Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study official title	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)
Study public title	Phase I/II trial of S64315 plus azacitidine in acute myeloid leukaemia
Test drug code	S64315
Indication	Acute Myeloid Leukaemia (AML)
Development phase	Phase I/II
Protocol code	CL1-64315-004
EudraCT Number	2019-004896-38
Universal Trial Number	Not applicable
Other register number (ISRCTN, CT. gov…)	NCT04629443
Investigational New Drug Application Number	136541
Sponsor	I.R.I.S.
International Coordinator	[redacted] Unité Hématologie 2 et Unité ETOH, Département d'Hématologie, Institut Paoli-Calmettes 232, boulevard Sainte Marguerite 13009 Marseille - FRANCE
Date of the document	14 October 2022
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Substantial Amendment(s) integrated

No.	Final version date	Countries concerned
1	22 February 2021	ALL
2	25 November 2021	ALL
3	12 April 2022	ALL
4	14 October 2022	ALL

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VERSION LIST

Protocol No.	Substantial amendment No.	Final version date	Countries concerned	Nature of modifications
1.0	NA	08 Apr 2020	ALL	Not Applicable
1.1	NA	15 Dec 2020	FRA	- Clarifications on follow-up of cardiac biomarkers and biochemistry assessments following French Competent Authority Request - See Appendix 9
2.0	1.0	22 Feb 2021	ALL	- Removal of non-screening criterion #6 (patients previously treated with HMA) - Modification of DLT definition for isolated AST or ALT elevation - Modification of treatment dose adaptations and re-administration criteria on AST or ALT values - Additional timepoints for monitoring of AST, ALT and total bilirubin - Update of criteria for study discontinuation during the LiD period - Update on pharmacokinetics timepoints - Clarification of inclusion criteria 29 - Update of exclusion criteria 43 - Additional recommendations for management of IRR - Update of the reporting of fatal events during inclusion period - Modification of the deadlines for obtaining certain exams for inclusion (Chest X-Ray, and hepatitis markers) - Table (8.12) 1: Clarification in case of TLS Grade 3 or 4 - Clarification on cardiac marker samples

Protocol No.	Substantial amendment No.	Final version date	Countries concerned	Nature of modifications
				- Update of the Table (4.4.1) 1 in accordance with the IMPD-Quality - Modification implemented in NS Amendment n°1 - Typo corrections
3.0	2.0	25 Nov 2021	ALL	- Updates following FDA's recommendations: o Addition of safety stopping rules and dose modification rules in expansion part o Addition of study safety stopping rules for any death suspected to be related to S64315 occuring within 30 days of study treatment administration o Monitoring of DLTs implemented at all cycles of treatment in escalation and expansion parts o Update of DLT definition for heamatologic toxicity and troponin increase o Update of eligibility criteria 16 and 43 o Update of management of S64315 dose modifications for QTc interval, creatine phosphokinase elevation and troponin elevation o Update of azacitidine dose modifications for non-hematologic toxicities o Sub-Arm A3 enroling patients with newly-diagnosed AML removed from the phase II expansion part o Phase II expansion part primary objective updated to Complete Remission rate

Protocol No.	Substantial amendment No.	Final version date	Countries concerned	Nature of modifications
				○ Clarifications added on study design for the expansion cohorts ○ Addition of treatment failure definition - Addition of recommendation in case of COVID-19 infection - Addition of recommendation in case of C1D9 infusion missed - Implementation of non-substantial amendment #2
4.0	3	12 April 2022	ALL	- To allow the possibility to include more than 6 DLT-evaluable patients in a cohort - To remove the collection of blood samples for PK that are considered unnecessary Other changes: - Update of blood sampling timepoints for PK - Update of blood sampling timepoints for PBMC assessment - Change in instructions that one of the two IMPs is permanently discontinued or discontinued for more than 28 days - Update for restarting of study treatment after COVID-19 infection - Clarification of wording related to treatment discontinuation during LID period (LID2 or C1D2) - Clarification about the investigations to be performed in the case of the need for an additional lead-in dose period - Clarification of the definition of dose-limiting toxicities

Protocol No.	Substantial amendment No.	Final version date	Countries concerned	Nature of modifications
				- Clarification about any new concomitant medication administration - Clarification in the wording of the one-week safety window between C1D2 of the first patient and C1D2 of subsequent patients in the same cohort - Clarification added in the situation where MTD is not be reached in some situations - Clarification for a secondary objective during expansion phase II: CRi is defined according to ELN recommendations - Update of statistical analysis sets for the expansion phase II part - Update for attesting authenticity of the data collected in the eCRF
5.0	4	14 October 2022	ALL	- Update of inclusion criteria #13 due to EU SmPC of azacitidine update (April 2022)

SYNOPSIS

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: S64315 (also named MIK665) Azacitidine	**Page:**	

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

Study Public Title*:* Phase I/II trial of S64315 plus azacitidine in acute myeloid leukaemia

International coordinator

National coordinators and investigators: listed in a separate document

Study centres:

Dose escalation phase I part
Approximately 8 centres
Approximately 4 countries

Expansion phase II part
To be further determined

Study period:

- Study duration: study treatment will be administered until the patient experiences unacceptable toxicity, progressive disease, treatment failure, investigator's or patient's withdrawal decision
- Study initiation date (planned date of first visit first patient)*:* September 2020
- Study completion date (planned date of end of follow-up period): March 2024

Study development phase:
Phase I/II

Objectives:
The purpose of this study is to determine the safety profile, the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT(s)) and to investigate the clinical activity of the combination of S64315 with azacitidine in patients with AML.
This study will be divided into two distinct arms:

- **Arm A** evaluating the combination of S64315 with azacitidine in the frame of a phase I/II trial.
  - The purpose of the **dose escalation phase I part** is to determine the safety profile, the MTD, DLT(s) and the recommended phase II dose (RP2D) in patients with relapsed/refractory AML
  - **phase II part** is to investigate the clinical activity of this combination in 2 distinct sub-arms in specific AML populations:
    - **sub-arm A1** enrolling patients with relapsed/refractory AML, HMA treatment-naïve
    - **sub-arm A2** enrolling patients with relapsed/refractory AML, previously treated with HMA
- **Arm B** [redacted] in the frame of a dose escalation phase I part in patients with newly diagnosed AML, not previously treated for AML and who are not candidate for intensive chemotherapy due to age or comorbidities. Details of this arm will be provided later, via an amendment.

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Arm A objectives

➢ **Dose escalation phase I part**

Primary objective

- To determine the safety profile and tolerability of S64315 in combination with azacitidine in patients with AML

Secondary objectives

- To determine the pharmacokinetic (PK) profile of S64315 and azacitidine administered in combination, and potential metabolites
- To evaluate the anti-leukemic activity of S64315 in combination with azacitidine

Exploratory objectives

- To assess measurable residual disease (MRD) and clonal evolution after treatment with S64315 in combination with azacitidine
- To evaluate the pharmacodynamic (PD) profile of S64315 in combination with azacitidine regarding:
  - the biological activity of S64315 in combination with azacitidine (target engagement)
  - the relationship between the anti-leukemic activity of S64315 in combination with azacitidine, chromosomal abnormalities (karyotypes) and other AML associated mutations or dysregulations
  - the relationship between [redacted]
- To explore PK/PD relationships for safety and activity
- To explore the relationship between DNA polymorphisms for proteins involved in absorption/ distribution/ metabolism/ excretion (ADME) and PK parameter variability

➢ **Expansion phase II**

Primary objective

- To evaluate the Complete Remission rate (CR) (proportion of patients who achieve a CR) of S64315 in combination with azacitidine

Secondary objectives

- To assess the anti-leukemic activity of S64315 in combination with azacitidine in terms of objective response rate (ORR) (including CR, complete remission with incomplete hematologic recovery (CRi) rates and Morphologic Leukemia Free State (MLFS)), overall survival (OS), duration of response (DOR), best overall response (BOR), progression-free survival (PFS), and disease-free survival (DFS)
- To assess the safety and tolerability of S64315 in combination with azacitidine
- To determine the PK profile of S64315 and azacitidine administered in combination, and potential metabolites

Exploratory objectives

- To assess MRD and clonal evolution after treatment with S64315 in combination with azacitidine
- To evaluate the PD profile of S64315 in combination with azacitidine regarding:
  - the biological activity of S64315 in combination with azacitidine (target engagement)
  - the relationship between the anti-leukemic activity of S64315 in combination with azacitidine, chromosomal abnormalities (karyotypes) and other AML associated mutations or dysregulations
  - [redacted]

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- To explore PK/PD relationships for safety and activity
- To explore relationships between DNA polymorphism for proteins involved in ADME and PK parameter variability

Arm B objectives

➢ **Dose escalation phase I part**

Primary objective

- To determine the safety profile and tolerability [redacted] in patients with AML

Secondary objectives

- To determine the PK profile of [redacted], and potential metabolites
- To evaluate the anti-leukemic activity of [redacted]

Exploratory objectives

- Exploratory objectives for Arm B will be further defined.

Methodology:

This phase I/II trial is designed as follows:

- **Arm A**: evaluating the combination of S64315 with azacitidine in the frame of a phase I/II trial and designed in two parts:
  - A dose escalation phase I part: a Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) will be used to guide the dose escalation of the combination.
  - An expansion phase II part with two sub-arms A1 and A2 previously described. A Bayesian two-stage adaptive design with one interim analysis for futility will be performed in each sub-arm.
- **Arm B:** [redacted] in the frame of a dose escalation phase I part. This arm will also be supported by a BLRM with EWOC.

Dose escalation methodology and dose-limiting toxicity (DLT) assessment in Arm A

The BLRM will be used to estimate the MTD(s) and/or the RP2D based on the occurrence of DLT (defined in section 4.1.3.5), including the S64315 lead-in dose (LID) period and the first cycle of treatment.

Toxicities are assessed according to NCI-CTCAE v5.0.

The MTD is defined as the highest dosage of S64315 in combination with azacitidine that is unlikely (< 25% posterior probability) to cause DLT in more than 33% of the treated patients up to the end of cycle 1. A maximum of 6 DLT-evaluable patients may be initially enrolled at a dose level, and a minimum of 3 DLT-evaluable patients must be treated at a given dose level before a new higher dose level may be evaluated. More than 6 DLT-evaluable patients may be treated in a cohort at dose levels considered safe according to the BLRM with overdose control in order to better characterize the safety, tolerability, PK, PD, or preliminary clinical activity of S64315 in combination with azacitidine. A minimum of 6 DLT-evaluable patients must have been evaluated at the dose level considered to be the MTD, and before treating patients with this dose in the Phase II part of the study.

Only the dose of S64315 will be escalated. The first S64315 weekly full tested dose will be 50 mg; azacitidine will be administered at a fixed dose (75 mg/m²/day for 7 days) in each cycle of treatment. A panel of S64315 doses from 25 mg (dose -1) to 250 mg may be tested according to the dose allocation of the BLRM. Intermediate doses may be proposed depending on available results during the study.

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Before testing a new dose level, an EoC meeting between the sponsor and the investigators will take place to discuss the DLTs, overall safety, PK, PD anti-leukemic activity observed in all patients, and to decide jointly the next dose level to be tested. Increments will not exceed 100% of the previous dose. A DSMB will review the data before each EoC meeting and provide recommendations.

For more details, see section 10.2.

Expansion phase II part methodology

The multi sub-arm expansion phase II part will start once the RP2D (MTD or suitable lower dose) of the combination Arm A has been determined during the dose escalation phase I part. A Bayesian two-stage design with one interim analysis for futility will guide the decision for each sub-arm and will be divided into two stages: stage 1 and stage 2.

During stage 1, patients will be enrolled and treated at the corresponding RP2D. At the end of stage 1, a Bayesian interim analysis for futility will be performed based on CR rate assessment.

According to futility interim analysis result in each sub-arm (A1 and A2), recruitment could be:

- Stopped, if results on CR rate are considered futile
- Continued if results on CR rate are considered not futile. In that case, one additional cohort of patients will be enrolled in stage 2 until the predefined end of study.

For more details, see section 10.3.

Safety data will be reviewed on an ongoing basis during dose expansion as described in section 10.3.2.

Number of included patients

Arm A

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

Arm B

The number of patients will be further defined.

Diagnosis and main criteria for inclusion

The criteria for dose escalation phase I part of **Arm A** are defined hereafter and should be adapted for expansion phase II part **(sub-arms A1 and A2)** according to results observed in the dose escalation phase I part. The criteria will be defined later for **Arm B** according to the results of Arm A.

Screening criteria

Demographic characteristics

1. Patients aged ≥ 18 years

Medical and therapeutic criteria

2. a. Patients with cytologically confirmed and documented de novo, secondary or therapy-related AML as defined by WHO 2016 classification (Arber, 2016) excluding acute promyelocytic leukaemia (APL, French-American-British M3 classification) with:
   - relapsed or refractory disease and without established alternative therapy or
   - secondary to MDS and without established alternative therapy
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (Appendix 3)

Informed consent

4. Written informed consent obtained prior to any study-specific procedure as described in section 13.3

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Non screening criteria

Medical and therapeutic criteria

5. Previous myeloproliferative syndrome (MPS)
6. *Criterion deleted in Substantial Amendment #1 (Amended Protocol V. 2.0)*
7. Patients previously treated with any Mcl-1 inhibitor

General criteria

8. Pregnant and lactating women
9. Unlikely to cooperate in the study
10. Participation in another interventional study requiring investigational treatment administration at the same time or within 2 weeks or at least 5 half-lives (whichever is longer) prior to the first IMP administration; participation in non-interventional registries or epidemiological studies is allowed. In case of donor lymphocyte infusions following allogeneic haematopoietic stem cell transplantation or biologic agents with a long half-life such as CART cells, immune checkpoint inhibitors, bispecific antibodies, a washout of 28 days is allowed.
11. Patients already enrolled (informed consent signed) and treated in the study

Inclusion criteria

General criteria

12. ECOG performance status ≤ 2 (Appendix 3)
13. Women of childbearing potential (WOCBP) must use a highly effective method of birth control (described in section 5.5), during study and up to 6 months after the last IMP administration. In case of use of oral contraception, women should have been stable on the same contraceptive drug (i.e. same active principle) for at least one month prior to the first IMP administration
14. Men with WOCBP partners must use a condom during the study and up to 3 months after the last IMP administration. In addition, contraception should be considered for their female partners. Contraceptive measures do not apply if the patient is sterile, vasectomized or sexually abstinent. Sperm donation will not be allowed during the study and up to 3 months after the last IMP administration.

Medical and therapeutic criteria

15. Adequate haematological function based on the last assessment performed within 7 days prior to the first 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)
16. a. 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/1.73m², determined by MDRD (Appendix 4)
17. Adequate hepatic function based on the last assessment within 7 days prior to the first IMP administration defined as:
    - AST and ALT < 1.5 x 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 are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN

Exclusion criteria

General criteria

18. Women of childbearing potential (WOCBP) tested positive in a serum pregnancy test within 7 days prior to the first day of IMP administration
19. Patients who have not recovered from toxicity of previous anticancer therapy, including Grade ≥ 2 toxicity (except alopecia of any grade) according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) version 5.0, prior to the first IMP administration

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Medical and therapeutic criteria

20. Severe or uncontrolled active acute or chronic infection
21. Uncontrolled hepatitis B or C infection
22. Known carriers of HIV antibodies
23. Known history of significant liver disease
24. Known active acute or chronic pancreatitis
25. Known active central nervous system disease
26. Clinically active severe skin diseases
27. Major surgery within 4 weeks prior to the first IMP administration or patients who have not recovered from side effects of the surgery
28. History of myocardial infarction (MI), unstable angina pectoris or coronary artery bypass graft (CABG) within 6 months prior to first IMP administration
29. a. Troponin I > ULN or Troponin T > ULN if Troponin I cannot be assessed
30. Clinically significant cardiac dysfunction (including NYHA class ≥ II heart failure, Left Ventricular Ejection Fraction (LVEF) < 50% as assessed by echocardiography (ECHO) or Multi-Gated Acquisition (MUGA) scan)
31. QT prolongation defined as QTc interval (corrected with Fridericia's formula) > 450 ms for males and > 470 ms for females, obtained from triplicate 12-lead ECG
32. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age
33. Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia, atrial fibrillation), complete left bundle branch block, high-grade atrioventricular block (AVB) (e.g. bifascicular block, Mobitz type II and third degree AVB)
34. Uncontrolled arterial hypertension (systolic blood pressure (SBP) > 150 mmHg or diastolic blood pressure (DBP) > 95 mmHg)
35. Unresolved CTCAE Grade ≥ 2 diarrhoea or presence of medical condition associated with chronic diarrhoea (such as irritable bowel syndrome or inflammatory bowel disease)
36. Coagulopathy that will increase the risk of bleeding complications according to investigator's judgment (e.g. disseminated intravascular coagulation)
37. Allogenic stem cell transplant within 3 months before the first IMP administration and/or patients who still receive immunosuppressive treatment and/or patients with active Graft-versus-host disease
38. Any previous anti-leukemic treatment for the studied disease within 2 weeks or at least 5 half-lives (whichever is longer) of this treatment prior to the first IMP administration (except for hydroxycarbamide). In case of donor lymphocyte infusions following allogeneic haematopoietic stem cell transplantation or investigational biologic agent with a long half-live such as CART cells, immune checkpoint inhibitors or bispecific antibodies, a wash-out of 28 days is allowed
39. Any radiotherapy within 2 weeks prior to the first IMP administration (except for palliative radiotherapy at localised lesions)
40. Malignant disease other than that being treated in this study. Exceptions include malignancies that were treated curatively, have not recurred within 2 years prior to study entry and not requiring ongoing therapy, completely resectable basal cell and squamous cell skin cancers, any malignancy considered to be indolent and that has never required therapy and completely resected carcinoma in situ of any type
41. Any clinically significant medical condition (e.g. organ dysfunction, gastric ulcer) or laboratory abnormality likely to jeopardize the patients' safety or to interfere with the conduct of the study, in the investigator's opinion
42. History of severe allergic or anaphylactic reactions to azacitidine or history of hypersensibility to excipient of S64315 or azacitidine, including egg, soybean, liposomal vehicle excipients or mannitol (E421)

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43. b. Patients receiving treatment medications listed in section 6.3.1 and that cannot be discontinued at least 1 week prior to the first IMP administration (at least 2 weeks for CYP3A4 inducers, see section 6.3.1 for details) and during the study period. Patients having received calcineurin inhibitors within 4 weeks before the first IMP administration.

For concomitant medication (prohibited or to be used with caution), refer to section 6.3.

Investigational Medicinal Products (IMPs)

Arm A

S64315 (test drug) and azacitidine administered in combination are both IMPs.

Dose and treatment schedule

- **S64315 lead-in dose period**

The lead-in dose period will last 2 weeks. S64315 LID1 will be administered on D-13 at 25 mg and LID2 on D-6 at 50 mg. LID1 and LID2 doses will be fixed all along the study.

- **Combination treatment period**

A treatment cycle will consist of 28 days for patients treated with S64315 in combination with azacitidine during the dose escalation phase I part:

- Weekly schedule for S64315 on CxD2, CxD9, CxD16 and CxD23
- Daily schedule for azacitidine from CxD1 to CxD7 followed by a 21-day rest period

S64315 will be administered via intravenous (IV) infusion over at least 2 hours.
The dose escalation will only concern S64315 during the combination treatment period. The starting dose will be 50 mg once weekly and doses up to 250 mg may be explored. For more details, see Table (4.1.3.3) 1.

Azacitidine will be administered at 75 mg/m² via subcutaneous (SC) injection, daily for 7 days from D1 to D7 of each cycle followed by a rest period of 21 days.

On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine should be administered 2h (±10 minutes (min)) prior to S64315.

For each cohort, if a dose/treatment combination schedule has not been tested yet, a one-week safety window should be observed between C1D2 of the first patient and C1D2 of subsequent patients in the same cohort. If no medically important or life-threatening toxicity occurs during the one-week observation period, the subsequent patients will be allowed to start treatment without further delays between subsequent patients.
Depending on the risk of the potential drug-drug interaction (DDI) between the IMPs or emergent safety issues, the dose of either or both IMPs may be modified.

Alternative dosing schedules may be further explored based on the observed clinical safety data, PK/PD data and non-clinical data (in vitro, in vivo, PK/PD modelling data).
In the expansion phase II part, patients will be treated at the RP2D (MTD or suitable lower dose) of S64315 in combination with azacitidine identified during the dose escalation phase I part.

Arm B

[redacted] are the IMPs.

Dose and treatment schedule

The dose and administrative schedule should be detailed via an amendment [redacted]

Prophylaxis, IMP administration/readministration criteria in Arm A phase I/II are defined hereafter. They will be further defined for **Arm B** via an amendment.

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Anti-emetic prophylaxis

Anti-emetic prophylaxis is strongly recommended prior to S64315 infusion and azacitidine administration to mitigate the risk of gastro-intestinal side effects. For more details, see section 8.2.8.1.

Tumour Lysis Syndrome (TLS) prophylaxis

TLS prophylaxis is required during each administration of IMPs for patients with active disease, in case of intra-patient dose escalation to a new assigned dose and in case of readministration after IMP interruption ≥ 28 days. TLS preventive strategies will start the day before the first S64315 infusion of the LID period. In addition to the recommendations described in the protocol, management of TLS will be based on international guidelines and published criteria (Cairo, 2010). For more details see section 8.2.9.

Infusion related reaction (IRR) prophylaxis

IRR prophylaxis is proposed prior to S64315 infusions. For more details, see section 8.2.10.

IMP administration/readministration criteria

Criteria to fulfil before each S64315 administration

- Before each S64315 infusion, all biological parameters should be checked in order to detect any toxicity (see Table (4.1.3.5) 1 and Table (8.12) 1).
- Patients with Grade ≥ 2 hypo/hypercalcemia and/or hypo/hypermagnesia and/or hypo/hyperkalaemia despite attempts at medical correction should not be treated with S64315
- Patients with white blood cell (WBC) count ≥ 10 G/L despite attempts at medical correction should not be treated with S64315. Hydroxycarbamide or leukapheresis may be used to reduce the circulating blast count before and throughout the study. WBC count must be checked twice a week during the LID period in order to maintain the WBC < 10 G/L
- AST and ALT ≤ 3 x ULN (except for LID1: AST and ALT ≤ 1.5 x ULN)
- Total bilirubin level ≤ 1.5 x ULN, except for patients with known Gilbert's syndrome, who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
- In the case of an S64315 interruption ≥ 28 days, its readministration must be preceded by a lead-in dose period (except for patients in CR/CRi). For more details, see section 6.1.2.

Criteria to fulfil before each first azacitidine administration (i.e. CXD1)

Patients should be monitored for haematological toxicity and renal toxicities. A delay in starting the next cycle or a dose adjustment due to haematological toxicity and/or renal toxicity may be necessary according to azacitidine E.U. SmPC (see Table (8.12) 2). WBC, absolute neutrophil count (ANC), platelets, serum creatinine, blood urea nitrogen (BUN) and serum bicarbonate will be assessed before starting the next treatment cycle.

Comparator: Not applicable

Duration of treatment

The planned duration of combination treatment is until disease progression, unacceptable toxicity, treatment failure or patient/physician decision.

- In case the patient becomes eligible for transplant, patient treatment discontinuation should be left to the investigator'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) will be allowed for bone marrow recovery at the investigator's discretion after discussion and approval from the Sponsor

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If one drug is permanently discontinued, both drugs should be discontinued. A patient should be withdrawn from the study if one of the IMPs is interrupted for more than 28 consecutive days for any reason. However, for patients with LVEF decline, IMP interruptions of up to 35 consecutive days are permitted.

If the patient is benefiting from the study treatment according to the investigator's judgement and if it is in the patient's best interest to continue the combination of S64315 with azacitidine, the patient may remain on study treatment.

A patient must discontinue the combination if the toxicity recurs with the same or worse severity after resumption of dosing, unless the investigator decides it is in the patient's best interest to continue the combination of IMPs and upon documented agreement with the Sponsor.

For each patient, once a dose reduction has occurred, the dose may not be re-escalated during the subsequent cycles unless in the opinion of the investigator it is in the patient's best interest to continue S64315, and upon documented agreement with the Sponsor.

Criteria for treatment discontinuation during the LID period:

- If the patient cannot receive the LID2 or the first S64315 C1D2 dose due to an AE, the S64315 infusion (either LID2 or C1D2) may be postponed by 1 to 5 days. If the LID2 is postponed for more than 2 days (5 days maximum), the C1D2 dose may not be postponed for more than 2 days. If S64315 C1D2 is postponed, azacitidine C1D1 dose should be postponed as well, whenever possible.
- If the AE is not recovered within this time period, the patient must be withdrawn from the study.

This study may be temporarily halted or prematurely discontinued at any time for any sufficiently reasonable cause. Stopping rules are described in corresponding sections 4.4.1, 4.4.2, 8.12, 10.2.8 and 10.3.

The end of trial is defined as the date of the last follow-up visit of the last patient, including a phone contact, or the date of the last contact attempt if the last patient is declared lost to follow-up.

Criteria for evaluation

Evaluation criteria in the dose escalation phase I part of Arm A are defined hereafter. They will be updated for the expansion phase II part for **sub-arms A1 and A2** according to results observed in the phase I part and for the dose escalation of **Arm B** according to the results of Arm A via an amendment.

Efficacy measurements

- All patients will be evaluated for response based on the 'Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel (Döhner, 2017) (see Appendix 5).
- A full blood count and a blood film examination, a bone marrow aspirate (BMA) and/or a bone marrow biopsy (BMB) (according to local medical practice) will be assessed for treatment response at defined time points.

For more details see section 7.

Safety assessments

Safety assessments will include:

- Incidence of DLTs
- Incidence and severity of AEs and SAEs according to NCI CTCAE 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, TLS monitoring, cardiac markers follow up
- Complete physical examination, ECOG performance status, vital signs measurements

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: S64315 (also named MIK665) Azacitidine	**Page:**	

- ECG parameters, cardiac function assessment
- Left ventricular ejection fraction (LVEF)
- Pregnancy test performed for women of childbearing potential
- Dose interruptions, reductions and dose intensity

For more details see section 8.

Pharmacokinetic measurements

Concentrations of S64315 and azacitidine for the Arm A will be determined in plasma using high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection at defined time points during the dose escalation phase I part. Expansion phase II part time points will be determined after PK results from phase I.
Blood sample time points for [redacted] PK measurements (with their potential metabolites, if applicable) for Arm B will be determined after PK results from the dose escalation phase I part of Arm A.

For more details see section 9.2.

Pharmacodynamic measurements

- Blood samples and bone marrow samples will be taken to determine:
  - The biological activity of S64315 in combination with azacitidine, by assessing target engagement and leukemic blast reduction kinetics
  - [redacted], by exploring Bcl-2 family member expression and somatic mutations, indels, copy number variations of Bcl-2 family members genes and other genes of interest (gene alteration analysis; control: saliva)
  - Minimal Residual Disease (MRD)
- Patient karyotype changes related to S64315 in combination with azacitidine will be evaluated by comparing available karyotype reports at diagnosis, at baseline and at progression

For more details see section 9.3.

Pharmacogenomics measurement (optional)

Pharmacogenomics analysis will be performed on a blood sample, to explore potential relationship between DNA polymorphism for proteins involved in ADME and variability on PK parameters.

For more details see section 9.4.

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: S64315 (also named MIK665) Azacitidine	**Page:**	

Contractual signatories

I, the undersigned, have read the foregoing amended protocol and the 'Participant information and consent form' documents attached to the amended protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice and the applicable regulatory requirements.

COORDINATOR

NAME	
CENTRE NUMBER	
DATE	
SIGNATURE	

HEAD OF ONCOLOGY R&D

NAME	[redacted]
DATE	18 October 2022
SIGNATURE	[redacted]

BIOSTATISTICIAN HEAD

NAME	[redacted]
DATE	18 October 2022
SIGNATURE	[redacted]

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List of abbreviations

%	:	percent
µmol	:	micromole
ADL	:	Activities of Daily Living
ADME	:	Absorption Distribution Metabolism Excretion
AE	:	Adverse Event
ALP	:	ALkaline Phosphatase
ALT	:	ALanine aminoTransferase
AML	:	Acute Myeloid Leukaemia
ANC	:	Absolute Neutrophil Count
APL	:	Acute Promyelocytic Leukaemia
aPTT	:	activated Partial Thromboplastin Time
AST	:	ASpartate aminoTransferase
AUC	:	Area Under the Curve
AUC24	:	Area Under the Curve at 24 hours
AUClast	:	Area under the concentration-time curve from time zero to time o last measurable concentration
AUC_{τ}	:	Area under the plasma concentration-time curve
AVB	:	AtrioVentricular Block
AZA	:	Azacitidine
ß hCG	:	ß Human Chorionic Gonadotrophin
BCL2	:	B-cell lymphoma 2 gene
Bcl-2	:	B-cell lymphoma 2 protein
BH3	:	Bcl-2 Homology domain 3
BLRM	:	Bayesian Logistic Regression Model
BMA	:	Bone Marrow Aspirate
BMB	:	Bone Marrow Biopsy
BMMC	:	Bone Marrow-derived Mononuclear Cells
BMI	:	Body Mass Index
BNP	:	Brain Natriuric Peptide
BP	:	Blood Pressure
BR	:	Best Response
bpm	:	beats per minute (heart rate unit)
BSA	:	Body Surface Area
BNP	:	Brain Natriuretic Peptide
BUN	:	Blood Urea Nitrogen
C	:	Cycle
CABG	:	Coronary Artery Bypass Graft
CAD	:	Coronary Artery Disease
CI	:	Confidence Interval
C_{inf}	:	Concentration at the end of infusion
CISO	:	Chief information security officer
CK	:	Creatine Kinase
CL	:	total CLearance
C_{last}	:	Last quantifiable observed concentration
CLL	:	Chronic Lymphocytic Leukaemia
cm	:	Centimetre
C_{max}	:	maximum Concentration

C_{min}	:	minimum Concentration
CMP	:	Clinical Monitoring Plan
CNS	:	Central Nervous System
CPK	:	Creatine Phosphokinase
CPK-MB	:	Creatine PhosphoKinase Myocardial Band
CR	:	Complete Remission
CRA	:	Clinical Research Associate
CRi	:	Complete Remission with incomplete haematologic recovery
CR_{MRD-}	:	Complete Remission without Minimal Residual Disease
CRO	:	Contract Research Organisation
CSR	:	Clinical Study Report
CTCAE	:	Common Terminology Criteria for Adverse Events
CT	:	Computed Tomography
CV	:	Curriculum Vitae
CXR	:	Chest X-Ray
D	:	Day
DBP	:	Diastolic Blood Pressure
DDI	:	Drug-Drug Interaction
DFS	:	Disease-Free Survival
DLT	:	Dose Limiting Toxicity
DLTES	:	Dose-Limiting Toxicity Evaluable Set
DSMB	:	Data Safety and Monitoring Board
DOR	:	Duration Of Response
DPO	:	Data Protection Officer
e.g.	:	Exempli gratia (for example)
ECG	:	ElectroCardioGram
ECHO	:	Echocardiogram
EAE	:	Emergent Adverse Event
eCRF	:	Electronic Case Report Form
ECOG	:	Eastern Cooperative Oncology Group
EMA	:	European Medicines Agency
EoC	:	End of Cohort
EoI	:	End of Infusion
ERIN	:	Event Requiring Immediate Notification
EWOC	:	Escalation With Overdose Control
FAS	:	Full Analysis Set
FDA	:	Food and Drug Administration
FFPE	:	Formalin-Fixed Paraffin-Embedded
FU	:	Follow-Up
FVFP	:	First Visit First Patient
g	:	Gram
G/L	:	Giga (10^9) per litre
GCP	:	Good Clinical Practice
GGT	:	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
GI	:	GastroIntestinal
GLP	:	Good Laboratory Practice
GLS	:	Global Longitudinal Strain
GMP	:	Good Manufacturing Practice
GVHD	:	Graft-versus-host disease

h	:	Hour
HBs	:	Surface antigen of Hepatitis B virus
hERG	:	Ether-à-go-go-Related Gene
HIV	:	Human Immunodeficiency Virus
HMA	:	HypoMethylating Agents
HNSTD	:	Highest Non Severely Toxic Dose
HPLC	:	High-Performance Liquid Chromatography
HR	:	Heart Rate
HSCT	:	Haematopoietic Stem Cell Transplant
IB	:	Investigator's Brochure
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonisation
ICTR	:	International Centre for Therapeutic Research
i.e.	:	id est (that is)
IEC	:	Independent Ethics Committee
IMP	:	Investigational Medicinal Product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial i.e. S64315 and azacitidine
INR	:	International Normalized Ratio
IRB	:	Institutional Review Board
I.R.I.S.	:	Institut de Recherches Internationales Servier
IRR	:	Infusion Related Reaction
IS	:	Included Set
IU	:	International Unit
IUD	:	IntraUterine (contraceptive) Device
IUS	:	IntraUterine hormone-releasing System
IV	:	IntraVenous (route)
kg	:	Kilogram
L	:	Litre
LDH	:	Lactate DeHydrogenase
LDL	:	Low-Density Lipoprotein
LFT	:	Liver Function Tests
LID	:	Lead-In Dose
LLN	:	Lower Limit of reference range
LV	:	Liposomal Vehicle
LVEF	:	Left Ventricular Ejection Fraction
MCL1	:	HGNC Approved Gene Symbol for Myeloid Cell Leukaemia Sequence 1
Mcl-1	:	Induced myeloid leukaemia cell differentiation protein
MDRD	:	Modification of Diet in Renal Disease
MDS	:	MyeloDysplastic Syndrome
MedDRA	:	Medical Dictionary for Regulatory Activities
mg	:	Milligram
MI	:	Myocardial Infarction
min	:	Minute
mL	:	Millilitre
mm	:	Millimetre
mmHg	:	Millimetre of mercury
mmol	:	Millimole
msec	:	Millisecond

MLFS	:	Morphologic Leukaemia-Free State
MM	:	Multiple Myeloma
MRD	:	Minimal (measurable) Residual Disease
MS/MS	:	tandem Mass Spectrometry
MTD	:	Maximum Tolerated Dose
MUGA scan	:	Multi-Gated Acquisition scan
NA	:	Not Applicable
NAE	:	Number of Adverse Events
NCA	:	Non-Compartmental Analysis
NCI	:	National Cancer Institute
NCT	:	EudraCT Number
NGS	:	Next Generation Sequencing
ng	:	Nanogram
NTI	:	Narrow Therapeutic Index
NS	:	Not statistically Significant
NYHA	:	New York Heart Association
OPM	:	OPerating Manual
ORR	:	Overall Response Rate
OS	:	Overall Survival
p.o.	:	per os (orally)
PBMC	:	Peripheral Blood-derived Mononuclear Cells
PBPK	:	Physiologically-based PharmacoKinetic
PD	:	PharmacoDynamics
PDX	:	Patient-Derived Xenograft
PFS	:	Progression Free Survival
PG	:	PharmacoGenomics
P-GP	:	P-glycoprotein 1
Ph. Eur.	:	European Pharmacopeia
PK	:	PharmacoKinetics
PR	:	Partial response
po	:	per os (orally)
PPS	:	Per Protocol Set
PS	:	Performance Status
QC	:	Quality Control
QD	:	Once daily
QTc	:	QT interval corrected for heart rate
QTcF	:	QTc interval corrected with Fridericia's formula
RBC	:	Red Blood Cells
RNA	:	Ribonucleic acid
RP2D	:	Recommended Phase II Dose
SAE	:	Serious Adverse Event
SBP	:	Systolic Blood Pressure
SC	:	SubCutaneous (route)
SD	:	Standard Deviation
SLL	:	Small Lymphocytic Lymphoma
SE	:	Standard Error
sec	:	Second
SmPC	:	Summary of Product Characteristics
SoI	:	Start of Infusion
SS	:	Safety Set

SUSAR	:	Suspected Unexpected Serious Adverse Reaction
T	:	Temperature
t½z	:	terminal half-life
TdP	:	Torsades de Pointes
test drug	:	Drug substance in a given dosage form, tested in a clinical trial, i.e. S64315
t_{last}	:	Time corresponding to C_{last}
TLS	:	Tumour Lysis Syndrome
t_{max}	:	Time corresponding to C_{max}
TPN	:	Total parenteral nutrition
TSH	:	Thyroid Stimulating Hormone
TTE	:	TransThoracic Echocardiography
TU	:	Therapeutic Unit
ULN	:	Upper Limit of reference range
USP-NF	:	United States Pharmacopeia and The National Formulary
Vd	:	Volume of distribution
WBC	:	White Blood Cells
WHO	:	World Health Organization
WHO-DD	:	World Health Organization, Drug Dictionary
WMA	:	World Medical Association
WOCBP	:	Woman of Child Bearing Potential
WV	:	Withdrawal Visit

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non sponsor parties, sponsors parties and CRO responsible for local management of the study are described in a separate document entitled 'Administrative part of clinical study protocol'.

The list of investigators for each country is given in separate documents attached to the protocol and entitled 'Investigators list for [*name of the country*]'.

The composition and role of the supervisory committee are described in sections 8.11 and 12.4.

2. BACKGROUND INFORMATION

2.1. Acute myeloid leukaemia

Acute myeloid leukaemia (AML) is the result of a multistep transforming process of hematopoietic precursor cells, which enables them to proceed through limitless numbers of cell cycles and to become resistant to cell death. Increased proliferation renders these cells vulnerable to acquiring mutations and may favour leukemic evolution. Deregulated cell cycle control contributes to increased proliferation in AML and favours genomic instability, a prerequisite to confer selective advantages to particular clones in order to adapt and independently proliferate in the presence of a changing microenvironment (Schnerch, 2012). A number of chromosomal and molecular genetic abnormalities has been described in this disease. Sub-classification based on these abnormalities guides prognosis (Döhner, 2017).

The yearly incidence of AML in European adults is 5-8 cases per 100 000 (Fey, 2013), 4.2 cases per 100,000 in US (Society AC. Cancer Facts & Figures, 2016) and 3.9 cases per 100,000 people in Australia (Australian Institute of Health and Welfare, 2012). Outcome for patients are poor with a 5-year survival rate of 26.9%. Untreated patients succumb to AML within weeks (Institute NC. Cancer Stat Facts: AML, 2017; Maldonado, 2015).

The incidence of AML increases approximately by 10-fold with age, from 1.3 cases per 100,000 people under 65 years of age to 12.2 cases per 100,000 in those over 65 years of age (De Kouchkowsky, 2016). AML is the most common acute leukaemia in the adult population, and largely affects older patients, with a median age at diagnosis of 68 years. Approximately 1/3 of all new diagnoses are aged 75 years and over (Institute NC. SEER Stat Facts Sheets: AML, 2016). In the elderly population, outcome is dismal with less than 5% survival at 5-years compared to a rate of 40% in younger patients (Alibhai, 2009). Long-term survival rate remains low with a median overall survival estimated at 7.0 months (Meyers, 2013). This is driven by the aggressive clinico-pathologic features of AML compounded with the comorbidities and frailty of this population.

The standard initial management for fitter patients with minimal comorbidities is intensive chemotherapy; older, less fit patients tolerate this poorly, resulting in limited effective treatment options (Cortes, 2019; Kantarjian, 2012). Historically, these patients have been referred for palliative or supportive care or treated with single-agent hypomethylating agents (HMAs) or low-dose cytarabine (LDAC), which have modest response rates.

AML is a biologically complex tumour with high rates of drug resistance. The goal of therapy is to reduce tumour burden and to re-establish normal bone marrow function and haematopoiesis. Evidence of minimal residual disease (MRD) places the patient at risk of relapse and short-term survival (Pettit, 2016). The central tenet of treatment is to cytoreduce with induction therapy while allowing the patient to emerge in a condition to tolerate subsequent more intensive consolidation therapy, which may include allogeneic haematopoietic stem cell transplantation (HSCT). Patients who do not receive consolidation therapy relapse within 6-9 months.

Initial treatment decisions are based on age, performance status, prior myelodysplastic syndrome and prior cytotoxic therapy.

Standard induction therapy for patients under the age of 60 usually consists of cytarabine and daunorubicin regimen. Overall outcomes for standard induction therapy are disappointing with complete response (CR) rate between 60-80% (Murphy, 2017). Half of those who do not reach complete remission experience fatal complications related to bone marrow aplasia or impaired recovery of normal haematopoiesis and the remaining population develop chemotherapy resistant disease.

Older patients present a particular challenge in the management of AML. In this population, AML is characterized by unfavourable karyotypes and higher mutational burden. Furthermore, the incidence of secondary AML, related to prior MDS or prior chemotherapy is higher in this population where current standard of care regimen may be difficult to tolerate, and treatment-related mortality may exceed expected anti-leukemic response.

Allogeneic HSCT, the only realistic hope of cure for these patients, is an option for a minority. Only patients with low tumour-burden and a long remission period (response rates > 12 months) appear to benefit from this treatment. Despite the curative intent, outcomes in these patients are sub-optimal. In a long-term follow-up study of post-allogeneic HSCT in AML and MDS patients, the reported relapse rate was 42% at 5 years (Finke, 2016). Besides allogeneic HSCT, no curative treatment exists for patients with relapsed AML. This is even more challenging in older patients, who usually experience short remissions (< 1 year) and are often considered unfit to tolerate intensive treatments (Ferrara, 2004).

Due to the high rates of relapse or recurrence in AML, there is a great need for effective salvage therapies.

In recent years, much has been learned about the genomic and epigenomic landscapes of AML, and the clonal architecture of both de novo and secondary AML has begun to be unravelled. Genetic studies in AML have revealed a variety of mutated or overexpressed proteins that, alone or in combination, contribute to leukemogenesis. New targeted therapies aimed at inhibiting these proteins are in development for treatment of AML. Since the past year, several novel agents have been approved by the US Food and Drug Administration (FDA) for use in patients with AML. Indeed I, 2017, the FLT3 inhibitor midostaurin, the antibody-drug conjugate gemtuzumab ozogamicin, CPX-351 (liposomal daunorubicin and cytarabine), and the IDH2 inhibitor enasidenib were approved. In 2018, other 4 new compounds were approved: the IDH1 inhibitor ivosidenib, the FLT3 inhibitor new generation gilteritinib, the first in class Hedghog pathway glasdegid, and the Bcl-2 inhibitor venetoclax. The latter received a granted accelerated approval in November 2018 in combination with azacitidine, decitabine or low-dose cytarabine (LDAC) for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy in the frame of a phase I/II.

This recent U.S. FDA approval of venetoclax with HMAs or LDAC in patients with AML who are previously untreated and older or unfit for chemotherapy has resulted in a promising therapy for these patients (DiNardo, 2018; Wei, 2019).

Despite advances in our understanding of the molecular basis for particular subtypes of AML and despite four new drugs approved for patients with FLT3 mutant, IDH2 mutant, CD33 positive AML, t-AML, and AML-MRC (Wei, 2017), a significant proportion of AML patients cannot be treated. New therapies are clearly needed, and in particular, there is a need to develop targeted therapies that avoid the use of cytotoxic drugs, many of which are also known mutagens.

2.2. Overview of S64315 (Mcl-1 inhibitor)

S64315 background

One of the cardinal features of cancer is a dysregulation of apoptosis (Hanahan, 2011) (Hanahan, 2011) Apoptosis is a physiological vital process for the maintenance of homeostasis in multicellular organisms, but it is also involved in a wide range of pathological processes, including cancer.

The regulation of apoptotic cell death is primarily controlled by the complex interactions of the Bcl-2 family of proteins (Kim, 2006; Kale, 2018). The Bcl-2 family comprises both pro (such as Bax, Bak, Noxa, PUMA, Bim, and Bid) and anti-apoptotic members, the latter (such as Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and Bfl-1/A1) are often overexpressed in cancer cells allowing a deregulated survival (Adams, 2018).

Small molecule selective Bcl-2 family inhibitors induce apoptotic cell death by releasing pro-apoptotic members (Tse, 2008; Danial, 2004; Green, 2004). Pharmacological inhibition of antiapoptotic Bcl-2 subfamily members in cancer has emerged as one of the strategies to induce apoptosis and cause tumour regression (Zhang, 2007).

Mcl-1 (induced myeloid leukaemia cell differentiation protein) was the second member of the Bcl-2 family discovered (Kozopas, 1993). Mcl-1 is highly expressed in a variety of human cancer cell lines, human haematopoietic, lymphoid cancers and solid tumours (Quinn, 2011). Mcl-1 overexpression is exploited by cancer cells to evade cell death, i.e. to survive, and as a mechanism for developing resistance to diverse chemotherapeutic agents (Akgus, 2009) Mcl-1 plays a crucial role in cell differentiation, regulation of apoptotic cell death, and has been shown to be critical to the development and maintenance of AML, making it an attractive therapeutic target in this disease.

In line with this observation, molecules targeting Mcl-1 such as S64315 (also named MIK665) are expected to be active in combination with conventional therapies (Hata, 2005).

2.2.1. Non clinical data

Pharmacology

S64315 (MIK665) is an innovative Bcl-2 Homology domain 3 (BH3) mimetic compound which selectively inhibits Mcl-1, a prosurvival member of the Bcl-2 family proteins.

S64315 is a synthetic small molecule which binds selectively to Mcl-1 with a very high affinity (IC_{50} range 3-6 nM in a displacement assay) and with low affinity to Bcl-2 and Bcl-xL.

In vitro, the ability of S64315 to inhibit cell growth was investigated in a panel of haematological cell lines including AML, lymphoma and multiple myeloma human cell lines. Most of the cell lines tested was sensitive to S64315, with IC_{50} below 100 nM.

In vivo, S64315 administered IV induced a rapid dose-dependent apoptotic response and tumour growth inhibition in an AML xenograft model. These data show that the *in vitro* potency of S64315 against haematological cell lines well translates to potent *in vivo* activity. For details, please refer to S64315 Investigator's Brochure.

S64315 was assessed for its off-target activity on receptors, enzymes and ion channels; however, the values obtained show that inhibition of the latter is unlikely in a clinical setting.

Pharmacokinetics and Metabolism

In preclinical IV studies, S64315 displayed a very high plasma protein binding across species (fraction unbound (fu) in plasma < 0.1% in mouse, rat, monkey and human) with more than 80% of the drug distributed in plasma. There was no concentration-dependency observed for rat, monkey and human plasma.

In a mouse distribution study using non-radiolabelled S64315, high liver exposure was observed with low to moderate uptake into muscle and adipose tissue and very low brain exposure.

In vitro, cross-species metabolism studies showed a moderate to high *in vitro* predicted hepatic clearance in mouse, rat, dog, monkey and human. Based on human hepatocyte data, S64315 is mainly metabolised through oxidative routes by CYP3A4 (50%) and CYP2C8 (20%). Direct glucuronidation of S64315 contributes to S64315 clearance for 30% or less. There is a moderate drug-drug interaction (DDI) risk when combining S64315 with CYP3A4 perpetrators and a low risk with CYP2C8 perpetrators.

Based on rat excretion data, renal clearance is predicted to be minor (less than 0.1% of the administered dose is excreted as unchanged S64315 within urine). The risk of DDI will have to be further investigated in clinic.

Toxicology

Preclinical cardiovascular safety pharmacology data do not indicate a risk for QTc prolongation or arrhythmogenicity based on the hERG assay, monkey telemetry studies, and ECGs evaluated in the 4-week GLP study in monkeys. There were no appreciable effects on CNS function or change in seizure threshold nor were there any effects on respiration observed in any study.

S64315 was devoid of *in vitro* and *in vivo* genotoxic potential.

In addition to the haematotoxicity, the principal target organs of toxicity following repeated S64315 administration (whatever the schedule of administration, either once weekly during 4 weeks or every 2 to 3 days during 2 weeks) to rats and monkeys include: bone marrow (depletion, hypocellularity), lymph organs (depletion and atrophy), liver (hepatocellular single-cell necrosis/apoptosis), gastrointestinal tract (epithelial cell single cell necrosis/apoptosis), pancreas (acinar cell single-cell necrosis/apoptosis), heart (increased staining of cardiomyocytes for cleaved caspase 3), testes (germ cell depletion), ovary (granulosa cell single-cell necrosis/apoptosis), skin (localized degeneration and cutaneous inflammation), eye (corneal degeneration and opacity and cataracts).

All these changes showed recovery after a 4-week dosing period.

For details, please refer to S64315 Investigator's Brochure (IB).

2.2.2. Clinical data

As of September 5th, 2019 (IB cut-off date), three clinical studies were ongoing in patients with haematological malignancies.

- Two phase I studies with S64315 as a single agent in patients with:
  - AML and myelodysplastic syndromes (MDS) conducted by Institut de Recherches Internationales Servier (CL1-64315-001). Thirty-eight (38) patients have been treated in this study with dose ranging 50-500 mg of S64315 as a weekly intravenous infusion. The dose of 500 mg was identified to be toxic, cardiotoxicity being the dose-limiting toxicity (see IB section 'Guidance for Investigator 7.11.6. Cardiovascular') and 300 mg has been established as the highest safe dose allowable by the EWOC criterion. No objective response was observed across the dose range, even though pharmacodynamics effects with bone marrow blast reduction were observed in 10/25 patients. Following the assessment of the benefit-risk of S64315 as single agent in AML/MDS patients, i.e. no objective response observed whereas toxic dose reached (i.e. 500mg), it was decided to definitively discontinue the development of S64315 in monotherapy in AML/MDS patients and therefore to discontinue the CL1-64315-001 study. Taking into account the mechanism of action, the role of the other BH3 mimetics proteins and the heterogeneity of the BCL2 family member's expression in AML, further development of S64315 in combination is considered in AML.
  - Lymphomas and multiple myeloma (MM) conducted by Novartis Pharmaceuticals (CMIK665X2101). Thirty-one (31) patients have been treated since the start of the study. The benefit-risk assessment of MIK665 as single agent in MM and lymphoma indication is currently under evaluation while the study is not recruiting new patients.
- One phase Ib study with S64315 in combination with a Bcl-2 inhibitor (venetoclax) in patients with AML conducted by Institut de Recherches Internationales Servier (CL1-64315-002). Twelve (12) patients have been treated since the start of the study. The benefit-risk assessment of S64315 in combination with venetoclax in AML patients is still considered favourable providing that additional safety measures, especially towards cardiac safety monitoring have been implemented.

The most frequently reported adverse events (AEs) (in ≥ 15% of the patients) irrespective of the relationship to the study drug involved the SOC gastrointestinal disorders and the SOC investigations. The most frequently reported preferred terms among gastrointestinal disorders were nausea, vomiting and diarrhoea and, among investigations, troponin I increased, alanine aminotransferase increased, and aspartate aminotransferase (AST/SGOT) increased. The most frequent severe AEs independently from the relationship to the study drug were febrile neutropenia, anaemia and neutropenia.

For more details on S64315 global safety, please refer to the last version of the IB (e.g. section 7: Guidance for investigator).

Pharmacokinetic properties

Preliminary PK data from the single agent studies were analysed by population PK modelling and were adequately described by a 3-compartment model with linear clearance estimated to 15.9 L/h.

High level interpretation based on the preliminary PK data and population PK modelling shows low to moderate variability (~30%) on exposure metrics (C_{max}, AUC). Exposure appears to increase proportionally with the dose, independently of the time and to be comparable between CMIK665X2101 and CL1-64315-001 studies. Exposure is quickly decreasing after end of infusion implying that AUC_{24h} is comparable to AUC_{tau}, deviating less than 5%.

2.3. Overview of the combination of a Mcl-1 inhibitor and a hypomethylating agent

2.3.1. Rationale of the combination of a Mcl-1 inhibitor and a hypomethylating agent

Hypomethylating agents have improved treatment options for patients with AML, both in relapsed/refractory as well as in first line settings for patients not eligible for intensive chemotherapy.

In relapsed/refractory AML, 16% of patients treated with HMA achieved CR/CRi with a median OS of 6.7 months. Used as first line therapy in elderly patients with AML (> 30% of bone marrow blasts), HMA achieved CR/CRi in 27.8% of patients, with a median OS of 21 months (Stahl, 2018).

Preclinical studies have demonstrated that decitabine, another HMA, exposure increased the expression of NOXA, a proapoptotic protein leading to neutralisation of MCL-1 and inducing apoptosis (Bogenberger, 2014). In addition, pharmacologic downregulation of MCL-1 via CDK-9 inhibition, as well as upregulation of the MCL-1 antagonist, NOXA, following decitabine exposure should result in enhanced antileukemic activity in MCL-1-dependent malignancies (Kim, 2018). These data support the potential synergistic activity of the combination of S64315 with hypomethylating nucleoside analogues.

2.3.2. Non clinical data

In translational studies, the combination of S64315 with the two HMAs, azacitidine and decitabine (cytidine analogues used in AML), has shown a good synergy between both compounds in different preclinical models (*in vitro*, *ex vivo* and *in vivo*) as presented below.

In vitro, the activity of S63845, tool compound of S64315 (less potent than S64315) was investigated in a panel of 13 AML cell lines in combination with decitabine. As shown in Table (2.3.2) 1, the combination was synergistic (synergy score >3) in 8 out of 13 AML cell lines, independently of the reported genetic profile.

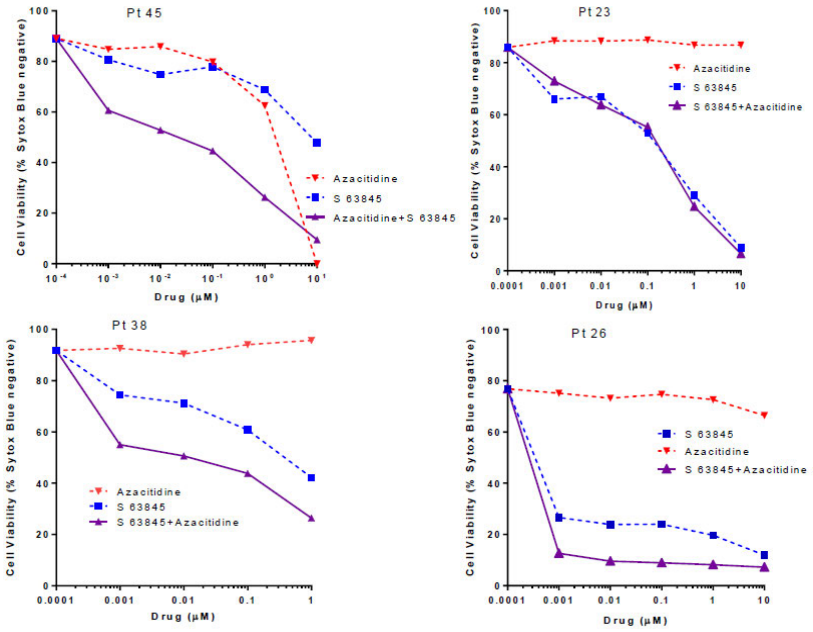
Table (2.3.2) 1 - Synergistic interactions of S63845 and decitabine were assessed using the Loewe additivity model to derive Synergy Score (SS), with SS > 3 indicating synergy and SS > 5 strong synergy

Cell line	Genetic profile	P53 status	S63845+ Decitabine Synergy score
MV4;11	FLT3 duplication and MLF-AFF1 fusion gene	-	**8.1**
MOLM13	FLT3 dup, CBL mut, MLL-MLLT3 fusion	wt	**5.4**
PL-21	FLT3 duplication	mut	**1.6**
ML-2	MLL-MLLT4 fusion gene	wt	**3.7**
Nomo1	MLL-MLLT3 fusion gene	mut	**4.1**
THP1	MLL-MLLT3 fusion gene	mut	**1.7**
HL-60	Cmyc expression and CDKN2A mutated	mut	**2.3**
Kasumi1	RUNX1-RUNX1T1 (AML1-ETO), Kit mut	mut	**4.8**
Oci-AML3	NPM1 mut (type A) and DNMT3A R882C mut	wt	**7.1**
EOL-1	MLL tandem dup; fusion FIP1L1-PDGFRA	-	**6.3**
GDM1	-	wt	**4.3**
KG1	-	-	**2.8**
KG1a	-	-	**2.7**

mut: mutated; wt: wild-type

The combination of S63845 and azacitidine was also tested in *ex vivo* AML primary patient samples Figure (2.3.2) 1. The combination mostly induces synergistic activity, even in samples resistant to azacitidine.

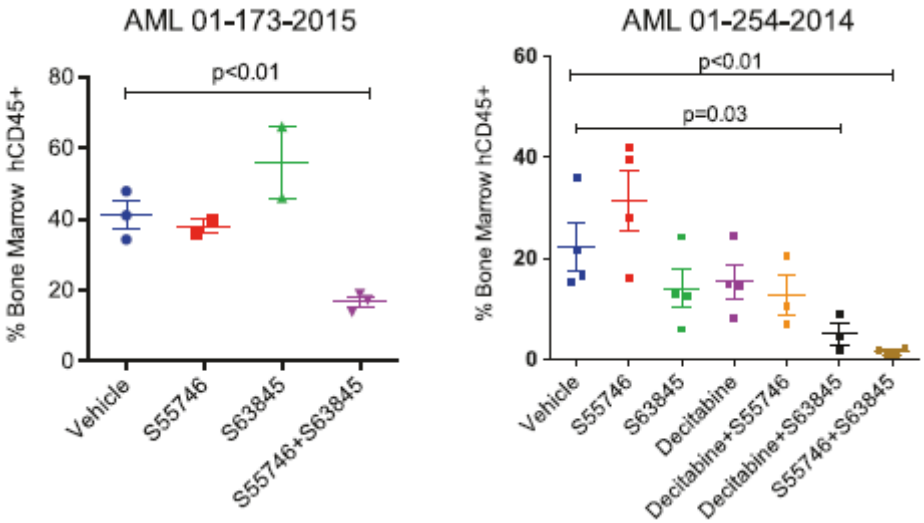
Figure (2.3.2) 1 - Ex vivo activity of S63845 in combination with azacitidine in primary AML samples [redacted]



Ficoll purified AML cells were exposed to drugs over a period of 48 hours. Viability was determined by cellular exclusion of SYTOX Blue Dead Cell Stain. Analysis was performed in 34 independent donors and 4 representative AML samples were represented.

Finally, the combination of S63845 and decitabine was tested in *in vivo* AML patient derived xenografts (PDX) as shown in Figure (2.3.2) 2. This combination induces more activity when compared to the single agents.

Figure (2.3.2) 2 - Combined S63845 and decitabine suppress leukaemia in vivo in NRG-SG3 patient-derived xenograft models of AML (Moujalled, 2019)



These data suggest that when S63845, tool compound of S64315, and decitabine are concomitantly administered, the Mcl-1 inhibitor may enhance the effect of the HMA in relapsed/refractory and treatment naive AML patients. This further supports the evaluation of the safety, tolerability, pharmacokinetics, pharmacodynamics and anti-leukemic activity of S64315 in combination with azacitidine in a clinical study.

2.3.3. Azacitidine clinical data

Azacitidine is an HMA commonly used in the treatment of AML. It is approved by the FDA and EMA. According to E.U SmPC, azacitidine is indicated for the treatment of adult patients who are not eligible for HSCT with AML with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification and AML with >30% marrow blasts according to the WHO classification.

Myelosuppression is the main dose-limiting toxicity for azacitidine. The risk is higher during the first 2 cycles and decreases when the patient's haematological function is restored. Less than 5% of patients required drug discontinuation due to haematological side effects. Close monitoring for haematological toxicity is recommended, including nadir counts, and supportive care provided when required. Doses for subsequent cycles should be adjusted based on nadir counts and haematological response (see E.U. azacitidine SmPC). Myelosuppression may lead to neutropenia and an increased risk of infection. Serious adverse reactions such as sepsis, including neutropenic sepsis and pneumonia, were reported in patients receiving azacitidine. Infections may be managed with the use of anti-infectives plus growth factor support (e.g. G-CSF) for neutropenia.

The most common non-haematological side effects are injection site reactions, nausea, vomiting, fatigue, and diarrhoea/ constipation. The gastrointestinal adverse reactions are to be managed symptomatically with anti-emetics for nausea and vomiting, anti-diarrhoeals for diarrhoea, and laxatives and/or stool softeners for constipation.

Severe hepatic failure has been reported in patients with extensive disease and hypoalbuminemia. Therefore, azacitidine is contraindicated in patients with advanced malignant hepatic tumours.

No clinically relevant difference in the frequency of adverse reactions was noted between subjects with normal renal function compared to those with renal impairment. Nevertheless, patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney, as some rare cases of renal tubular dysfunction have been reported.

2.3.4. Expected overlapping toxicities

Based on preclinical data from both drugs, clinical data from azacitidine as a single agent in monotherapy as well as preliminary clinical data available from ongoing studies with S64315, bone marrow and lymphoid organs are identified as primary target organs for toxicity; overlapping myelosuppression may be observed. The risk of tumour lysis syndrome (TLS) has also to be considered. Other overlapping toxicities such as gastrointestinal disorders may be observed (see section 8 for toxicity prophylaxis).

Even if pharmacology investigations indicate the potential for synergistic toxicity, no dedicated combination toxicity study had been considered since the safety of azacitidine is well known. The measures implemented, including clinical monitoring and described in the section 8 of this document are deemed sufficient to mitigate the risk and to predict clinical dose adjustments.

2.3.5. Pharmacokinetics and metabolism

When coadministered, *in vitro* results show an inhibition of hepatic efflux (P-GP) of S64315 by azacitidine. With limited *in vitro*/*in vivo* information for azacitidine, population based pharmacokinetic (PBPK) simulations have been performed to quantify this impact. PBPK simulations show a very limited DDI risk between azacitidine and S64315 with concomitant administration. Thus, from a PK point of view, there is no recommendation of starting dose adaptation due to DDI risk.

2.3.6. Starting dose rationale & administration schedule

In the study CL1-64315-001 assessing S64315 as a single agent in a weekly schedule without lead-in dose period, doses from 50 to 500 mg were tested. Based on all the DLT data collected since the beginning of the study across 38 evaluable patients with AML or MDS, 500 mg was identified to be a toxic dose and 300 mg was the highest dose considered safe by the statistical model i.e. BLRM with EWOC criterion. Nevertheless, considering the global safety observed at 300 mg (except DLT), it was decided not to overpass S64315 weekly dose of 250 mg.

- **Arm A evaluating the combination of S64315 with azacitidine in the frame of a phase I/II trial**
  - **Dose escalation phase I part**

    The choice of the starting dose of S64315 in the Arm A is based on the first clinical data (safety and PK profile) from the administration schedule assessing weekly S64315 as a single agent, taking into account the anticipated activity, the limited DDI risk between S64315 and azacitidine and the potential risk of overlapping toxicity regarding the haematotoxicity and GI toxicity. Thus, following a conservative approach, the started dose of S64315 proposed to assess the combination of S64315 and azacitidine will be 50 mg once a week as full tested dose. The dose escalation will be preceded by a 2-week lead-in dose (LID) period of weekly S64315 at a fixed dose of 25 mg for LID1 and 50 mg for LID2.

    The introduction of the LID period with fixed low doses of S64315 aims:
    - to allow an early detection of patients with cardiac sensitivity to S64315 and to prevent subsequent administrations with higher doses to these patients
    - to improve the overall tolerance to S64315
    - to reduce the risk of tumour lysis syndrome (TLS)
    - Azacitidine will be administered via subcutaneous injection at the dose of 75 mg/m², daily from day 1 to day 7, followed by a rest period of 21 days (28-day cycles), according to the current E.U SmPC.

    With regards to the administration schedule of the combination, there is an interest to administer azacitidine before the targeted dose of S64315 in order to sensitize the tumour cells to S64315 (Caenepell, 2018). For this reason, the administration schedule starting from cycle 1 onwards, over 28-day cycles is, as follows:
    - Azacitidine daily administered via a subcutaneous injection, from day 1 to day 7 (D1 to D7), followed by a rest period of 21 days
    - S64315 administered intravenously weekly, on day 2, day 9, day 16 and day 23 (D2, D9, D16, D23)
  - **Expansion phase II part**

The dose of S64315 tested during the expansion phase II part will be the MTD/RP2D identified during the dose escalation phase I part, whichever the sub-arm (A1 or A2).

The administration schedule will be the same as for the dose escalation phase I part.

2.3.7. Expansion phase II part design rationale

The expansion phase II part will be divided in two distinct parts according to a Bayesian two-stage design: stage 1 and stage 2. A futility analysis will be performed at the end of stage 1 for sub-arms A1 and A2 based on the rate of CR observed after 4 cycles of combination treatment. This analysis will support the decision to stop the evaluation of the combination or to continue the evaluation during the stage 2.

Azacitidine has demonstrated a CR rate of 17,9% to 19,5% in the first-line treatment of patients with newly diagnosed AML (Schuh, 2017; Di Nardo, 2020). In patients with relapsed/refractory AML the CR rate is approximately 11% (Stahl, 2018). In order for combination therapy with azacitidine + S64315 to be considered a clinically meaningful improvement over azacitidine alone, the CR rate in relapsed/refractory AML should be at least doubled, and closer to the level of activity observed in the first-line setting, i.e., around 20%.

Therefore, dose expansion arms A1 and A2 will each treat 23 patients in the first stage of analysis. If there is evidence that the CR rate is < 20% the treatment is stopped in the relevant arm in the first stage. Twenty-three patients in stage 1 provides a > 50% chance to stop the trial early, without exposing more patients, if the true CR rate is less than 20%. If there is evidence that the CR rate >= 20%, 27 additional patients will be treated to better estimate the CR rate. The treatment of these additional patients will provide a better estimate of the true rate of CR with S64315 + azacitidine.

Statistical considerations are further described in section 10.3.2. and in Appendix 8.

2.4. Overview of the [redacted]

2.4.1. Rationale [redacted]

Venetoclax, the most advanced Bcl2 inhibitor to date, was FDA approved in 2018 for use in combination with azacitidine or decitabine or low dose cytarabine for the treatment of older adult patient with newly-diagnosed AML ineligible for intensive chemotherapy. In the pivotal clinical trials evaluating venetoclax either in combination with LDAC or with HMA, the rates of complete remission (CR) plus CR with incomplete haematological recovery were 54% and 67%, respectively and the median overall survival (OS) was 10.4 months and 17.5 months, respectively, comparing favourably with outcomes in clinical trials evaluating single-agent LDAC or HMA (Richard-Carpentier, 2019). The results of this phase Ib has been confirmed by the positive outcome of the confirmatory phase III trial just a week ago.

The median overall survival for patients treated with venetoclax plus hypomethylating agents was still only 17.5 months, which for an otherwise fit and healthy 75-year-old person, is a devastating outcome. In the high-risk subsets, including those with TP53 mutations and adverse risk cytogenetics, the outcomes are much worse than this, and highlight the ongoing unmet need for this group of patients with AML. [redacted]

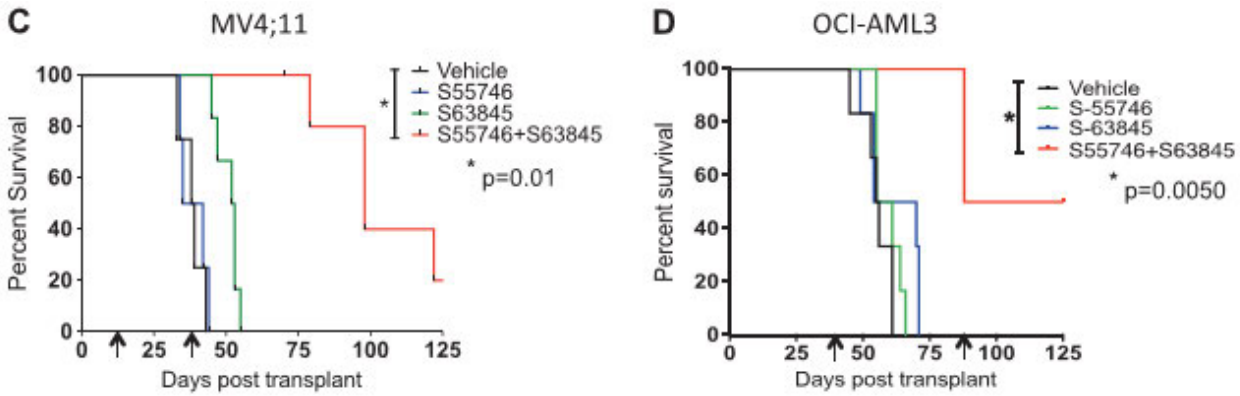
2.4.2. Rationale for the combination of a Mcl-1 inhibitor and a Bcl-2 inhibitor

Given its selectivity for BCL-2, an intrinsic mechanism of venetoclax resistance is due to increased AML blast dependency on the anti-apoptotic proteins, BCL-xL and MCL-1. In the phase II trial of venetoclax monotherapy in relapsed/refractory AML patients, both BCL-xL and MCL-1 expression levels were negatively correlated with response to venetoclax (Konopleva, 2016). A numbers of novel therapies tested in pre-clinical models in combination with venetoclax have demonstrated synergistic effects by downregulating MCL-1 expression (Sillar, 2019).

Indeed, azacitidine has also been shown to reduce MCL-1 expression (Tsao, 2012). Hence, directly targeting MCL-1 makes logical sense in combination with a Bcl-2 inhibitor in AML. As proof of concept, a recent study investigated the role of BCL-2 and MCL-1 in AML survival by combining inducible lentiviral vectors expressing BH3-only proteins and venetoclax to differentially target anti-apoptotic BCL-2 family members, BCL-2 and MCL1 emerged as critical and complementary proteins regulating cell survival in acute myeloid leukaemia. Dual targeting of BCL-2 and MCL1, but not either alone, prolonged survival of leukaemia-bearing mice. Targeting BCL-2 and MCL-1 improved survival in a mouse xenograft model, whereas other combinations including BCL-2/BCL-XL/BCL-W or MCL-1 alone, did not. Hence, combining venetoclax with an MCL-1 inhibitor is an exciting prospect for the treatment of patients with AML (Teh, 2018).

In pre-clinical studies, we have demonstrated the anti-leukemic efficacy of a novel BCL-2 inhibitor S55746 which demonstrates synergistic pro-apoptotic activity in combination with the MCL1 inhibitor S63845 (related analogue of S64315). Activity of the combination was caspase and BAX/BAK dependent, superior to combination with standard cytotoxic AML drugs and active against a broad spectrum of poor risk genotypes, including primary samples from patients with chemoresistant AML. Co-targeting BCL-2 and MCL-1 was more effective against leukemic, compared to normal hematopoietic progenitors, suggesting a therapeutic window of activity. Finally, S55746 combined with S63845 prolonged survival in xenograft models of AML Figure (2.4.2) 1. Combined S55746 and S63845 suppresses leukaemia in vivo in NRG-SG3 patient-derived xenograft models of AML but not normal hematopoietic cells in bone marrow of engrafted mice.

Figure (2.4.2) 1 - Combined targeting of BCL-2 and MCL-1 improves the survival of mice xenografted with human AML



These results suggest that targeting both BCL2 and MCL1 using small molecule inhibitors to suppress human AML in vivo may have less severe adverse effects on normal bone marrow hematopoietic function than standard cytotoxic drugs (Moujalled, 2019).

This provide proof-of-concept demonstration that targeting BCL-2 and MCL-1 simultaneously can lead to rapid suppression of diverse AML subtypes, with limited toxicity to normal human bone marrow cells, thereby providing strong rationale for further clinical development.

In conclusion, a dual BH3-mimetic approach is feasible, highly synergistic, and active in diverse models of human AML. This approach has strong clinical potential to rapidly suppress leukaemia, with reduced toxicity to normal hematopoietic precursors compared to cytotoxic drugs.

2.4.3. Rationale for the [redacted]

AML survival is BCL2-dependent and, in a subset of patients, MCL1-codependent. HMAs in combination with Bcl2 inhibitor like Venetoclax have demonstrated clinical responses in AML (Dinardo, 2019; Dinardo, 2018). Preclinical studies indicate potential mechanism of resistance to venetoclax including overexpression of Mcl-1 (Konopleva, 2006).

Direct or indirect targeting of BCL2 alternative proteins, particularly MCL1, in combination with venetoclax may result in greater efficacy and may overcome resistance in patients with AML (Pollyea, 2019; Gurnari, 2020). Various mechanisms of resistance to venetoclax have been identified so far and mainly involve MCL-1 or BCL-XL upregulation. Treating patients prior to the emergence of resistant disease is likely to be highly beneficial.

Preclinical studies evaluating the combination of pevodenistat, an inhibitor of Nedd8 which inhibit Mcl1 by inducing NOXA a pro-apoptotic protein leading to neutralization of Mcl1 inducing apoptosis, and venetoclax against AML cell lines have demonstrated synergistic effect (Knorr, 2015). We hypothesize that the [redacted] would enhance the therapeutic efficacy by overcoming resistance to apoptosis.

In a recent publication it was reported that AML cells can apparently switch from BCL2 to MCL1 dependence to drive energy metabolism as cells acquire a more differentiated developmental state. This finding suggests developmental and dynamical heterogeneity is a previously underappreciated factor in determining therapeutic response (Pei, 2020).

It was also reported that responses to venetoclax and azacitidine in AML patients correlate closely with developmental stage, where phenotypically primitive AML is sensitive, but monocytic AML is more resistant. Mechanistically, resistant monocytic AML has a distinct transcriptome profile, loses expression of venetoclax target BCL2 and relies on MCL1 to mediate oxidative phosphorylation and survival. This differential sensitivity drives a selective process in patients which favours the outgrowth of monocytic subpopulations at relapse. Based on these findings, resistance to venetoclax and azacitidine can arise due to intrinsic molecular/metabolic properties of monocytic AML cells, and that such properties can potentially be targeted with alternative strategies. Further preclinical data assessing the combination of S64315 and Blc-2 inhibitors are ongoing.

The starting doses of S64315 and the Blc-2 inhibitor, as well as the administration schedule in the dose escalation phase I part of [redacted] will be further defined according to the results of combination Arm A (RP2D, clinical activity) and [redacted]

The study will be conducted in compliance with the protocol, GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary objective

Refer to Table (3.4) 1, Table (3.4) 2 and Table (3.4) 3.

3.2. Secondary objectives

Refer to Table (3.4) 1, Table (3.4) 2 and Table (3.4) 3.

3.3. Exploratory objectives

Refer to Table (3.4) 1, Table (3.4) 2 and Table (3.4) 3.

3.4. Endpoints

Table (3.4) 1 - Endpoints for dose escalation phase I part – Arm A

	Objectives	Endpoints
Primary	To determine the safety profile and tolerability of S64315 in combination with azacitidine in patients with AML	- Incidence of DLTs starting from the LID period to the end of the first cycle of treatment of S64315 in combination with azacitidine - Incidence and severity of AEs and SAEs according to NCI CTCAE 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, TLS monitoring, cardiac markers follow up - Complete physical examination, ECOG performance status, vital signs measurements - ECG parameters, cardiac function assessment - Left ventricular ejection fraction (LVEF) - Dose interruptions, reductions and dose intensity
Secondary	To determine the PK profile of S64315 and azacitidine administered in combination, and potential metabolites	PK parameters of S64315 and azacitidine administered in combination, and potential metabolites if applicable, in plasma (e.g. C_{inf}, t_{inf}, AUC_{last}, t_{last}, C_{last}, AUC, $t_{1/2,z}$, CL and Vd)
	To evaluate the anti-leukemic activity of S64315 in combination with azacitidine	- CR rate, ORR (including CR/CRi/MLFS), Best Overall Response (BOR), Duration of Response (DOR), Progression Free Survival (PFS), Overall survival (OS) - Anti-leukemic activity assessment using blood, BMA and BMB if available according to ELN 2017 response criteria (Döhner, 2017)

	Objectives	Endpoints
Exploratory	To assess MRD and clonal evolution after treatment with the combination of S64315 with azacitidine	Detection and quantification of residual leukemic cells by gene expression and genomic alterations analysis
	To evaluate the PD profile of S64315 in combination with azacitidine in relation to:	
	- the biological activity (target engagement)	- Leukemic blast reduction kinetic assessment - Absolute total and B lymphocyte count
	- the relationship between the expression level of Bcl-2 family members (in blood, and bone marrow samples) and the anti-leukemic activity	- Bcl-2 family member protein expression
	- the relationship between the anti-leukemic activity, karyotypes and AML associated genes mutations or dysregulations	- Somatic mutations, indels, rearrangements and amplifications and expression of BCL-2 family member genes and in a panel of cancer-related genes and karyotype analysis
	To explore PK/PD relationships for safety and efficacy	PK/PD relationship related to haematological/ AE findings and to activity
	To explore relationships between DNA polymorphism for proteins involved in ADME and variability of PK parameters	Pharmacogenomics on blood sample (optional part)

Table (3.4) 2 - Endpoints for expansion phase II part – sub-arms A1 and A2

	Objectives	Endpoints
Primary	To evaluate the CR rate of the combination of S64315 with azacitidine	CR rate (proportion of patients who achieve CR)
Secondary	To assess anti-leukemic activity of the combination of S64315 with azacitidine	- ORR (including CR/ CRi and MLFS), BOR, DOR, PFS, OS - Anti-leukemic activity assessment using blood/BMA and BMB if available according to ELN 2017 response criteria (Döhner, 2017)
	To determine the safety and tolerability of the combination of S64315 with azacitidine in patients with AML	- Incidence of DLTs - Incidence and severity of AEs and SAEs according to NCI CTCAE v5.0 - Laboratory tests: haematology with differential, blood biochemistry, thyroid function, blood coagulation and urinary analysis, hepatitis markers, TLS monitoring, cardiac markers follow up - Complete physical examination, ECOG performance status, vital signs measurements - ECG parameters, cardiac function assessment - LVEF

		- Dose interruptions, reductions and dose intensity
	To determine the PK profile of S64315 and azacitidine administered in combination, and potential metabolites if applicable	PK parameters of S64315 and azacitidine administered in combination, and potential metabolites if applicable, in plasma
Exploratory	To assess MRD and clonal evolution after treatment with the combination of S64315 with azacitidine	Detection and quantification of residual leukemic cells by gene expression and genomic alterations
	To evaluate the PD profile of the combination of S64315 with azacitidine in relation to:	
	- the biological activity (target engagement)	- Leukemic blast reduction kinetic assessment - Absolute total and B lymphocyte count
	- the relationship between the expression level of Bcl-2 family members (in blood, and bone marrow samples) and the anti-leukemic activity	- Bcl-2 family member protein expression
	- the relationship between the anti-leukemic activity and karyotypes and AML associated gene mutations or dysregulations	- Somatic mutations, indels, rearrangements and amplifications and expression of BCL-2 family member genes and in a panel of cancer-related genes and karyotype analysis
	To explore PK/PD relationships for safety and efficacy	PK/PD relationship related to haematological/ AE findings and to activity
	To explore relationships between DNA polymorphism for proteins involved in ADME and variability of PK parameters	Pharmacogenomics on blood sample (optional part)

Table (3.4) 3 - Endpoints for dose escalation phase I part – Arm B

	Objectives	Endpoints
Primary	To determine the safety profile and tolerability of [redacted] in patients with AML	- Incidence of DLTs starting from the LID period to the end of the first cycle of treatment of S64315 in combination with azacitidine - Incidence and severity of AEs and SAEs according to NCI CTCAE 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, TLS monitoring, cardiac markers follow up - Complete physical examination, ECOG performance status, vital signs measurements - ECG parameters, cardiac function assessment - LVEF - Dose interruptions, reductions and dose intensity

Secondary	To determine the PK profile of [redacted] and potential metabolites	- PK parameters of [redacted] and potential metabolites if applicable, in plasma (e.g. C_{inf}, t_{inf}, AUC_{last}, tlast, C_{last}, AUC, $t_{1/2,z}$, CL and Vd)
	To evaluate the anti-leukemic activity of [redacted]	- CR rate, ORR (including CR/CRi/MLFS), Best Overall Response (BOR), Duration of Response (DOR), Progression Free Survival (PFS), Overall survival (OS) - Anti-leukemic activity assessment using blood, BMA and BMB if available according to ELN 2017 response criteria (Döhner, 2017)
Exploratory	To assess MRD and clonal evolution after treatment with [redacted]	Detection and quantification of residual leukemic cells by gene expression and genomic alterations analysis
	To evaluate the PD profile of [redacted] in relation to:	
	- the biological activity (target engagement)	- Leukemic blast reduction kinetic assessment - Absolute total and B lymphocyte count
	- the relationship between the expression level of Bcl-2 family members (in blood, and bone marrow samples) and the anti-leukemic activity	- Bcl-2 family member protein expression
	- the relationship between the anti-leukemic activity and karyotypes and AML associated genes mutations or dysregulations	- Somatic mutations, indels, rearrangements and amplifications and expression of BCL-2 family member genes and in a panel of cancer-related genes and karyotype analysis
	To explore PK/PD relationships for safety and efficacy	PK/PD relationship related to haematological/ AE findings and to activity
	To explore relationships between DNA polymorphism for proteins involved in ADME and variability of PK parameters	Pharmacogenomics on blood sample (optional part)

4. STUDY DESIGN

4.1. Investigational Plan

4.1.1. Study plan

This trial is an international, open-label, multicentre, non-randomised, non-comparative phase I/II study assessing S64315 in combination with azacitidine and conducted in patients with AML.

The study design will allow the characterization of the safety, tolerability and anti-leukemic activity of [redacted].

This study will therefore be divided into two distinct arms:

- **Arm A** evaluating the combination of S64315 with azacitidine in the frame of a phase I/II trial
  - The purpose of the **dose escalation phase I part** is to determine the safety profile, the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT(s)) and the Recommended Phase II Dose (RP2D) in patients with relapsed/refractory AML
  - The purpose of the **expansion phase II part** is to investigate the clinical activity of this combination in 2 distinct AML populations:
    - **Sub-arm A1** targeting patients with relapsed/refractory AML, HMA treatment-naïve
    - **Sub-arm A2** targeting patients with relapsed/refractory AML previously treated with an HMA

The study plan of Arm A is shown in Figure (4.1.1) 1.

The study plan of sub-arms A1 and A2 will be further defined according to dose escalation phase I part via an amendment.

[redacted]

The study plan of Arm B will be further defined according to the results of Arm A via an amendment.

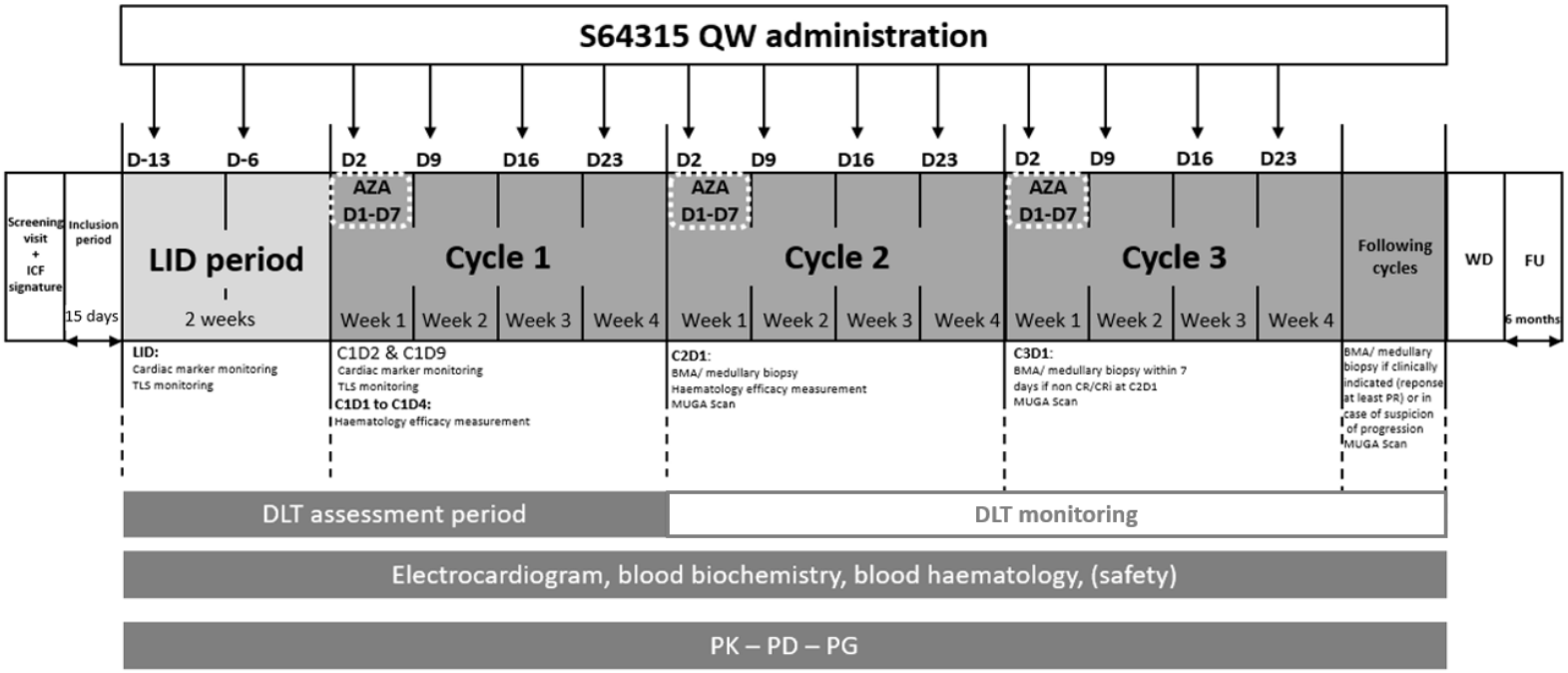
The overall study plan is shown in Figure (4.1.1) 2.

Figure (4.1.1) 1 - Study plan for S64315 administration schedule in combination with azacitidine (dose escalation phase I part – Arm A)

Study treatments:

S64315 administered via IV infusion, weekly during the 2-week lead-in dose period on **D-13** and **D-6** and then on **D2, D9, D16, D23** of each 28-day combination cycle
Azacitidine administered via SC injection, daily from **D1 to D7,** at the dose of 75mg/m² of each 28-day combination cycle

Study periods:



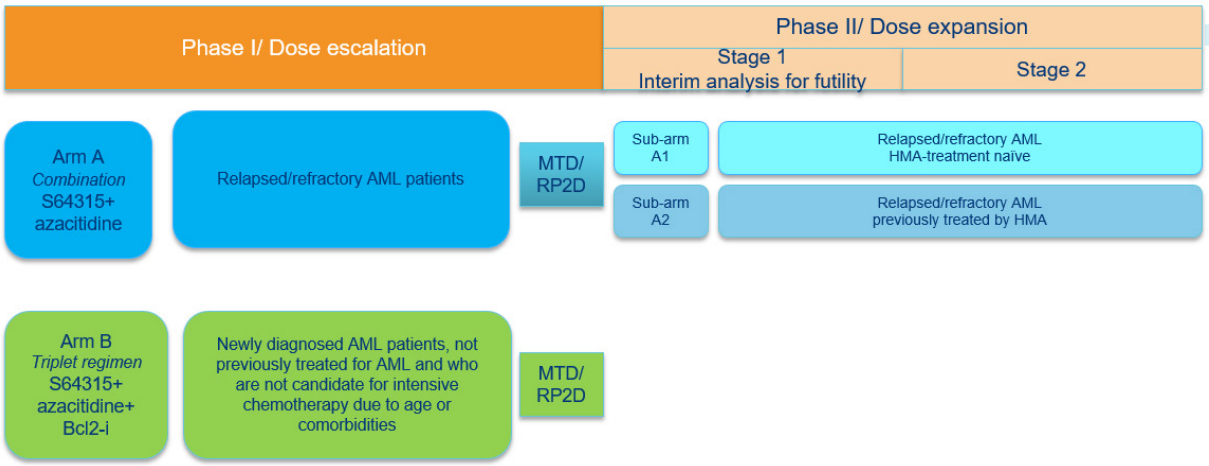
: S64315 lead-in-dose period : combination treatment period

S64315 infusion on D-13, D-6, CxD2, CxD9, CxD16, CxD23
Azacitidine administration from CxD1 to CxD7
PK: pharmacokinetic measurements (see section 9.2)
PD: pharmacodynamics measurements (see section 9.3)
PG: optional pharmacogenomics measurements (see section 9.4)

AZA: Azacitidine

AZA: Azacitidine
D: day
FU: post-withdrawal follow-up
LID: Lead-in dose (see section 4.1.3.2)
W: week
WV: withdrawal visit

Figure (4.1.1) 2 - Overall study plan



The study start is defined as the date of the first visit of the first patient, corresponding to ICF signature. It will be divided into the following periods for each patient of Arm A.

Screening visit

The screening eligibility criteria will be checked after the patient informed consent is obtained.

Inclusion period

The inclusion and exclusion criteria will be checked. The inclusion period can last up to 15 days before starting the LID period. The patient is included when he/she has met all the inclusion criteria.

S64315 lead-in dose period

The lead-in dose period will last 2 weeks. S64315 LID1 will be administered on D-13 at 25 mg and LID2 on D-6 at 50 mg. LID1 and LID2 doses will be fixed all along the study.

Combination treatment period

A treatment cycle will consist of 28 days for patients treated with S64315 in combination with azacitidine during the dose escalation phase I part:

- Weekly schedule for S64315 on CxD2, CxD9, CxD16 and CxD23
- Daily schedule for azacitidine from CxD1 to CxD7 followed by a 21-day rest period

The administration schedule for the expansion phase II part will be defined according to what is observed during the dose escalation phase I part.

The planned duration of combination treatment is until disease progression, unacceptable toxicity, treatment failure (defined as failure to achieve CR, CRi, PR, or MLFS after at least 6 cycles of study treatment) or patient/physician decision. In case of myelosuppression within the context of non-active AML, a 4-week interruption of administration of one or both IMP(s) will be allowed for bone marrow recovery at the investigator's discretion after discussion and approval from the Sponsor.

If the patient is benefiting from the study treatment according to the investigator's judgement and if it is in the patient's best interest to continue the combination of S64315 with azacitidine, the patient may remain on study treatment. In case the patient becomes eligible for transplant, patient's treatment discontinuation should be left at the investigator's decision.

Withdrawal visit (WV): up to 28 days after the last dose of IMP

Post-withdrawal follow-up

After the withdrawal visit, a contact or telephone call will be done for the patients:

- every 3 months (±15 days) from the WV and up to 6 months, except in case of consent withdrawal for the dose escalation phase I part
- every 3 months (±15 days) from the WV and up to 12 months, except in case of consent withdrawal for the expansion phase II part

End of Trial (EoT)

The EoT is defined as the date of the last follow-up of the last patient (including a phone contact), or the date of the last contact attempt if the last patient is declared lost to follow-up.

4.1.2. Investigation schedule

Table (4.1.2) 1 describes the efficacy, safety and other assessments performed during the dose escalation phase I part of the study for **Arm A**.

Investigation schedule for the expansion phase II part for **sub-arms A1 and A2** will be further defined according to what is observed during the dose escalation phase I part.

Investigation schedule for **Arm B** will further defined according to the results of Arm A.

Table (4.1.2) 1 - Investigation schedule for arm A

	Protocol section	Screening visit	Inclusion period	S64315 Lead-in dose period		Cycle 1					Cycle 2 and cycle 3					Cycle 4 and beyond					In case of suspected progression	WV	FU
				D-13	*D-6*	*D1*	*D2*	*D9[1]*	*D16*	*D23*	*D1*	*D2*	*D9*	*D16*	*D23*	*D1*	*D2*	*D9*	*D16*	*D23*			
Informed consent(s)	13 3	X																					
Screening / non screening criteria	5	X																					
Demography	5 1 1	X																					
Inclusion / exclusion criteria	5		X																				
Current medical condition	8 2 1		X																				
Relevant medical / surgical & radiotherapy history	5 / 8		X																				
Previous treatments	6 3		X																				
Concomitant treatments	6 3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy measurements																							
Haematology [A]	7 2		X			X AZA predose	X 4h after S64315 EoI +D3 AZA predose +D4 AZA predose				X AZA predose											X	
BMA and BMB (if available) [B]	7 2		X								X C2D1 AZA predose + C3D1 AZA predose if non-CR/CRi on C2D1					+ C7D1 AZA predose if non-CR/CRi/MLFS or PR at any other cycle					X	X	
Safety measurements																							
Vital signs (temperature, HR, BP)	8		X	X Predose, EoI, 2h and 24h after EoI	X Predose, EoI, 2h and 24h after EoI	X AZA predose	X S64315 predose, EoI, 2h and 24h after EoI	X S64315 predose, EoI, 2h after EoI	X S64315 predose, EoI, 2h after EoI	X S64315 predose, EoI, 2h after EoI	X AZA predose	X S64315 predose, and EoI	X S64315 predose	X S64315 predose	X S64315 predose	X AZA predose	X S64315 predose	X S64315 predose	X S64315 predose	X S64315 predose		X	
ECOG PS	8		X	X Predose		X AZA predose					X AZA predose					X AZA predose						X	

	Protocol section	Screening visit	Inclusion period	S64315 Lead-in dose period		Cycle 1					Cycle 2 and cycle 3					Cycle 4 and beyond					In case of suspected progression	WV	FU
				D-13	*D-6*	*D1*	*D2*	*D9[l]*	*D16*	*D23*	*D1*	*D2*	*D9*	*D16*	*D23*	*D1*	*D2*	*D9*	*D16*	*D23*			
Height	8		X																				
Body weight	8		X			X AZA predose					X AZA predose					X AZA predose						X	
DLT assessment	4 1 3 6			X during LID period and cycle 1							X (DLT monitoring)												
Adverse events	8 3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory examinations																							
Blood haematology	8		X [C]	X [D] Predose*, 24h and 48h after EoI	X [D] predose*, 24h and 48h after EoI	X AZA predose*	X S64315 predose* and EoI	X S64315 predose*	X S64315 predose*	X [p] S64315 predose*	X AZA predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*	X AZA predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*		X	
Blood biochemistry (fasted when applicable[k])	8		X [C]	X Predose*, 8h[k] 24h and 48h after EoI	X Predose*, 8h[k], 24h and 48h after EoI	X AZA predose*	X S64315 predose* EoI, 8h[k], 24h[k] and 72h[k] after EoI[k]	X S64315 predose* 24h after EoI[k]	X S64315 predose*	X S64315 predose*	X Aza predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*	X Aza predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*	X S64315 predose*		X	
Cardiac markers (troponin, CPK-MB and BNP)	8		X [CJ]	X Predose*, 6h, 24h, 48h and 72h after EoI	X Predose*, 6h, 24h, 48h and 72h after EoI	X AZA predose*	X S64315 predose*, 6h, 24h, 48h and 72h after EoI	X S64315 predose*, 6h, 24h, 48 and 72h after EoI	X [E] S64315 predose*	X [E] S64315 predose*	X Aza predose*	X [E] S64315 predose*	X [E] S64315 predose*	X [E] S64315 predose*	X [E] S64315 predose*	X Aza predose	X [E] S64315 predose*	X [E] S64315 predose*	X [E] S64315 predose*	X [E] S64315 predose*			
TLS monitoring - laboratory parameters (haematology & biochemistry)	8 2 8			X Predose*, 2h, 4h, 8h, 24h,	X Predose*, 2h, 4h, 8h, 24h,	X AZA predose, 1h30, 6h post injection	X S64315 predose*, 2h, 4h, 8h and 24h after S64315 EoI	X S64315 predose*, 2h, 4h, 8h and 24h after S64315 EoI	X [F]	X [F]		X [F]	X [F]	X [F]	X [F]		X [F]	X [F]	X [F]	X [F]			
Blood coagulation	8		X [C]	X Predose*		X AZA predose*					X AZA predose*					X AZA predose*						X	
Thyroid function	8		X [C]	X Predose*		X AZA predose*					X AZA predose*					X AZA predose* until C6, then every 4 cycles							
Hepatitis markers	8		X [C]																				
Urinary analysis	8		X [C]	X Predose*		X AZA predose*					X AZA predose*					X AZA predose*						X	
Pregnancy test	8		X [C] Serum								X serum or urine					X serum or urine						X serum	

	Protocol section	Screening visit	Inclusion period	S64315 Lead-in dose period		Cycle 1					Cycle 2 and cycle 3					Cycle 4 and beyond					In case of suspected progression	WV	FU
				D-13	*D-6*	*D1*	*D2*	*D9*[I]	*D16*	*D23*	*D1*	*D2*	*D9*	*D16*	*D23*	*D1*	*D2*	*D9*	*D16*	*D23*			
Chest X-Ray	8 2 1		X																				
ECG (triplicate) [G]	8		X [C]	X predose, EoI, 1h, 2h, 6h, 24h after EoI	X predose, EoI, 1h, 2h, 6h, 24h after EoI	X AZA predose	X S64315 predose, EoI, 1h, 2h, 6h, 24h after EoI	X S64315 predose, EoI, 1h, 2h, 6h, 24h after EoI	X S64315 predose, EoI	X S64315 predose, EoI		X S64315 predose, EoI					X S64315 predose, EoI					X	
ECHO/MUGA scan	8		X [C]								X Aza predose					X Aza predose every 2 cycles						X	
Pharmacokinetic measurements **																							
Blood samples [H]	9 2 1			X EoI, 4h and 24h after EoI			X S64315 predose, 10 , 30 after SoI, EoI, 30 , 1h, 2h, 4h, 7h ±1h after EoI +D3: S64315 24h after EoI																
Pharmacodynamics measurements **																							
BMB	9 3		X								X in case of response, at least PR										X		
Blood samples (protein expression)	9 3			X predose		X AZA predose	X AZA predose, S64315 predose, 1h and 24h ±2h after EoI				X AZA predose	X AZA predose, S64315 predose, 1h and 24h ±2h after EoI				X AZA predose	X AZA predose, S64315 predose, 1h and 24h ±2h after EoI				X		
Blood samples (genomic alterations and MRD)	9 3			X predose		X AZA predose					X C2D1 and C3D1 AZA predose and anytime in case of CR when CR achieved and every 3 months during study treatment period					Anytime in case of CR when CR achieved and every 3 months during study treatment period					X		

	Protocol section	Screening visit	Inclusion period	S64315 Lead-in dose period		Cycle 1					Cycle 2 and cycle 3					Cycle 4 and beyond					In case of suspected progression	WV	FU
				D-13	*D-6*	*D1*	*D2*	*D9*[I]	*D16*	*D23*	*D1*	*D2*	*D9*	*D16*	*D23*	*D1*	*D2*	*D9*	*D16*	*D23*			
Absolute total and B lymphocyte count	9 3			X predose		X AZA predose	X AZA predose, S64315 predose, 4h, 6h, 24h and 72h after EoI	X predose 24h after EoI	X predose		X AZA predose			X predose		X AZA predose			X predose				
BMA (protein expression)	9 3		X								X in case of response, at least PR										X		
BMA (genomic alterations and MRD)	9 3		X								X C2D1 and C3D1 AZA predose and anytime in case of CR when CR achieved and every 3 months during study treatment period					Anytime in case of CR when CR achieved and every 3 months during study treatment period					X		
Saliva (DNA sequencing)	9 3		X								X in case of CR												
Copy of karyotype report (if available)	9 3		X																		X		
Pharmacogenomics measurements (optional)																							
PG measurements	9 4					X AZA predose																	
IMP circuit																							
S64315 dispensation / administration / compliance [I]	6 1 1			X	X		X	X	X	X		X	X	X	X		X	X	X	X			
Azacitidine dispensation / administration / compliance [I]	6 1 1					X Daily from D1 to D7					X Daily from D1 to D7					X Daily from D1 to D7							

SoI: start of infusion
EoI: end of infusion
AZA: azacitidine
A: (Efficacy measurements) Predose exams to be performed within 24h prior to C1D1; ideally in the morning on C1D2 and C1D3 and within 3 days prior to C2D1 and C3D1
B: (Efficacy measurements) BMA and BMB predose to be performed within 2 days prior to C2D1 and within 7 days prior to C3D1 and C7D1
C: (Safety measurements) Exams to be performed within 7 days prior to inclusion and results available for inclusion
D: (Safety measurements) WBC count must be checked twice a week during the LID period in order to maintain this level < 10 G/L

E: (Safety measurements) In case of any troponin increase observed after any of the two first infusions of cycle 1, it will be recommended to assess cardiac markers at 48h and 72h after S64315 EoI and after each subsequent infusion (before discharge and beyond, if needed), on a regular basis
F: (Safety measurements) Applicable for all patients with a risk of developing TLS according to the investigator's judgment: prior to each S64315 infusion (predose) and 2h, 4h, 8h and 24h±2h after each S64315 EoI
G: (Safety measurements) ECG predose could be performed within 24 hours before any S64315 infusion or after azacitidine before S64315 CXD2 infusion
H: (Pharmacokinetic measurements) PK predose time points should be collected 5-30 minutes before infusion/injection; PK S64315 EoI time points should be collected within 5 to 10 minutes before the end of infusion
I: (IMP circuit) On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine should be administered 2 hours (±10 minutes) prior to S64315
J: Except CPK-MB and BNP
K: (Biochemistry) Assessments should be limited to AST, ALT and total bilirubin for 8h timepoints after LID1 and LID2 EoI, 8h, 24h and 72h timepoint after C1D2 EoI and 24h timepoint after C1D9 EoI. Fasting conditions are not required for these timepoints.
L: If Day 9 administration is not performed, all scheduled assessments should be performed at the next S64315 infusion (2nd S64315 infusion in cycle 1).
*: Predose laboratory examinations to be performed within 3 days prior to LID1 or LID2, within 24h prior to S64315 C1D2 and within 3 days prior to any other IMP administration
**: In case of an additional lead-in dose period (see section 6.1.2), all investigations must be performed except those for Pharmacokinetic and Pharmacodynamics measurements.

Table (4.1.2) 2 - Pharmacokinetic measurements for arm A

	Protocol section	Lead-in dose period	*D1*	*D2*	*D3*	*D9*	*D10*
S64315 blood samples	9.2.1	LID1 EoI**, 4h and 24h after LID1 EoI**	*NA*	Predose*, 10' and 30' after SoI, EoI**, 30', 1h, 2h, 4h and 7h ± 1h after EoI**	24h after EoI**	*NA*	*NA*

AZA: azacitidine; LID1: Lead-in dose 1; SoI: Start of infusion; EoI: End of Infusion; NA: not applicable
*PK predose time points should be collected 5-30 minutes before infusion/injection
**PK S64315 EoI timepoints should be collected within 5 to 10 minutes before the end of infusion

For further practical details, methods of measurement are provided in sections 7, 8 and 9.

The maximum total volume of blood collected per patient during the study will be around 918 mL until Cycle 3, around 180 mL per additional cycle, around 30 mL in case of suspicion of disease progression and around 20 mL in case of withdrawal visit.

4.1.3. Dose escalation phase I part procedure for Arm A

The following sections are applicable for the **Arm A** dose escalation phase I part. They will be updated for **Arm B** dose escalation phase I part, according to the results of Arm A.

4.1.3.1. General points

The sponsor will be responsible for the coordination of the clinical trial and will provide regular updates to the centres on the study progress.

The dose escalation phase I part will be conducted in clinical centres which have a proven expertise in phase I studies in oncology. Multicentre study will allow improving patient's recruitment.

During the dose escalation phase I part, at each new dose level, the IMPs will be firstly administered to one patient. If no medically important or life-threatening toxicity occurs during a 1 week observation period, the subsequent patients will be allowed to start treatment without further delays between subsequent patients. The dose increase between two dose levels will be guided by the observed toxicities.

A specific monitoring of potential cardiac, haematological, liver, etc. toxicities will be set up as described in section 8.

4.1.3.2. Dose administration schedules

The initial schedule will consist of a 2-week S64315 lead-in dose 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.

Alternative dosing schedules based on the observed clinical safety, PK/PD data and non-clinical data (in vitro, in vivo, PK/PD modelling data) may be further explored. They should be integrated in the protocol via an amendment.

S64315 will be administered via intravenous (IV) infusion over at least 2h once every week, as follows:

- **2-week lead-in dose period** i.e. fixed lead-in dose 1 (LID1) of 25 mg on D-13 and fixed lead-in dose 2 (LID2) of 50 mg on D-6
- followed by the **combination treatment period over 28-day cycles**, i.e. on CxD2, CxD9, CxD16 and CxD23

The starting dose will be 50 mg. A panel of dose from 25 mg (-1) and up to 250 mg could be explored according to the dose escalation process of the BLRM. For more details, please refer to Table (4.1.3.3) 1.

A minimum of 5 days between two infusions of S64315 is required.

An infusion could be postponed in case of 1-day delay and should be discussed with the Sponsor in case of 2-day delay, for any reason other than medical / toxicity.

Azacitidine will be administered during the combination treatment period at 75 mg/m² via subcutaneous (SC) injection, daily for 7 days, i.e. from CxD1 to CxD7, followed by a rest period of 21 days (28-day cycle).

On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine should be administered 2h (±10 min) prior to S64315.

4.1.3.3. Dose escalation scheme

An adaptive Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) will be used to guide the dose escalation of S64315 in combination with azacitidine. The dose escalation will only concern S64315.

All available data on DLTs (assessed from the LID period and up to the end of cycle 1) will be 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 Dose-Limiting Toxicity Evaluable Set (DLTES) (see section 4.1.3.5). If a patient is not eligible for inclusion in the DLTES, this patient must be replaced.

The dose allocation methodology is detailed in section 10.

A maximum of 6 DLT-evaluable patients may be initially enrolled at a new dose level, and a minimum of 3 DLT-evaluable patients must be treated at a given dose level in order to begin treatment of patients at a new, higher dose level. To better characterize the safety, tolerability, PK, PD, or preliminary clinical activity of S64315 in combination with azacitidine, more than 6 DLT-evaluable patients may be treated in a cohort. If the starting dose of the combination is not well tolerated, a dose level-1 will be considered. Intermediate doses may be tested, if needed. For more details, please refer to Table (4.1.3.3) 1. A minimum of 6 DLT evaluable patients must have been evaluated at the dose considered to be the MTD, and before treating patients with this dose in the Phase II part of the study.

Table (4.1.3.3) 1 - Provisional dose levels of S64315

Dose level	Proposed dose*	Increment from previous dose
-1**	25 mg	-50%
1	50 mg	Starting dose
2	100 mg	100%
3	200 mg	100%
4	250 mg	25%

**It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts can be added at any dose level below or at the MTD in order to better understand safety, PK or PD*
***No dose reduction below dose level -1 is permitted for this study*

4.1.3.4. Intra-patient dose escalation

Intra-patient dose escalation of S64315 is not permitted at any time within the first 4 cycles of treatment. After Cycle 4 is completed, individual patients may be considered for treatment at a dose of S64315 higher than the dose initially assigned. For a patient to be treated at a higher dose of S64315, he/she must have tolerated its originally assigned dose for at least the last 4 cycles of therapy prior to the intra-patient dose escalation (i.e. he/she must not have experienced any S64315-related or S64315/azacitidine-related toxicity CTCAE Grade ≥ 2 at the originally assigned dose). Moreover, the newly assigned higher dose with which the patient is to be treated must have been validated, i.e. it should be a dose lower than the dose of the combination currently tested and considered safe according to the EWOC criterion at the time of the decision to escalate the dose of the patient. S64315 dose increase can occur as often as deemed necessary. For any further increase after the initial intra-patient dose escalation, the same rules should be applied.

Consultation and agreement with the Sponsor must occur prior to any intra-patient dose escalation. Data from the first cycle of treatment at the new dose levels will not be formally included into the statistical model describing the relationship between doses combined and occurrence of DLT. However, this data will be incorporated into the clinical assessment of safety within a dose escalation EoC meeting.

4.1.3.5. DLT definition

A dose-limiting toxicity (DLT) is defined as a clinically significant adverse event graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, observed following the administration of the test drug, assessed as unrelated to disease progression, intercurrent illness, or concomitant medications, considered at least possibly related to the test drug by the investigator and that meets any of the criteria included in Table (4.1.3.5) 1.

For each patient, an assessment of DLT will be performed at the end of the first cycle of treatment, through C1D28. This assessment will include all toxicities observed starting from the LID period through C1D28. Only DLTs occurring during the LID period + Cycle 1 will be included in the Bayesian logistic regression model (BLRM) that estimates the relationship between dose and DLTs. However, monitoring for DLTs that occur after Cycle 1 will continue, in case there is evidence for delayed or cumulative toxicity.

Table (4.1.3.5) 1 - Toxicity criteria according to NCI CTCAE grading

TOXICITY	DLT CRITERIA
Eye disorders: blurred vision; cataract; corneal ulcer; dry eye; eye pain	Grade ≥ 3 confirmed by an ophthalmologic examination
GI disorders	Grade ≥ 3 nausea, vomiting or diarrhoea resulting in hospitalization, tube-feeding or use of total parenteral nutrition (TPN)
	Grade 4 diarrhoea
Renal abnormalities	Grade ≥ 3 serum creatinine
Hepatic abnormalities	AST or ALT ≥ 3xULN along with a total bilirubin > 2.0xULN and confirmed Hy's law cases according to FDA guidance; For patients with elevated baseline AST or ALT or total bilirubin: [AST or ALT > 2.0xbaseline AND > 3.0xULN] OR [AST or ALT > 8.0xULN], whichever is lower, combined with [total bilirubin > 2.0 x baseline AND > 2.0xULN]
	Isolated Grade 3 AST or ALT which does not resolve within 7 days to Grade ≤1
	Isolated Grade 4 AST or ALT
For any Grade ≥3 hepatic toxicity which does not resolve within 7 days to Grade ≤ 1 level or baseline, an abdominal CT scan or hepatic echography must be performed.	
Pancreatic abnormalities	Grade ≥ 3 serum lipase and/or serum amylase
	Grade ≥ 3 pancreatitis
For any Grade 3 or Grade 4 pancreatic toxicity, which does not resolve within 7 days to Grade ≤1 level or baseline, an abdominal CT scan must be performed	
Creatine kinase (CK) / Creatine phosphokinase (CPK)	Grade ≥ 3 serum CK/CPK
	Grade 3 isolated electrolyte abnormalities (i.e. those occurring without clinical consequence) not recovered with or without intervention, to Grade < 2 level within 72 hours

TOXICITY	DLT CRITERIA
Electrolyte abnormalities (including magnesium, calcium, phosphorus, etc.) **clinically significant**	Any Grade 4 electrolyte abnormality
Cardiac disorders	QTcF interval ≥ 501 ms or increase of > 60 ms from baseline on at least two separate ECG assessments (1 assessment = triplicate ECG)
	Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline AND LVEF < 50%
	Asymptomatic, absolute decrease in LVEF of 20% or greater from baseline
	Troponin increase > 10xULN or a troponin increase consistent with the diagnosis of a myocardial infarction (Grade 3)
	Symptomatic congestive heart failure
Skin and subcutaneous tissue disorders	Grade ≥ 3 rash
Haematological abnormalities	Grade 4 neutropenia and/or thrombocytopenia persisting for 28 days after the start of azacitidine dosing in a cycle of therapy in the absence of active AML (< 5% blasts) or active MDS or myelofibrosis
Other AEs	Any Grade ≥ 3 AE
	Single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in a cycle may be considered to be DLT by the Investigators and the Sponsor, even if not Grade ≥ 3
	Failure to restart test drug administration at the same dose due to drug-related toxicity
	Failure to restart test drug administration at the same dose within one cycle (i.e. 28 days) of the first missed dose due to delayed recovery from drug-related toxicity
	Failure to initiate cycle 1 after completing the LID period or failure to receive LID2 after receiving the LID1, due to drug-related toxicity
NCI CTCAE v5.0 will be used for grading	

The following criteria will not be considered as DLT:

- Grade 3 nausea, vomiting, diarrhoea, anorexia or constipation that do not result in hospitalization, tube-feeding or use of TPN
- Grade 3 fatigue, asthenia, fever
- Grade 3 isolated electrolyte abnormalities (i.e. those occurring without clinical consequence) that resolve, with or without intervention, to Grade < 2 level in 72 hours

Patients who meet any of the criteria included in Table (4.1.3.5) 2 at the end of Cycle 1 will not be evaluable for DLT and therefore will be replaced during the dose escalation phase I part of the study, but not in the expansion parts of the study.

Table (4.1.3.5) 2 - Non evaluability criteria

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 - see Table (4.1.3.5) 3
If a patient received more than the assigned IMP doses from study entry to DLT occurrence during the DLT assessment period, non-evaluability criteria will be reassessed by Sponsor and investigator - see Table (4.1.3.5) 3

Table (4.1.3.5) 3 - Minimum number of S64315 and azacitidine doses to meet minimum exposure until the end of cycle 1

Schedule description	Minimum number of doses
S64315 during the 2-week LID period (LID1 on D-13 and LID2 on D-6)	2 out of 2
S64315 (D2, D9, D16 and D23 in 28-day cycle)	3 out of 4
Azacitidine (D1 to D7 in 28-day cycle)	5 out of 7

4.1.3.6. DLT management

Study treatments must be delayed for any patient who experienced a DLT. Conditions to resume treatment are described in section 8.12.

All DLT will be reported to I.R.I.S. within 24h via the DLT form in the electronic Case Report Form (eCRF). The eCRF 'Adverse Event' page should then be filled in, without waiting for the results of the clinical outcome or of additional investigations. When data of the DLT form are submitted, an e-mail will be immediately and automatically sent to the sponsor.

If the eCRF is unavailable when the investigator is informed of the DLT, he/she should:

- report the DLT on a paper 'DLT form'
- send the form by fax immediately to I.R.I.S. at the following number: +33.1.55.72.50.04

As soon as the eCRF becomes available again, the investigator must enter the data in the eCRF.

4.1.3.7. Decision process and decision rules

Before testing a new dose level during the dose escalation phase, an EoC meeting between the Sponsor (Therapeutic Area Oncology and Immuno Oncology, Medical Safety Leader, Methodology Department and Clinical Pharmacokinetics department), the coordinator and the investigators will take place to discuss the toxicities in terms of DLTs, safety data, the PK and available PD and the preliminary efficacy data observed in all patients. This meeting will support the decision to escalate to the next dose level of the treatment, to decide jointly of the next dose level to be tested, the go/no go for the expansion phase II part.

If a dose/treatment schedule has not yet been tested, a one-week period should be respected between the C1D2 of the first patient and the C1D2 of subsequent patients of the cohort (between the first and the second infusion in patient of S64315 at the full tested dose). If no medically important or life-threatening toxicity occurs during the one-week observation period, the subsequent patients will be allowed to start treatment without further delays between subsequent patients.

A template of 'Dose allocation meeting minutes' is available in Appendix 6.

A Data Safety and Monitoring Board (DSMB) will be set up and will review the safety data before each EoC meeting and provide recommendations to the Sponsor.

4.1.4. Expansion phase II part for sub-arms A1 and A2

The RP2D of S64315 in combination with azacitidine and its administration schedule will be defined according to results observed in the dose escalation phase I part in terms of safety, activity and, if appropriate, PK data.

The expansion phase II part will be divided in two distinct parts according to a Bayesian two-stage design: stage 1 and stage 2.

A futility analysis will be performed at the end of stage 1 for sub-arms A1 and A2 based on the rate of CR observed after 4 cycles of combination treatment. This analysis will support the decision to stop the evaluation of the combination or to continue the evaluation during the stage 2. The rationale for the expansion phase II part design is described in section 2.3.7.

Up to 50 patients will be treated in each sub-arm (A1 and A2) at the RP2D as follows (more detail on this topic is provided in section 10.5.2 and Appendix 8):

- Twenty-three patients will be treated in the first stage of analysis; if there is evidence that the CR rate is < 20% (if there are fewer than 5/23 patients who achieve a CR), treatment will be stopped in the relevant arm
- If there is evidence that the CR rate >= 20%, 27 additional patients will be treated to better estimate the rate of CR.

After at least 4 patients have been treated during dose expansion at the RP2D, if the observed rate of DLT through the end of Cycle 1 exceeds 33% (including the patients treated at this dose during dose escalation), the BLRM will be updated to determine whether the RP2D still satisfies the EWOC principle. If the RP2D is estimated to have a ≥25% posterior probability of generating excessive toxicity (DLT rate between 33% and 100%) during the first cycle of treatment, then enrollment to the study will be paused. A risk assessment will be conducted by the DSMB, the investigators and sponsor, and consideration will be given to reducing the RP2D.

In addition, monitoring will continue for DLTs that may occur after the first cycle of treatment. After at least 4 patients have had the opportunity to receive a second cycle of treatment, if the posterior probability is greater than 25% that the true rate of DLT occurring after Cycle 1 is >33%, enrollment to the study will be paused. Patients should have received at least three doses of S64315 from Cycle 2 to be evaluable, unless dosing was limited by the occurrence of a DLT. Evaluable patients treated at this dose during escalation will also be included in this assessment. The study will also be paused if the cumulative rate of Grade ≥3 treatment-related cardiac adverse events at the RP2D exceeds 20%. In either case, the safety of the RP2D will be re-evaluated by the DSMB, the investigators and sponsor, and consideration will be given to reducing the RP2D.

More detail on this topic is provided in section 10.3.2.

4.2. Measures to minimise bias

During the study:

- International multicentre study
- Triplicate 12-lead ECGs will be recorded on site and analysed by a central reading CRO for ECGs tracings
- PK sample analyses will be performed in a specific central laboratory, which will minimise the variability of measurements
- PD sample analyses (protein and gene expression, gene alteration and determination of complex dissociation analysis) will be centrally stored and sent to a specific analytical centre for analyses, to minimise the variability of measurements
- Genes implicated in ADME analyses (optional) will be performed in a specific central laboratory

4.3. Study products and blinding systems

4.3.1. Products administered

Arm A

S64315 (test drug) and azacitidine administered in combination are both IMPs in Arm A.

Azacitidine will be provided as marketed boxes.

Les Laboratoires Servier Industrie (Gidy, France) will:
- pack, release and supply S64315 Therapeutic Units (TUs);
- relabel, release and supply azacitidine marketed boxes.

Table (4.3.1) 1 provides a description of the IMPs.

Table (4.3.1) 1 - Description of the IMPs (S64315 and azacitidine)

	S64315 Organic concentrate	S64315 Liposomal vehicle	Azacitidine
Pharmaceutical form	Concentrate of solution for infusion	Intravenous infusion	Powder for suspension for injection
Unit dosage	209.95 mg/3.4mL	2.39 gram of egg phospholipids in 23.9 mL	100 mg
Appearance, colour	Colourless to greenish, yellowish or slightly brownish, clear solution	A yellow to brown turbid solution	White lyophilized powder
Composition	Each vial contains an overfill volume of 0.4 mL, so it actually contains 234.65 mg of S64315. The vials contain a clear, colourless to greenish, yellowish or slightly brownish solution comprising of the active ingredient S64315, propylene glycol, anhydrous ethanol, DMPG (1,2-Dimyristoyl-sn-1-glycero)-3-phospho-rac-glycerol sodium salt), PEG 300 (Polyethylene glycol 300)	Each vial contains 2.39 gram of egg phospholipids. The liposomal vehicle comprises egg phospholipids, sucrose, L-histidine and water for injections. Sodium hydroxide for injections and hydrochloric acid are also used for pH adjustment. The egg phospholipids comprising liposomal vehicle form small liposomes in aqueous environment and are used as a solubilizing vehicle, able to dissolve S64315 in an aqueous environment after mixing with S64315 liquid in the vial	Each vial contains 100 mg azacitidine. After reconstitution, each mL of suspension contains 25 mg azacitidine. Excipient: <

Table (4.3.1) 2 provides a description of the packaging of the IMPs.

Table (4.3.1) 2 - Description of packaging

Number of units of the pharmaceutical form per primary packaging	- 3.8 mL of S64315 concentrate for solution for infusion in individual 6 mL glass vial - 23.9 mL of liposomal vehicle in individual 30 mL glass vial - 100 mg of azacitidine powder for suspension for injection in individual vial
Number of primary packaging per secondary packaging	1 vial of S64315 concentrate per box 1 vial of S64315 liposomal vehicle per box 1 vial of azacitidine per box
Number of secondary packaging per patient and per treatment period	The number of S64315 concentrate vials and liposomal vehicle and the number of azacitidine boxes per patient and per administration will depend on the dose level and the administration schedule

The labelling of packages complies with the regulatory requirements of each country involved in the study.

[redacted]

4.3.2. IMP management

Arm A

Both IMPs will be sent by Les Laboratoires Servier Industrie (Gidy, France) either directly to the investigational centres or to sub-distribution centres or to local pharmacies depending on the geographic areas and the local regulatory requirements.

IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to section 6.2), accountability and collection are the responsibility of the investigator and/or pharmacist of the medical institution.

For any information regarding azacitidine management, please refer to azacitidine SmPC.

Handling conditions and cleaning procedures

Specific handling conditions and cleaning procedures will be described in the Pharmacy Manual.

Stability and storage

The IMPs should be stored in a secure area with restricted access. Specific storage conditions are mentioned on IMP labelling and are detailed in S64315 Investigator's Brochure and in azacitidine SmPC.

The investigator/pharmacist is responsible for the IMP temperature monitoring on a daily basis using a 'Therapeutic Unit temperature log sheet – centre' (recording Min-Max temperatures every working day) or an equivalent document.

In case of temperature deviation, the investigator/pharmacist should immediately:
- Place the concerned IMPs in quarantine
- Alert the monitor or the local project manager if the monitor is absent, forward him all needed information and implement the received instructions

Furthermore, the investigator/pharmacist must put in place an adequate corrective/preventive action once the first temperature deviation occurs, in order to avoid recurrence.

IMP management will be verified on a regular basis by the study monitor.

The investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must complete in real time all the documents provided by the Sponsor concerning IMP management (therapeutic unit tracking form or an equivalent document). Therapeutic unit tracking form, or an equivalent document, is the source document to fill.

The investigator and/or the pharmacist of the medical institution should only use the IMPs provided for the patients involved in the study by the Sponsor (or Gidy).

All defects or deterioration of IMPs or their packaging are to be reported to the study monitor. The investigator will notify the monitor of all complaints set out by a patient (appearance, etc.).

In the event of anticipated IMP return to the Sponsor (batch recall), the Sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study centre. On receipt of the letter, the investigator and/or the pharmacist will identify the patients in possession of the IMPs at the moment the incident becomes known, by using, among other tools, the therapeutic unit tracking form, or an equivalent document, and will contact them immediately.

Destruction

Destruction of the IMPs is the responsibility of the Sponsor or the pharmacist of the medical institution.

Remaining treatments (used and unused IMPs) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMPs management.

A certificated destruction will be performed according to standard modalities for that class of product and the attestation must be sent to the Sponsor. The practical procedures for destruction of unused IMPs will be defined by the Sponsor and adapted to the centre. An IMP collection and destruction form will be completed before the shipment of IMPs to destruction. Destruction of IMPs may be possible (after drug accountability and Sponsor authorization) when the product has been used or damaged, has expired, or after at least the last visit of the last treated patient.

Arm B

Details regarding [redacted] via an amendment.

4.3.3. Management of blinding systems

Not applicable

4.4. Discontinuation of the study

4.4.1. Premature discontinuation of the study or temporary halt

This study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause. Stopping rules during the study are described in section 8.12 for any patient throughout the study, in section 10.2.7 for the dose escalation phase I part, in section 10.3 for the expansion phase II part and in section 4.4.2. Moreover, the DSMB could also give recommendations, based on the review of the safety data, to suspend or to prematurely terminate the study/treatment arms in case of serious concerns about patient safety.

After having informed the coordinator, the sponsor or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or the Competent Authorities may terminate the study before its scheduled term. Two copies of the written confirmation will be dated and signed by the coordinator. The IRB/IECs and Competent Authorities will be informed according to local regulations.

If the study is prematurely discontinued, the ongoing patients should be seen as soon as possible, and the same assessments as described in section 5.8 should be performed.

Under some circumstances, the investigator may be informed of additional procedures to be followed, in order to ensure that adequate consideration is given to the protection of the patient's interests.

In case of study suspension (temporary halt), the study may resume once concerns about safety, protocol compliance and data quality are addressed and satisfy the Sponsor, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authorities.

4.4.2. Criteria for stopping or pausing the study

The study will be paused and the health authorities will be notified if:

- Any death suspected to be related to S64315 occurs within 30 days of study treatment administration
- The observed cumulative rate of Grade ≥3 treatment-related cardiac adverse events at the RP2D (including patients treated in both dose escalation and dose expansion) exceeds 20%, after at least 4 patients have been treated with S64315 in dose expansion

4.4.3. Discontinuation of the study in the event of objective reached

Not applicable

4.5. Source data

Patient's medical file (e.g. ECG reports, clinical laboratory examination reports and all other patients' examination results, copies of karyotype reports, requisition forms, registration forms, exam recording (and the result report when applicable) provided by the CRO to the centre, and the result report when applicable, will be considered as source documents.

Source data and source documents of the centre should be clearly identified in a specific, detailed and signed document before the beginning of the study.

5. SELECTION AND WITHDRAWAL OF PATIENTS

The criteria for dose escalation phase I part of **Arm A** are defined hereafter and should be adapted for expansion phase II part (**sub-arms A1 and A2**) according to results observed in the dose escalation phase I part. The criteria will be defined later for **Arm B** according to the results of Arm A.

5.1. Screening criteria

5.1.1. Demographic characteristics

1. Patients aged ≥ 18 years

5.1.2. Medical and therapeutic criteria

2. a. Patients with cytologically confirmed and documented de novo, secondary or therapy-related AML as defined by WHO 2016 classification (Arber, 2016) excluding acute promyelocytic leukaemia (APL, French-American-British M3 classification) with:
   - relapsed or refractory disease and without established alternative therapy or
   - secondary to MDS without established alternative therapy
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (Appendix 3)

5.1.3. Informed consent

4. Written informed consent obtained prior any study-specific procedure as described in section 13.3

5.2. Non-screening criteria

5.2.1. Medical and therapeutic criteria

5. Previous myeloproliferative syndrome (MPS)
6. *Criterion deleted in Substantial Amendment #1 (Amended Protocol V. 2.0)*
7. Patients previously treated with any Mcl-1 inhibitor

5.2.2. General criteria

8. Pregnant and lactating women
9. Unlikely to cooperate in the study
10. Participation in another interventional study requiring investigational treatment administration at the same time or within 2 weeks or at least 5 half-lives (whichever is longer) prior to the first IMP administration; participation in non-interventional registries or epidemiological studies is allowed. In case of biologic agents with a long half-life such as CART cells, immune checkpoint inhibitors, bispecific antibodies, a washout of 28 days is allowed
11. Patients already enrolled in the study (informed consent signed) and treated in the study

5.3. Inclusion criteria

5.3.1. General criteria

12. ECOG performance status ≤ 2 (Appendix 3)
13. Women of childbearing potential (WOCBP) must use a highly effective method of birth control (described in section 5.5), during study and up to 6 months after the last IMP administration. In case of use of oral contraception, women should have been stable on the same contraceptive drug (i.e. same active principle) for at least one month prior to the first IMP administration
14. Men with WOCBP partners must use a condom during the study and up to 3 months after the last IMP administration. In addition, contraception should be considered for their female partners. Contraceptive measures do not apply if the patient is sterile, vasectomized or sexually abstinent. Sperm donation will not be allowed during the study and up to 3 months after the last IMP administration

5.3.2. Medical and therapeutic criteria

15. Adequate haematological function based on the last assessment performed within 7 days prior to the first IMP administration, defined as:
    - Circulating white blood cell count < 10 G/L (only use of hydroxycarbamide or leukapheresis before study drug initiation is allowed to achieve this inclusion criterion)
16. a. Adequate renal function based on the last assessment performed within 7 days prior to the first IMP administration defined as calculated creatinine clearance > 60 mL/min/1.73m², determined by MDRD (Appendix 4)
17. Adequate hepatic function based on the last assessment performed within 7 days prior to the first IMP administration defined as:
    - AST and ALT < 1.5 x 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 are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN

5.4. Exclusion criteria

5.4.1. General criteria

18. Women of childbearing potential (WOCBP) tested positive in a serum pregnancy test within 7 days prior to the first day of IMP administration
19. Patients who have not recovered from toxicity of previous anticancer therapy, including Grade ≥ 2 toxicity (except alopecia of any grade) according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) v5.0, prior to the first IMP administration

5.4.2. Medical and therapeutic criteria

20. Severe or uncontrolled active acute or chronic infection
21. Uncontrolled hepatitis B or C infection
22. Known carriers of HIV antibodies
23. Known history of significant liver disease
24. Known active acute or chronic pancreatitis
25. Known active central nervous system disease
26. Clinically active severe skin diseases

27. Major surgery within 4 weeks prior to the first IMP administration or patients who have not recovered from side effects of the surgery
28. History of myocardial infarction (MI), unstable angina pectoris or coronary artery bypass graft (CABG) within 6 months prior to first IMP administration
29. a. Troponin I > ULN or Troponin T > ULN if Troponin I cannot be assessed
30. Clinically significant cardiac dysfunction (including NYHA class ≥II heart failure, Left Ventricular Ejection Fraction (LVEF) < 50% as assessed by echocardiography (ECHO) or Multi-Gated Acquisition (MUGA) scan)
31. QT prolongation defined as QTc interval (corrected with Fridericia's formula) > 450 ms for males and > 470 ms for females, obtained from triplicate 12-lead ECG
32. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age
33. Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia, atrial fibrillation), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third degree AV block)
34. Uncontrolled arterial hypertension (SBP > 150 mmHg or DBP > 95 mmHg)
35. Unresolved CTCAE Grade ≥ 2 diarrhoea or presence of medical condition associated with chronic diarrhoea (such as irritable bowel syndrome or inflammatory bowel disease)
36. Coagulopathy that will increase the risk of bleeding complications according to investigator's judgment (e.g. disseminated intravascular coagulation)
37. Allogenic stem cell transplant within 3 months before the first IMP administration and/or patients who still receive immunosuppressive treatment and/or patients with active Graft-versus-host disease
38. Any previous anti-leukemic treatment for the studied disease within 2 weeks or at least 5 half-lives (whichever is longer) of this treatment prior to the first IMP administration (except for hydroxycarbamide). In case of donor lymphocyte infusions following allogeneic haematopoietic stem or investigational biologic agent with a long half-live such as CART cells, immune checkpoint inhibitors or bispecific antibodies, a wash-out of 28 days will be acceptable
39. Any radiotherapy within 2 weeks prior to the first IMP administration (except for palliative radiotherapy at localised lesions)
40. Malignant disease other than that being treated in this study. Exceptions include malignancies that were treated curatively, have not recurred within 2 years prior to study entry and not requiring ongoing therapy, completely resectable basal cell and squamous cell skin cancers, any malignancy considered to be indolent and that has never required therapy and completely resected carcinoma in situ of any type
41. Any clinically significant medical condition (e.g. organ dysfunction) or laboratory abnormality likely to jeopardize the patients' safety or to interfere with the conduct of the study, in the investigator's opinion
42. History of severe allergic or anaphylactic reactions to azacitidine or history of hypersensibility to excipient of S64315 or azacitidine, including egg, soybean, liposomal vehicle excipients or mannitol (E421)
43. b. Patients receiving treatment medications listed in section 6.3.1 and that cannot be discontinued at least 1 week prior to the first IMP administration (at least 2 weeks for CYP3A4 inducers, see section 6.3.1 for details) and during the study period. Patients having received calcineurin inhibitors within 4 weeks before the first IMP administration.

For concomitant medications, refer to section 6.3.

5.5. Definition of women of childbearing potential and contraception methods

Women of childbearing potential

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Contraception methods

- Definition of highly effective contraception methods for the study:

Highly effective methods of birth control refer to those which result in a low failure rate (i.e. less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception when associated with inhibition of ovulation (oral, injectable, implantable), some intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), bilateral tubal occlusion, male sterilization (vasectomy).

- Definition of acceptable contraception methods for the study:

Acceptable contraception methods for the study are those considered as highly effective methods, male or female condom with or without spermicide, cap, diaphragm or sponge with spermicide.

5.6. Retest management during screening period

A patient who has a laboratory result that does not satisfy the entrance criteria may have the test repeated providing that the investigator judges it relevant according to the patient previous result or medical history and if s/he considers laboratory abnormalities are likely to be transient. Results of the test(s) repeated should be obtained within the allowed screening period. In this case the patient will not be required to sign another informed consent and the original patient identification number assigned by the investigator will be used.

In any case, the last result available for each parameter must be considered for the patient inclusion.

5.7. Additional information recorded at the inclusion visit

Not applicable

5.8. Patient withdrawal

5.8.1. Withdrawal criteria

Information to be collected during the last visit of these patients is given in section 5.8.2. These follow-up modalities are used to ensure the efficacy and safety evaluation of all patients who received the IMPs.

The reasons for premature discontinuation of IMPs are:

- **Adverse events** incompatible with continuation of one of the IMPs according to the judgment of the investigator, including no recovery in safety parameters. Criteria for treatment discontinuation are implemented during the LID period in order to avoid treating a patient in medical condition that could jeopardize his/her safety or interfere with the conduct of the study. If the patient cannot receive the LID2 or the first S64315 C1D2 dose due to an AE, the S64315 infusion (either LID2 or C1D2) may be postponed by 1 to 5 days. If the LID2 is postponed for more than 2 days (5 days maximum), the C1D2 dose may not be postponed for more than 2 days. If S64315 C1D2 is postponed, azacitidine C1D1 dose should be postponed as well, whenever possible. If the AE has not recovered within this time period, the patient must be withdrawn from the study.
- **Pregnancy** (for reporting, see section 8.9.2.3)
- **Protocol deviation** if it interferes with the study evaluations and/or if it jeopardises patient's safety, e.g. any medical event requiring administration of an unauthorised concomitant treatment (see section 6.3)
- **Disease progression** at the discretion of the investigator
- **Treatment failure,** defined as failure to achieve CR, CRi, MLFS or PR after at least 6 cycles of study treatment
- **Non-medical reason** (to be thoroughly described) e.g. consent withdrawal, patient's removal
- **Other, physician decision** (for reasons that cannot be included in any of the criteria listed above, for example: availability of a better therapeutic alternative for the patient)

If the patient becomes eligible for transplant, patient treatment discontinuation should be left to the investigator's decision.

If the patient is benefiting from the study treatment according to the investigator's judgement and if it is in the patient's best interest to continue the combination of S64315 with azacitidine, the patient may remain on study treatment. A patient must discontinue the combination if the toxicity recurs with the same or worse severity after resumption of dosing, unless the investigator decides it is in the patient's best interest to continue the combination of IMPs and upon documented agreement with the Sponsor.

If one IMP is permanently discontinued, both drugs should be permanently discontinued. A patient must be withdrawn from the study if one the IMPs is interrupted for more than 28 consecutive days from C1D2, for any reason. However, for patients with LVEF decline, IMP interruptions of up to 35 consecutive days are permitted.

5.8.2. Procedure

Upon discontinuation of the IMPs, the investigator must:

- notify the Sponsor immediately by recording this information in the eCRF
- indicate the main reason, if there are several reasons

Patients should return for the Withdrawal visit (WV) as soon as possible and up to 28 days of the last dose of IMP. If the decision to discontinue occurs at a regular scheduled visit, that visit may become the WV rather than having the patient returns for an additional visit.

After the withdrawal visit, patients will continue in the follow-up period; the date of death and the progression date will be recorded in the eCRF, if applicable. Study discontinuation for another reason than disease progression will be recorded in the eCRF.

In the case of premature withdrawal from the study due to an AE (event requiring immediate notification or not), the investigator must make every effort to collect the information relating to the outcome of the AE. If necessary, the information will be collected afterwards (see section 8.9). This information is recorded in the 'AEs' eCRF form. If the investigator cannot collect the information during a patient visit, he must collect it from the patient's doctor in charge of his/her follow-up.

If the study is stopped/one of the IMPs is discontinued as a result of an event requiring immediate notification, the procedure described in section 8.9.2.5 is to be implemented.

The dispositions to be taken after the IMPs discontinuation are described in section 6.5.

5.8.3. Lost to follow-up

When the investigator has no news of the patient, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones, etc.), to establish the reason of the IMPs discontinuation and suggest to the patient to come to a withdrawal visit. If all these attempts to contact the patient fail, the investigator can then declare the patient 'lost to follow-up'. The investigator should document all these attempts in the corresponding medical file.

6. TREATMENT OF PATIENTS

The following sections are applicable for dose escalation phase I part of **Arm A** and. They could be refined for expansion phase II part (**sub-arms A1 and A2**) according to results observed in the dose escalation phase I part, as well as for **Arm B** according to the results of Arm A. They will be described in an amendment to the protocol.

6.1. IMPs administered

6.1.1. IMP administration schedule

S64315 and azacitidine will be administered in combination in patients with AML. The administration schedule of the combination is detailed in section 4.1.3.2.

Azacitidine will be administered via SC injection, once a day over 7 days i.e. from CxD1 to CxD7, followed by a rest period of 21 days, over 28-day cycle during the combination treatment period, according to E.U. SmPC recommendations.

S64315 will be administered via IV infusion over at least 2h, once a week, i.e. during the 2-week lead-in dose period (on the days of LID1 and LID2) and then during the combination treatment period on CxD2, CxD9, CxD16, and CxD23 over 28-day cycle.

As data will emerge during the study regarding clinical safety and PK data, the administration schedule and the infusion duration may be changed. Any change will be implemented through an amendment to the protocol.

The assignment of a patient to a particular cohort will be coordinated by the Sponsor. No randomisation will be performed in this study. Information about infusion duration as well as treatment schedule will be reported in the Patient Registration Form (Appendix 2).

For IMP dose adaptations due to toxicities, please refer to section 8.12.

6.1.2. Administration/re-administration criteria

- Criteria to fulfil before each S64315 infusion
  - Before each S64315 infusion, biological parameters should be checked in order to detect any toxicity (see Table (8.12) 1)
  - Patients with Grade ≥ 2 hypo/hypercalcemia and/or hypo/hypermagnesia and/or hypo/hyperkalaemia despite attempts at medical correction should not be treated with S64315
  - Patients with WBC ≥ 10 G/L despite attempts at medical correction should not be treated with S64315. Hydroxycarbamide can be used to reduce the circulating blast count before and throughout the treatment period
  - AST and ALT ≤ 3 x ULN (except for LID1: AST and ALT ≤ 1.5 x ULN)
  - Total bilirubin level ≤ 1.5 x ULN, except for patients with known Gilbert's syndrome, who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
  - In the case of an S64315 interruption ≥ 28 days, its readministration must be preceded by a lead-in dose period (except for patients in CR/CRi) which is called additional Lead-In dose period. See Table (4.1.2) 1 for more details on safety assessments required.
- Criteria to fulfil before each first azacitidine administration (i.e. CxD1)

Patients should be monitored for haematological toxicity and renal toxicities. A delay in starting the next cycle or a dose adjustment due to haematological toxicity and/or renal toxicity may be necessary according to E.U. SmPC (see Table (8.12) 2). WBC, absolute neutrophil count (ANC), platelets, serum creatinine, BUN and serum bicarbonate will be assessed before starting the next treatment cycle.

6.2. IMP dispensing

S64315 and azacitidine will be dispensed by the pharmacist/responsible of the healthcare establishment upon prescription of the investigator only.

The investigator may only use the IMPs provided for the patients involved in the study and treated under his/her responsibility or that of a designated co-investigator.

For each patient, the IMPs will only be dispensed during the study.

Further instructions for the preparation and dispensation of S64315, as well as the description of the tubing and infusion sets compatible with S64315, are described in the Pharmacy Manual.

All dosages of S64315 and azacitidine prescribed to the patient and all dose changes during the study must be recorded in the eCRF.

The detachable portion of the label on the IMPs box must be stuck by the investigator/responsible person on an IMP label collection form or on the prescription form where the IMPs are dispensed by a pharmacist.

6.3. Previous and concomitant treatments

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited. Concomitant medication administration could result in DDI that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication, as of S64315 and/or azacitidine.

A list of prohibited and unauthorized treatment by drug class can be consulted in the eCRF, it includes the 'guidance on use of co-medications for clinical study CL1-64315-004' to be used as reference before prescribing any concomitant treatment to a patient. Patients must not have taken calcineurin inhibitors for at least 4 weeks before the first dose of S64315 in order to be eligible.

Before any new concomitant medication administration, the investigator should assess any potential DDI with S64315 and azacitidine (if applicable) using this concerned medication SmPC, from 7 days before the first IMP intake to 7 days following last IMP intake. For CYP3A4 inducers comedications, the wash out period is defined as at least 2 weeks. For concomitant CYP3A4 inducer drugs with a long elimination half-life (> 40 h), a wash out period of 1 week and additional 5 half-lives must be applied before initiation of S64315 therapy. Contraindicated comedication drugs with a long elimination half-life are flagged in the "Guidance on use of comedication for clinical study CL1-64315-004" that can be consulted in the eCRF.

Regularly updated lists of the co-administered medications that should be contraindicated or used with caution will be shared through the eCRF during the clinical study. These lists are not exhaustive and only meant to be used as a guide (for example, pro-drugs of the listed drugs should be considered as their active substance). The Sponsor should be contacted in case of any doubt. If a medication appears on both 'prohibited' and 'to be used with caution' lists, the medication is prohibited.

6.3.1. List of prohibited medications during the IMP treatment period

Medications prohibited from at least 7 days before the first IMP administration and up to 7 days following the last IMP administration:

- Strong CYP3A4 inducers
- Dual strong CYP3A4 and CYP2C8 inhibitors and inducers
- Listed dual 'strong CYP3A4 inhibitors' and 'CYP2C8 and/or P-GP inhibitors'
- Listed herbal preparations/medications
- OATP substrates
- QT prolonging drugs with a known risk to induce Torsades de Pointes (TdP)
- Other investigational and anti-leukemic therapies

Medications prohibited from 7 days before the first IMP administration and up to the end of cycle 1:

- Haematopoietic growth factors

6.3.2. List of medications to be used with caution during the IMP treatment period

Medications to be used with caution from at least 7 days before the first IMP administration and up to 7 days following the last IMP administration:

- Strong CYP3A4 inhibitors
- Moderate CYP3A4 inducers
- Dual P-GP inhibitors and strong/selected moderate CYP3A4 inhibitors
- Drugs with possible and conditional risk for TdP

Medications to be used with caution during the IMP treatment period:

- CYP2C8 sensitive and Narrow Therapeutic Index (NTI) substrates
- Multi-transporter substrates (including OATPs) with no reported in vivo DDI reported
- MATE1 sensitive and NTI substrates

- BCRP substrates (IV administration)
- P-GP NTI substrates
- Warfarin (unknown risk for plasma proteins displacement due to co-administration of S64315, leading to higher free concentrations of warfarin (Prothrombin Time and International Normalized Ratio (PT/INR) monitoring is required)
- Listed herbal preparations/medications

The information regarding the administration of such medications, the occurrence of therapeutic drug monitoring, the need of dose adaptation and the magnitude of the adaptation when applicable must be recorded in the eCRF.

6.3.3. List of permitted concomitant medications

- Hydroxycarbamide used to control leucocytosis is allowed
- Haematopoietic growth factors used in the centre may be prescribed after Cycle 1 for the subsequent cycles
- Anti-emetics are strongly recommended for prophylaxis prior each S64315 administration and dexamethasone mandatory at least before S64315 LID1, LID2 and CID2 (see section 8.2.8.1)
- Anti-diarrhoeals should be prescribed if clinically indicated except for prophylaxis prior to first dose of S64315. If prophylaxis or treatment is required subsequently to the first S64315 administration, it may be administered at the discretion of the investigator (see section 8.2.8.2)

The patient must be informed to notify the investigational site about any new medications he/she takes after having signed the ICF of the study. All medications (other than IMPs) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed in the eCRF.

Treatments received for the studied disease and after the last IMPs administration are to be recorded in 'Post-withdrawal follow-up' eCRF form.

6.4. IMP compliance

The number of vials and volume infused are to be counted by the investigator or a designated person from his/her team and recorded in the eCRF and on the therapeutic unit tracking form, or an equivalent document.

The compliance will be assessed from the method described above.

6.5. IMP discontinuation

After the discontinuation of the IMPs, patient's treatment is left to the physician's discretion. S64315 is not licensed and not available on the market. Azacitidine is licensed and available on the market.

Specific rules may be followed in some countries according to local regulation.

7. ASSESSMENT OF EFFICACY

The efficacy assessments hereafter are applicable for dose escalation phase I part of **Arm A** They could be refined for expansion phase II part (**sub-arms A1/ A2**) according to results observed in the dose escalation phase I part, as well as for **Arm B** according to the results of Arm A. They will be described in an amendment to the protocol.

7.1. Efficacy measurements

Efficacy measurements performed during the study will use AML criteria: 'Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel' (Döhner, 2017) (Appendix 5). They are described in Table (4.1.2) 1.

7.2. Methods and measurement times

- A full blood count and blood film examination will be assessed for treatment response at the following time points:
  - Baseline
  - C1D1 azacitidine predose (within 24h prior to C1D1)
  - C1D2 4h after S64315 EoI
  - C1D3 and C1D4 azacitidine predose (ideally in the morning)
  - From Cycle 2 onwards: D1 azacitidine predose of each cycle (within 3 days prior to CxD1)
  - WV
- A bone marrow aspirate (BMA) and/or a bone marrow biopsy (BMB) (according to local medical practice) will be assessed at the following time points:
  - Baseline
  - C2D1 azacitidine predose (within 2 days prior to C2D1)
  - C3D1 azacitidine predose if non-CR/CRi on C2D1 (within 7 days prior to C3D1)
  - C7D1 azacitidine predose if non-CR/CRi/MLFS or PR at any previous cycle (within 7 days prior to C7D1)
  - Any time if clinically indicated or in case of suspected disease progression at the investigator's discretion
  - WV

8. ASSESSMENT OF SAFETY

The safety assessments hereafter are applicable for dose escalation phase I part of **Arm A** They could be refined for expansion phase II part (**sub-arms A1/ A2**) according to results observed in the dose escalation phase I part, as well as for **Arm B** according to the results of Arm A. They will be described in an amendment to the protocol.

All adverse events and other situations relevant to the safety of the patients must be followed up and fully and precisely documented, in order to ensure that the sponsor has the needed information to continuously assess the benefit-risk balance of the clinical trial.

Table (8) 1 - Mitigation strategies of the identified risks

Risk	Mitigation strategy
Cardiac	See section 8.2.5 ECG recording Echocardiography and GLS / MUGA scan Cardiac markers MRI Holter
Hepatic	See section 8.2.6
Gastrointestinal	See section 8.2.8
TLS	See section 8.2.9
IRR	See section 8.2.10

8.1. Specification of safety parameters

Safety measurements of S64315 in combination with azacitidine performed are indicated in Table (4.1.2) 1. They include:

- DLTs assessment at the end of Cycle 1 (DLTs will be continued to be monitored at all cycles), which will drive the MTD/RP2D identification
- Record of AEs and toxicity according to NCI CTCAE. The severity of each AE will be graded according to version 5.0 on a five-point scale (Grade 1 to 5)
- Recording of any change or addition of a new concomitant medication
- Laboratory tests: haematology, blood biochemistry, blood coagulation parameters, urinalysis, hepatitis markers, TLS monitoring, cardiac marker follow up
- Local assessment of ECGs by the investigators and central ECG reading
- LVEF evaluation by echocardiography or MUGA scan; Global Longitudinal Strain (GLS) assessment will be assessed during the echocardiography, whenever possible (not mandatory), as a means to follow left ventricular systolic dysfunction at the time points already defined in the study protocol for echocardiography
- Physical examination, ECOG PS (Appendix 3), vital signs measurements
- Pregnancy test for women of childbearing potential

Any significant abnormality detected during safety assessments from the patient ICF signature must be reported on the adequate eCRF page by the investigator at each visit (AE, medical history or sign & symptoms).

8.2. Methods and measurement times

Relevant medical history will be reported to identify any medical condition which could make an individual unsuitable for inclusion:

- Initial diagnosis, relevant medical history at screening (baseline)
- Previous chemotherapies, bone marrow transplants, surgeries, radiotherapies, or procedures related to the studied disease (screening)
- Concomitant signs and symptoms linked to the studied disease
- Previous and concomitant treatments

Clinical examination and vital signs measurements

- Serum/urine pregnancy test (ß hCG) only for WOCBP
- Complete clinical examination (including examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological), height and body weight measurement and ECOG PS assessment
- Vital signs measurements including blood pressure (BP) measurements, heart rate (HR) and temperature, HR and BP measured by an automatic device in supine position after a 5-min rest

Laboratory tests

The laboratory assessments detailed in Table (8.2) 1 will be performed as indicated in sections 8.2.2 and 8.2.3. Additional tests could be repeated if clinically indicated.

Table (8.2) 1 - Local Clinical laboratory parameters collection plan

Test Category	Test Name
Haematology	Haematocrit, Haemoglobin, Red blood cells, WBC, Platelets, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Blasts in absolute value and in %)
Total and B-lymphocytes	Total and B-lymphocyte count
Biochemistry	Albumin, Alkaline Phosphatase (ALP), ALT, AST, Bicarbonates, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Total Calcium, Ionized Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine (including creatinine clearance), CK/CPK, Total Bilirubin, Total Cholesterol, LDL, HDL, Triglycerides, BUN or Urea, Uric Acid Amylase, Lipase, Glucose
Cardiac markers	BNP, CPK-MB, Troponin I or T*
Urinary analysis	Macroscopic Panel (Dipstick) (Blood, Glucose, Ketones, Protein) If the dipstick test is at least 2+ on one or more parameter(s), quantitative urinary biochemistry tests will be performed on the abnormal parameter(s)
Blood coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Thyroid	T3 [free], T4 [free], TSH
Hepatitis markers	HbsAg, HbsAb, HbcAb, if HbsAg or HbcAb positive check viral load (HBV-DNA) at baseline, HCV RNA-PCR, HEV RNA-PCR
Pregnancy Test	When effective contraception is required, pregnancy testing is mandatory at inclusion (serum), on CxD1 predose of every cycle from Cycle 2 onwards (serum or urine) and at WV (serum)

*The same subtype (either I or T) should be used throughout the study. If, for a given centre, both troponin I and T can be assessed, priority should be given to troponin I

All samplings for biochemistry should be taken in fasting conditions, unless cholesterol, LDL, HDL, triglycerides and glucose are not measured (e.g. TLS monitoring).

All laboratory tests performed during the study period will be assayed in an identified laboratory at hospital. Inter-visits laboratory tests could be assayed by local laboratories.

In all cases, the full validated set of normal ranges values will be collected, as well as any update in these values during the study and must be documented in the corresponding eCRF pages.

Any laboratory abnormality that has a clinical impact on the patient, e.g. results in delay of study medication dosing, study discontinuation, requires treatment due to abnormal values, or is considered by the investigator to be medically important, must be reported as an AE, unless it is considered as a supporting lab to a clinical diagnosis already reported as an AE. If there is a question or concern, please call the Sponsor. All laboratory data will be analysed using NCI CTCAE grade criteria v5.0.

During the course of the study, the results of laboratory tests should be available before the following S64315 administration and/or azacitidine CxD1 predose.

Electrocardiograms (see section 8.2.5.1) will be assessed following the collection plan detailed in Table (8.2) 2.

Table (8.2) 2 - Central ECGs collection plan

Period	Day	Time	ECG Type
Inclusion	ICF signature to LID1	Anytime*	12-Lead, triplicate
LID1	-13	S64315 predose**	
	-13	S64315 EoI	
	-13	1h after S64315 EoI	
	-13	2h after S64315 EoI	
	-13	6h after S64315 EoI	
	-12	24h after S64315 EoI	
LID2	-6	S64315 predose**	
	-6	S64315 EoI	
	-6	1h after S64315 EoI	
	-6	2h after S64315 EoI	
	-6	6h after S64315 EoI	
	-5	24h after S64315 EoI	
Cycle 1	1	Azacitidine predose	
	2	S64315 predose***	
	2	S64315 EoI	
	2	1h after S64315 EoI	
	2	2h after S64315 EoI	
	2	6h after S64315 EoI	
	3	24h after S64315 EoI	
	9#	S64315 predose**	
	9#	S64315 EoI	
	9#	1h after S64315 EoI	
	9#	2h after S64315 EoI	
	9#	6h after S64315 EoI	
	10#	24h after S64315 EoI	
	16	S64315 predose**	
	16	S64315 EoI	
	23	S64315 predose**	
	23	S64315 EoI	
Cycle 2	2	S64315 predose***	
	2	S64315 EoI	
Cycle 3 and beyond	2	S64315 predose***	

Period	Day	Time	ECG Type
	2	S64315 EoI	
Withdrawal visit	WV	Anytime	
Unscheduled sample****		Anytime	

EoI: End of Infusion
NOTE: A PK sampling is to be performed in conjunction with ECG whenever applicable (N/A 6h after S64315 EoI)
*to be collected within 7 days prior to inclusion and results available for inclusion
**to be collected within 24 hours before S64315 infusion
***to be collected after azacitidine administration on day of coadministration
****A PK sample should be collected immediately following an ECG performed due to an unexpected cardiac signal (one for S64315 and one for azacitidine dosing purpose on days of coadministration; otherwise only one for S64315 dosing purpose)
or next S64315 infusion if Day 9 administration is not performed

Echocardiography: LVEF parameter (see section 8.2.5.2)

8.2.1. Screening period and inclusion visit

Prior to the inclusion and after ICF signature, the clinical assessments will include:

- Medical, surgical and radiotherapy history
- Previous and concomitant treatments
- Complete physical examination (including examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological examination including sensory and motor evaluation functions)
- Clinical evaluation including vital signs (temperature, HR, BP), body weight, height, and ECOG PS within 7 days before the inclusion
- Laboratory tests: blood haematology with differential, blood biochemistry (fasted) blood coagulation, thyroid function, urinary analysis within 7 days before inclusion and available for inclusion and hepatitis markers within inclusion period
- Cardiac markers (limited to troponin only)
- Serum pregnancy test for female of childbearing potential within 7 days before inclusion and available for inclusion
- Cardiac function assessment performed by echocardiography or MUGA scan; GLS assessment will be recommended during echocardiography, whenever possible, as a means to follow left ventricular systolic dysfunction
- Chest X-Ray (CXR), a chest X-Ray performed prior to ICF signature but no more than 21 days prior to the first day of IMP administration is acceptable
- Triplicate ECGs (i.e. 3 ECGs within 10 min): see Table (8.2) 2

8.2.2. During the treatment period

S64315 LID period

- Clinical examination:
  - Vital signs (temperature, HR, BP): LID1 and LID2 predose*, LID1 and LID2 End of Infusion (EoI), 2h and 24h after LID1 and LID2 EoI
  - ECOG PS at LID1 predose*

- Laboratory tests:
  - Blood haematology with differential and blood biochemistry (fasted): LID1 and LID2 predose*, 24h and 48h after LID1 and LID2 EoI. A blood haematology sample should be obtained between LID1 and LID2 and between LID2 and C1D1 to ensure WBC are < 10 G/L during the LID period
  - Blood biochemistry limited to AST, ALT and total bilirubin: 8h after LID1 and LID2 EoI
  - Cardiac markers (including troponin, CPK-MB and BNP): LID1 and LID2 predose*, 6h, 24h, 48h and 72h after LID1 and LID2 EoI
  - TLS laboratory parameters monitoring (WBC, creatinine, phosphorus, calcium, potassium, uric acid, LDH): LID1 and LID2 predose*; 2h, 4h, 8h and 24h± 2h after LID1 and LID2 EoI
  - Blood coagulation, thyroid function and urinary analysis at LID1 predose*

*Predose exams to be performed within 3 days prior to LID1 or LID2

- Triplicate ECGs: see Table (8.2) 2

Cycle 1

- Clinical examination:
  - Vital signs (temperature, HR, BP):
    - D1: azacitidine predose*
    - D2, D9, D16 and D23: S64315 predose*, S64315 EoI and 2h after S64315 EoI
  - ECOG PS on D1 azacitidine predose*
  - Body weight on D1 azacitidine predose*
- Laboratory tests:
  - Blood haematology with differential and blood biochemistry:
    - D1: azacitidine predose*
    - D2: S64315 predose* and EoI
    - D9, D16 and D23: S64315 predose*
  - Blood biochemistry limited to AST, ALT and total bilirubin: 8h, 24h and 72h after S64315 C1D2 EoI and 24h after C1D9 EoI
  - Blood coagulation, thyroid function and urinary analysis on D1 predose*
  - Cardiac markers (including troponin, CPK-MB and BNP)[#]: D1: azacitidine predose*, D2 and D9: S64315 predose*, 6h, 24h, 48h and 72h after EoI, D16 and D23: S64315 predose*

    [#]In case of any troponin increase observed after the two first S64315 infusions of cycle 1, it will be recommended to assess cardiac markers at 48h and 72h after S64315 EoI, and after each subsequent infusion (before discharge and beyond, if needed), on a regular basis according to investigator's judgment.
  - TLS laboratory parameters monitoring (WBC, creatinine, phosphorus, calcium, potassium, uric acid, LDH):
    - D1: predose*, 1h30 and 6h after azacitidine administration
    - D2: predose*, 2h, 4h, 8h, 24h±2h after S64315 EoI
    - beyond D2 (applicable for all patients with a risk of developing TLS according to the investigator's judgment): prior to each S64315 infusion (predose) and 2h, 4h, 8h, 24h±2h after each S64315 EoI

*Predose exams to be performed within 24h prior to S64315 C1D2 and 3 days prior to any other IMP administration

- Triplicate ECGs: see Table (8.2) 2

If Day 9 administration is not performed, all scheduled assessments should be performed at the next S64315 infusion (2nd S64315 infusion in cycle 1).

Cycle 2 and cycle 3

- Clinical examination:
  - Vital signs (temperature, HR, BP): D1 azacitidine predose*, D2 S64315 predose* and EoI, D9 S64315 predose*, D16 S64315 predose*, D23 S64315 predose*
  - ECOG PS on D1 azacitidine predose*
  - Body weight on D1 azacitidine predose*
- Laboratory tests:
  - Blood haematology with differential and blood biochemistry: D1 predose*, D2 predose*, D9 predose*, D16 predose*, D23 predose*
  - Blood coagulation, thyroid function and urinary analysis on D1 predose*
  - Cardiac markers (including troponin, CPK-MB and BNP) #: D1 predose*, D2 predose*, D9 predose*, D16 predose*, D23 predose*

  # in case of any troponin increase observed after the two first S64315 infusions of cycle 1, it will be recommended to assess cardiac markers at 48h and 72h after S64315 EoI, and after each subsequent infusion (before discharge and beyond, if needed), on a regular basis according to investigator's judgment
  - TLS laboratory parameters monitoring (WBC, creatinine, phosphorus, calcium, potassium, uric acid, LDH), applicable for all patients with a risk of developing TLS according to investigator's judgment, prior to each S64315 infusion; 2h, 4h, 8h, 24h ± 2h, after each S64315 EoI

* Predose exams to be performed within 3 days prior any IMP administration

- Pregnancy test for women of childbearing potential (serum or urine) on D1
- Triplicate ECGs: see Table (8.2) 2
- Cardiac function assessment performed by echocardiography or MUGA scan on D1 predose within 2 days prior to the IMP administration

Cycle 4 and beyond

- Clinical examination:
  - Vital signs (temperature, HR, BP) on D1 and D2 predose*
  - ECOG PS on D1 predose*
  - Body weight on D1 predose*
- Laboratory tests:
  - Blood haematology with differential and blood biochemistry: D1 predose*, D2 predose*, D9 predose*, D16 predose*, D23 predose*
  - Blood coagulation and urinary analysis on D1 predose*
  - Cardiac markers (including troponin, CPK-MB and BNP)#: D1 predose*, D2 predose*, D9 predose*, D16 predose*, D23 predose*

  # in case of any troponin increase observed after the two first S64315 infusions of cycle 1, it will be recommended to assess cardiac markers at 48h and 72h after S64315 EoI, and after each subsequent infusion (before discharge and beyond, if needed), on a regular basis according to investigator's judgment
  - Thyroid function on D1 predose* of each cycle until cycle 6, then if no effects on the thyroid function is observed on D1 predose* every 4 cycles from cycle 6 onwards
  - TLS laboratory parameters monitoring (WBC, creatinine, phosphorus, calcium, potassium, uric acid, LDH), applicable for all patients with a risk of developing TLS according to investigator's judgment

* Predose exams to be performed within 3 days prior to any IMP administration
- Pregnancy test for women of childbearing potential (serum or urine) on D1
- Triplicate ECGs: see Table (8.2) 2
- Cardiac function assessment performed by echocardiography or MUGA scan every 2 cycles; from cycle 4 onwards on D1 predose and within 2 days before azacitidine administration

8.2.3. Withdrawal visit

- Clinical examination: vital signs (temperature, HR, BP), ECOG PS and body weight
- Laboratory tests: blood haematology with differential, blood biochemistry, blood coagulation and urinary analysis
- Pregnancy test for women of childbearing potential (serum)
- Triplicate ECGs: see Table (8.2) 2
- Cardiac function assessment performed by echocardiography or MUGA scan (only if the previous assessment was performed more than 3 weeks ago)

8.2.4. Post-withdrawal follow-up

After the withdrawal visit, a contact or telephone call will be done with the patients:
- every 3 months (±15 days) from the WV, up to 6 months, except in case of consent withdrawal for the dose escalation phase I part
- every 3 months (±15 days) from the WV, up to 12 months, except in case of consent withdrawal for the expansion phase II part

The following information will be collected:
- the patient's survival
- the date of first disease progression
- the first line of therapy administered after withdrawal and its starting date

8.2.5. Cardiac safety

8.2.5.1. Central ECG recording

In order to monitor the potential of S64315 infusion in combination with azacitidine to delay cardiac repolarisation, serial triplicate 12-lead ECGs (i.e. 3 ECGs within 10 min) will be performed for the measurement of the QT and QTc interval (correction according to Fridericia's formula). 12-lead ECG parameters with at least 3 to 5 QRS complexes for each lead will be evaluated by Core Reading Centre: HR, PR interval, QRS duration, QT interval, RR interval, corrected QT, using Fridericia's formula.

Three print-out ECGs will be produced with at least 6 complexes recorded for each. The ECG recordings will be centrally read by a CRO, specialised in cardiac monitoring. The CRO will provide a 12-lead digital recorder, will train and certify the centres in terms of equipment and will employ a trained independent cardiologist to read the ECGs.

At each time point described in Table (8.2) 2, the triplicate 12-lead ECG will be obtained after resting for 10 min prior to the recordings and in supine position. Predose ECG should be collected:
- within 7 days prior to inclusion and results available for inclusion
- after azacitidine injection and before S64315 infusion on CxD2 (day of coadministration)
- with 24h prior to any other S64315 infusion

Detailed instructions on ECG recordings are provided in the ECG manual.

In the event that an ECG abnormality is observed, additional examinations could be performed at the discretion of the investigator (e.g. a blood sample for ionogram (Na, K, Cl) in case of QTc prolongation).

The management of the patient/the study treatment will be based on the local reading of the ECGs; all the ECGs will be sent by the site on a regular basis to the central reading CRO. The final analysis of the QTc values throughout the study will be based on the central reading analysis.

At inclusion visit

The mean QTc will be calculated for each triplicate ECG according to Fridericia's formula. If the mean QTc is > 450 ms in men or > 470 ms in women, then 3 other ECGs (in 10 min) should be repeated 3 h later. The mean QTc will be recalculated. If the abnormality is confirmed, the patient will not be included.

During the study

Triplicate ECGs will be carried-out at the time points defined in Table (8.2) 2. The mean QTc will be calculated to detect a possible QTc prolongation. Toxicity grading of QTc interval prolongation is defined by the CTCAE v 5.0 as follows:

Table (8.2.5.1) 1 - Toxicity grading of QTc interval prolongation is defined by the CTCAE (v 5.0)

Grade	Definition
1	QTc 450 - 480 ms
2	QTc 481 - 500 ms
3	QTc ≥ 501 ms on at least two separate ECGs
4	Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

In the event of prolongation of the QTc interval according to Fridericia's formula, management of treatments will be performed as explained in the Table (8.12) 1.

The recommendations described in the Table (8.12) 1 are not intended to supersede the clinical judgment of the investigator and the treating physician, who will determine the appropriate management for the patient. ECG abnormalities considered clinically significant by the investigator will be reported in the eCRF as adverse events.

8.2.5.2. Echocardiography/ MUGA scan

An echocardiography or a MUGA scan will be performed during the study to assess cardiac function. The same technique (either echocardiography or MUGA) should be used throughout the study for a given patient.

At inclusion visit, if LVEF is < 50%, the patient is ineligible.

During the study, the management of decrease in LVEF is based on the measured LVEF and LVEF change from baseline described in section 8.12.

GLS assessment will be assessed during echocardiography, whenever possible (not mandatory), to follow left ventricular systolic dysfunction, at the time points already defined for echocardiography.

8.2.5.3. Cardiac marker follow-up

In order to monitor a potential cardiac toxicity, a cardiac marker assessment, including troponin, CPK-MB and BNP, will be performed at predose, 6h, 24h, 48 and 72h after S64315 EoI on the days of LID1 (D-13) and LID2 (D-6), C1D2 and C1D9 and at each pre-dose assessments for the following visits.

Either troponin I or T assessment can be used, but it should be ultra-sensitive, whenever possible. The same subtype (either I or T) should be used throughout the study. If, for a given centre, both troponin I and T can be assessed, priority should be given to troponin I.

In case of troponin increase observed after any of the first two S64315 infusions during cycle 1 (C1D2 or C1D9), it will be recommended to assess these cardiac markers at 48h and 72h S64315 EoI and after each subsequent S64315 infusions (before discharge and beyond, if needed) on a regular basis according to the investigator's judgment.

In case of troponin increase > 10xUNL or a troponin increase consistent with the diagnosis of a myocardial infarction (Grade 3), the patient should discontinue study treatment (see section 8.12).

8.2.5.4. MRI assessment

A cardiac MRI should be performed at the time of the event (as far as possible within 48 to 72h) in case of troponin increase > 10xULN or in case of troponin increase > ULN associated with clinical signs or LVEF decrease or ECG abnormality, to detect a potential acute structural effect related to S64315. Another cardiac MRI should be performed 5 or 6 weeks later, to detect any long-term damage related to S64315.

In case of MRI abnormality in this context of troponin increase, the patient should discontinue study treatment (see section 8.12).

8.2.5.5. 24-hour Holter assessment

A 24-hour Holter should be set-up in case of troponin increase > 10xULN (immediately once detected) or troponin > ULN associated with clinical signs or LVEF decrease or ECG abnormality to detect arrhythmia. Abnormalities considered clinically significant by the investigator and/or local cardiologist will be reported in the eCRF as adverse events.

8.2.6. Hepatic safety

Considering the results of the GLP toxicity studies showing some hepatotoxic effect of the drug, the hepatic safety will be closely monitored. An increase in serum liver enzymes should be followed by repeated testing including all the usual serum measures (at least ALT, AST, ALP and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing as follows:

- For isolated Grade 3 total bilirubin increase (> 3xULN) or isolated Grade 3 AST or ALT increase (> 5xULN), the patient should be weekly monitored, including LFT: albumin, ALT, AST, total bilirubin, fractionated if total bilirubin > 2.0xULN, ALP, fractionated if ALP > 2.0xULN, and GGT, or more frequently if clinically indicated, until values have resolved to baseline or stabilised over 4 weeks
- For AST or ALT > 3.0xULN combined with total bilirubin > 2.0xULN, repeat LFT as soon as possible, preferably within 48h from awareness of the abnormal results, then with weekly monitoring of LFT, or more frequently if clinically indicated, until AST, ALT, or bilirubin values have resolved to baseline or stabilised over 4 weeks

Clinically significant abnormalities should be carefully documented in the patient's medical file.

Additional tests to evaluate liver function such as INR (or biopsy if appropriate) may be performed as appropriate. Close observation and documentation also include:

- obtaining a more detailed history of symptoms and prior or concurrent diseases, obtaining a history of concomitant drug use (including non-prescription and herbal and dietary supplement preparations), alcohol use
- performing liver imaging (ultrasound, magnetic resonance or computerized tomography) to evaluate biliary tract or liver disease
- ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; NASH; and biliary tract disease
- considering gastroenterology or hepatologist consultations

The recommendations towards the study according to the level and evolution of hepatic abnormalities are detailed in section 8.12.

8.2.7. Monitoring of infections that may occur with neutropenia

A possible co-toxicity on bone marrow and lymphoid organs, identified as primary target organs for both compounds in the toxicology studies, should be considered. Therefore, WBC count should be closely monitored, and caution should be exercised in assessing the possibility of infections in the patients receiving S64315 in combination with azacitidine.

Early initiation of empirical broad-spectrum antibacterial antibiotics is recommended in the event of fever. If fever persists for 4 to 7 days, an antifungal treatment should also be considered. Investigators should employ these agents in compliance with best medical practices and institutional guidelines and standards. Before initiating these treatments, the list of non-authorized treatments must be consulted. For quinolone agents, besides the possible DDI, the possible risk of prolongation of the QTc interval must be assessed (refer to section 6.3 and 'Guidance on use of co-medication for CL1-64315-004 clinical study').

The use of recombinant hemopoietic growth factors, specifically prohibited in Cycle 1, may be used beyond Cycle 1 at the discretion of the Investigator.

8.2.8. Gastrointestinal disorders

8.2.8.1. Nausea and vomiting management

Considering the GLP toxicity studies and the preliminary clinical data with S64315 (as of September 5, 2019, 23 (60.5%) and 19 (50%) out of 38 patients treated in the S64315 single agent AML and MDS study experienced nausea and vomiting respectively), nausea/vomiting prophylaxis is strongly recommended before each S64315 infusion.

Dexamethasone administration is mandatory at least 1h before S64315 infusion on the days of LID1 and LID2, and on C1D2.

Based on international guideline (ASCO, 2011), this prophylaxis consists in a two-drug combination of palonosetron and dexamethasone, before each S64315 infusion, followed by dexamethasone maintenance for two days after each S64315 infusion.

According to azacitidine E.U. SmPC, patients should be premedicated with anti-emetics for nausea and vomiting.

The recommended prophylaxis is displayed in the Table (8.2.8.1) 1.

Table (8.2.8.1) 1 - Treatments schedule for nausea/vomiting prophylaxis

LID1 and LID2	Palonosetron 0.25 mg IV or 0.5 mg p.o.+ Dexamethasone 8 mg p.o. / IV 1h before each S64315 infusion, followed by dexamethasone 8 mg p.o. / IV during two days after each S64315 infusion, as required
CxD_1	Metoclopramide IV before azacitidine administration
CxD_2	Palonosetron 0.25 mg IV or 0.5 mg per os (p.o.) before azacitidine administration + Dexamethasone 8 mg p.o. / IV. 1h before S64315 infusion
CxD_3	Dexamethasone 8 mg p.o. / IV. as required
CxD_4	Dexamethasone 8 mg p.o. / IV. as required
CxD_9 CxD_{16} CxD_{23}	Palonosetron 0.25 mg IV or 0.5 mg p.o.+ Dexamethasone 8 mg p.o. / IV before each S64315 infusion, followed by dexamethasone 8 mg p.o. / IV during two days after each S64315 infusion, as required

If palonosetron is not available, clinicians may substitute with a first-generation 5-HT3 serotonin receptor antagonist (i.e. granisetron/ dolasetron/ tropisetron, to be used with caution according to 'Guidance on use of co-medication for CL1-64315-004 clinical study').

Limited evidence also supports adding aprepitant to the combination, if the above combination does not provide sufficient nausea/vomiting control.

As a reminder, ondansetron is prohibited along the study due to the risk of QTcF prolongation (see 'Guidance on use of co-medication for CL1-64315-004 clinical study').

For patients who experience nausea and/or vomiting despite optimal prophylaxis, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications and consider adding lorazepam or alprazolam or adding a dopamine antagonist to the regimen.

Please refer to sections 6.3.1 and 6.3.2 for more information about the prohibited medications and the medications to be used with caution during IMP treatment.

8.2.8.2. Diarrhoea management

Considering the GLP toxicity studies and the preliminary clinical data with S64315 (17/38, 44.7%) patients treated in the S64315 monotherapy AML and MDS study experienced diarrhoea), diarrhoea should be closely monitored.

The patient should be instructed to contact the physician/other study personnel in case of severe diarrhoea.

In case of diarrhoea, management and treatment approaches should be implemented according to routine practice and applicable guidelines. In case no guideline is available, investigators should refer to ESMO clinical practice guidelines for diarrhoea in adult cancer patients.

Guidance for diarrhoea management (ESMO, 2018) is summarised in Appendix 7.

8.2.9. Tumour Lysis Syndrome management

Tumour Lysis Syndrome (TLS) prophylaxis is required during the administration of S64315 in combination with azacitidine for patients with active disease, in case of intra-patient dose escalation to a new assigned dose(s) and in case of readministration after one or both IMPs interruption ≥ 28 days.

Even if only patients with low/intermediate risk of TLS are included, TLS prophylaxis for intermediary risk should be implemented for any patient considering the expected overlapping toxicity of the combination. TLS management will be based on institutional guidelines and published criteria (Cairo, 2010) and on the recommendations described below.

Hydration

Adequate hydration should be ensured for all patients according to routine clinical practice and international guidelines (Cairo, 2010).

In order to prevent the risk of TLS, hydration will be made mandatory during the LID period and during the two first infusions of S64315 at the full tested dose (LID1, LID2, C1D2 and C1D9). Patients should be encouraged to drink up to 1.5 to 2.0 L of water daily starting the day before the S64315 infusion, and 24 hours after. Intravenous fluids at 50cc/hour or higher are recommended to be administered for at least 12 hours prior to the S64315 infusion, then IV fluid should be continued according to the investigator's judgement. The rate of IV fluids should be adjusted per clinical judgment.

Anti-hyperuricaemic agents

Allopurinol is recommended for patients with active disease throughout the study. Patients who develop laboratory TLS should receive rasburicase unless clinically contraindicated (Cairo, 2010).

Laboratory assessments (see section 8.2.2).

Before and following S64315 infusions during the LID period (LID1 on D-13 and LID2 on D-6):
WBC, serum uric acid, serum calcium, serum phosphorus, serum potassium, serum creatinine and LDH must be monitored at the following time points:

- Prior to S64315 administration (LID1 and LID2 predose)
- 2h, 4h and 8h after S64315 EoI (LID1 and LID2)
- 24h (± 2h) after S64315 EoI (LID1 and LID2)

Before and following the first azacitidine administration (C1D1) and first S64315 infusion (C1D2) of cycle 1:
WBC, serum uric acid, serum calcium, serum phosphorus, serum potassium, serum creatinine and LDH must be monitored at the following time points:

- Prior to azacitidine first injection (C1D1 predose)
- 1h30 and 6h after azacitidine first injection (C1D1)
- After azacitidine second injection and prior to first S64315 infusion (C1D2)
- 2h, 4h and 8h after S64315 EoI (i.e. C1D2)
- 24h (± 2h) after S64315 EoI (i.e. C1D3)

Beyond the first infusion of S64315 (applicable for all patients with a risk of developing TLS according to the investigator's judgment):
WBC, serum uric acid, serum calcium, serum phosphorus, serum potassium, serum creatinine and LDH must be monitored at the following time points:

- Prior to each S64315 infusion (i.e. CxD9, CxD16, CxD23 predose)
- 2h, 4h and 8h after each S64315 EoI (i.e. CxD9, CxD16, CxD23)
- 24h (± 2h) after each S64315 EoI (i.e. CxD10, CxD17, CxD24)

Electrolyte abnormalities should be corrected promptly.

Hospitalization

To enable close in-patient TLS monitoring and management, patients must be hospitalized:

- at least 12h before the day of LID1 and for at least 24h after LID1
- at least 12h before the day of LID2 and for at least 24h after LID2

- at least 12h before C1D1 and for at least 24h after C1D2 S64315 infusion (including C1D1, C1D2 and C1D3)

If a biological or clinical TLS develops, additional measures should be implemented according to guidelines (Howard, 2011), including dialysis if clinically indicated.

In case of intra-patient dose escalation, the patient will be hospitalized for at least 3 days.

8.2.10. Infusion Related Reaction management

As the risk of Infusion Related Reaction (IRR) is not yet well characterized, it is challenging at this stage to propose a standardized prophylactic treatment before the first S64315 infusions. However, before S64315 infusion during LID period, cycle 1, and during following cycles at the investigator's discretion according to conventional practices, patients should receive the following:

- Hydration: already planned in the frame of TLS prophylaxis (see section 8.2.9)
- Corticoids (dexamethasone): already planned in the frame of nausea/vomiting prevention (see section 8.2.8.1)
- Additionally, according to investigator's opinion, anti H1 and/or anti H2 could be administered before S64315 infusion
- Patient's risk factors to develop IRR such as age-related factors, concomitant diseases (e.g. chronic respiratory diseases, cardiovascular diseases, severe atopic disease) and concomitant medications (e.g. β-adrenergic blockers and angiotensin-converting enzyme inhibitors), should be assessed before treating the patient

In addition, patient vital signs (BP, HR, temperature) should be monitored as follows:

- during the LID period for each S64315 infusion: EoI, at least 2h and 24h after EoI (LID1 and LID2)
- during Cycle 1 for each S64315 infusion: EoI and at least 2h after EoI (C1D2, C1D9, C1D16, C1D23)

In case of occurrence, IRR management will be performed according to ESMO guidelines (ESMO, 2017) as presented in Figure (8.2.10) 1 or according to local practice guidelines. If the patient experiences an IRR of grade 1 or 2, the infusion rate should be immediately decreased by 50% of the initial rate without exceeding 3 hours of total infusion time or infusion immediately stopped according to the investigator judgment and based on the severity of symptoms. The patient's vital signs (eg: blood pressure, heart rate, respiration, temperature) should be monitored every 15 minutes until the event has resolved.

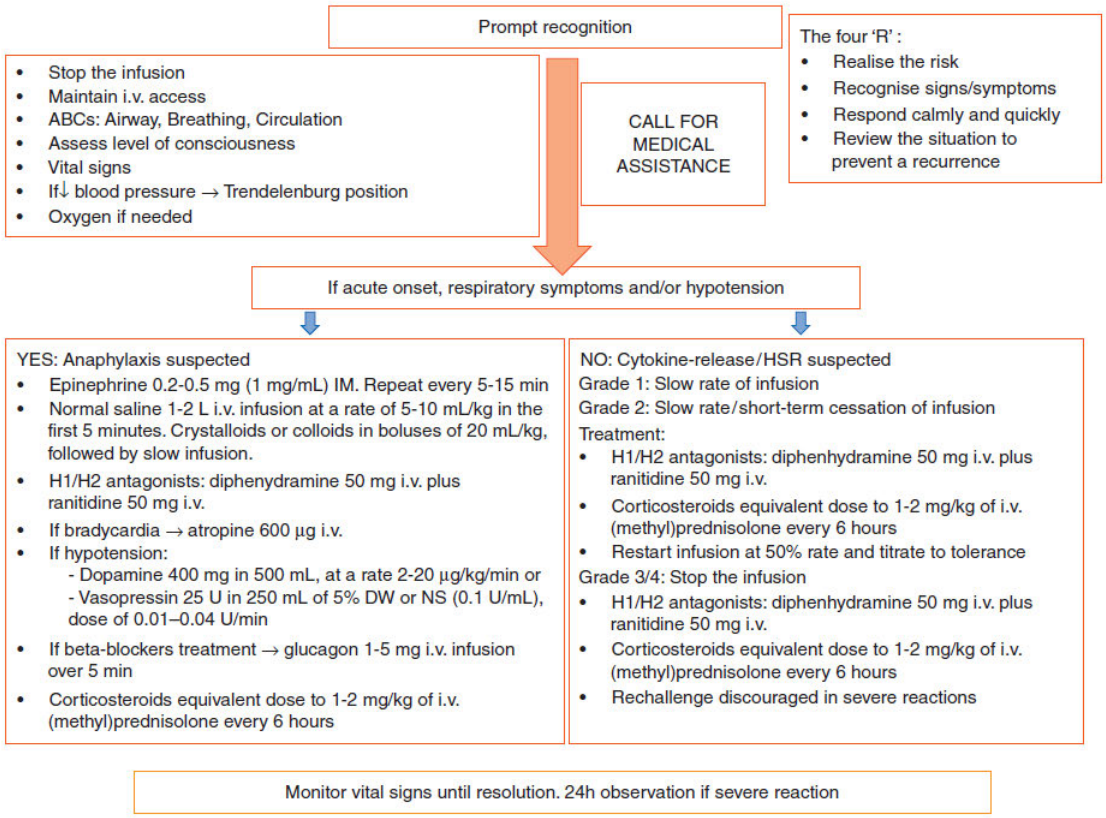
To allow better characterization of IRR, it is recommended to perform blood samplings for the measurement of tryptase levels optimally 15 min to 3h after the onset of the IRR. A new sample should be obtained from 48h to 72h after the onset of the event (baseline value).

With regards to rechallenge, the following guidelines should be considered:

- Grade 1 IRR: adequate prophylaxis should be implemented before each subsequent S64315 infusion
- Grade 2 IRR: adequate prophylaxis should be implemented before each subsequent S64315 infusion

- Grade 3 IRR:
  - If serious adverse event: no rechallenge is permitted
  - If non-serious adverse event: rechallenge is permitted according to the expected benefit risk ratio and provided that an adequate prophylaxis is implemented before each subsequent S64315 infusion, and upon sponsor's approval
- Grade 4 IRR: rechallenge is not permitted.

Figure (8.2.10) 1 - Management of IRR to systemic anticancer therapy ESMO clinical practice guidelines



8.2.11. Specific COVID-19 situation

In case of highly suspected COVID-19 infection (based on typical symptoms or typical chest CT scan images) or confirmed COVID-19 infection (based on positive COVID-19 biological testing), the study treatment(s) should be immediately interrupted.

The study treatment(s) could be restrated if patient is asymptomatic for at least 15 days after the diagnosis or with a negative test.

8.3. Definition of adverse events

An adverse event is defined as any untoward medical occurrence in a patient participating in a clinical study, whether or not there is a causal relationship with the IMPs and/or experimental procedures, occurring or detected from the date the patient signs the information and consent form, irrespective of the period of the study.

An adverse event can therefore be:

- any unfavourable and unintended sign (including an abnormal finding from an additional examination such as lab tests, X-rays, ECG, etc.) which is deemed clinically relevant by the investigator
- any symptom or disease
- any worsening during the study of a symptom or a disease already present when the patient entered the study (increase in frequency and/or intensity), including the studied pathology
- and detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in patient's diary or safety evaluation scale)

Of note:

- Any **hospitalisation for administration of anti-tumour treatment and/or associated protocol (during or after the study) or other care measures for cancer (e.g. overnight hospital stay to receive a blood or platelets transfusion), for social reasons, educational purpose** (e.g. learning of diabetes management by the patient) or routine check-up should not be considered as an adverse event and should not be reported in the eCRF.
- The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, **should not be reported in the eCRF and kept in the source data (or patient file)**:
  - therapeutic procedures related to a non-aggravated medical history (e.g. cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study)
  - prophylactic procedures (e.g. sterilisation, wisdom teeth removal)
  - comfort procedures (e.g. cosmetic surgery)
  - control procedures of a pre-existing condition without aggravation (e.g. colonoscopy to control the remission of colon cancer)

8.4. Definition of Serious adverse events

A Serious Adverse Event (SAE) is any adverse event that, at any dose:

- results in death
- is life-threatening(1)
- requires inpatient hospitalization or prolongation of existing hospitalization
- is medically significant(2)
- results in persistent or significant disability/incapacity(3)
- is a congenital anomaly/birth defect(4)

(1) Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(2) Any event that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to sponsor.

(3) Disability/incapacity in this context refers to any event that seriously disrupts the ability of the patient to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the patient's body functions or structure, physical activity and/or quality of life.

(4) Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

8.5. Definition of overdose

This refers to any intake of a quantity of IMP or a product other than the IMP taken as part of the protocol (NIMP) which is above the maximum dose recommended in the study protocol, independently of the occurrence of any adverse event.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol. For instance, if the study protocol requires a unique daily administration, one administration of twice the dose or two administrations of the full tested dose on the same day should be both considered as overdoses.

8.6. Definition of Adverse event of special interest

Not applicable

8.7. Definition of Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (i.e. without delay and **within 24h** at the latest) to the sponsor if it is:

- a SAE
- an overdose of the IMP even if asymptomatic
- any intake of the IMP by a person around the patient
- a pregnancy

8.8. Classification of an adverse event (seriousness, severity, causality, expectedness)

It is important that the investigator gives his/her own opinion regarding the **seriousness**, the **intensity** of the event as well as the **cause-effect relationship** between an adverse event and the IMPs. This evaluation must be assessed by the investigator and reported in the AE form. In addition, the sponsor will be responsible for the evaluation the **expectedness** of the event (see section 8.10).

The Seriousness should be evaluated according to international guidance (see definition in section 8.4, in accordance with ICH Topic E2A and DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April).

The severity of all AEs will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI CTCAE) on a five-point scale (Grade 1 to 5):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[1]

[1] Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

The causal relationship to the IMPs, to the experimental procedures or to disease progression must be assessed when reporting the AE in the AE form. Cases ticked 'related' by the investigator or judged by the sponsor as having a reasonable suspected causal relationship to the IMPs (AE linked to the mechanism of action of the test drug, etc.), will be considered as suspected Adverse Drug Reaction. In general, if a relationship between AE and drug is at least reasonably possible (i.e. the relationship cannot be ruled out) it is to be considered as 'related'.

8.9. Reporting procedures

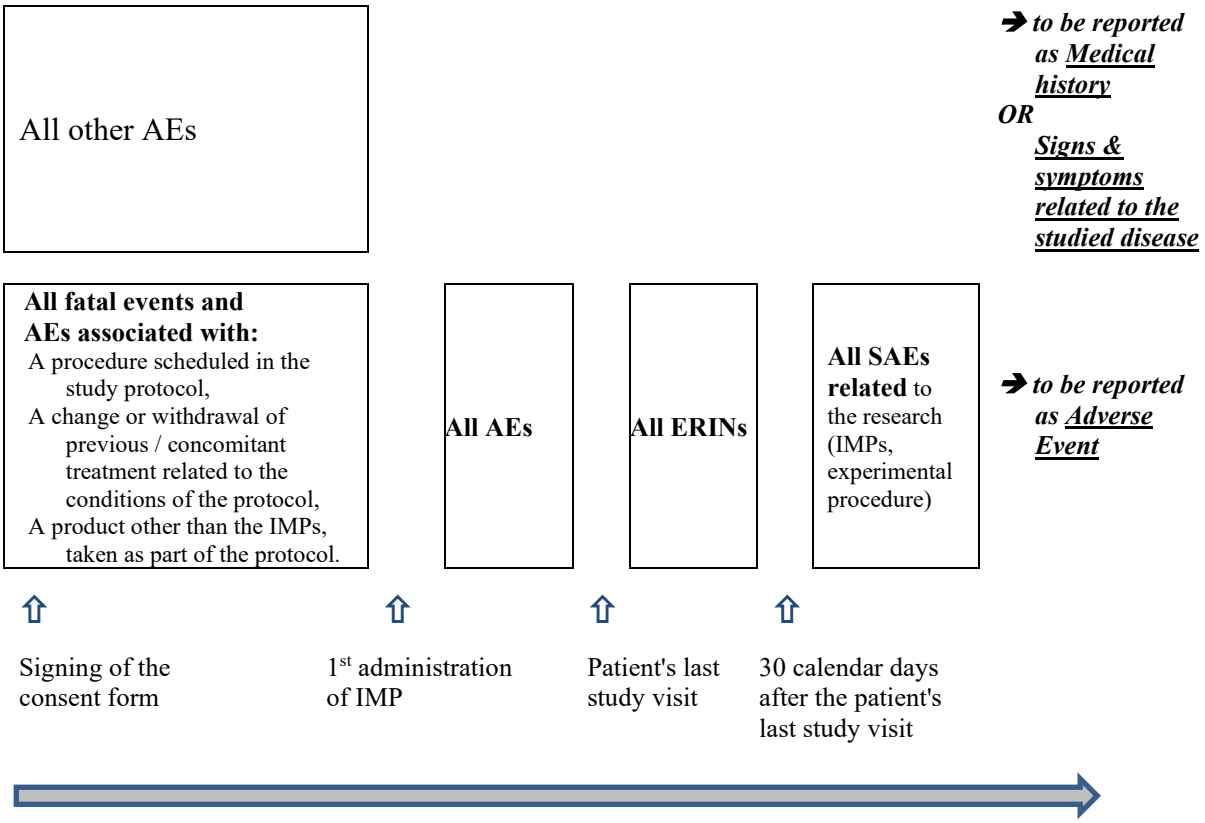
8.9.1. Time frame for AE reporting

Any event meeting the above mentioned definitions (see sections 8.3 to 8.7) must be reported to the sponsor on an adverse event form if it occurred:

- before the first intake of the IMP, and after the signature of the ICF, for event associated with any procedure/condition required by the study protocol: procedure (BMA, blood samples, MRI, etc.), change or withdrawal of previous/concomitant treatment relating to the conditions of the protocol
- at any time after the first intake of the IMP up to the patient's last study visit for all events
- after the patient's last study visit:
  - up to 30 calendar days after the patient's last study visit for all ERINs, regardless of the supposed role of the research (IMP or experimental procedure)
  - irrespective of the time of onset after the end of the study for all SAEs related to the research (IMP or experimental procedure)

Of note, events occurring between the signature of the ICF and the first administration of the IMP for which the investigator does not consider an association with any procedure/condition required by the study protocol must be reported as medical history or as signs or symptoms related to the studied disease in the dedicated eCRF form. Fatal event, related or not to the research, occurring between ICF signature and before first IMP administration, must be reported on AE form.

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.



8.9.2. Responsibilities of the investigator

For any adverse event and special situation mentioned above the investigator must:

- **Note in the patient's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the patient or a third person, …) and any other relevant information which he/she has learned of the event
- **Assess** the event in terms of seriousness, intensity and causality
- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately)
- **Document** the event with additional useful information
- Ensure the **follow-up** of the event
- **Fulfil his/her regulatory obligations** to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations

Moreover, the investigator must report to the sponsor and/or to the IRB/IEC and/or to the Competent Authorities in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the test drug or that would be sufficient to consider changes in the test drug administration or in the overall conduct of the clinical investigation.

8.9.2.1. Documentation of the event

The investigator must ensure that all events are well documented. In particular for ERIN, he/she should provide the sponsor, as they become available, with anonymized copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis, where possible, the results from pre-test drug assessments should be appended for comparison with the results obtained under test drug, or the autopsy report, if autopsy is performed.

8.9.2.2. Follow-up of adverse events

The investigator must ensure that follow-up of the patient is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on the 'Adverse event' page previously created for the event.

If the adverse event has not resolved at the patient's final visit in the study, the patient must be followed up suitably and any information on the outcome of the event will be noted on the 'Adverse Event' page previously created for the event. An adverse event ongoing at the time of a participant's death is considered to be Not Recovered.

If the patient's follow-up is not done by the investigator him/herself (hospitalisation, followed by a specialist or the patient's general practitioner, etc.), the investigator will do everything to establish/maintain contact with the person/department in charge of the patient's follow-up.

8.9.2.3. Special situations (pregnancy, overdoses, intake of IMP by a person around the patient)

Pregnancy

If a female patient in the study becomes pregnant, the investigator must:

- stop immediately the IMPs
- report it on an 'Adverse Event' page as well as on the specific paper pregnancy form (1st age) to be notified immediately (ERIN)
- contribute to the follow-up of this pregnancy and provide the sponsor with information concerning this follow-up (notably using the 2nd page of the specific paper pregnancy form)

If the partner of a patient becomes pregnant during the course of the study, the pregnancy should not be reported in the eCRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed

Overdose of IMP

- In case of overdose, the investigator should report it on an 'Adverse Event' page to be notified immediately (ERIN)
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
  - dose details (number of units, duration, etc.) and, if multiple overdose, details regarding other medicinal products or substance
  - context of occurrence, i.e. intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage)

  - related signs and symptoms ('No related adverse events' to be reported otherwise)
  - outcome
- In so far as possible, an additional PK blood sampling should be collected for assay of the taken IMP

Intake of IMP by a person around the patient

This event should not be reported in the eCRF. The investigator should immediately contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

8.9.2.4. Recording methods in the eCRF

Adverse events must be documented on the eCRF 'Adverse Event' page.

In case of chronic disease:
- if the disease is known when the patient enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event
- if the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the 'Adverse Event' page previously created for the event which will clearly describe the diagnosis

8.9.2.5. Procedure for an event requiring an immediate notification

In case of an event requiring an immediate notification, the investigator must:
- **immediately** after being informed of this event, **fill in** the **patient's medical file** as well as the eCRF **'Adverse Event' page** according to the general instructions available in the eCRF, without waiting for the results of the clinical outcome or of additional investigations. When data is submitted into Inform®, an e-mail will be immediately and automatically sent to the sponsor
- provide the sponsor (person designated in the contact details provided in the investigator's study file), as they become available, with anonymized copies of the documents which provide additional useful information
- fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations

If an adverse event initially non-serious worsens and becomes a SAE, this must be reported **immediately** on the eCRF 'Adverse event' page.

In case the eCRF is unavailable when the investigator was informed of the ERIN, he/she should:
- **Immediately** fill in a paper 'Adverse event' page
  - For serious event on a paper 'Adverse event – Initial information' page
  - For event initially non-serious on a paper 'Adverse event – Initial information' page, and the worsening leading to seriousness on a paper 'Adverse event – Additional information' page
- Immediately send them by fax or by e-mail to the person(s) designated in the contact details provided in the investigator's study file or outside working hours, the 24-hour phone line (01.55.72.60.00 for a call from France, or +33.1.55.72.60.00 for a call from outside France, and/or the specific phone line as specified in the instructions provided to each centre)
- As soon as the eCRF becomes available, enter this information in the eCRF 'Adverse Event' page

8.10. Responsibilities of the sponsor

In accordance with international guidance, the assessment of the seriousness and the causality of adverse events are usually made by the investigator but falls also under sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The sponsor will review the seriousness of the adverse events and the causality of (at least) the SAEs, whether reported by the investigator or upgraded by the sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of documents providing useful information such as reports of further consultations, laboratory tests reports, reports of other examination aiding diagnosis may be asked for the event assessment. If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report (CSR).

In addition, the sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMPs.

Independently of the regulatory obligations of the investigator, the sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit /risk balance of the product, required in ICH Good Clinical Practice guidelines and local regulations, to the appropriate Authorities, to all the investigators involved and to the patients involved, through the investigators, as mentioned in section 13.4.

The concerned Authorities will be notified as soon as possible by the sponsor of the DSMB recommendations if any, where relevant for the safety of patients (i.e. modification or termination of the study).

8.11. Responsibilities of Data Safety and Monitoring Board

Taken into account the innovative character of such a combination, the limited data from animal studies, the potential important safety risks associated with the administration of both IMPs, the vulnerability of the treated population, a DSMB will be set-up to review periodically the patients' safety and efficacy data throughout the conduct of the study in order to ensure that the patients' potential benefit is not compromised by safety concerns.

In accordance with the DSMB charter and the rules for DSMB functioning, the DSMB is an independent group of experts who provides expertise and recommendations to the Sponsor. Their primary responsibility is to review safety and efficacy data in the light of the benefit-risk ratio on a regular basis and after the last patient of each cohort has completed the first cycle of treatment. After each meeting they will provide written recommendations to the International Coordinator/Investigators and the Sponsor regarding the progress and conduct of the study (continuation, modification or termination). Indeed, the DSMB can recommend escalating, de-escalating the doses or extending a given cohort to additional patients according to the adopted study design. The DSMB could also give recommendations on the possible modification of the study protocol based on the review of the safety and efficacy data and suspend or early terminate the study in case of serious concerns about patient safety. The DSMB members will ensure their availability in case of any required extraordinary meeting.

The role and the composition of the DSMB are detailed in section 12.4.

8.12. Management of treatment dose adaptations due to toxicities

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatments.

Dose modifications recommendations for S64315 are summarised in Table (8.12) 1.

A patient must discontinue treatment with S64315 if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity, unless in the opinion of the investigator it is in the patient's best interest to continue S64315, and upon documented agreement with the Sponsor.

For each patient, once a dose reduction has occurred, the dose may not be re-escalated during the subsequent cycles unless in the opinion of the investigator it is in the patient's best interest to continue S64315, and upon documented agreement with the Sponsor.

When a patient meets the criteria for S64315 discontinuation described in the table, he/she must discontinue both IMPs.

Dose modifications for azacitidine must be done according to azacitidine E.U. SmPC (see Table (8.12) 2).

These dose changes must be recorded in the eCRF.

Table (8.12) 1 - Criteria for interruption and re-initiation of S64315

Recommended dose modifications for S64315	
Worst toxicity **CTCAE Grade[a] (unless otherwise specified)**	**During a cycle of therapy**
Investigations (Renal)	
Serum creatinine	
Grade 2 (> 1.5 – 3 x ULN or > 1.5 – 3 x baseline)	Omit dose until resolved to Grade ≤ 1 or baseline, then: - If resolved in ≤ 14 days, then maintain dose level - If resolved in > 14 days, then ↓ 1 dose level
Grade 3 (> 3 – 6 x ULN or > 3 x baseline)	Omit dose until resolved to Grade ≤ 1 or baseline, then ↓ 1 dose level
Grade 4 (> 6 x ULN)	Discontinue patient from test drug treatment
Note: If intercurrent illness, e.g. dehydration due to diarrhoea or febrile infections, leads to prerenal insufficiency, this should not be considered drug related and the criterion for dose modification not fulfilled	
Investigations (Hepatic)	
Isolated Total Bilirubin elevation[b]	
Grade 2 (> 1.5 - 3.0 x ULN if baseline was normal, >1.5 - 3.0 x baseline if baseline was abnormal)*	Omit dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 14 days, maintain dose - If resolved in > 14 days, ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 14 days, ↓ 1 dose level - If resolved in > 14 days, discontinue patient from test drug treatment The patient should be weekly monitored (including Liver Function Tests (LFT)[f]), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilised over 4 weeks
Grade 4 (> 10.0 x ULN)	Discontinue patient from test drug treatment The patient should be weekly monitored (including LFT), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilised over 4 weeks
Isolated AST or ALT elevation	
AST or ALT > 3.0 – 5 x ULN	Omit dose S64315 until resolved to ≤ 3 x ULN, then maintain dose
Grade 3 (> 5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal)	Omit dose until resolved to ≤ 3 x ULN, then - If resolved in ≤ 14 days, maintain dose - If resolved in > 14 days, ↓ 1 dose level.
Grade 4 (> 20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal)	Discontinue patient from test drug treatment

Combined[c] elevations of AST or ALT and total bilirubin[e]	
AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN and confirmed Hy's law cases according to FDA guidance	- For patients with normal baseline ALT or AST or total bilirubin value If AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis[d]: - Permanently discontinue patient from test drug treatment For patients with elevated baseline AST or ALT or total bilirubin value If [AST or ALT > 2.0 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN: - Permanently discontinue patient from test drug treatment. Repeat LFT[f] as soon as possible, perform liver imaging to assess biliary tract or liver disease (if possible), preferably within 48h from awareness of the abnormal results, then with weekly monitoring of LFT[f], or more frequently if clinically indicated, until AST, ALT or bilirubin has resolved to baseline or stabilised over 4 weeks
Investigation (Pancreatic)	
Amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	May maintain dose level
> 1.5 - 2.0 x ULN	May maintain dose level
> 2.0 - 5.0 x ULN and asymptomatic	Omit dose until resolved to Grade ≤ 1 or baseline then: - If resolved in ≤ 14 days, maintain dose level - If resolved in > 14 days, ↓ 1 dose level
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms or >5.0 x ULN and asymptomatic)	Discontinue patient from test drug treatment
Grade 4 (> 5.0 x ULN and with signs or symptoms)	Discontinue patient from test drug treatment
Note: A CT scan to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any Grade ≥ 3 amylase and/or lipase, or as clinically indicated	
Investigation (Metabolic)	
Creatine (phospho)kinase elevation	
Grade 3	Omit dose until resolved to Grade ≤ 2, then: - If resolved in ≤ 14 days, maintain dose level - If resolved in > 14 days, ↓ 1 dose level
Grade 4	Omit dose until resolved to Grade ≤ 2, then: - If resolved in ≤ 14 days, then ↓ 1 dose level - If resolved in > 14 days, then discontinue patient from test drug treatment

Gastro intestinal	
Pancreatitis	
Grade ≥ 3	Discontinue patient from test drug treatment
Diarrhoea	
Grade 1 and 2[g]	Maintain dose level, treat the patient per institutional diarrhoea management protocol
Grade 3	Omit dose until resolved to Grade ≤ 1, treat the patient per institutional diarrhoea management protocol, then: - If resolved in ≤ 5 days, maintain dose level - If resolved in > 5 days despite the use of optimal anti-diarrhoea therapy, ↓ 1 dose level
Grade 4	Discontinue patient from test drug treatment.
Grade ≥ 3 Vomiting	Maintain dose level, if not resolved to Grade ≤ 2 within 48h after start of optimal anti-emetic therapy, then omit dose until resolved to Grade ≤ 2, and then ↓ 1 dose level
Metabolism and nutrition disorders	
Electrolyte abnormalities (if clinically significant)	
Grade 3	Omit dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days, maintain dose level - If resolved in > 7 days, ↓ 1 dose level
Grade 4	Discontinue patient from test drug treatment
Skin and subcutaneous tissue disorders	
Rash /photosensitivity	
Grade 1	Maintain dose level Consider initiating appropriate skin toxicity therapy (e.g. antihistamines and topical corticosteroids) as per local institutional guidelines Consider skin biopsy for evaluation
Grade 2	Maintain dose level but initiate/intensify appropriate skin toxicity therapy (e.g. antihistamines, topical corticosteroids and low-dose systemic corticosteroids) as per local institutional guidelines and monitor closely Consider skin biopsy for evaluation
Grade 3, despite skin toxicity therapy	Omit dose and reassess the patient weekly until resolved to Grade ≤ 1, then: - If resolved in ≤ 14 days, ↓ 1 dose level - If resolved in > 14 days, discontinue patient form test drug treatment Consider referral to dermatologist and manage rash per dermatologist's recommendations Consider skin biopsy for evaluation

Grade 4, despite skin toxicity therapy	Discontinue patient from study treatment Consider referral to dermatologist and manage rash per dermatologist's recommendations Consider skin biopsy for evaluation
Cardiac disorders	
QTcF Prolongation	
QTcF interval ≥ 481ms or increase of > 60 ms from baseline on at least two separate ECG	Omit S64315 dose, correct the possible electrolytes abnormalities (e.g. potassium, magnesium, etc.) and perform frequent ECGs* until resolves to Grade ≤ 1, then: - If resolved in ≤ 14 days, ↓ 1 dose level. Triplicate ECGs must be monitored on D1 of each cycle throughout the study - If resolved in > 14 days, discontinue patient from test drug treatment *Perform at least weekly ECGs until 2 weeks following resolution of the QTc prolongation
LVEF Decrease	
Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and LVEF <50%	Omit dose, obtain consultation with a cardiologist, and repeat cardiac imaging after 4 weeks - If improved to ≤ 10% from baseline and ≥ 50% within 4 weeks, then ↓ 1 dose level. Monitor LVEF on D1 of each subsequent cycle for at least 3 cycles; if no recurrence of LVEF decline and if agreed by the cardiologist, the frequency may then be decreased to every other cycle. - If not improved to ≤ 10% from baseline and ≥ 50% within 4 weeks, then discontinue patient from test drug treatment
Absolute decrease in LVEF of 20% or greater from baseline and LVEF < 40% OR Symptomatic congestive heart failure	Discontinue patient from test drug treatment and obtain consultation with a cardiologist
NOTE: Upon discontinuation due to LVEF decrease, closely monitor LVEF until resolution. The same cardiac imaging modality (i.e. transthoracic echocardiography (TTE) or MUGA scan) used at baseline is to be used for all subsequent assessments	
Cardiac MRI abnormality	In case of cardiac MRI abnormality clinically significant according to the cardiologist (e.g. compatible with ischemia or left ventricular dysfunction), in a context of troponin elevation, discontinue patient from study drug treatments
Cardiac biomarkers	
Grade 1 troponin I or T elevation	Omit dose, evaluate and treat patient per institutional guidelines. Follow Troponin I/T to resolution per institutional guidelines - If no evidence of LVEF decrease from baseline of 10% or greater on TTE or MUGA* and Troponin I/T resolves to normal in ≤ 7 days, then maintain dose level - If no evidence of LVEF decrease from baseline of 10% or greater on TTE or MUGA* and Troponin I/T resolves to normal in > 7 days, then ↓ 1 dose level. Consult with a cardiologist prior to re-initiating test drug - If evidence of LVEF decrease from baseline of 10% or greater on TTE or MUGA, follow guidelines for LVEF decrease

	*exams to be performed once per cycle or according to physician decision A clear investigation is required in case of isolated increase in troponin in order to consider the possible confounding factors before considering the abnormality as related to the test drug
Troponin I or T elevation > ULN associated with clinical signs or LVEF decrease or ECG abnormality	A cardiac MRI should be performed at the time of the event (as far as possible within 48h to 72h) and 5 to 6 weeks later, for functional cardiac assessment A 24-h Holter should be performed at the time of the event
Troponin I or T elevation > 10 x ULN or troponin increase consistent with the diagnosis of a myocardial infarction (Grade 3)	Discontinue the patient from test drug treatments A cardiac MRI should be performed at the time of the event (as far as possible within 48h to 72h) and 5 or 6 weeks later, for functional cardiac assessment A 24-hour Holter should be performed at the time of the event
Eye Disorders (Results and images of ophthalmic examinations should be made available upon request)	
Other ocular/visual toxicity	
Grade 1 or 2	Maintain dose level and increase ophthalmic monitoring frequency to at least every 14 days Refer the patient to an ophthalmologist within one week for evaluation
Grade 3	Omit dose until resolved to Grade ≤ 1, and increase ophthalmic monitoring frequency to at least once a week, and refer the patient to an ophthalmologist within one week for further evaluation, then: - If resolved in ≤ 14 days, ↓ 1 dose level - If resolved in > 14 days, discontinue patient from test drug treatment
Grade 4	Discontinue test drug treatment and refer the patient to an ophthalmologist for monitoring
Haematological abnormalities (myelosuppression)	
Neutropenia and thrombocytopenia Grade 4	If bone marrow clearance, omit dose and/or interrupt azacitidine until count recovery: - If resolved in < 28 days, then maintain the dose level - If resolved in > 28 days, then consider discontinuing patients from study unless the patient has evidence of clinical benefit and in discussion with the Sponsor a decision is made to continue therapy at a lower dose
Other AEs	
Grade 3	If Grade 3 (except those correctable within 7 days and deemed by the investigator to be not clinically important), hold treatment until resolved to Grade ≤ 1 or baseline, then: - If resolved in ≤ 14 days, ↓ 1 dose level - If resolved in > 14 days, discontinue patient from test drug treatment
Grade 4	Discontinue test drug treatment
NOTE In some particular cases, a patient with a Grade 3 or Grade 4 AE may resume treatment at the lower dose level if in the opinion of the Investigator and after discussion with the Sponsor, the event is not life-threatening, and the patient can be managed and monitored for recurrence of the AE. In case of TLS Grade 3 or 4, the dose adaptation of the study drugs will be discussed between the sponsor and the investigator according to the patient's benefit/risk assessment.	

All dose modifications should be based on the worst preceding toxicity.

Patients may receive supportive care (e.g. packed red blood cells) as per local institutional guidelines.

[a] Common Toxicity Criteria for Adverse Events (CTCAE v5.0)

[b] If Grade 3 or 4 hyper-bilirubinaemia is due to the indirect (non-conjugated) component only, and haemolysis as the aetiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator

[c] 'Combined' defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

[d] 'Cholestasis' defined as: ALP elevation [> 2 x ULN and R value < 2] in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury)

[e] If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, restart the treatment either at the same dose or at one dose lower if a criterion for dose reduction is met.

[f] LFT include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), ALP (fractionated if ALP > 2.0 x ULN) and GGT. For isolated elevations of any grade of ALP and/or GGT, maintain dose level.

[g] Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhoea.

* Note: Patients enrolled with Gilbert's syndrome and elevated baseline bilirubin between > 1.5 x ULN and ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN can continue treatment.

Table (8.12) 2 - Criteria for interruption and re-initiation of azacitidine (see E.U. azacitidine SmPC)

Dose adjustment due to haematological toxicity

Haematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets ≤ 50.0 x 10^9/L and/or absolute neutrophil count (ANC) ≤ 1 x 10^9/L.
Recovery is defined as an increase of cell line(s) where haematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (i.e. blood count at recovery ≥ nadir count + (0.5 x [baseline count – nadir count]).

Patients without reduced baseline blood counts (i.e. WBC ≥ 3.0 x 10^9/L and ANC ≥ 1.5 x 10^9/L, and platelets ≥ 75.0 x 10^9/L) prior to the first treatment

If haematological toxicity is observed following azacitidine treatment, the next cycle of the therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

Nadir counts		% Dose in the next cycle, if recovery* is not achieved within 14 days
ANC (x 10^9/L)	Platelets (x 10^9/L)	
≤ 1.0	≤ 50.0	50%
> 1.0	> 50.0	100%

*Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10^9/L or ANC < 1.5 x 10^9/L or platelets < 75.0 x 10^9/L) prior to the first treatment

Following azacitidine treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is ≤ 50%, or greater than 50% but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC or ANC or platelets is greater than 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced according to the following table:

Bone marrow cellularity	% Dose in the next cycle if recovery is not achieved within 14 days	
	Recovery* ≤ 21 days	Recovery* > 21 days
15-50 %	100%	50%
< 15%	100%	33%

*Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

Following dose modifications, the cycle duration should return to 28 days.

Dose adjustment due to non-hematologic toxicities:
Renal abnormalities and electrolyte imbalance:

- If unexplained reductions in serum bicarbonate levels to less than 20 mmol/L occur, the dose should be reduced by 50% on the next cycle.
- If unexplained elevations in serum creatinine or blood urea nitrogen (BUN) to ≥ 2-fold above baseline values and above upper limit of normal (ULN) occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

The assessments hereafter are applicable for dose escalation phase I part of **Arm A** They could be refined for expansion phase II part (**sub-arms A1/ A2**) according to results observed in the dose escalation phase I part, as well as for **Arm B** according to the results of Arm A. They will be described in an amendment to the protocol.

9.1. Assessments related to inclusion criteria.

Not applicable

9.2. IMPs concentration measurements

9.2.1. Blood samples

Concentrations of S64315 and azacitidine administered in combination, and of potential metabolite(s) will be determined in plasma using high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection, according to a separate bioanalytical sample analysis plan established with the dedicated analytical laboratory.

Blood samples should be collected from the arm opposite from the IMP infusion if peripheral access is used, or from another site, such as an arm, if the patient displays a central vein line for the IMP infusion.

The accurate date and time of sample collection will be recorded on documents provided with the lab kits associated to each visit, called the requisition forms. All problems associated with sample collection or processing should be noted on the requisition forms and reported to the Sponsor's monitor.

A blood sample should be collected immediately following an ECG performed due to an unexpected cardiac signal, to assess drug concentration.

- **Dose escalation phase I part**

For each patient, concentrations of S64315 and azacitidine administered in combination, and of potential metabolite in plasma, will be measured as described in Table (9.2.1) 1.

Each patient will have a total of 13 PK samples collected.

Table (9.2.1) 1 - Time points for drug concentration assessment during dose escalation phase I part

Once a week administration of S64315 in combination with azacitidine (28-day cycle)	
Number of blood samples to be collected (3 mL each)	13 samples
	S64315
S64315 LID1	EoI**
	4h after EoI
	24h after EoI
C1D2: Second azacitidine injection First S64315 infusion (within 2h ±10 minutes after azacitidine injection)	Predose*
	[Start of S64315 Injection]
	10 min after SoI

Once a week administration of S64315 in combination with azacitidine (28-day cycle)	
Number of blood samples to be collected (3 mL each)	13 samples
	S64315
	30 min after SoI
	EoI**
	30 min after EoI
	1h after EoI
	2h after EoI
	4h after EoI
	7h ±1h after EoI
C1D3: Third azacitidine injection	24h after EoI

SoI Start of Infusion *EoI End of Infusion*
**i.e. 5-30 min before infusion/injection* ** *i.e. within 5 to 10 min before the EoI*

Detailed instructions for sample collection, processing, handling, and shipment of samples will be provided in a laboratory manual.

Residual plasma used for PK analysis (e.g. S64315 and azacitidine plasma concentration) may also be used for exploratory analysis. This could include using leftover plasma for protein binding analysis, metabolite profiling, co-medication PK analysis or exploratory biomarker analysis, if there are sufficient samples remaining. Plasma samples remaining from the analysis may be retained by the Sponsor for additional investigations (i.e. long-term stability, reproducibility).

- **Expansion phase II part**

Measurement of drug concentration during the expansion phase II part of the study will be determined according to results observed in the dose escalation phase I part.

9.2.2. Identification and transfer of samples

Each sample will be clearly labelled with a double identification (aliquots 1 and 2) and will be shipped with a requisition form. It will be clearly labelled with the centre number, the patient number, date and hour of collection. Aliquots 1 and 2 will have to be sent in different shipments.

All PK samples will be shipped to the logistic platform (shipments at approximately -80°C). The logistic platform will then ship the aliquot 1 sample to the analytical laboratories. Aliquot 2 will be at logistic platform on interim storage until Sponsor request. At the latest 3 months after bioanalytical report signature and upon request of I.R.I.S., the logistic platform and the analytical laboratory will be responsible for the destruction of the samples received.

9.3. Pharmacodynamics measurements

Exploratory biomarkers, i.e. assessments planned to improve the knowledge of the combination of S64315 with azacitidine and/or the disease are detailed in Table (9.3) 1.

Table (9.3) 1 - Biomarker sample collection plan

Sample type	Visit / time points	Volume	Marker	Purpose
Blood samples (PBMCs or fixed/lysed blood samples)	LID1: S64315 predose CxD1: azacitidine predose CxD2: azacitidine predose, S64315 predose, 1h and 24h ±2h EoI Any time in case of disease progression****	10 mL (EDTA K2 tube) at each time point	Bcl-2 family members protein expression	To characterize PD markers and identify potential predictors of efficacy
	L1D1: predose C1D1: azacitidine predose C2D1: azacitidine predose C3D1: azacitidine predose In case of CR and every 3 months during study treatment period after CR for MRD only Any time in case of disease progression****	10 mL (EDTA K2 tube) at each time point	Genomic alterations of Bcl-2 family members and cancer related genes	To assess potential mechanisms of treatment resistance
			Detection and quantification of residual leukemic cells by gene expression and genomic alterations	To assess MRD
Blood samples	LID1: S64315 predose C1D1: azacitidine predose C1D2: azacitidine predose, S64315 predose, 4h, 6h, 24h and 72h after EoI C1D9: predose and 24h after EoI C1D16: predose Other cycles: CXD1 Aza predose; CXD16 predose	According to local procedures (2 - 4mL maximum)	Absolute count of Total and B lymphocytes	To assess potential surrogate response marker of biological activity as additional evidence of MCL-1 response
Bone Marrow Aspirate (BMA)* (BMMCs or fixed/lysed BMA samples)	Baseline*** Any time in case of response (at least PR) In case of disease progression****	2-5 mL (EDTA K2 tube) at each time point	Bcl-2 family members protein expression	Exploratory analysis for potential predictive markers of response
	Baseline*** C2D1: predose C3D1: predose In case of CR and every 3 months during study treatment period after CR for MRD only Any time in case of disease progression****	2-5 mL (EDTA K2 tube) at each time point	Genomic alterations of Bcl-2 family members and cancer related genes	To assess potential mechanisms of treatment resistance
			Detection and quantification of residual leukemic cells by gene expression and genomic alterations	To assess MRD
Archived BMB sample (and corresponding pathology report if needed)** (if available)	Before screening	FFPE tumour block or 15-20 unstained slides	Bcl-2 family members protein expression	To assess potential Bcl-2 family members expression due to prior therapy
BMB sample** (if available)	Baseline*** Any time in case of response (at least PR) In case of disease progression****	FFPE tumour block or 15-20 unstained slides	Bcl-2 family members protein expression	Exploratory analysis for potential predictive markers of response To assess potential mechanisms of treatment resistance

Sample type	Visit / time points	Volume	Marker	Purpose
Saliva sample	Baseline*** In case of CR	Patient kit	DNA/RNA sequencing	Comparator to allow identification of somatic DNA variants in tumour
Copies of karyotype reports (if available)	Diagnosis and/or baseline*** In case of disease progression****	N/A	Chromosomal abnormalities	To assess potential modifications in karyotypes

BMMCs: Bone Marrow-derived Mononuclear Cells; BMB: Bone Marrow Biopsy, PBMCs: Peripheral Blood-derived Mononuclear Cells; FFPE: Formalin-Fixed Paraffin-Embedded
CR: complete response; PR: partial response
*If enough material is available from the BMA performed for the evaluation of efficacy measurement (anti-leukemic activity)
** If enough material is available from the BMB performed for the evaluation of efficacy measurement (anti-leukemic activity)
***Before the first IMP administration
**** N/A for LID period

9.3.1. Mandatory assessments

Tumour samples will be analysed at the molecular and cellular levels as well as to determine how baseline biomarker values/levels and changes from baseline may relate to exposure, clinical outcomes, and resistance. Potential predictive markers of efficacy will also be explored. In addition, MRD (Ivey, 2016) assessment will be explored for detection, as well as the quantification, of residual leukemic cells and their clonal evolution.

Participation in the CL1-64315-004 study implies a systematic participation in the mandatory investigation. All patients will have to consent to this investigation by signing the main information and consent form for participation in the study. In addition, in case of consent withdrawal, related samples will be destroyed after mandatory assessment is completed.

In this investigation, the analysis of an association between the biomarkers (BCL-2 family member genes, proteins and other genes of interest), the investigated disease (AML) and the treatment response will be assessed. For this purpose, samples from all patients will be collected in order to extract DNA, RNA and/or proteins and to analyse biomarkers (such as variations of DNA, proteins and RNA characteristics). Overall validated results of the biomarkers assessment may be transmitted to the patient upon his/her request at the end of the study. There will be no communication of individual results neither to the investigator nor to the patient unless these results are proven to impact the therapeutic strategy.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g. inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of the Sponsor.

9.3.1.1. Sampling and storage

Archived and newly obtained tumour samples but also blood samples will be collected before and during treatment with S64315 in combination with azacitidine upon disease progression to investigate the effect of the combination.

- Archived and/or newly BMB:

An archived tumour sample, Formalin-Fixed Paraffin-Embedded (FFPE) block, or unstained slides if it's not possible to obtain FFPE block, is requested from all patients before screening, if available. The BMB main anatomo-pathological characteristics will be collected via the eCRF. If needed, corresponding copies of anonymized pathology reports should be sent to the Sponsor by fax or email to the following number / address: +33.1.55.72.50.04 / CL1-64315-004@servier.com. An additional archived sample may be requested if the original sample provided is of insufficient quantity or quality to complete the planned analysis. All FFPE blocks and unstained slides will be stored and sent at approximately +4°C.

- Bone marrow aspiration (BMA) samples and blood samples:

The BMA main anatomo-pathological characteristics will be collected via the eCRF. If needed, corresponding copies of anonymized pathology reports should be sent to the Sponsor by fax or email to the following number / address: +33.1.55.72.50.04 / CL1-64315-004@servier.com. BMMCs (bone marrow-derived mononuclear cells) or fixed/lysed cells and PBMCs (peripheral blood-derived mononuclear cells) or fixed/lysed cells collections from BMA and blood samples respectively are requested for all patients at various predose time points as described in Table (9.3) 1. PBMCs and BMMCs (or fixed/lysed cell) samples will be stored at approximately ≤ -70°C on site before shipment and sent on dry ice.

- Saliva:

Patient's saliva will be collected as defined in Table (9.3) 1. Patient's saliva kit will be stored on site before shipment and sent at ambient temperature.

- Karyotype for AML patients:

The main chromosomal abnormalities will be collected via the eCRF. If needed, copies of anonymized karyotype reports should be sent to the Sponsor by fax or email to the following number / address: +33.1.55.72.50.04 / CL1-64315-004@servier.com, if performed at the following time points: diagnosis, baseline (before the first infusion of S64315) and at disease progression.

The samples will be stored during the study in a logistic platform/central laboratory. Then, the samples will be kept deep frozen (except for biopsy samples) in a central bio-repository specialized in storage of biological samples until further notification from the Sponsor and may be retained up to 25 years after study closure.

9.3.1.2. Labelling and shipments

All sample collection information must be entered as required on the appropriate sample collection eCRF page(s) and requisition form(s). Detailed instructions for the collection, handling, and shipment of tumour or other samples are outlined in the laboratory manual for the study.

All tubes will be produced by the logistic CRO, and will be clearly labelled with the centre number, the patient number, date and hour of collection. Samples will be single coded with a number and thus will not carry any personal identifiers.

Samples will be sent to the logistic CRO to be stored until their analysis by different analytical laboratories depending on their aim:

- on dry ice for PBMCs and BMMCs (or fixed/lysed cells) from blood and BMA samples respectively
- at +4°C for archived and/or newly obtained tumour samples (BMB)
- at ambient temperature for patients' saliva samples

9.3.1.3. Biomarker assessments

- Archived and/or newly BMB

Collection of the archived samples may allow monitoring of the changes potentially occurring in Bcl-2 family member's expression, between the time of the collection of archived and newly obtained BMB. This could allow assessing potential Bcl-2 family member's expression changes due to prior therapy.

Newly BMB will be collected for exploratory analysis of potential predictive biomarkers of efficacy (response and non-response) which include but are not limited to expression of Bcl-2 family proteins or other proteins related to cancer.

Additional biomarkers or methods may be utilized if indicated by new findings from the literature as well as from I.R.I.S. internal data.

- BMA samples and blood samples

  BMMCs and PBMCs isolated from BMA and blood (or fixed/lysed cells) samples respectively will permit exploratory analysis of:
  - Predictive markers of efficacy (response and non-response) which may include, but are not limited to expression of Bcl-2 family proteins, genomic alterations of BCL-2 family member genes and other genes related to cancer using technologies such as next generation sequencing (NGS),
  - MRD and residual leukemic cells clonal evolution.

Moreover, PBMCs isolated from blood samples will also be collected prior to and after dosing of S64315, on the time points indicated in Table (9.3) 1 to allow assessment of pharmacodynamics biomarkers.
A dose-dependent decrease of B-cells counts following S64315 treatment has been observed in toxicological studies in rats. Moreover, based on literature, hypomethylating agents do not significantly reduce the B-cell population (N. Daver et al. Leukemia (2018)). Therefore, absolute count of total and B lymphocytes will be assessed locally as potential surrogate response markers for MCL1 inhibition.

For patients who have disease progression after demonstrating clinical benefit, tumour samples may be collected and used to evaluate determinants of resistance and outcome as described above. Refractory tissue samples containing tumour (i.e. blood, BMA or BMB) will be compared to pre-treatment biopsy samples.

Additional markers or methods may be utilized if indicated by new findings from the literature as well as from Sponsor's internal data.

- Saliva

For gene alteration analysis, patient's saliva will be used as a comparator to allow identification of somatic DNA variants in tumour.

- Karyotype

The changes in karyotypes of AML patients related to S64315 treatment will be evaluated by comparing karyotypes at diagnosis or at baseline and at progression.

The samples may be used after the end of the study for other genomic assessments in relation to the test drug or the disease (AML) not specified in the protocol in light of new scientific knowledge or technology but will not be used for the elaboration of a DNA bank.

9.3.1.4. Transfer of analytical results

Final analytical results will be transferred to Data Management according to section 12.2.

9.3.2. Optional assessments

During the trial, in addition to the biomarkers specified above, exploratory biomarker research may be conducted on any remaining BMA, tumour and/or blood samples. These studies would extend the search for the potential of other relevant biomarkers for S64315 in combination with azacitidine effects and/or safety. This may also include research to help develop ways to detect, monitor and/or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

Participation in the CL1-64315-004 study does not imply a mandatory or systematic participation in these optional investigations. All voluntary patients will have to sign a specific informed consent form for **optional retrospective genomic biomarker analyses**. The consent given to these assessments can be withdrawn at any moment without compromising the participation in the overall clinical study investigations. In addition, in case of consent withdrawal, related samples will be destroyed before any optional assessment is completed.

The samples will not be used for any investigations not specified in this protocol or for the elaboration of a DNA bank.

If the patient agrees, the remaining biological samples from blood, bone marrow or tumour may be stored for up to 25 years and further analysed to address scientific questions related to the S64315 compound and/or cancer. This may also include research to help develop ways to detect, monitor or treat cancer. A decision to perform such exploratory biomarker research studies will be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

9.3.2.1. Sampling and storage

See section 9.3.1.1.

9.3.2.2. Labelling and shipments

See section 9.3.1.2.

9.3.2.3. Transfer of analytical results

See section 9.3.1.4.

9.4. Pharmacogenomics measurements

In order to improve the knowledge of factors influencing S64315 pharmacokinetics in humans and in accordance with the guideline 'Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products' (Guideline EMA-EMA/CHMP/37646, 2009), an analysis of genetic variations among patients is recommended. This investigation focuses on genes encoding proteins involved in absorption, distribution, metabolism and excretion (ADME) will be requested if a high inter-individual variability would be observed in pharmacokinetics data not explain by other factors (as gender, age, body weight, etc.). Therefore, depending on the results obtained during the study, sample analysis may be omitted at I.R.I.S. discretion.

Participation in the CL1-64315-004 study does not imply a mandatory or systematic participation in the optional investigation. All voluntary patients will have to sign a specific informed consent form for **optional genomic biomarkers (ADME genotyping) analysis**. The consent given to this assessment can be withdrawn at any moment without compromising the participation in the overall clinical study investigations. In addition, in case of consent withdrawal, related samples will be destroyed before any optional assessment is completed.

The samples will not be used for any investigations not specified in this protocol or for the elaboration of a DNA bank.

Overall results of the pharmacogenomics ADME biomarkers assessment may be transmitted to the patient upon his/her request at the end of the study. There will be no communication of individual results neither to the investigator nor to the patient.

9.4.1. Sampling and storage

One blood sample (2 mL) per patient will be collected into an EDTA K3 tube according to the study centre's practice at C1D1 azacitidine predose. The accurate sample collection date and time must be recorded on the requisition forms and entered on the sample collection eCRF page.

The blood sample will be immediately stored on site before shipment and sent on dry ice.

9.4.2. Labelling and shipments

Each sample tubes will be clearly labelled with a double identification (aliquot number, Sponsor's name, country code, centre number, protocol number and patient number) and will be shipped with a requisition form. Samples will be single coded with a number and thus will not carry any personal identifiers.

The whole blood samples will be stored on site before shipment at approximately ≤ 70°C and sent on dry ice to the appropriate logistic CRO that will store the samples at approximately ≤-70°C at reception, until shipment to the laboratory for DNA extraction and analysis. The extracted remaining DNA samples will then be shipped and kept deep frozen in a central bio-repository specialized in storage of biological samples or not until further notification from the Sponsor and may be retained up to 25 years after study closure.

The samples may be used after the end of the study for ADME genomic assessments in relation to the IMPs not specified in the protocol in light of new scientific knowledge or technology.

After a maximum period of 25 years after the end of the study or on the simple demand of the patient to the investigator, all DNA extracts stored at a central bio-repository will be destroyed.

9.4.3. Transfer of analytical results

If the analysis is required during the study, final analytical results will be transferred to Data Management; otherwise no data will be transferred.

10. STATISTICS

This part will describe the planned analysis for the **Arm A** and the **sub-arms A1 and A2**. **Arm B** will be introduced through an amendment and the associated statistical part will be defined later.

10.1. Overall consideration

The purpose of this study is to determine the safety profile, the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT(s)), the RP2D and to investigate the clinical activity of the combination of S64315 with azacitidine in patients with AML.

The dose escalation phase I part will be followed by an expansion phase II part into two sub-arms: A1 and A2. A DSMB will assess the overall data of the study and provide recommendations on the conduct of the study (see section 8.11). The statistical analyses corresponding to the dose allocation processes will be carried out using R® software with the rjags R package (Rjags R) by the Center of Excellence Methodology and Valorisation of Data of I.R.I.S.

10.2. Dose escalation phase I part

10.2.1. Dose escalation phase I part considerations

An adaptive Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) will be used to guide the dose escalation phase I part and estimate the MTD(s) based on occurrence of DLT until C1D28 (Neuenschwander, 2008; Babb, 1998).

The BLRM is a well-established method to estimate the MTD in patients with cancer. The adaptive BLRM will be guided by the escalation with overdose control principle to control the risk of DLT in future patients on study. The dose recommended by the model at any stage of the trial is based on the entire history of all available DLT information from previous cohorts as opposed to only the number of DLTs observed in the last group of patients. Moreover, historical data/co-data can also be used to enrich the prior of the BLRM. Operational characteristics of the design are presented in Appendix 8.

This study is currently planned to administer S64315 once a week during a 28-day cycle in combination with azacitidine, with a lead-in dose period of 2 weeks for S64315.

Based on the emerging clinical safety and PK data, other dosing schedules may also be assessed in this study. If the decision is made to switch to a different dosing schedule a new model and its operating characteristics will be communicated via a new document similar to Appendix 8 along with the documentation provided as formal notification of the change in dosing schedule (e.g. minutes of the corresponding dose escalation meeting, etc.), or it will be explicitly indicated in such documentation with suitable rationale that the new regimen has no changes to the initial model.

The MTD/RP2D will be based on:
- The MTD estimated by the BLRM model stated above and
- An overall clinical assessment of all available safety, tolerability, PK, PD and preliminary activity data

10.2.2. Statistical model

This part contains a quick presentation of the model; more details about the model and assumptions are presented in Appendix 8, as well as the operational characteristics of the chosen models.

A 5-parameter adaptive Bayesian logistic regression model guided by the escalation with overdose control principle (EWOC) will be fitted on DLT during LID period and during Cycle 1 data to make dose recommendations and estimate the MTD/ RP2D for the combination of S64315 (agent 1) and azacitidine (agent 2, fixed dose).

The model has three components:
- S64315 single agent toxicity, represented by parameters α1 and β1
- azacitidine single agent toxicity, represented by parameters α2 and β2
- the interaction between S64315 and azacitidine, represented by parameter η12

The two single agent dose-DLT relationships are modelled as in a single agent study:

$$logit\big(\pi 1(d1)\big) = log(\alpha 1) + \beta 1\, log(d1/d1*), \alpha 1 > 0, \beta 1 > 0$$
$$logit\big(\pi 2(d2)\big) = log(\alpha 2) + \beta 2\, log(d2/d2*), \alpha 2 > 0, \beta 2 > 0$$

where π1(d1) is the probability of DLT if S64315 is given as a single agent at a total weekly dose of d1 and π2(d2) is the probability of DLT if azacitidine is given as a single agent at a total daily dose of d2.

The parameter α1 (respectively α2) is then the single-agent odds of a DLT at the reference dose for S64315 (respectively azacitidine), and β1 (respectively β2) is the increase in the log-odds of a DLT by a unit increase in log-dose for S64315 (respectively azacitidine). As there is only one tested dose of azacitidine and this tested dose is chosen as the reference dose, $\log(d_2/d_2^*) = 0$ and β_2 will not be estimated. Then, the model is simplified from a 5-parameter model to a 4-parameter model.

The dose-DLT relationship of the combination of S64315 and azacitidine is modelled as:

$$Odds(\pi 12(d1,d2))) = \frac{\pi 12(d1,d2)}{1 - \pi 12(d1,d2)}$$
$$= exp(\eta 12 \frac{d1}{d1*}\frac{d2}{d2*}) \left(\frac{\pi 1(d1) + \pi 2(d2) - \pi 1(d1)\pi 2(d2)}{(1 - \pi 1(d1))(1 - \pi 2(d2))}\right)$$

This study is currently planned to administer S64315 once weekly with a 28-day cycle preceded by a LID period of 2-weeks, with one infusion of 25 mg on D-13 and one infusion of 50 mg on D-6. Azacitidine will be administered at 75 mg/m² via SC injection, daily for 7 days, from D1 to D7 followed by a rest period of 21 days (28-day cycle). However, based on the emerging clinical safety and PK data, other dosing schedules may also be assessed in this study.

If the decision is made to switch to a different dosing schedule before determination of the MTD in the planned schedule, then the initial total weekly S64315 dose will be a dose that has previously been tested and that is considered safe according to the EWOC criterion. Unless otherwise justified, it will be assumed that different schedules can have different effects on patient safety and dose allocation based on the new schedule will then be guided by a new model.

The new model and its operating characteristics would be communicated via a new document similar to Appendix 8 along with the documentation provided as formal notification of the change in dosing schedule (e.g. minutes of the corresponding dose escalation meeting, etc.), or it would be explicitly indicated in such documentation with suitable rationale that the new regimen has no change to the initial model.

The MTD is the highest dose of the combination treatment that is unlikely (< 25% posterior probability) to cause DLT in more than 33% of the treated patients during the LID period and the first cycle of S64315 treatment in combination with azacitidine.

10.2.3. Provisional dose levels

This study currently plans and expects to complete dose escalation of S64315 in combination with azacitidine with the provisional dose levels described in Table (10.2.3) 1.

Table (10.2.3) 1 - Provisional dose levels

Dose level	-1	1*	2	3	4
Weekly dose of S64315 (mg)	25	50*	100	200	250

*Starting dose level according to the power prior obtained by integrating all data from weekly S64315 in the single agent CL1-64315-004 study validated at the last EoC meeting

Intermediate dose levels could be added during the course of the study.

Azacitidine will be administered at a fixed dose of 75 mg/m² via SC injection, daily for 7 days, from D1 to D7 followed by a rest period of 21 days (28-day cycle).

S64315 full starting dose will be 50 mg. This dose is considered safe (i.e. fulfilling the EWOC criterion) according to the power prior obtained by integrating all data from the weekly schedule of S64315 as a single agent in CL1-64315-001 study validated in an EoC meeting (see Appendix 8 for details on power prior calculation and power prior obtained from single agent study data as of 26 November 2019).

10.2.4. Prior specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which includes the single-agent parameters for S64315 (α1, β1), for azacitidine (α2, β2), and the interaction parameter (η12). A weakly informative prior will be used for S64315 prior and data from study CL1-64315-001 will be used to enrich this same weakly informative prior. Details on the derivation of the weakly informative prior that will be used are provided in Appendix 8. A weakly informative prior will be used for azacitidine.

10.2.5. Integration of data from CL1-64315-001 study as co-data

Available clinical data from CL1-64315-001 study will be used to enrich the weakly informative prior used in our combination, in a down weighted fashion. The power prior obtained after integration of the previous study data will be used as prior information for S64315: it will be derived at the time of evaluation of each once a week cohort in combination with azacitidine, based on all data from the weekly monotherapy schedule (study CL1-64315-001) validated in an EoC meeting at that time.

The given data will be incorporated through down-weighting using the following weight 'w' (Chen, 2006; Neuenschwander, 2010):

$$w = \frac{1}{1 + 2n\tau^2/\sigma^2}$$

where n is the sample size of external data, σ is the 'outcome standard deviation' for one observation and τ is the between-trial standard deviation. While σ is the standard deviation of all external data which include several dose levels, σ^2 can be approximated by variance of log(α). For this dose escalation, σ was then chosen as 2 and τ was set as 0.25 to correspond to moderate between-trial variability.

See Appendix 8 for details on power prior calculation and the power prior obtained study CL1-64315-001 data as of 26 November 2019.

10.2.6. Dose proposed by the model

The dose allocation will start at the dose combination of 50 mg and 75 mg/m^2 respectively for S64315 and azacitidine.

A maximum of 6 DLT-evaluable patients may be initially enrolled at a dose level, and a minimum of 3 DLT-evaluable patients must be treated at a given dose level before a new higher dose level may be evaluated.

All available data on DLTs, assessed starting from the LID period to C1D28 will be used for updating the model. Before making a dose allocation decision, all patients from a cohort must:

- have been treated with LID1 and LID2, 3 out of 4 S64315 infusions and 5 out of 7 azacitidine injections or
- have had a DLT within the LID period or the first cycle

If a patient is not eligible for inclusion in the Dose-Limiting Toxicity Evaluable Set (DLTES), she/he must be replaced.

If a DLT occurred at LID1, the DLT will be considered as relative to 25 mg of S64315 in monotherapy. If a DLT occurred at LID2, the DLT will be considered as relative to 50 mg of S64315 in monotherapy. In that case, the patient will be replaced to ensure the minimal number of patients needed in the cohort at the full tested dose. Those DLTs will be considered for dose recommendation during the EoC meeting.

At any time during the study, if DLTs occur in the first 2 evaluable patients of a cohort (whether it happened during the LID period or cycle 1), the BLRM could be updated in order to re-evaluate the current dose level before enrolment of any additional patients in the cohort. Once each cohort of patients is completed, the dose recommendation by the model will be based on posterior summaries including the mean, median, standard deviation, 95%-credible interval, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0,16%) under-dosing
- [16%,33%) targeted toxicity
- [33%,100%] excessive toxicity

Following the principle of EWOC, after each cohort of patients, the dose combinations fulfilling the EWOC criterion (i.e. it is unlikely (<25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval) will be identified by the model. A dose not fulfilling the EWOC criterion cannot be recommended.

In addition, admissible dose increments for the next cohort will not exceed 100% of the previous dose of S64315.

The set of allowed doses for the next cohort is thus defined as the intersection between the dose levels admissible according to this protocol (escalation rule defined above) and the dose levels allowed by the model (EWOC criterion fulfilled). The dose recommendation made by the adaptive BLRM should then be regarded as guidance and information to be integrated with a clinical assessment of the toxicity and activity profiles observed, so that a dose is selected for the next cohort among the allowed doses.

More than 6 DLT-evaluable patients may be treated in a cohort at dose levels considered safe according to the BLRM with overdose control in order to better characterize the safety, tolerability, PK, PD, or preliminary clinical activity of S64315 in combination with azacitidine.

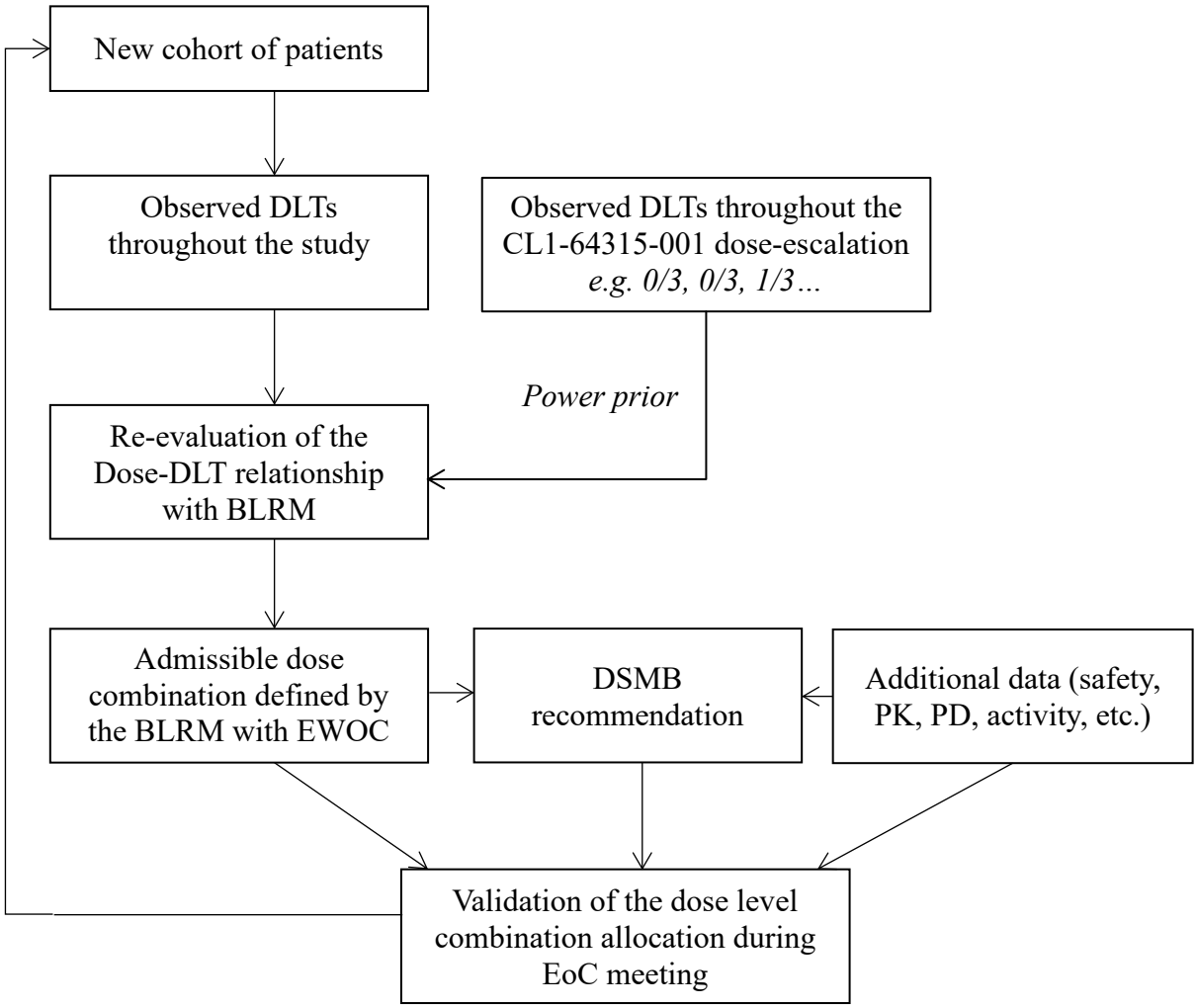
10.2.7. Dose allocation process

Once evaluation of a given dose level has been completed, and before testing a new dose level, an EoC meeting between the Sponsor (Therapeutic Area Oncology and Immuno Oncology, Medical Safety Leader, Methodology Department and Clinical Pharmacokinetics Department) and the investigators will take place to decide jointly the next dose level to be tested according to:

- the admissible doses allowed by the BLRM (based on single agent study CL1-64315-001 data through the power prior)
- all safety data
- PK data
- PD data
- activity data

The dose allocation process is described in Figure (10.2.7) 1.

Figure (10.2.7) 1 - Dose-allocation process



10.2.8. Final recommendation and stopping rules

Dose escalation will continue until identification of the MTD or suitable lower dose levels for the expansion phase II (RP2D). This will occur when the following conditions are met:

1. at least 6 patients have been treated at this dose and are evaluable for the DLT
2. one of the following conditions is fulfilled:

   a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses or

   b. a minimum of 18 patients have already been treated and evaluable for the DLT on the dose escalation of Arm A
3. it is the dose recommended for patients, either per the model or by review of all patient clinical data during an EoC meeting

Of note, the dose escalation phase I part could be stopped earlier by a joint decision from the sponsor and the investigators during a dose escalation meeting, by taking into account the model estimations and a global assessment of the safety, PK, PD and preliminary activity data. Note that it is possible that the MTD may not be reached in some situations and a suitable dose level may be defined as a recommended dose for the phase II dose expansion part after evaluation of all data collected during the phase I dose escalation part.

10.3. Expansion phase II part

10.3.1. Expansion design

The expansion phase II part will be performed at the MTD or suitable lower dose levels (RP2D) in order to gain more information about the overall safety and tolerability of S64315 in combination with azacitidine in Arm A, to provide additional PK and PD data and to provide preliminary activity data.

Therefore, an expansion phase II part will be performed at the final recommended dose (RP2D) and schedule of administration in order to better evaluate anti-tumour activity and cumulative toxicity if any of S64315 in combination with azacitidine in sub-arms A1/A2. New patients will be enrolled in a two-stage expansion phase II part with a Bayesian interim analysis for futility at the end of stage 1 in each arm.

During stage 1, in each arm, patients will be enrolled and treated at the corresponding RP2D. The interim analysis for futility will occur when the patients included in stage 1 have completed at least 4 cycles or early discontinued. Of note, the recruitment could be stopped before the interim analysis if the minimal number of responders is impossible to be met.

Then, a Bayesian analysis will be performed on the rate of CR. Decision rules will be based on clinical threshold defined on the posterior distribution of the rate of CR (see section 8.5 for details on the determination of sample size).

According to results of futility interim analysis performed at the end of stage 1, the expansion phase II part could be:

- Stopped, if results on the rate of CR are considered futile
- Continued if results on the rate of CR are considered not futile. In that case, additional patients will be enrolled in stage 2

10.3.2. Criteria to re-evaluate the RP2D during the expansion phase

Subjects in the dose expansion phase will be followed for DLT (as defined in section 4.1.3.5).

After at least 4 subjects have been treated during dose expansion at the RP2D, if the observed rate of DLT through the end of Cycle 1 exceeds 33% across (including the patients treated at this dose during dose escalation), the BLRM will be updated to determine whether the RP2D still satisfies the EWOC principle. If the RP2D is estimated to have a ≥25% posterior probability of generating excessive toxicity (DLT rate between 33% and 100%) during the first cyle of treatment, then enrollment to the study will be paused. A risk assessment will be conducted by the DSMB, the investigators and sponsor, and consideration will be given to reducing the RP2D.

In addition, monitoring will continue for DLTs that may occur after the first cycle of treatment. After at least 4 subjects have had the opportunity to receive a second cycle of treatment, if the posterior probability (based on a beta-binomial distribution, using a Jeffrey prior) is greater than 25% that the true rate of DLT occurring after Cycle 1 is >33%, enrollment to the study will be paused. Subjects should have received at least three doses of S64315 from Cycle 2 to be evaluable, unless dosing was limited by the occurrence of a DLT. Evaluable patients treated at this dose during dose escalation will also be included in this assessment. The study will also be paused if the cumulative rate of Grade ≥3 treatment-related cardiac adverse events at the RP2D exceeds 20%.

In either case, the safety of the RP2D will be re-evaluated by the DSMB, the investigators and sponsor, and consideration will be given to reducing the RP2D.

If the assessment of all available data warrants a change in the RP2D, 23 subjects will be treated at the new RP2D in each arm involved. These subjects will be monitored as reported above.

10.4. Statistical analysis

A Statistical Analysis Plan will be written after finalising the protocol and definitively completed before the first database lock. These specifications will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol.

The statistical analysis will be mainly descriptive. It will be carried out using SAS® software by I.R.I.S. Pole of Expertise Methodology & Data Valorisation and/or designated CRO.

The study data will be analysed and reported in the CSR once the study is terminated (at the end-of-study, defined as the date of the last follow-up of the last patient). However, some intermediate analyses might be performed during the conduct of the study.

10.4.1. Evaluation criteria

10.4.1.1. Safety criteria

10.4.1.1.1. Dose escalation phase I part

- Incidence of DLT during the LID period and Cycle 1
- Incidence and severity of AEs and SAEs
- Change or addition of a new concomitant treatment
- Laboratory tests: haematology with differential, blood biochemistry, thyroid function, blood coagulation, urinary analysis, hepatitis markers, TLS monitoring, cardiac markers
- Complete physical examination, ECOG PS
- Vital signs
- ECG and cardiac function parameters
- LVEF
- Pregnancy test for WOCBP
- Dose interruptions, reductions and dose intensity

10.4.1.1.2. Expansion phase II part

Evaluation criteria for expansion phase II part for sub-arms A1 and A2 will be further defined according to the dose escalation phase I results of Arm A.

- Incidence and severity of AEs and SAEs
- Change or addition of a new concomitant treatment
- Laboratory tests: haematology with differential, blood biochemistry, thyroid function, blood coagulation, urinary analysis, hepatitis markers, TLS monitoring, cardiac markers
- Complete physical examination, ECOG PS
- Vital signs
- ECG and cardiac function parameters
- LVEF
- Pregnancy test for WOCBP
- Dose interruptions, reductions and dose intensity

10.4.1.2. Activity criteria

The efficacy endpoints are defined according to guidelines (Guideline EMA, 2012) and (ICH E9, 1998).

10.4.1.2.1. Dose escalation phase I part

During the dose escalation phase I part, efficacy is only assessed as a secondary objective.

The following endpoints are assessed according to the previous part of the protocol.

- Best Overall Response (BOR) observed during the treatment period, as defined by standard disease-specific criteria
- Objective Response Rate (ORR) will be defined as the proportion of patients who achieve a complete remission (CR), complete remission with incomplete hematologic recovery (CRi) and morphologic leukemia-free state (MLFS) according to 'Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel' (Döhner, 2017)
- Complete Remission (CR) rate will be defined as the proportion of subjects who achieve complete remission (Döhner, 2017)
- Duration of response (DOR) will be calculated from the date of first response to the date of progression or the date of death (whatever the reason of death), whichever occurs first
- Progression-Free Survival (PFS) will be calculated from the date of first IMP administration to the date of progression or the date of death (whatever the reason of death), whichever occurs first
- Overall Survival (OS) will be calculated from the date of first IMP administration to the date of death (whatever the reason of death)
- Disease-Free Survival (DFS) will be defined on responders by the time from primary response to relapse

10.4.1.2.2. Expansion phase II part

The following endpoints are assessed according (Guideline EMA, 2012) and (ICH E9, 1998).

- **Primary endpoint:**
  - Complete Remission rate will be defined as the proportion of subjects who achieve complete remission
- **Secondary endpoints**:
  - Objective Response Rate (ORR) will be defined as the proportion of patients who achieve a complete remission (CR), complete remission with incomplete hematologic recovery (CRi) or morphologic leukemia free-state (MLFS)

- Best Overall Response (BOR) observed during the treatment period, as defined by standard disease-specific criteria
- Duration of response (DOR) will be calculated from the date of first response to the date of progression or the date of death (whatever the reason of death), whichever occurs first
- Overall survival (OS) will be calculated from the date of first IMP administration to the date of death (whatever the reason of death)
- Progression Free Survival (PFS) will be calculated from the date of first IMP administration to the date of progression or the date of death (whatever the reason of death), whichever occurs first
- Disease-Free Survival (DFS) will be defined on responders by the time from primary response to relapse

10.4.2. Statistical elements

The following descriptive statistics will be provided depending on the nature of variables:

- Quantitative variable: number of observed values, mean and standard deviation, minimum and maximum and if necessary, median, first and third quartiles
- Qualitative or ordinal variable: number and percentage by class

10.4.3. Analysis sets

The following analysis sets are defined according to (ICH E9, 1998) guidelines.

10.4.3.1. Dose escalation phase I part

- Included Set 1 (IS1) corresponds to all included patients during the dose escalation phase I part
- Safety Set 1 (SS1) corresponds to patients who received at least one dose of IMP during dose escalation phase I part. It will be used for all safety and efficacy analyses
- Dose-Limiting Toxicity Evaluable Set (DLTES) corresponds to patients from the SS 1 who are evaluable for DLT according to the criteria defined in section 4.1.3.6

10.4.3.2. Expansion phase II part

- Included Set 2 (IS2) corresponds to all included patients during the expansion phase II part
- Safety set 2 (SS2) corresponds to patients who received at least one dose of IMP during the expansion phase II part
- Per protocol set (PPS) corresponds to patients of SS2 that do not have any significant protocol deviations that may impact the primary endpoint (CR rate). The list of deviations will be reviewed for the determination of their significance prior to the database lock

10.4.4. Statistical methodology

All the following analyses will be performed separately. When they are done on expansion phase II part, analyses will be done on each sub-arm A1 and A2 separately.

10.4.4.1. Study outcome

The study outcome analyses will be carried out on the IS sets, IS1 and IS2, by dose level and overall.

Patients characteristics including demography, disease characteristics at diagnosis and assessment criteria baseline values will be described.

Number of cycles, dose intensity, dose interruptions, patient status, withdrawal reason, protocol deviations and concomitant treatments will be described.

10.4.4.2. Safety

The safety analyses will be performed on the SS sets, SS1 and SS2, by dose level and overall.

DLT until the end of Cycle 1

Number and percentage of patients in the DLTES with DLT occurrence from the LID period to the end of the first cycle will be tabulated by dose level and overall.

DLT after the end of Cycle 1

Number and percentage of patients evaluable for DLTs, with occurrence of DLT after the end the first cycle will be tabulated by dose combination and overall.

Emergent adverse event

NCI CTCAE v5.0 will be used to classify all adverse events.

Number of Emergent adverse event (EAE), number and percentage of patients reporting at least one EAE will be summarised by System Organ Class and Preferred Term, overall and by dose level. The same analysis will be performed for serious EAEs and SAEs.

Some analyses will be performed by worst on-treatment grade, severity, relationship to the IMP, outcome and action taken.

Clinical laboratory evaluation

Laboratory parameters will be graded according to NCI CTCAE v5.0. For laboratory tests where grades are not defined by NCI CTCAE v5.0, results will be classified according to the laboratory reference ranges.

The following summaries will be generated separately for each haematology and biochemistry tests:

- for laboratory tests where grades are defined by NCI CTCAE v5.0, shift tables comparing the worst on-treatment grade to the grade at baseline
- for laboratory tests where grades are not defined by NCI CTCAE v5.0, shift tables comparing the classification according to the laboratory normal ranges to baseline

Urinalysis abnormalities will be described using shift tables comparing the worst on-treatment value (Positive, Trace, Negative) to the value at baseline.

Physical examination including vital signs, body weight and ECOG PS

These criteria will be described using baseline value, worst on-treatment value and change from baseline to worst on-treatment value.

ECG parameters and LVEF

Quantitative parameters (QT interval corrected and LVEF) and qualitative parameters (ECG abnormalities) will be described.

10.4.4.3. Activity

One of the objectives of the study is to assess preliminary anti-tumour activity of S64315 in combination with azacitidine.

10.4.4.3.1. Dose escalation phase I part

CR rate, BOR and ORR will be analysed on the SS1 by dose level, overall and per population (relapsed/refractory and 1st line) depending of the number of patients. They will be evaluated according to the investigator assessments of response during the treatment period. They will be described using proportion and the corresponding exact binomial 95% confidence interval will be provided.

The survival function of the time-dependent parameters will be estimated via Kaplan-Meier curve. In addition, 95% confidence interval for median duration will be computed depending of the number of observations

10.4.4.3.2. Expansion phase II part

The primary endpoint Complete Remission rate will be analysed on the SS2 and on the PPS depending of the number of patients per treatment status.

Patients without post-baseline assessment will be considered as non-responders.

The Complete Remission rate will be described using proportion along with the corresponding exact binomial 95% confidence interval. Bayesian statistics based on the posterior distribution will also be provided.

The secondary endpoints, ORR, BOR, DOR, OS, PFS and DFS will be analysed on the SS2 and on the PPS, overall and per treatment status (R/R and 1st line) depending of the number of patients per treatment status.

BOR will be described using proportion along with the corresponding exact binomial 95% confidence interval.

The distribution of the survival endpoints (OS, DOR, DFS and PFS) will be estimated with the Kaplan-Meier product-limit method. Summary statistics (median, 95% confidence interval) and Kaplan-Meier curves will be presented.

All endpoints will be evaluated according to the investigator assessments of response during the period of interest.

10.4.4.4. Biomarkers

The relationship between the expression level of Bcl-2 family members, genomic alterations of Bcl-2 family member genes and other cancer-related genes in blasts (from blood and bone marrow samples) as well as target-engagement biomarker and the antineoplastic activity of S64315 in combination with azacitidine could be studied using descriptive statistics if relevant, and quantitative systems pharmacology analyses. The relationship between the biomarkers just mentioned and S64315 toxicity could also be studied using descriptive statistics.

10.5. Determination of sample size

No formal statistical power calculations to determine sample size were performed for this study. Overall, a maximum of 180 patients will be enrolled in the dose escalation phase I part of Arm A (up to 30 patients) followed by sub-arms A1and A2 (50 per sub-arms, up to 150 patients overall).

10.5.1. Dose escalation phase I part

During the dose escalation phase I part, the cohort size will be between 3 and 6 evaluable patients. At least 6 patients will be treated at the MTD/RP2D level, as described in section 10.2.

According to the simulations performed, at least 18 patients should be considered evaluable in the dose escalation phase I part to have reasonable operating characteristics for the determination of the MTD. However, in some situations, the MTD/ RP2D could be declared with fewer patients.

10.5.2. Expansion phase II part

In the expansion phase II part, up to 50 patients will be enrolled in each sub-arm (A1 and A2) at the RP2D. In each of these arms, there will be two stages:

- 23 patients are planned to be included in stage 1 based on the following Bayesian rules for futility: the posterior probability of CR rate <20% must be lower than 60% (i.e. >4 (so at least 5) responders /23 patients) to consider there is enough evidence of S64315 in combination with azacitidine activity to enrol a new cohort in stage 2
- In case of no futility at the end of stage 1, 27 additional patients are planned to be included in stage 2. This number of patients ensures detecting enough evidence of S64315 in combination with azacitidine activity based on a posterior probability of CR rate >20% greater than 70%. Moreover, this number of patients has been identified to ensure a minimal precision of 23% around the CR rate

10.6. Pharmacokinetic analyses and PK/PD analysis

10.6.1. Pharmacokinetic interpretation

The dataset needed for the final analysis will be prepared by extraction from the clinical Business Intelligence Department using SAS® program and following the clinical PK project manager specifications. The non-compartmental pharmacokinetic analysis (NCA) will be performed by the Clinical Pharmacokinetics and Pharmacometrics Department using PhoenixWinNonlin® version 6.4 or later or Excel 2010 on the individual plasma concentration-time data of S64315 and azacitidine after the IV administration of S64315 and SC administration of azacitidine.

For S64315 and azacitidine preliminary NCA analysis, the theoretical administration and sampling times will be used.
The exact administration and sampling times will be used for the final NCA analysis for S64315 and azacitidine.

Descriptive statistics, tables and figures will be generated using SAS 9.2® and Excel® 2010. The NCA will be performed according to operating manual (OPM) of clinical Pharmacokinetics and Pharmacometrics Department.

Any suspicious concentration will be investigated and kept in the PK analysis if possible. All excluded concentrations will be justified in the report.

For each patient, the following parameters will be calculated on the individual plasma concentration-time profiles of azacitidine: C_{max}, t_{max}, AUC_{last}, AUC_{τ}, AUC, t_{last}, C_{last}, $t_{1/2,z}$, CL and Vd.

For each patient, the following parameters will be calculated on the individual plasma concentration-time profiles of S64315: C_{inf}, t_{inf}, AUC_{last}, AUC_{τ}, AUC, t_{last}, C_{last},, $t_{1/2,z}$, CL and Vd.

Descriptive statistics (n, mean, SD, min, median, max, coefficient of variation) will be calculated for these PK parameters as well as on concentrations-time profiles using SAS and Excel®.

S64315 plasma concentrations from the present study that could be pooled with data from previous studies will be analysed by population approach, described in a separate Data Analysis Plan, in order to assess S64315 PK and to investigate potential sources of variability through a covariate analysis.

10.6.2. PK/PD interpretation when applicable

Any potential PK/PD relationships with activity, efficacy and safety will be investigated through an exploratory analysis, and if relevant, a PK/PD Data Analysis Plan will be set up.

Description of analyses will be done in a separate PK/PD protocol.

PK/PD relationship will be assessed for clinical and biological efficacy endpoints including:
- Clinical response according to (Cheson, 2003)
- Biological response: bonne marrow blast decrease
- Blood markers: WBC, neutrophils, platelets
- Any other clinically relevant endpoint

PK/PD relationship will be assessed for clinical and biological safety endpoints including:
- Cardiac events following narrow and broad definitions as in section 8.2.5
- Plasma troponin I and troponin T
- Left ventricular ejection fraction
- Neutrophil count
- Hepatic safety parameters (i.e. AST, ALT)
- Any other clinically relevant endpoint

Assessment of the PK/PD relationship for listed safety endpoints will be updated after each new cohort completion, when assessment of PK/PD relationship for efficacy will be performed at the end of dose escalation.

PK and relevant biomarker data may also be analysed in a Quantitative Systems Pharmacology analysis, which will be described in a separate protocol.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the IRB/IEC, and of the Competent Authorities to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data is accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the structure mentioned in the monitoring guide.

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

12.1.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

Training sessions may be organised for the investigators and/or instruction manuals may be given to the investigators.

12.1.2. During the study

The investigator will allow the monitor to:
- review of the study site's processes and procedures
- verify appropriate clinical investigator supervision of study site staff and third party vendors
- inspect the site, the facilities and the material used for the study
- meet all members of his/her team involved in the study
- consult the documents relevant to the study
- have access to the eCRF (i.e. access to an analogic phone line or his/her computer)
- check that the eCRF has been filled out correctly
- directly access source documents for comparison of data therein with the data in the eCRF
- verify that the study is carried out in compliance with the protocol and local regulatory requirements

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and/or the investigation schedule, and arranged between the investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (i.e. audit trail). The investigator will save data at regular intervals.

The investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the sponsor, the investigator undertakes:
- at the start of the study, to print the medical files of all patients allowing a reliable verification of the study criteria (e.g. medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol)
- during the study, to print in real time each data entry and each data change

The investigator will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the investigator will provide all the print-outs of the medical files of the patients. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the patients and the records of the changes made. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the sponsor, the investigator undertakes to give access to the monitor to the computerised medical files of all patients. If the monitor cannot access to the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the patients. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

The investigator undertakes to keep:
- all medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the sponsor
- if the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the sponsor or when the monitor cannot access to the audit trail in the computer system
- all original source-documents (originals of specific examinations, informed consent forms, therapeutic unit tracking form, etc.)

12.3. Audit - Inspection

The investigator should be informed that an audit may be carried out during or after the end of the study.

The investigator should be informed that the Competent Authorities may also carry out an inspection in the facilities of the sponsor and/or the study centre(s). The sponsor will inform the investigators concerned immediately upon notification of a pending study centres inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The investigator must allow the representatives of the Competent Authorities and persons responsible for the audit:
- to inspect the site, facilities and material used for the study
- to meet all members of his/her team involved in the study
- to have direct access to study data and source documents
- to consult all of the documents relevant to the study

If the computerised medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the patients and, if the computer system used allows, the record of the changes made during the study.

If the computerised medical file is considered as validated, the investigator undertakes to:

- give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerised medical files of all patients
- provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer

12.4. Supervisory committees

The DSMB will be composed of 3 members expert in haematology, gastroenterology/hepatology and cardiology. One of these experts will be the chairperson of this committee and his/her role is to coordinate, lead the DSMB meetings and deliver the minutes of the meetings to the Sponsor.

According to the protocol design, the DSMB will meet after the last patient of each cohort has completed Cycle 1 during the dose escalation phase I part and then every 3 months, according to the recruitment rate, during the expansion phase II part. The eCRF should be completed for each patient on an ongoing basis and mandatorily after the last visit of Cycle 1.

Extraordinary meetings may also occur during the conduct of the study in case of any event requiring the DSMB recommendations. The DSMB recommendations and meeting minutes will be shared immediately with all Investigators/sites. The final recommendations from the DSMB will be made available before each EoC meeting during the dose escalation phase (see section 4.1.3.3).

An initial or kick-off DSMB meeting will be performed before the study start to agree on the DSMB charter, which will define the quorum that must be in attendance for the validity of the meeting, the format and content of the data to be reviewed, the frequency and the modalities of the meetings (teleconferences, face-to-face meetings or email exchanges), the timelines and format of the minutes.

The DSMB charter will provide extended details on the composition and the role and responsibilities of the DSMB, as well as the organization of the DSMB meetings.

DSMB recommendations will be forwarded to the IRB/IEC / Competent Authorities on an expedited basis only if relevant for the safety of patients.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the 'Participant information and consent form' documents, the list of investigators document, the insurance documents, the SmPC and the Investigator's Brochure of administered IMPs will be submitted to IRBs/IECs by the investigators or the sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IRB/IECs has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (see Appendix 1), with the GCP and with the applicable regulatory requirements.

13.3. Participant information and informed consent

In any case, the patient (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the investigator.

The investigator or a person designated by him/her is to collect written consent from each patient before his/her participation in the study. Prior to this, the investigator or his/her delegate must inform each patient of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs.

The patient will be provided with an ICF in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

Two original copies per ICF must be completed, dated and signed personally by the patient and by the person responsible for collecting the informed consent. The patient will be given one and the second will be kept by the investigator.

If the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. The patient must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent. A copy of the ICF in the language(s) of the country is given in the 'Participant information and consent form' document attached to the protocol.

13.4. Modification of the information and consent form

Any change to the ICF constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the Competent Authorities.

A copy of the new version of the ICF in the language(s) of the country will be given in the amendment to the 'Participant Information and consent form'.

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, with the exception of an amendment required eliminating an immediate risk to the study patients.

Each patient affected by the amendment must complete, date and sign two original copies of the new version of the ICF together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the ICF.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

A 21 CFR Part 11-compliant electronic data capture system is going to be used for this study. An eCRF is designed to record the data required by the protocol and collected by the investigator.

The eCRF will be produced by I.R.I.S. in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the eCRF use by the sponsor.

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the patient's Medical File.

Upon entry, data will be transmitted via the Internet from the study centre to the study database.

The investigator or the designated person from his/her team agrees to complete the eCRF, at each patient visit, and all other documents provided by the sponsor (e.g. documents relating to the IMP management, etc.).

Data recorded directly in the eCRF and considered as source data (see section 4.5) must be collected immediately in the eCRF. The other eCRF forms must be completed as soon as possible following each visit.

All corrections of data in the eCRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of Inform® software, including date, reason for modification and identification of the person who has made the change.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the sponsor or third parties. The investigator or co-investigator must attest the authenticity of the data collected in the eCRF by entering his/her username and password after the last visit of the patient and, as much as possible, either before starting a new level dose or at the time of yearly cut-off for DSUR (Development Safety Update Report).

Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However, the investigator has the possibility to modify a data if deemed via a request to the sponsor.

After the last visit of the patient, the investigator or co-investigator must attest the authenticity of the data collected in the eCRF by entering his/her username and password.

After the database lock, the investigator or an authorized member of his/her team will have to download from the eCRF an electronic file containing patient data from his/her centre for archiving it in the study file (see section 14.3).

14.2. Data management

Data is collected via an eCRF and stored in a secured database.

For data collected in the eCRF, I.R.I.S. Clinical Data Management is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

For data transferred from dedicated providers (central reading ECG, central laboratory, PK, PD and PG analysis), I.R.I.S. Clinical Data Management is responsible for data transfer: centralised laboratory, central reading centre provide electronic transfer of computerised data to I.R.I.S. Clinical Data Management. Data is transferred according to a transfer protocol issued by I.R.I.S. data manager.

I.R.I.S. Medical Review Department is responsible for data coding including:

- medical / surgical history, adverse events and procedures using MedDRA,
- medications using World Health Organization, Drug Dictionary (WHO-Drug).

The coding process is described in a specification manual.

The investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC it cannot be implemented. All important protocol deviations will be recorded and reported in the CSR.

When data validation is achieved, a review of the data is performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked and the IMP codes will be unblinded and made available for data analysis.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 25 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the investigator or an authorized member of his/her team will download an electronic copy of each patient's data from the eCRF and should keep it in a reliable, secure and durable location. The file includes all data and comments reported in the eCRF, the history of all queries and signatures and the full audit trail reports.

The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage or deterioration for the duration of the archiving period.

15. INSURANCE

I.R.I.S., or any parent company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by LES LABORATOIRES SERVIER to cover its liability as sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any parent company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation is included in the file submitted to any authorities' approval of which is required.

16. OWNERSHIP OF THE RESULTS – DATA SHARING POLICY AND PUBLICATION POLICY

I.R.I.S., acting as the study sponsor, assumes full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

I.R.I.S. will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to the sponsor in accordance with the guidelines set forth in the applicable publication policy or financial agreement.

The investigator, who submitted the project, shall take the sponsor's comments into due consideration.

As the study is a multicentre one, the first publication must be performed only with data collected from several centres and analysed under I.R.I.S. responsibility. The investigator commits himself/herself not to publish or communicate data collected in only one centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other investigators and I.R.I.S. has been provided.

Data Sharing Policy is available at https://clinicaltrials.servier.com/data-request-portal/. Researchers can ask for a study protocol, patient-level and/or study-level clinical trial data including CSR.
They can ask for all interventional clinical studies:

- submitted for new medicines and new indications approved after 1 January 2014 in the European Economic Area (EEA) or the United States (US)
- where Servier or an affiliate are the Marketing Authorization Holders (MAH). The date of the first Marketing Authorization of the new medicine (or the new indication) in one of the EEA Member States will be considered within this scope

The datasets generated and/or analysed during the current study will be available upon request from www.clinicaltrials.servier.com after the Marketing Authorisation has been granted.

Summary results and a lay summary will be published on www.clinicaltrials.servier.com within 12 months after the end of the study. The results will be submitted for publication in scientific literature within 18 months after the end of the study.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigator

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

With the agreement of the patient, the investigator will inform the patient’s general practitioner about his/her patient’s participation in a clinical study.

17.1.2. Substantial protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by the coordinator and the sponsor.

The substantial protocol amendment must be drafted in accordance with the sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigators or the coordinator or the sponsor, in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can only be implemented after a favourable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, with the exception of a measure required to eliminate an immediate risk to the study patients.

When the submission is performed by the investigator or the coordinator, the latter must transmit a copy of IRB/IEC new written opinion to the sponsor, immediately upon receipt.

Furthermore, any substantial amendment and amended protocol are to be submitted to the Competent Authorities in accordance with local regulations.

17.1.3. Final study report

The study report will be drafted by I.R.I.S. Pole of Expertise Methodology and Data Valorisation in compliance with I.R.I.S. standard operating procedure.

The sponsor's representative and the international coordinator must mutually agree on the final version. One copy of the final report must be dated and signed by the international coordinator and the Director of the Therapeutic Area Oncology and Immuno Oncology.

The clinical study report, the summary of the results of the clinical trial together with a summary that is understandable to a layperson will be submitted where applicable within 1 year after the end of the clinical trial worldwide.

If the clinical trial is still ongoing but ended in the European countries, the statistical analysis will not be relevant before the end of the study worldwide. Therefore, the CSR, the summary of the results of the clinical trial together with a summary that is understandable to a layperson will be submitted where applicable within 1 year after the end of the clinical trial worldwide.

17.2. Concerning the sponsor

The sponsor undertakes to:

- supply the investigator with adequate and sufficient information concerning the IMPs administered during the study to enable him/her to carry out the study
- supply the investigator with investigator's brochure if the test drug is not marketed
- supply the investigator with SmPC, the one best suited to ensure patient safety, and any potential updated version during the study:
  - for the marketed IMP, to be appended to Investigator's brochure (Section 4. Guidance for the investigator)
  - for all reference products used in the study
- obtain any authorisation to perform the study and/or import licence for the administered IMPs that may be required by the local authorities before the beginning of the study
- provide the investigator or coordinator annually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s)
- take all the necessary precautions to maintain the safety of the processed data, in particular their confidentiality, their integrity and their availability, by assessing risks identified concerning personal data protection. The following non-exhaustive measures will be implemented:
  - Management of authorisation to access to personal data (eCRF)
  - Identification and authentication measures before accessing personal data (eCRF)
  - Traceability measures for the access to and modification of personal data (eCRF)
  - Secured data transfer
  - Time limit for storing personal data

- handle any security breach by implementing an internal committee (including CISO, DPO, communication department, etc.) in order to qualify the security incident (Information systems, nature and number of personal data impacted), to define an action plan for corrective actions and to notify to relevant person (authority and/or if needed individuals)

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to S64315 and study CL1-64315-004 are strictly confidential.

The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.

He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.

In case patient wants to exercise his/her rights regarding personal data protection, he/she will contact the investigator. The investigator will forward the request to the sponsor.

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study patients. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the sponsor.

The investigator must not disclose any information without the prior written consent from I.R.I.S., except to the representatives of the Competent Authorities, and only at their request. In the latter case, the investigator commits himself/herself to informing I.R.I.S. prior to disclosure of information to these authorities.

A patient screening log and a full identification and enrolment list of each patient will be completed and kept in a safe place by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The patient screening log must be completed from the moment the investigator checks that a patient could potentially take part in the study (by assessment of patient medical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse, etc.) and any other person involved in the study for this centre (cardiologist, pharmacist, etc.) must figure in the ‘Organisation of centre’ document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the centre.

17.3.3. Documentation supplied to the sponsor

The investigator undertakes before the study begins:

- to provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s)
- to provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the measured parameters
- to provide any other document required by local regulation (e.g. Food & Drug Administration 1572 form)
- to send a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members

The CVs of other members of the team involved in the study (if possible in English) will be collected during the course of the study (at least, members involved in the patients' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

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19. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predic Adams risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Patient Registration Form

PATIENT REGISTRATION FORM / PROTOCOL CL1-64315-004

Centre: |__|__|__|__|

Please complete Section A and return by fax to Oncology department +33.1.55.72.50.04 or by e-mail to CL1-64315-004@servier.com

Section A/To be completed after Informed Consent Form signature

Identification of the patient:

Patient number (= eCRF n°): |__|__|__|__|__| Gender: ☐ Male ☐ Female

Year of birth: |__|__|__|__|

Diagnosis of the primary tumour type*:……*

Date patient signed Informed Consent Form (dd/mm/yyyy): |__|__| / |__|__| / |__|__|__|__|

Expected date baseline period completed (dd/mm/yyyy): |__|__| / |__|__| / |__|__|__|__|

Section A completed by:……

Please complete Section B and return by fax to Oncology department +33.1.55.72.50.04 or by e-mail to CL1-64315-004@servier.com

Section B/To be completed after baseline period

Name of the investigator: ……

Fax number: *(NA if by email)*……..

Does the patient comply with all inclusion/exclusion criteria? ☐ Yes ☐ No

If yes, date of inclusion (dd/mm/yyyy): |__|__| / |__|__| / |__|__|__|__|

Section B completed by:……

Date: |__|__| / |__|__| / |__|__|__|__| Signature:……..……..

Section C: Sponsor or its designee

Identification of the investigator

Name of the investigator: ……

Fax number ……

Identification of the patient

Patient number: |__|__|__|__|__| Gender: ❒ Male ❒ Female

Year of birth: |__|__|__|__|

Cohort number: |__|__|__|

S64315 LID1: |_2_|_5_| mg

S64315 LID2: |_5_|_0_| mg

Full tested dose of S64315: |__|__|__| mg

Section C completed by:……

Date: |__|__| / |__|__| / |__|__|__|__| Signature:…….…….

Appendix 3: Patient performance status

Status Karnofsky	Grade		Status ECOG* - ZUBROD / WHO
Normal, no complaints; no evidence of disease.	100		
		0	Fully active, able to carry on all pre-disease performance without restriction.
Able to carry on normal activity; minor signs or symptoms of disease.	90		
Normal activity with efforts; some signs or symptoms of disease.	80		
		1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
Cares for self; unable to carry on normal activity or to do active work.	70		
Requires occasional assistance but is able to care for most of his personal needs.	60		
		2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires considerable assistance and frequent medical care.	50		
Disabled; requires special care and assistance.	40		
		3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Severely disabled; hospital admission is indicated although death not imminent.	30		
Very sick; hospital admission necessary; Active supportive treatment necessary.	20		
		4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Moribund; fatal processes progressing rapidly.	10		
Dead	0	5	Dead

* As published in Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Appendix 4: MDRD formula (Levey et al, 2006)

The reexpressed 4-variable MDRD study equation for GFR, expressed in L/min/1.73m^2, with serum creatinine (Scr) expressed in mg/dL, is as follows:

GFR (mL/min/1.73 m^2) = 175 x (Scr)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if black)

Appendix 5: Response criteria in acute myeloid leukemia according to Diagnosis and Management of AML in Adults: 2017 ELN Recommendations from an International Expert Panel

Category	Definition	Comment
Response		
CR without minimal residual disease (CR_{MRD-})	If studied pre-treatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥ 1.0 x 10^9/L (1000/µL); platelet count ≥ 100 x 10^9/L (100,000/µL)	MRD positive or unknown
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L [1000/µL]) or thrombocytopenia (< 100 x 10^9/L [100,000/µL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
Primary refractory disease	No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine (see Table 8, Döhner, 2017) are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CRi, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 months

Category	Definition	Comment
Progressive disease (PD)[a,b]	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • ≥ 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10^9/L [500/μL], and/or platelet count to > 50 x 10^9/L [50,000/μL] non-transfused); or • > 50% increase in peripheral blasts (WBC x % blasts) to > 25 x 10^9/L (> 25,000/μL) (in the absence of differentiation syndrome)[b]; or • New extramedullary disease	Category mainly applies for older patient given low intensity or single-agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 weeks apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cut-off values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

[a] The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

[b] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

Appendix 6: Dose allocation meeting minutes template

Protocol: CL1-64315-004
Meeting decision on dose allocation at the end of Cohort No. ____: ____mg

Date of meeting / conference call:

Attendees:		
Centre(s): **Oncology Centre for Therapeutic Innovation** **Methodology Department** **PK analyst**	**Name(s):**	**Role(s):**

Cumulative Summary of Patients Treated

Patient No.	Treatment Start Date	Treatment Stop Date	Dose	DLT	Comment

Dose proposed by Methodology department

Dose proposed = ____ mg

Documents reviewed during the meeting:

- Interim safety report (*date*)
- Preliminary PK report (plasma/urine) *(date)*
- Core laboratory or clinical data e.g. QT, echo data
- Others….

Details on safety issues (by patient No.)

1. **Patient No.**
2. **Patient No.**
3. **Patient No.**

Decision at the end of the cohort meeting:

❑ Dose allocation continued ☐ ❑ Dose allocation stopped ☐	**Next cohort = ____ mg**

Comments:

e.g. Following review of the documents and data raised after the administration of x mg of S64315 in combination with azacitidine from dd/mm/yyyy to dd/mm/yyyy, it has been confirmed that the dose has been well tolerated and that the escalation to the next dose level (x mg of S64315 as full tested dose from Cycle 1 onwards) is appropriate.
Date: |__|__| / |__|__| / |__|__|__|__|
Signature(s):……

Appendix 7: Guidance for diarrhoea management (ESMO, 2018)

Algorithm for diagnostic exams of chemotherapy related diarrhoea:

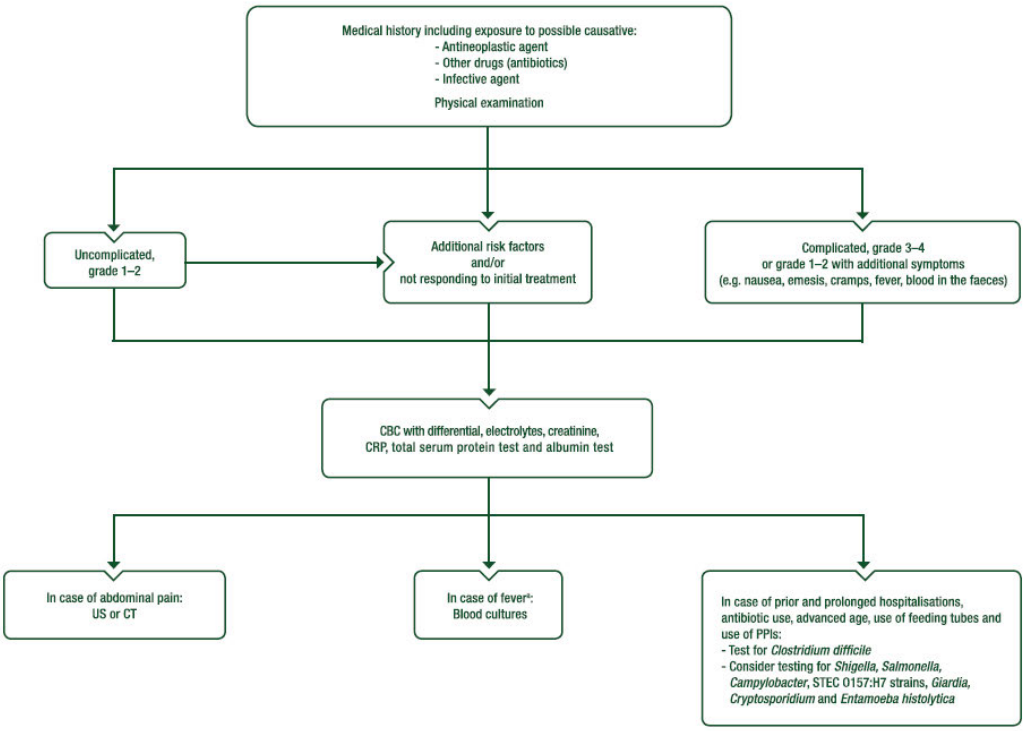


Figure 1. Algorithm for diagnostic exams of ChT-related diarrhoea.
[a]In case of neutropaenic fever, management according to ESMO guidelines on management of febrile neutropaenia [11].
CBC, complete blood count; ChT, chemotherapy; CRP, C-reactive protein; CT, computed tomography; ESMO, European Society for Medical Oncology; PPI, proton pump inhibitor; STEC, Shiga toxin-producing *Escherichia coli*; US, ultrasound.

Algorithm for therapeutic approach:

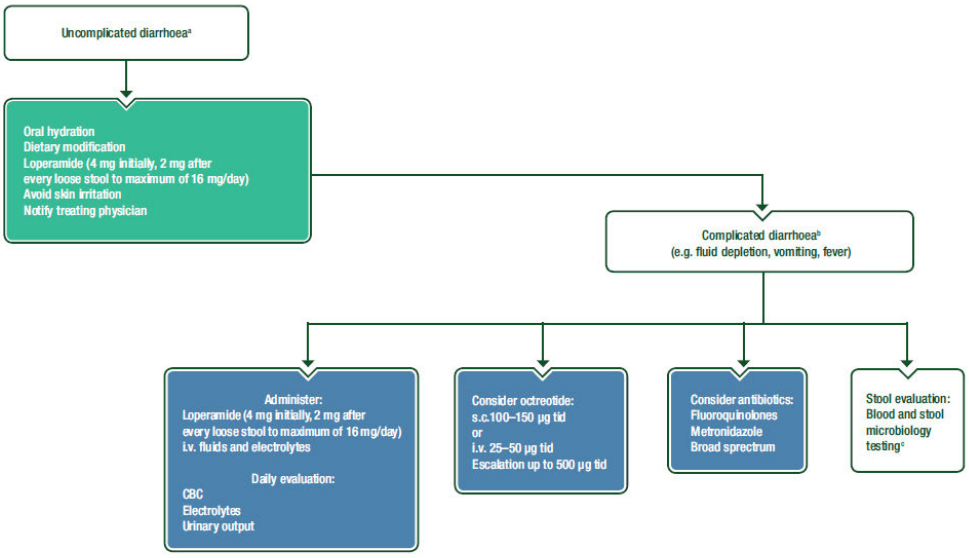


Figure 2. Algorithm for therapeutic approach.
[a]Treatment setting: ambulatory and/or outpatient supportive care outpatient unit.
[b]In-hospital treatment.
[c]Consider *Clostridium difficile*, *Salmonella*, *Campylobacter* and other causes of infectious colitis.
CBC, complete blood count; i.v., intravenous; s.c., subcutaneous; tid, three times a day.

Appendix 8: Statistical aspects for the dose escalation phase I part and the expansion phase II part with an interim analysis for futility

1. Dose escalation phase I part – ARM A: Operating characteristics of the Bayesian Logistic Regression Model (BLRM)

1.1. BLRM details – prior specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single-agent parameters for S64315 (α1, β1) and those for azacitidine (α2, β2), and the interaction parameter (η12). Derivation of these priors is provided in the following subsections.

1.1.1. Prior for S64315

The bivariate normal prior for the BLRM parameters (α_1, β_1) is based on clinical knowledge.

1.1.1.1. Prior specification

The Bayesian approach requires the specification of prior distributions for the two model parameters: α and β.

The same weakly informative prior as the one used in CL1-64315-001 study will be used and also data from CL1-64315-001 study will be used to enrich this same weakly informative prior (see section 1.1.1.2 for details).

The weakly-informative prior bivariate normal prior for the model BLRM parameters (log(α), log(β)) with a reference dose level of 1400mg is obtained as follows:

- The median DLT rate at the S64315 reference dose (1400 mg) was assumed to be 20%, i.e. $\text{mean}(\log(\alpha_1)) = \log(0.25)$
- A doubling in dose was assumed to double odds of DLT, i.e. $\text{mean}(\log(\beta)) = 0$
- The standard deviation of $\log(\alpha)$ was set to 2, and the standard deviation of $\log(\beta)$ to 1, which allows for considerable prior uncertainty for the dose-toxicity profile
- The correlation between $\log(\alpha)$ and $\log(\beta)$ was set to 0

Table (1.1.1.1) 1 summarizes these prior parameters. Table (1.1.1.1) 2 describes the prior obtained for S64315 agent. The effective sample size (ESS) calculated at each dose level is less than 2 patients (weakly-informative prior).

Table (1.1.1.1) 1 - Prior parameters for bivariate normal distribution of model parameters (α_1,β_1)

Parameters	Means	Standard deviations	Correlation
$\log(\alpha_1), \log(\beta_1)$	(-1.386, 0.000)	(2.000, 1.000)	0

Table (1.1.1.1) 2 - Prior distribution summaries derived from priors in Table (8.1.1) 1

S64315 dose (mg)	Prior probabilities that Pr(DLT) is in interval:					Quantiles			
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50%	97.5%	ESS[1]
25	0.897	0.049	0.054	0.057	0.140	0.000	0.003	0.548	1.755
50*	0.874	0.059	0.067	0.070	0.155	0.000	0.006	0.610	1.726
100	0.841	0.072	0.086	0.087	0.172	0.000	0.011	0.674	1.700
200	0.795	0.090	0.114	0.111	0.192	0.000	0.022	0.740	1.680
250	0.776	0.098	0.126	0.122	0.200	0.000	0.028	0.761	1.676

*: Starting dose
[1]: Effective Sample Size

1.1.1.2. Integration of CL1-64315-001 study data as co-data

Available clinical data from CL1-64315-001 study of the present study will be used to enrich the weakly informative prior used for S64315, in a downweighted fashion. The power prior obtained after integration of the CL1-64315-001 study data will be used as prior information for S64315.

The CL1-64315-001 study data will be incorporated through down-weighting using the following weight "w" (Chen, 2006; Neuenschwander, 2010):

$$w = \frac{1}{1 + 2n\tau^2/\sigma^2}$$

where n is the sample size of external data, σ is the "outcome standard deviation" for one observation and τ is the between-study standard deviation. While σ is the standard deviation of all external data which include several dose levels, σ^2 can be approximated by variance of log(α). For this dose-escalation, σ was then chosen as 2. The between-study standard deviation τ was set at 0.25 to correspond to a moderate between-trial variability, as a similar frequency of administration of S64315 is planned in the two studies.

All once a week monotherapy data (CL1-64315-001 study) validated in an End of Cohort meeting at the time of assessment of a cohort from combination S64315 and azacitidine will be considered to assess this cohort.

For information, the once a week monotherapy data available as of 26 November 2019, date of the last EoC meeting, are presented in Table (1.1.1.2) 1. Of note, based on these data, the highest allowed dose of S64315 in monotherapy in the once a week escalation in monotherapy is 300 mg, the highest dose tested being 500 mg.

Table (1.1.1.2) 1 - CL1-64315-001 study data

Dose of S64315 (QW, mg)	Number of DLT(s) / Number of evaluable patients
50	1/6
100	1/5
200	0/5
250	0/5
300	1/5
400	1/3
500	3/3

When accounting for these data, the power prior parameters obtained are presented in Table (1.1.1.2) 2.

Table (1.1.1.2) 2 - Power prior parameters for bivariate normal distribution of model parameters

Parameters	Means	Standard deviations	Correlation
$\log(\alpha), \log(\beta)$	(-0.092, -0.507)	(0.982, 0.694)	0.705

The corresponding power prior distribution is summarized in Table (1.1.1.2) 3.

Table (1.1.1.2) 3 - Power prior distribution summaries derived from power prior parameters in Table (1.1.1.2) 2

S64315 dose (mg)	Prior probabilities that Pr(DLT) is in interval:			Mean	SD	Quantiles			ESS[1]
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]			2.5%	50%	97.5%	
25	0.877	0.112	0.011	0.081	0.075	0.000	0.062	0.277	12.1
50*	0.791	0.185	0.025	0.108	0.088	0.001	0.088	0.333	11.4
100	0.650	0.291	0.059	0.147	0.103	0.006	0.127	0.402	10.7
200	0.447	0.411	0.143	0.203	0.120	0.026	0.182	0.490	10.2
250	0.372	0.440	0.188	0.226	0.126	0.038	0.205	0.522	10.0

* Starting dose level (provided this dose is considered safe (i.e. fulfilling the EWOC criterion) according to the power prior obtained by integrating all data from the once-a-week monotherapy study (CL1-64315-001 study) validated in an End of Cohort meeting)

[1]: Effective sample size

Note: none of the doses meet the overdose criterion (more than 25% chance of excessive toxicity) with the power prior information only.

The starting dose of S64315 for the combination with azacitidine is 50 mg. This dose is indeed considered safe according to the power prior calculated (see Table (1.1.1.2) 3 above).

1.1.2. Prior for azacitidine

The normal prior for the BLRM parameters (α_2, β_2) of the dose-DLT relationship of azacitidine is defined as a weakly-informative prior. The information available on azacitidine (e.g. SmPC) have been used to define the prior parameter alpha. As there is only one dose for azacitidine, and as the reference dose is equal to this only dose, there is no estimation of β_2, then there is now only one parameter estimated for this agent. However, a prior has been defined anyway on β_2 to keep the opportunity to add another dose of azacitidine, if the matter appears in the future.

With a reference dose level of 75 mg/m^2, the prior parameters are obtained as follows:

- The median DLT rate at the azacitidine reference dose (75 mg/m^2) was fixed such that the mean DLT rate at this dose, with the considered standard deviation, was equal to 8%, leading to a median DLT rate of 2.3, i.e. mean(log(α_2)) = log (0.023/0.977) (see prior distribution in Table (1.1.2) 2)
- A doubling in dose was assumed to double odds of DLT, i.e. mean(log(β_2)) = 0
- The standard deviation of log(α_2) was set to 2 which allows for strong prior uncertainty for the dose-toxicity profile of azacitidine
- The correlation between log(α_2) and log(β_2) was set to 0

Table (1.1.2) 1 summarizes these prior parameters.

Table (1.1.2) 1 - Prior parameters for bivariate normal distribution of model parameters (α_2,β_2) for azacitidine

Parameters	Means	Standard deviations	Correlation
log(α_2), log(β_2)	(-3.75, 0)	(2, 1)	0

Resulting distribution and associated summary statistics are presented in Table (1.1.2) 2.

Table (1.1.2) 2 - Prior distribution summaries for azacitidine derived from priors in Table (1.1.1.2) 1

Azacitidine dose (mg/m^2)	Prior probabilities that Pr(DLT) is in interval:					Quantiles			
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50%	97.5%	ESS[1]
75	0.8574	0.0795	0.0631	0.0803	0.1404	5,00E-04	0.0230	0.5417	2.7493

[1]: Effective sample size

1.1.3. Prior for interaction parameter

A normal prior distribution for the interaction parameter η_{12} is derived to reflect the current uncertainty about the toxicity profile of the combination of S64315 and azacitidine:

- η_{12} is normally distributed and centred on 0 (reflecting an assumption of no PK drug-drug interaction a priori)
- 97.5th percentile of η_{12} is selected such that there is a 2-fold increase in odds of DLT due to interaction compared to independence at the dose combination (50 mg of S64315, 75 mg/m^2 of azacitidine), allowing for enough uncertainty in case an interaction exists

Consequently, the mean and standard deviation of the normal prior distribution for η_{12} turn out to be 0 and 9.902 respectively.

Table (1.1.3) 1 summarizes this prior parameter. Table (1.1.3) 2 shows the prior median and 95% credible interval for the interaction term $\exp(\eta_{12}(d_1/d_{1*})(d_2/d_{2*}))$ = $\exp(\eta_{12}(d_1/d_{1*})$ (as $d_2=d_{2*}$) at all provisional dose level combinations.

Table (1.1.3) 1 - Prior parameters for normal distribution of model parameters (η_{12})

Parameters	Means	Standard deviations
η_{12}	0	9.902

Table (1.1.3) 2 - A priori interaction at the provisional dose levels

S64315 (mg)	Azacitidine (mg/m^2)
	75
25	1 (0.71,1.4)
50*	1 (0.5,2)
100	1 (0.25,4)
200	1 (0.063,16)
250	1 (0.031,31)

*median (95% credible interval) of interaction parameter $\exp(\eta_{12}(d_1/d_{1^*})(d_2/d_{2^*})$ at dose combination (50 mg of S64315, 75 mg/m² of azacitidine)

1.1.4. Prior for combination

Combining the priors of the five parameters and including data on S64315 from CL1-64315-001 study as of 26 November 2019 (power prior), the distribution of the DLT rates for provisional dose combinations is summarized in Table (1.1.4) 1.

The greater effective sample size at lower dose combinations illustrate the greater amount of information brought by the CL1-64315-001 study data at these low dose combinations (32 patients indeed treated at doses between 50 mg and 500 mg in CL1-64315-001 study, among which 21 at 250 mg or below).

Table (1.1.4) 1 - Distribution summaries derived from Table (1.1.1.2) 3, Table (10.4.4.4) 2, Table (10.4.4.4) 3

S64315 dose (mg)	Prior probabilities that Pr(DLT) is in interval:					Quantiles			
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50%	97.5%	ESS[1]
	Azacitidine = 75 mg/m^2**								
25	0.661	0.239	0.101	0.156	0.148	0.008	0.112	0.588	5.0
50*	0.577	0.280	0.143	0.184	0.158	0.012	0.140	0.626	5.0
100	0.472	0.286	0.241	0.231	0.187	0.017	0.179	0.722	4.1
200	**0.397**	**0.216**	**0.387**	**0.312**	**0.262**	**0.012**	**0.234**	**0.898**	**2.1**
250	**0.390**	**0.183**	**0.427**	**0.345**	**0.294**	**0.008**	**0.257**	**0.948**	**1.6**

*: Starting dose for S64315 (provided this dose is considered safe (i.e. fulfilling the EWOC criterion) according to the power prior obtained by integrating all data from the once-a-week monotherapy study (CL1-64315-001 study) validated in an End of Cohort meeting)
**: Starting dose for azacitidine
[1]: Effective Sample Size
Note: bold values indicate dose combinations not meeting the overdose criterion (more than 25% chance of excessive toxicity) with the prior information only.

1.2. Operating characteristics

1.2.1. Introduction

This section presents the operating characteristics illustrating the precision of the design in estimating the MTD under various assumed true dose-toxicity relationships.

1.2.2. True dose-DLT scenarios

Simulations were performed on five different true dose-toxicity relationships representing hypothetical scenarii where the data are more or less in agreement with what can be expected from the prior information considered (for S64315, azacitidine and interaction) and data collected on S64315 (data of CL1-64315-001 study as of as of 26 November 2019). The summary of the DLT rates obtained from the combination of these priors and the CL1-64315-001 data considered (see section 1.1.4) represents what can be expected. The scenarii are:

a. MTD is reached at late provisional dose level: the odds of DLT are lower than expected; only the last dose level is in the target interval
b. MTD is reached at middle provisional dose level: the odds of DLT are similar with what is expected (c.f. what was estimated mean DLT rate after adding the once a week monotherapy data to the prior information, see section 1.1.4)
c. MTD is reached at early-middle provisional dose level: the odds of DLT are aligned with what is expected at low dose levels only; at higher dose levels the odds of DLT are higher than expected (dose levels not fulfilling the EWOC criterion in the power prior combination as of 26 November 2019, see section 1.1.4)
d. MTD is reached at early provisional dose level: the odds of DLT are higher than expected; only the starting and back-up dose levels are safe
e. All doses are considered overtoxic

Table (1.2.2) 1 - True underlying DLT probabilities

Scenario a		**S64315 (mg)**				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	0.05	0.07	0.09	0.12	0.18
Scenario b		**S64315 (mg)**				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	0.19	0.22	0.29	0.35	0.40
Scenario c		**S64315 (mg)**				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	0.20	0.27	0.40	0.50	0.60
Scenario d		**S64315 (mg)**				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	0.25	0.45	0.5	0.55	0.60
Scenario e		**S64315 (mg)**				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	0.45	0.5	0.55	0.6	0.65

Note: Grey shading indicates dose combinations with true DLT probability within the targeted toxicity interval [16%. 33%)
*Starting dose level combination
[1]Azacitidine

Note that scenarii *a* (very little toxic), *d* and *e* (very toxic) represent unlikely scenarii in combination with azacitidine based on the data already collected on the S64315 in monotherapy (CL1-64315-001 study once a week monotherapy data).

1.2.3. Simulation parameters

For each dose combination-DLT scenario, 5000 clinical trial replications were generated using R software version 3.4.1 on a x86-64 architecture on a Linux OS. The MCMC estimation is obtained using Rjags R package with 5000 burnin and 10000 iterations on 2 chains (5000 each), per scenario. Each clinical replication is numbered from SimulationNumber = 1 to 5000. The seed used for data generation is 1234*SimulationNumber and the seed used for MCMC estimation is 1 for chain 1 and 2 for chain 2.

The following trial simulation parameters were used:

- Cohort size: 3
- Starting dose: 50 mg of S64315 combined to 75 mg/m^2 of azacitidine

The dose allocation rule used in the simulations is the dose having the highest posterior probability of the DLT rate falling in the targeted interval [16%, 33%) among the admissible doses fulfilling EWOC (note that in practice any admissible dose fulfilling EWOC could be recommended).

1.2.4. Evaluation metrics

Operating characteristics were reviewed for the simulations to compare the relative performance of the design under each true dose-DLT relationship. The following metrics were:

- Probability of recommending as the MTD:
  - an undertoxic dose level combination, i.e. a dose combination with true probability of DLT in the under-dosing toxicity interval [0%, 16%) (sponsor risk)
  - a targeted dose level combination, i.e. a dose combination with true probability of DLT in the targeted toxicity interval [16%, 33%) (correct final decision)
  - an overtoxic dose level combination, i.e. a dose combination with true probability of DLT in the excessive toxicity interval [33%, 100%] (patient risk)
- Average number of patients per trial exposed at:
  an undertoxic dose level combination, as defined above
  a targeted dose level combination, as defined above
  an overtoxic dose level combination, as defined above
- Summary of the total number of patients per trial (average, 1st quartile, median, 3rd quartile)
- Average total number of DLTs observed per trial

1.2.5. Operating characteristics of the design

Operating characteristics of the final design are reviewed to investigate performance of the model under each true dose-DLT scenario. Table (1.2.5) 1 summarises the results from the simulations performed according to the rules defined in section 1.2.3. Table (1.2.5) 2 details the selection probability of each dose combination in each scenario.

Table (1.2.5) 1 - Summary metrics of the simulations performed

True dose-DLT scenario	Probability of recommending a dose combination with true P(DLT)			No MTD recommend-ation	Average number of patients per trial receiving a dose combination with true P(DLT)			Average number of patients	
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]		[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Per trial (Q1 - Median - Q3)	Experiencing a DLT per trial
a	31.24	67.02	NA	1.74	12.45	5.56	NA	18.01 (18 - 18 - 18)	2.18
b	NA	75.12	6.04	18.84	NA	9.77	1.84	11.61 (6 - 12 - 15)	3.15
c	NA	51.18	20.52	28.30	NA	5.78	3.94	9.71 (6 - 9 - 15)	3.18
d	NA	1.56	34.02	64.42	NA	0.38	6.00	6.37 (3 - 6 - 6)	2.87
e	NA	NA	25.30	74.70	NA	NA	5.62	5.62 (3 - 3 - 6)	2.82

Overall, the BLRM with the specified prior is performing reasonably well in all pre-specified scenarios: the performance is good in scenario b and c (the most likely), with a high chance to select the right dose while minimizing the probability of overtoxicity, and correct in scenarii a, d and e, yet less likely.

In scenario a, only the highest dose combination falls into the target interval and this dose is recommended 67% of the time. By looking more in detail at the probabilities of selection of each dose combination in Table (1.2.5) 2, we can see that the dose combinations (200 mg of S64315, 75 mg/m^2 of azacitidine) – 12% true toxicity rate, and (100 mg of S64315, 75 mg of azacitidine) – 9% true toxicity rate, both close to the target interval, are often recommended. The scenario a is unlikely as the data from the CL1-64315-001 study already collected are more toxic. The minimum number of patients that could trigger a stopping rule is also low (18) so that the escalation may stop before reaching the highest dose, even without seeing toxic data. In practice the stopping rule could be “ignored” in this situation, to pursue escalation.

Table (1.2.5) 2 - Probability of recommending each dose combination in the simulations performed

Scenario a		S64315 (mg)				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	0.00	5.06	20.54	5.64	67.02
Scenario b		S64315 (mg)				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	0.72	36.60	37.80	1.42	4.62
Scenario c		S64315 (mg)				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	1.42	49.76	20.00	0.30	0.22
Scenario d		S64315 (mg)				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	1.56	30.00	3.94	0.04	0.04
Scenario e		S64315 (mg)				
	A[1] (mg/m²)	**25**	**50**	**100**	**200**	**250**
	75	0.80	22.26	2.20	0.04	0.00

Note: Grey shading indicates dose combinations with true DLT probability within the targeted toxicity interval [16%. 33%)
*Starting dose level combination
[1]Azacitidine

The probability of recommending a dose in the overtoxic interval [0.33, 1] is more important in scenario d as only one dose combination (back-up one) falls into the target interval, all the other ones being too toxic. In this scenario, the starting dose combination (50 mg of S64315, 75 mg of azacitidine) presenting a 45% true toxicity rate is indeed recommended 30% of the time. This true toxicity rate of 45% is not so far from the upper boundary of the target interval (33%), explaining why this dose combination is sometimes recommended. The fact that the starting dose is already too toxic may also have an impact as 6 patients can be quickly included at this dose and check the condition of a probability to be in the target interval >50%, leading the model to stop and the dose to be declared as MTD. Additional patients could be included at the dose in practice if judged necessary before declaring the MTD.

In scenario e, 74% of the time the trial is stopped for overtoxicity, as no dose combination falls into the target interval, all dose combinations being too toxic. The average number of patients per trial indicates that on average, less than 2 cohorts of three patients are necessary to see that no dose can be recommended, preventing us from exposing too many patients to overtoxic doses. An overtoxic dose combination is recommended 25% of the time, and it can be explained similarly as in scenario d: in scenario e, the starting dose is already too toxic and is recommended 22% of the time.

Note that the results of the simulations performed here are dependent on the dose escalation rules that were used, as well as on the data from the ongoing CL1-64315-001 study that were considered. During the study, many other parameters than the model are considered to recommend the dose for the next cohort, as for instance PK data, PD data, safety data other than DLTs (see section 10.2.7 in the protocol) and also potential patients having DLT in the lead-in period. And as specified in section 1.1.2, all available data from the ongoing CL1-64315-001 study will be included.

1.3. Hypothetical dose allocation scenarios in early cohorts

Aside from the overall operating characteristics studied above, the design should make reasonable decisions during a study based on the observed DLTs. After completion of a given cohort, the dose allocation for the subsequent cohort will depend on the recommendation of the model and medical review of all available data.

Some scenarios to illustrate on-study dose allocation are presented in Table (1.3) 1. These scenarios assume that the first cohort will include 5 patients and then each cohort has 3 valuable patients and the next recommended dose is based on the dose escalation rules defined in section 1.2.3. However, during the study, it may be possible to include 3 to 6 patients by cohort and to add new provisional dose levels.

Table (1.3) 1 - Hypothetical dose allocation scenarios in early cohorts

Cohort	Dose S64315 (mg)-azacitidine (mg/m^2)	Nb of DLT(s)/Nb of patients	Next dose level (NDL) proposed (mg)	Decision (S64315-azacitidine)	P(Target) NDL	P(Overtox) NDL	Median DLT rate at NDL
1	50 - 75	0/5	100 - 75	E-S	0,2526	0,0666	0,1061
		1/5	100 - 75	E-S	0,3941	0,2246	0,1996
		2/5	25 - 75	D-S	0,4456	0,2032	0,2045
		3/5	--*	--*	--*	--*	--*
		4/5	--*	--*	--*	--*	--*
		5/5	--*	--*	--*	--*	--*
2a (0/5 DLT in cohort 1 (50mg – 75 mg/m^2))	100 - 75	0/3	200 - 75	E-S	0,2020	0,1312	0,0926
		1/3	100 - 75	S-S	0,3911	0,1118	0,1606
		2/3	50 - 75	D-S	0,4784	0,0918	0,1762
		3/3	50 - 75	D-S	0,5436	0,2295	0,2356
2b (1/5 DLT in cohort 1 (50mg – 75 mg/m^2))	100 - 75	0/3	200 - 75	E-S	0,2741	0,2370	0,1655
		1/3	50 - 75	D-S	0,4874	0,0969	0,1793
		2/3	25 - 75	D-S	0,4805	0,1472	0,1923
		3/3	--*	--*	--*	--*	--*
2c (2/5 DLT in cohort 1 (50mg – 75 mg/m^2))	25 - 75	0/3	50 - 75	E-S	0,5043	0,1471	0,1976
		1/3	25 - 75	S-S	0,5178	0,2217	0,2265
		2/3	--*	--*	--*	--*	--*
		3/3	--*	--*	--*	--*	--*
3a (0/5 DLT in cohort 1 (50mg – 75 mg/m^2) and 0/3 in cohort 2 (100mg – 75 mg/m^2))	200 - 75	0/3	250 - 75	E-S	0,1467	0,0628	0,0555
		1/3	200 - 75	S-S	0,3492	0,2039	0,1786
		2/3	100 - 75	D-S	0,4881	0,0966	0,1811
		3/3	50 - 75	D-S	0,3375	0,0360	0,1310
3b (0/5 DLT in cohort 1 (50mg – 75	100 - 75	0/3	200 - 75	E-S	0,2958	0,2294	0,1707
		1/3	100 - 75	S-S	0,4942	0,1469	0,1969

mg/m²) and 1/3 in cohort 2 (100mg – 75 mg/m²))		2/3	50 - 75	D-S	0,5317	0,0912	0,1869
		3/3	50 - 75	D-S	0,5819	0,2140	0,2380
3c (0/5 DLT in cohort 1 (50mg – 75 mg/m²) and 2/3 in cohort 2 (100mg – 75 mg/m²))	50 - 75	0/3	100 - 75	E-S	0,4869	0,2069	0,2170
		1/3	50 - 75	S-S	0,5663	0,1178	0,2011
		2/3	25 - 75	D-S	0,5267	0,1457	0,1990
		3/3	--*	--*	--*	--*	--*
3d (0/5 DLT in cohort 1 (50mg – 75 mg/m²) and 3/3 in cohort 2 (100mg – 75 mg/m²))	50 - 75	0/3	50 - 75	S-S	0,5564	0,1101	0,1975
		1/3	25 - 75	D-S	0,4927	0,1118	0,1836
		2/3	25 - 75	D-S	0,5325	0,2389	0,2390
		3/3	--*	--*	--*	--*	--*
4a (1/5 DLT in cohort 1 (50mg – 75 mg/m²) and 0/3 in cohort 2 (100mg – 75 mg/m²))	200 - 75	0/3	250 - 75	E-S	0,2047	0,1011	0,0898
		1/3	100 - 75	D-S	0,4846	0,0789	0,1745
		2/3	100 - 75	D-S	0,5720	0,2320	0,2447
		3/3	50 - 75	D-S	0,5445	0,1117	0,1968
4b (1/5 DLT in cohort 1 (50mg – 75 mg/m²) and 1/3 in cohort 2 (100mg – 75 mg/m²))	50 - 75	0/3	100 - 75	E-S	0,4843	0,1691	0,2023
		1/3	50 - 75	S-S	0,5496	0,1341	0,2044
		2/3	25 - 75	D-S	0,5300	0,1804	0,2135
		3/3	--*	--*	--*	--*	--*
4c (1/5 DLT in cohort 1 (50mg – 75 mg/m²) and 2/3 in cohort 2 (100mg – 75 mg/m²))	25 - 75	0/3	50 - 75	E-S	0,5660	0,1421	0,2099
		1/3	25 - 75	S-S	0,5374	0,1734	0,2120
		2/3	--*	--*	--*	--*	--*
		3/3	--*	--*	--*	--*	--*
5a (2/5 DLT in cohort 1 (50mg – 75 mg/m²) and 0/3 in cohort 2 (25 mg – 75 mg/m²))	50 - 75	0/3	100 - 75	E-S	0,4483	0,2222	0,2140
		1/3	50 - 75	S-S	0,5749	0,1672	0,2189
		2/3	25 - 75	D-S	0,5546	0,2072	0,2310
		3/3	--*	--*	--*	--*	--*
5b (2/5 DLT in cohort 1 (50mg – 75 mg/m²) and 1/3 in cohort 2	25 - 75	0/3	50 - 75	E-S	0,5732	0,1849	0,2246
		1/3	25 - 75	S-S	0,5687	0,2454	0,2445
		2/3	--*	--*	--*	--*	--*
		3/3	--*	--*	--*	--*	--*

(25 mg – 75 mg/m²))							
Note: Decision for each agent, E = Escalate, S = Stay, D = Deescalate **P(Target) NDL: Posterior probability that the true DLT rate for the next recommended dose lies in the targeted interval [16%, 33%)** **P(Overtox) NDL: Posterior probability that the true DLT rate for the next recommended dose lies in the excessive toxicity interval [33%, 100%]** ***: No doses are considered safe according to the EWOC condition**							

Overall, the dose recommendation leads to decisions that are in agreement with clinical sense. In general, when no DLTs are observed on 3 patients in a dose level, the decision is to increase the dose combination. When 1 DLT is observed on 3 patients in a dose level combination, the decision is to stay at the current dose level combination. When more than 1 DLT is observed on 3 patients in a dose level, the decision is to decrease the dose level.

2. Expansion phase II part

2.1. Introduction

Once the RP2D (MTD or suitable lower dose) has been determined, new patients will be enrolled in a two-stage expansion phase II part in three sub-arms A1 and A2. A Bayesian interim analysis for futility will be performed at the end of the first stage in each sub-arm. The following methodology will be applied for each the three sub-arms.

During stage 1, the patients will be enrolled and treated at the corresponding RP2D (identified during the dose escalation phase I part). One interim analysis for futility will occur when:

- All patients included in stage 1 have completed at least four cycles or early discontinued
- The CRs reached during this time must be confirmed

Then, Bayesian analysis will be performed on CR rate. Decision rules will be based on clinical threshold defined on the posterior distribution of CR rate (see section 2.3 determination of sample size for details).

According to results of futility interim analysis performed at the end of stage 1, the expansion phase II part could be:

- Stopped, if results on CR rate are considered futile
- Continued if results on CR rate are considered not futile. In that case, one additional cohort of patients will be enrolled in stage 2 and treated at the corresponding RP2D

2.2. Methodology

2.2.1. Bayesian approach

The observed response is a binary variable, either a success or failure outcome from the administered treatment. With n being the number of observed patients, the number of observed responses s, is a binomial variable (n, π), where π is the probability of response.

Let π, a random variable with the prior distribution Beta(a,b) where a and b>0. The values of a and b are fixed at the beginning of the trial (see 2.2.3 Prior specification for details). The mean and the variance of the Beta(a,b) distribution are given by $E(\pi)=a/(a+b)$ and $Var(\pi)=ab/((a+b)^2(a+b+1))$.

After n patients are included into the trial, the posterior distribution of the probability of response, is given by Beta(a+s,b+n-s), with its mean defined by $E(\pi)=(a+s)/(a+b+n)$.

2.2.2. Futility rule

Stop for futility if there is a high probability that the estimated response rate is lower than a minimal response rate threshold.

That is, $P(\pi \leq R_L|data)>\tau$ where R_L is a minimal response rate threshold, fixed before the beginning of the trial by clinical development team.

τ is chosen to be enough restrictive for further stop if flagrant futility is observed, but not too much to allow the possibility for activity analysis at study end, by including more patients in stage 2.

2.2.3. Prior specification

In a Bayesian framework, a prior distribution needs to be defined. In this situation, we choose a Jeffreys prior, a non-informative prior distribution, e. g. a=0.5 and b=0.5.

2.3. Operating characteristics

2.3.1. Clinical and Statistical assumptions

According to the information given by the clinical development team, the response rate is partitioned as follows:

• [0%; R_L%): No activity on CR rate– results are considered futile

• [R_L%; 100%]: improvement on CR rate – results are not considered futile - one additional cohort of patients will be enrolled in stage 2

The thresholds R_L have been defined from literature and given the current information, will be the same for the three sub-arms:

Table (2.3.1) 1 - Choice of response rate threshold RL

Threshold R_L	References
20%	(Schuh, 2017)

The susmentionned threshold might evolve given the information available before the start of phase II part, independently for sub-arms A1 and A2, based on more recent published data if available.

In a Bayesian framework, threshold needs to be defined on the posterior distribution, as previously explained for the dose-escalation part appendix. In our case, it is defined as the minimum probability to observe less than the fixed threshold CR rate. In our case, if the probability of observing CR rate < R_L% is over the threshold of 60% (P(CR rate < R_L %) > 60%), we will declare results as futile.

2.3.2. Simulations parameters

5000 clinical trials under several scenarios were generated using R software version 3.4.1 on a x86-64 architecture on a Linux OS. Several scenarios will be investigated in order to perform a sensitivity analysis on the number of patients to enhance the performance of the model.

2.3.3. Operating characteristics of the design for stage 1

2.3.3.1. Probability to stop for futility according to true response rate

Results of 5000 clinical trials with a true response rate R_L were simulated assuming a binomial distribution with parameters (n_1, R_L) with n_1 corresponding to the number of patients in stage 1. For each clinical trial, the posterior probability of true response rate < R_L is compared to the threshold of 20%. Then, among the 5000 simulations, the probability to stop for futility at interim analysis (i.e. the probability that the posterior probability of true response rate < R_L is over 60%) is calculated. Results are presented in table below for different value of n_1.

Table (2.3.3) 1 - Probability of stopping for futility at R_L at the interim depending on the number of patients

Probability (%) stopping for futility at interim (P(CR rate < R_L %) > 60%)

True response rate for futility (R_L)	20 pts	21 pts	22 pts	**23 pts**	24 pts	25 pts
20	0,411	0,368	0,331	**0,503**	0,466	0,423

A minimal number of 23 patients have been fixed to ensure enough evidence for futility analysis in a Bayesian framework with a vague prior.

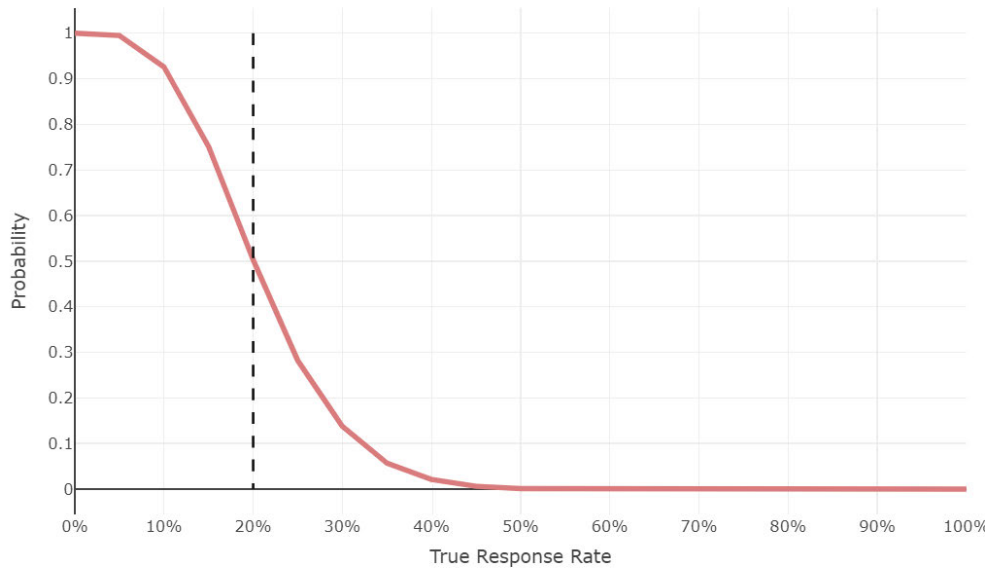
For clinical trials simulated with true response rate equal to R_L, the probability to stop for futility at interim is maximized with n_1= 23 patients in stage 1. These probabilities are equal to 50%.

Thus, considering n_1= 23 patients in stage 1 allows to obtain good operating characteristics for a futility analysis.

The same calculations as above were performed for clinical trials simulated with different true response rate (from 0% to 100%). Results are presented below for n_1= 23 patients for stage 1.

Figure (2.3.3) 1 - Probability to stop for futility during the trial according to the true CR rate (n = 23)

n =23



According to graphic representations, with n_1 =23 patients enrolled in stage 1, the probability to stop for futility at interim rapidly decreases for true response rate above the threshold R_L, with a slope of -4.7 at R_L. Moreover, probability to stop for futility at interim analysis is less than 14% for true response rate equal to R_L + 10%.

2.3.3.2. Minimal number of responders out of 23 patients to continue in stage 2

Table (2.3.3) 2 - Minimal number of responders out of 23 patients to continue in stage 2

N	Observed Responses (N (%))	Posterior mean [90% Credible interval]	Probability of the true rate falling within [0; 0.20[	Probability of the true rate falling within [0.20; 1]
23	3 (13%)	0.1458 [0.0487; 0.2769]	0.7930	0.207
	4 (17.4%)	0.1875 [0.0754; 0.3296]	0.6034	0.3966
	5 (21.7%)	0.2292 [0.1048; 0.3797]	0.3980	0.602
	6 (26.1%)	0.2708 [0.1361; 0.4277]	0.2253	0.7747

The futility decision will be overpassed if we observe at least 5 responders out of 23 patients during stage 1. In that case (5 responders/23 patients), the posterior probability for true response rate to be ≥20% is equal to 60% which provides enough evidence for non-futility of the d in the context of interim analysis.

Thus, according to all analyses presented above, with n $_1$ = 23 patients in stage 1, the operating characteristics of the design are considered sufficient and do not justify a further increase in the sample size for stage 1.

2.3.4. Operating characteristics of the design for stage 2

In case of no futility decision at interim analysis, one additional cohort of patients will be enrolled in stage 2 and treated at the corresponding RP2D. In the following sections, the operating characteristics of the design will be checked in case of enrolment of 27 additional patients in stage 2 ($\boldsymbol{n_2 = 27}$), giving an overall sample size of n=$\boldsymbol{n_1 + n_2}$ = 50 patients for the expansion phase II part.

2.3.4.1. Operating characteristics according to true response rate

The same simulation analyses as the ones performed for stage 1 have been done.

Results of 5000 clinical trials with a true response rate R_L (same as stage 1) were simulated assuming a binomial distribution of parameters (n, R_L), with $\boldsymbol{n = 50}$, corresponding to the overall number of patients of expansion phase II part, e.g. first 23 patients included at stage 1 and then 27 more. The posterior probability of true response rate > R_L is compared to different thresholds (70%, 80%), for the overall number of subject 50. Then, among the 5000 simulations, the probability that the posterior probability of true response rate > R_L is over the threshold is calculated, with R_L=20%. Results are presented in table below.

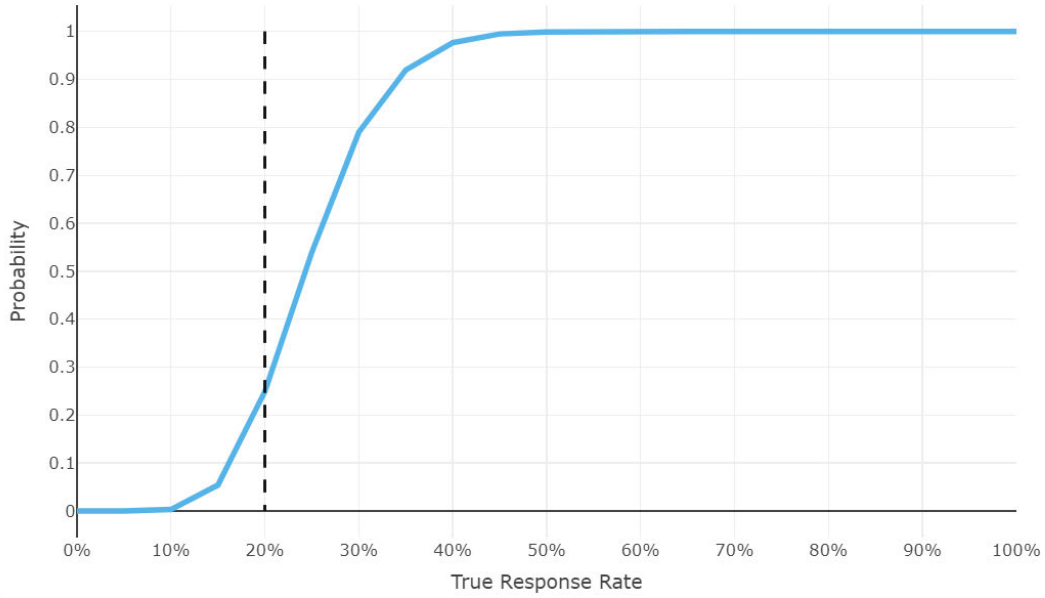
Table (2.3.4.1) 1 - Probability of having a posterior probability of true response rate R_L over a threshold Y

Overall number of subject	Probability (%) for P(CR >20) > Y % at study end	
	Y=70%	Y=80%
50	24.7	17.0

Considering a threshold of 70% (respectively 80%), there is 25% probability (respectively 17% probability) that the posterior probability of true response rate be greater than $R_{L,}$ for clinical trials simulated with a true response rate equal to the futility boundary R_L.

Same calculations were performed for clinical trials simulated with different true response rates (from 0% to 100%). Results are presented below for n=50 patients and for 70% boundary.

Figure (2.3.4) 1 - Probability for P(CR rate > R_L) > 70% at study end according to the true CR rate



According to graphic representations, with $n = 50$ patients for the expansion phase II part, the chance that the posterior probability of true response rate be greater than $R_{L,}$ rapidly increases for true response rate above the threshold R_L: these probabilities reach 80% for true response rate equal to R_L + 10%.

According to these results, we consider that 50 patients for expansion phase II part provide enough evidence for activity.

2.3.4.2 Justification based on precision of the estimate

Moreover, the length of the credibility interval has also been checked with 50 patients included for the expansion phase II part per sub-arm.

50 patients enrolled in the expansion phase II part per sub-arm ensure a maximal length of the 90% credibility interval on the posterior distribution (i.e. a minimal precision) of 23% around the estimated response rate at each sub-arms end.

2.3.4.3. Conclusion for overall number of patients in expansion phase II part

Thus, according to all analyses presented above, n = 50 patients for each sub-arm of the expansion phase II part allow to have sufficient operating characteristics of the design for activity assessment, so N=150 overall for the expansion phase II part.

Appendix 9: Local modification of the clinical study protocol

FINAL VERSION DATE: 14 December 2020

COUNTRY*(COUNTRIES)* CONCERNED: FRANCE

NATURE OF MODIFICATIONS

- Paragraphs impacted: **Synopsis – Non screening criteria, 5.2.2. General criteria**
- Amended text:

SYNOPSIS

[…]

Non screening criteria

[…]

9a. Unlikely to cooperate in the study or legally incapacitated person under guardianship or trusteeship or judicial protection.

5.2.2. General criteria

[…]

9a. Unlikely to cooperate in the study or legally incapacitated person under guardianship or trusteeship or judicial protection.

Appendix 10: Instructions to investigator for handling data rights requests

DATA PROTECTION / GDPR (General Data Protection Regulation of 27 April 2016 n°2016/679)–

INSTRUCTIONS TO INVESTIGATOR FOR HANDLING DATA RIGHTS REQUESTS

In the framework of a research study/clinical trial, a participant to the study may exercise his/her rights, i.e. may ask I.R.I.S. (as data controller) for:

- access to his/her data
- rectification of inaccurate/incomplete information
- restriction of processing of data
- objection to processing of data
- data portability (receiving his/her data in a readable format)

In accordance with the Informed Consent Form and information notice provided to participant, we requested participant to contact you first for exercising their rights.

Request for exercise of rights:

- has to be a **written** one (either originating from an (e)-mail from a participant or from request expressed orally to you and put in written)
- has to be sent **by you** by e-mail or by mail **to** I.R.I.S. (as data controller) to central address dataprivacy@servier.com or local Servier address as mentioned in ICF/information notice provided/available

DO **Instructions to be followed by you**	**DON'T** **What you should not do**
E-mail title: Data protection rights	Do not forward participant e-mail (if applicable)
Study name/number	
Participant number	**No information regarding participant identity**: No participant's name, e-mail address, participant's signature
As soon as possible without exceeding a week	

I.R.I.S. and INVESTIGATOR responsibilities

GDPR requirement:
It is mandatory for I.R.I.S. as data controller to provide an answer to participant/volunteer within 1 month following the request (article 12 of GDPR)
Clinical trials requirements:
It is prohibited for I.R.I.S. as a sponsor to know the identity of the participants/volunteer participating to studies

	I.R.I.S. responsability	**Investigator responsability**
Forward/inform I.R.I.S. of the request		YES
Timelines	Answer within 1 month once expressed by the participant	Request: transmitted to I.R.I.S. as soon as expressed by the participant Answer: transmitted by you to participant as soon as sent by I.R.I.S.
Answer the request	YES	