syndrome and without established alternative therapy
- ECOG performance status ≤ 2.
- Able to comply with study procedures.
- Adequate haematological function based on the last assessment performed within 7 days prior to the first investigational medicinal product (IMP) administration, defined as:
  - Circulating white blood cell count < 10 G/L (only use of hydroxycarbamide or leukapheresis before first IMP administration is allowed to achieve this inclusion criterion)
- Adequate renal function based on the last assessment within 7 days prior to the first IMP administration defined as calculated creatinine clearance > 60 mL/min/1.73 m², determined by modification of diet in renal disease (MDRD)
- Adequate hepatic function based on the last assessment within 7 days prior to the first IMP administration defined as:
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 1.5 x upper limit of normal (ULN) and
  - Total serum bilirubin level < 1.5 x ULN, except for patients with known Gilbert's syndrome (confirmed by the UGT1A1 polymorphism analysis) who were excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
- Women of childbearing potential has been tested negative in a serum pregnancy test within 7 days before the first day of IMP administration.

Investigational Medicinal Products

Azacitidine was administered via subcutaneous (SC) injection, once a day over 7 consecutive days.

S64315 was administered via intravenous (IV) infusion over at least 2 hours, once a week.

The initial schedule consisted of a 2-week S64315 LID period followed by a 28-day cycle with the combination, i.e. a weekly regimen for S64315 and a daily regimen for azacitidine over 7 days.

The schedule was as follows:

- A 2-week LID period with S64315 fixed LID1 of 25 mg on Day -13 (D -13) and S64315 fixed LID2 of 50 mg on D -6, followed by
- 28-day cycles (Cx) of combination treatment period with S64315 administered on CxD2, CxD9, CxD16 and CxD23, and 75 mg/m² of azacitidine administered daily for 7 days from CxD1 to CxD7 followed by a rest period of 21 days.

On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine was administered 2 hours (±10 min) prior to S64315. The starting dose of S64315 after the lead-in period was 50 mg. A panel of doses from 25 mg (-1) and up to 250 mg could have been explored according to the dose escalation process of the Bayesian Logistic Regression Model (BLRM).

During the dose escalation phase, at each new dose level, the IMPs were first administered to one patient. If no medically important or life-threatening toxicity occurred during a 1-week observation period, the subsequent patients were allowed to start treatment without further delays between subsequent patients. The dose increase between 2 dose levels was guided by the observed toxicities.

An adaptive BLRM with escalation with overdose control (EWOC) was used to guide the dose escalation of S64315 in combination with azacitidine. The dose escalation only concerned S64315. The purpose of the dose escalation Phase I part was to determine the safety profile, the MTD, the DLTs and the RP2D in patients with relapsed/refractory AML. All available data on DLTs (assessed from the LID period and up to the end of Cycle 1) were used for updating the model. Before making a decision regarding dose escalation, the minimum number of patients required from a cohort must have been treated with one cycle of the combination and be fully evaluable for treatment-related toxicities according to the minimum requirements for inclusion in the DLTES. If a patient was not eligible for inclusion in the DLTES, this patient must have been replaced.

Comparator: Not applicable

Duration of treatment:

Screening period/inclusion: within 15 days before starting LID period.

S64315 lead-in dose period: 2 weeks. S64315 LID1 was administered on D-13 at 25 mg and LID2 on D-6 at 50 mg. LID1 and LID2 doses were fixed all along the study.

Combination treatment period:
The planned duration of combination treatment was until disease progression, unacceptable toxicity, treatment failure or patient's/physician's decision. In case of myelosuppression within the context of non-active AML, a 4-week interruption of administration of one or both IMP(s) was allowed for bone marrow recovery at the investigator's discretion after discussion and approval from the Sponsor. If the patient was benefiting from the study treatment according to the investigator's judgment and if it was in the patient's best interest to continue the combination of S64315 with azacitidine, the patient could remain on study treatment. In case the patient became eligible for transplant, patient's treatment discontinuation should be left at the investigator's decision.

Withdrawal and Follow-up (FU) period:
- Withdrawal visit (WV): up to 28 days after the last dose of IMP.
- Post-withdrawal FU: after the WV, a contact or telephone call was done every 3 months (up to 6 months), except in case of consent withdrawal for the dose escalation Phase I part.

Statistical methodology:

Analysis Sets:
- **Screened Set:** All patients who signed the informed consent form (ICF), whether they were included or not at the end of the screening period.
- **Included Set (IS):** All patients who signed the ICF, whose eligibility was confirmed at the end of the screening period, and who were included in the dose escalation Phase I part of the study.
- **Safety Set (SS):** All patients who signed the ICF and who received at least one dose of IMP (S64315 or azacitidine) during the dose escalation Phase I part of the study.
- **DLT-Evaluable Set (DLTES):** All patients from the SS who were evaluable for DLT according to the DLT assessment at the end of Cycle 1. A patient was not considered evaluable for DLT if he/she:
  - Permanently discontinued treatment before C1D28 for reasons other than DLT.
  - Did not undergo a DLT assessment at the end of Cycle 1.
  - Did not receive the minimum exposure criteria i.e., minimum number of doses according to the dose administration schedule of both IMPs prescribed from study entry to DLTs assessment visit (end of Cycle 1 D28), unless treatment was stopped for a DLT.
  - Did receive more than the assigned IMP doses from study entry to DLT occurrence during the DLT assessment period, non-evaluability criteria would have been reassessed by Sponsor and investigator.

Study patients (disposition, baseline characteristics, and follow-up): Descriptive statistics were provided by dose level and overall.

Pharmacokinetic (PK) analysis: PK parameters were estimated by non-compartmental analysis (NCA) on the individual plasma concentration and actual time data of S64315 and azacitidine after administration of IV S64315 and SC azacitidine. Details about the PK analyses are described in the PK Report.

Safety analysis: All safety analysis was performed on the SS (resp. DLTES for DLT analysis) by treatment dose level group and overall.

Summary of results and Conclusions

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 31 patients were screened, 29 patients were selected, and 17 patients were included in the study. All included patients were treated. The overall disposition of patients is presented in **Table 1**.

Table 1 - Overall patient disposition – Included Set (N = 17)

Status		50 mg of S64315 + 75 mg/m² of azacitidine (N = 5)	100 mg of S64315 + 75 mg/m² of azacitidine (N = 7)	190 mg of S64315 + 75 mg/m² of azacitidine (N = 5)	All (N = 17)
Included	**n**	**5**	**7**	**5**	**17**
Withdrawn on treatment due to	**n (%)**	**5 (100)**	**7 (100)**	**5 (100)**	**17 (100)**
adverse event	n (%)	2 (40.0)	1 (14.3)	2 (40.0)	5 (29.4)
progressive disease	n (%)	2 (40.0)	3 (42.9)	3 (60.0)	8 (47.1)
other, physician decision	n (%)	1 (20.0)	3 (42.9)	-	4 (23.5)

N: number of patients by dose combination
n: number of patients with non-missing data.
Percentages are based on n.

Included and Safety Sets consisted of 17 patients, each, and DLTES of 13 patients.

BASELINE CHARACTERISTICS

For included patients, the mean ± Standard Deviation (SD) age was 64.9 ± 12.5 years, and most patients (58.8%) were between [65-85[years. More than half of the patients were male (58.8%), and all were white.
Overall, 17 patients were included with AML disease and classified as follows: 10 patients (58.5%) as 'AML, not otherwise specified', 5 (29.4%) as 'AML with myelodysplasia-related changes', 1 (5.9%) as 'AML with recurrent genetic abnormalities', and 1 (5.9%) as 'therapy-related myeloid neoplasms'. Eleven patients (64.7%) had de novo AML and 6 patients (35.3%) had secondary AML. The mean disease duration since diagnosis was 1.6 ± 2.4 years. At entry in the study, 9 patients (52.9%) were in relapse, 7 (41.2%) were refractory to the previous treatment, and 1 (5.9%) was treatment naive. The cytogenetic risk category was adverse for 8 patients (50%), intermediate for 7 (44%), and favourable for 1 (6%). Also, 1 patient was included with cytogenetic risk category unknown.
Among the 15 patients with a bone marrow (BM) blast value at baseline, 2 patients (13.3%) had a BM blast value in the range of [5-20%[, 6 patients (40.0%) had a value in the range of [20-50%[and 7 patients (46.7%) had a value of ≥ 50%.
With regards to number of treatment lines for AML, 1 patient (5.9%) had no previous treatment line. For those who had previous lines of treatment, 7 patients (41.2%) had 1 line, 3 patients (17.6%) had 2 lines, 3 patients (17.6%) had 3 lines, and 3 patients (17.6%) had 4-7 lines.

EXTENT OF EXPOSURE

The mean ± SD treatment duration with S64315 was 15.4 ± 18.4 weeks ranging from 1.0 to 57.4 weeks. Treatment duration with azacitidine was similar to the one with S64315.
During the overall treatment duration, the mean relative dose intensity (RDI) for S64315 was 80.4% ± 12.0% and most of the patients (82.4%) had an RDI between 65% and 100%. During the overall treatment duration, the mean RDI for azacitidine was 114.8 ± 54.5%: 8 patients (50.0%) had an RDI ≥ 100% and 6 patients (37.5%) had an RDI between 85% and 100%.

EFFICACY RESULTS

Efficacy endpoints

In the context of the study discontinuation and abbreviated clinical study report, no statistical analyses were planned in the Statistical Analysis Plan (SAP) for efficacy.

Pharmacokinetic results

S64315 was administered once weekly at dose levels of 50 mg, 100 mg and 190 mg by IV infusion in combination with azacitidine at daily doses of 75 mg/m² subcutaneously over 7 days. The infusion duration of S64315 ranged from 0.68 hours to 2.47 hours depending on the patient's weight and toxicities observed during the infusion.

For S64315, an increase in exposure was observed with the increased doses from 50 to 190 mg. High variability was observed around the end of infusion timepoint probably due to several imprecisions during sample collection i.e., the end of infusion timepoint often collected out of the time window recommended in the protocol. Maximal concentrations were not always observed at the end of infusion. Area under the concentration-time curve from time zero to time of last measurable concentration also increased with the increased doses. Very few data (n = 1) were available at Day 9 across the cohorts; therefore, no conclusions can be made regarding the accumulation between Day 2 and Day 9. Overall, PK profiles seemed to be consistent between Day 2 and Day 9 which suggests that the co-administration of S64315 with azacitidine did not seem to have an impact on S64315's PK. The mean geometric elimination half-life of S64315 ranged from 2.7 to 5.4 hours across the cohorts.

Azacitidine, was rapidly absorbed after subcutaneous administration (T_{max} ranging from 0.22 hours to 0.52 hours across all cohorts and both days). Azacitidine PK parameters and their observed moderate to high variability were consistent with the literature data. As expected, the co-administration of S64315 with azacitidine did not seem to have an impact on the PK of azacitidine.

SAFETY RESULTS

Dose-limiting toxicities

During dose escalation, S64315 was tested in combination with azacitidine at dose levels ranging from 50 to 190 mg for S64315 and 75 mg/m^2 for azacitidine. At the end of Cycle 1, 13 patients were evaluable for DLTs, out of whom 2 patients experienced DLTs: 1 patient in the S64315 100 mg + 75 mg/m^2 azacitidine dose level group and 1 patient in the S64315 190 mg + 75 mg/m^2 azacitidine dose level group.

Treatment-emergent adverse events (TEAEs)
Main results for AEs in the SS are described in **Table 2**.

Table 2 - Overall summary of treatment-emergent adverse events in the Safety Set

	ALL (N = 17) n (%)
Participants having reported at least one:	
TEAE	17 (100)
Treatment-related* TEAE	14 (82.4)
Serious TEAE (including death)	16 (94.1)
Treatment-related* serious TEAE (including death)	3 (17.6)
Severe (Grade ≥ 3) TEAE	17 (100)
Treatment-related* severe (Grade ≥ 3) TEAE	4 (23.5)
TEAE leading to treatment withdrawal	6 (35.3)
TEAE leading to dose reduction	1 (5.9)
TEAE leading to dose delay	6 (35.3)
TEAE leading to temporary IMP interruption	11 (64.7)
Participants who died during the study	
During the treatment and follow-up period	9 (52.9)
During treatment period	3 (17.6)
Treatment-related* TEAE leading to death	-

** related to S64315 or azacitidine*
IMP investigational medicinal product, TEAE treatment-emergent adverse event.
Note 1 patient experienced an SAE before the first IMP intake, and 2 patients experienced SAEs after 30 days from the last IMP intake (non- TEAEs).

All patients reported at least one TEAE. The ***most frequently affected system organ class (SOC) (≥ 50% of patients overall)*** were Investigations (82.4%), Infections and infestations (64.7%), Blood and lymphatic system disorders (52.9%) and Gastrointestinal disorders (52.9%).

The ***most commonly reported TEAEs (≥ 20% of the patients overall)*** were ALT increased (10 patients, 58.8%), AST increased, and febrile neutropenia (7 patients, 41.2%, each), constipation (6 patients, 35.3%), and diarrhoea, hypokalaemia, hypophosphatemia, and oedema peripheral (4 patients, 23.5%, each).

All patients reported at least one ***severe TEAE***. The ***most commonly reported severe TEAEs (≥ 25% of the patients overall)*** were febrile neutropenia (7 patients, 41.2%), and ALT increased (5 patients, 29.4%).

Overall, 14 patients (82.4%) experienced at least one ***treatment-related TEAE***. The ***most commonly reported treatment-related TEAEs (≥ 10% of the patients overall)*** were ALT increased (6 patients [35.3%]), AST increased (5 patients [29.4%]), constipation (4 patients [23.5%]), and blood bilirubin increased, troponin T increased, diarrhoea, and nausea (2 patients [11.8%], each). Overall, 4 patients (23.5%) experienced at least one severe treatment-related TEAE: AST increased (2 patients [11.8%]), and ALT increased, blood bilirubin increased, troponin I increased, neutropenia, and thrombocytopenia (1 patient, 5.9%, each).

TEAEs leading to treatment withdrawal were reported in 6 patients (35.3%). Each of those TEAEs were reported in no more than one patient (5.9%) except ALT increased which was reported in 2 patients (11.8%). All TEAEs leading to treatment withdrawal were severe events. Overall, serious TEAEs leading to treatment withdrawal were reported in 4 patients (23.5%). Each of those TEAEs were reported in no more than one patient (5.9%). All TEAEs leading to treatment withdrawal were not treatment-related, except for one serious troponin I increased event.

Overall, 1 patient (5.9%) reported at least one ***TEAE leading to dose reduction***. This patient was in the 50 mg S64315 + 75 mg/m^2 azacitidine dose level group and had 2 TEAEs of neutropenia leading to dose reduction of azacitidine only.

TEAEs leading to dose delay were reported in 6 patients (35.3%). Each of those TEAEs leading to dose delay were reported in no more than one patient except for ALT increased (2 patients, 11.8%).

A total of 35 ***serious TEAEs*** were experienced by 16 patients (94.1%) during the study. The serious TEAEs reported in at least 2 patients overall were febrile neutropenia (7 patients, [41.2%]), pneumonia and sepsis (2 patients, [11.8%], each). Overall, 3 patients (17.6%) reported at least ***one serious treatment-related TEAE***: neutropenia, ALT increased, AST increased, blood bilirubin increased and troponin I increased (1 patient [5.9%] each).

A total of 9 ***deaths*** (52.9%) were reported during the study: 3 patients (17.6%) died during the treatment period and 6 (35.3%) during the FU period. None of the deaths were considered treatment related.

Laboratory tests

For ***haematological gradable parameters***, treatment-emergent severe (Grade ≥ 3) abnormal values were detected for low leukocytes (12 patients [70.6%]: 2 patients [11.8%] rated Grade 3 and 10 patients [58.8%] Grade 4), low haemoglobin (10 patients [58.8%]: all Grade 3), low lymphocytes (9 patients [52.9%]: 3 patients [17.6%] Grade 3 and 6 patients [35.3%] Grade 4), low platelets (8 patients [47.1%]: all Grade 4), and low neutrophils (5 patients [29.4%]: all Grade 4).

For ***blood biochemical gradable parameters***, the most frequent treatment-emergent severe abnormal values (≥ 10% of overall patients) were observed for low potassium and high ALT (4 patients [23.5%], each), low ionized calcium (2 patients [18.2%]), high AST (3 patients [17.6%]) and high gamma-glutamyltransferase (2 patients [11.8%]).

Other safety evaluation

Vital signs, clinical examination and ECOG performance status

Overall, the mean ± SD change from baseline in highest heart rate value was 22.6 ± 12.5 beats per minute (bpm) with worst highest value on treatment of 95.5 ± 14.4 bpm.

The majority of patients (64.8%) had ECOG performance status maintained on treatment and 6 patients had worsening of their ECOG performance.

Electrocardiogram

No patient had a clinically significant treatment-emergent ECG abnormality. QTc interval corrected with Fridericia's (QTcF) values within]450-480] ms were detected on treatment in 1 patient (5.9%). A QTcF change from baseline within]30-60] ms was detected in 4 patients (23.5%) overall.

LVEF

At baseline, all patients had an LVEF ≥ 50%. All patients assessable for LVEF under treatment (n = 10) had worst lowest values ≥ 50%. The mean ± SD change from baseline was -7.4% ± 9.3% (ranging from -22% to 8%).

Biomarkers assessments

For **blood cardiac markers**, the most frequent emergent out-of-reference range values were detected for high brain natriuretic peptide (50.0%).

Conclusion:

This was an international, open-label, multicentre, non-randomised, non-comparative Phase I/II study aimed to characterize the safety profile (including DLT, MTD), tolerability, and to determine the RP2D of intravenously administered S64315 in combination with azacitidine in patients with AML.

A total of 17 patients were treated with a 2-week S64315 LID period followed by 28-day cycles with the combination of a weekly regimen for S64315 (tested at 50 mg, 100 mg and 190 mg, IV) and a daily regimen for azacitidine (75 mg/m², SC) over 7 days.

Two patients reported at least one DLT which were ALT increased, AST increased, blood bilirubin increased for 1 patient and troponin I increased for the other patient (all Grade 3). The MTD could not be determined.

During the dose escalation, the Sponsor decided to discontinue the study for strategic reasons. This decision was not a consequence of any safety concerns.

In overall treated patients, the most common treatment-related TEAEs were ALT increased, AST increased, constipation, blood bilirubin increased, troponin T increased, diarrhoea and nausea. The only severe treatment-related TEAE reported in more than one patient was AST increased. All serious treatment-related TEAEs were reported in no more than one patient. None of the reported TEAEs leading to death were related to study treatment.

Date of the report: 09 February 2024