2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France **Local Sponsor: Laboratorios Servier, S.L., Avenida de los Madroños, 33 - 28043 Madrid - Spain**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** S64315 (MIK665)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Phase I, international, multicentre, open-label, non-randomised, non-comparative study of intravenously administered S64315, a Mcl-1 inhibitor, in patients with Acute Myeloid Leukaemia (AML) or Myelodysplastic Syndrome (MDS)
Protocol No.: CL1-64315-001
EudraCT No.: 2016-003768-38
The description of the study protocol given hereafter includes the modifications implemented through the 8 substantial amendments to the protocol.

International coordinator: [redacted]

Study centres:
Four countries included 40 patients: Australia (n = 13), France (n = 11), Spain (n = 10) and the United States of America (USA) (n = 6).

Publication (reference):
Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 17 March 2017 (first visit first patient) Completion date: 11 May 2020 (last follow-up visit last patient)	Phase I

Objectives:

Primary objectives:
To determine the safety profile (including Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD)(s)) and tolerability of S64315 in patients with AML, and MDS, and determine the Recommended Phase 2 Dose (RP2D).

Secondary objectives:

- To determine the pharmacokinetic (PK) profile of S64315 and potential metabolite(s) in plasma and urine.
- To evaluate preliminary anti-neoplastic activity of S64315 using the response criteria proposed by 'Clinical Application and Proposal for Modification of the International Working Group response criteria in myelodysplasia' (Cheson *et al.*, 2006) and the 'Revised Recommendations of the International Working Group for diagnosis standardisation of Response Criteria Treatment outcomes and reporting standards for therapeutic trials in AML' (Cheson *et al.*, 2003).

Exploratory objectives:

- To determine the pharmacodynamic (PD) profile of S64315 according to:
  - The biological activity of S64315.
  - The relationship between the expression level of Bcl-2 family members in blasts (from blood, and bone marrow samples) and the anti-neoplastic activity of S64315.
  - The relationship between the anti-neoplastic activity of S64315 and genomic aberrations in the Bcl-2 gene family and the other cancer related genes.
  - Identification of genetic abnormalities potentially induced by S64315.
  - Target engagement by S64315 (Arm A: only in expansion part; Arm B: in both dose escalation and expansion parts).
- To assess pharmacogenomics (PG), inter-patient variation in genes encoding for proteins involved in absorption/distribution/metabolism/excretion.
- To explore any potential PK/PD relationship for safety and efficacy.

Methodology:
This was an international, multicentre, open-label, non-randomised, non-comparative phase I study, with a Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) to guide the dose escalation and determine the MTD(s) and/or recommended dose for expansion (RDE).

This study was planned to explore two different administration schedules:

- Arm A: S64315 administered once a week (QW) with a dose escalation in patients with AML or MDS. An alternative regimen [redacted] could be tested, depending on the results observed in the initial arm A (QW) dose-escalation phase.
- Arm B: S64315 administered twice a week (BIW) with a dose escalation in patients with AML or MDS. Alternative BIW regimen could be tested, depending on the results observed in the arm B dose-escalation phase.

Following determination of the MTD(s) and/or RDE, an expansion phase was planned in each arm (A and B).

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

In August 2019, due to the occurrence of cardiotoxicity in AML patients treated with S64315, the Food and Drug Administration (FDA) requested the partial clinical hold of the studies conducted in the USA with S64315 and the conduction of a benefit-risk evaluation. The Sponsor also decided to proactively extend this recruitment halt to all countries participating in the study.

Following the assessment of the benefit-risk of S643145 as single agent in AML/MDS patients (no objective response observed, even at the maximum tested dose of 500 mg where 3 out of 4 patients had experienced a DLT), the Sponsor I.R.I.S decided to discontinue the development of MIK665 (S64315) as monotherapy in AML/MDS patients and therefore to discontinue this study (last visit last patient: 11 May 2020).

Only the arm A dose escalation was conducted, and the corresponding dose expansion part of the study was not initiated. On the date of the partial clinical hold, no patient was receiving treatment and 5 patients were on-going in the follow-up period and were followed according to the clinical study protocol.

In this context, an **abbreviated clinical study report** was written.

Number of patients:
Planned: a maximum of 80 patients.
Included: 40 patients (Arm A).

Diagnosis and main criteria for inclusion:

- Male or female aged ≥ 18 years.
- Patients with cytologically confirmed and documented de novo, secondary or therapy-related AML as defined by World Health Organisation (WHO) 2016 classification, excluding acute promyelocytic leukaemia (APL, French-American British M3 classification):
  - With relapsed or refractory disease without established alternative therapy or
  - Secondary to MDS treated at least by hypomethylating agent and without established alternative therapy or
  - ≥ 65 years not previously treated for AML and who are not candidates for intensive chemotherapy nor candidates for established alternative chemotherapy

  OR

  Patients with cytologically confirmed and documented MDS as defined by WHO 2016 classification, in relapse or refractory after previous treatment line including at least one hypomethylating agent, and had ≥ 10% bone marrow blasts and who were not candidate for any established alternative therapy.
- Patients having an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
- Patients having circulating white blood cells (WBC) < 10.10^9/L.
- Patients having adequate renal function defined as serum creatinine ≤ 1.5 x upper limit of normal laboratory reference range (ULN) or calculated creatinine clearance (determined by modification of diet in renal disease (MDRD) > 50 mL/min/1.73 m^2.
- Patients having lactate dehydrogenase (LDH) < 2 x ULN and serum creatine kinase (CK)/ creatine phosphokinase (CPK) ≤ 2.5 x ULN.
- Patients having adequate hepatic function defined as:
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 x ULN.
  - Total bilirubin level ≤ 1.5 x ULN, except for patients with known Gilbert's syndrome (confirmed by the UDP-glucuronosyltransferase (UGT) 1A1 polymorphism analysis), who were excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN.

Test drug:

Two administration schedules were initially planned to be tested in two separated arms:

- Arm A: S64315 was administered intravenously (IV) once a week (Day 1, Day 8, Day 15 of each 21-day cycle) via IV infusion within 30 minutes. The duration of infusion could be extended up to 3 hours depending on the patient's weight and toxicities observed once every week.
- Arm B: S64315 was planned to be administered IV twice a week, for three weeks, followed by one week off (Day 1, Day 4, Day 8, Day 11, Day 15, Day 18 of each 28-day cycle) via IV infusion within 30 minutes. The duration of infusion could be extended up to 3 hours depending on the patient's weight and toxicities observed twice a week.

In the end, only the arm A (once a week regimen) was evaluated.

Alternative dosing regimens planned to be explored based on the observed clinical safety and preliminary PK data [redacted] were not carried out in the end.

Batch numbers: S64315 organic concentrate: L0065842, L0068618, L0070229, L0071032, L0072253, L0074009, L0074389, L0074390.

Precaution for the first S64315 administration

Each patient had to be hospitalised for at least 3 days in arm A (and at least 5 days in arm B) and in case of intra-patient dose escalation, to enable close in-patient tumour lysis syndrome (TLS) monitoring and management, in accordance with institutional guidelines and published criteria.

Dose allocation methodology

Two separate dose escalations were planned in arm A and B. In each arm, an adaptive BLRM with EWOC was planned to guide dose escalation and estimate the MTD(s) based on the occurrence of DLTs during cycle 1.

In each arm, the MTD was to be the highest drug dosage that is unlikely (< 25% posterior probability) to cause DLT in more than 33% of the treated patients in the first cycle of S64315 treatment. A minimum of 3 patients who meet the eligibility criteria was enrolled in each cohort, and the total number of patients per cohort (3 to 6 evaluable patients) depended on safety and PK data.

The first weekly dose tested in arm A was 50 mg, and then a panel of doses from 50 to 1350 mg could be tested according to the dose allocation process of the BLRM. Intermediate doses could be proposed depending on available results during the study.

The starting dose in arm B should have been based on the data already collected in the once a week schedule (arm A). In any case it should not exceed half of the highest dose tested considered safe in the once a week schedule (arm A). A panel of doses from 50 to 400 mg twice a week could be tested according to the dose allocation process of the BLRM. Intermediate or lower doses could be proposed depending on available results during the study.

Irrespective of the treatment arm, before testing a new dose level, an end of cohort meeting (EoC) between the Sponsor, the coordinators and the investigators was organised to discuss the toxicities in terms of DLT, safety and PK data observed in all patients, and to decide jointly the next dose level to be tested.

A minimum of 6 evaluable patients should be treated at the MTD(s) in each arm.

The planned dose expansion part of the study was not initiated.

DLT assessment

Toxicities were assessed according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

A DLT was defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications, that occurred during the first cycle following the first dose of S64315, and that met any of the criteria defined in the study protocol.

Comparator:

Not applicable.

Duration of treatment:
The planned duration of treatment was until disease progression. Patients were discontinued from treatment with the study drug earlier due to unacceptable toxicity and/or investigator's/patient's decision. The total number of cycles was at the discretion of the investigator. If the patient was clearly benefiting from the study treatment and in the opinion of the investigator it was in the patient's best interest to continue S64315, the patient remained on study treatment.

A patient was discontinued from the study if the study drug was interrupted for more than 21 days for any reason (except in case of myelosuppression). However, for patients with left ventricular ejection fraction (LVEF) decline, study drug interruptions of up to 35 days were permitted.

Criteria for evaluation:
Efficacy measurements:

- **Patients with AML** were evaluated for response based on the "Revised Recommendations of the International Working Group for diagnosis standardisation of Response Criteria Treatment outcomes and reporting standards for therapeutic trials in AML".
- **Patients with MDS** were evaluated for response based on the "Clinical Application and Proposal for Modification of the International Working Group response criteria in myelodysplasia".
- Haematological parameters in peripheral blood and bone marrow (BM) blasts in Bone Marrow Aspirate (BMA) were assessed at baseline and during the study.

Safety measurements:
The safety criteria were DLTs at the end of cycle 1, MTD assessment, adverse events (grading according to CTCAE v 4.03), laboratory tests (haematology, blood biochemistry, thyroid function, coagulation parameters, hepatitis markers, urinalysis), weight, ECOG performance status, vital signs (blood pressure, heart rate, temperature), 12-lead ECG parameters (corrected QT interval according to Fridericia's formula (QTcF) prolongation), cardiac function (LVEF).
Following cardiac adverse events observed at the dose of 500 mg QW, management of cardiac toxicity was implemented in the study protocol through the amendment n°8 dated 11 June 2019. The cardiac parameter troponin was closely monitored. In case of troponin increase observed after the two first infusions, it was recommended to assess troponin at 48h and 72h post-infusion and after each subsequent infusion (before discharge and beyond, if needed), on a regular basis. In addition, hepatic safety was to be closely monitored.
Nausea/vomiting prophylaxis was strongly recommended before each S64315 infusion, and diarrhoea was to be closely monitored according to routine practice and applicable guidelines.
Also, management of TLS was reinforced through the study protocol amendment n°8, with the implementation of a prophylactic treatment and laboratory assessments at each S64315 infusion.

Pharmacokinetic measurements:
Concentrations of S64315 and potential metabolite(s) were determined in plasma and urine.

Pharmacodynamic measurements:
Blood samples and bone marrow samples (BMA and BM biopsy) were taken at baseline and during the study to assess the exploratory biomarkers.
The exploratory analysis is presented in a separate report and included as biomarkers: Bcl-2 family members protein expression (blood, BM), genomic alterations of Bcl-2 family members and cancer related genes (blood, BM), Mcl-1/Bak complexes measurement in blood, DNA/RNA sequencing in saliva, chromosomal abnormalities (in karyotypes of AML and MDS patients). Only the evolution over time of bone marrow (BM) blasts are presented in the present abbreviated clinical study report.

Pharmacogenomic measurements (optional): Pharmacogenomic analysis, on blood, of inter-patient variation in genes encoding ADME involved proteins.

Statistical methods:

Analysis Sets:
Safety Set (SS): all patients having received at least one dose of S64315.
DLT Evaluable Set (DLTES): all patients of the SS who were evaluable for DLTs according to the DLT assessment at the end of cycle 1. A patient was not considered evaluable if:

- He/she discontinued treatment during the DLT assessment period for reasons other than DLTs.
- He/she did not receive the minimum number of doses according to the regimen of test drug prescribed doses from study entry to the DLT assessment visit, unless treatment was stopped for a DLT.
- He/she did receive more than the assigned test drug doses from study entry to DLT occurrence during the DLT assessment period.

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

Efficacy analysis: efficacy analysis was carried out in the SS. The best overall response (BOR), overall response rate (ORR), time to BM blast relative change and other observations related to efficacy were provided in tables or listings for each dose level and overall. In addition, a waterfall plot of the best BM blast relative change from baseline according to the dose level was presented during the treatment period for AML patients.

Safety analysis: descriptive statistics were provided in the SS (except for DLT analysis in the DLTES) by dose level and overall.

Pharmacokinetic analysis: PK analysis is described in a separate PK report.

Pharmacodynamic analysis: analyses for BM blasts were provided for patients by dose level and overall in the Bone Marrow Safety Set (BMSS) (this set corresponded to all SS patients with an analysable value based on BM blasts). The best decrease as well best relative decrease and time-point related to best decrease were presented. The best decrease was estimated (estimate and 95% Confidence Interval (CI) using the Hodges & Lehmann one-sample non-parametric approach and tested using the Wilcoxon signed-rank test (only for the overall population).

Pharmacogenomic analysis: PG analysis is not presented in this study report.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Table 1 - Overall disposition of patients and analysis sets

Status		**S64315 (N = 40)**
Included	**n**	**40**
In conformity with the protocol	n (%)	5 (12.5)
With protocol deviation(s) before or at inclusion	n (%)	35 (87.5)
Withdrawn on treatment due to	**n**	**40**
Progressive disease	n (%)	21 (52.5)
Physician decision	n (%)	10 (25.0)
Adverse event	n (%)	8 (20.0)
Non-medical reason	n (%)	1 (2.5)
Withdrawn on follow-up due to*	**n**	**27**
Death	n (%)*	27 (100)
Follow-up completed	**n**	**10**

N Number of patients overall
n number of patients
*Percentages are based on N except * based on the number of patients included in the follow-up*
Of note, 3 patients did not perform the follow-up i.e. 2 patients included but not treated and 1 patient who withdrew consent at the end of cycle 1.

			S64315							
Analysis sets			**50 mg**	**100 mg**	**200 mg**	**250 mg**	**300 mg**	**400 mg**	**500 mg**	**Not treated**
Included Set	**(N = 40)**	n (%)	6 (15.0)	6 (15.0)	5 (12.5)	6 (15.0)	7 (17.5)	4 (10.0)	4 (10.0)	2 (5.0)
SS	**(N = 38)**	n (%)	6 (15.8)	6 (15.8)	5 (13.2)	6 (15.8)	7 (18.4)	4 (10.5)	4 (10.5)	-
DLTES	**(N = 32)**	n (%)	6 (18.8)	5 (15.6)	5 (15.6)	5 (15.6)	5 (15.6)	3 (9.4)	3 (9.4)	-
BMSS	**(N = 37)**	n (%)	6 (16.2)	6 (16.2)	4 (10.8)	6 (16.2)	7 (18.9)	4 (10.8)	4 (10.8)	-

Percentages are based on N

In the Included Set (IS), 38 out of the 40 patients were treated with S64315 and assigned to arm A (once a week regimen). In the end, arm B and the alternative planned regimens were not finally tested.

BASELINE CHARACTERISTICS

For included patients, the mean age was 65.7 ± 16.3 years (median age was 70.5 years), and the majority of the patients were male (57.5%), and White (85.0%). Among included patients, 39 patients had AML and 1 patient had MDS.

Among AML patients, 19 were diagnosed 'AML with myelodysplasia-related changes', 12 'AML, not otherwise specified', 5 'therapy-related myeloid neoplasms' and 3 'AML with recurrent genetic abnormalities'. Twenty patients presented de novo AML and 19 patients had secondary AML (mainly secondary to MDS in 73.7% of the patients). At the time of inclusion, the mean disease duration since diagnosis was 1.8 ± 2.6 years. At study entry, 51.3% of the patients were refractory to previous treatment, 35.9% were in relapse and 12.8% were treatment naive. Overall, the treatment-free interval was 63.4 ± 51.9 days. The cytogenetic risk category was adverse for 43.2% of the patients, intermediate for 29.7%, favourable for 10.8%.and not assessable for 16.2%.

One patient was diagnosed with MDS disease with excess blasts, with a disease duration of 1.6 years and a treatment free interval of 123 days. At study entry, the status of the disease of this patient was in relapse and the cytogenetic risk category was poor.

The majority of included patients had a baseline BM blasts value in the range [20-50[% (44.1%) and ≥ 50% (35.3%). A total of 2.9% had a baseline BM blasts value < 5%, and 17.7% had a baseline BM blasts value in the range [5-20[%.

The majority of included patients (87.5%) received at least one previous therapy mostly drug treatment only (70.0%), and graft with drug treatment (17.5%). Among the 40 included patients, 12.5% did not received previous therapy, 22.5% received one line of prior treatment, 25.0% 2 lines, 37.5% between 3-7 lines and 2.5% (*i.e.* 1 patient) more than 7 lines.

Most of included patients (94.9%) had an ECOG performance status at baseline ≤ 2 (mainly equal to 1 in 66.7% of the patients), and 2 patients (5.1%) had an ECOG performance status equal to 3 at baseline (but their ECOG status was equal to 2 at inclusion).

Due to the small number of patients per S64315 dose level group, no comparative observations between the S64315 dose level groups could be carried out.

This Phase I study was conducted in patients with AML/MDS disease, for which baseline characteristics were in accordance with the target population defined in the study protocol.

EXTENT OF EXPOSURE

The mean treatment duration with S64315 was 6.5 ± 5.2 weeks (median = 5.5 weeks), ranging from 1.0 week to 24.1 weeks. Patients received on average 2.5 ± 1.6 cycles (median = 2.0), ranging from 1 to 8 cycles. Overall, 4 patients (10.6%) had at least one cycle delayed, and 2 patients (5.3%) had one dose reduced.
The mean relative dose intensity (RDI) was 87.6 ± 17.7% (median = 97.5%) and most of the patients (76.3%) had a RDI between 65% and 100%.

EFFICACY RESULTS

Efficacy was part of the secondary objectives of the study.

- **Best Overall Response**
  For most of the patients with AML (81.1%), the BOR was treatment failure, and was missing (*i.e.* best response missing or early treatment assessment under the studied period) for the other patients (18.9%), in the SS. For the patient with MDS, the BOR was progressive disease. No ORR could be determined (*i.e.* 0% of the patients).
- **Time to BM blast relative change**
  In the SS, the mean time to BM blast relative change ≥ +50% (change referring to an increase of BM blasts) observed for 12 patients was 6.8 ± 5.2 weeks and the mean time to BM blast relative change ≤ -50% (change referring to a decrease of BM blasts) observed for 4 patients was 3.7 ± 1.5 weeks.
- **Change in tumour assessment: evolution over time of BM blasts**
  In the SS, best relative changes from baseline of BM blasts during the treatment period ranged from -92.0% to 215.4% (mean best relative change from baseline = 21.7 ± 78.8%, and median = 11.1%).

SAFETY RESULTS

- **Dose Limiting Toxicities**

During dose escalation, S64315 was tested at doses from 50 mg to 500 mg in the arm A, once a week schedule. At the end of cycle 1, 32 patients were evaluable for DLTs out of whom 7 patients experienced DLTs at 50 mg, 100 mg, 300 mg, 400 mg and 500 mg. At the highest S64315 dose level of 500 mg, 3 patients experienced DLTs related to cardiac disorders: one Grade 1 troponin T increased in a patient with AML, one Grade 2 cardiac failure in a patient with AML and one Grade 4 blood CPK MB increased in the patient with MDS. Consequently, the BLRM model recommended de-escalating to a weekly dose of 300 mg.

- **Emergent adverse events (EAEs)**

Main results for adverse events in the SS are described in Table 2.

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

		S64315 (N = 38)
Patients having reported at least one:		
EAE	n (%)	38 (100)
Treatment-related EAE	n (%)	34 (89.5)
Severe* EAE	n (%)	37 (97.4)
Treatment-related	n (%)	17 (44.7)
Serious AE (including death)	n (%)	31 (81.6)
Serious EAE (including death)	n (%)	31 (81.6)
Treatment-related	n (%)	13 (34.2)
EAE leading to treatment withdrawal	n (%)	9 (23.7)
Severe* EAE	n (%)	6 (15.8)
Serious EAE	n (%)	5 (13.2)
Treatment-related EAE	n (%)	4 (10.5)
Treatment-related serious EAE	n (%)	3 (7.9)
Treatment-related severe* EAE	n (%)	3 (7.9)
Patients who died during the study	n (%)	27 (71.1)
During treatment period	n (%)	2 (5.3)
During the follow-up period	n (%)	25 (65.8)

**CTCAE grade 3 or 4*

All patients reported at least one EAE. The ***most frequently affected System Organ Classes (SOCs) (≥ 30% of the patients overall)*** were Gastrointestinal disorders (84.2%), Investigations (81.6%), Blood and lymphatic system disorders (71.1%), Infections and infestations (47.4%), General disorders and administration site conditions and Metabolism and nutrition disorders (both SOCs: 42.1%).

The ***most commonly reported EAEs (≥ 10% of the patients overall)*** were nausea (60.5%), febrile neutropenia, vomiting (47.4% each), diarrhoea (44.7%), alanine aminotransferase increased (39.5%), neutropenia, troponin I increased (31.6% each), aspartate aminotransferase increased (28.9%), anaemia (26.3%), constipation (18.4%), gamma-glutamyltransferase increased (15.8%), asthenia, blood alkaline phosphatase increased, blood creatine phosphokinase increased, thrombocytopenia, troponin increased (13.2% each), chills, ejection fraction decreased, hyponatremia, malignant neoplasm progression, pyrexia, troponin T increased and tumour lysis syndrome (10.5% each).

Most of the patients (97.4%) reported at least one ***severe EAE***. Blood and lymphatic system disorders was the most frequently affected SOC mostly including the following severe EAEs: febrile neutropenia (47.4% of the patients, with 42.1% Grade 3 and 5.3% Grade 4), neutropenia (28.9%, 2.6% Grade 3 and 26.3% Grade 4), and anaemia (23.7% Grade 3).

Overall, 89.5% of the patients had at least one ***treatment-related EAE***. The most commonly reported treatment-related EAEs (≥ 10% of the patients overall) were nausea (44.7%), vomiting (42.1%), diarrhoea (36.8%), troponin I increased (28.9%), alanine aminotransferase increased (26.3%), aspartate aminotransferase increased (15.8%), blood creatine phosphokinase increased and troponin increased (10.5% each). Of note, the treatment-related EAEs febrile neutropenia (7.9% of the patients), tumour lysis syndrome, troponin T increased and rash maculo-papular (5.3% each) were reported in at least 2 patients in either S64315 dose level group.

Of note, considering the treatment-related EAEs 'troponin increase', 11 patients (28.9%) reported 13 events troponin I increase, 4 patients (10.5%) reported 5 events troponin increase, and 2 patients (5.3%) reported 3 events troponin T increase.

Overall, 44.7% of the patients had at least one ***severe treatment-related EAE***. The most commonly reported severe treatment-related EAEs (≥ 5% of the patients overall) were febrile neutropenia, troponin I increased (7.9% each), neutropenia, anaemia, alanine aminotransferase increased, amylase increased, white blood cell count decreased and tumour lysis syndrome (5.3% each).

Overall, 81.6% of the patients had at least one ***serious EAE including death***. The serious EAEs reported in at least 2 patients in either S64315 dose level group were febrile neutropenia (4 patients, 66.7% in the S64315 50 mg dose level group, 1 patient, 16.7% in the S64315 100 mg dose level group, 1 patient, 20.0% in the S64315 200 mg dose level group, 4 patients, 66.7% in the S64315 250 mg dose level group, 3 patients, 42.9% in the S64315 300 mg dose level group, 2 patients, 50.0% in the S64315 400 mg dose level group, 1 patient, 25.0% in the S64315 500 mg dose level group), and tumour lysis syndrome (1 patient, 16.7% in the S64315 50 mg dose level group, 1 patient, 16.7% in the S64315 250 mg dose level group, 2 patients, 50.0% in the S64315 400 mg dose level group).

A total of 13 patients (34.2%) reported at least one ***treatment-related serious EAE***. The treatment-related serious EAEs were reported in a single patient except febrile neutropenia, troponin I increased and tumour lysis syndrome reported in 2 patients (5.3%) each.

A total of 27 patients (71.1%) **died** during the study. Overall, 2 patients (5.3%) died during the treatment period: one patient in the S64315 50 mg dose level group died due to progressive disease (having 3 EAEs with fatal outcome: malignant neoplasm progression, acute kidney injury and dyspnoea) and one patient in the S64315 100 mg dose level group died due to other reason (having an EAE of septic shock with fatal outcome). All deaths occurring during the treatment period were considered as not treatment-related.
During the follow-up period, 25 patients (65.8%) died: 17 patients for progressive disease and 8 patients for other reason. These deaths affected 4 patients each in the S64315 50 mg, 100 mg, and 200 mg dose level group, 5 patients each in the S64315 250 mg and 300 mg dose level group, 2 patients in the S64315 400 mg dose level group, and 1 patient in the S64315 500 mg dose level group. Of note, 5 of these deaths occurring during the follow-up period were reported as fatal outcome of EAE(s).

EAEs leading to IMP withdrawal were reported in 9 patients (23.7%). Each EAE was only reported in one patient (2.6%) except EAEs alanine aminotransferase increased, which were reported in 2 patients (5.3%, both patients in the S64315 300 mg dose level group).
Treatment-related EAEs leading to IMP withdrawal were reported in 4 patients (10.5%): rectal haemorrhage, colitis ulcerative, troponin I increased, neutropenia, bronchopulmonary aspergillosis, pyrexia, and cardiac failure, reported in one patient (2.6%), each.
Severe EAEs leading to IMP withdrawal, and treatment-related severe EAEs leading to IMP withdrawal were reported in 6 patients (15.8%) and 3 patients (7.9%), respectively.
Serious EAEs leading to IMP withdrawal and treatment-related serious EAEs leading to IMP withdrawal were reported in 5 patients (13.2%) and 3 patients (7.9%), respectively. Each EAE occurred in a single patient (2.6% each).

EAEs led to dose reduction in 2 patients (5.3%), to cycle delay in 7 patients (18.4%), to dose reduction and cycle delay in 2 patients (5.3%), and to temporarily interruption of IMP in 21 patients (55.3%).

- **Laboratory tests**

For **blood biochemical parameters** rated according to the CTCAE version 4.03 grading, emergent severe (Grade ≥ 3) abnormal values were sparsely distributed. The most frequent emergent severe abnormal values (reported in at least 2 patients) were high ALT and low sodium (2 patients, 33.3% in the S64315 50 mg dose level group, each), high amylase (2 patients, 40.0% in the S64315 100 mg dose level group), high GGT (2 patients, 28.6% in the S64315 300 mg dose level group) and high AST (2 patients, 50.0% in the S64315 500 mg dose level group). All were Grade 3, except the following Grade 4 values reported for high lipase (1 patient, 25.0% in the S64315 100 mg dose level group), high glucose (1 patient, 14.3% in the S64315 300 mg dose level group), high CPK (1 patient, 14.3% in the S64315 300 mg dose level and 1 patient, 25.0% in the S64315 500 mg dose level group) and high uric acid (1 patient, 25.0% in the S64315 400 mg dose level group).

Of note, regarding non-gradable biochemical parameters in relation with cardiac toxicity, high troponin I was reported in 50.0% of the patients overall, and high troponin T in 33.3%.

For **blood haematological parameters**, emergent severe abnormal values were detected for low neutrophils (59.3% of the patients: 3.7% of the patients rated Grade 3 and 55.6% Grade 4), low WBC (55.3%: 15.8% Grade 3 and 39.5% Grade 4), low haemoglobin (47.4%: Grade 3), low platelets (42.1%: 7.9% Grade 3 and 34.2% Grade 4) and low lymphocytes (33.3%: 25.9% Grade 3 and 7.4% Grade 4).

Of note, regarding non-gradable haematological parameters, emergent out-of-range values were detected for high monocytes (20.8% of the patients), high leucocytes (15.8%), and high lymphocytes (14.8%).

- **Other safety evaluation**

Vital signs, clinical examination and ECOG performance status

A clinically relevant decrease in mean value over time was detected for weight, the mean worst lowest value on treatment being 67.9 ± 14.3 kg compared to a mean baseline value of 69.5 ± 13.8 kg.

No clinically relevant changes in mean values over time were detected for blood pressure and heart rate.

The majority of the assessable patients had their baseline ECOG performance status maintained during the study (23 patients, 62.2%). A total of 11 patients (29.7%) had a worsening of their ECOG performance status from baseline to treatment period: 6 patients (16.2%) (ECOG 0 to ECOG 1), 3 patients (8.1%) (ECOG 1 to ECOG 2) and 2 patients (5.4%) (ECOG 1 to ECOG 3).

Electrocardiogram

At post-baseline, the QTcF value within]450 ; 480] ms was detected on treatment in 4 patients (10.5%) overall, and a QTcF value within]480 ; 500] ms was detected in 1 patient (2.6%). Of note, one patient had one EAE reported "electrocardiogram QTc prolonged" rated Grade 1.

LVEF

At baseline, all assessable patients had an LVEF ≥ 50%, and under treatment, one patient (2.9%) had an LVEF in the [40 -50% [range and one patient (2.9%) had an LVEF < 40%.

Overall, 4 EAEs 'Ejection fraction decreased' rated according to the NCI CTCAE version 4.03 definitions were reported by the investigator in 4 patients (10.5%) (*i.e.* 3 patients, 7.9% with Grade 2 rated event and 1 patient, 2.6% with Grade 3 rated event).

CONCLUSION

In this international, multicentre, open-label, non-randomised, non-comparative, phase I, dose-escalation study, a total of 37 patients with AML and one patient with MDS were treated intravenously with once weekly dose of S64315 during a 21-day cycle (arm A). In the end, arm B of the study and other alternative regimens initially planned in the study protocol were not performed.

The AML/MDS patients received S64315 treatment for a median of 2 cycles, and most of the patients (76.3%) had a mean relative dose intensity between 65% and 100%. All patients were withdrawn from the treatment, mostly for progressive disease (52.5%).

For most patients with AML (81.1%), the BOR was treatment failure, and it was missing for the other patients. For the patient with MDS, the BOR was progressive disease.

During dose escalation, DLTs were reported in a total of 7 patients who received S64315 at 50 mg, 100 mg, 300 mg, 400 mg and 500 mg. Three patients (2 patients with AML and 1 patient with MDS) experienced DLTs related to cardiac disorders at the 500 mg dose level. Consequently, the BLRM model recommended de-escalating to a weekly dose of 300 mg.

All patients reported at least one EAE. The most commonly reported severe EAEs (*i.e.* rated Grade 3 and 4 according to CTCAE) affected the SOC Blood and lymphatic system disorders, mostly including febrile neutropenia (47.4% of the patients, with 42.1% Grade 3 and 5.3% Grade 4), neutropenia (28.9%, 2.6% Grade 3 and 26.3% Grade 4), and anaemia (23.7% Grade 3).

Overall, 89.5% of the patients had at least one treatment-related EAE. The most commonly reported treatment-related EAEs (≥ 10% of overall patients) were nausea, vomiting, diarrhoea, troponin I increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatine phosphokinase increased, and troponin increased.

Overall, 81.6% of the patients had at least one serious EAE including death. The serious EAEs reported in at least 2 patients in either dose were febrile neutropenia and tumour lysis syndrome.

Following the assessment of the benefit-risk of S64315 as single agent in AML/MDS patients (no objective response observed, even at the maximum tested dose of 500 mg where 3 out of 4 patients experienced a DLT), the Sponsor I.R.I.S decided to discontinue the development of S64315 as monotherapy in AML/MDS patients and therefore to discontinue this study. The RP2D could not be determined during the study.

Date of the report: 12 November 2020
Version of the report: Final version